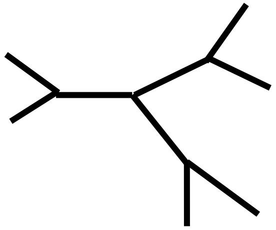
Adaptive search heuristic for ML phylogenetic tree inference based on the predicted difficulty of dataset.

Anastasis Togkousidis, Alexandros Stamatakis

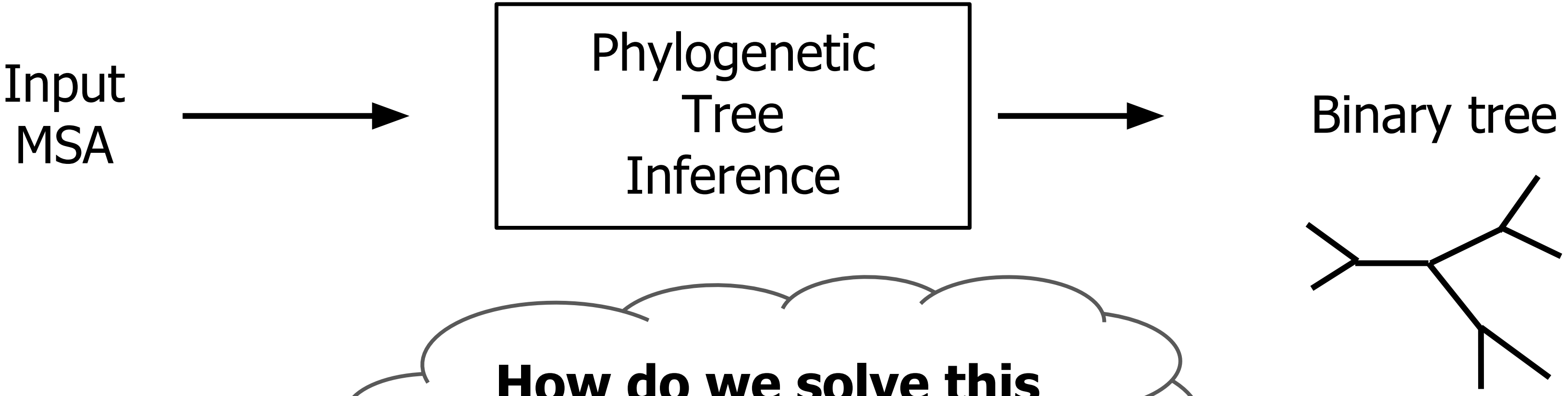
Introduction

Introduction

Input MSA → Phylogenetic Tree Inference → Binary tree



Introduction



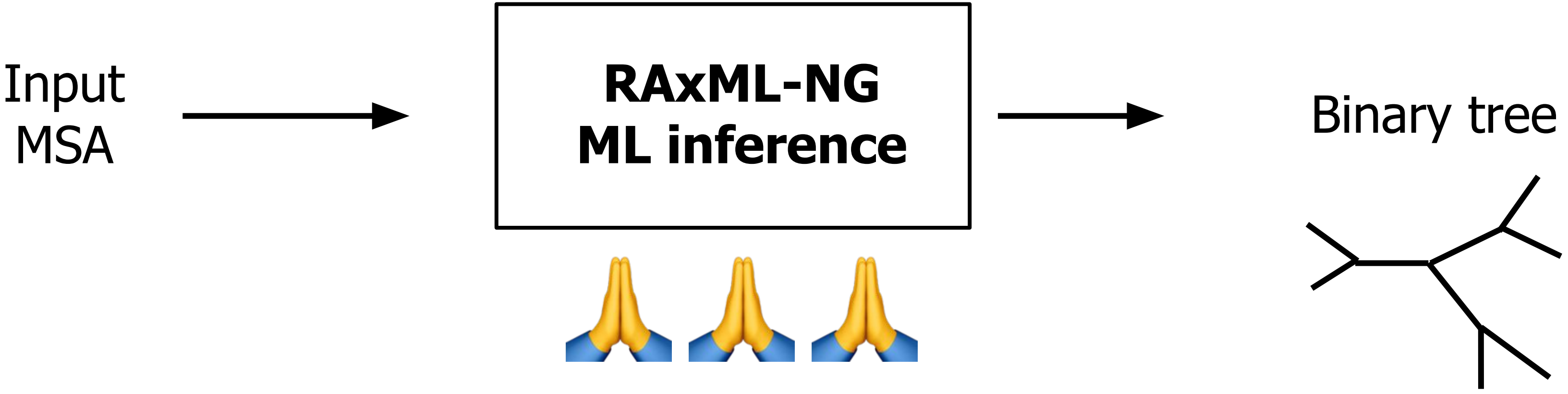
Input MSA

Phylogenetic Tree Inference

Binary tree

How do we solve this difficult problem ?

Introduction



Input MSA

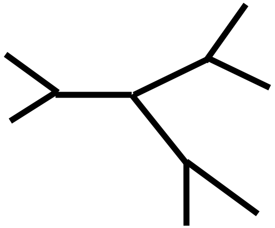
RAxML-NG
ML inference

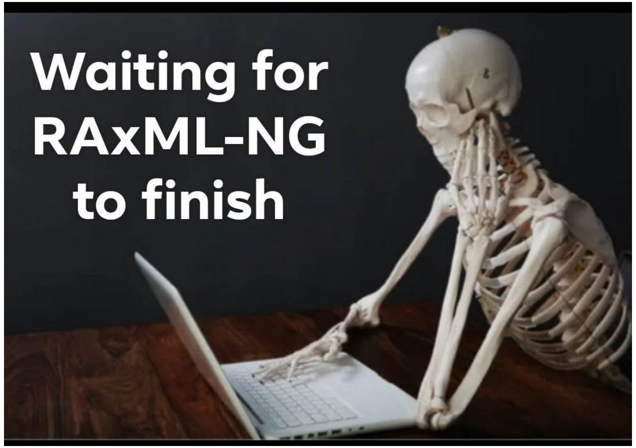
🙏🙏🙏

Binary tree

Introduction

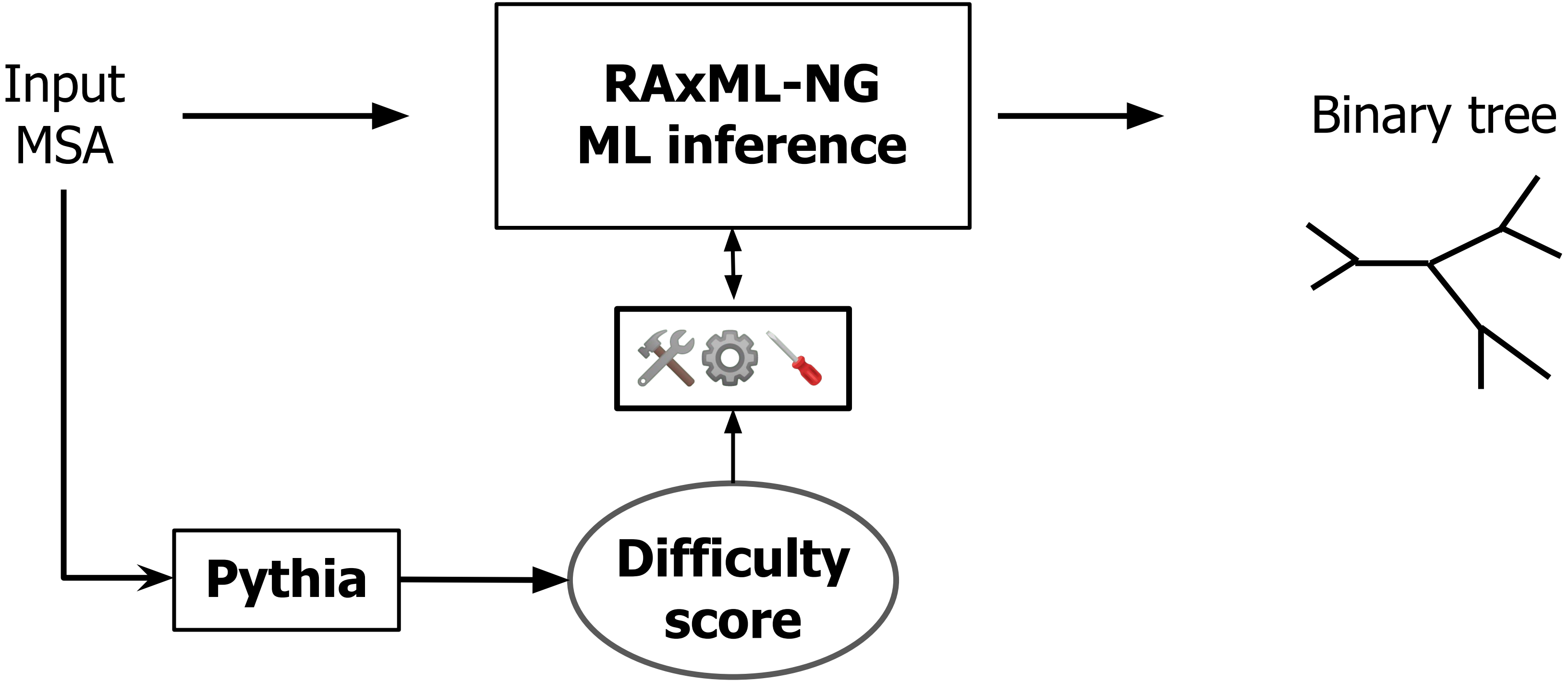
Input MSA → **RAxML-NG ML inference** → Binary tree





Introduction

IDEA



Input
MSA

RAxML-NG
ML inference

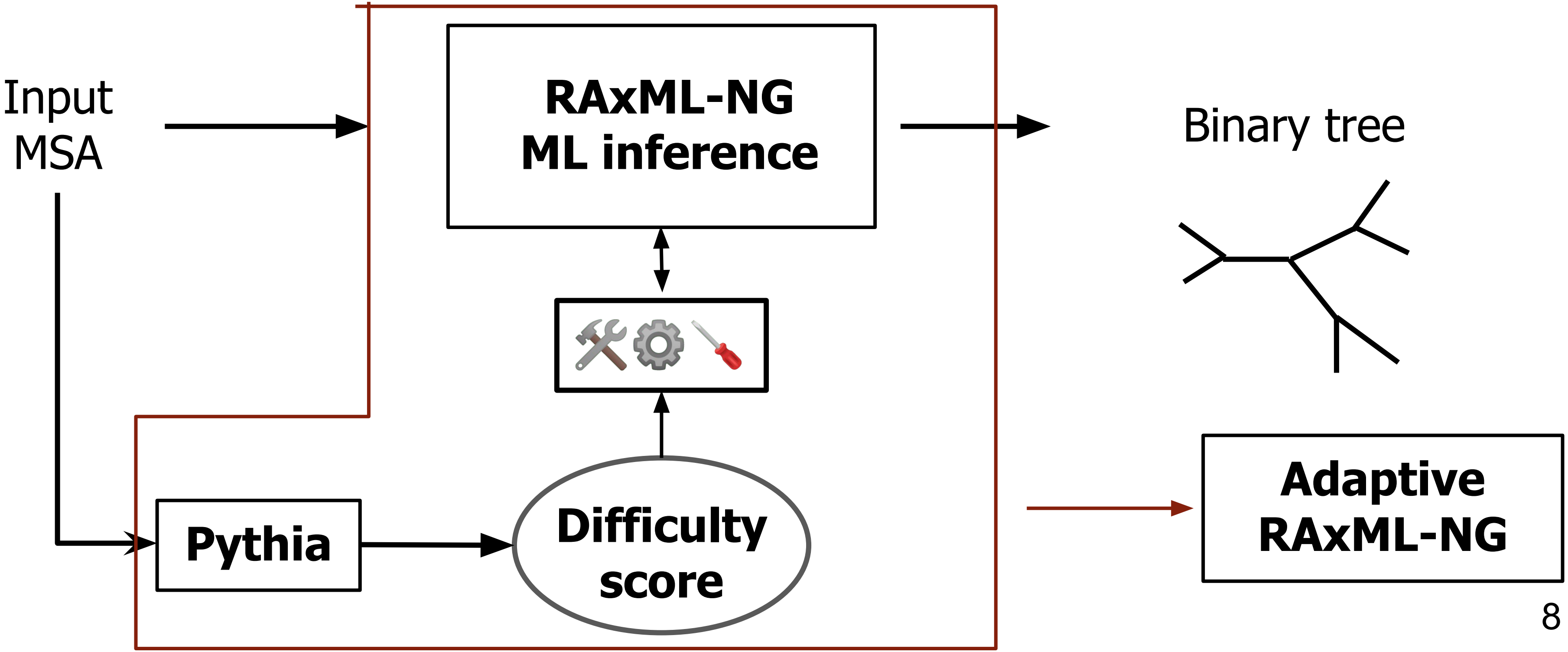
Binary tree

Pythia

Difficulty
score

Introduction

IDEA



Input MSA

RAxML-NG ML inference

🛠 ⚙ 🪛

Pythia

Difficulty score

Binary tree

Adaptive RAxML-NG

Background

The concept of difficulty

- For some datasets, independent ML tree searches starting from different trees, converge to a **single - or topologically similar - tree(s)**
- This implies **a single**, well distinguishable, **globally optimal peak** on the likelihood surface, associated with a single tree topology
- We say that these datasets exhibit a “**clear phylogenetic signal**”

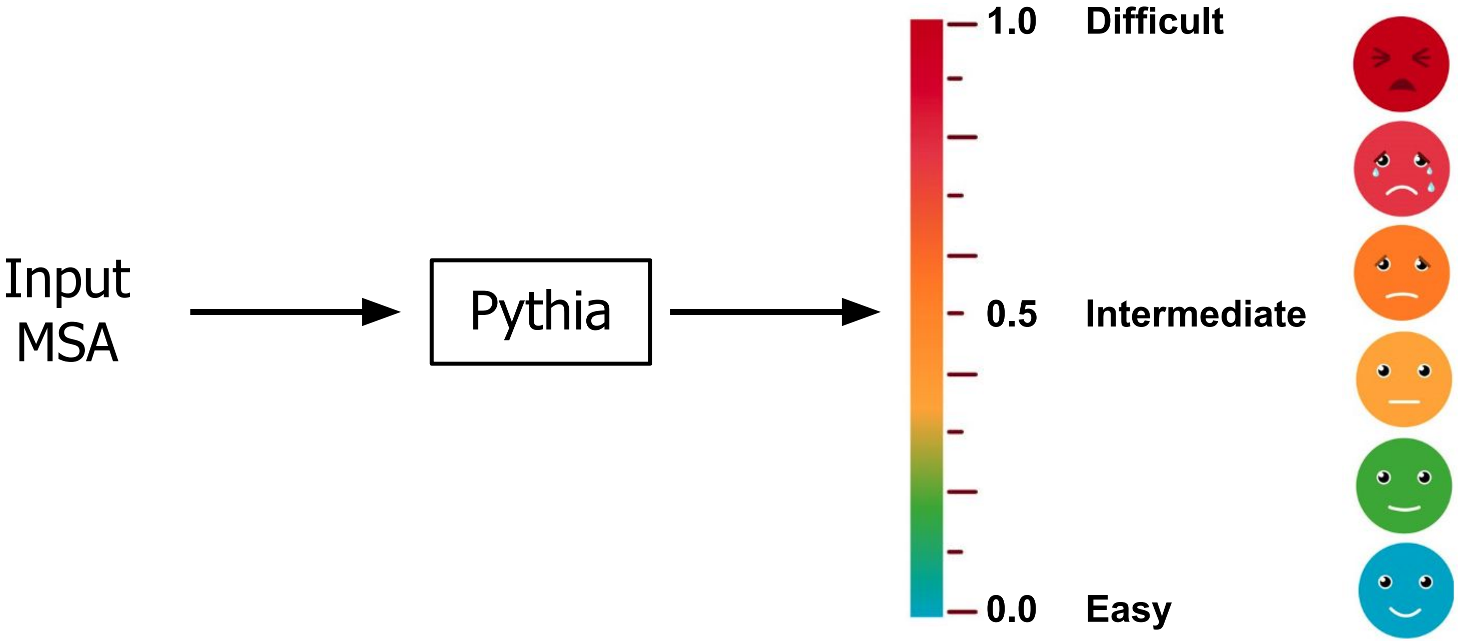
The concept of difficulty

- Other datasets yield **topologically highly distinct**, yet **equally likely trees**
- These trees are also **statistically indistinguishable** based on IQ-TREE 2 significance tests
- This implies a “**rugged**” likelihood surface, with **multiple local optima** associated with contradicting topologies

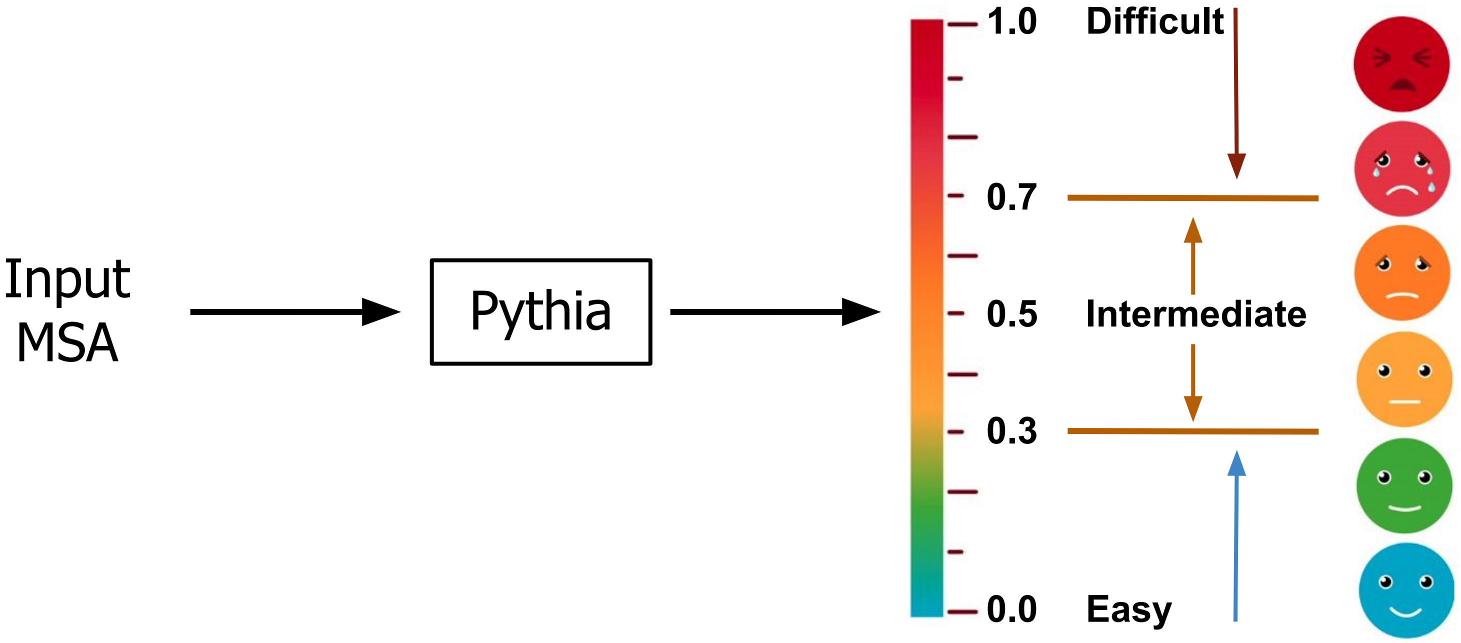
Comments

- These two examples demonstrate two extreme-case dataset types
- There is a whole spectrum of **in-between dataset** cases (for example datasets with multiple local optima, albeit only a small proportion of them being significantly better)
- This diverse **behavior** is essentially **quantified** by **pythia**

Difficulty prediction (Haag *et al.*)



Difficulty prediction (Haag *et al.*)

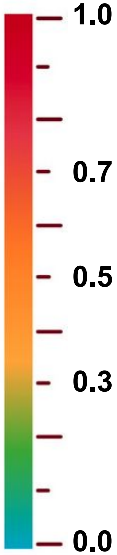


Höhler *et al.* (preprint)

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

Höhler *et al.* (preprint)

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



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

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

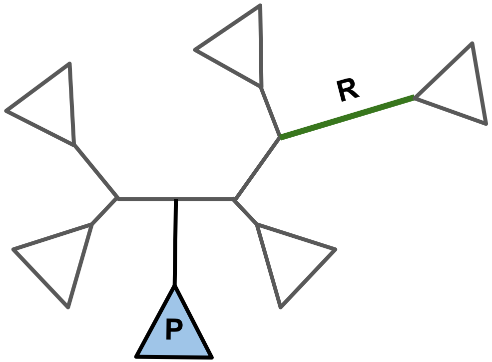
Standard RAxML-NG

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

Standard RAxML-NG

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

Subtree Prune and Regraft (SPR) move

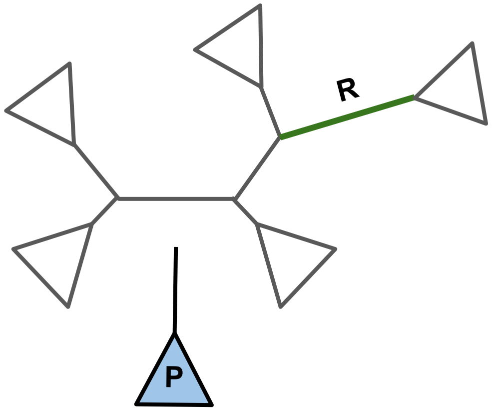


Initial tree topology

Standard RAxML-NG

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

Subtree Prune and Regraft (SPR) move

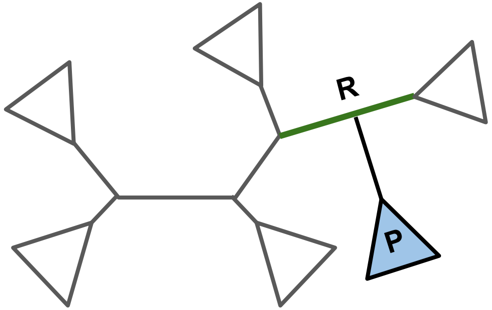


Prune

Standard RAxML-NG

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

Subtree Prune and Regraft (SPR) move

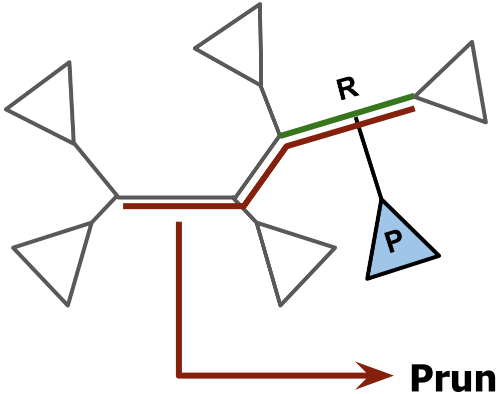


Regraft

Standard RAxML-NG

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

Subtree Prune and Regraft (SPR) move



Regraft

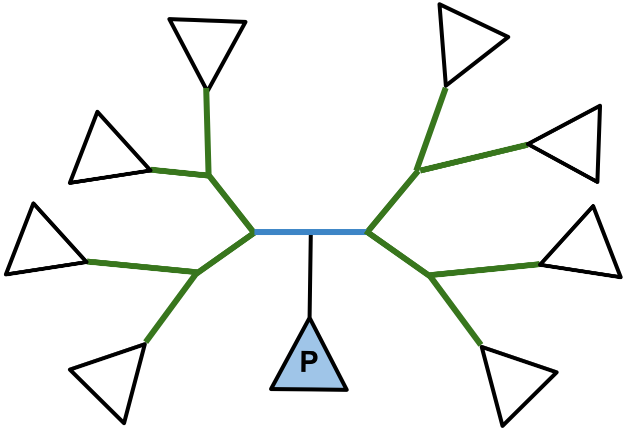
Prune-Regraft distance: 2

SPR round

- Sequence of SPR moves
- Hill-climbing - greedy heuristic
- Two types of SPRs round in 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**

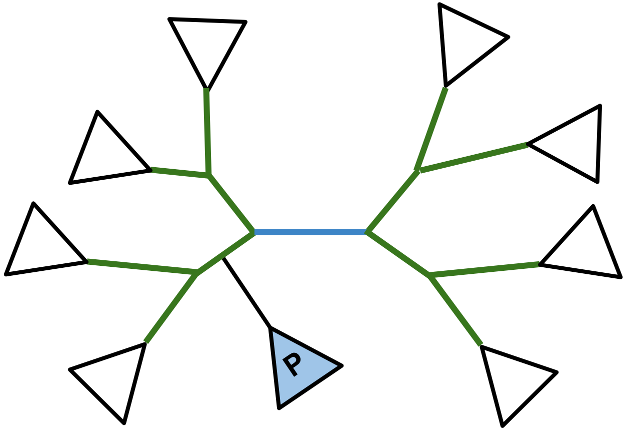


🟦 **Pruning edge**
🟩 **Regrafting edge**

- 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

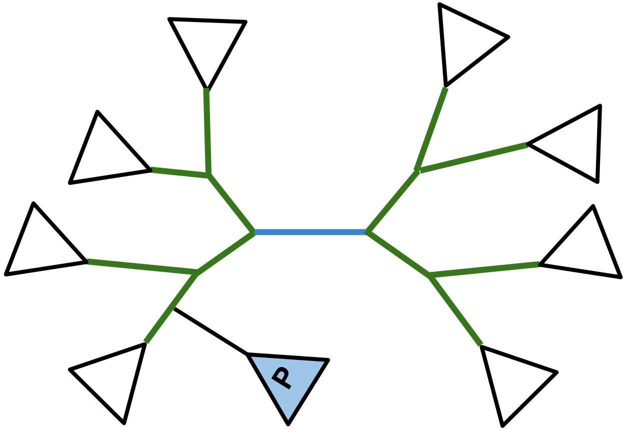
- Example with SPR **radius = 2**



- 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

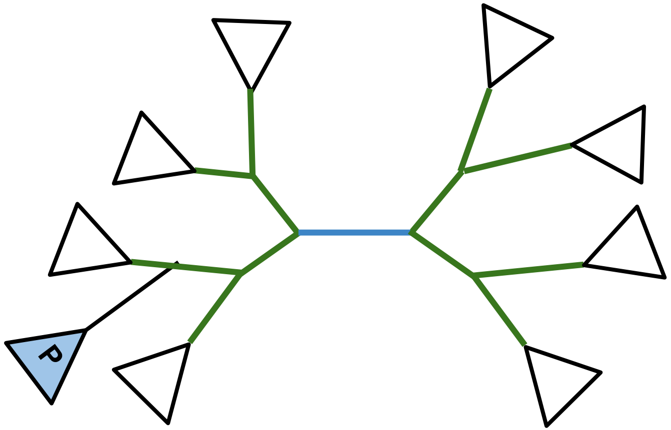
- Example with SPR **radius = 2**



- 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**

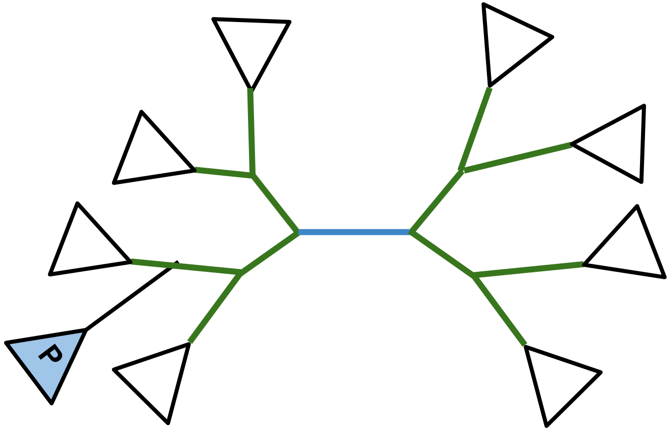


- In an SPR round, RAxML-NG tests **all** possible **regrafting** (green) **edges** up to a certain distance (**radius**)
- It accepts the topology with the highest likelihood score

SPR radius

- Example with SPR **radius = 2**

🟦 **Pruning edge**
🟩 **Regrafting edge**

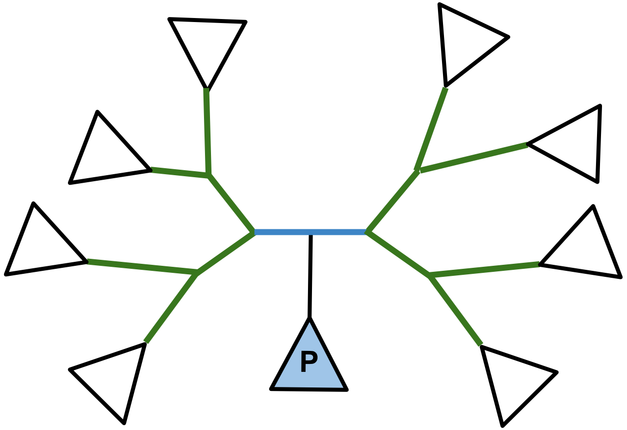


- In an SPR round, RAxML-NG tests **all** possible **regrafting** (green) **edges** up to a certain distance (**radius**)
- It accepts the topology with the highest likelihood score

And so on ….

Fast SPR round

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



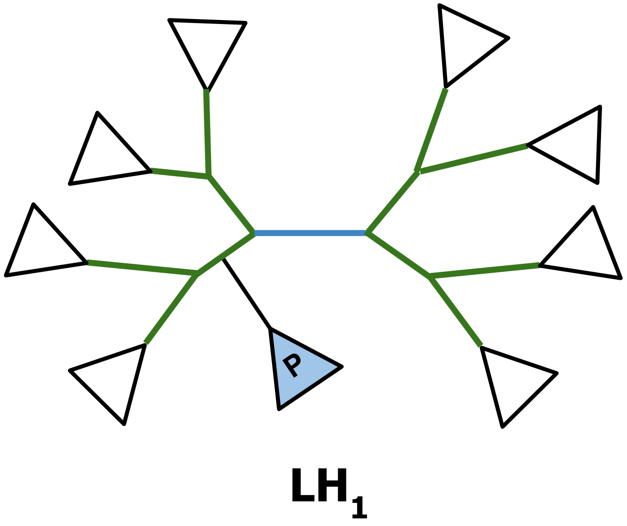
LH_0

List of LH scores:

- LH_0

Fast SPR round

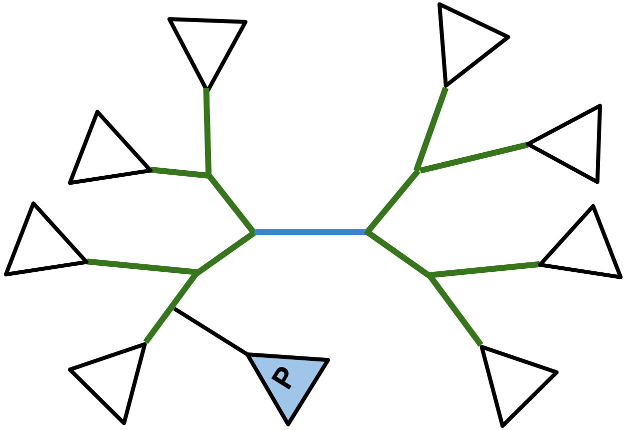
- In **Fast SPR** round, RAxML-NG computes the likelihood using the **branch lengths** of the **initial tree** topology



List of LH scores:
- LH$_0$
- LH$_1$

Fast SPR round

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



LH_2

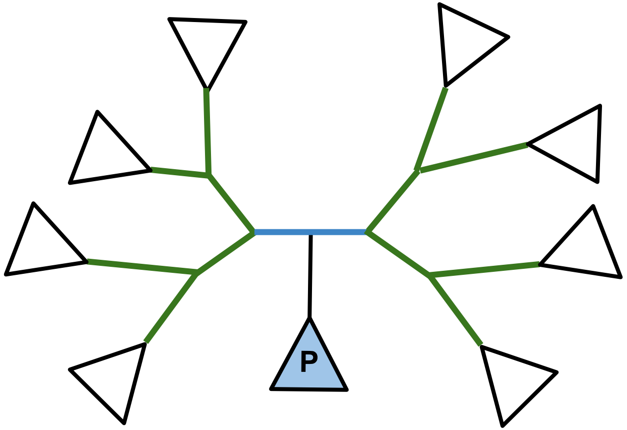
List of LH scores:

- 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**



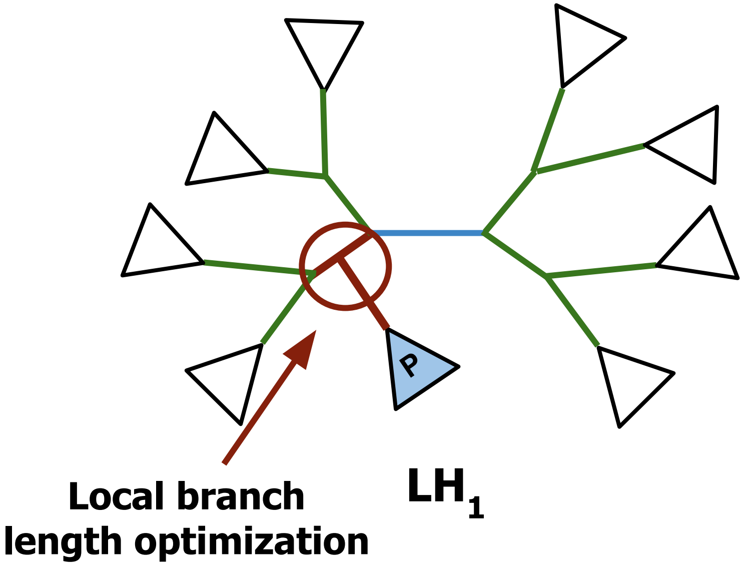
LH$_0$

List of LH scores:

- LH$_0$

Slow SPR round

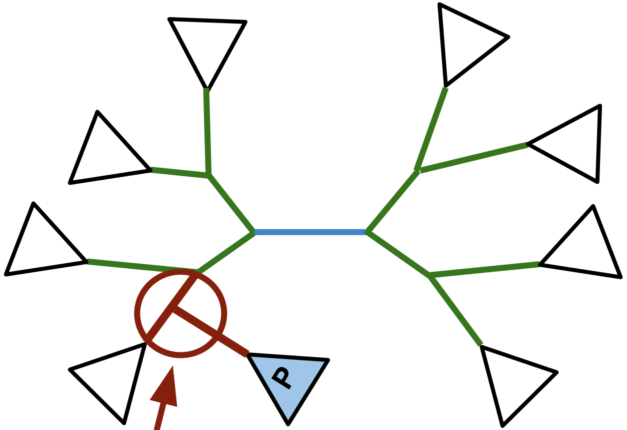
- In **Slow SPR** round, RAxML-NG computes the likelihood using the **branch lengths** of the **initial tree** topology



List of LH scores:
- LH_0
- LH_1

Slow SPR round

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



Local branch length optimization

LH_2

List of LH scores:

- LH_0
- LH_1
- LH_2

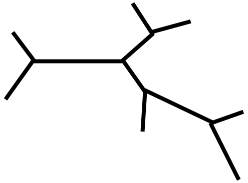
And so on ….

Slow SPR round

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

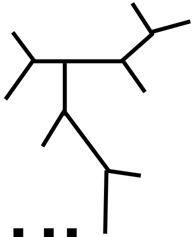
Top-20 topologies:

1.



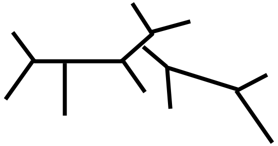
LH_1

2.



LH_2

3.

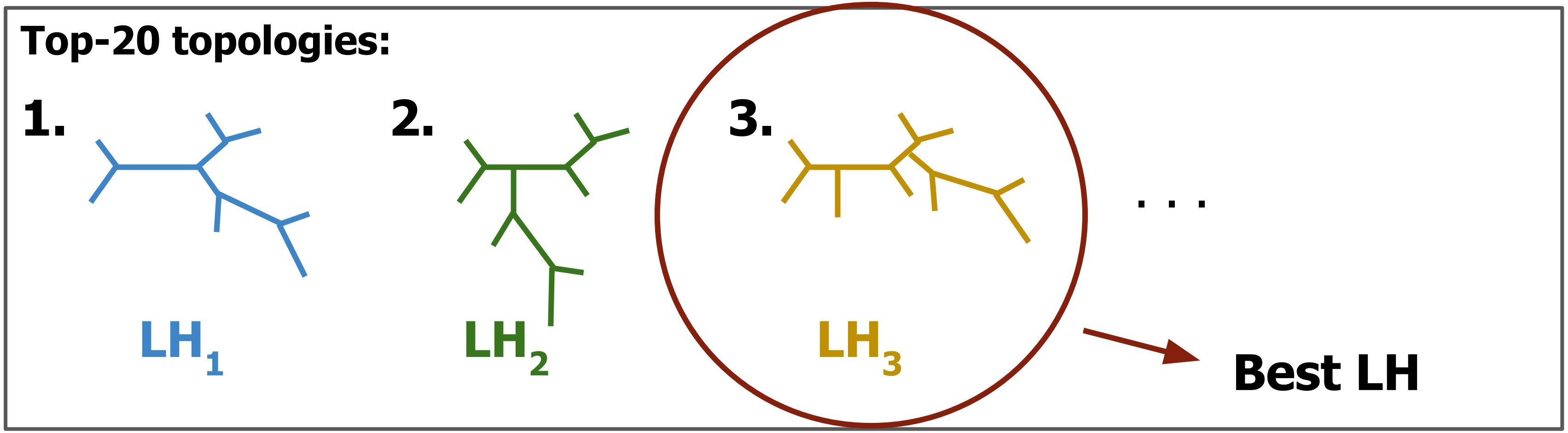


LH_3

. . .

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

. . .

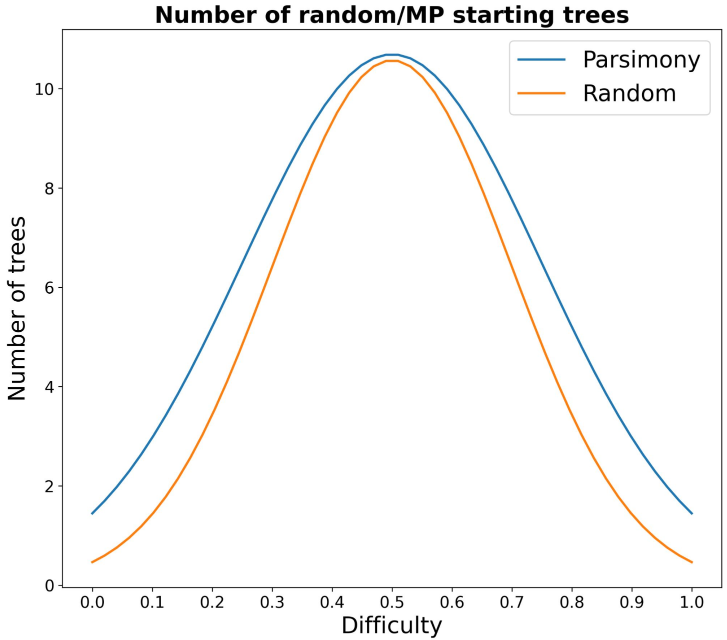
Best LH

Adaptive heuristic in RAxML-NG

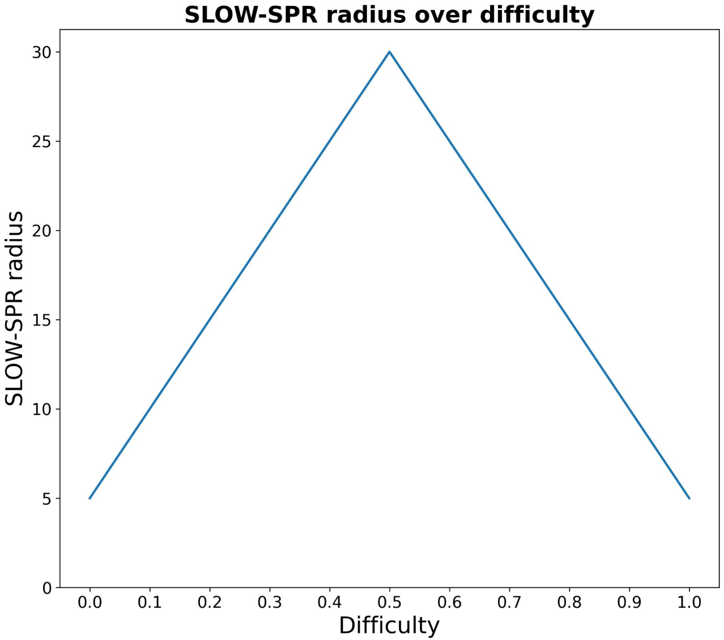
- We **modify** (with respect to difficulty) :
    - the **number** of **ML tree searches**
    - the radius in Slow SPR round

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

Adaptive heuristic in RAxML-NG

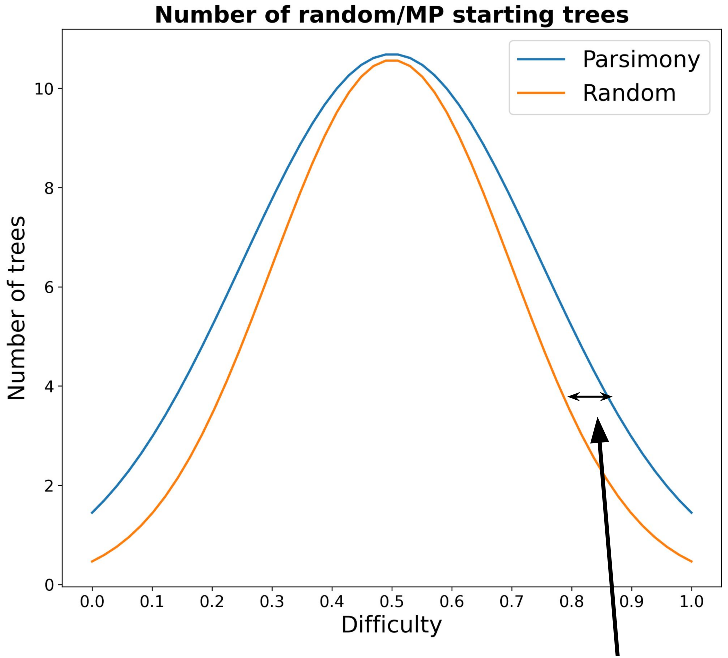


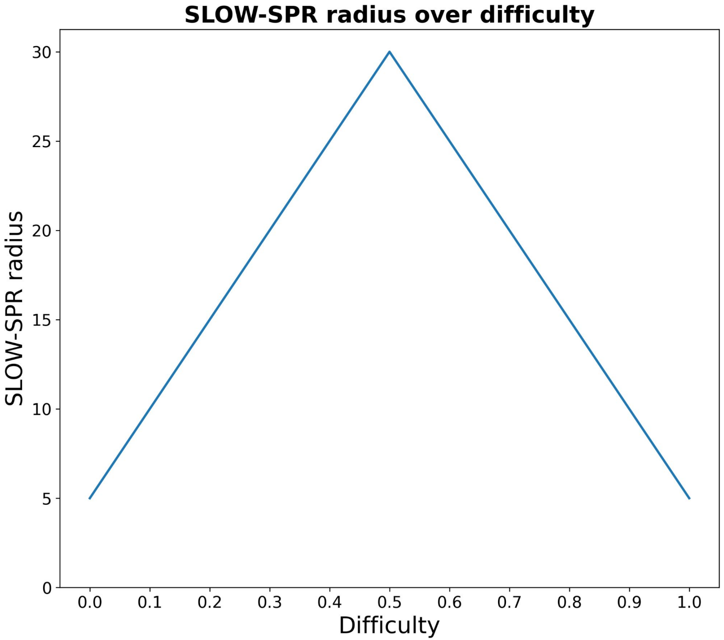
Number of random/MP starting trees



SLOW-SPR radius over difficulty

Adaptive heuristic in RAxML-NG

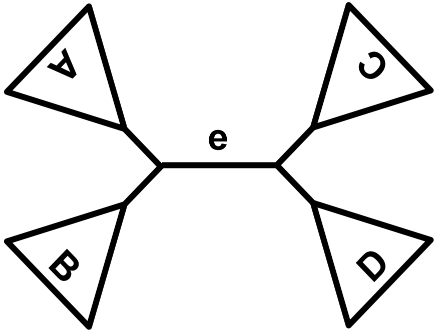




The MP starting trees curve is wider, due to the observation made by Morel *et al.*

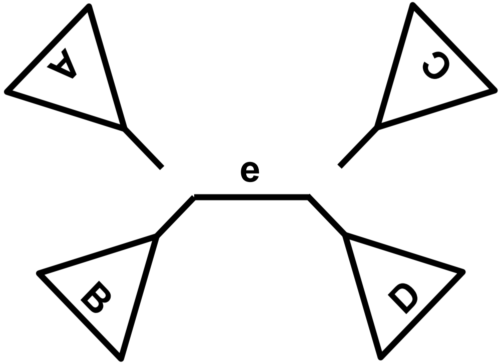
Nearest Neighbor Interchange (NNI) move

- Around a central branch *e*



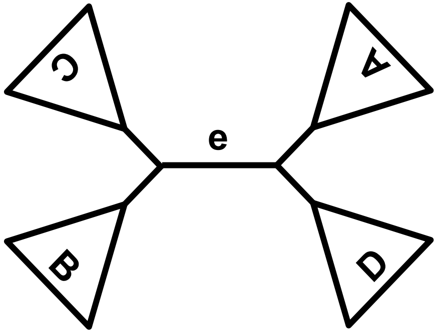
Nearest Neighbor Interchange (NNI) move

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



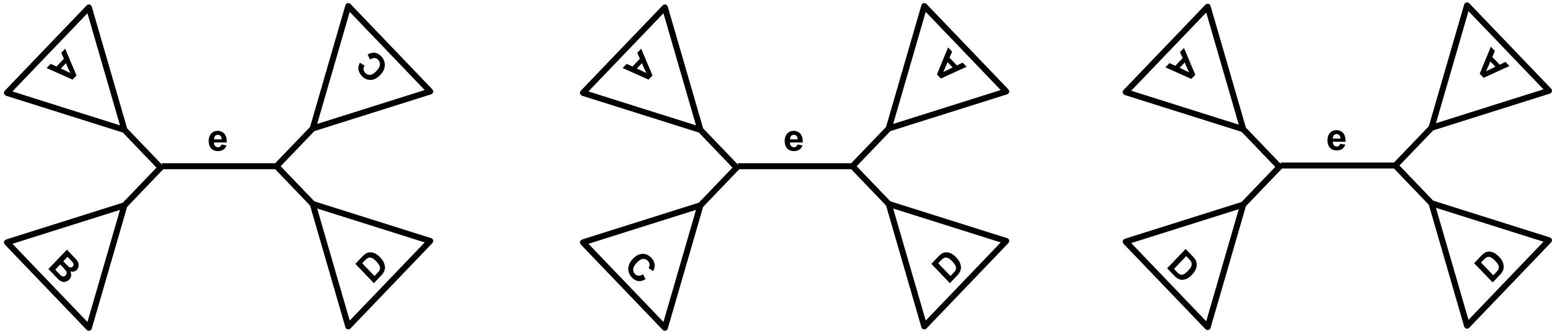
Nearest Neighbor Interchange (NNI) move

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



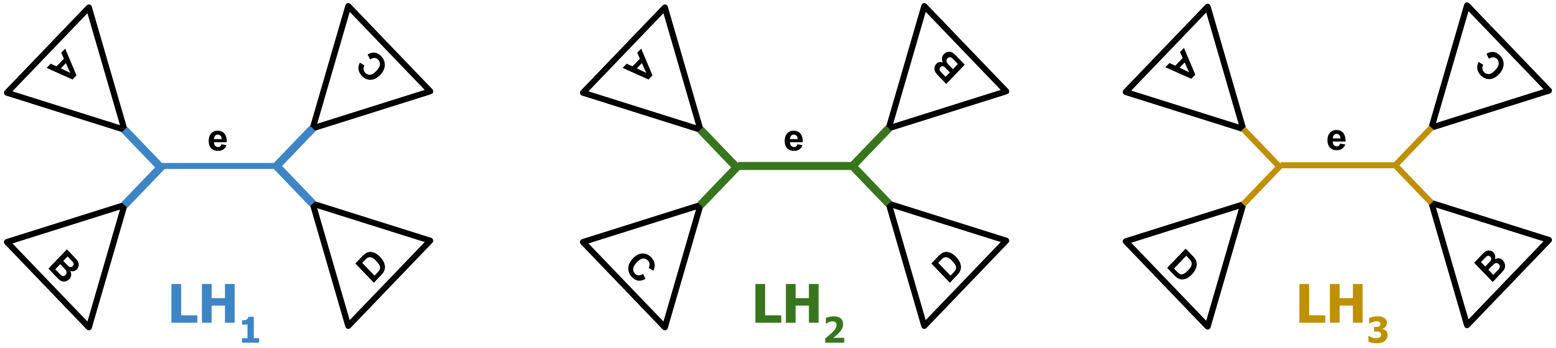
NNI round

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



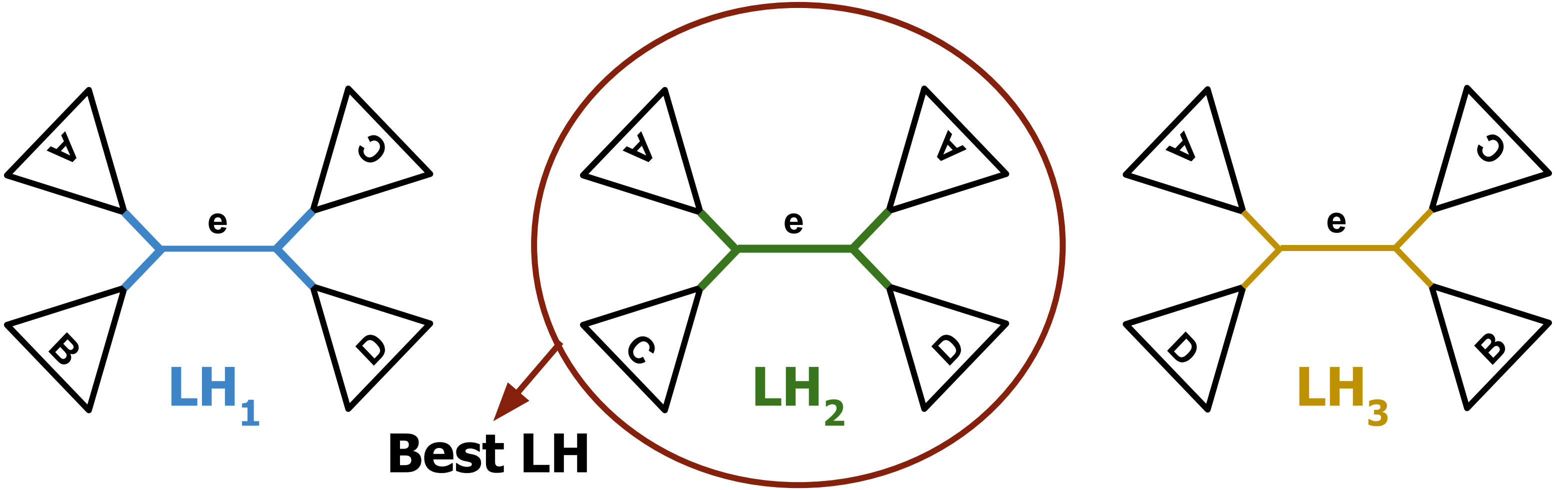
NNI round

- 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

- 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)

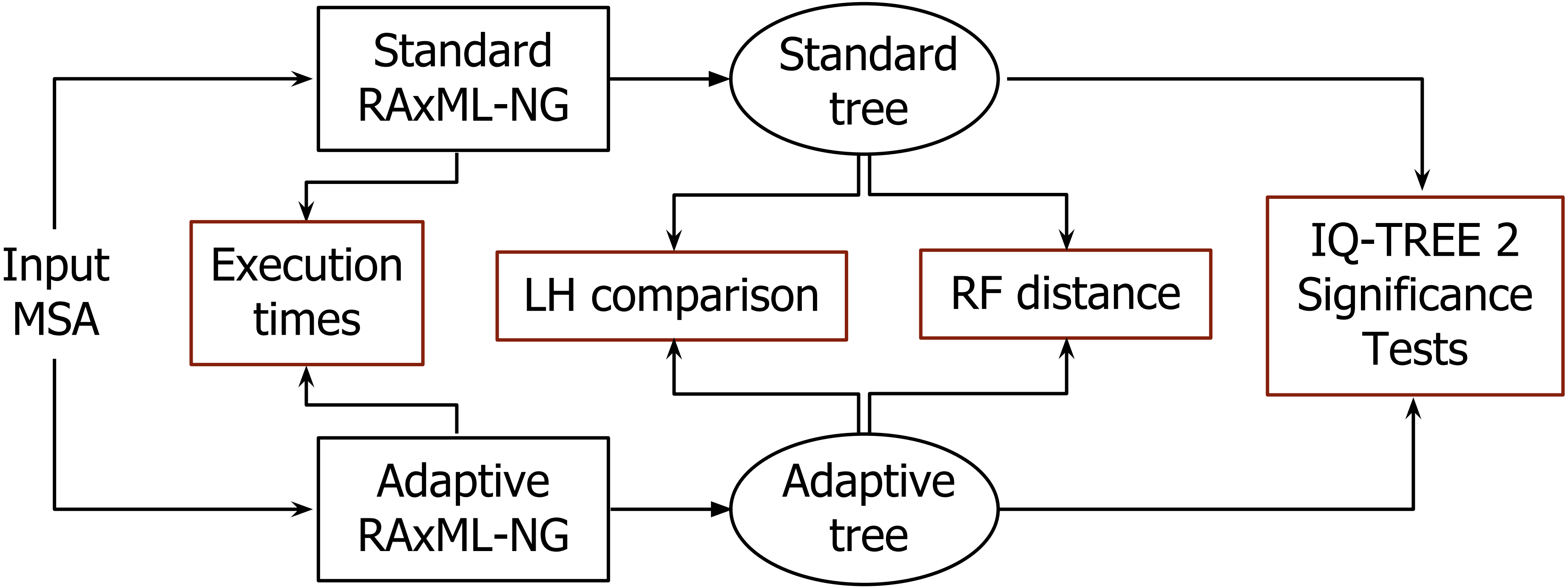
10,000 empirical
5,000 simulated

Filtering

9,192 empirical
4,991 simulated

We present the results
from filtered datasets

Experimental pipeline



Input MSA

Standard RAxML-NG

Adaptive RAxML-NG

Standard tree

Adaptive tree

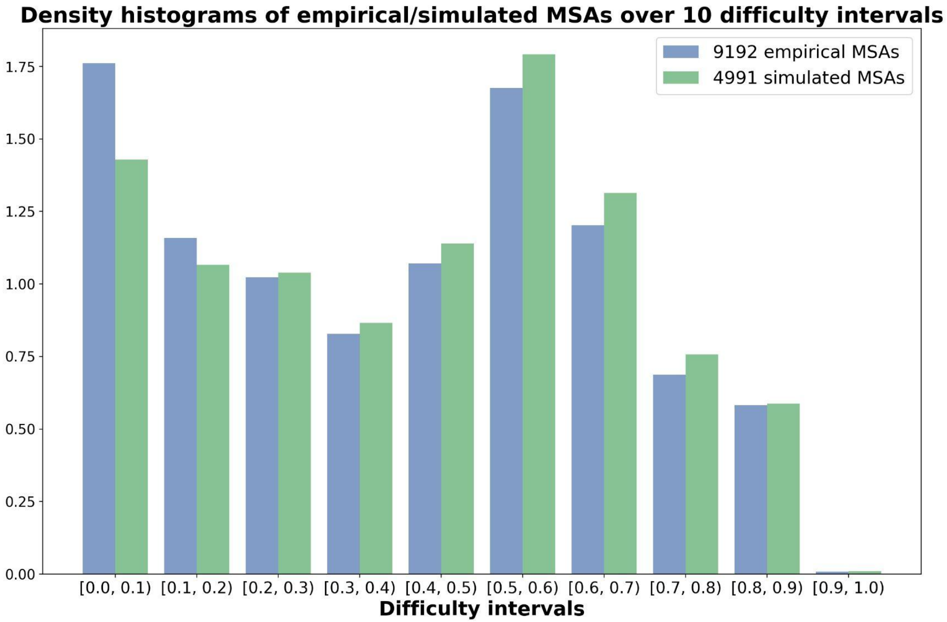
Execution times

LH comparison

RF distance

IQ-TREE 2 Significance Tests

Difficulty score distribution



Likelihood score comparison

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

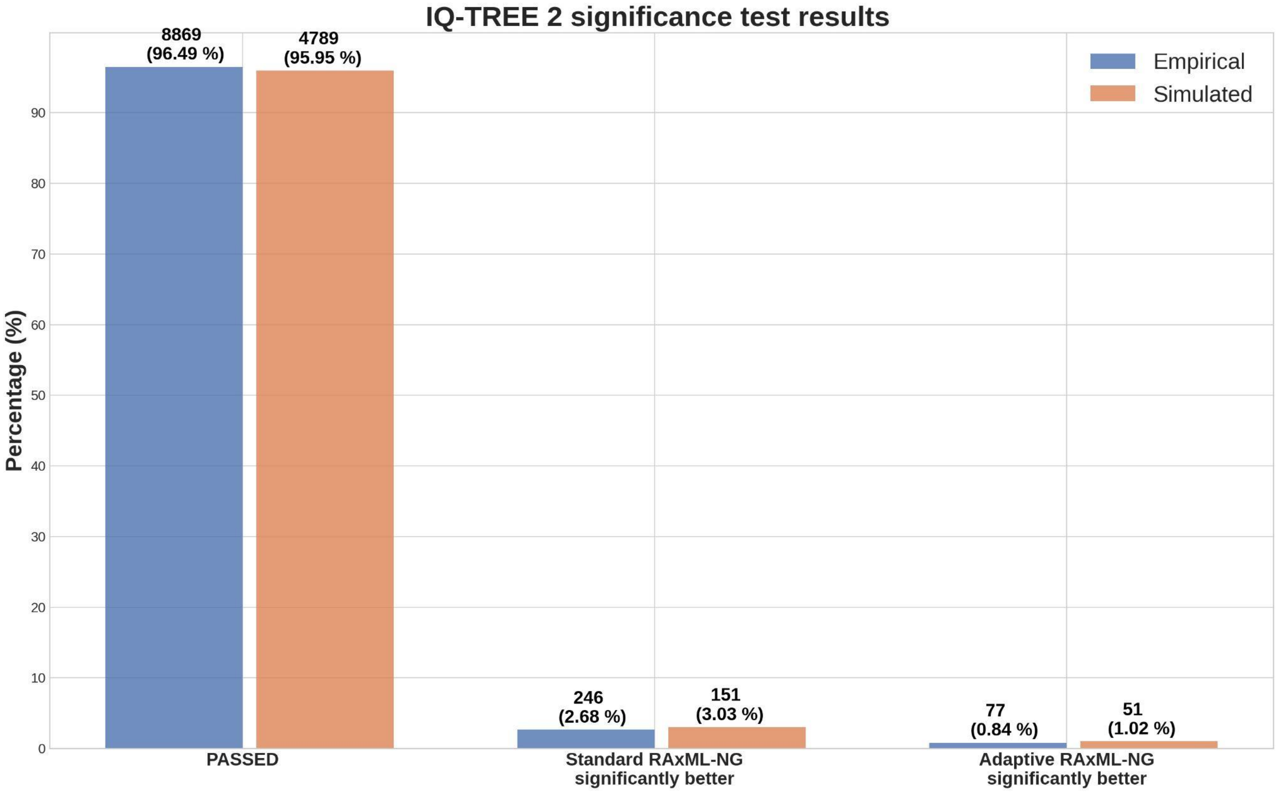
$$\boxed{LD = LH_S - LH_A}$$

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

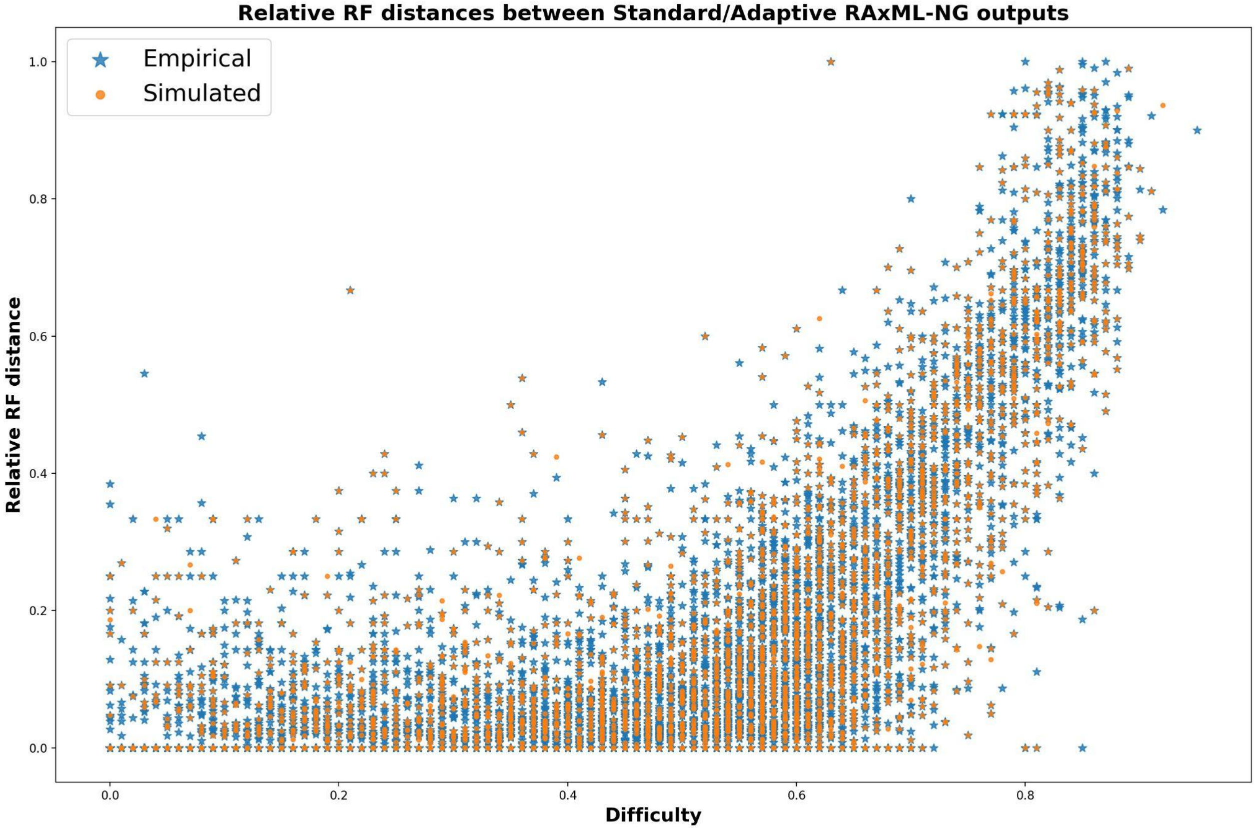
$$\boxed{RLD = \frac{LH_S - LH_A}{|LH_S|}}$$

- 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%)

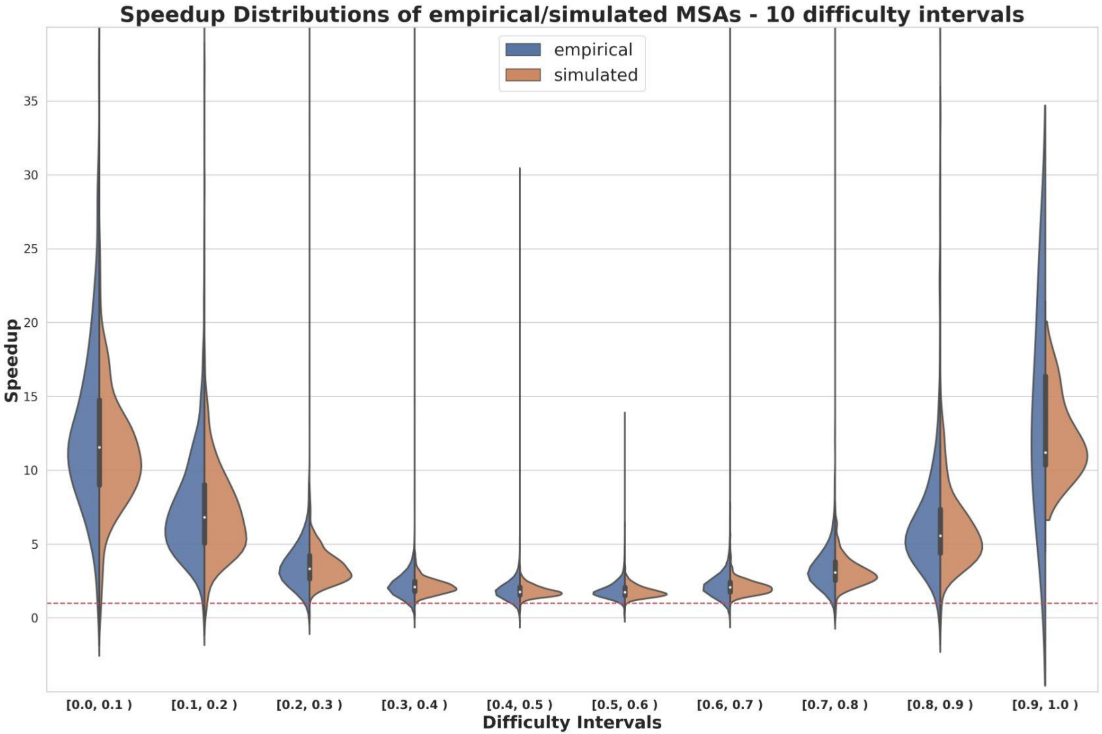
IQ-TREE 2 significance tests



Relative RF distances



Speedups


Speedup Distributions of empirical/simulated MSAs - 10 difficulty intervals
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:
    - More focus on heuristics
    - Experiment with statistical tests for early termination of the tree search
    - Efficient parallelization of adaptive RAxML-NG
    - Insert checkpoints
    - Import it into RAxML-NG

For now

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

- Manuscript under preparation:
  - Togkousidis, A., Kozlov, A. M., Stamatakis. A., (2023). Adaptive search heuristic for ML phylogenetic tree inference based on the predicted difficulty of dataset.

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

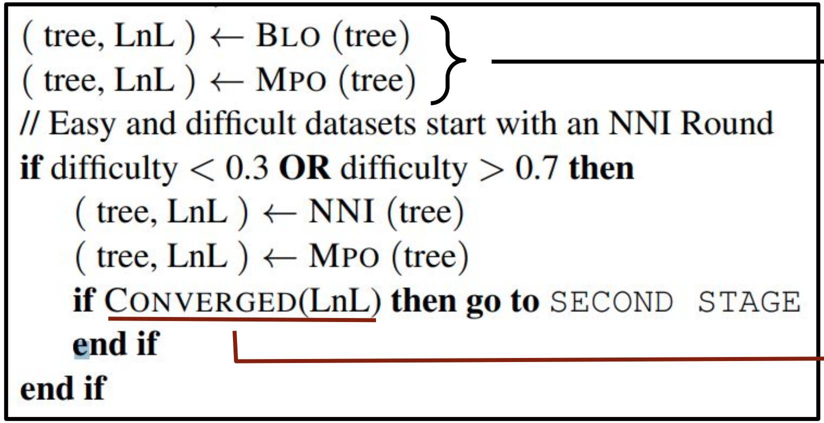
- Based on the difficulty score, one can classify MSAs into **easy**, **intermediate** and **difficult** (hard/hopeless) to analyze.
- Our suggestion:
  - Easy datasets (Difficulty < 0.3)
  - Intermediate (0.3 ≤ Difficulty ≤ 0.7)
  - Difficult datasets (Difficulty > 0.7)
- The concept of difficulty provides 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



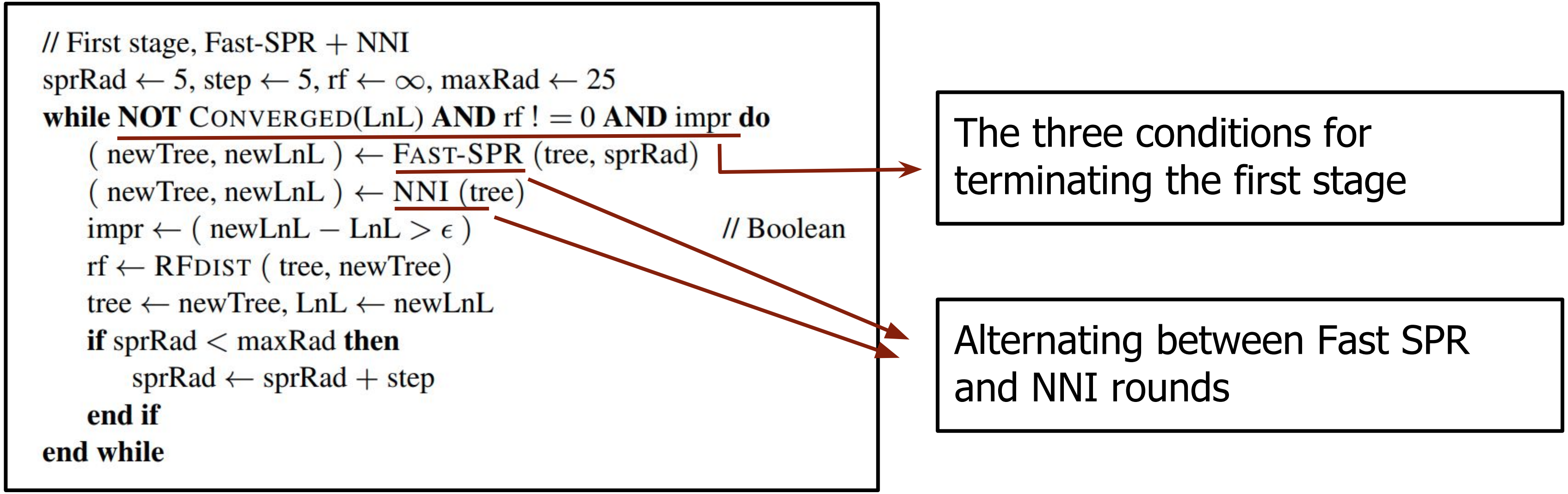
```
( tree, LnL ) ← BLO (tree)
( tree, LnL ) ← MPO (tree)
// Easy and difficult datasets start with an NNI Round
if difficulty < 0.3 OR difficulty > 0.7 then
    ( tree, LnL ) ← NNI (tree)
    ( tree, LnL ) ← MPO (tree)
    if CONVERGED(LnL) then go to SECOND STAGE
    end if
end if
```

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



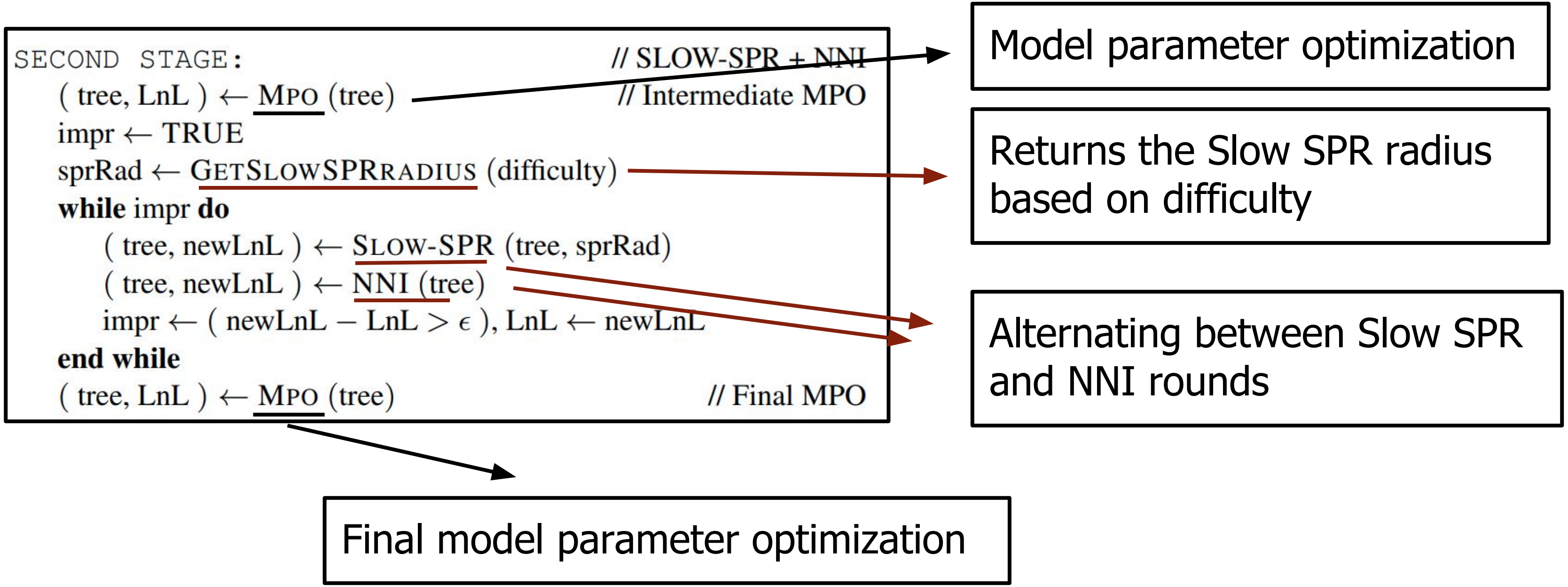
```
// First stage, Fast-SPR + NNI
sprRad ← 5, step ← 5, rf ← ∞, maxRad ← 25
while NOT CONVERGED(LnL) AND rf != 0 AND impr do
    ( newTree, newLnL ) ← FAST-SPR (tree, sprRad)
    ( newTree, newLnL ) ← NNI (tree)
    impr ← ( newLnL − LnL > $\epsilon$ )                // Boolean
    rf ← RFDIST ( tree,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

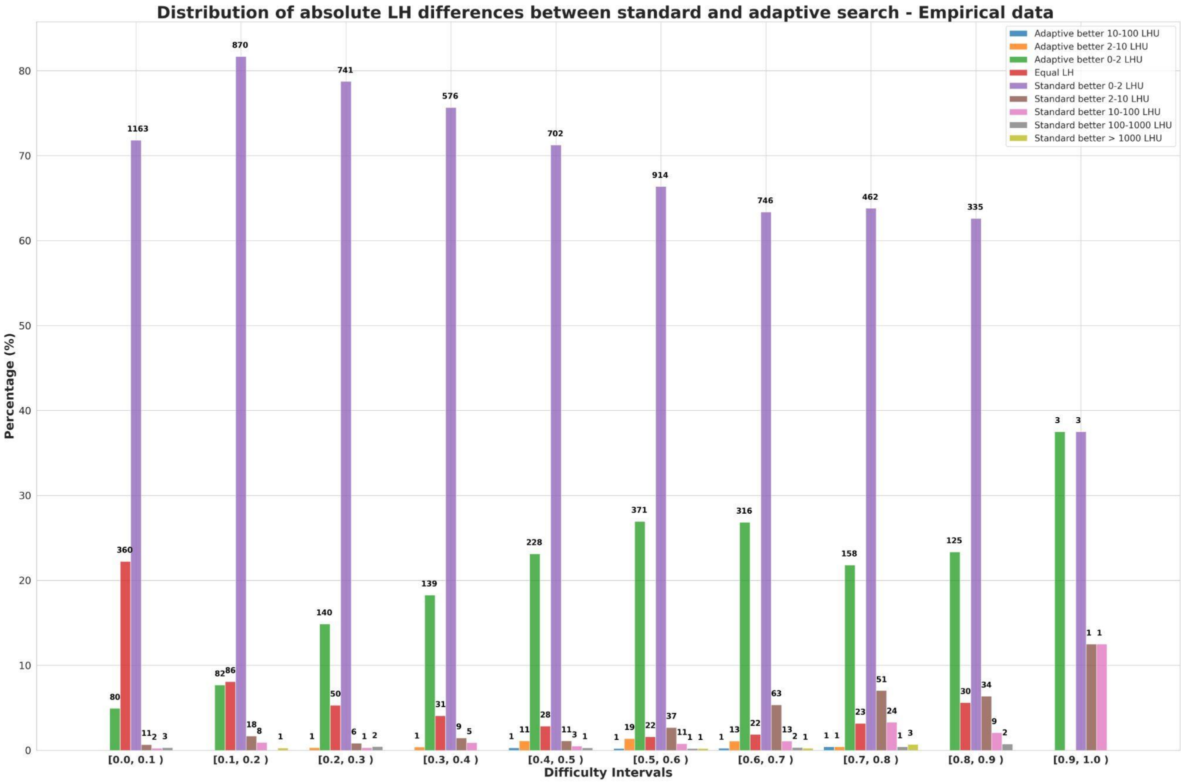
Pipeline + Filtering

- 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

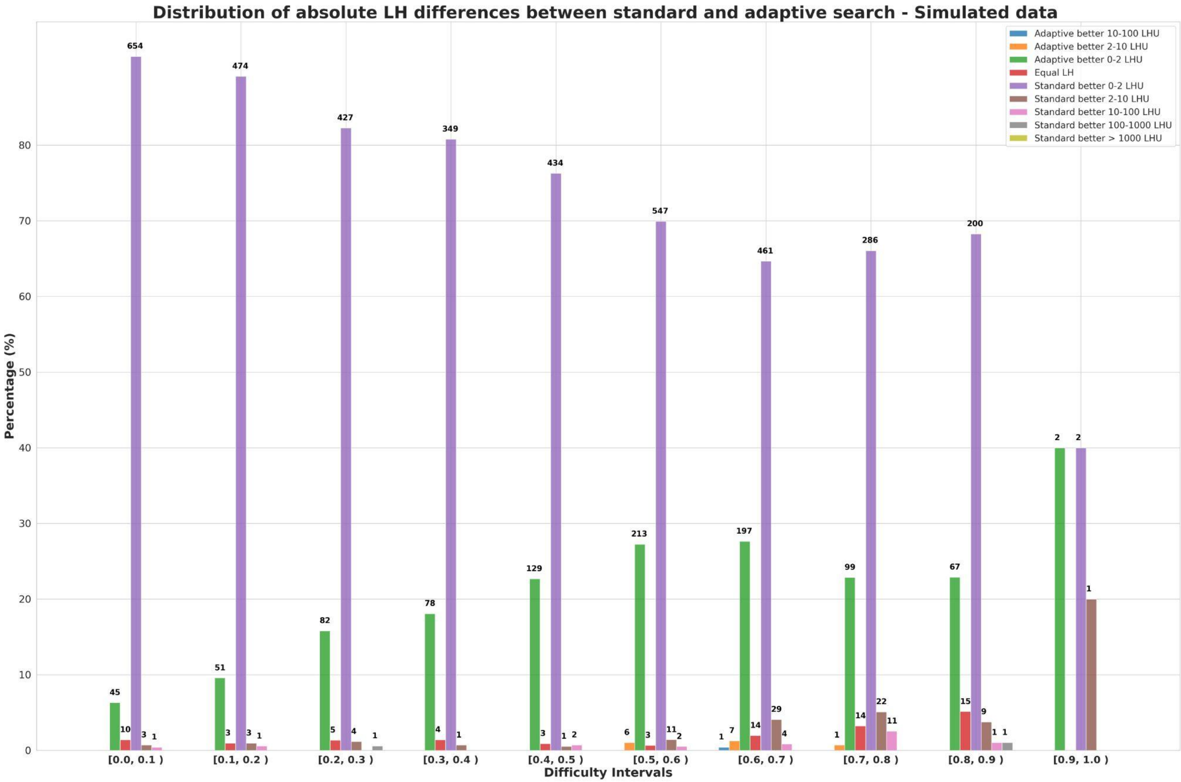
Standard/Adaptive RAxML-NG comparison

- 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**)

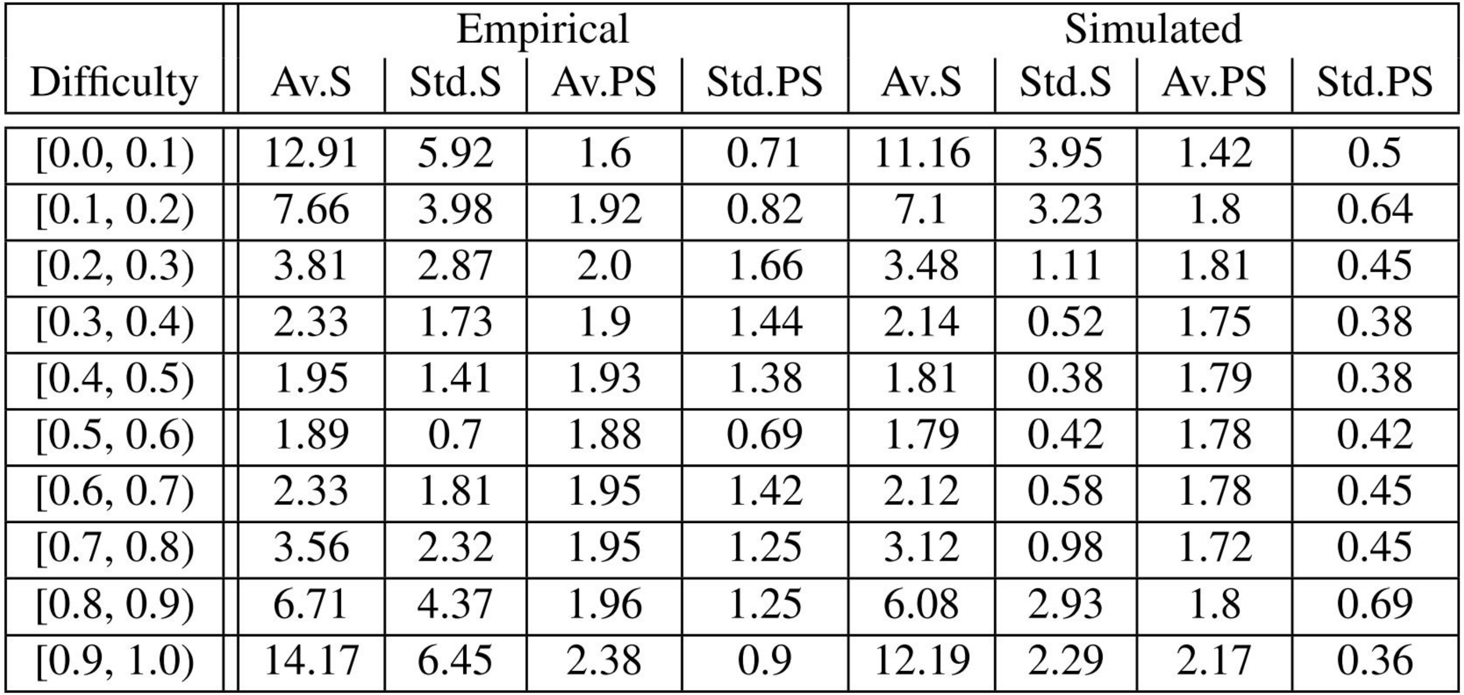
Likelihood score comparison



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