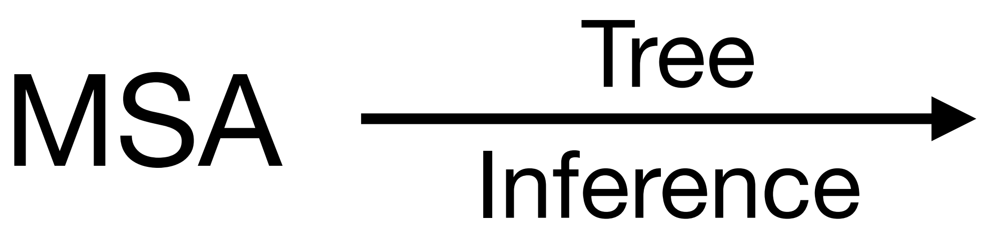
From Easy to Hopeless

Predicting the Difficulty of a Phylogenetic Analysis

Julia Haag

HITS Heidelberg

What does difficult mean?

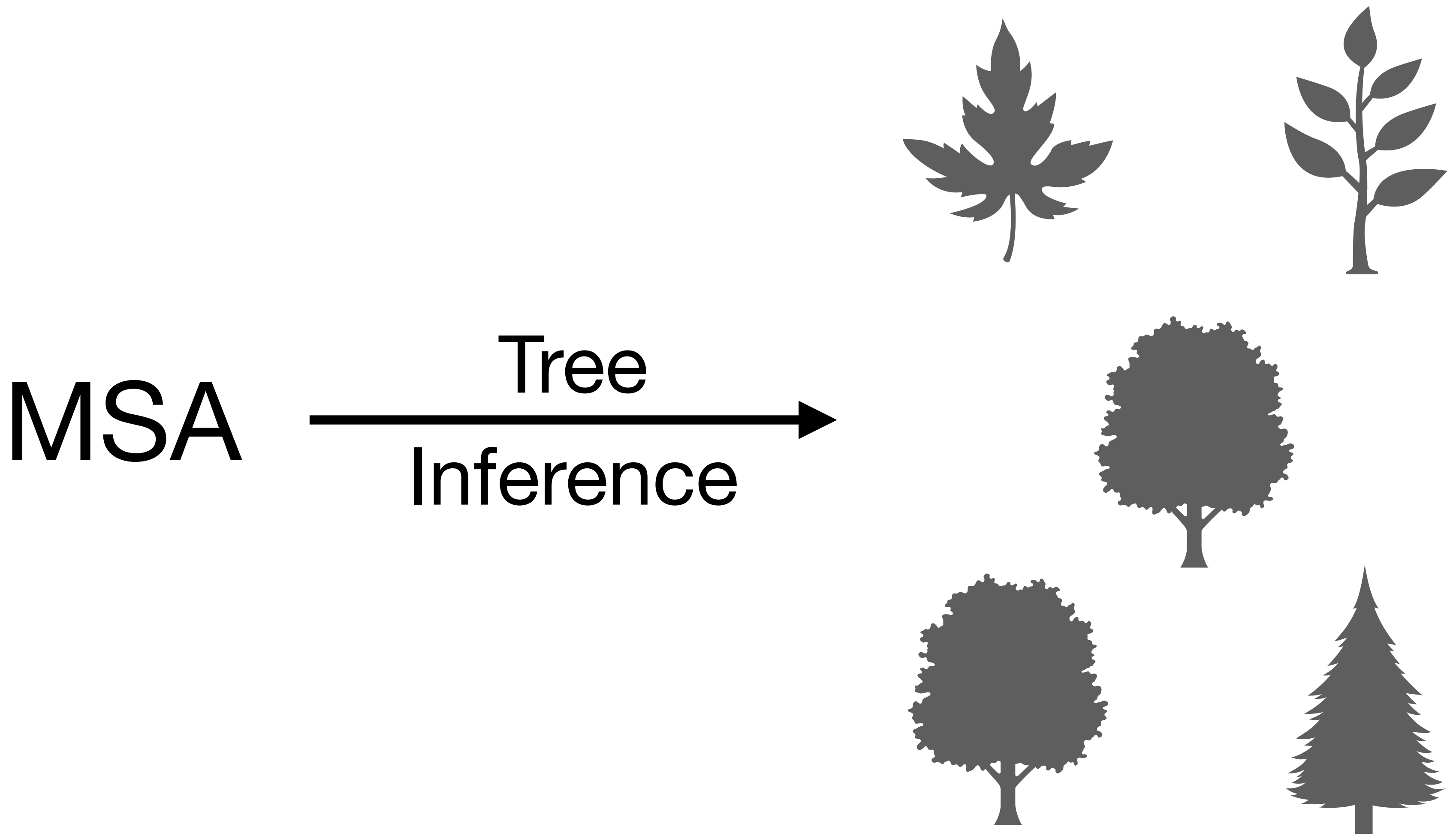


MSA

Tree

Inference

What does difficult mean?



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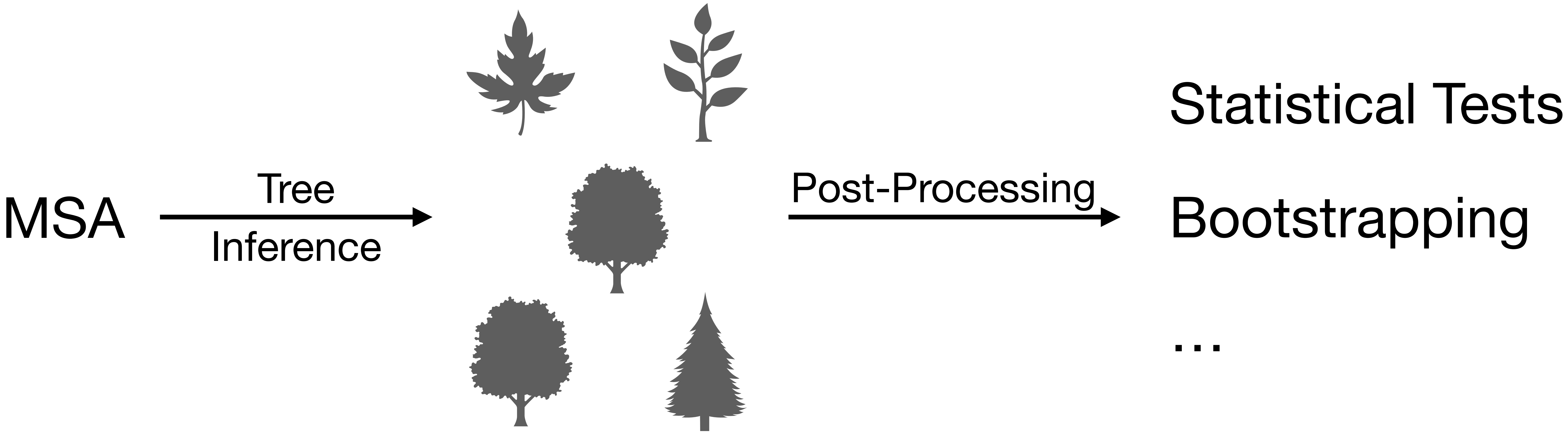

MSA

Tree Inference

Post-Processing

Statistical Tests

Bootstrapping

…

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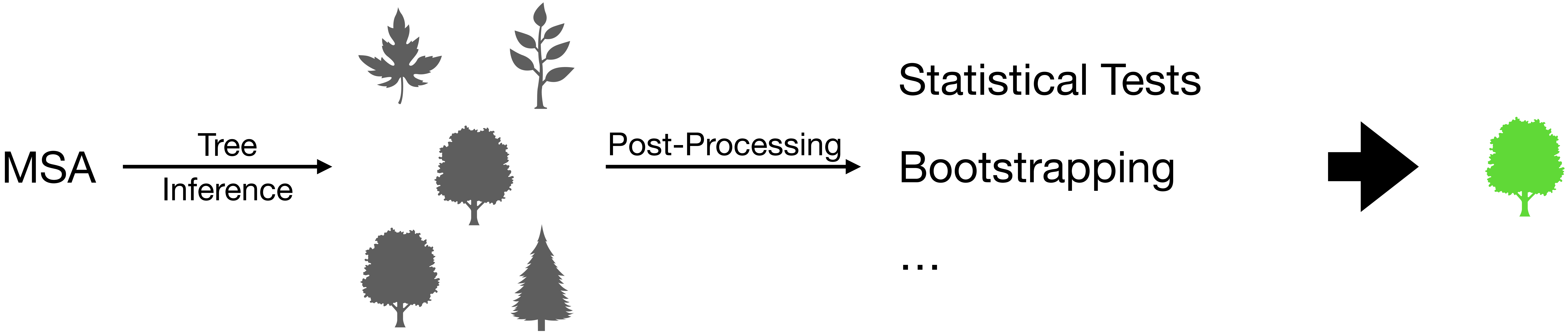

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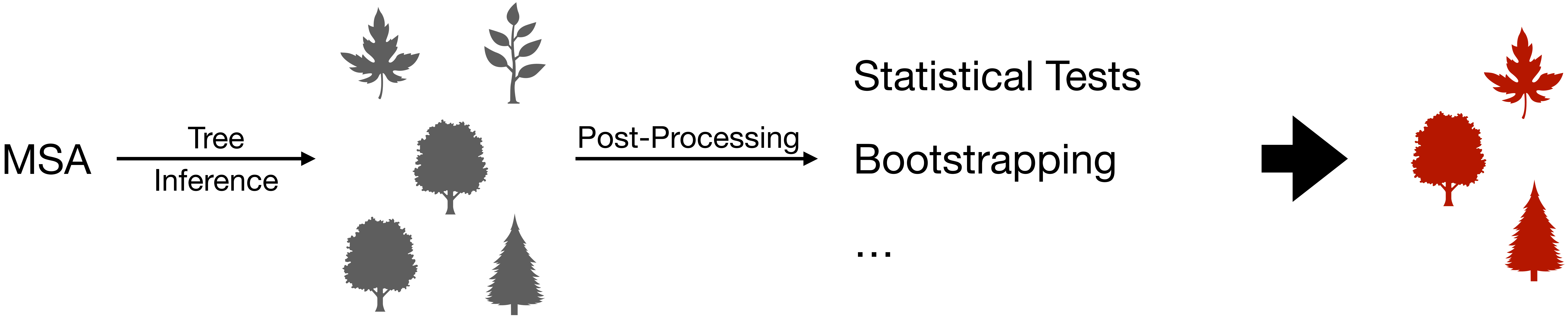

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What does difficult mean?

Difficulty = ruggedness of the tree space

Easy

Difficult

- Few highly similar tree topologies
- Single likelihood peak

- Highly distinct topologies, statistically indistinguishable
- Multiple likelihood peaks

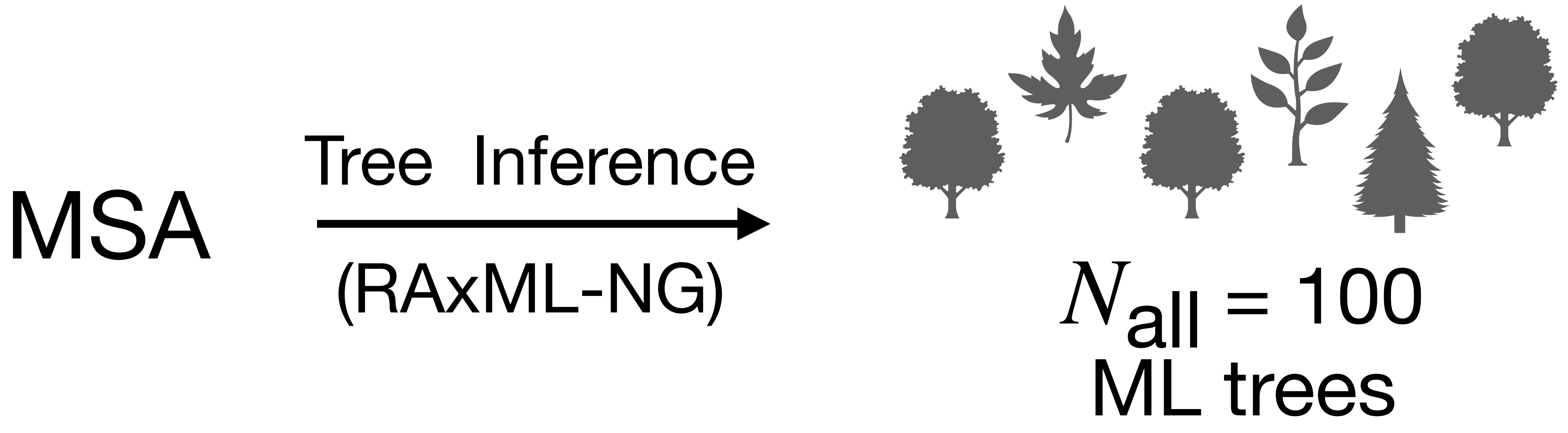
Pythia

The oracle of difficulty

Pythia

- Pythia = Boosted Tree Regressor
- Supervised regression task:
  - predict difficulty from 0.0 (easy) to 1.0 (difficult)
  - ground-truth difficulty as target for training based on 100 ML tree inferences
- Trained on ~4k empirical MSAs
  - Mean absolute percentage error 2.5%

How to quantify difficulty?



MSA

Tree Inference

(RAxML-NG)

N_{all} = 100

ML trees

difficulty(MSA) =

How to quantify difficulty?

$$\text{MSA} \xrightarrow[\text{(RAxML-NG)}]{\text{Tree Inference}}$$

$N_{\text{all}} = 100$
ML trees

$$\Big\downarrow \text{RF-Distance}$$

RF_{all} N^*_{all}

difficulty(MSA) =

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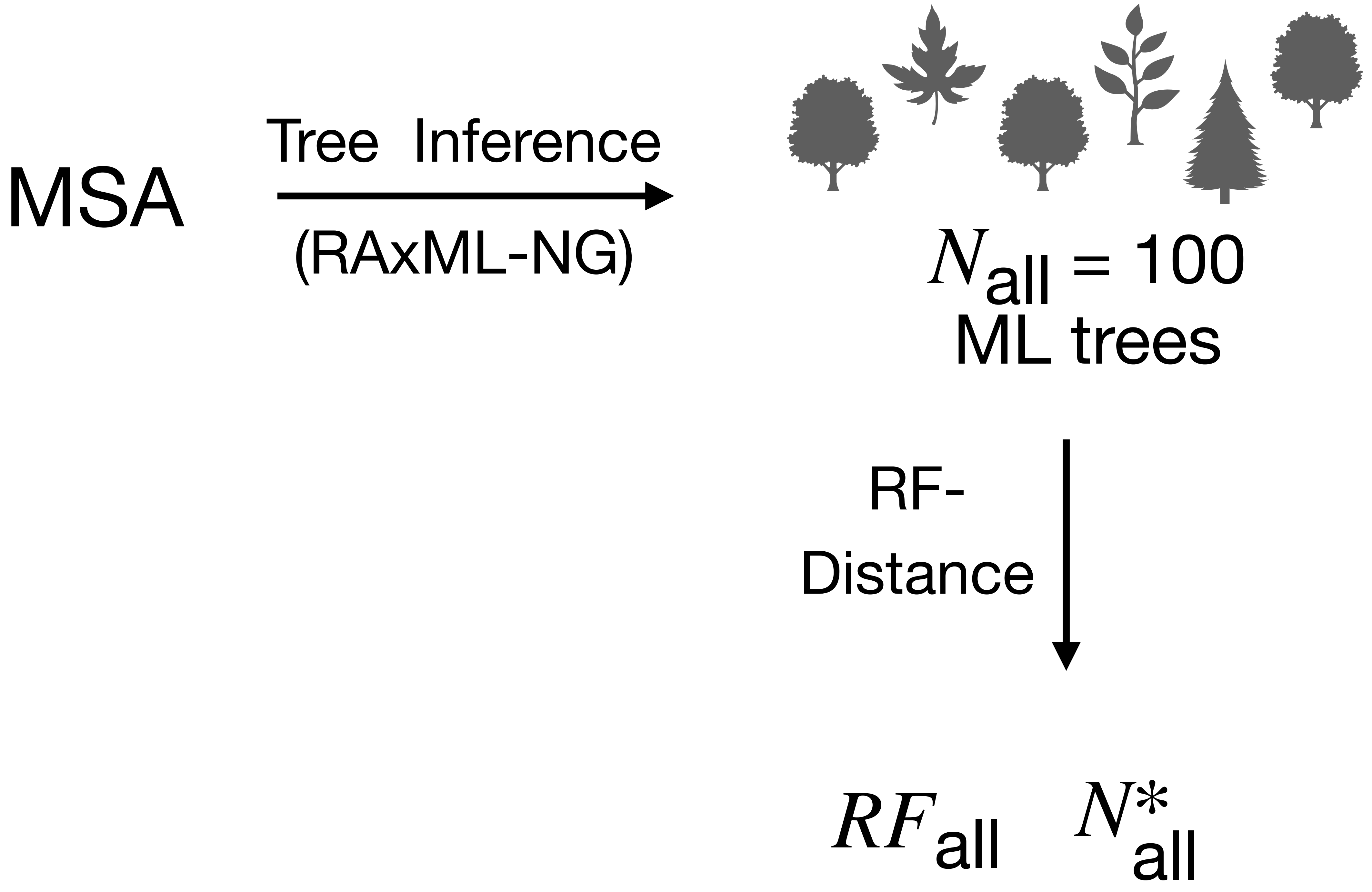

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ML trees

RF-Distance

RF_{all} N^{*}_{all}

$$\text{difficulty(MSA)} = RF_{\text{all}}$$

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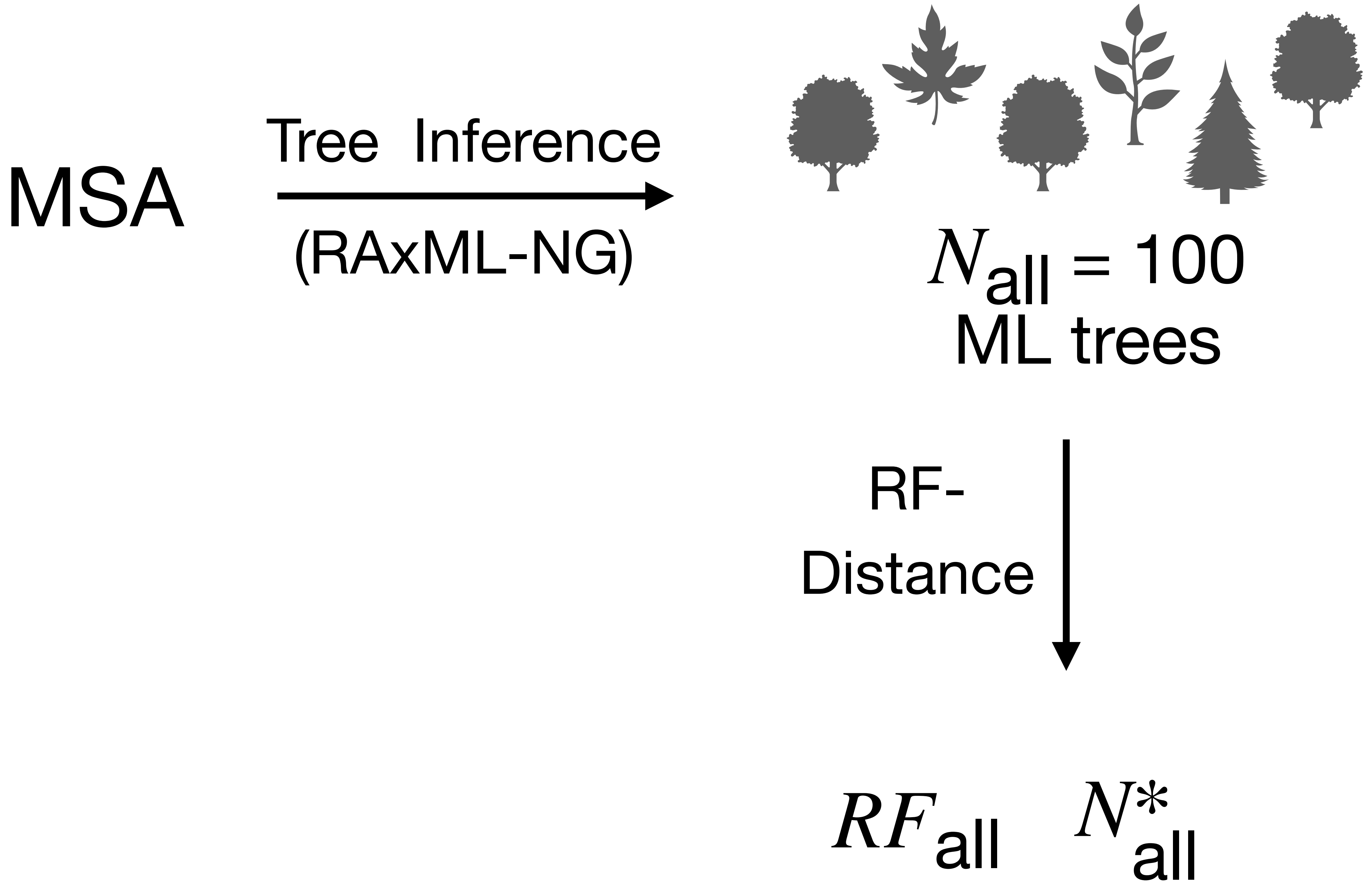

MSA $\xrightarrow[\text{(RAxML-NG)}]{\text{Tree Inference}}$

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ML trees

RF-Distance

RF_{all} N^*_{all}

$$\text{difficulty(MSA)} = \quad RF_{\text{all}} + \frac{N^*_{\text{all}}}{N_{\text{all}}}$$

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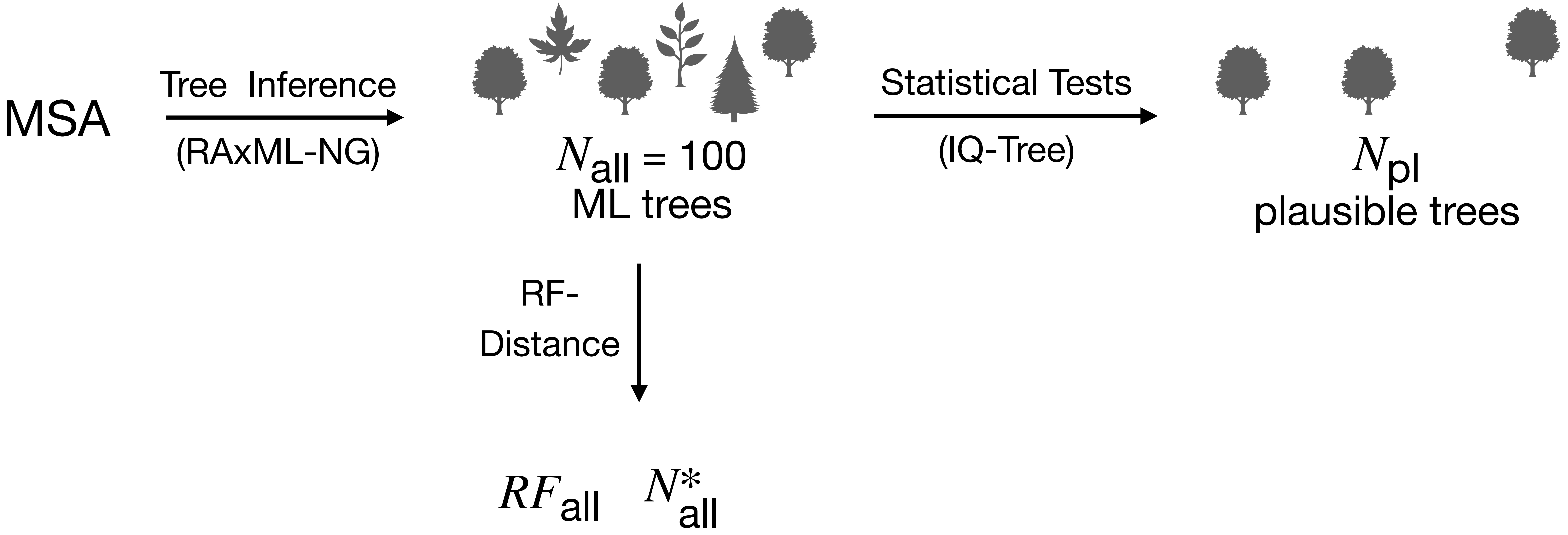

MSA

Tree Inference

(RAxML-NG)

$N_{\text{all}} = 100$

ML trees

Statistical Tests

(IQ-Tree)

N_{pl}

plausible trees

RF-

Distance

RF_{all} N^*_{all}

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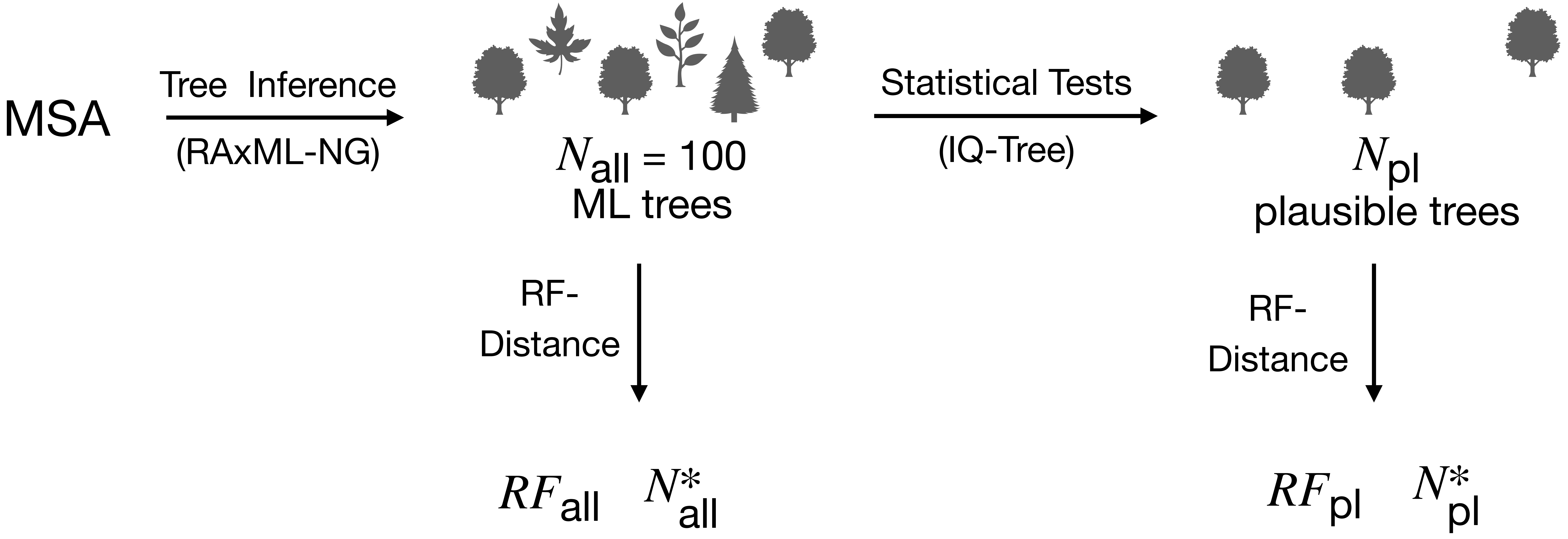

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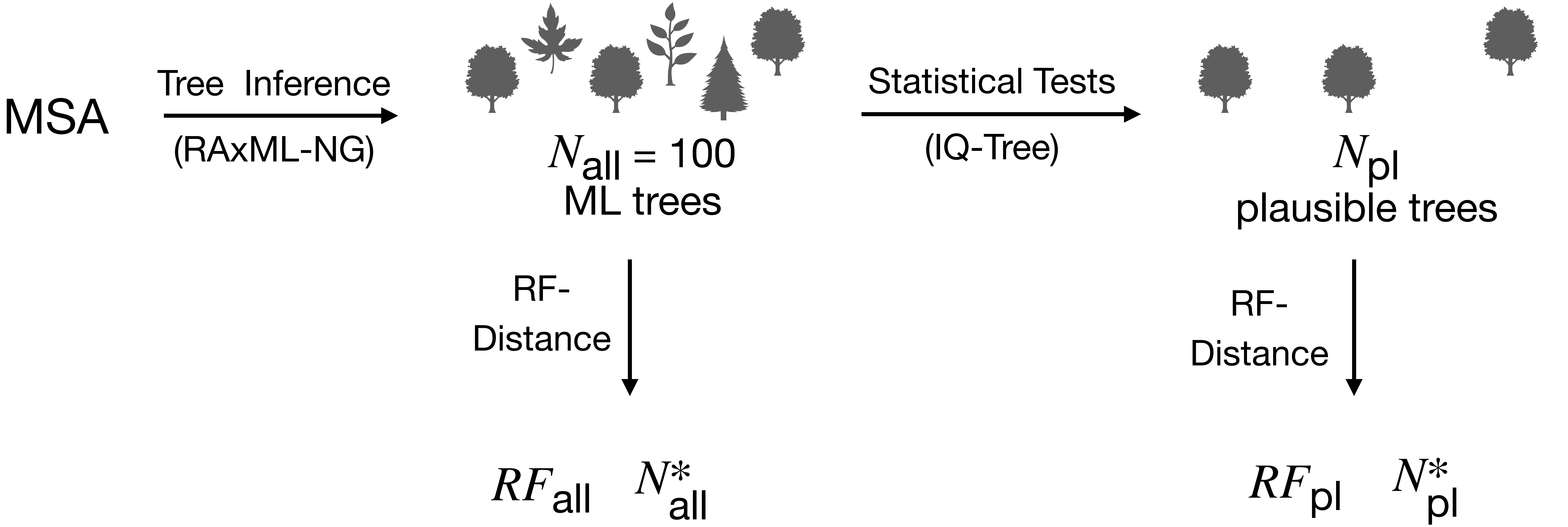

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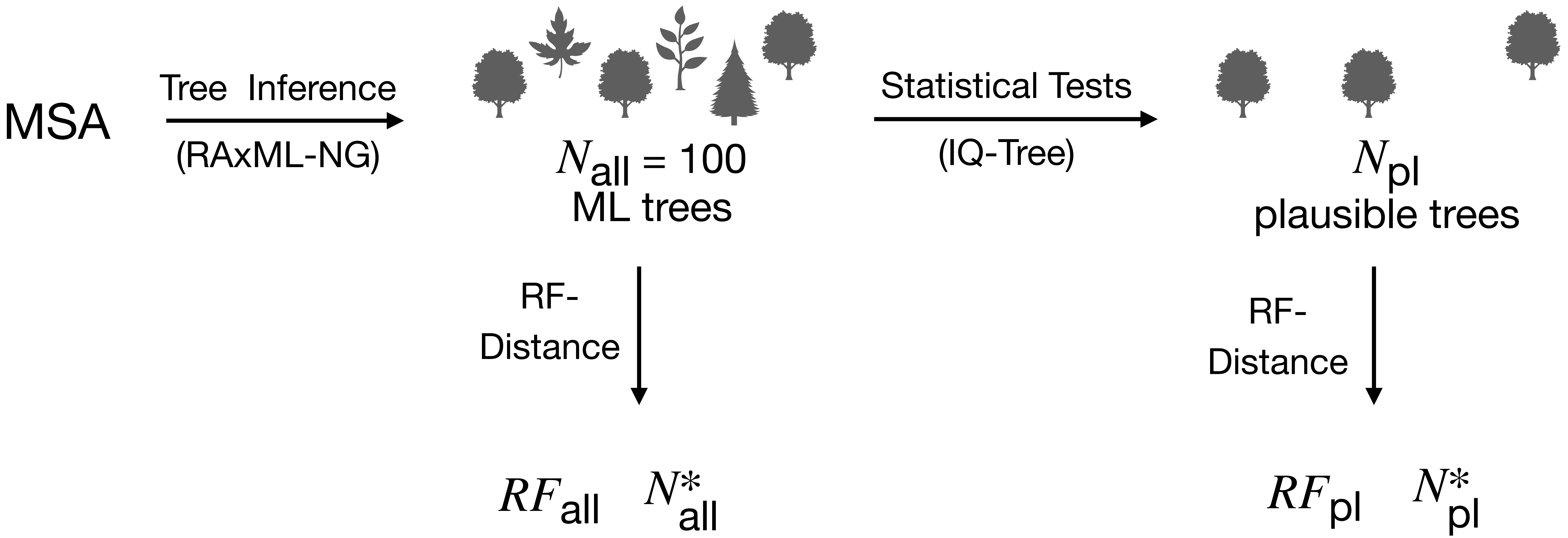

MSA

Tree Inference (RAxML-NG)

$N_{\text{all}} = 100$ ML trees

Statistical Tests (IQ-Tree)

N_{pl} plausible trees

RF-Distance

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RF_{all} N^*_{all}

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$$\text{difficulty(MSA)} = RF_{\text{all}} + \frac{N^*_{\text{all}}}{N_{\text{all}}} + RF_{\text{pl}} + \frac{N^*_{\text{pl}}}{N_{\text{pl}}}$$

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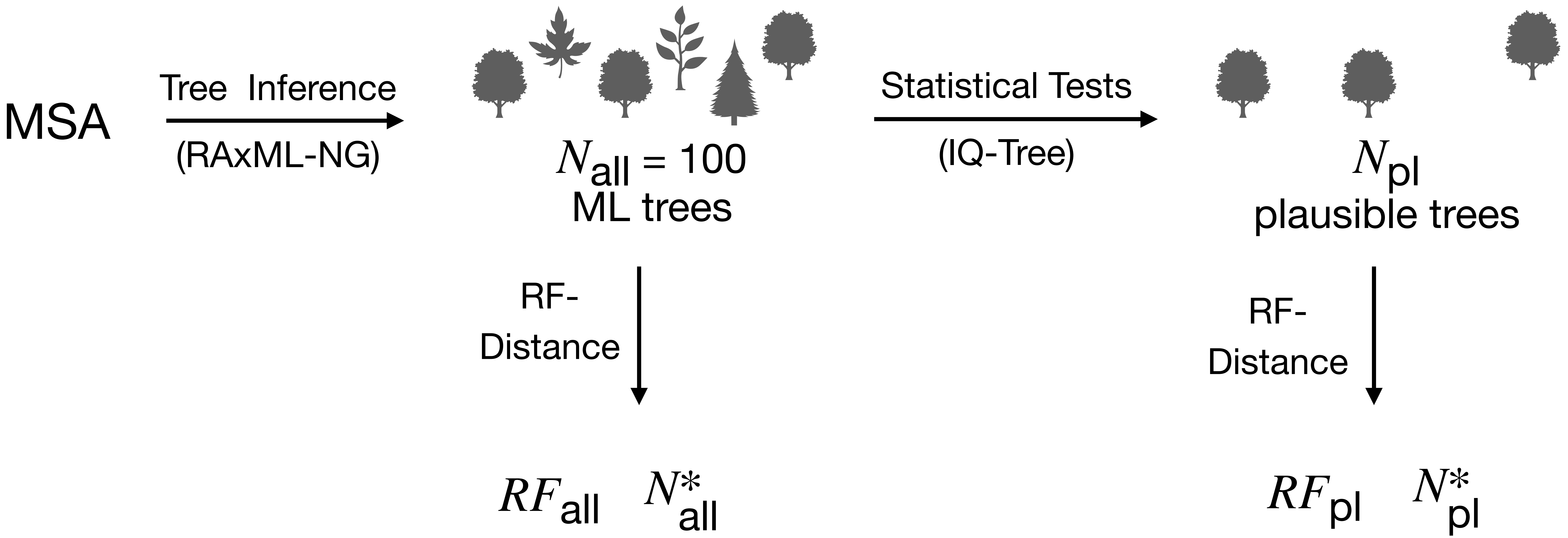

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$$\text{difficulty(MSA)} = RF_{\text{all}} + \frac{N^*_{\text{all}}}{N_{\text{all}}} + RF_{\text{pl}} + \frac{N^*_{\text{pl}}}{N_{\text{pl}}} \quad \cdot \frac{N_{\text{pl}}}{N_{\text{all}}}$$

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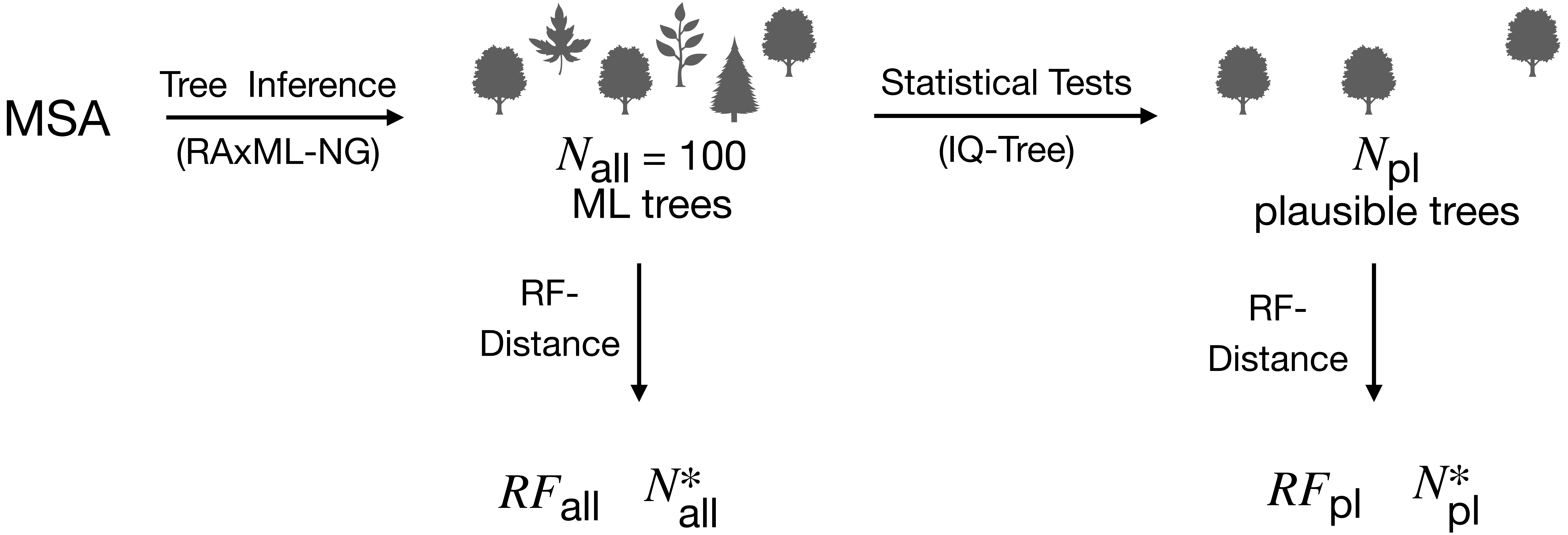

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$$\text{difficulty(MSA)} = \quad RF_{\text{all}} + \frac{N^*_{\text{all}}}{N_{\text{all}}} + RF_{\text{pl}} + \frac{N^*_{\text{pl}}}{N_{\text{pl}}} + \left(1 - \frac{N_{\text{pl}}}{N_{\text{all}}}\right)$$

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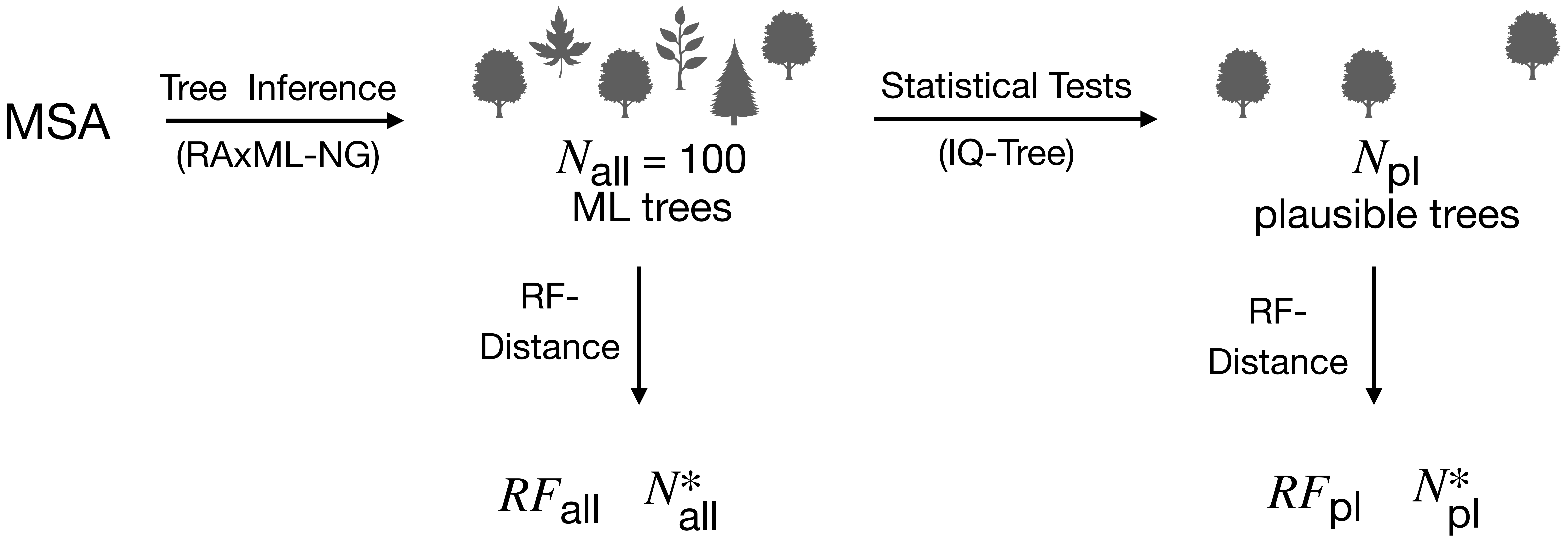

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RF-
Distance

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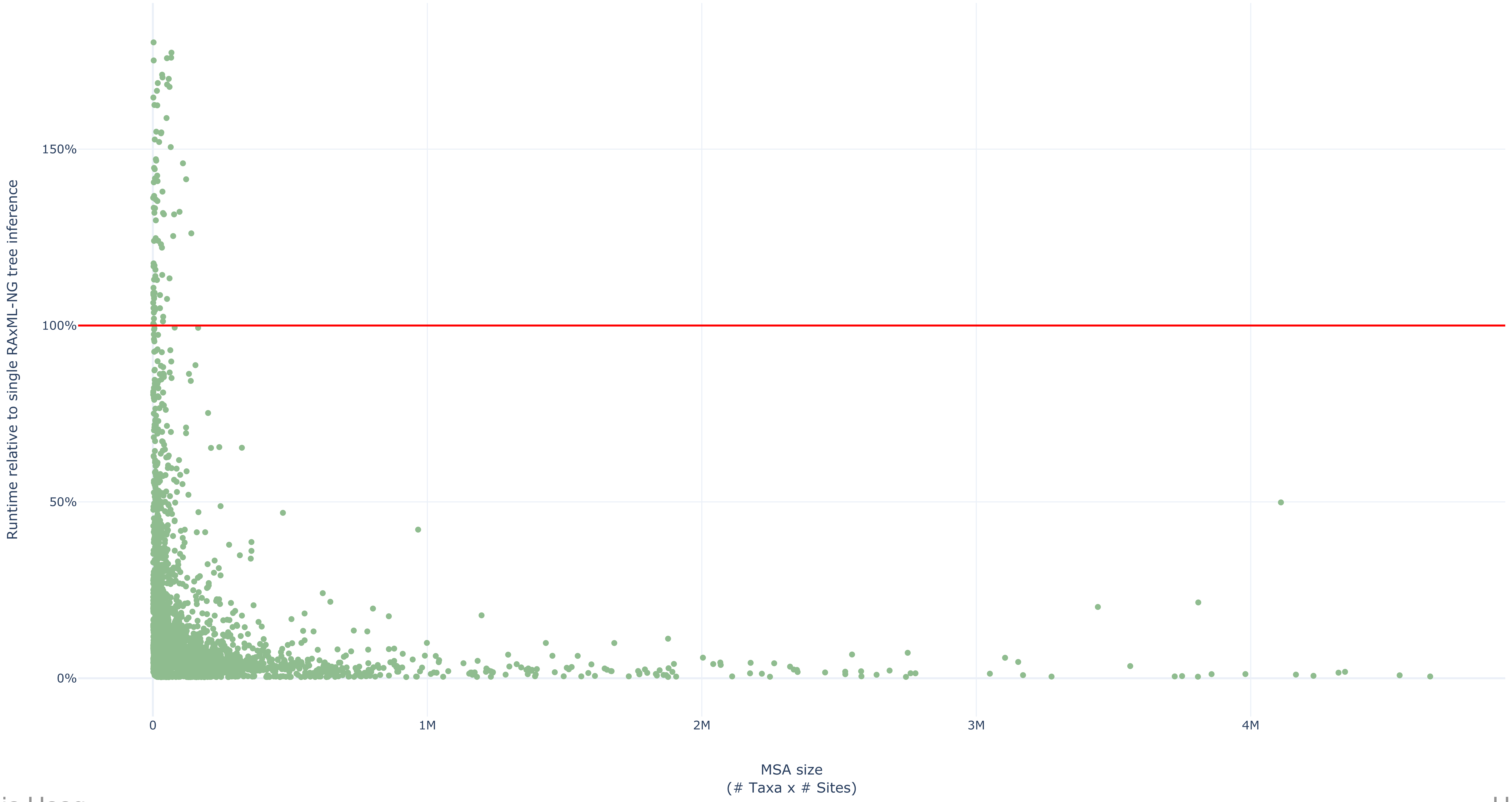
RF_{pl} N^*_{pl}

$$\text{difficulty(MSA)} = \frac{1}{5} \cdot \left[RF_{\text{all}} + \frac{N^*_{\text{all}}}{N_{\text{all}}} + RF_{\text{pl}} + \frac{N^*_{\text{pl}}}{N_{\text{pl}}} + \left(1 - \frac{N_{\text{pl}}}{N_{\text{all}}} \right) \right]$$

Prediction Features

- Eight features:
    - 4 MSA attributes:
        - sites-over-taxa, patterns-over-taxa, % gaps, % invariant sites
    - 2 MSA information metrics:
        - Shannon entropy, Bollback multinomial test statistic
    - 2 Parsimony-tree-based features:
        - Infer 100 parsimony trees → average RF-Distance, % unique topologies

Prediction Features: Runtime



Example: Covid Data

"*Phylogenetic Analysis of SARS-CoV-2 Data Is Difficult*" (https://doi.org/10.1093/molbev/msaa314)

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The predicted difficulty for MSA examples/covid.fasta is: 0.84.

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num_taxa: 4869

num_sites: 28361

[ ... ]

num_sites/num_taxa: 5.82

[ ... ]

avg_rfdist_parsimony: 0.79

proportion_unique_topos_parsimony: 1.0

Feature computation runtime:    1830.182 seconds

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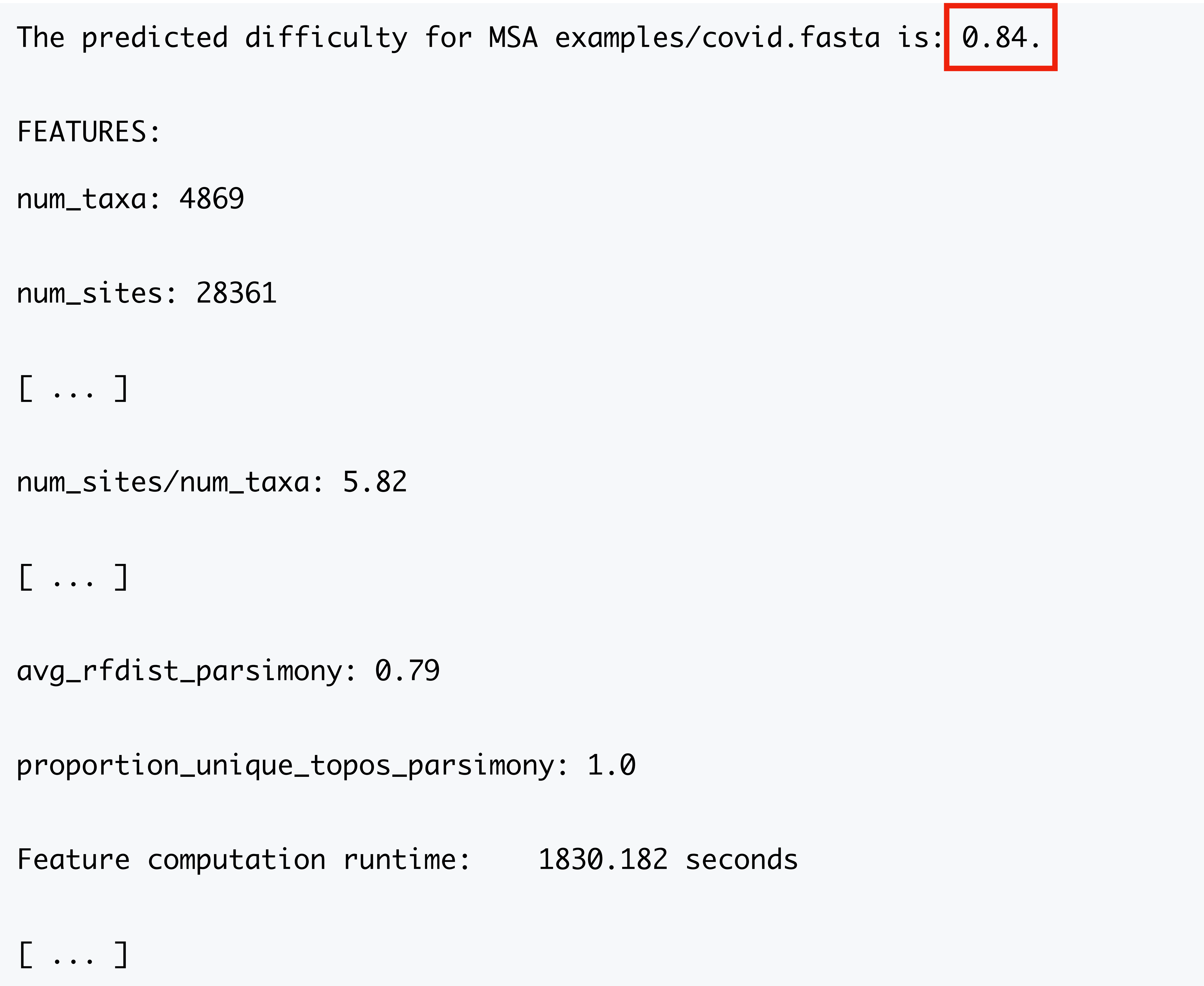

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~31min ≪ 12 hours

Use and Misuse of Pythia

- ✅ Prior to tree inferences
- ✅ Choose inference + post-processing setup
- ✅ Adjust MSA

- ❌ Difficulty equals number of tree inferences

Outlook

- Next Pythia version:
  - trained on ~12k MSAs
  - additional Features (e.g. patterns-per-site ratio)
  - Hopefully even higher accuracy ☺
- Difficulty-aware search heuristic in RAxML-NG

Summary

- Pythia = difficulty predictor
- Difficulty = ruggedness of the tree space
- Prediction *prior* to time-intensive tree inference
- Accurate and fast
  - faster than a *single* ML tree inference
- Paper: https://doi.org/10.1093/molbev/msac254
- Pythia on Github: https://github.com/tschuelia/PyPythia