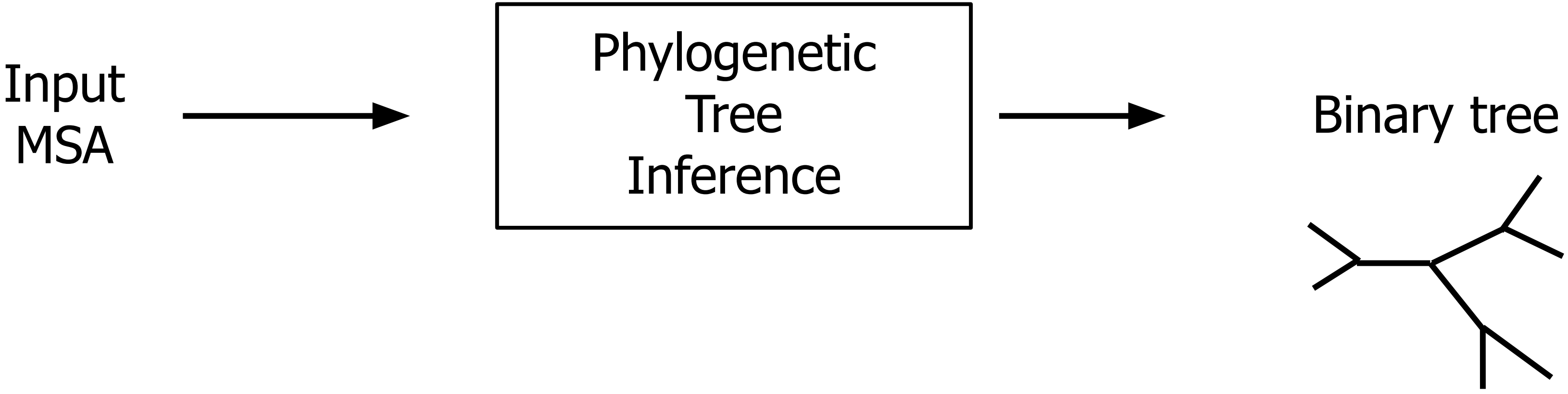
Adaptive RAxML-NG: Accelerating Phylogenetic Inference under Maximum Likelihood using dataset difficulty

Anastasis Togkousidis, Oleksiy M Kozlov, Julia Haag,
Dimitri Höhler, Alexandros Stamatakis

HITS

Introduction

Introduction

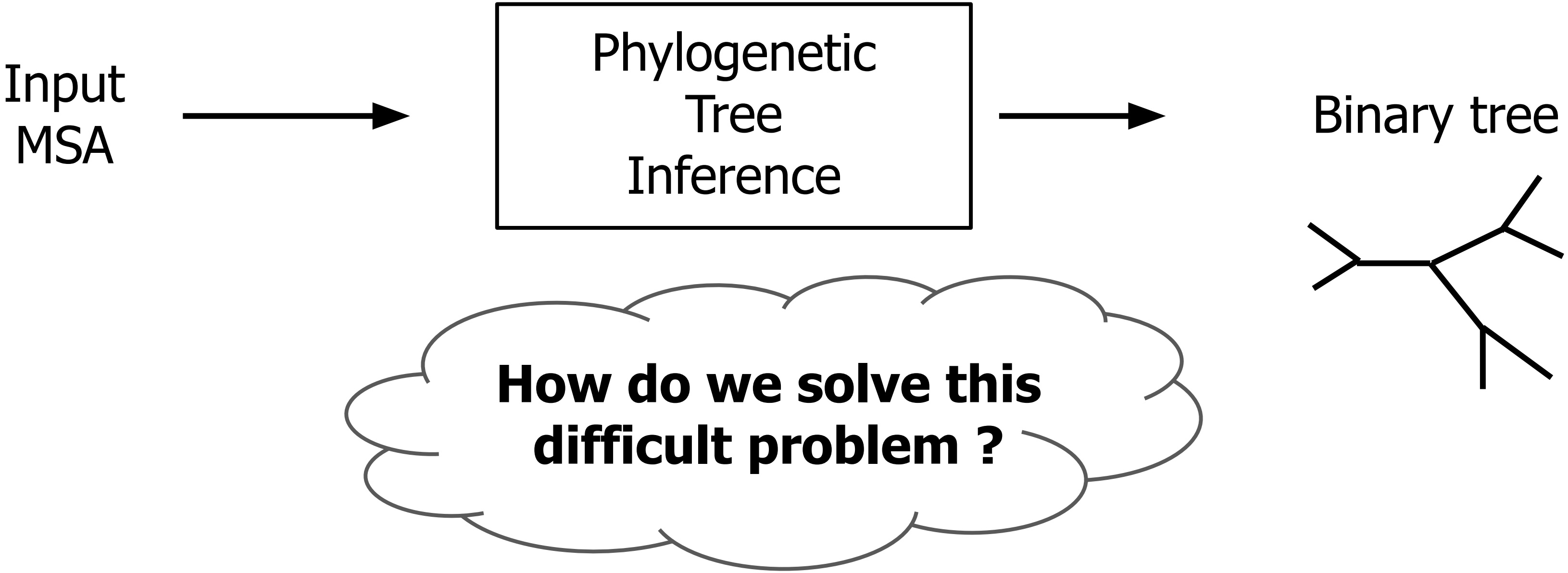


Input MSA

Phylogenetic Tree Inference

Binary tree

Introduction



Input
MSA

Phylogenetic
Tree
Inference

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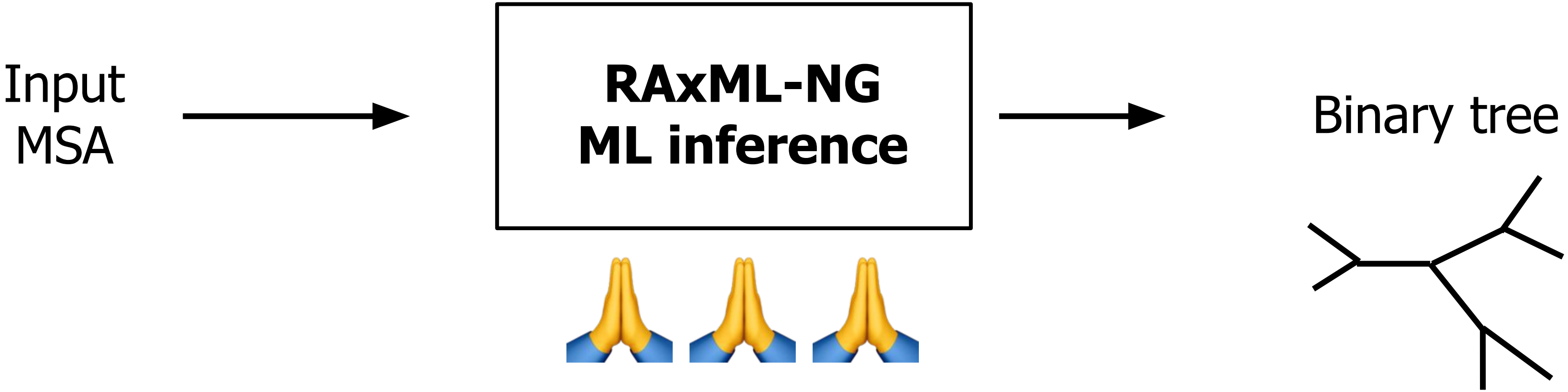
How do we solve this difficult problem ?

Introduction



Input
MSA

RAxML-NG
ML inference

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Binary tree

Introduction

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MSA

→

RAxML-NG
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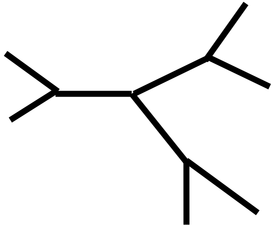
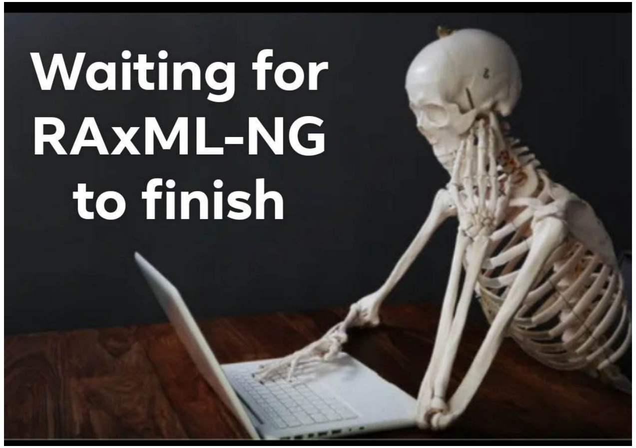
→

Binary tree





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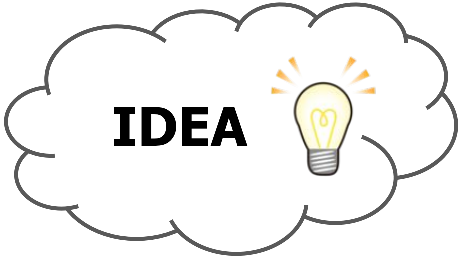
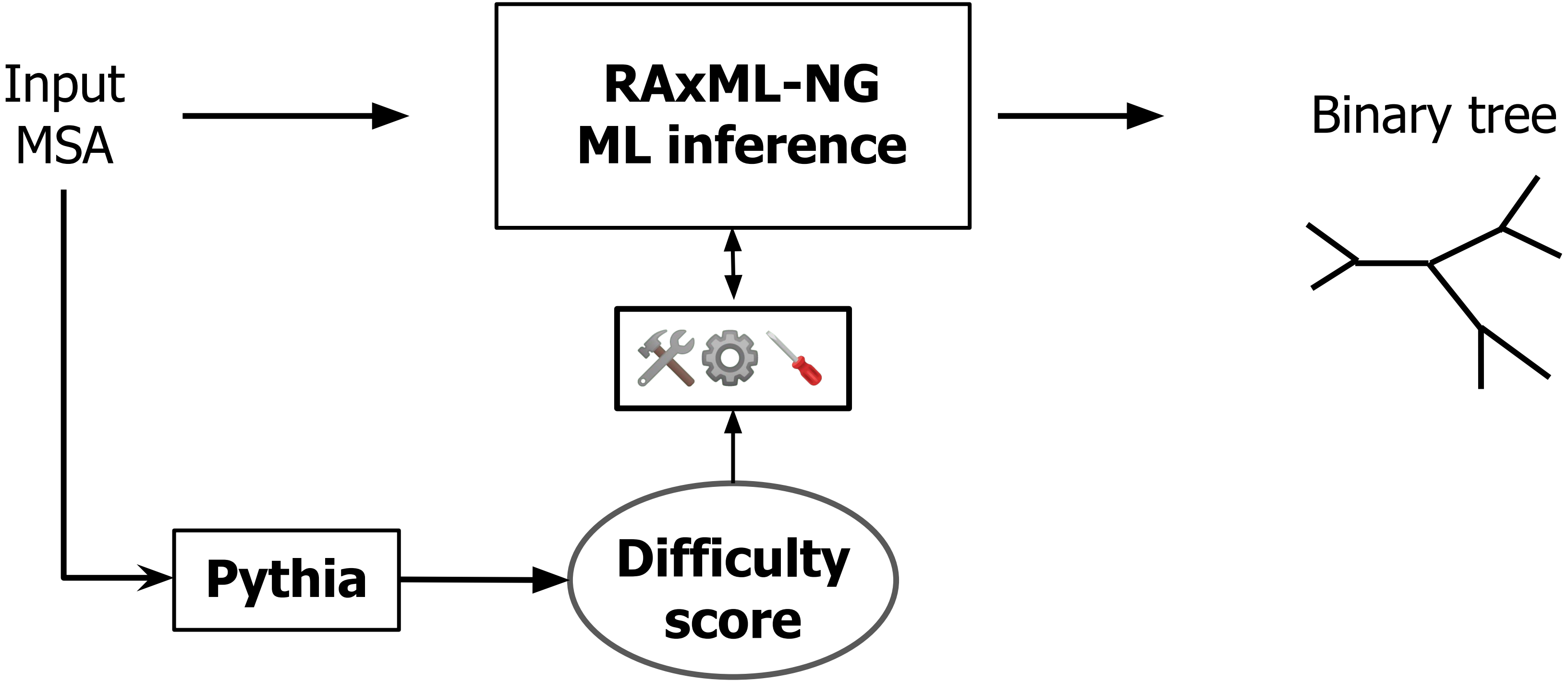
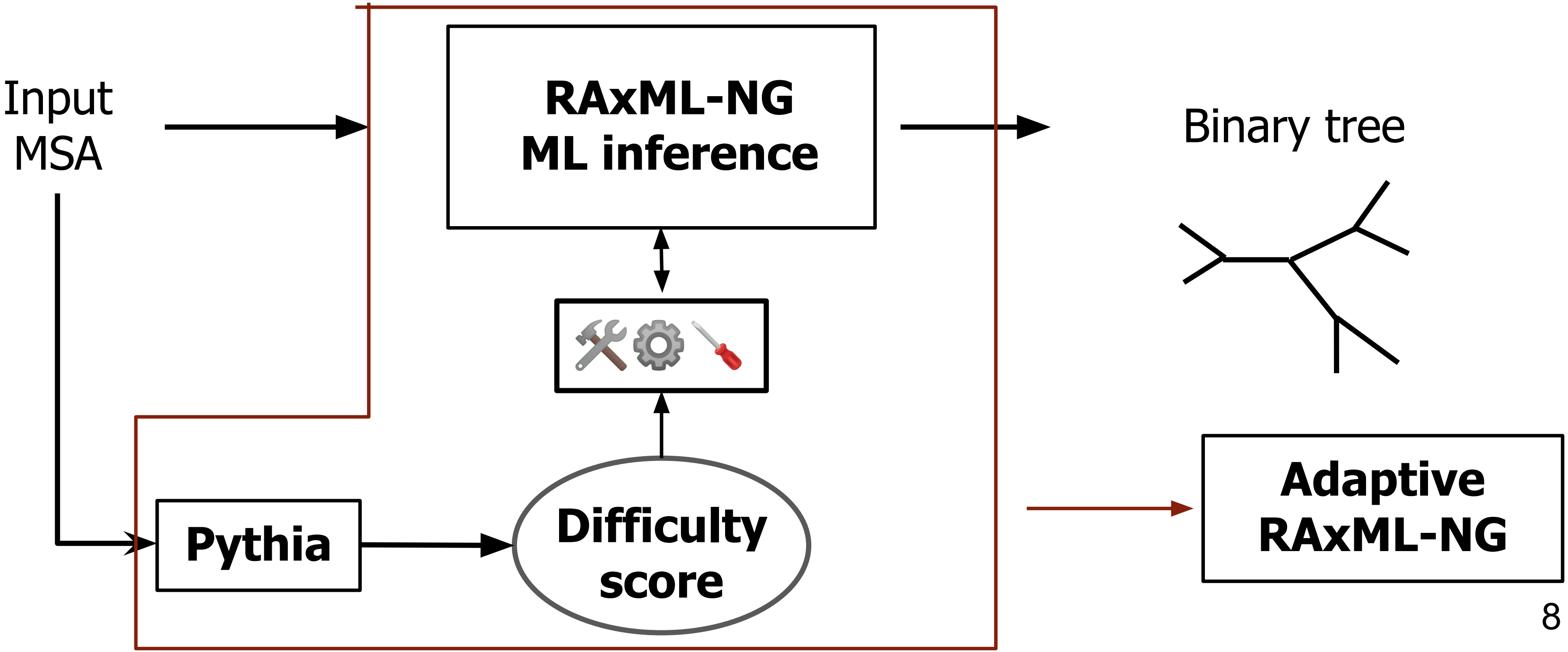




Introduction

IDEA



Input
MSA

RAxML-NG
ML inference

Binary tree

Pythia

Difficulty
score

Adaptive
RAxML-NG

Background

Tree inference

1.

Taxon1: AACAGTAC--AA
Taxon2: ATCATTACC-AA
Taxon3: AAGAGTACC-AA
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TaxonN: AGCAGTAC--AA

MSA

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MSA

→

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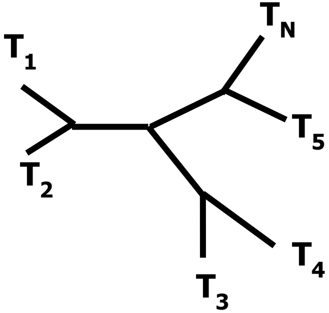
LH = -100



Initial tree
(Random, MP)

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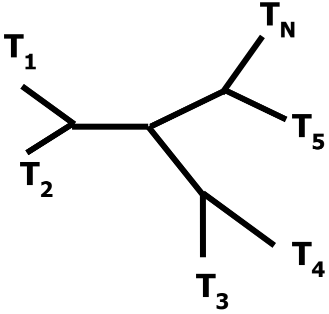

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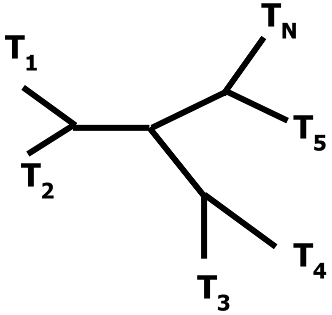

Intermediate Trees
(Topological moves)

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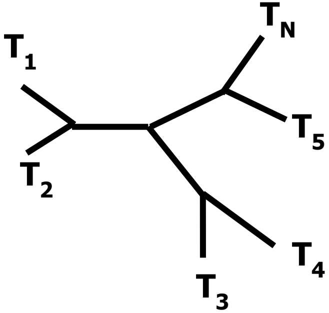

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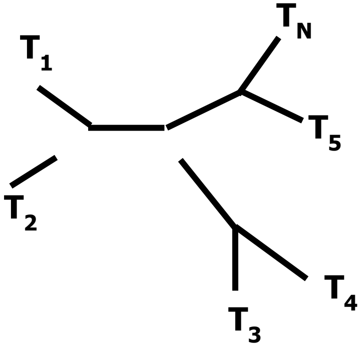

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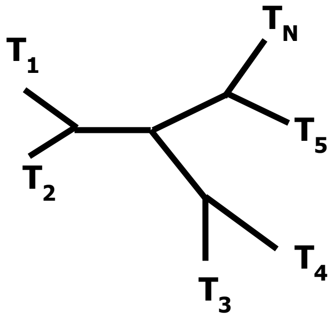

Initial tree
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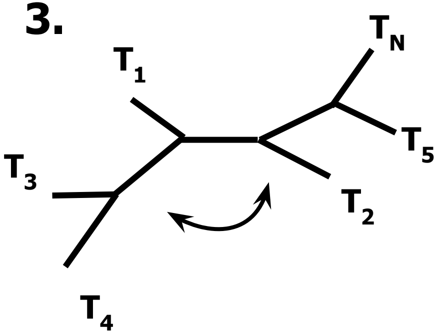

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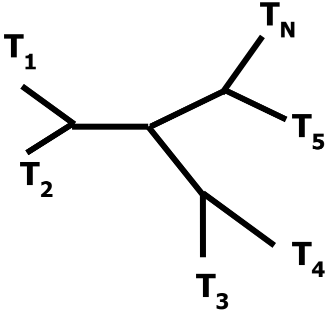

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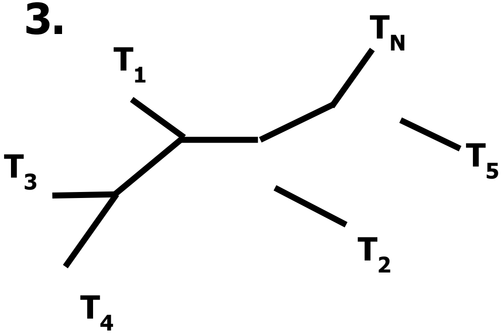

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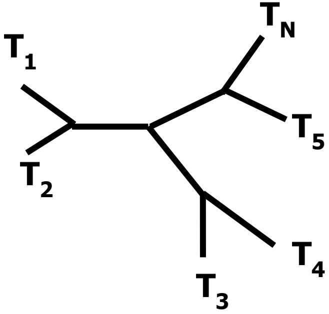

Initial tree
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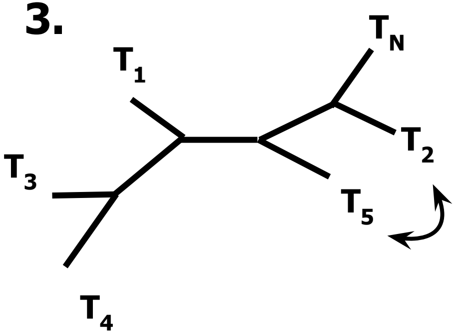

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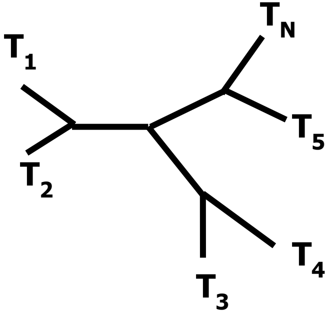

Initial tree
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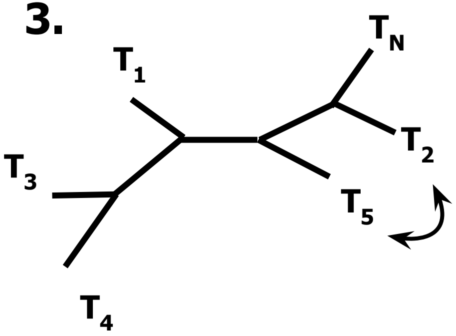
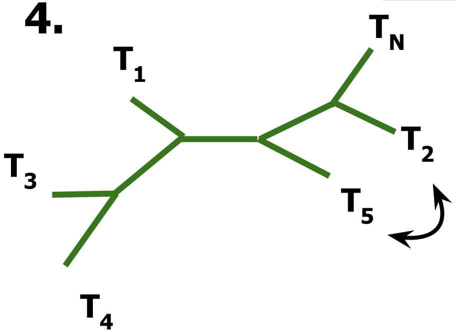


Intermediate Trees
(Topological moves)

4.

LH = -35



Branch-Length Optimization

Tree inference

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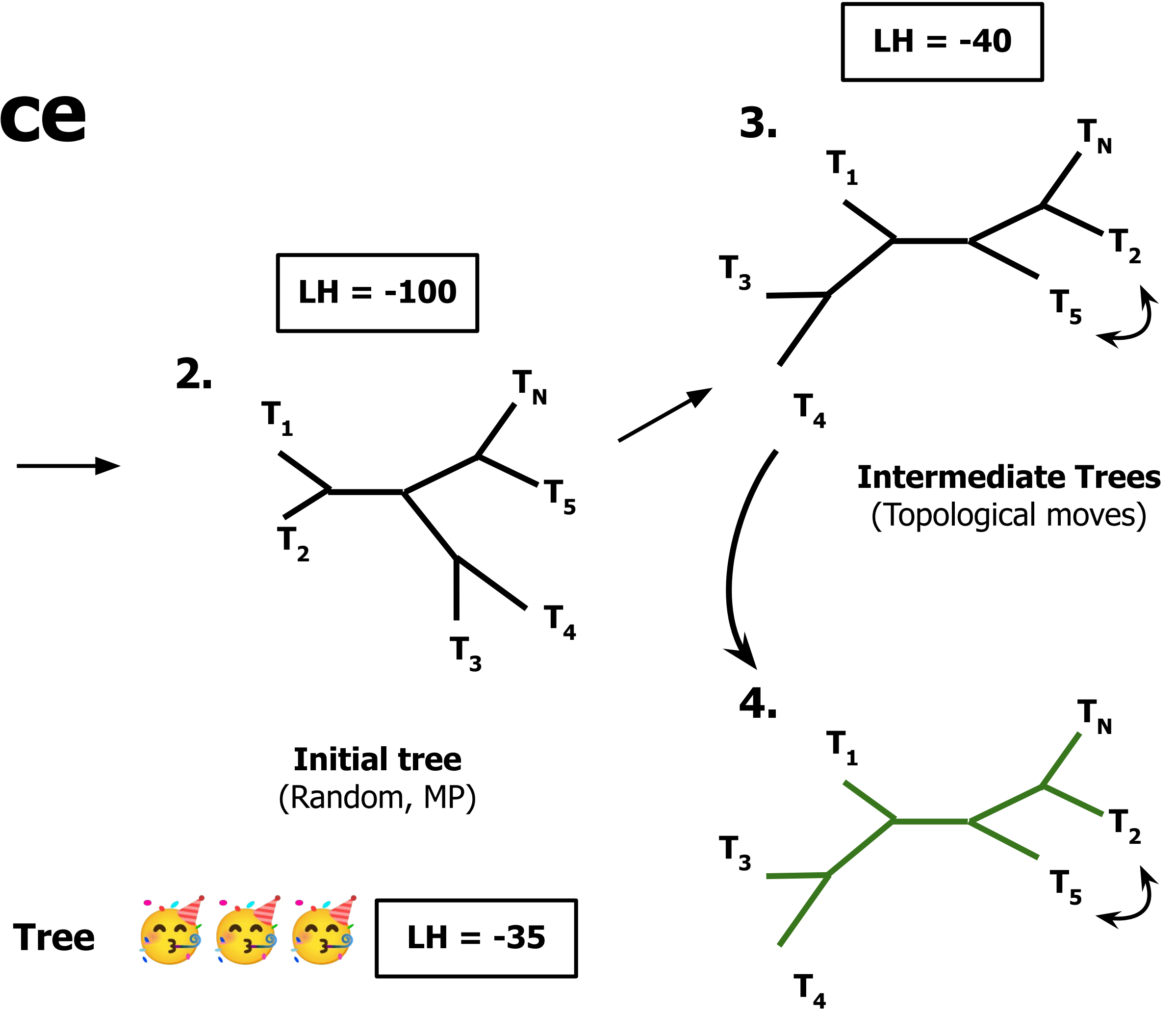
TaxonN: AGCAGTAC--AA

MSA



Initial tree
(Random, MP)

Intermediate Trees
(Topological moves)

Final Tree 🥳🥳🥳 **LH = -35**

The concept of difficulty

Easy datasets:

- For some datasets, independent ML tree searches starting from different trees, converge to a **single - or topologically similar - tree(s)**
- We say that these datasets exhibit a “**clear phylogenetic signal**”

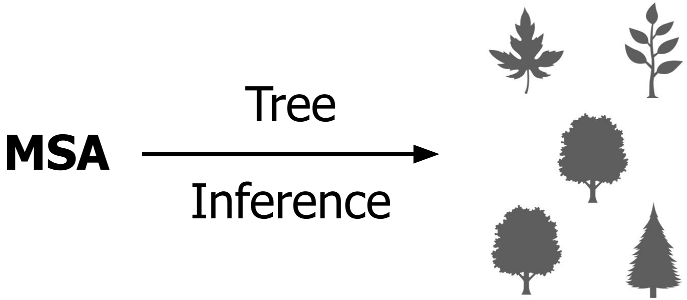
The concept of difficulty

Easy datasets:

MSA $\xrightarrow[\text{Inference}]{\text{Tree}}$

The concept of difficulty

Easy datasets:



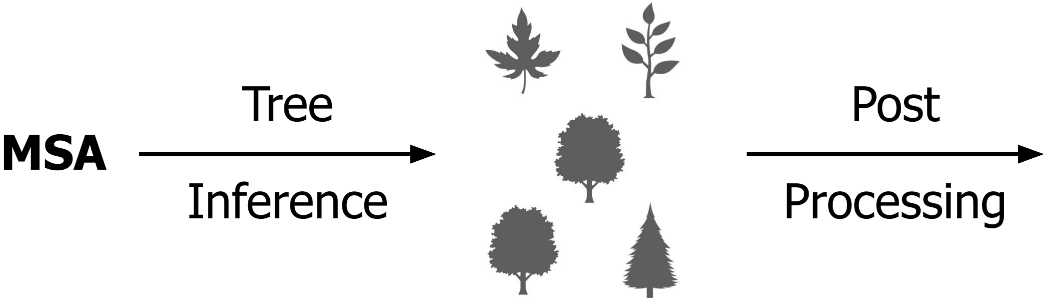
MSA

Tree

Inference

The concept of difficulty

Easy datasets:



MSA

Tree

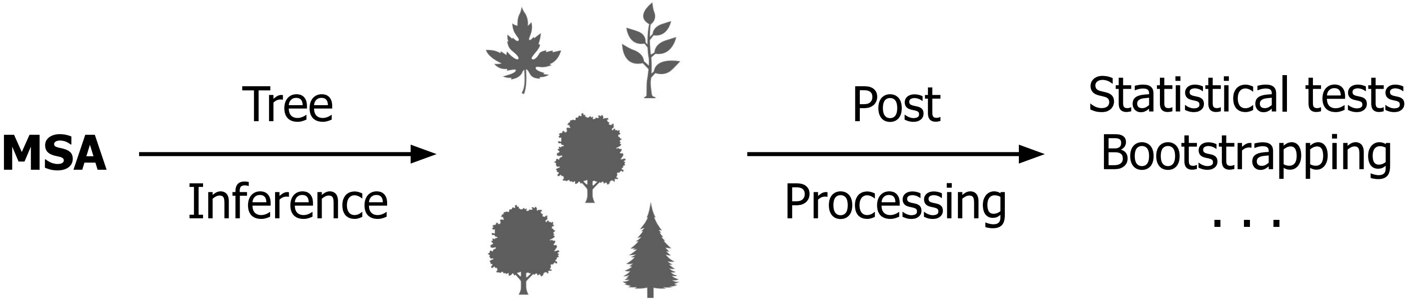
Inference

Post

Processing

The concept of difficulty

Easy datasets:



The concept of difficulty

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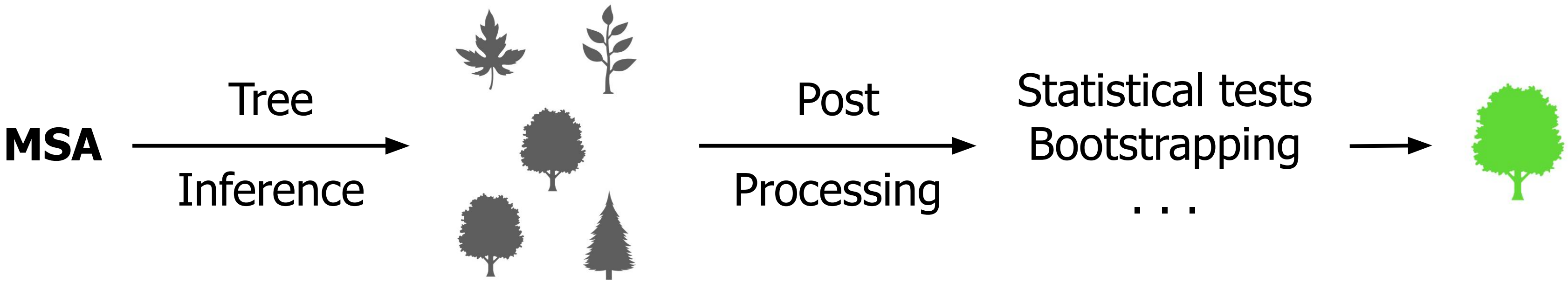


MSA

Tree Inference

Post Processing

Statistical tests
Bootstrapping
. . .

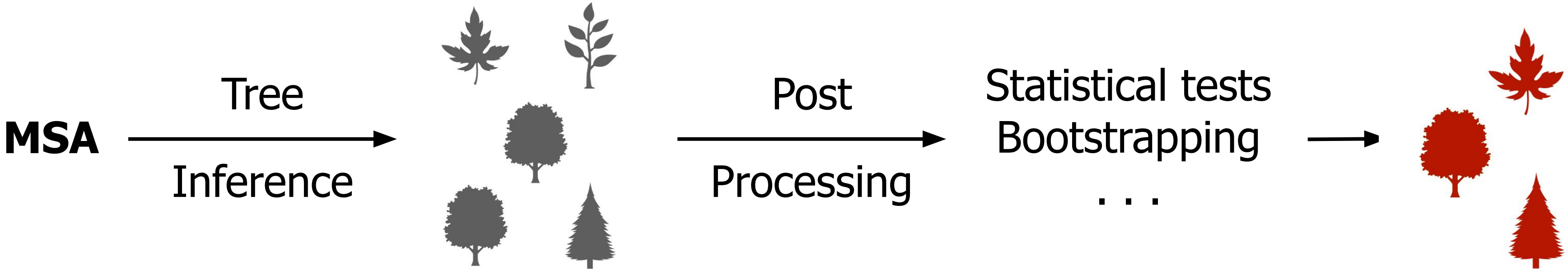
The concept of difficulty

Difficult datasets:

- Other datasets yield **topologically highly distinct**, yet **equally likely trees** (equal score)
- These trees are also **statistically indistinguishable** based on IQ-TREE 2 significance tests

The concept of difficulty

Difficult datasets:



MSA

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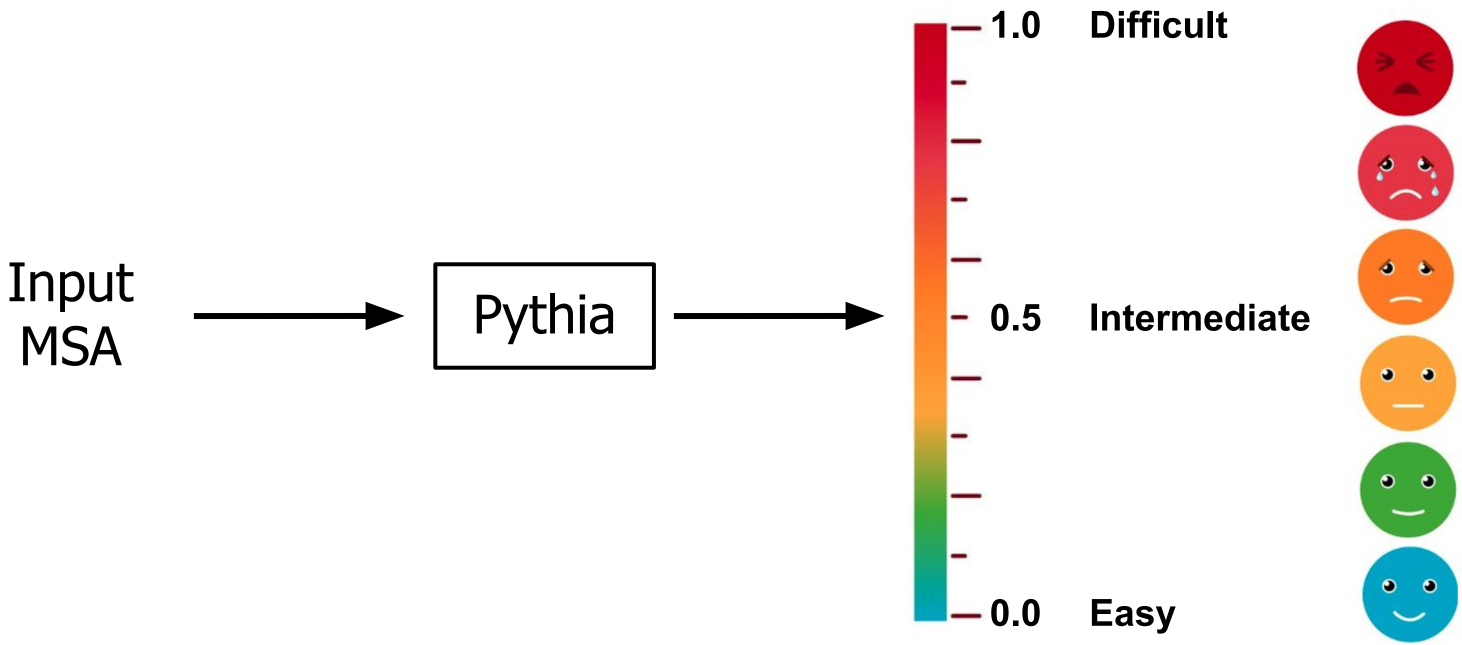
. . .

Comments

- These two examples demonstrate two extreme-case dataset types
- There is a whole spectrum of **in-between dataset** cases (intermediate datasets)
- This diverse **behavior** is essentially **quantified** by **pythia**

Difficulty prediction (Haag *et al.*)



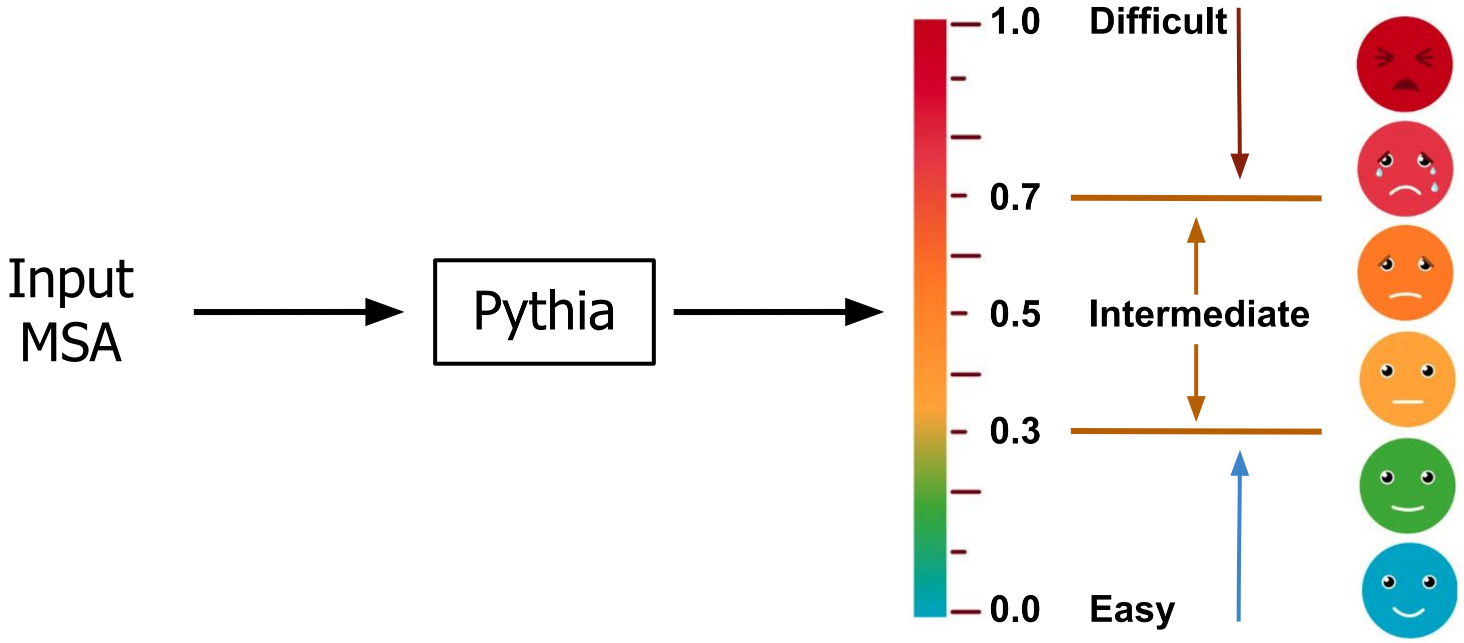
Input MSA → Pythia →

1.0 Difficult

0.5 Intermediate

0.0 Easy

Difficulty prediction (Haag *et al.*)



Input MSA

Pythia

1.0 Difficult

0.7

0.5 Intermediate

0.3

0.0 Easy

Höhler *et al.* (preprint)

- Compared RAxML-NG, IQ-TREE 2 and FastTree 2 on **datasets** with **varying difficulty**.

Höhler *et al.* (preprint)

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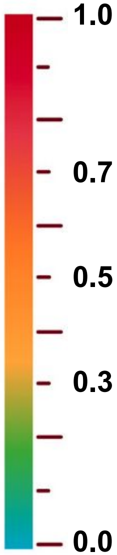

On **difficult** MSAs, all tools perform **similarly** but **only** in terms of **likelihood** score

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On **intermediate** MSAs, **RAxML-NG** and **IQ-TREE 2** infer significantly **better trees**

On **easy** MSAs, all tools perform **similarly** in terms of **likelihood** score and **topological accuracy**

Adaptive RAxML-NG

Standard RAxML-NG

- Initiates **10 random** + **10 MP** starting trees
- Applies a tree search **heuristic** to each of them, using exclusively **SPR** moves

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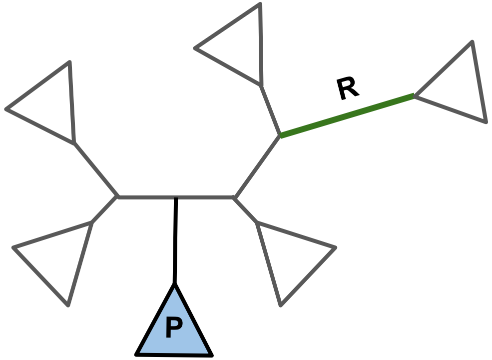
Subtree Prune and Regraft (SPR) move



Initial tree topology

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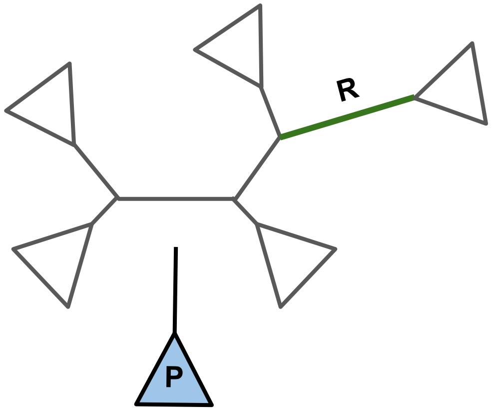

Prune

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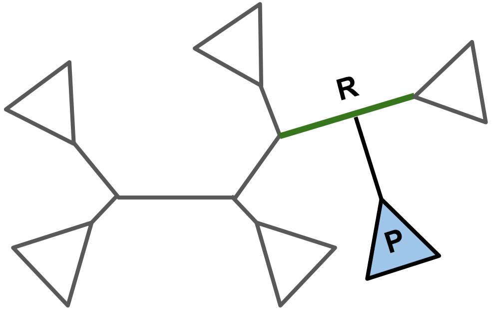
Subtree Prune and Regraft (SPR) move



Regraft

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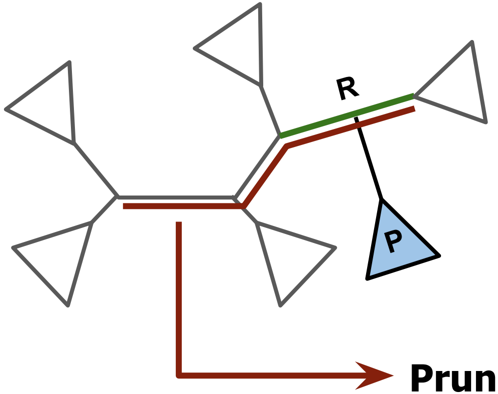


Regraft

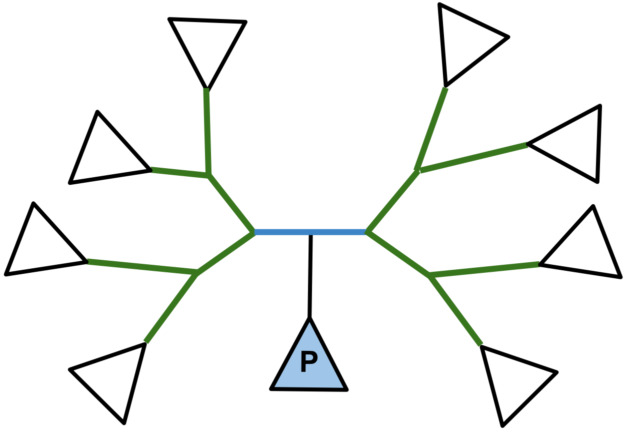
Prune-Regraft distance: 2

SPR round

- Sequence of SPR moves
- Hill-climbing - greedy heuristic
- Two types of SPRs round in **adaptive** RAxML-NG: **Fast** and **Slow** SPR round
- SPR radius: parameter of SPR rounds, denotes the **maximum distance** between the **pruning** and **regrafting** edge

SPR radius

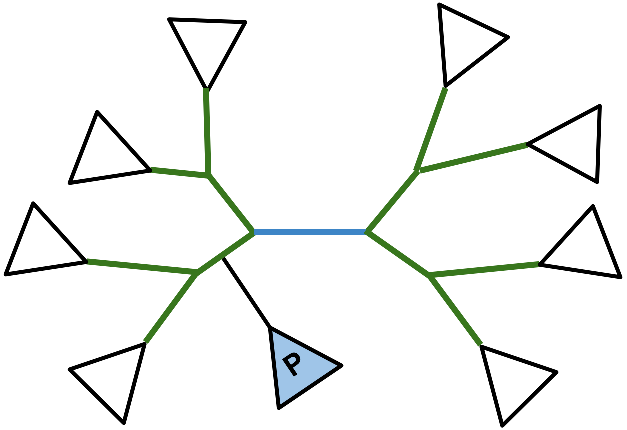
- Example with SPR **radius = 2**



- In an SPR round, RAxML-NG tests **all** possible **regrafting** (green) **edges** up to a certain distance (**radius**)
- It accepts the topology with the highest likelihood score

SPR radius

- Example with SPR **radius = 2**



━ **Pruning edge**
━ **Regrafting edge**

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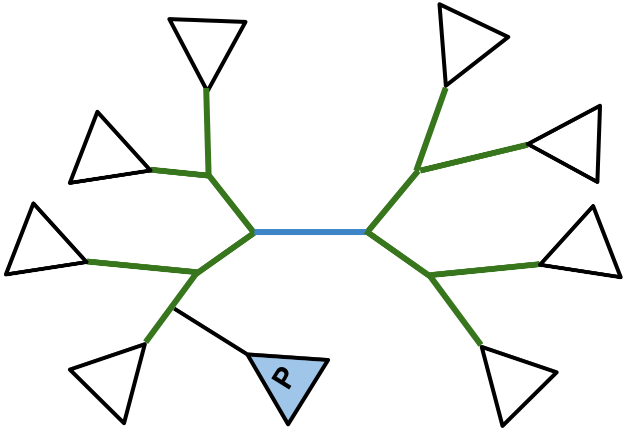

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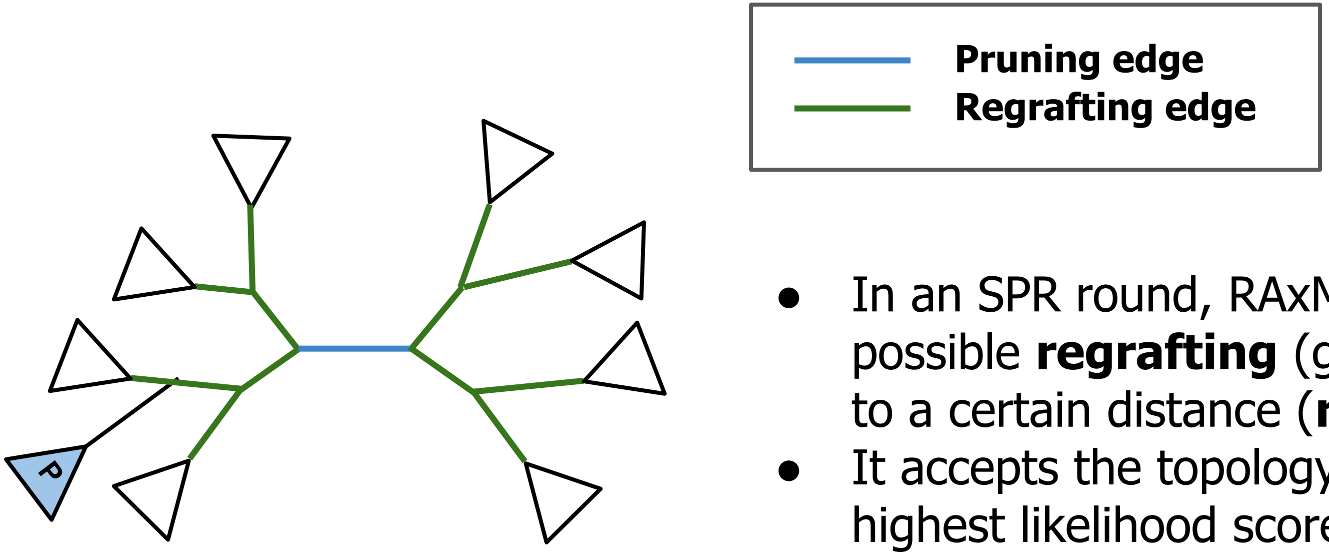

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SPR radius

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🟦 **Pruning edge**
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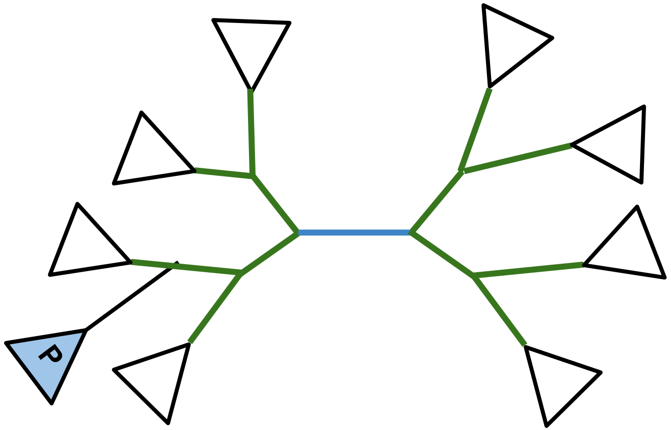

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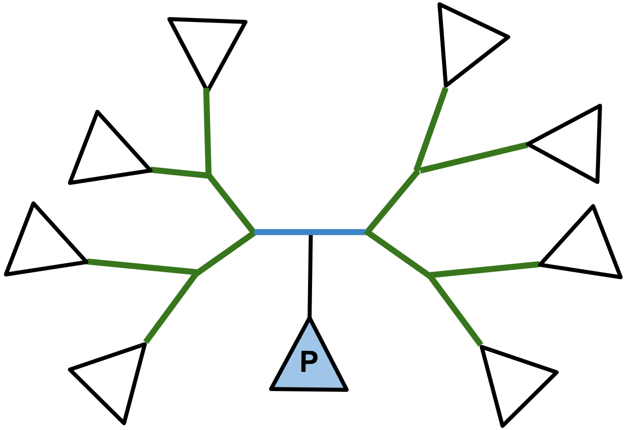
And so on ….

Fast SPR round

- In **Fast SPR** round, RAxML-NG computes the likelihood using the **branch lengths** of the **initial tree** topology



LH_0

List of LH scores:
- LH_0

Fast SPR round

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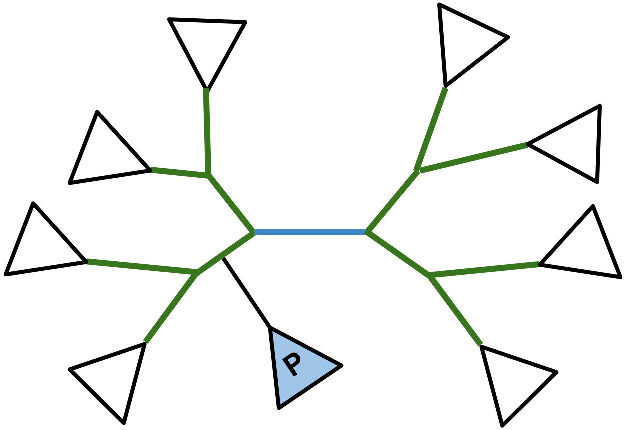

LH_1

List of LH scores:

- LH_0
- LH_1

Fast SPR round

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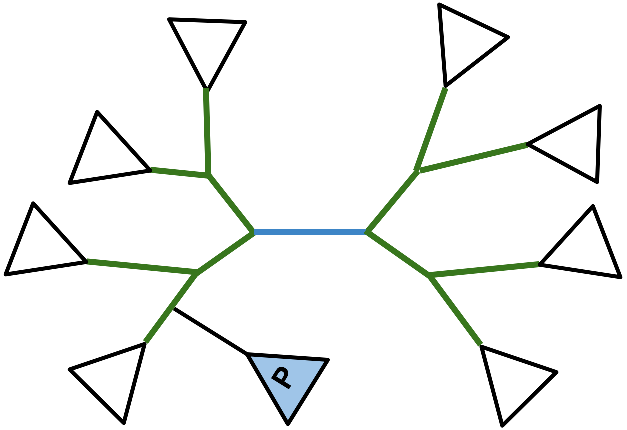


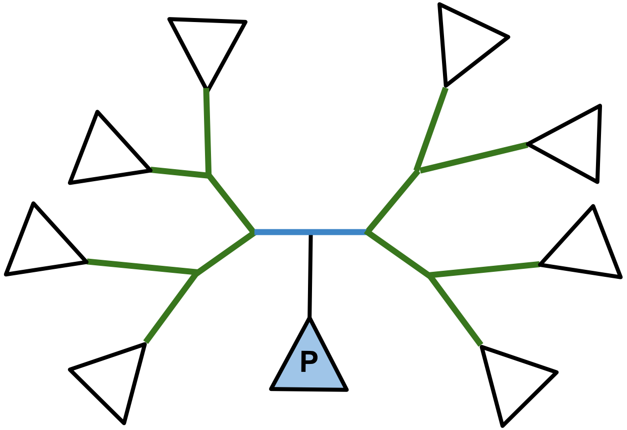
LH_2

List of LH scores:
- LH_0
- LH_1
- LH_2

And so on ….

Slow SPR round

- In **Slow SPR** round, RAxML-NG computes the likelihood by **optimizing** the **three branch lengths** around the **insertion node**



LH_0

List of LH scores:

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Slow SPR round

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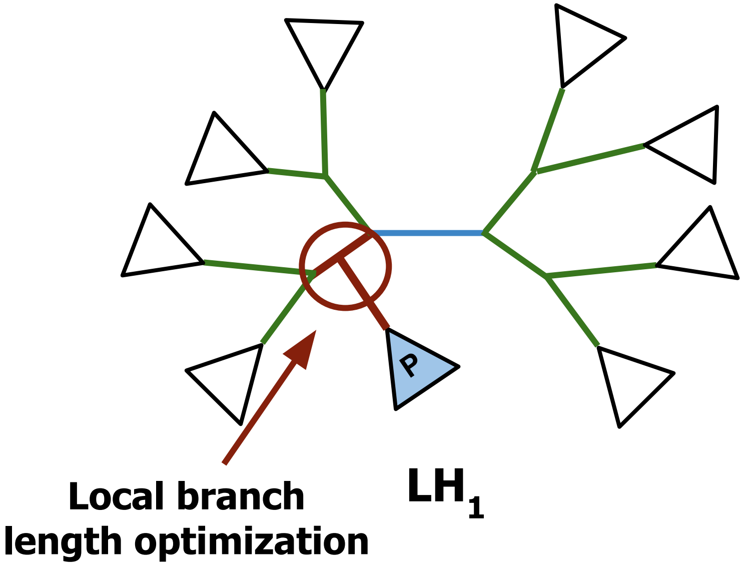


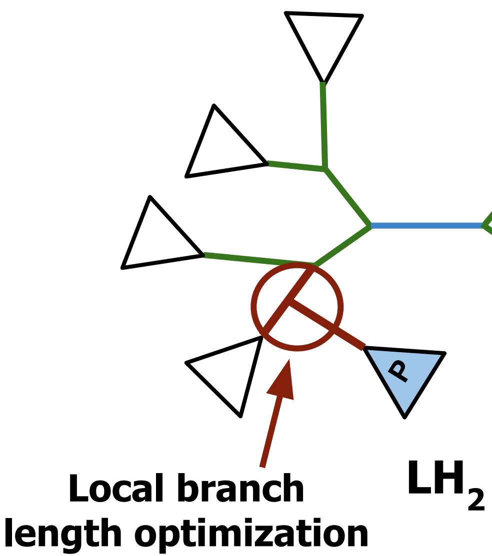
Local branch length optimization

LH_1

List of LH scores:
- LH_0
- LH_1

Slow SPR round

- In **Slow SPR** round, RAxML-NG computes the likelihood using the **branch lengths** of the **initial tree** topology



List of LH scores:
- LH_0
- LH_1
- LH_2

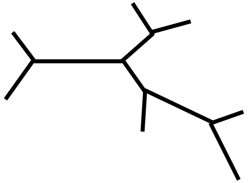
And so on ….

Slow SPR round

- Also, in **Slow SPR** round, RAxML-NG stores the **top-20** best-scoring **topologies** on a list

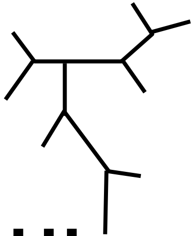
Top-20 topologies:

1.



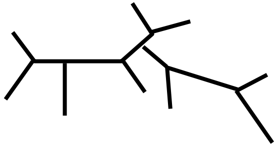
LH_1

2.



LH_2

3.

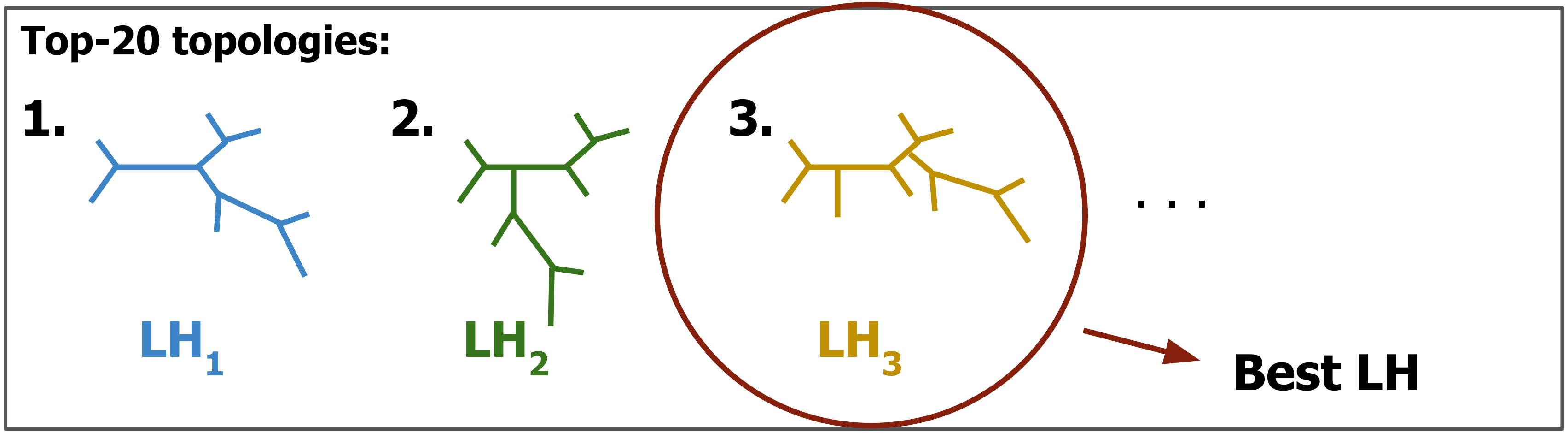


LH_3

. . .

Slow SPR round

- Also, in **Slow SPR** round, RAxML-NG stores the **top-20** best-scoring **topologies** on a list
- At the end of the round, **branch lengths** are **optimized** in all top-20 topologies to check whether any of them gives a **higher LH score**



Top-20 topologies:

1. LH_1

2. LH_2

3. LH_3

. . .

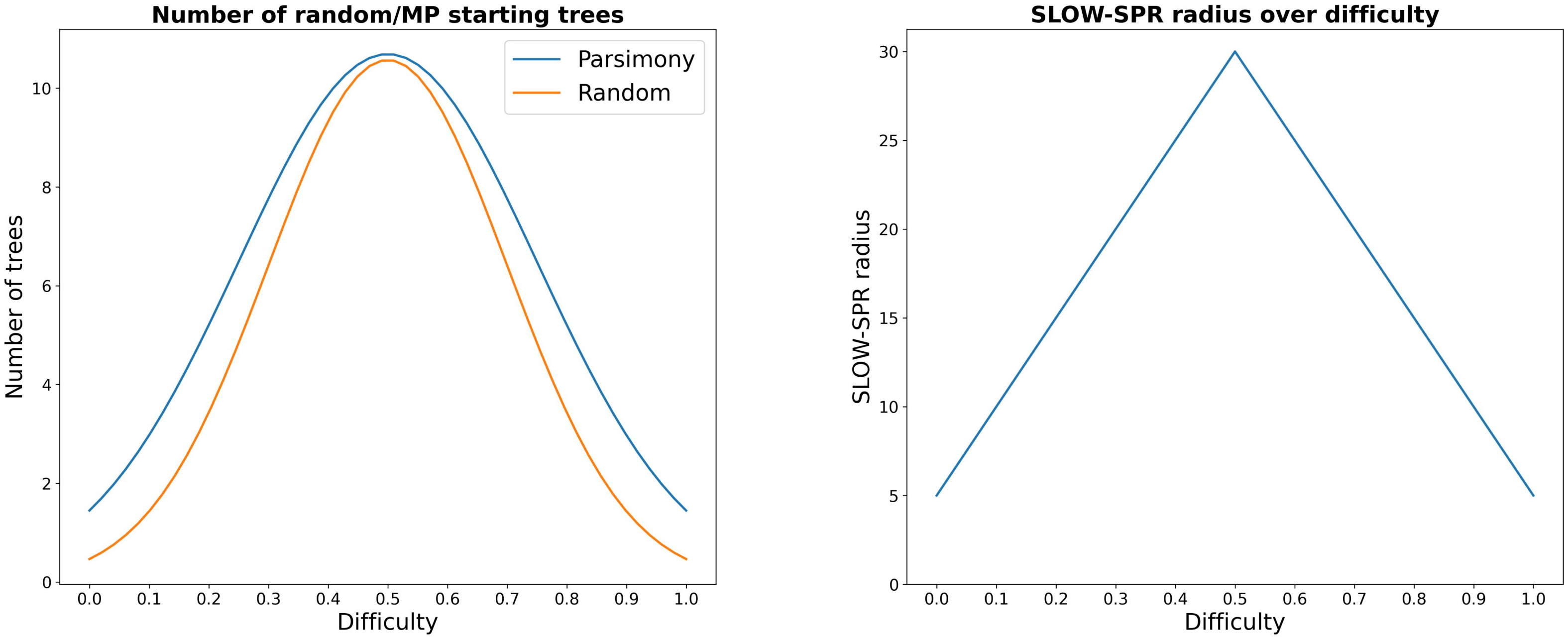
Best LH

Adaptive heuristic in RAxML-NG

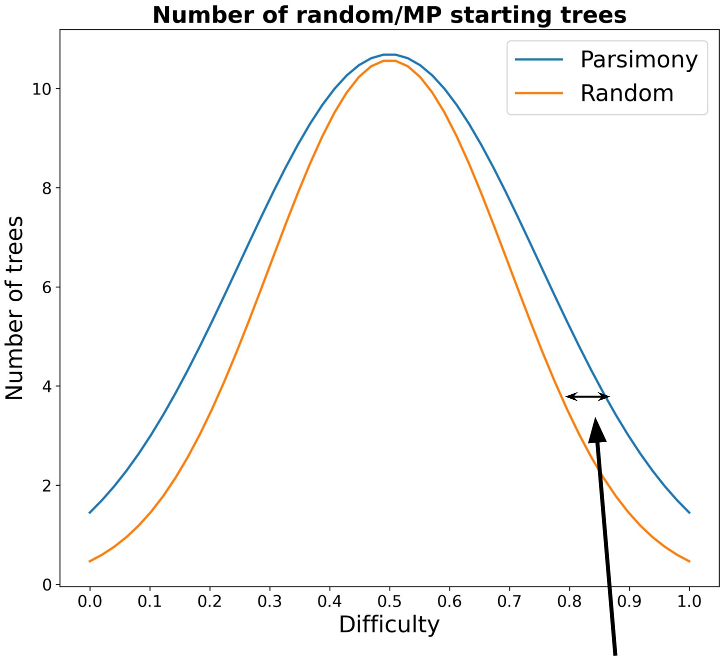
- We **modify** (with respect to difficulty) :
    - the **number** of **ML tree searches**
    - the radius in Fast/Slow SPR rounds

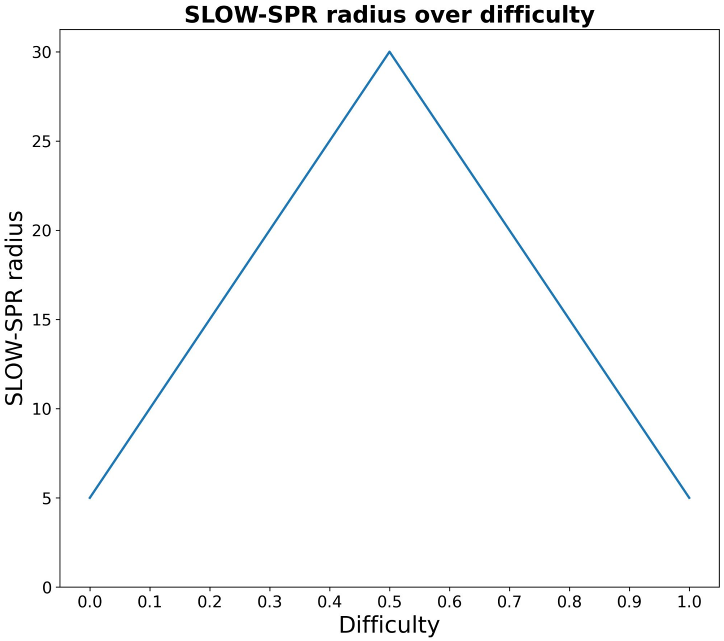
- We further **introduce**:
    - The **NNI moves**

Adaptive heuristic in RAxML-NG



Adaptive heuristic in RAxML-NG

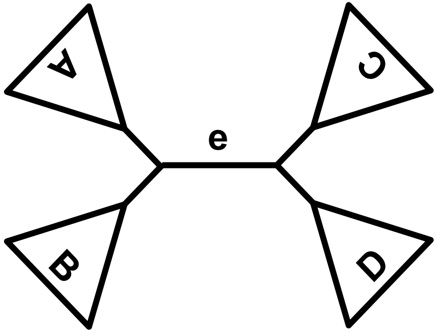




The MP starting trees curve is wider, due to the observation made by Morel *et al.*

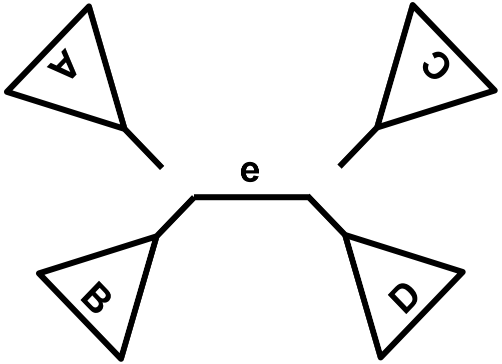
Nearest Neighbor Interchange (NNI) move

- Around a central branch *e*



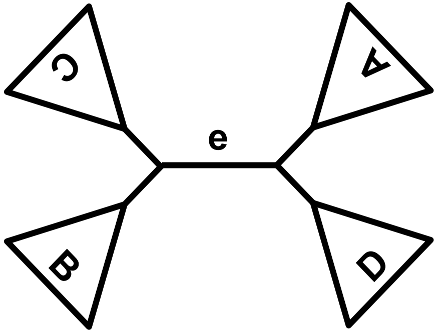
Nearest Neighbor Interchange (NNI) move

- Around a **central** inner **branch *e***
- Pick one subtree from each side



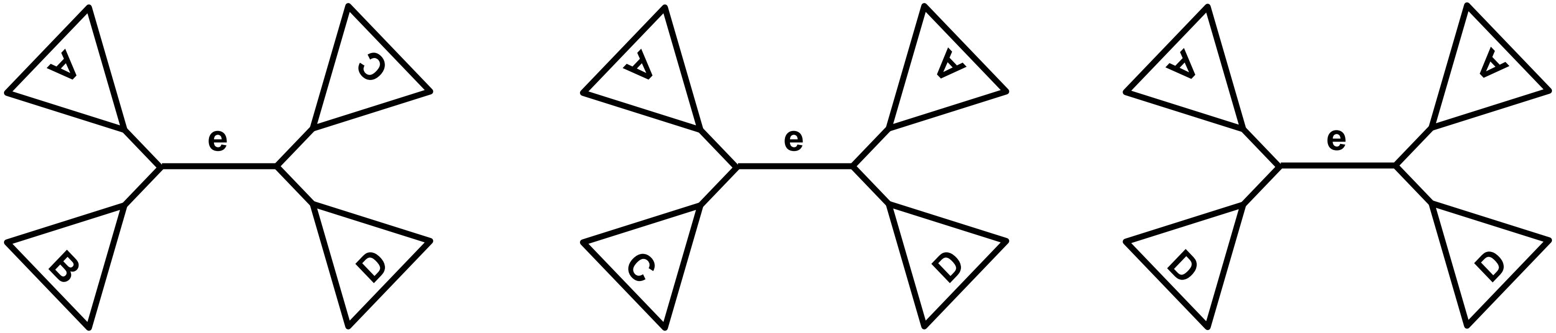
Nearest Neighbor Interchange (NNI) move

- Around a **central** inner **branch *e***
- Pick one subtree from each side
- And **interchange** them



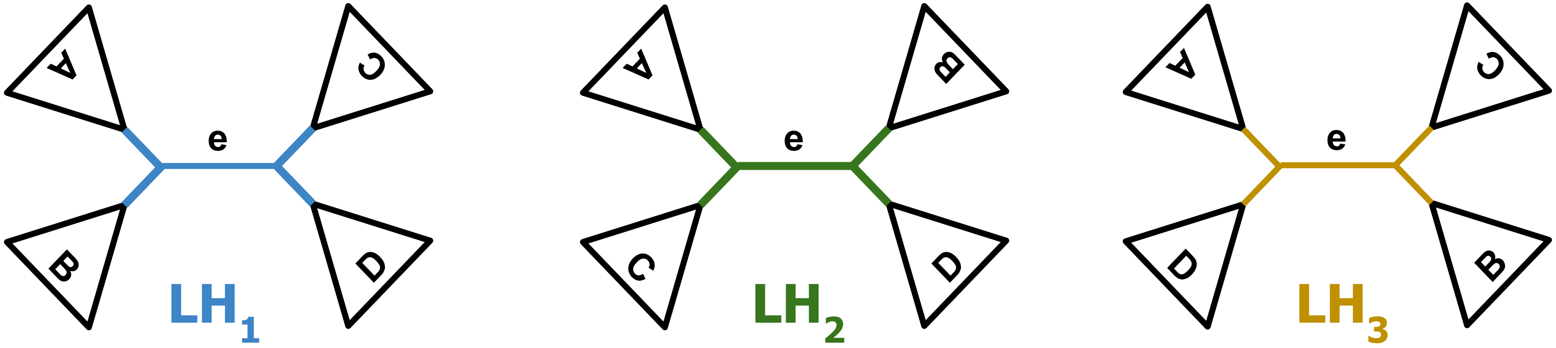
NNI round

- Sequence of NNI moves (hill-climbing/greedy heuristic)
- For each inner branch *e*, we check all three neighboring NNI topologies



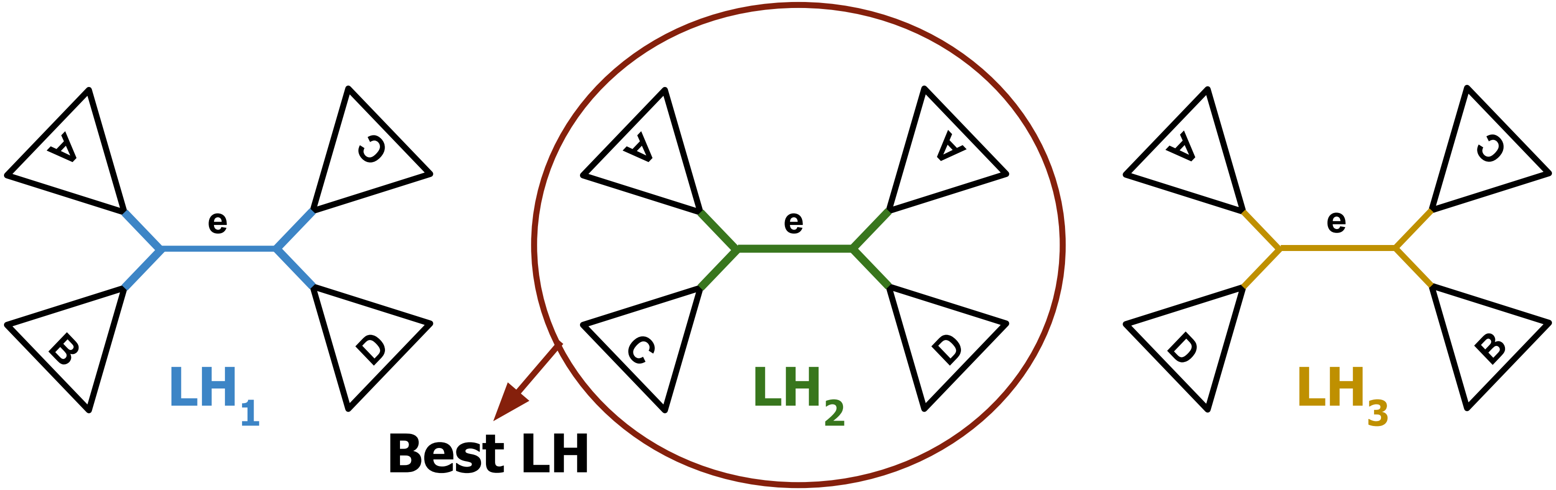
NNI round

- Sequence of NNI moves (hill-climbing/greedy heuristic)
- For each inner branch *e*, we check all three neighboring NNI topologies
- We optimize the five central branches and calculate the likelihoods



NNI round

- Sequence of NNI moves (hill-climbing/greedy heuristic)
- For each inner branch *e*, we check all three neighboring NNI topologies
- We optimize the five central branches and calculate the likelihoods
- Accept the best-scoring topology. Proceed to adjacent inner branches



Adaptive heuristic in RAxML-NG

- We **alternate** between **SPR** and **NNI rounds**
- The alternation between SPR and NNI rounds achieves faster likelihood convergence, while maintaining the accuracy
- On **easy** and **difficult** datasets, we **begin** with an **NNI round**, since the probability of rapid convergence on those datasets is comparatively high

Results

Experimental setup

Experimental setup

- ~10,000 empirical - 5,000 simulated datasets
- Empirical data from TreeBASE [DNA/AA, single/multi partitioned]
- Simulated data from Höhler *et al.* (RAxML Grove reference trees)

Experimental setup

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- Empirical data from TreeBASE [DNA/AA, single/multi partitioned]
- Simulated data from Höhler *et al.* (RAxML Grove reference trees)

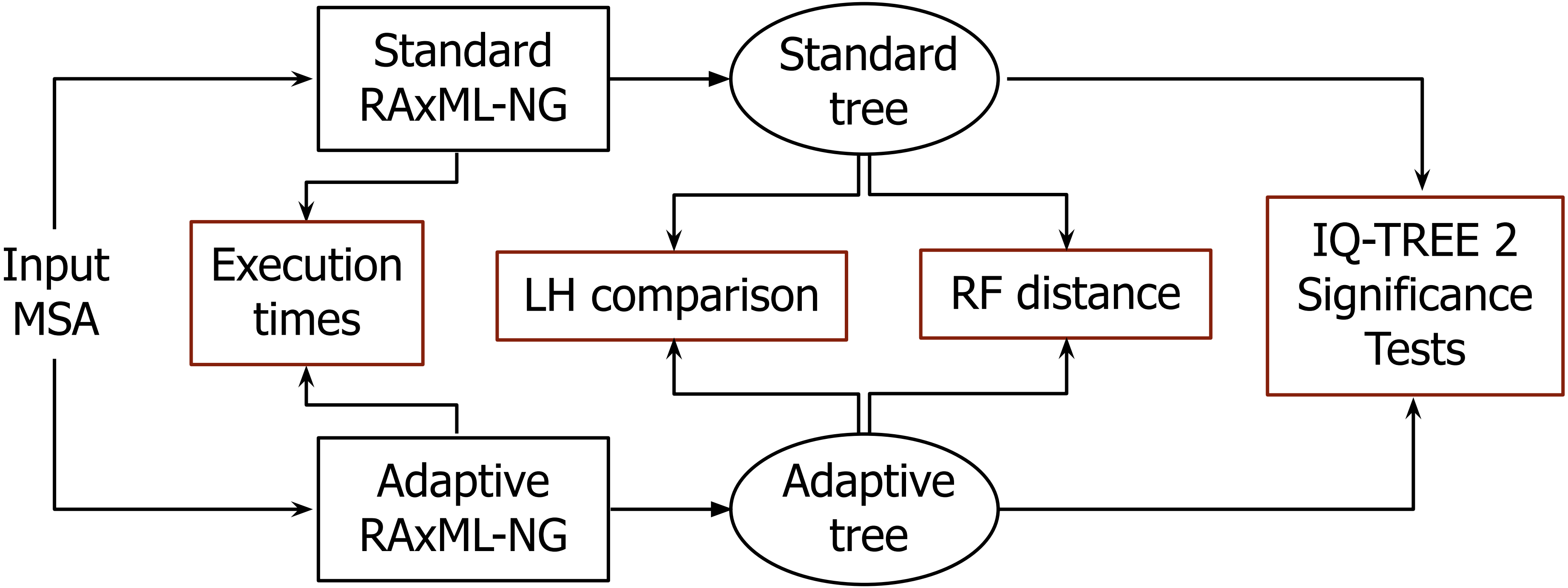
10,000 empirical
5,000 simulated

Filtering

9,515 empirical
5,000 simulated

We present the results
from filtered datasets

Experimental pipeline



Input
MSA

Standard
RAxML-NG

Adaptive
RAxML-NG

Standard
tree

Adaptive
tree

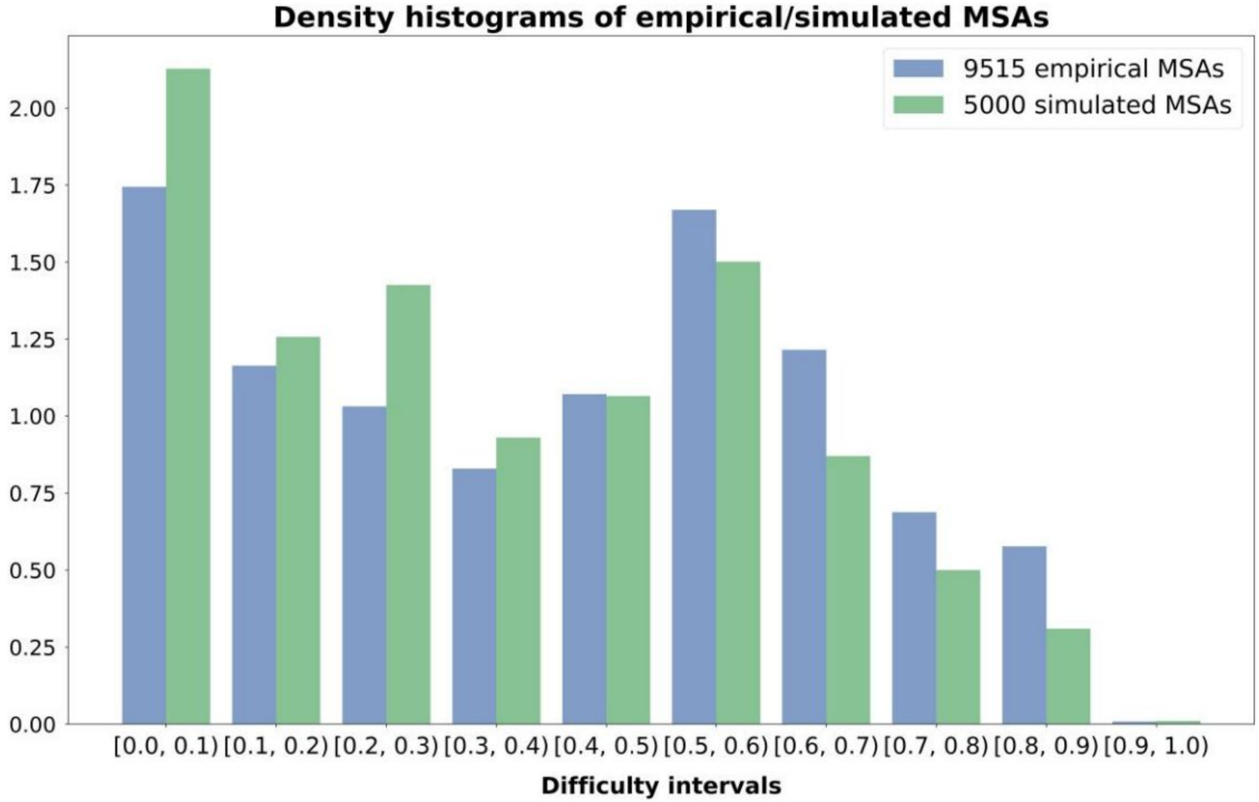
Execution
times

LH comparison

RF distance

IQ-TREE 2
Significance
Tests

Difficulty score distribution



Likelihood score comparison

- Log-likelihood difference metric (**LD**):

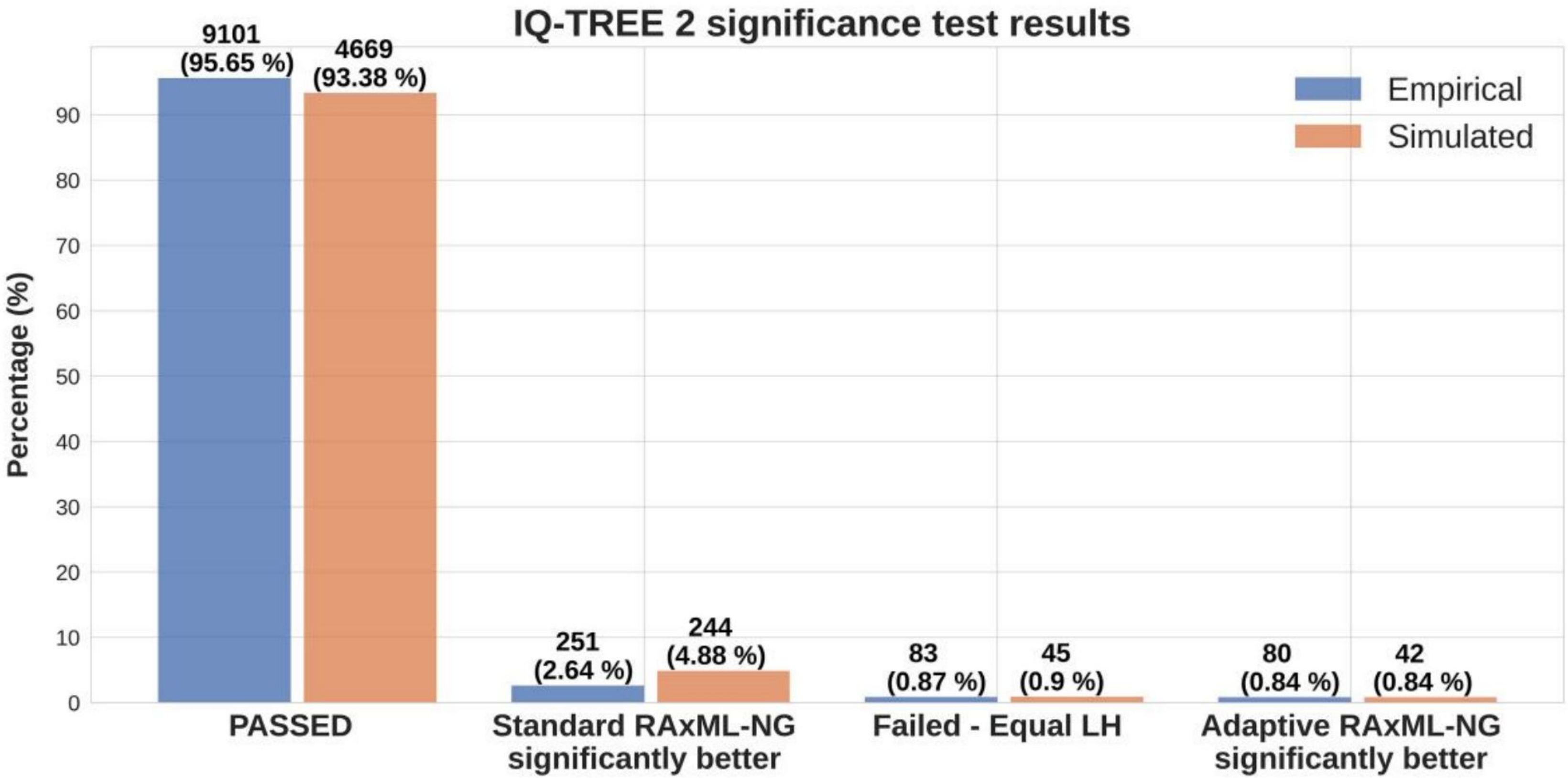
$$\boxed{LD \;=\; LH_S - LH_A}$$

- Relative log-likelihood difference metric (**RLD**):

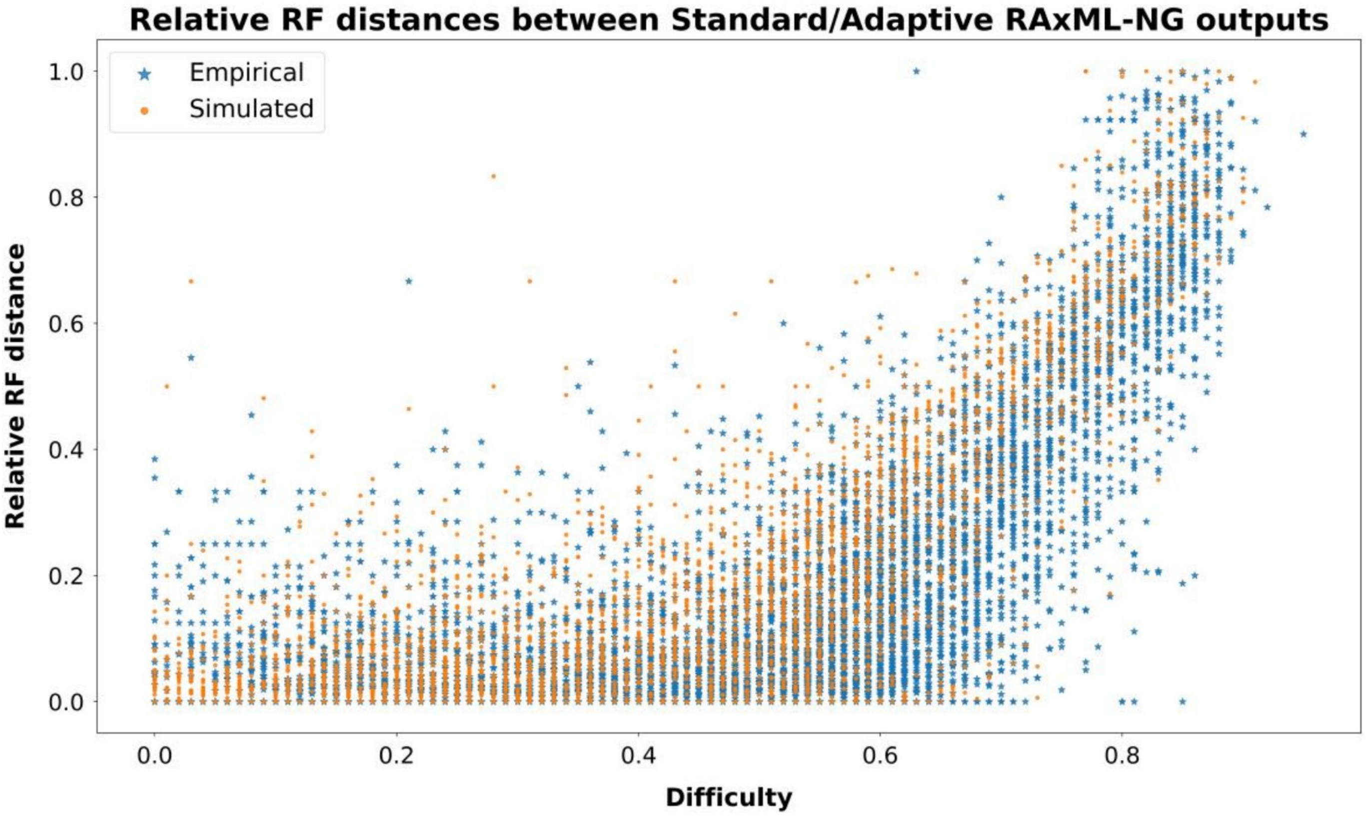
$$\boxed{RLD = \frac{LH_S - LH_A}{|LH_S|}}$$

- In cases the adaptive tree has higher LH, LD<0 and RLD<0
- In **~98%** of empirical/simulated data, **LD < 2 LHU**
- In ~**99%** of the cases (on empirical/simulated data) **RLD<10^{-3}** (0.1%), while in **all** cases, **RLD<10^{-2}** (1%)

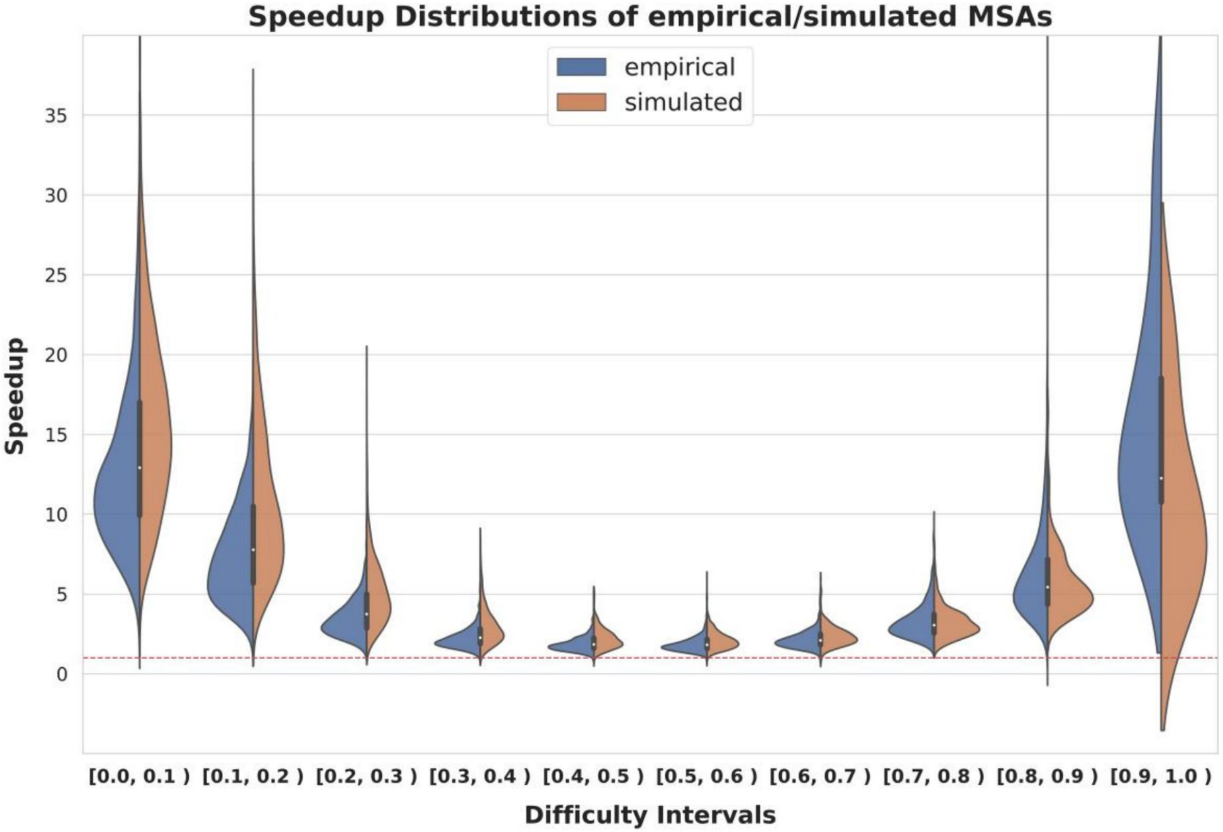
IQ-TREE 2 significance tests



Relative RF distances



Speedups


Speedup Distributions of empirical/simulated MSAs
empirical
simulated
Speedup
35
30
25
20
15
10
5
0
[0.0, 0.1)
[0.1, 0.2)
[0.2, 0.3)
[0.3, 0.4)
[0.4, 0.5)
[0.5, 0.6)
[0.6, 0.7)
[0.7, 0.8)
[0.8, 0.9)
[0.9, 1.0)
Difficulty Intervals

Future work

Future work

- Concerning our future work, we intend to:
    - Play a little bit with adaptive RAxML-NG heuristic
    - Experiment with **statistical tests** for **early termination** of the tree search
    - Consider the **sequence error rate** during the inference

Availability

- Adaptive RAxML-NG is currently available under GNU GPL:
  - https://github.com/togkousa/raxml-ng/tree/adaptive

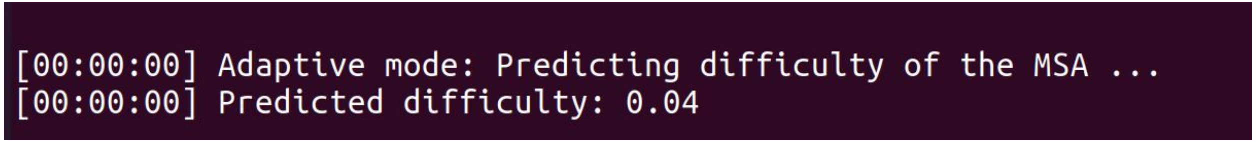
- Manuscript:
  - Togkousidis, A., Kozlov, O. M., Haag, J., Höhler, D., & Stamatakis, A. (2023). Adaptive RAxML-NG: Accelerating Phylogenetic Inference under Maximum Likelihood using Dataset Difficulty. Molecular Biology and Evolution, 40(10), msad227.

Demo

- In order to execute the adaptive version of RAxML-NG, the user needs to invoke the `--adaptive` option in the command line:

```
./bin/raxml-ng --adaptive --threads 4 --msa ../seminar-datasets/easy/alignment.phy --model LG --seed 0 --nofiles
```

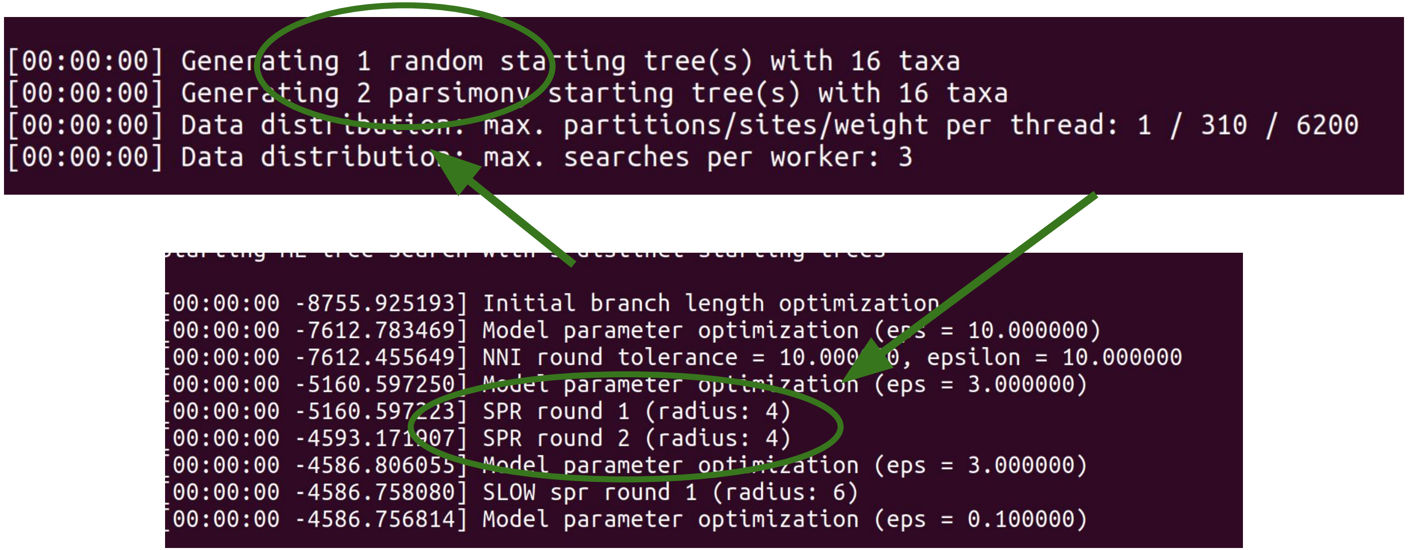
- The predicted difficulty is printed out directly at the beginning of the execution:



```
[00:00:00] Adaptive mode: Predicting difficulty of the MSA ...
[00:00:00] Predicted difficulty: 0.04
```

Demo

- The number of independent tree searches and the SPR radius are modified according to the predicted difficulty score:

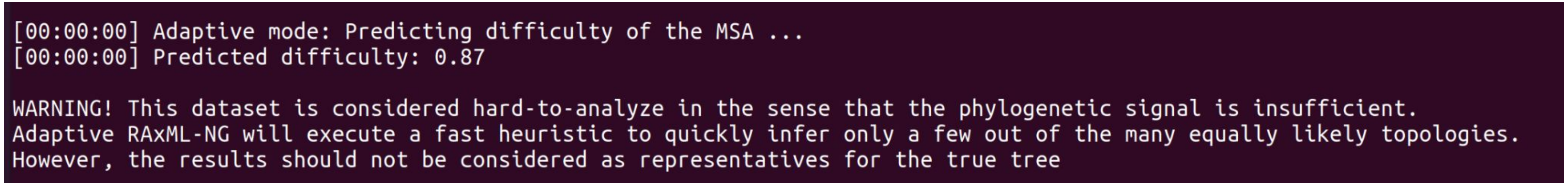


```
[00:00:00] Generating 1 random starting tree(s) with 16 taxa
[00:00:00] Generating 2 parsimony starting tree(s) with 16 taxa
[00:00:00] Data distribution: max. partitions/sites/weight per thread: 1 / 310 / 6200
[00:00:00] Data distribution: max. searches per worker: 3
```

```
[00:00:00 -8755.925193] Initial branch length optimization
[00:00:00 -7612.783469] Model parameter optimization (eps = 10.000000)
[00:00:00 -7612.455649] NNI round tolerance = 10.000000, epsilon = 10.000000
[00:00:00 -5160.597250] Model parameter optimization (eps = 3.000000)
[00:00:00 -5160.597223] SPR round 1 (radius: 4)
[00:00:00 -4593.171907] SPR round 2 (radius: 4)
[00:00:00 -4586.806055] Model parameter optimization (eps = 3.000000)
[00:00:00 -4586.758080] SLOW spr round 1 (radius: 6)
[00:00:00 -4586.756814] Model parameter optimization (eps = 0.100000)
```

Demo

- In case the predicted difficulty score is higher than 0.7, a warning is printed to inform the user that the phylogenetic signal in the input MSA is insufficient



```
[00:00:00] Adaptive mode: Predicting difficulty of the MSA ...
[00:00:00] Predicted difficulty: 0.87

WARNING! This dataset is considered hard-to-analyze in the sense that the phylogenetic signal is insufficient.
Adaptive RAxML-NG will execute a fast heuristic to quickly infer only a few out of the many equally likely topologies.
However, the results should not be considered as representatives for the true tree
```

Thank you

BACK UP
SLIDES

Difficulty prediction (Haag *et al.*)

- Recently, Haag *et al.* proposed a definition for the difficulty of analyzing an MSA
- The **difficulty score** essentially **quantifies** the amount of phylogenetic **signal** on a given MSA
- Difficulty score is a real number between **0.0 (easy MSAs)** and **1.0 (difficult MSAs)**
- They also implemented and published **Pythia**, a Random-Forest Regressor able to accurately predict the difficulty score of an MSA

Summary of their work

- Quantified difficulty on ~3,000 empirical MSAs from TreeBASE. For each dataset they:
    - conducted 100 ML RAxML-NG tree searches
    - extracted the *plausible tree set (PST)*

$$\boxed{Difficulty = \frac{1}{5}\left(RF_{all} + RF_{pl} + \frac{N_{all}^{*}}{N_{all}} + \frac{N_{pl}^{*}}{N_{pl}} + \left(1 - \frac{N_{pl}}{N_{all}}\right)\right)}$$

- Trained and tested Pythia on the inferred difficulty labels

Using Pythia

- Pythia uses **eight features** to represent each dataset as a data point
- Six of them are dataset’s attributes (fast-to-compute)
- For the remaining two features, Pythia conducts **100 MP tree inferences**
- The two remaining features are attributes of the MP output tree set
- **Predicting the difficulty** is on average **five times faster than a single ML tree inference** in RAxML-NG

Beyond Pythia

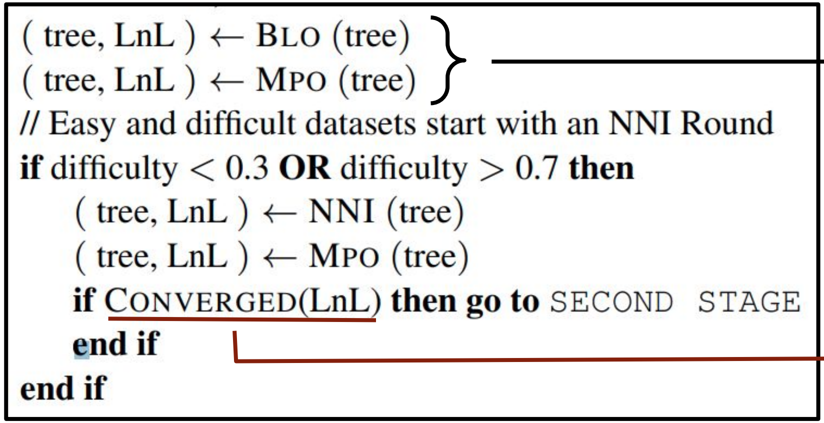
- Based on the difficulty score, one can classify MSAs into **easy**, **intermediate** and **difficult** (hard/hopeless) to analyze.
- Our suggestion:
  - Easy datasets (Difficulty < 0.3)
  - Intermediate (0.3 ≤ Difficulty ≤ 0.7)
  - Difficult datasets (Difficulty > 0.7)
- The concept of difficulty provides adequate explanation for the ambiguities arising from different tool performance-assessment studies

Our idea

- The three observations made in Höhler *et al.* study indicate that one can **modify** the **thoroughness** of the tree search **heuristic based on** the predicted **difficulty** of the MSA
- On **easy** and **difficult** datasets, **fast heuristics** perform equally well
- On easy datasets, tree searches converge rapidly
- Difficult datasets are hopeless to analyze, and thus it suffices to quickly infer only a few out of the many equally likely trees, to reduce overall execution time

Heuristic step by step

- Adaptive RAxML-NG begins with a BLO and MPO round. In case the dataset is easy or difficult, it applies an NNI round + MPO. If likelihood convergence is achieved, it proceeds directly to the second stage



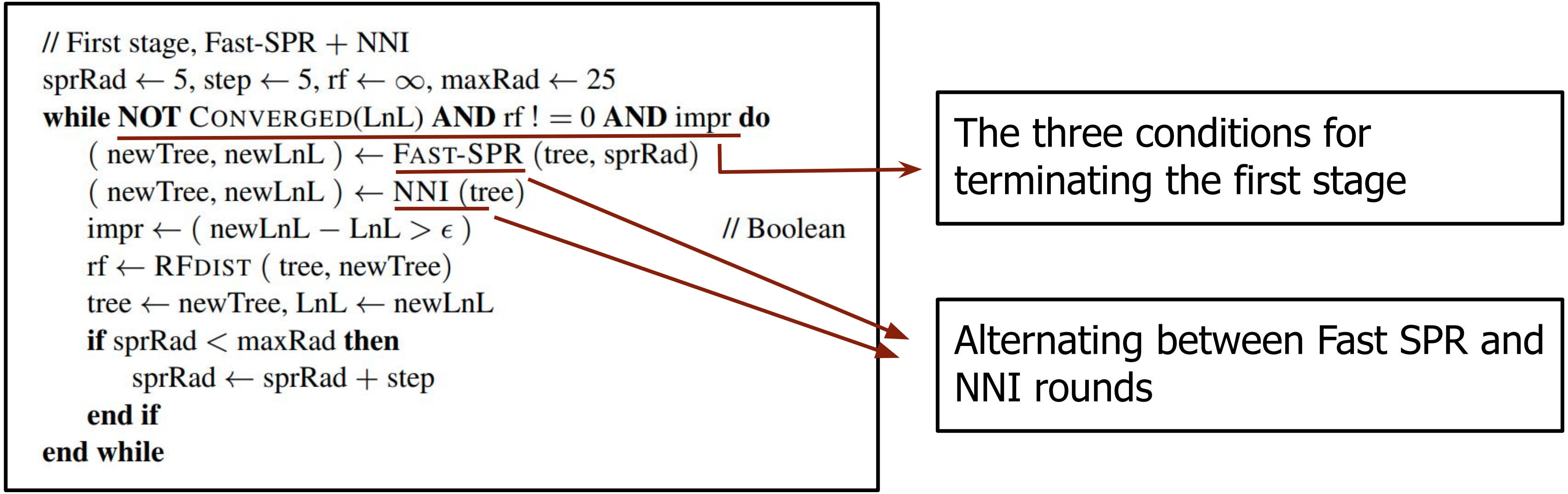
```
( tree, LnL ) $\leftarrow$ BLO (tree)
( tree, LnL ) $\leftarrow$ MPO (tree)
// Easy and difficult datasets start with an NNI Round
if difficulty $< 0.3$ OR difficulty $> 0.7$ then
    ( tree, LnL ) $\leftarrow$ NNI (tree)
    ( tree, LnL ) $\leftarrow$ MPO (tree)
    if CONVERGED(LnL) then go to SECOND STAGE
    end if
end if
```

Branch-length optimization
Model parameter optimization

Checks if likelihood convergence was achieved (1% likelihood convergence interval). If so, it skips the first stage

Heuristic step by step

- During the first stage, Fast-SPR round are alternated with NNI rounds



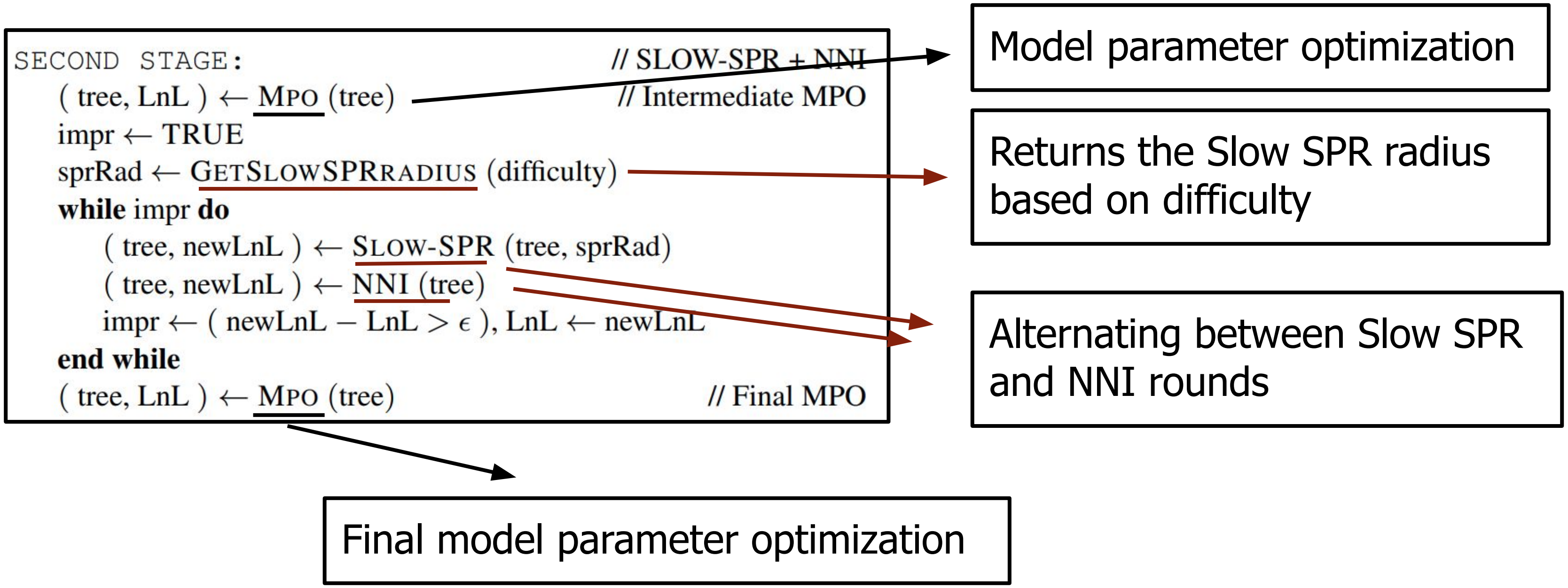
```
// First stage, Fast-SPR + NNI
sprRad ← 5, step ← 5, rf ← $\infty$, maxRad ← 25
while NOT CONVERGED(LnL) AND rf != 0 AND impr do
    ( newTree, newLnL ) ← FAST-SPR (tree, sprRad)
    ( newTree, newLnL ) ← NNI (tree)
    impr ← ( newLnL − LnL > $\epsilon$ )                // Boolean
    rf ← RFDIST ( tree, newTree)
    tree ← newTree, LnL ← newLnL
    if sprRad < maxRad then
        sprRad ← sprRad + step
    end if
end while
```

The three conditions for terminating the first stage

Alternating between Fast SPR and NNI rounds

Heuristic step by step

- During the first stage, Fast-SPR round are alternated with NNI rounds



```
SECOND STAGE:                                                // SLOW-SPR + NNI
    ( tree, LnL ) ← MPO (tree)                               // Intermediate MPO
    impr ← TRUE
    sprRad ← GETSLOWSPRRADIUS (difficulty)
    while impr do
        ( tree, newLnL ) ← SLOW-SPR (tree, sprRad)
        ( tree, newLnL ) ← NNI (tree)
        impr ← ( newLnL − LnL > ϵ ), LnL ← newLnL
    end while
    ( tree, LnL ) ← MPO (tree)                               // Final MPO
```

Model parameter optimization

Returns the Slow SPR radius based on difficulty

Alternating between Slow SPR and NNI rounds

Final model parameter optimization

Adaptive heuristic in RAxML-NG

- The heuristic is divided into **two stages**. During the **first stage**, **Fast-SPR** rounds are alternated with **NNI** rounds.
- The first stage is terminated if:
  - The likelihood improvement is less than ε *OR*
  - The RF distance between two consecutive tree topologies is 0 *OR*
  - The likelihood is less than 1% lower from the score of the best ML tree found so far from a finished tree inference (**1% likelihood convergence interval**)

Adaptive heuristic in RAxML-NG

- During the **second stage**, **Slow-SPR** rounds are alternated with **NNI** rounds.
- The second round is terminated if the likelihood improvement is less than ε
- Before and after each stage, adaptive RAxML-NG conducts Branch-Length Optimization (BLO) and Model Parameter Optimization (MPO)

Adaptive heuristic in RAxML-NG

- On **easy** and **difficult** datasets, adaptive RAxML-NG begins with an NNI round + MPO
- The probability of achieving likelihood convergence with only an NNI round is comparatively high on such datasets

Experimental setup

- We collected **10,000 empirical** MSAs from TreeBASE and used the **5,000 simulated** MSAs from Höhler *et al.* study.
- We apply some **filtering** process (which we will describe on the next slide). After filtering, we end up with **9,192 empirical** and **4,991 simulated** MSAs.
- All simulated data are single-partitoned DNA datasets
- Out of the 9,192 (final) empirical MSAs.
    - 7,769 are single-partitioned DNA
    - 614 are multi-partitioned DNA
    - 801 are single-partitioned AA
    - 8 are multi-partitioned AA

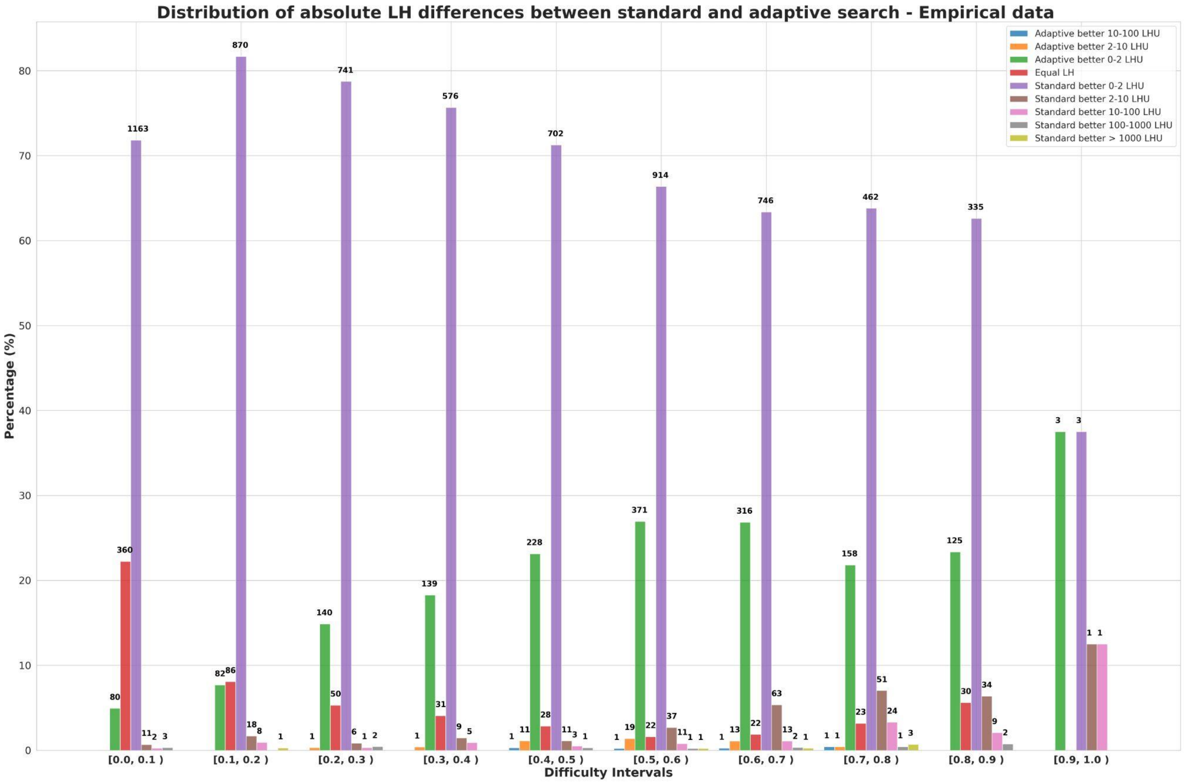
Pipeline + Filtering

- We ran both **standard** and **adaptive RAxML-NG** on each one of the datasets (sequentially, 24 hours threshold)
- We filtered out those MSAs in which either:
    - The execution of standard/adaptive RAxML-NG took longer than 24 hours *OR*
    - At least one of the RAxML-NG executions failed for whatever reason
- We ran IQ-TREE 2 significance tests (Tree Topology Tests) on all pairs of standard/adaptive output trees. Those datasets in which the execution of IQ-TREE 2 failed were also filtered out
- We end up with 9,192 empirical and 4,991 simulated MSAs

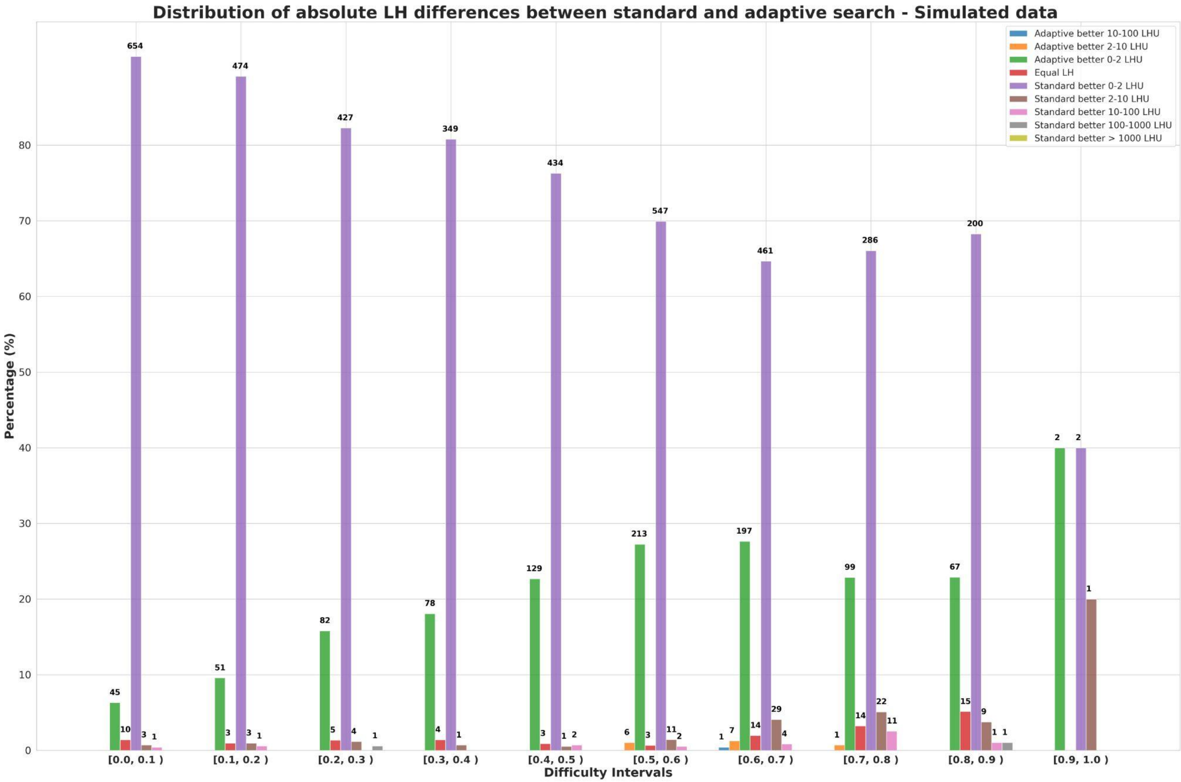
Standard/Adaptive RAxML-NG comparison

- We **compare** the two versions of RAxML-NG based on:
  - The **likelihood score** of the output tree
  - The result IQ-TREE 2 **significance tests** (We consider the two output trees to be **statistically indistinguishable** if the pair passes **all** significance tests)
  - The relative **RF-distance** between the output trees
  - The execution times (**Speedups**)

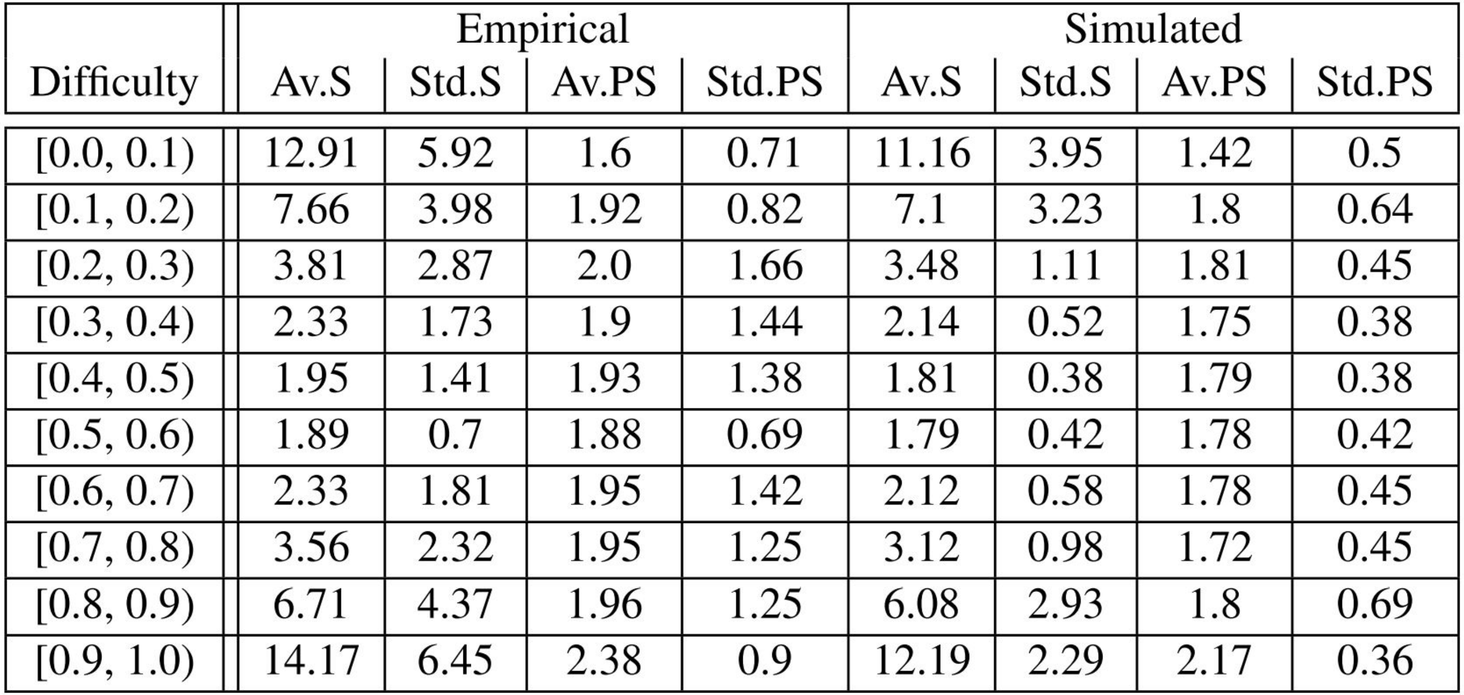
Likelihood score comparison


Distribution of absolute LH differences between standard and adaptive search - Empirical data

Likelihood score comparison



Speedups



	Empirical				Simulated			
Difficulty	Av.S	Std.S	Av.PS	Std.PS	Av.S	Std.S	Av.PS	Std.PS
[0.0, 0.1)	12.91	5.92	1.6	0.71	11.16	3.95	1.42	0.5
[0.1, 0.2)	7.66	3.98	1.92	0.82	7.1	3.23	1.8	0.64
[0.2, 0.3)	3.81	2.87	2.0	1.66	3.48	1.11	1.81	0.45
[0.3, 0.4)	2.33	1.73	1.9	1.44	2.14	0.52	1.75	0.38
[0.4, 0.5)	1.95	1.41	1.93	1.38	1.81	0.38	1.79	0.38
[0.5, 0.6)	1.89	0.7	1.88	0.69	1.79	0.42	1.78	0.42
[0.6, 0.7)	2.33	1.81	1.95	1.42	2.12	0.58	1.78	0.45
[0.7, 0.8)	3.56	2.32	1.95	1.25	3.12	0.98	1.72	0.45
[0.8, 0.9)	6.71	4.37	1.96	1.25	6.08	2.93	1.8	0.69
[0.9, 1.0)	14.17	6.45	2.38	0.9	12.19	2.29	2.17	0.36