Pythia

Predicting the Difficulty of Phylogenetic Analyses

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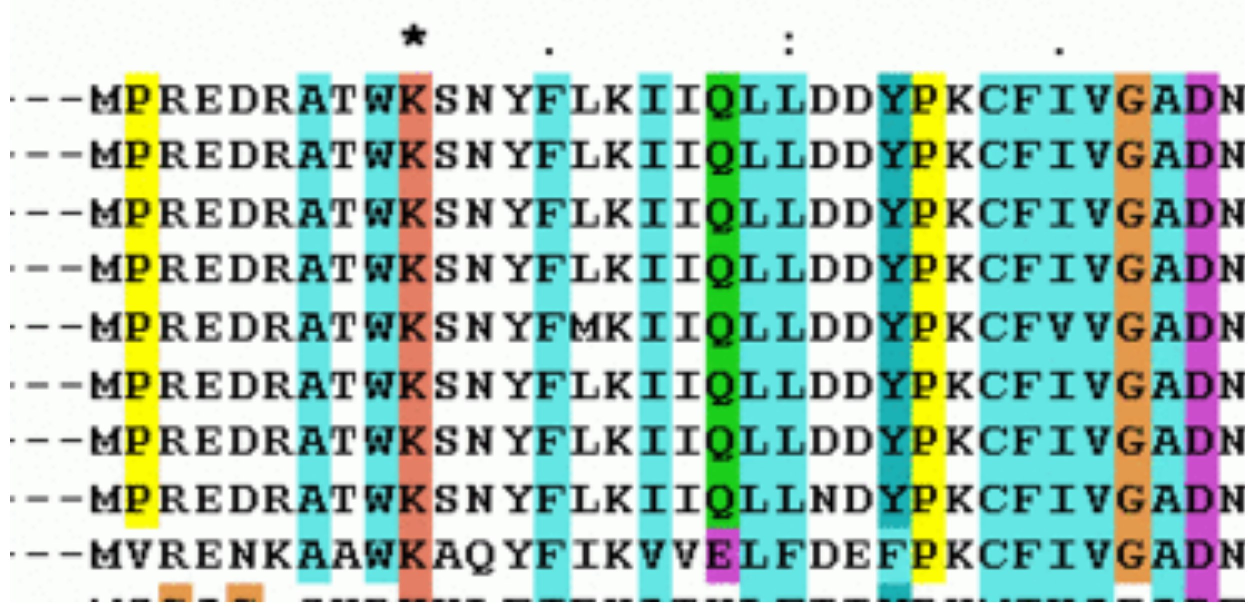
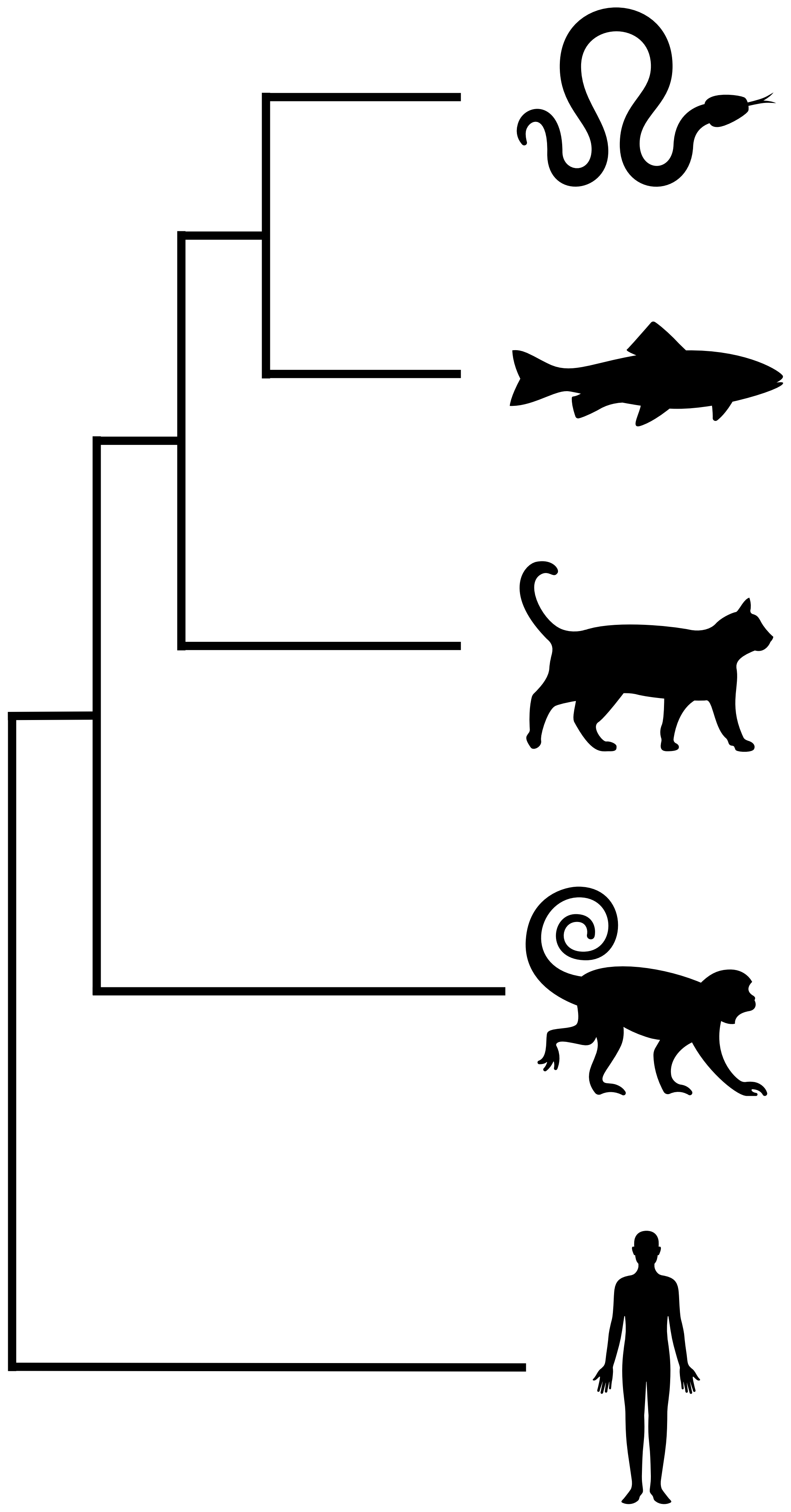
Phylogenetic Analysis

Sequence Data



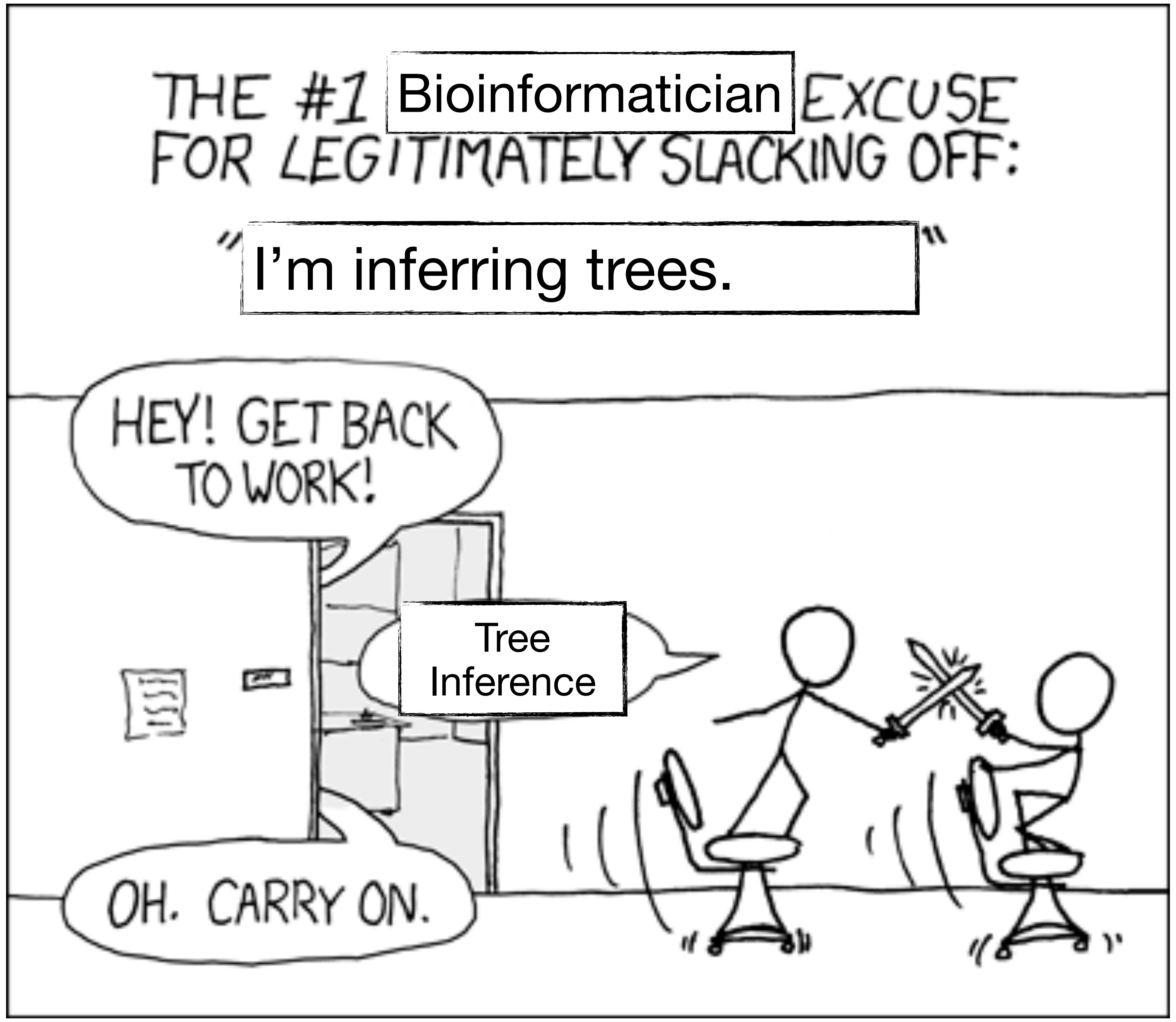
```
            *   .      :       .
---MPREDRATWKSNYFLKIIQLLDDYPKCFIVGADN
---MPREDRATWKSNYFLKIIQLLDDYPKCFIVGADN
---MPREDRATWKSNYFLKIIQLLDDYPKCFIVGADN
---MPREDRATWKSNYFLKIIQLLDDYPKCFIVGADN
---MPREDRATWKSNYFMKIIQLLDDYPKCFVVGADN
---MPREDRATWKSNYFLKIIQLLDDYPKCFIVGADN
---MPREDRATWKSNYFLKIIQLLDDYPKCFIVGADN
---MPREDRATWKSNYFLKIIQLLNDYPKCFIVGADN
---MVRENKAAWKAQYFIKVVELFDEFPKCFIVGADN
```

Phylogenetic Tree



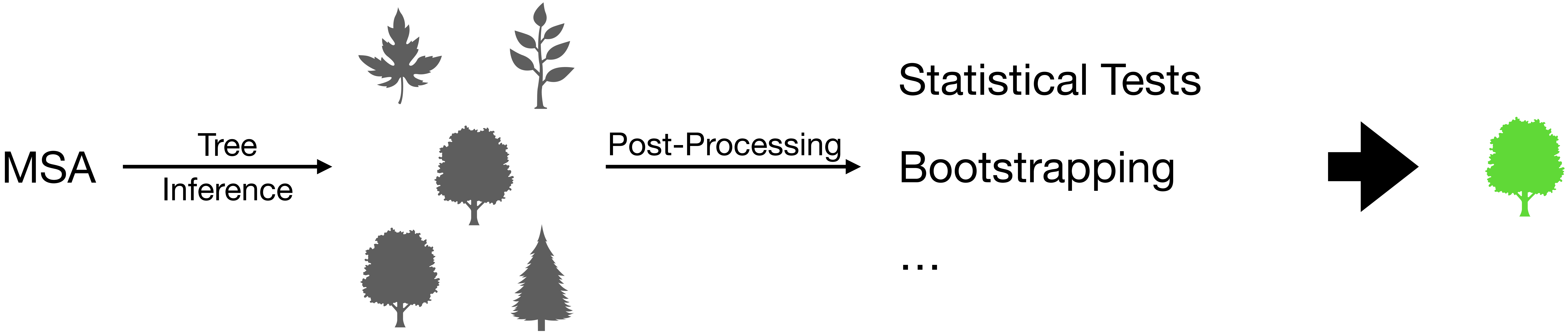
Phylogenetic Analysis

- Fast, but less accurate methods:
  - Maximum Parsimony
  - Neighbor Joining
  - …
- Slow, but more accurate methods:
  - Maximum Likelihood (e.g. RAxML-NG)
  - Bayesian Methods (e.g. MrBayes)
  - …



Based on "Compiling" https://xkcd.com/303/

What does difficult mean?



MSA

Tree Inference

Post-Processing

Statistical Tests

Bootstrapping

…

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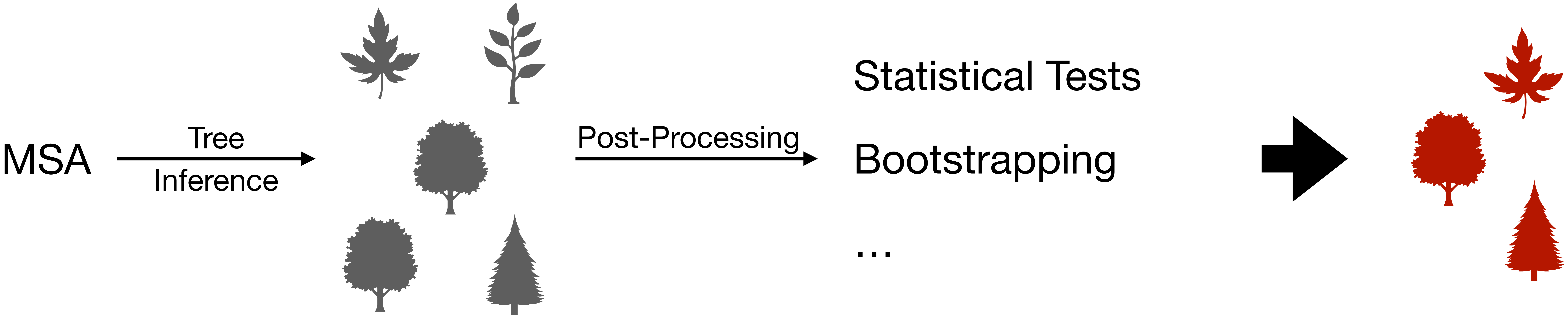

MSA

Tree Inference

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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

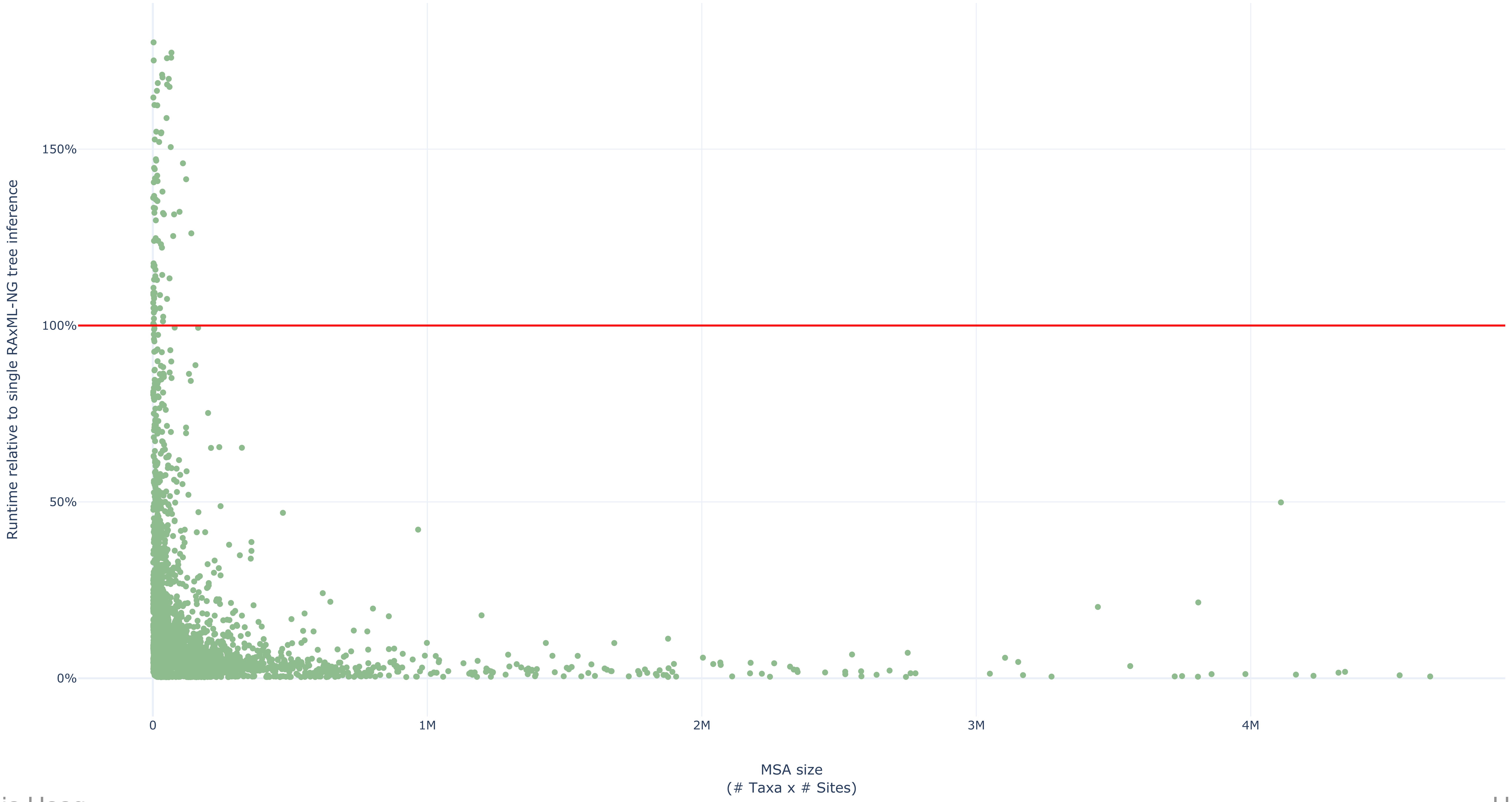
Pythia

- 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 ~12.5k empirical MSAs
  - Mean absolute percentage error 1.7%

Prediction Features

- 10 features:
  - 5 MSA attributes:
    - sites-over-taxa, patterns-over-taxa, patterns-over-sites % gaps, % invariant sites
  - 3 MSA information metrics:
    - Shannon entropy, Bollback multinomial test statistic, Entropy-like pattern metric
  - 2 Parsimony-tree-based features:
    - Infer 100 parsimony trees → average RF-Distance, % unique topologies

Prediction Features: Runtime



How to use Pythia

- 3 options:
  - **Command Line Interface**, Python module: https://github.com/tschuelia/PyPythia
  - C library: https://github.com/tschuelia/CPythia
- Phylip or FASTA format
- DNA, Protein, or morphological data

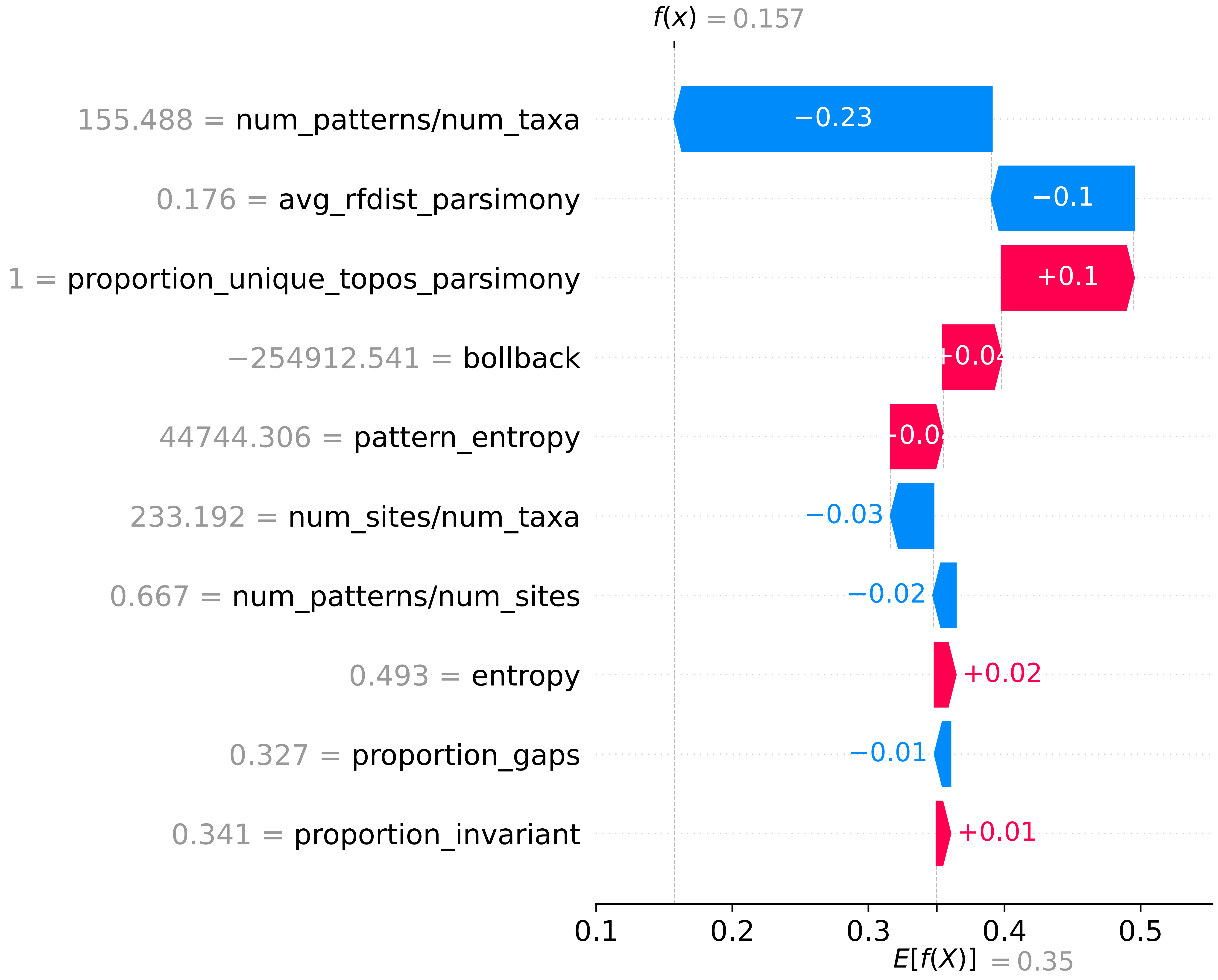
How to use Pythia: example MSA

```
pythia -h

pythia -m examples/example.phy -r path/to/raxml-ng -v -b –shap
```

- Single likelihood peak → easy (difficulty = 0.16)
- Runtime:
  - Pythia: ~10 seconds
  - 1 tree inference: ~16 minutes

Shapley Values: example.phy



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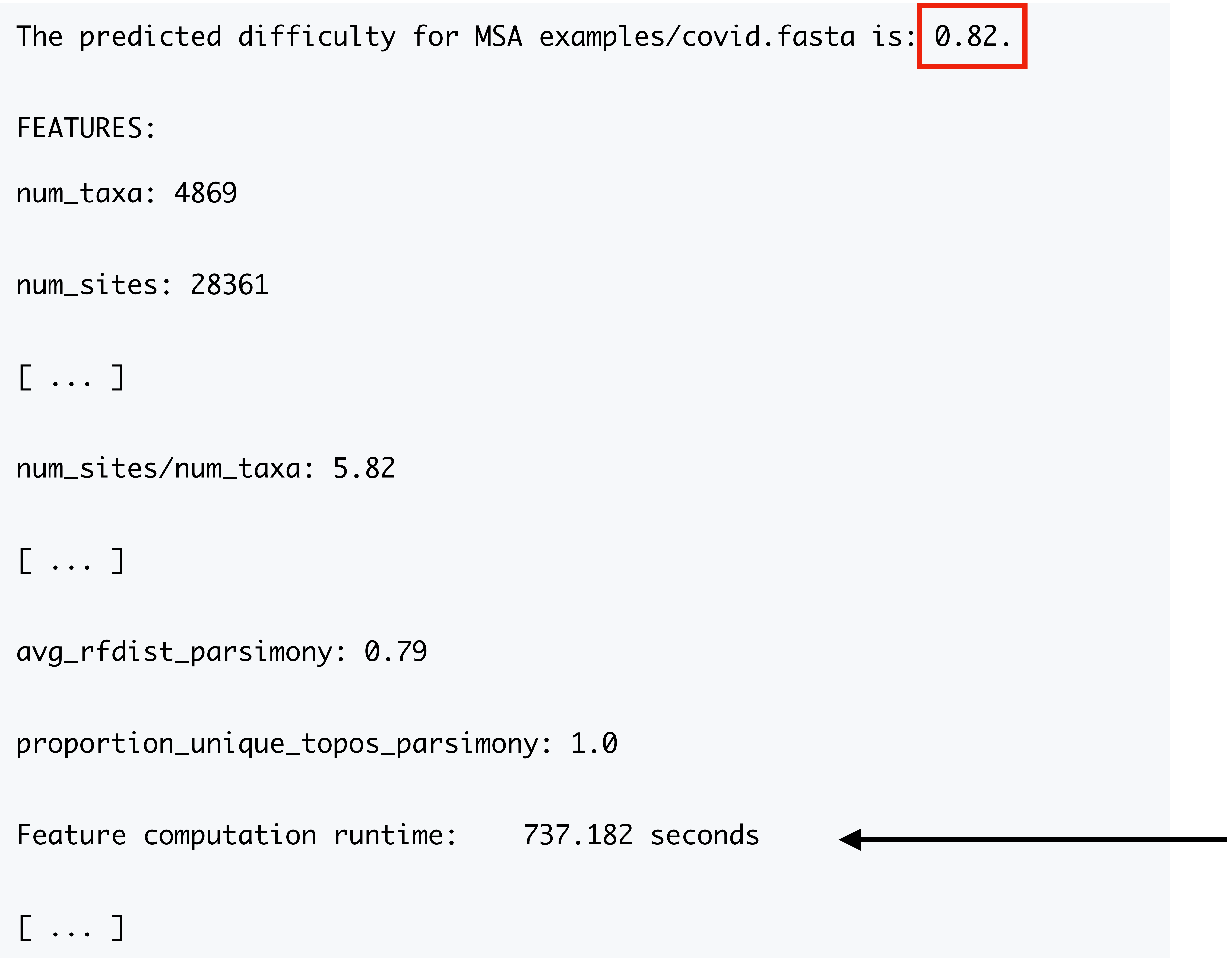
Example: Covid Data

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



```
The predicted difficulty for MSA examples/covid.fasta is: 0.82.

FEATURES:

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:    737.182 seconds

[ ... ]
```

~12min ≪12 hours

Use and Misuse of Pythia

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

- ❌ Difficulty equals number of tree inferences

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