Phylogenetic Inference with Markov Chain Monte Carlo

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Goals

- **Simulate** phylogenetic data → phylogenetic trees of aligned sequences
- Perform **inference** on simulated data → reconstruct the tree from the sequences

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Outline

- **Introduction** → What is phylogenetics? What are the main things to consider?
- **Development** → How can we simulate and infer phylogenetic trees?
- **Results** → What can we say about our simulated / inferred trees?
- **Conclusion** → Did we achieve our goals?

INTRODUCTION

The problem of phylogenetics

What is **phylogenetics**?

- Sequences from different organisms → infer a tree that describes their **evolutionary history**
  - DNA, proteins, morphology
  - Aligned

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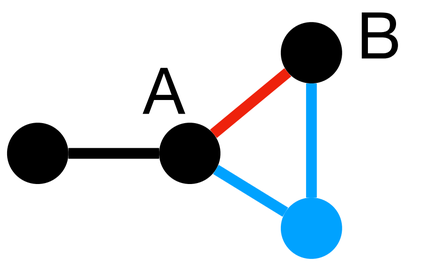
- Inference → deterministic / probabilistic approaches
  - Definition of sequence *similarity*
  - Model of sequence evolution

The problem of phylogenetics

What is a **tree**?

Connected graph with no *cycles* → any two nodes are connected by a single path



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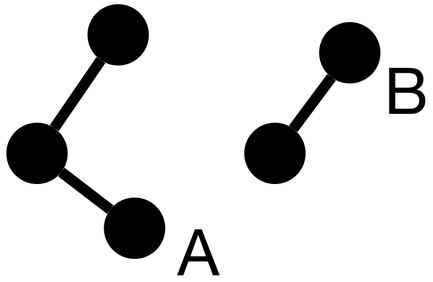

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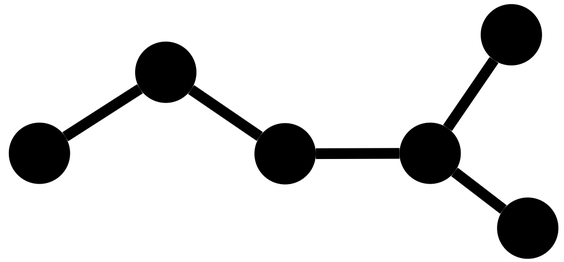

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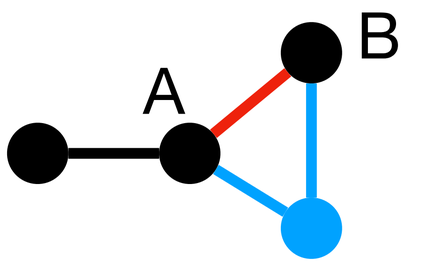

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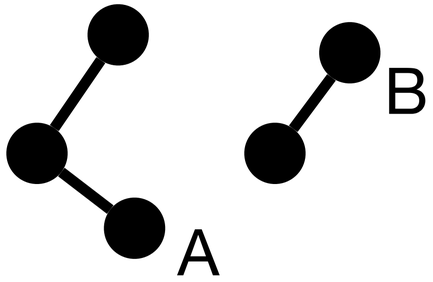

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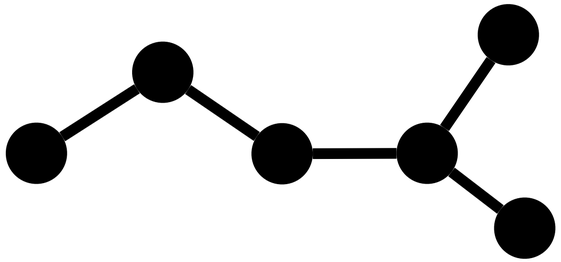
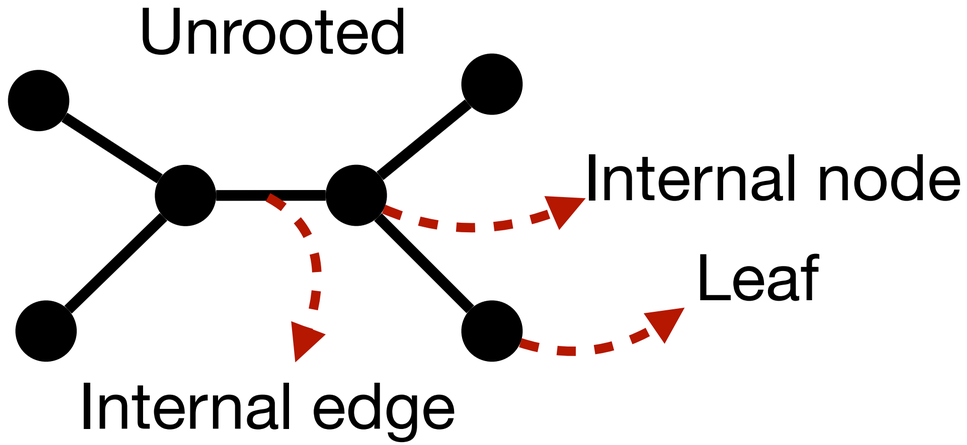
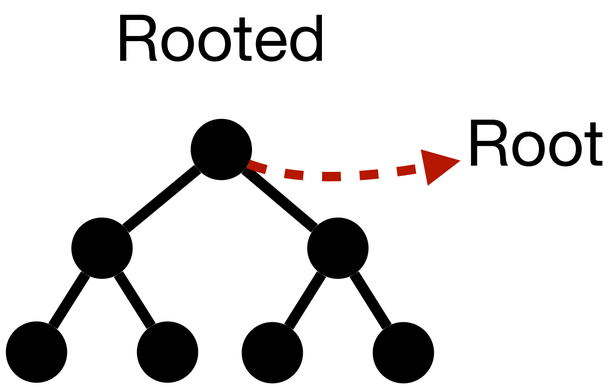


Tree

Binary tree → every internal node has degree 3 (except maybe for the *root*)





Probabilistic models of DNA mutation

Evolution of sequence sites → conditional probabilities

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- Base probability distribution → $\overrightarrow{p_0}$
- Rate matrix → Q
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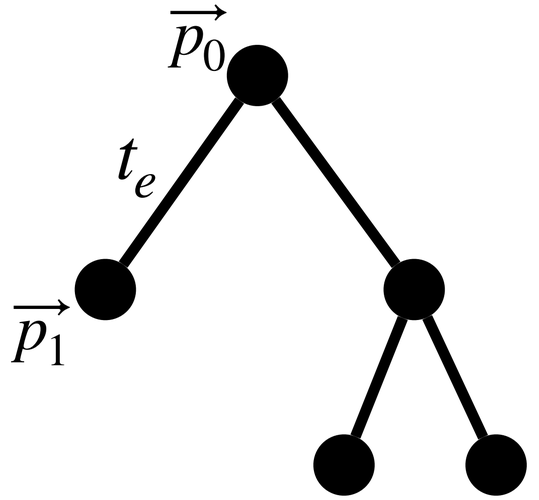
Only mechanism considered is substitution, others are excluded (deletion, insertion, …)

Application to a tree



$$\overrightarrow{p_1} = \overrightarrow{p_0} M(t_e)$$

The Jukes-Cantor model

Simplest Markov model of base substitution

- Uniform root distribution $\rightarrow \left(\overrightarrow{p_\rho}\right)_i = |\chi|^{-1}, \forall i$
- Uniform transition rates $\rightarrow Q_{ij} = -\alpha\delta_{ij} + (\alpha/3)(1-\delta_{ij})$

$|\chi|$: Size of the alphabet

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Since $\overrightarrow{p_\rho}M(t) = \overrightarrow{p_\rho}, \forall t$ $\rightarrow$ the base distribution remains uniform at every node.

The Markov Chain Monte Carlo approach

MCMC for tree inference → **Metropolis—Hastings** algorithm

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4. Accept proposal with probability:

$$A = \min\left[1, \underbrace{\frac{P(S \mid T', \{\theta'\})}{P(S \mid T, \{\theta\})}}_{\text{Likelihood}} \cdot \underbrace{\frac{P(T', \{\theta'\})}{P(T, \{\theta\})}}_{\text{Prior}}\right]$$

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5. Repeat steps 3-4 N_{MC} times to generate samples

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How can we calculate the likelihood? → **Felsenstein's pruning algorithm**

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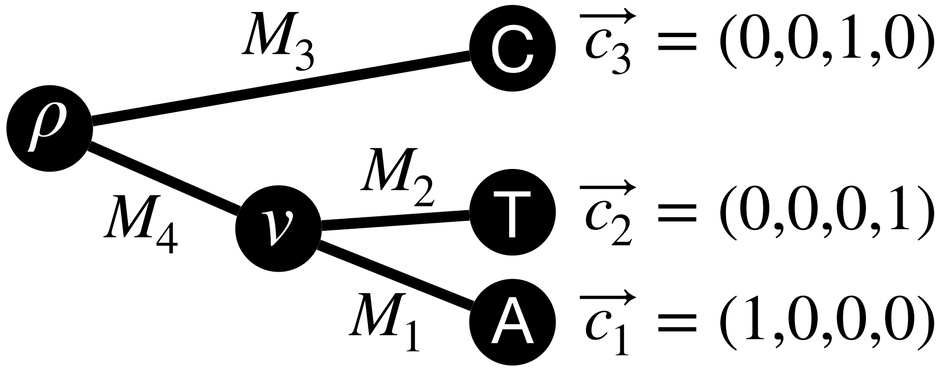

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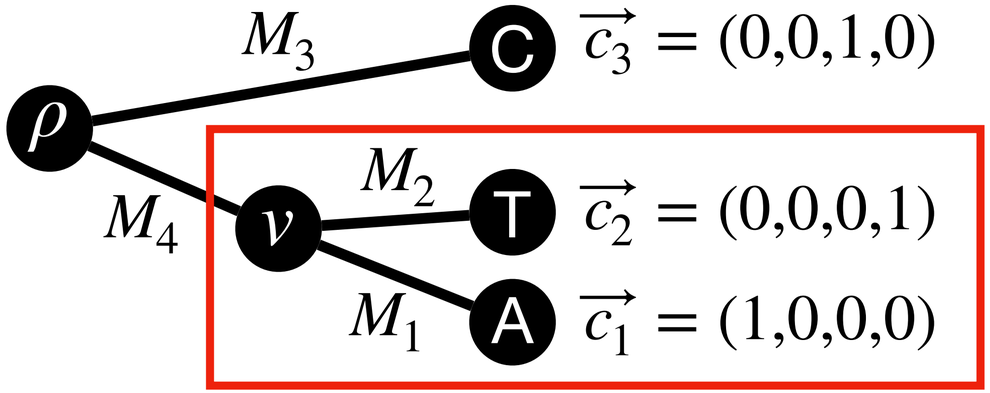

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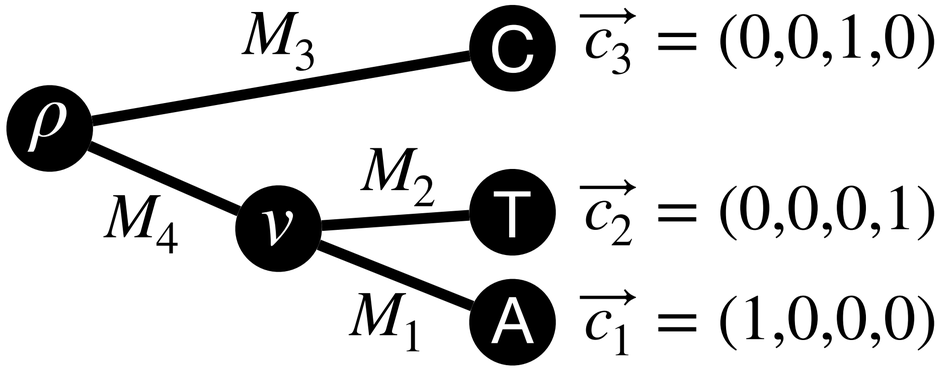

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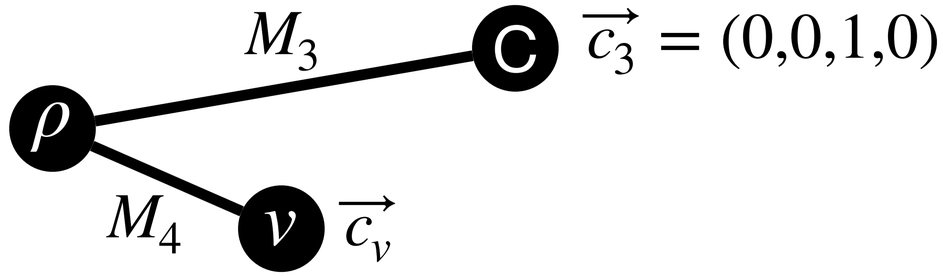

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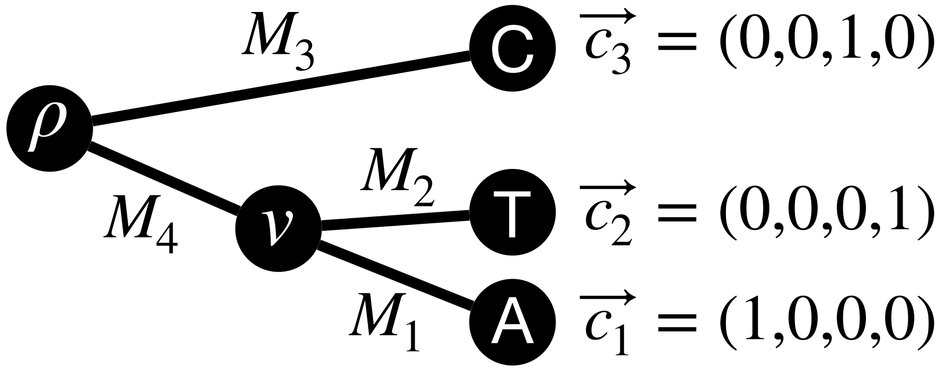

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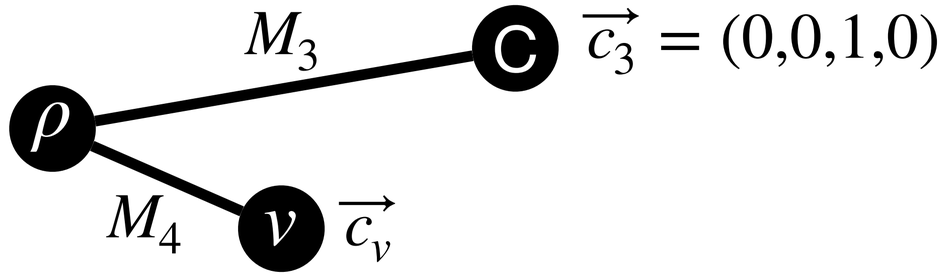

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3. $P(S \mid T, \{\theta\}) = \vec{p}_\rho \cdot \vec{c}_\rho$

Tree space

For a fixed collection X of n taxa $\rightarrow$ space of distinct topological trees

- Unrooted binary trees $\rightarrow (2n-5)!!$
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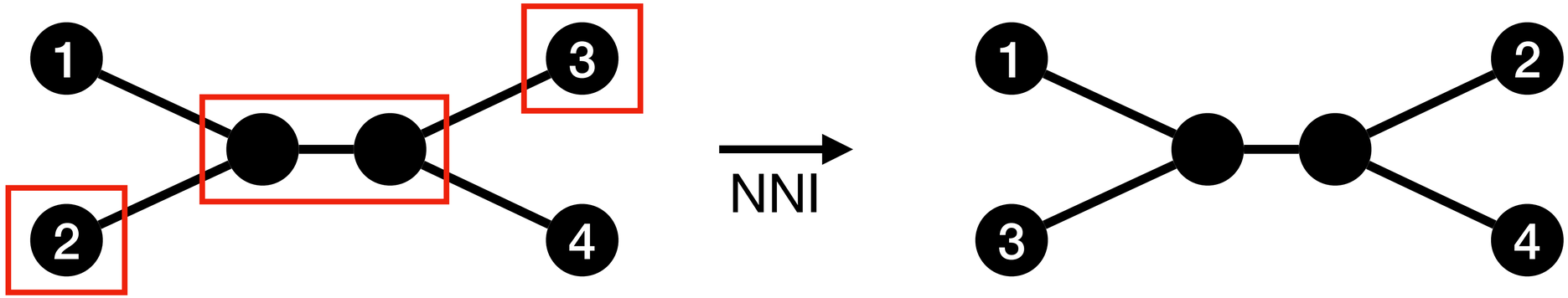

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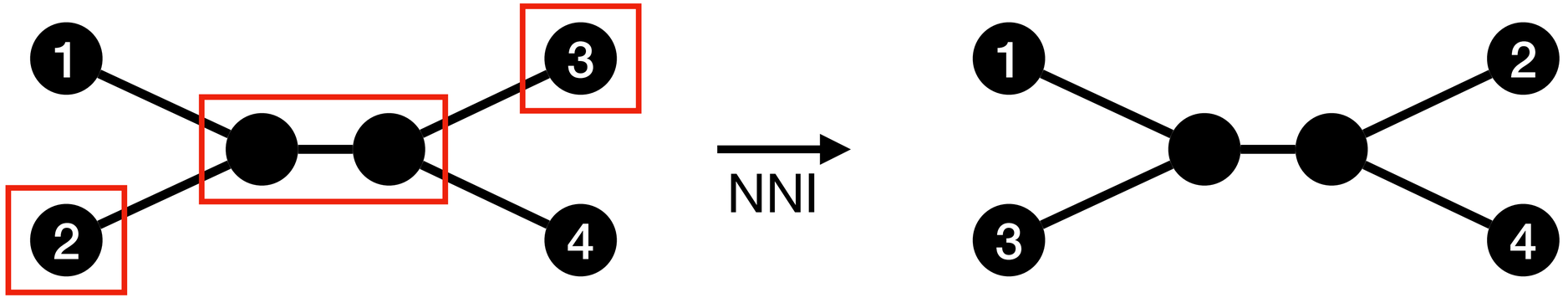

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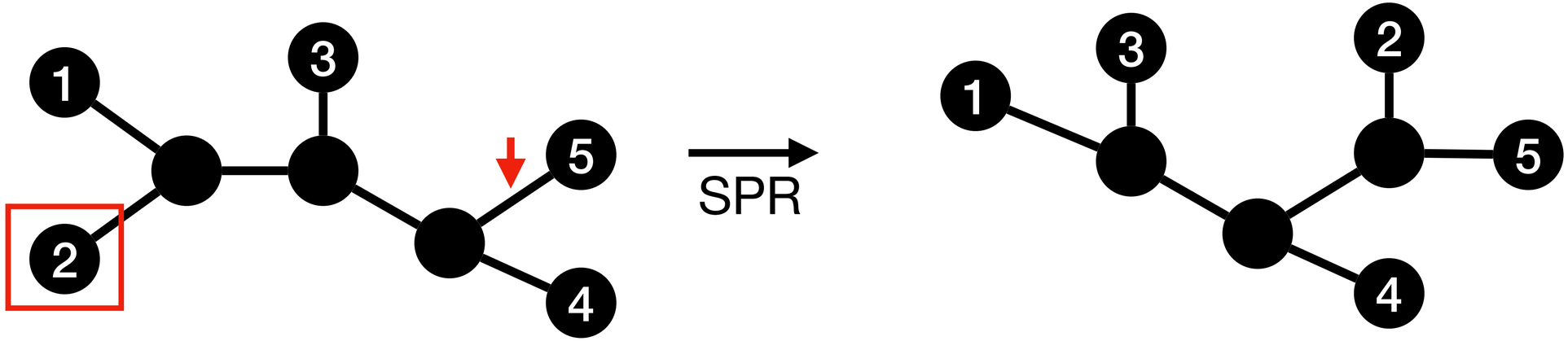

DEVELOPMENT

Generating binary tree topologies

First, we need $G_T(n) \rightarrow$ generates a rooted binary tree with n leaves

Can we sample the tree space uniformly?

- Only way I could think of was to build all possible trees and choose one uniformly at random

  ➡ Very inefficient

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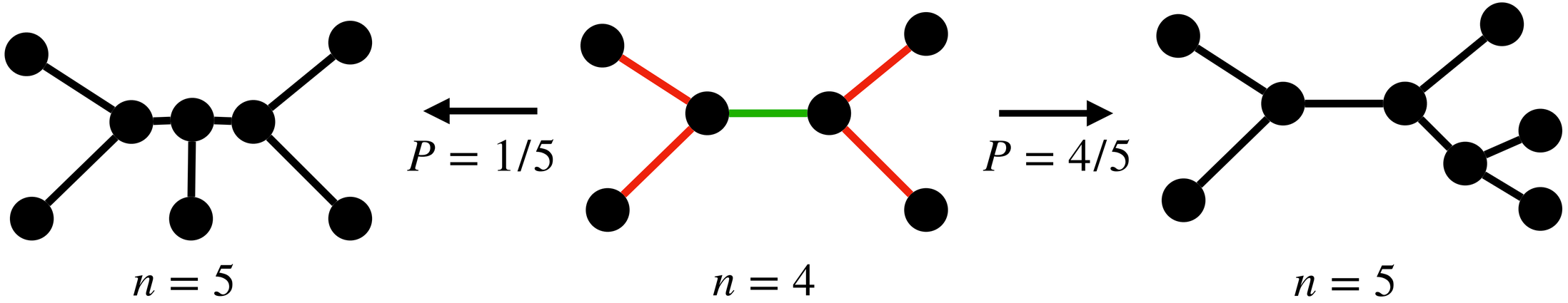

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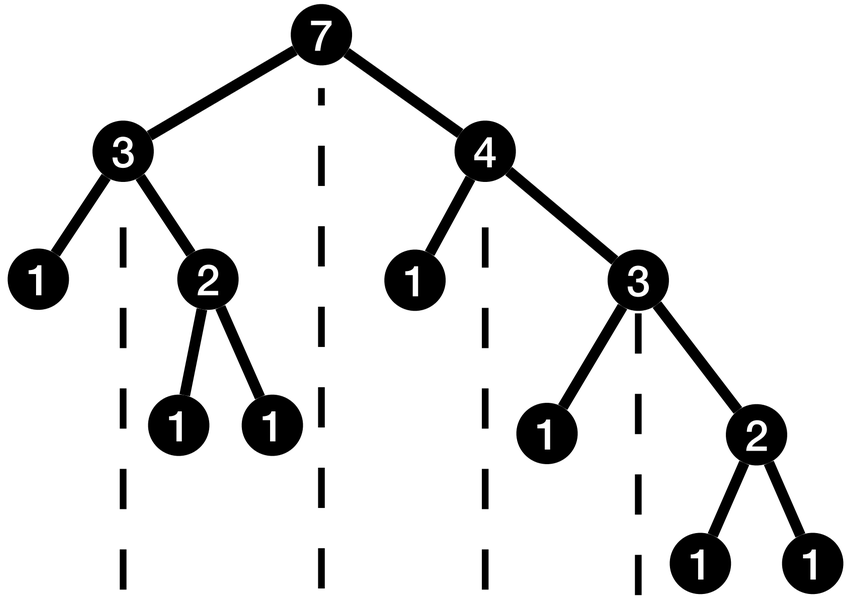

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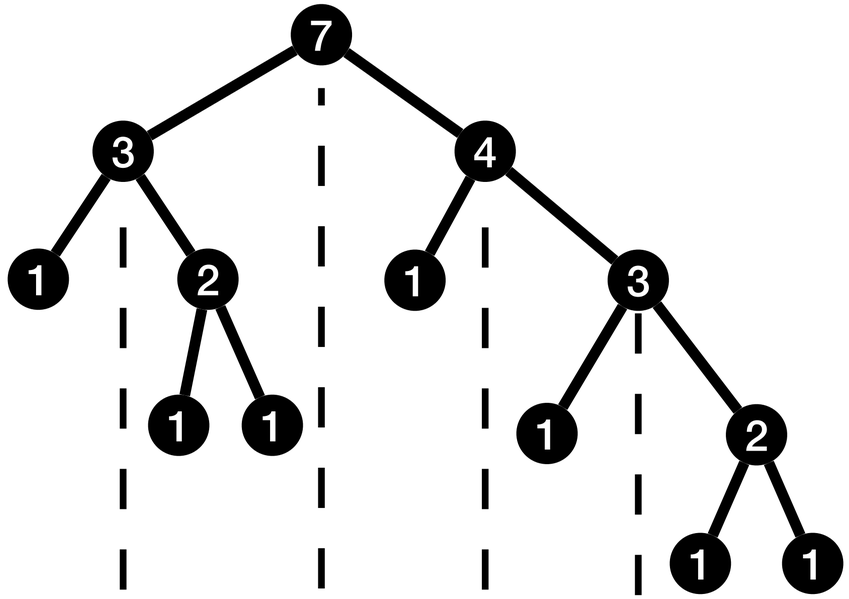

$$7$$

$$3 \,|\, 4$$

$$1 \,|\, 2 \,\big|\, 1 \,|\, 3$$

$$1 \,\big|\, 1 \,|\, 1 \,\big|\, 1 \,\big|\, 1 \,|\, 2$$

$$\cdots$$

Largest *trivial* representation

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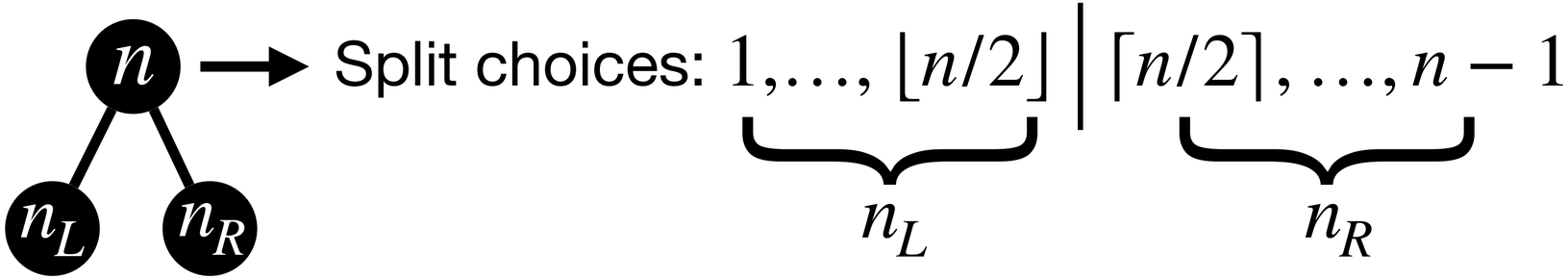

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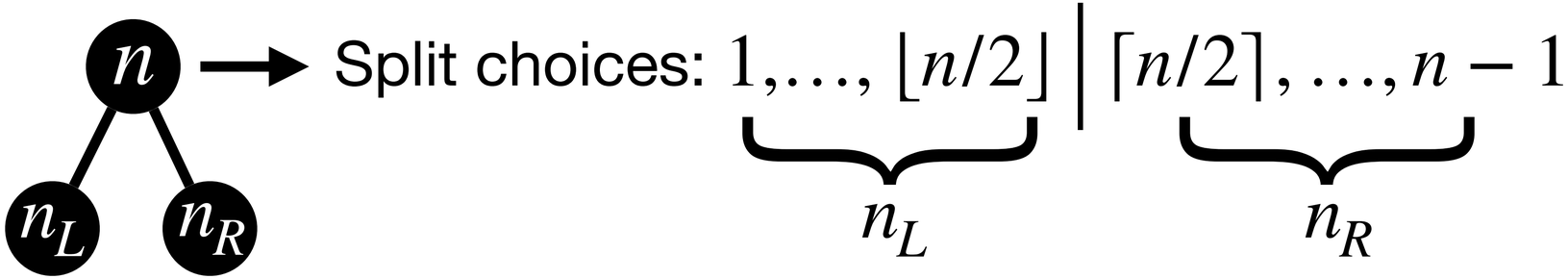

- Assign a weight to every possible split $(n_L, n_R) \rightarrow w_i = \max(1, \lfloor n_L/2 \rfloor) \cdot \lfloor n_R/2 \rfloor$
- Then, sample each split with probability $p_i = w_i \,/ \sum_j w_j$

➡ Splits that lead to more topologies are favored

Generating phylogenetic binary trees

Now, we need to assign the length to each edge in the topology

- Same distribution as the prior for inference
- Exponential distribution $\rightarrow P(t) = \lambda \exp(-\lambda t)\ ,\ t \geq 0$
- What is a good choice for the scale parameter λ? $\rightarrow$ More on this later…

Generating phylogenetic binary trees

Finally, we need to generate leaf sequences with length m

- Initialize the root sequence $\rightarrow S_{\rho,i} \sim U(A, G, C, T)\ ,\ i = 1,\ldots,m$
- Draw children sequences $\rightarrow S_{child,i} \sim \vec{p}_i = \vec{c}_{\rho,i} M(t_e)\ ,\ i = 1,\ldots,m$
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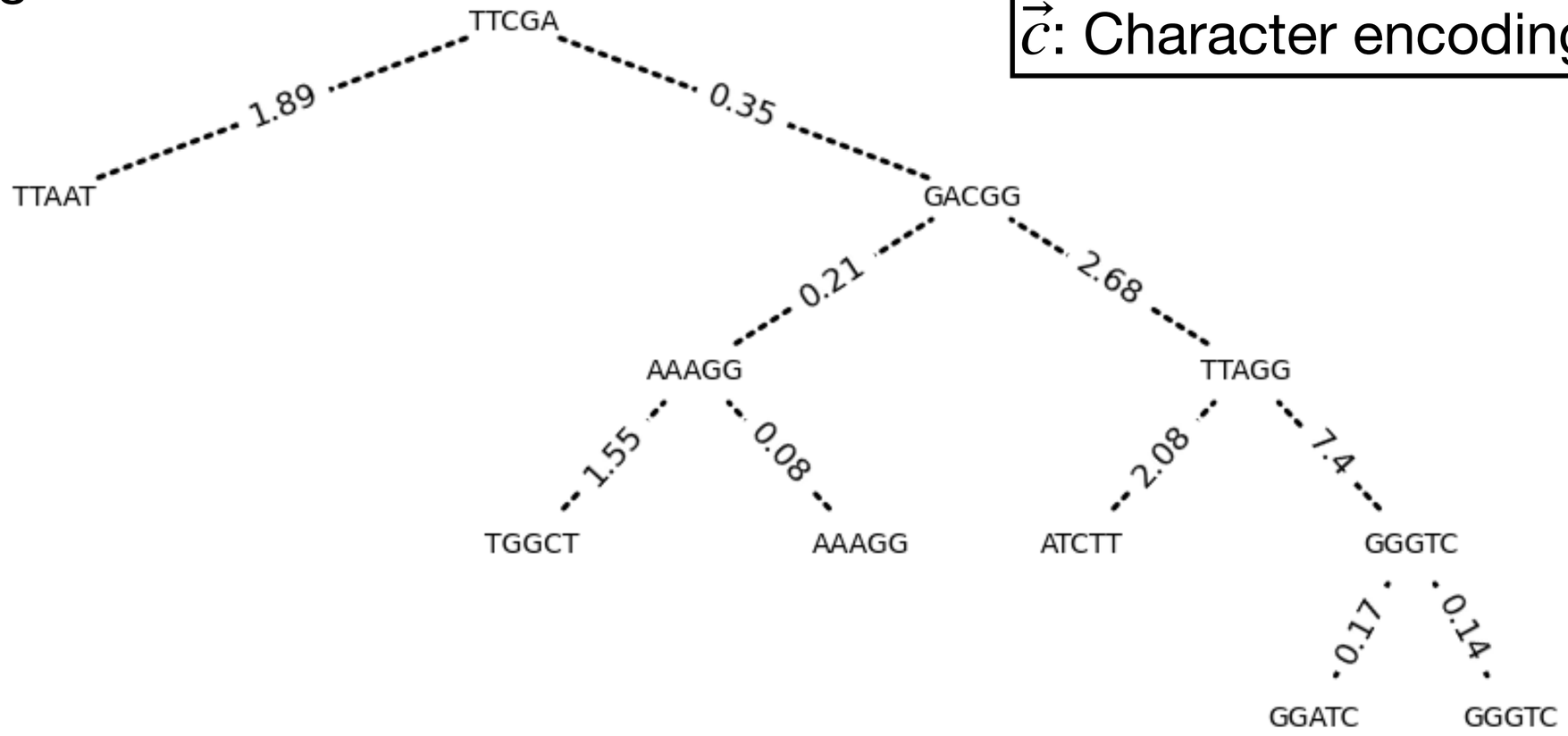
$\vec{c}$: Character encoding



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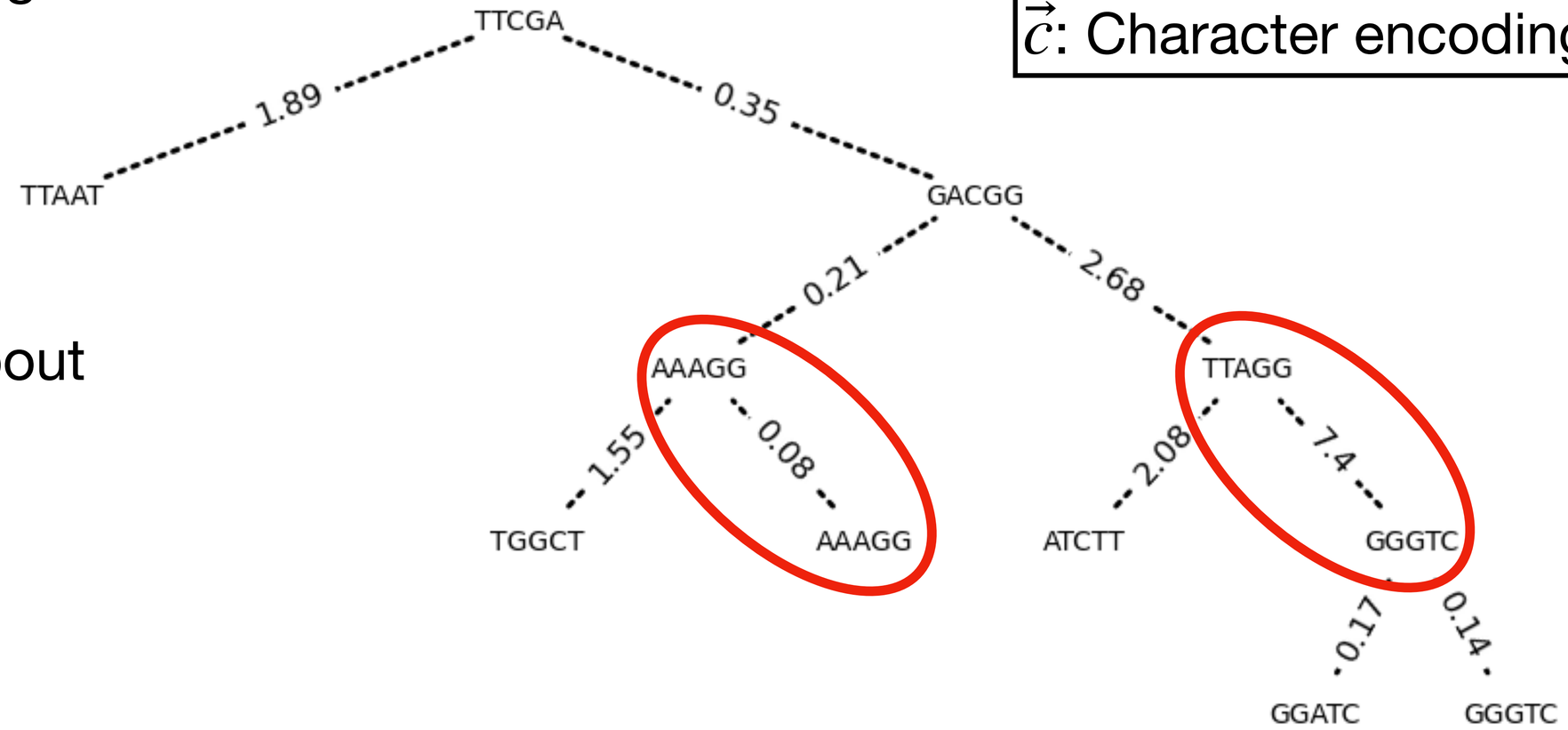
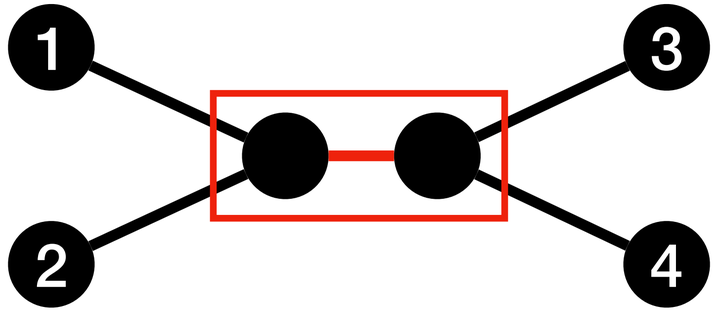


Notice something about the sequences?

Tree moves for MCMC inference

External MCMC step → exploration of tree space

- NNI move:
    1. Choose an internal edge and gather the two nodes



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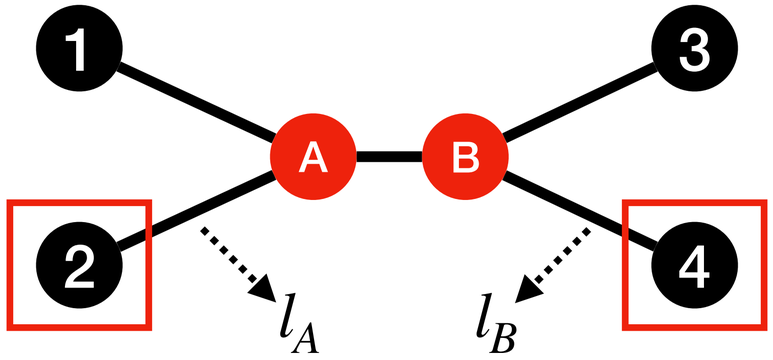

Tree moves for MCMC inference

External MCMC step → exploration of tree space

- NNI move:
  1. Choose an internal edge and gather the two nodes
  2. Select one external component for each node uniformly at random, and register edge lengths
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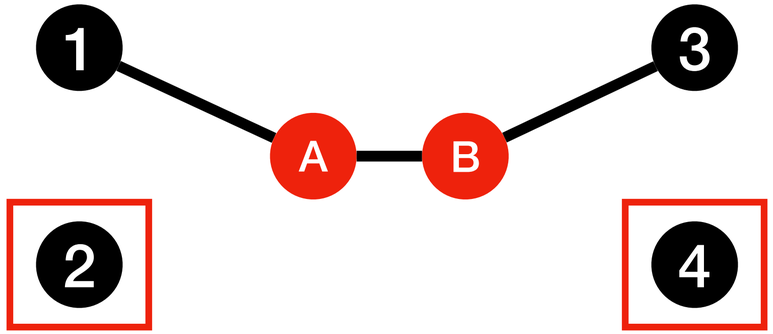

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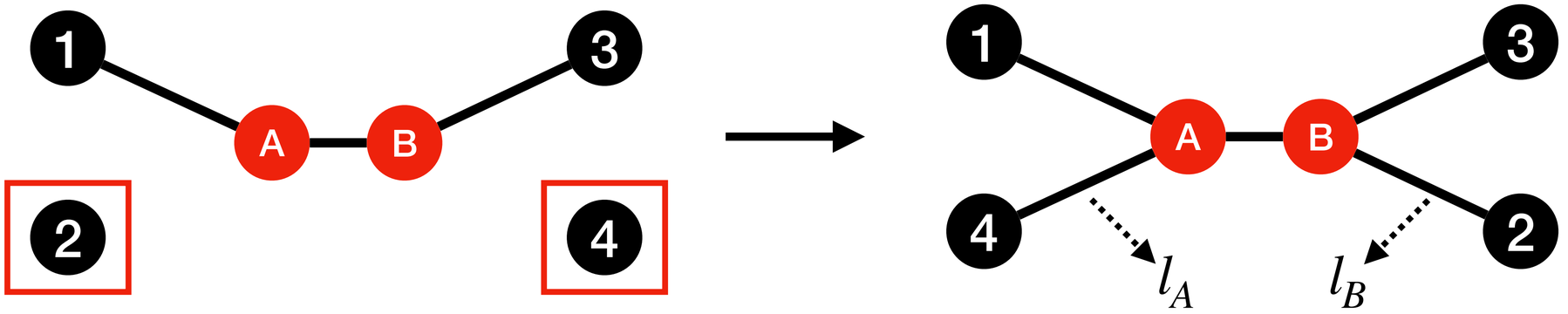
  4. Remap components to their new parents, and assign edge length registered for that parent



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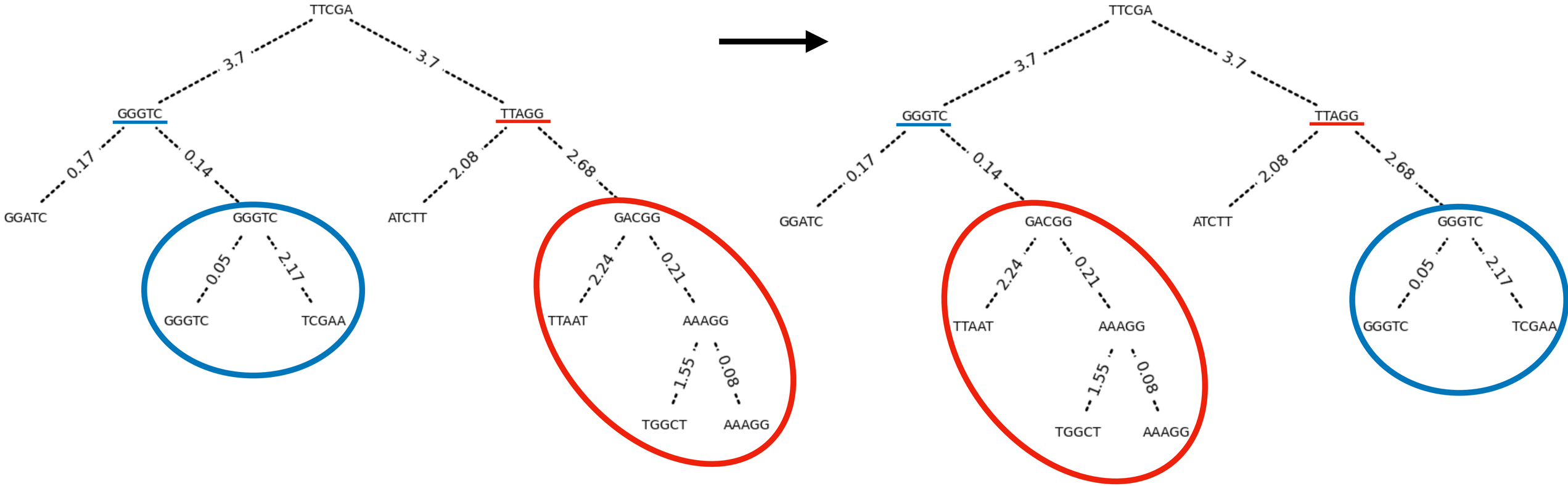

Tree moves for MCMC inference

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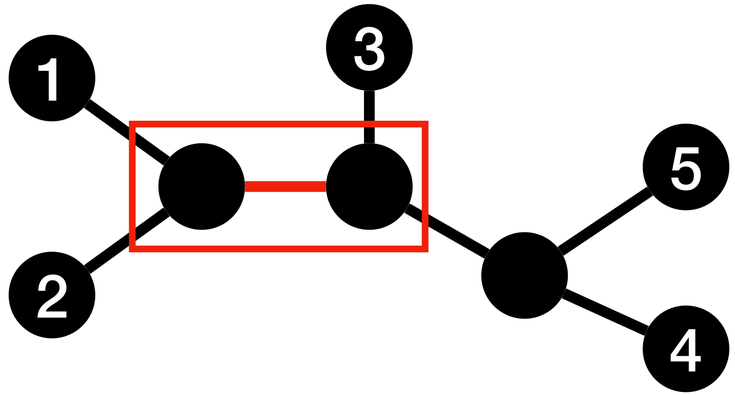

Tree moves for MCMC inference

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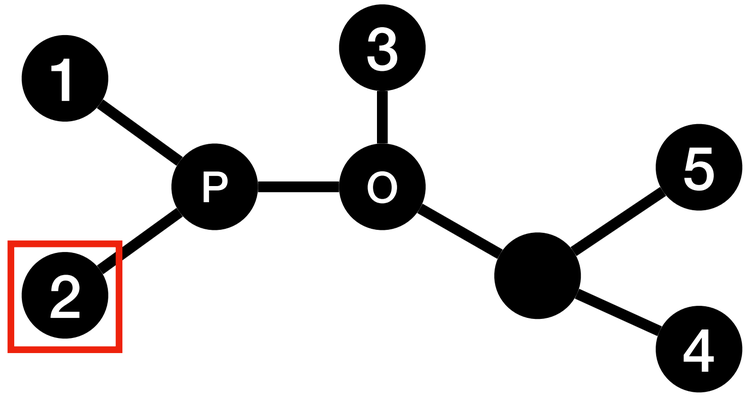

P: prune, O: origin

Tree moves for MCMC inference

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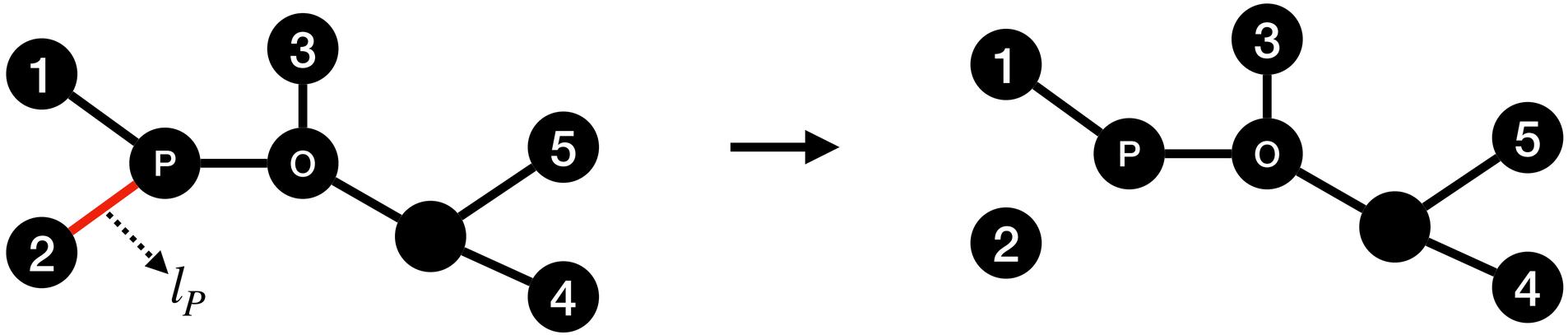

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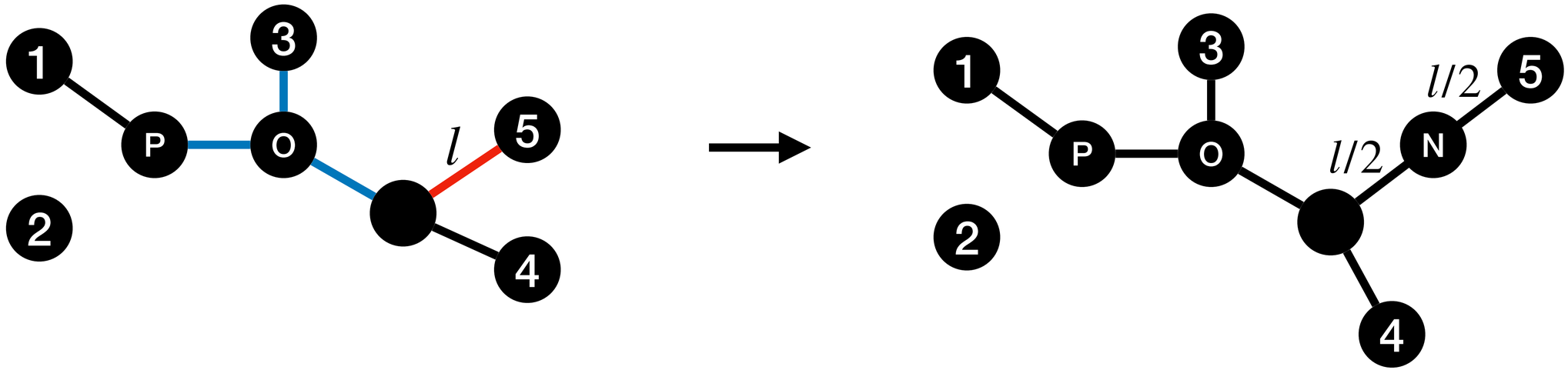

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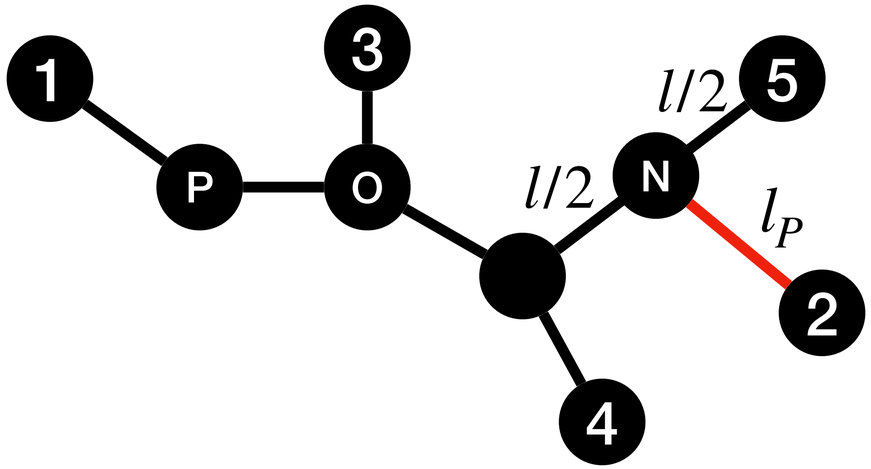

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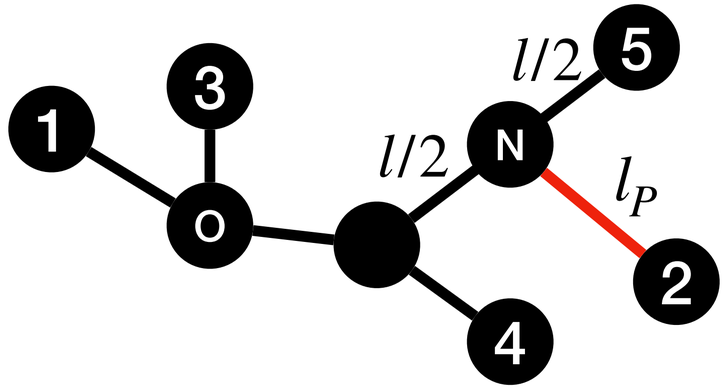
  5. Regraft pruned subtree and assigned the registered length to the edge
  6. Simplify → remove redundant nodes



Tree moves for MCMC inference

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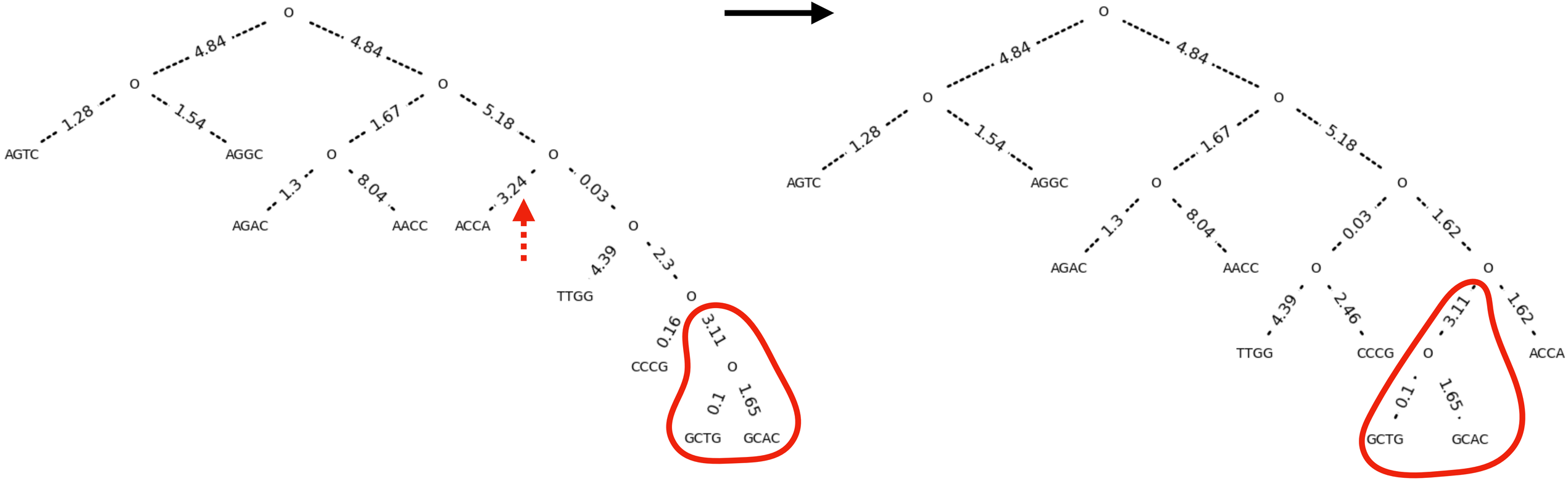

Edge length exploration for MCMC inference

Internal MCMC step → exploration of internal degrees of freedom (edge lengths)

- Initializing edges with *reasonable* values
- Defining the edge length prior, $P(t)$
- Defining the edge length proposal distribution, $P(t' \mid t)$

But first, we need to get a better understanding of the effect of the edge length…

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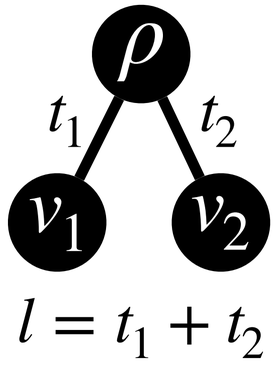
But first, we need to get a better understanding of the effect of the edge length…

Note → JC model:

- α and t only appear as αt in $a(t) = \frac{3}{4}\left(1 - \exp\left(-\frac{4}{3}\alpha t\right)\right)$
- Since we cannot infer α independently, we set $\alpha = 1$

Effect of the edge length on evolution

Consider a simple scenario → tree with a root and two leaves



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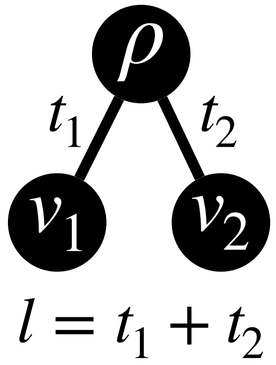

- v_1, v_2 encode 1-character sequences → example $S_1 = A, S_2 = G$

- For $S_1 \neq S_2$, the likelihood can be shown to be:

$$L = \frac{1}{16}\left[1 - \exp\left(-\frac{4}{3}l\right)\right]$$

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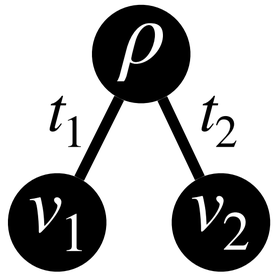

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  - $l \to 0 \Rightarrow L = 0$, because it is impossible for the sequences to be different
  - $l \to \infty \Rightarrow L \to 1/16$, any possible outcome is equally likely
  - $L = 1/16$ is the maximum likelihood for $S_1 \neq S_2$

➡ $l \to \infty$ is a “lazy” maximum, because it does not “commit” to a relationship between S_1 and S_2.

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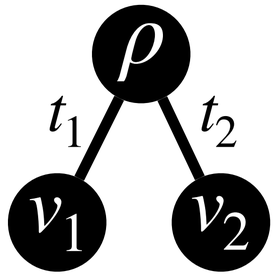

$l = t_1 + t_2$

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- For $S_1 = S_2$, the likelihood can be shown to be:

$$L = \frac{1}{16}\left[1 + 3\exp\left(-\frac{4}{3}l\right)\right]$$

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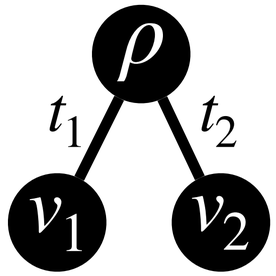

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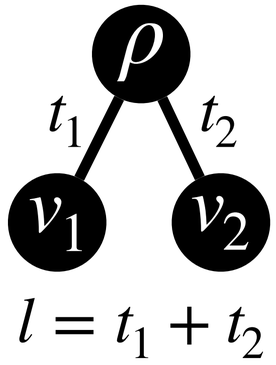

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- Let us consider S_1, S_2 with n characters. If S_1, S_2 have n^+ matching characters and n^- mismatched characters, then the likelihood is:

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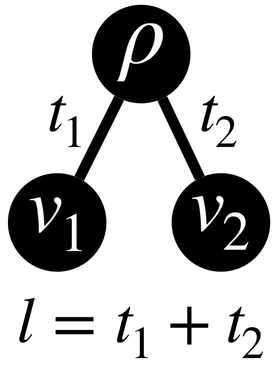

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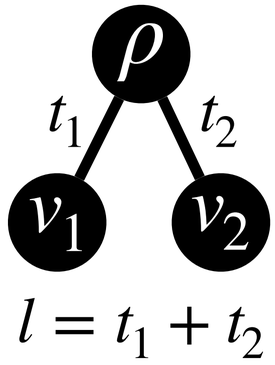
  - The maximum likelihood is given by: $l^* = -\frac{3}{4} \ln \left[\frac{1}{3n}(n^+ - 3n^-)\right]$
  - No solution if $n^+ \leq 3n^-$

- We can already use this notion to initialize edge lengths to **reasonable** values.

Effect of the edge length on evolution

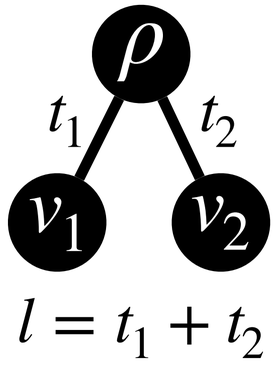


Let us generate *useful* synthetic data from our new understanding

- JC model → What is the probability that we generate $S_1 = S_2$?
  Assume we have $t_1 = t_2 = l/2$...

$$P(S_1 = S_2) = 1 - 2a(l/2) + \frac{4}{3}a^2(l/2)$$

Effect of the edge length on evolution



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- Since the process is independent for each site, then n^+ follows a *Binomial* distribution with mean:

$$\mathbb{E}[n^+] = nP(S_1 = S_2)$$

- Our condition for a non-“lazy” maximum-likelihood was: $n^+ > 3n^- \Leftrightarrow n^+ > 3n/4$

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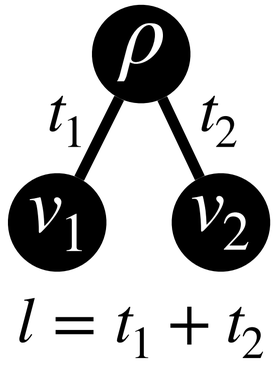

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- **Upper boundary** to generate synthetic data that can be reconstructed with inference:

$$l^* < -\frac{3}{4}\ln\left(\frac{2}{3}\right)$$

Distribution of edge lengths

From the upper bound we found, we may propose the edge length distribution

$$P(t) = \lambda e^{-\lambda t} \quad ; \quad \lambda = \frac{1}{t^* + \delta_t} \quad ; \quad t^* = \frac{l^*}{2} = -\frac{3}{8} \ln\left(\frac{2}{3}\right) \approx 0.15$$

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- Used for data generation and as prior for inference
- δ_t determines how closely related the daughter and parent sequences are:
  - $\delta_t > 0 \rightarrow n^+/n^-$ decreases and sequences are less correlated
  - $\delta_t < 0 \rightarrow n^+/n^-$ increases and sequences are more correlated

Proposal distribution for edge lengths

We want the following qualities from our proposal:

- Symmetric $\rightarrow P(t' \mid t) = P(t \mid t')$
- Avoids proposing negative values $\rightarrow P(t' < 0 \mid t) = 0, \forall t$

Let us propose $t' = t \cdot e^{\gamma}$, with $\gamma \sim U(-\gamma_0, \gamma_0)$

➡ Then, $P(t' \mid t) = P(\gamma = \ln(t'/t))$ and fulfills our constraints

Complete MCMC inference scheme

1. Initialize tree topology and edge lengths from $P(t)$.
2. Propose N_{seq} sequence assignments for the tree and keep the one with maximum likelihood.
3. Perform N_{burn} MC steps for burn-in.
4. Perform $N_{samples}$ MC steps for sampling.

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Each MC step consists of:

a. **External** MC step: attempt $N_{int,e}$ NNI moves and N_{SPR} SPR moves.

b. **Internal** MC step: attempt N_e edge changes, picked uniformly at random.

c. **Register** sample for the specific topology.

Complete MCMC inference scheme

Let us define the following log-ratios:

$$\Delta_P = \ln[P(S\,|\,T', \{t'_e\})] - \ln[P(S\,|\,T, \{t_e\})] \qquad \Delta_t = \ln[\exp(t')] - \ln[\exp(t)] = t' - t$$

Then, the acceptance probabilities are given by:

- External MC steps ($\{t'_e\} = \{t_e\}$) $\rightarrow$ $A_{ext} = \exp(\Delta_P)$
- Internal MC steps ($T' = T$) $\rightarrow$ $A_{int} = \exp(\Delta_P - \lambda\Delta_t)$

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In this context, λ can be interpreted as modulating the reward of shorter edges (“bold” claims for the data) and the cost of longer edges (“lazy” claims).

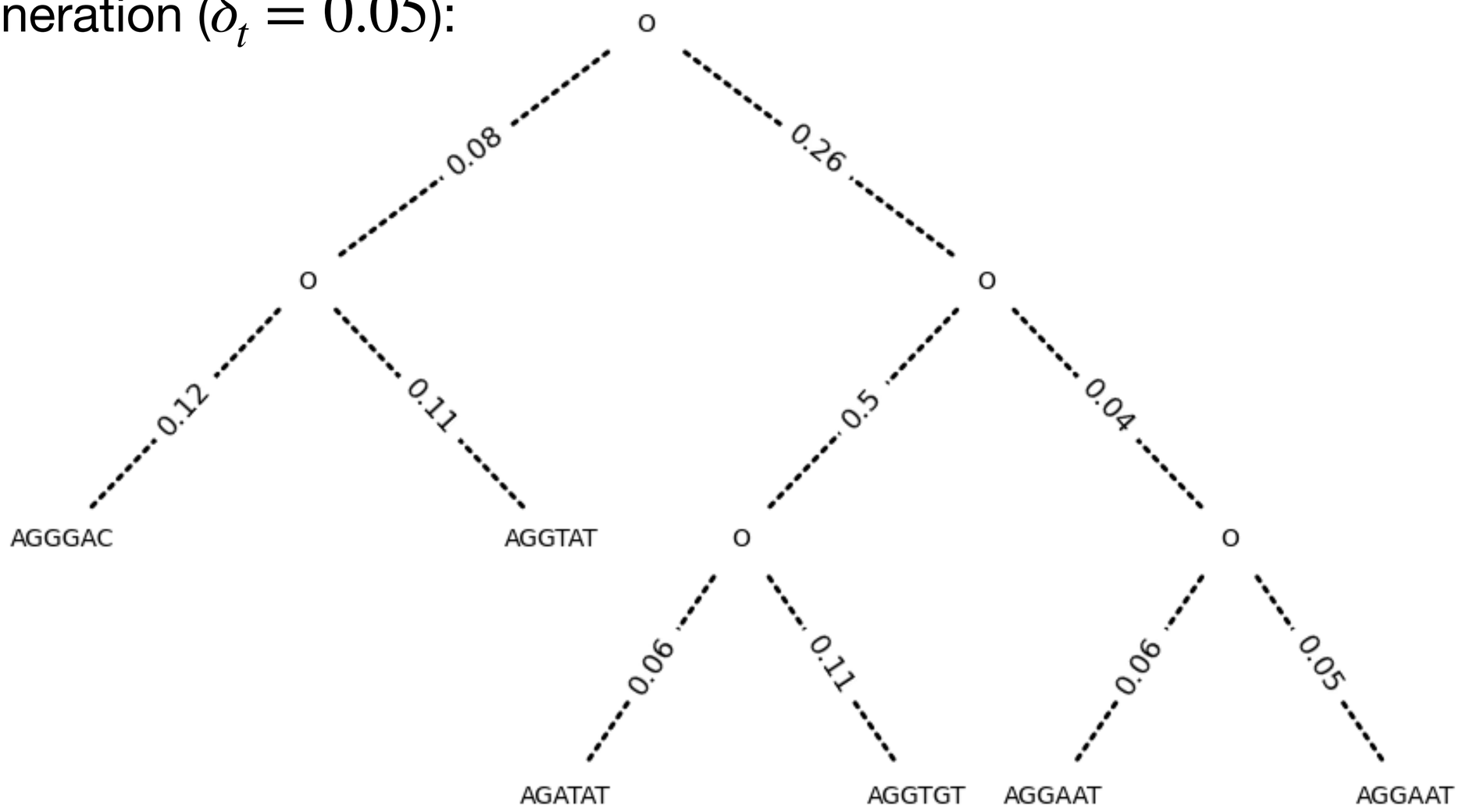
RESULTS

Initial testing

Small test case $\rightarrow n = 6$ leaves, with $m = 6$ sites per sequence

- Synthetic data generation ($\delta_t = 0.05$):

  ➡ $\langle t \rangle \approx 0.2$



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- MCMC inference:
  - 5×10^2 burn-in steps
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  - $\gamma_0 = 2.5, N_{SPR} = 2$

Execution time ≈ 100 s

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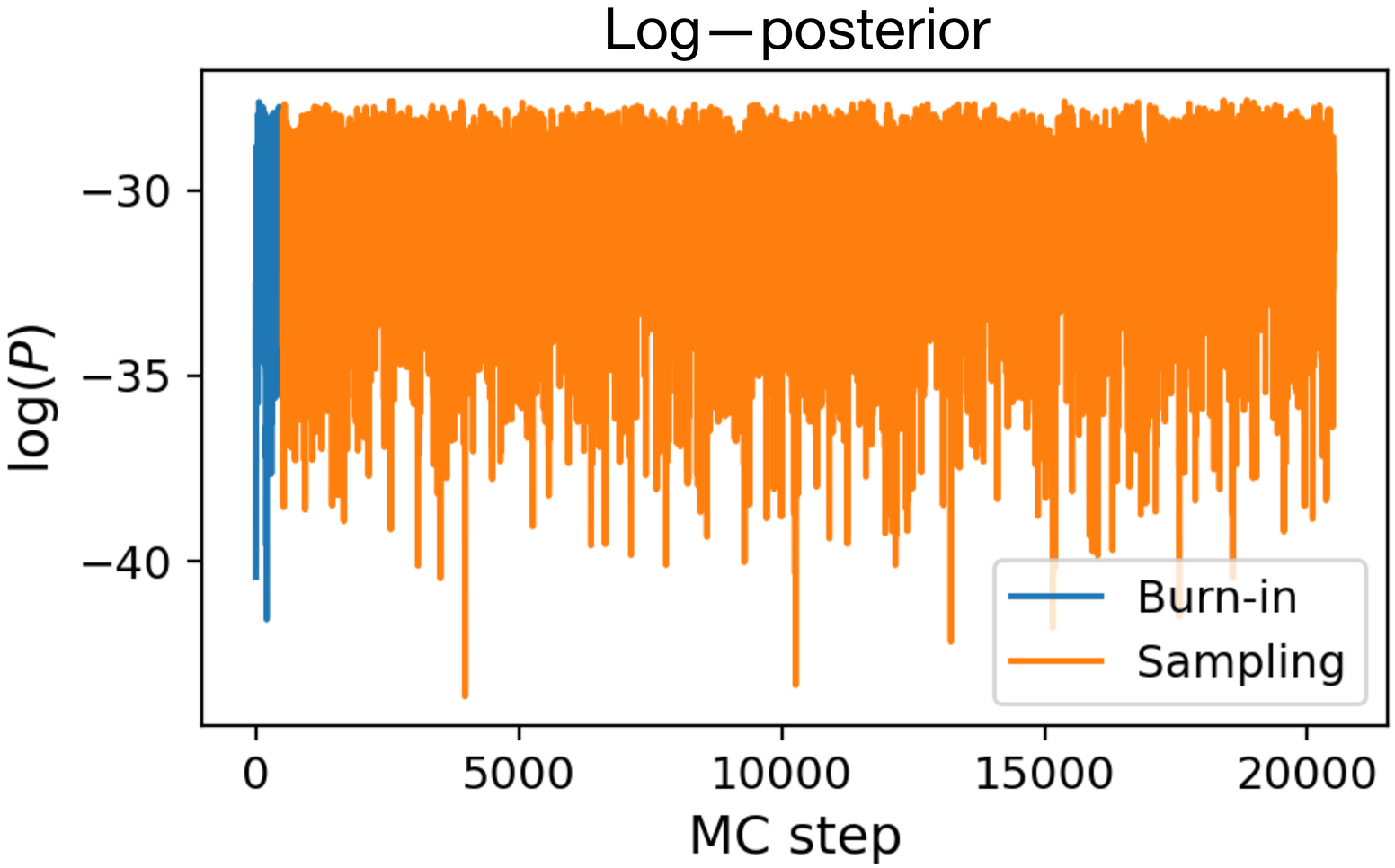

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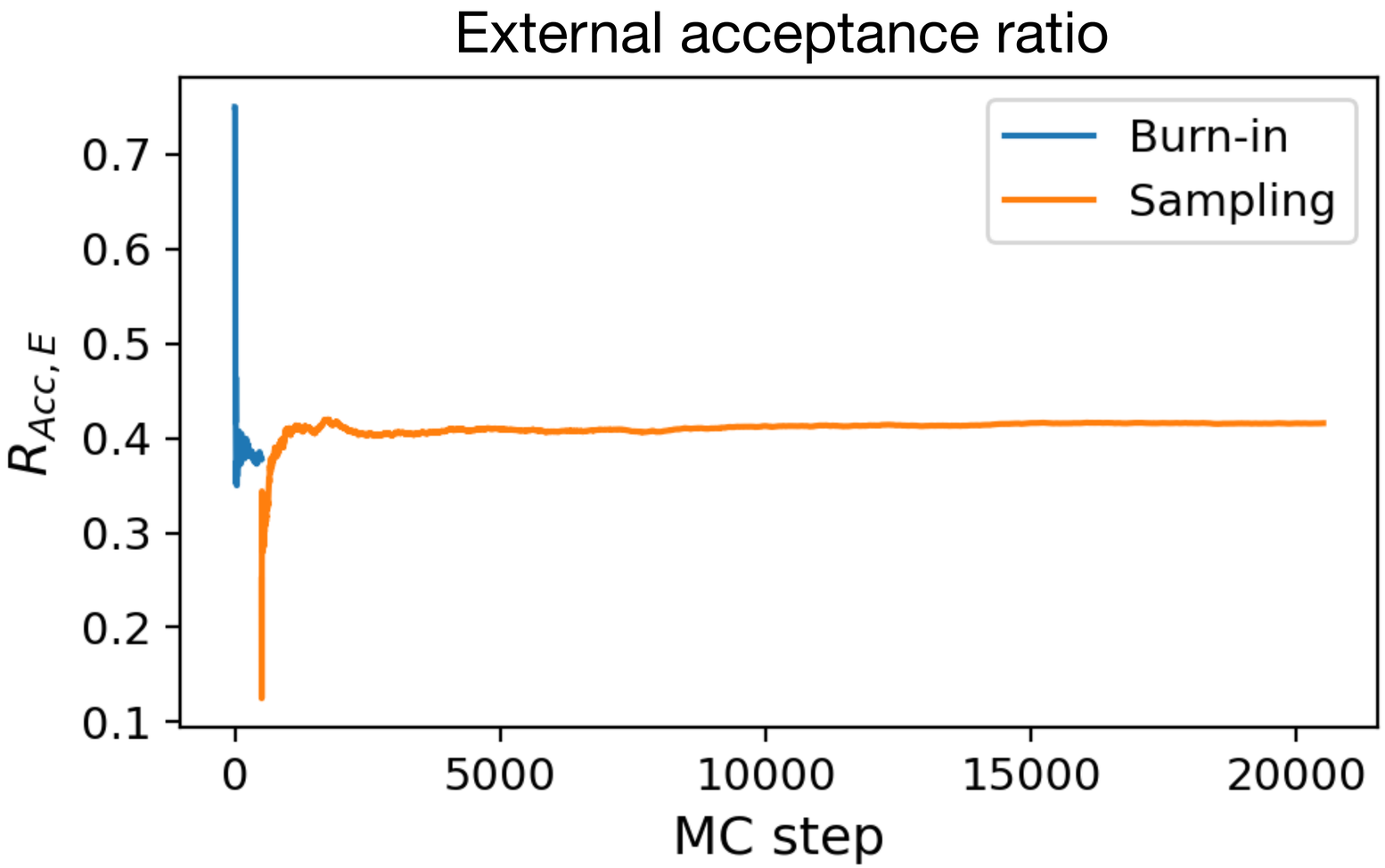

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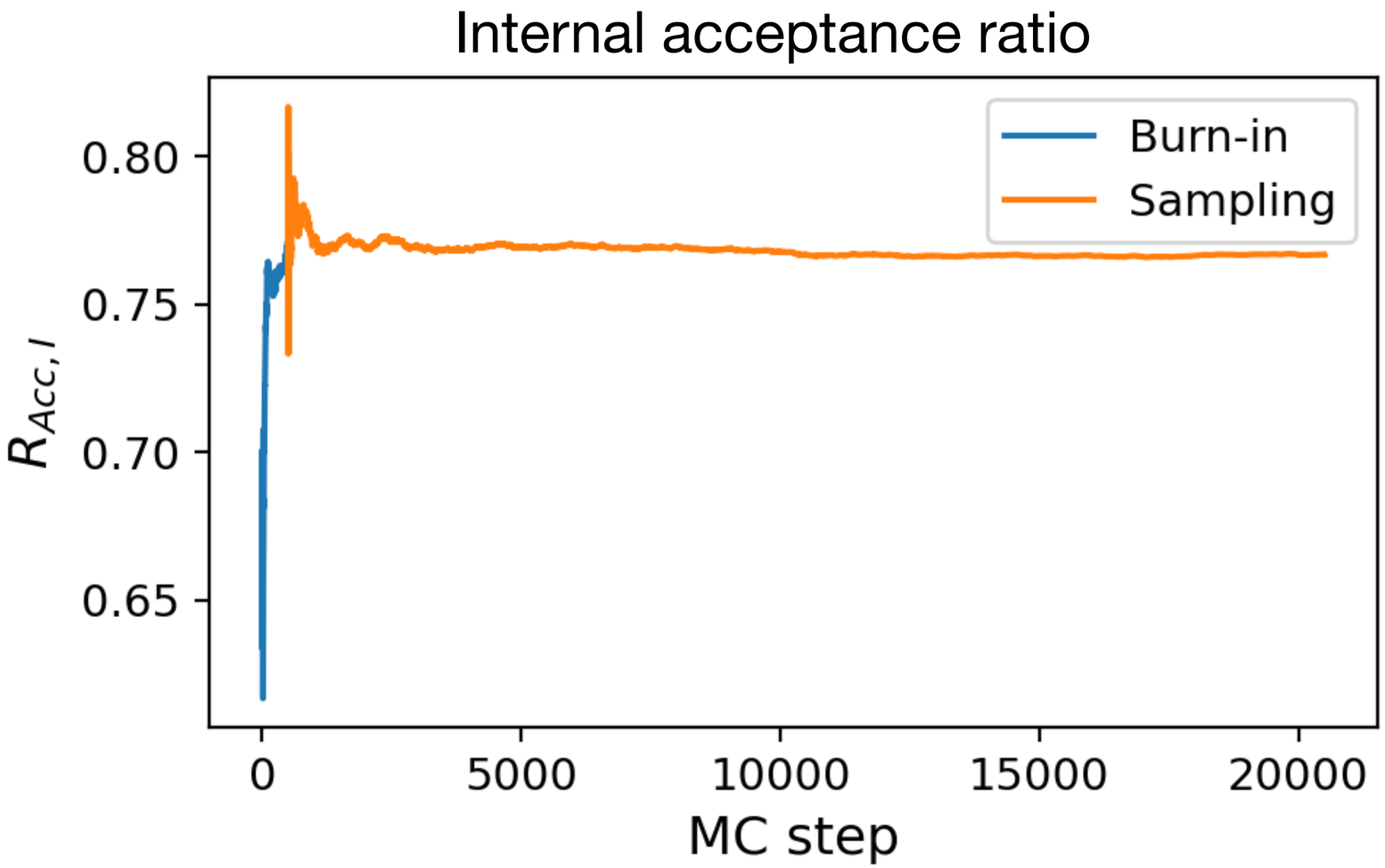
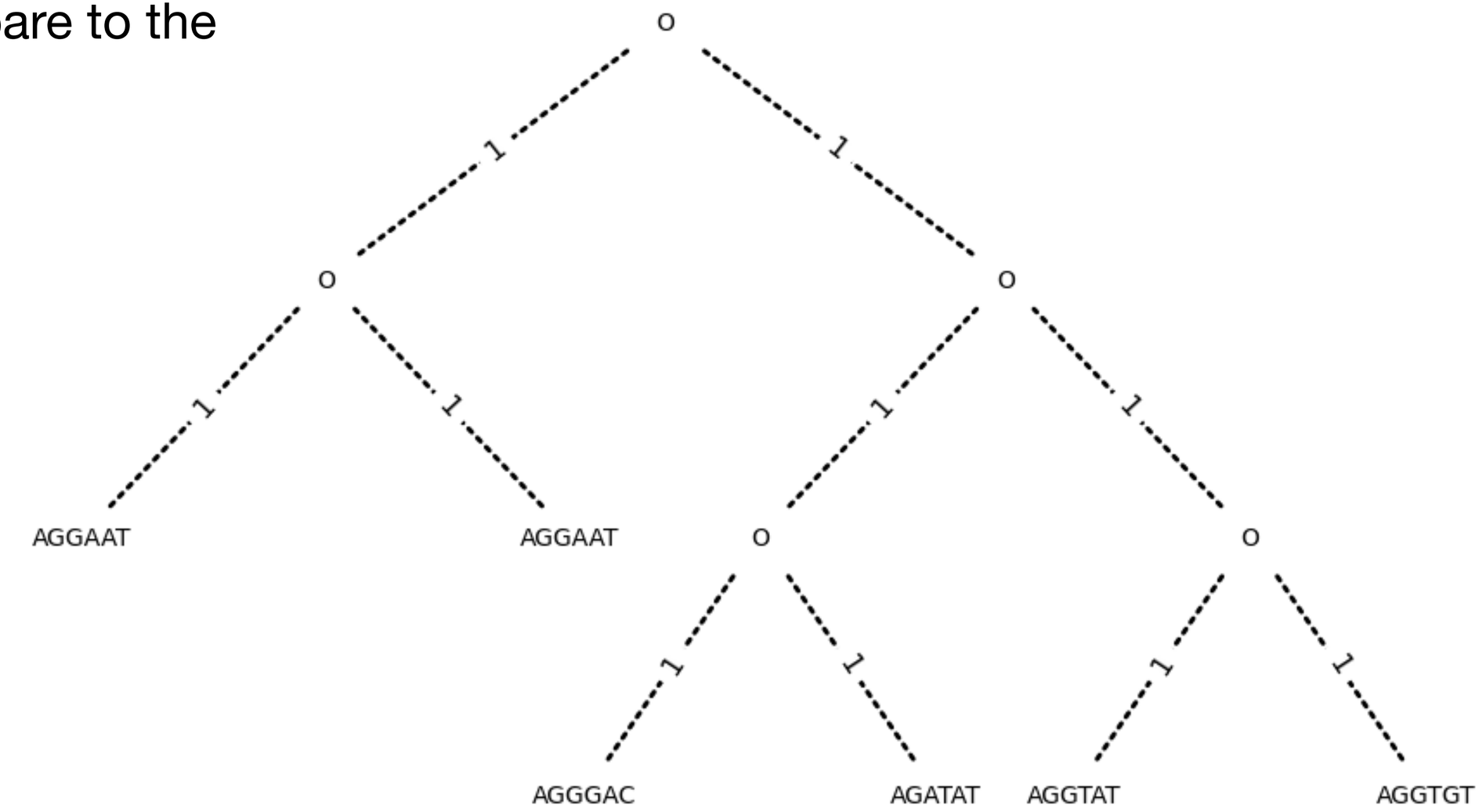


Initial testing

Maximum a posteriori (MAP) tree → Sampled topology with highest posterior

- How does it compare to the original tree?



Initial testing

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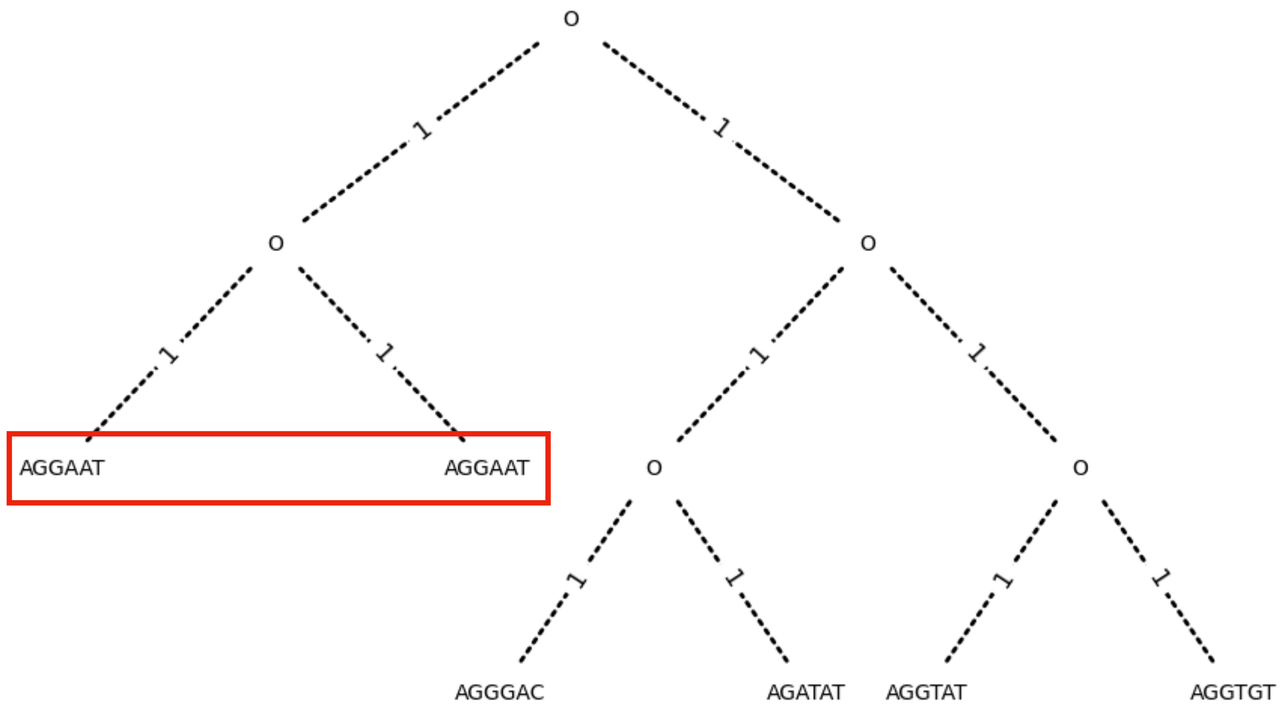
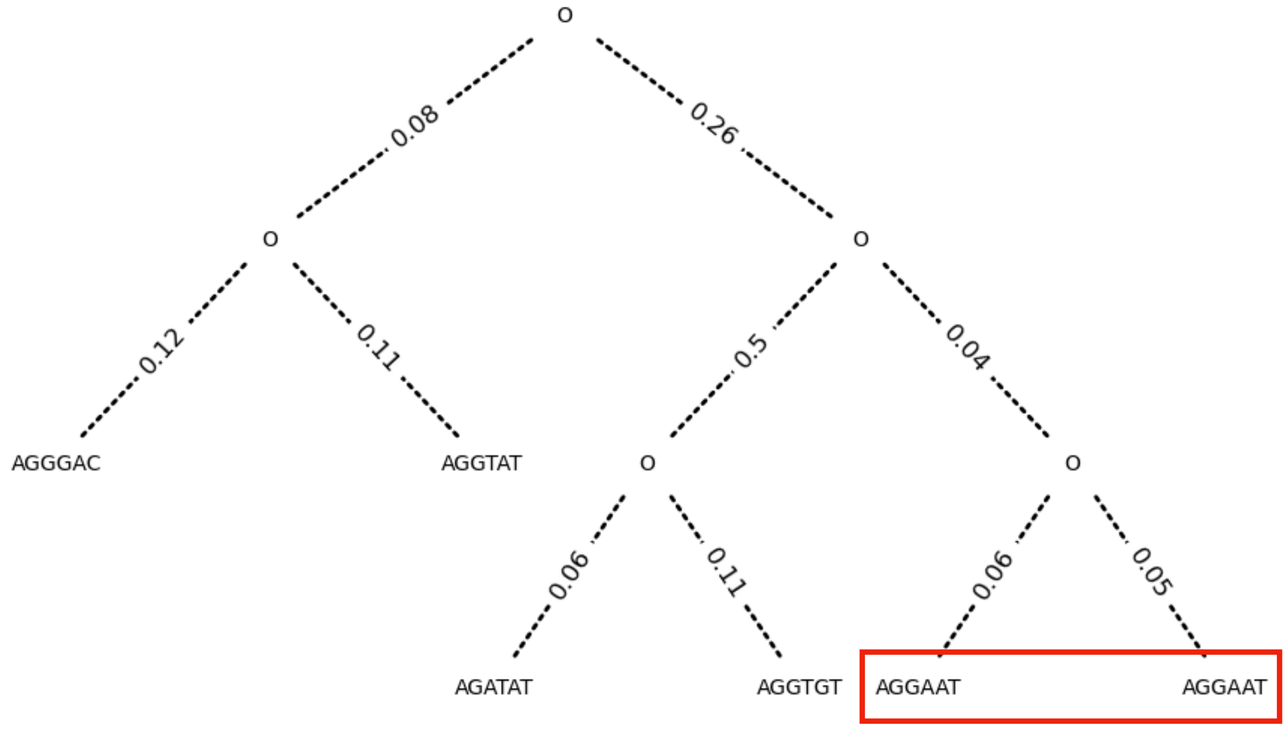


Original



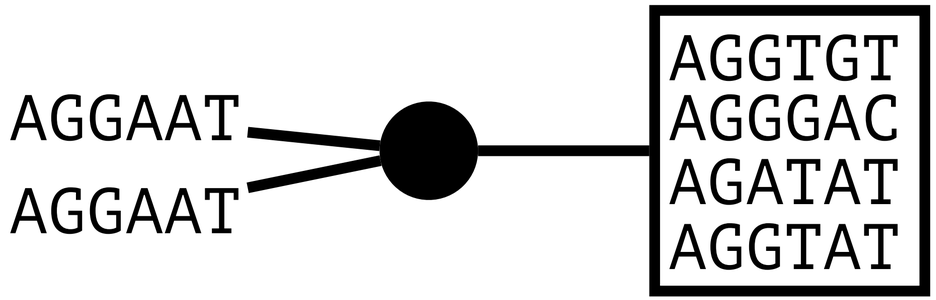
Ranking by $\log(P)$: 259 out of 267

Initial testing

Splits $\rightarrow$ any partition of X into two non—empty disjoint subsets

- Majority—rule consensus: accept the splits that appear in $> 50\,\%$ of the trees

```
((AGGAAT,AGGAAT),(AGGTGT,AGGGAC,AGATAT,AGGTAT))
```



- Original splits:

```
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((AGGGAC,AGGTAT),(AGGAAT,AGATAT,AGGTGT,AGGAAT))
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```

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Inference of edge lengths for the MAP tree → Sample with *internal* MC steps

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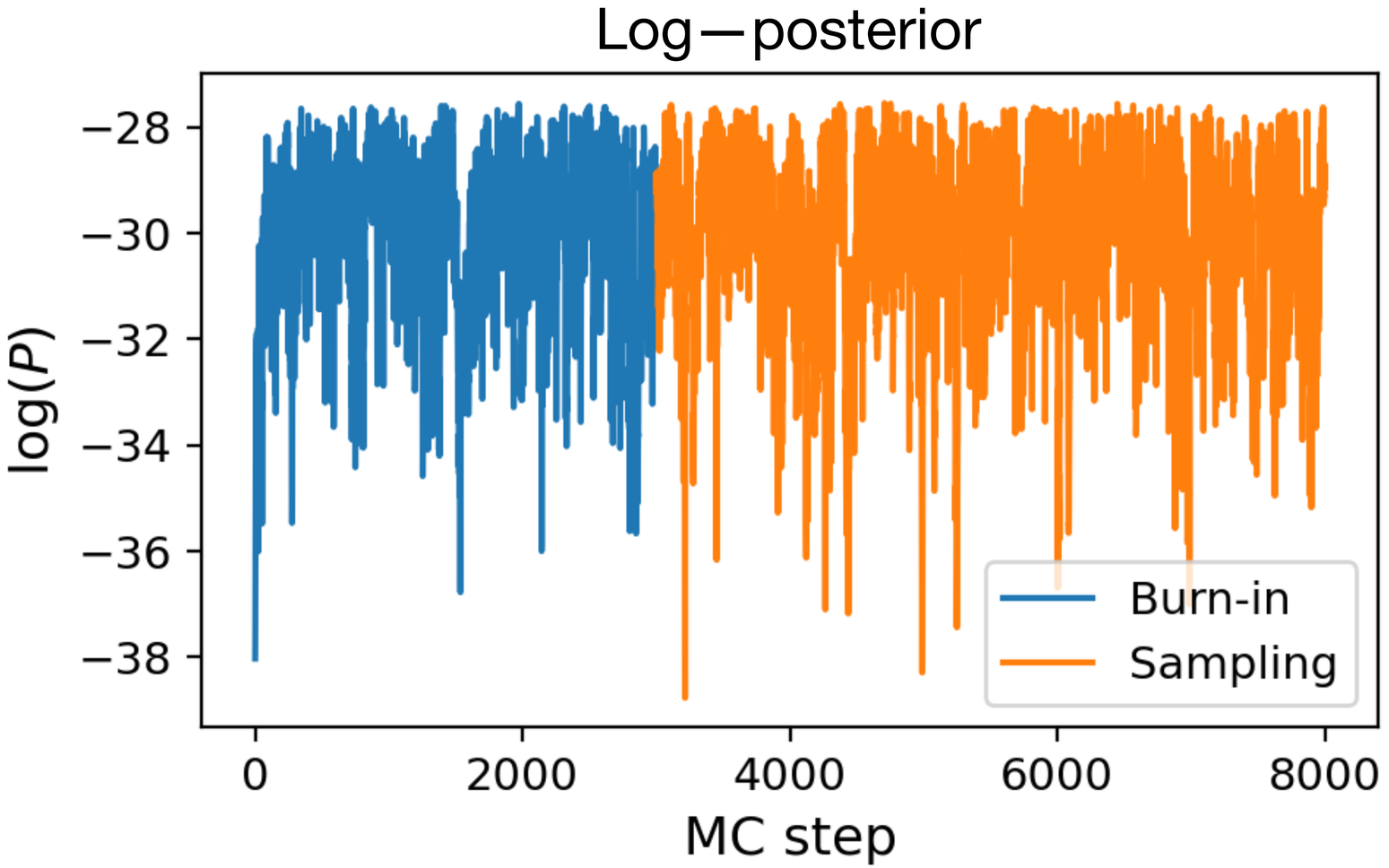

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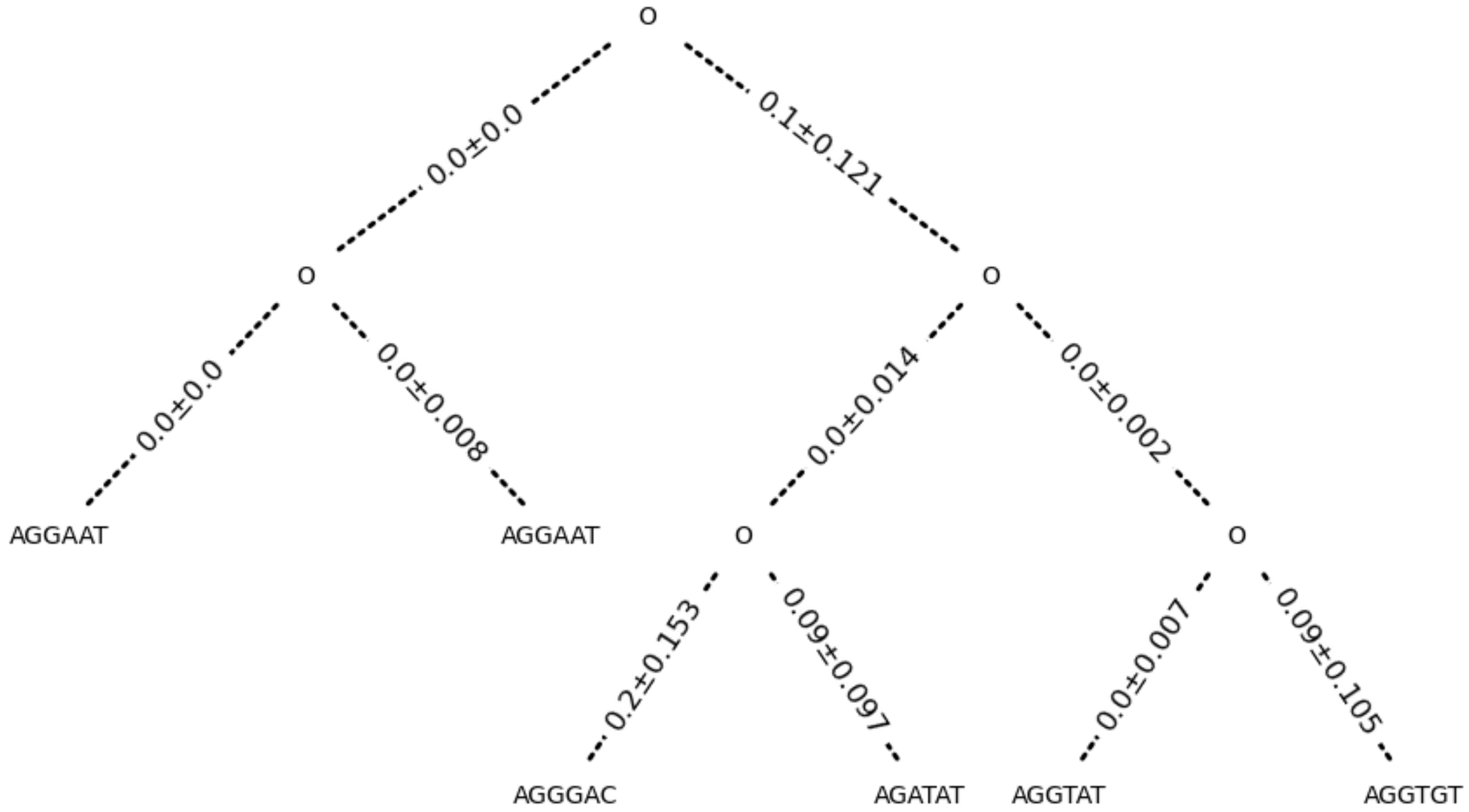
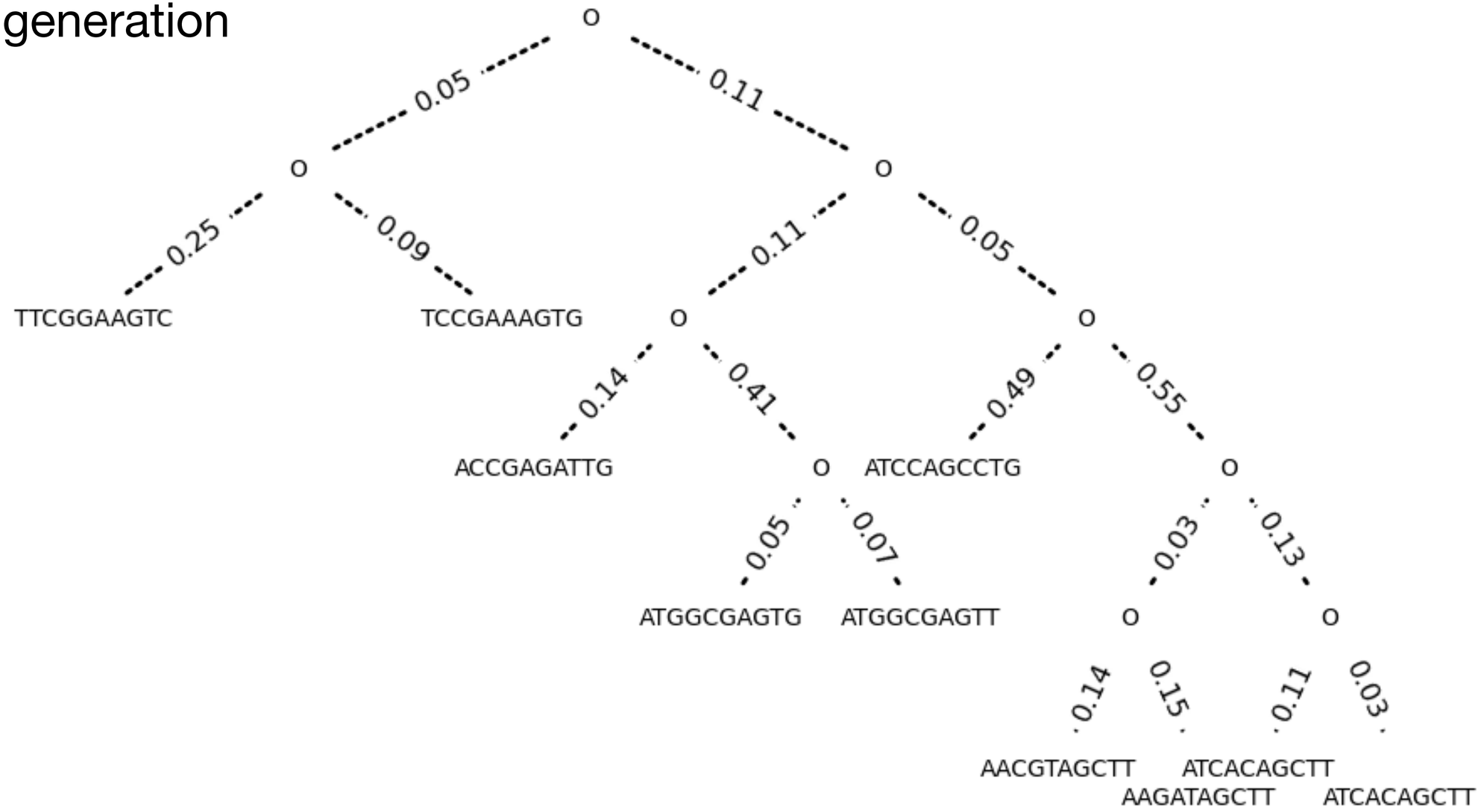


Case study

More complex scenario $\rightarrow n = 10$ leaves, with $m = 10$ sites per sequence

- Synthetic data generation ($\delta_t = 0.01$):

  ➡ $\langle t \rangle \approx 0.16$



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More complex scenario $\rightarrow n = 10$ leaves, with $m = 10$ sites per sequence

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Execution time ≈ 4.7 min

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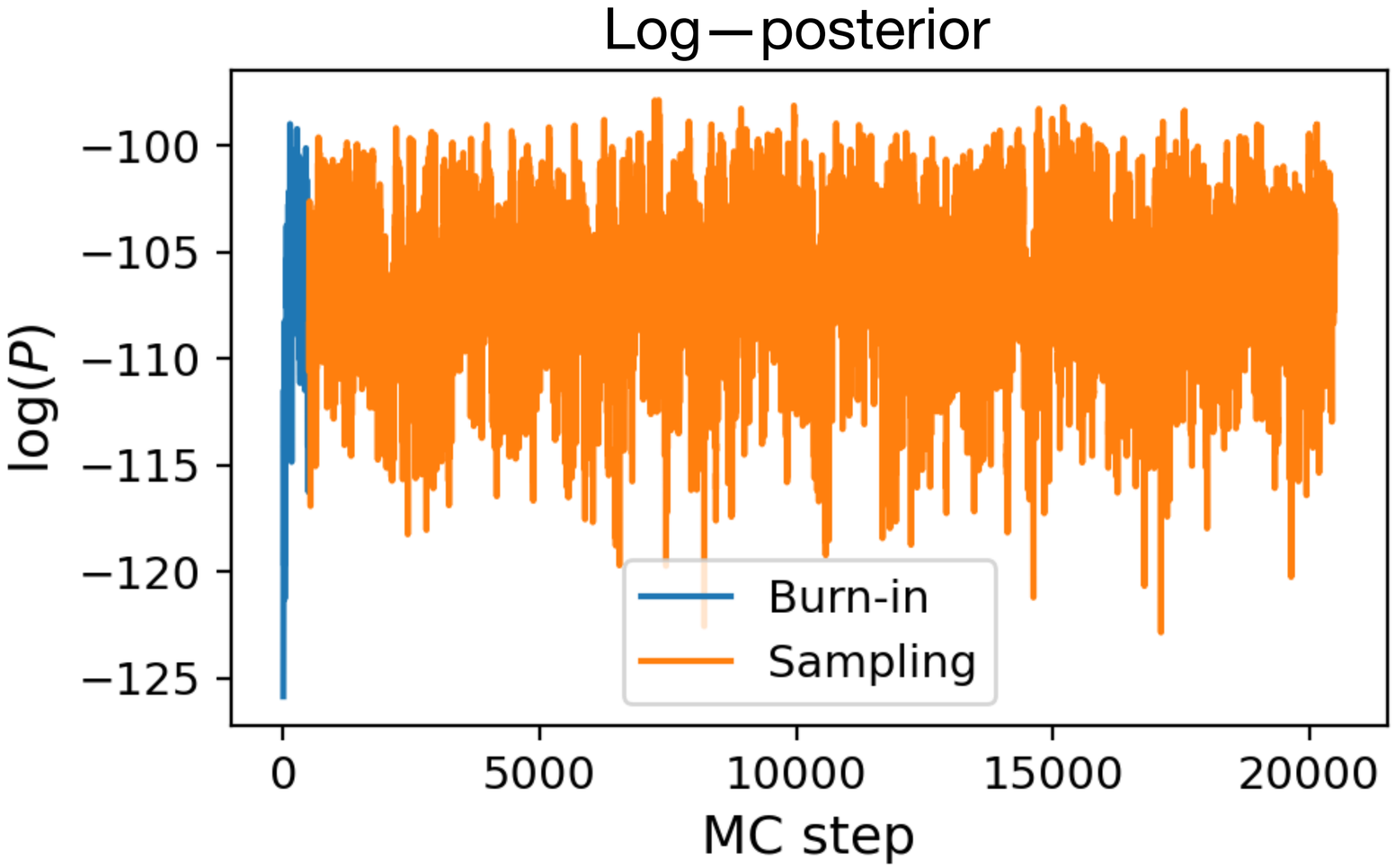

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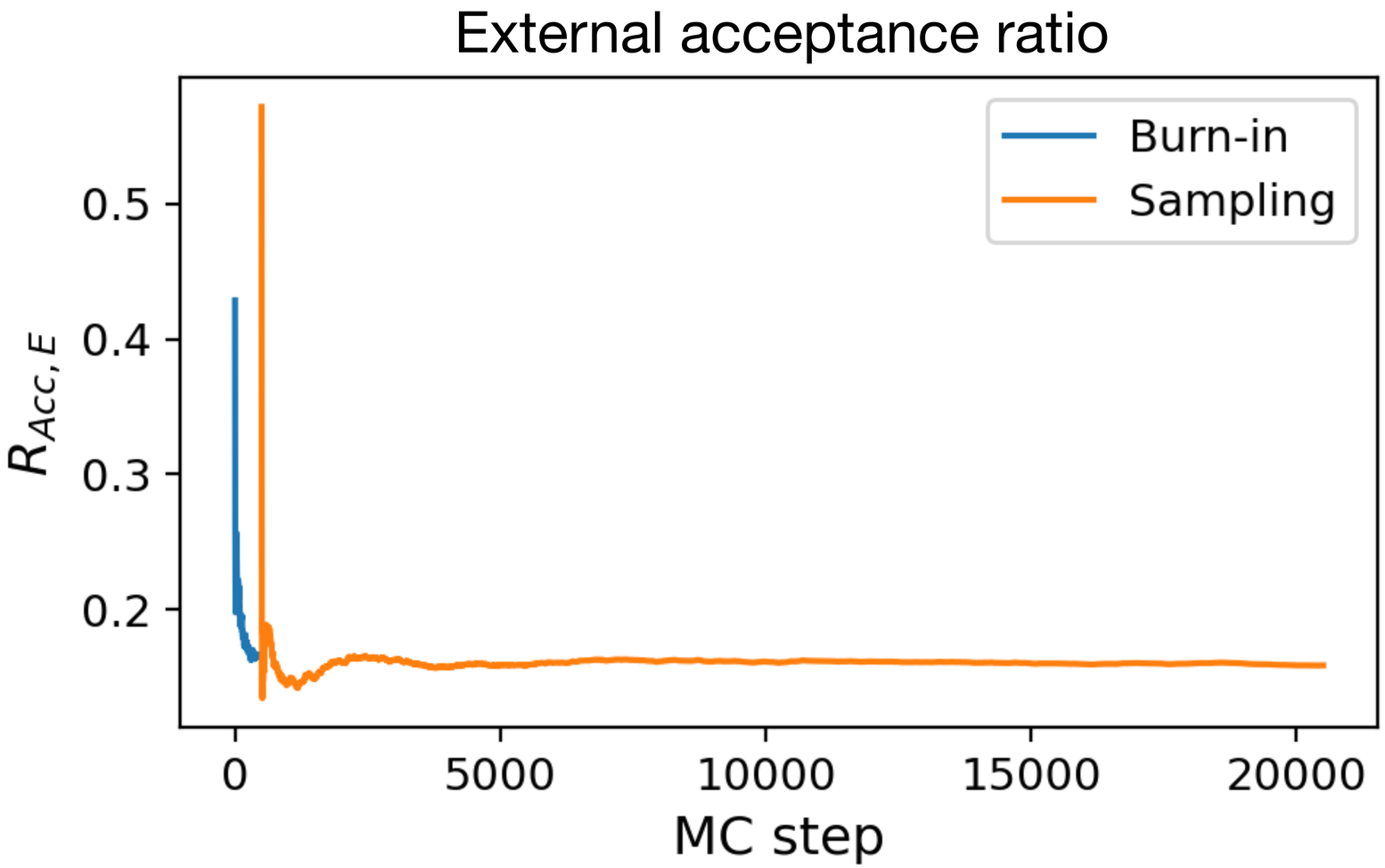

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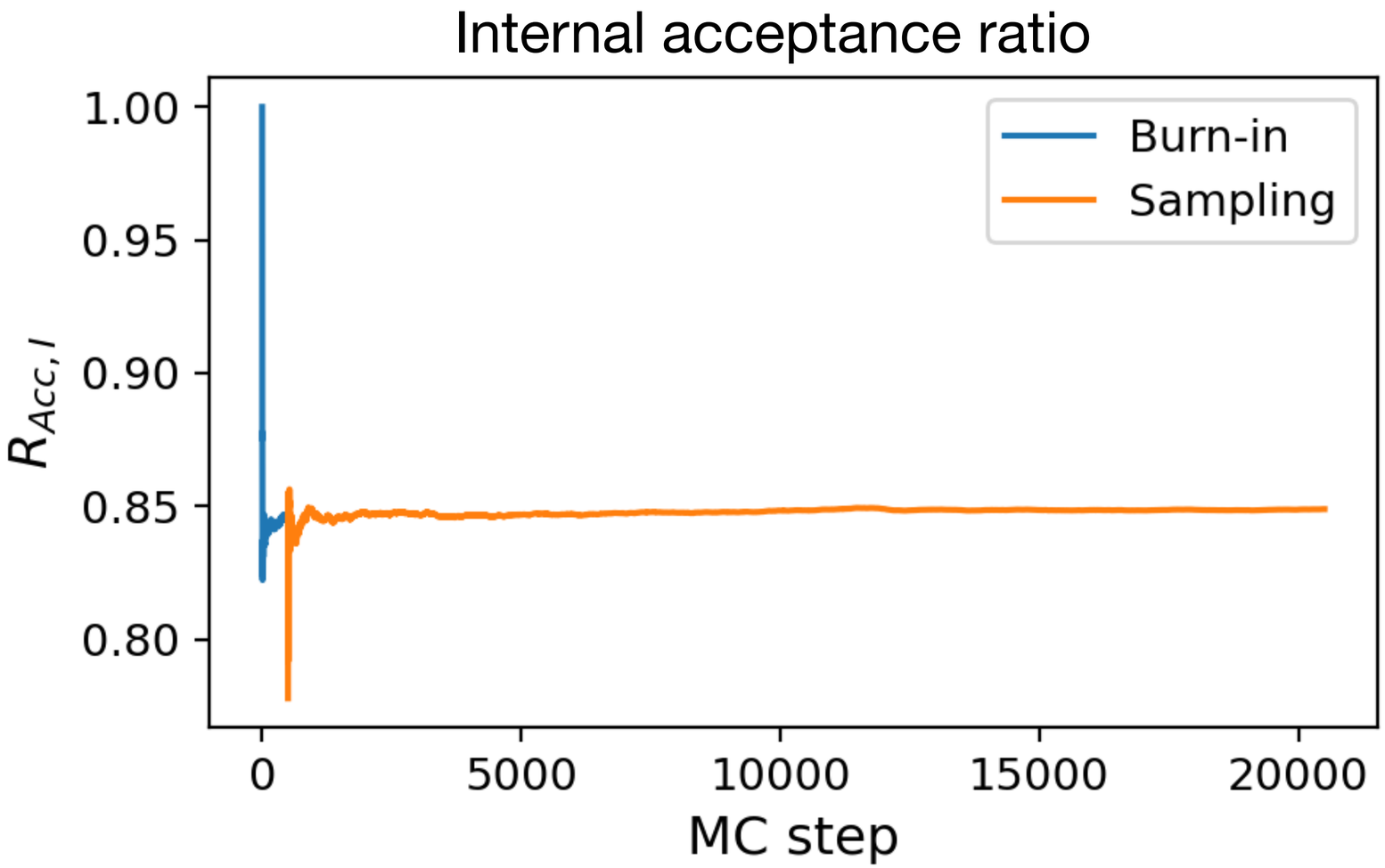

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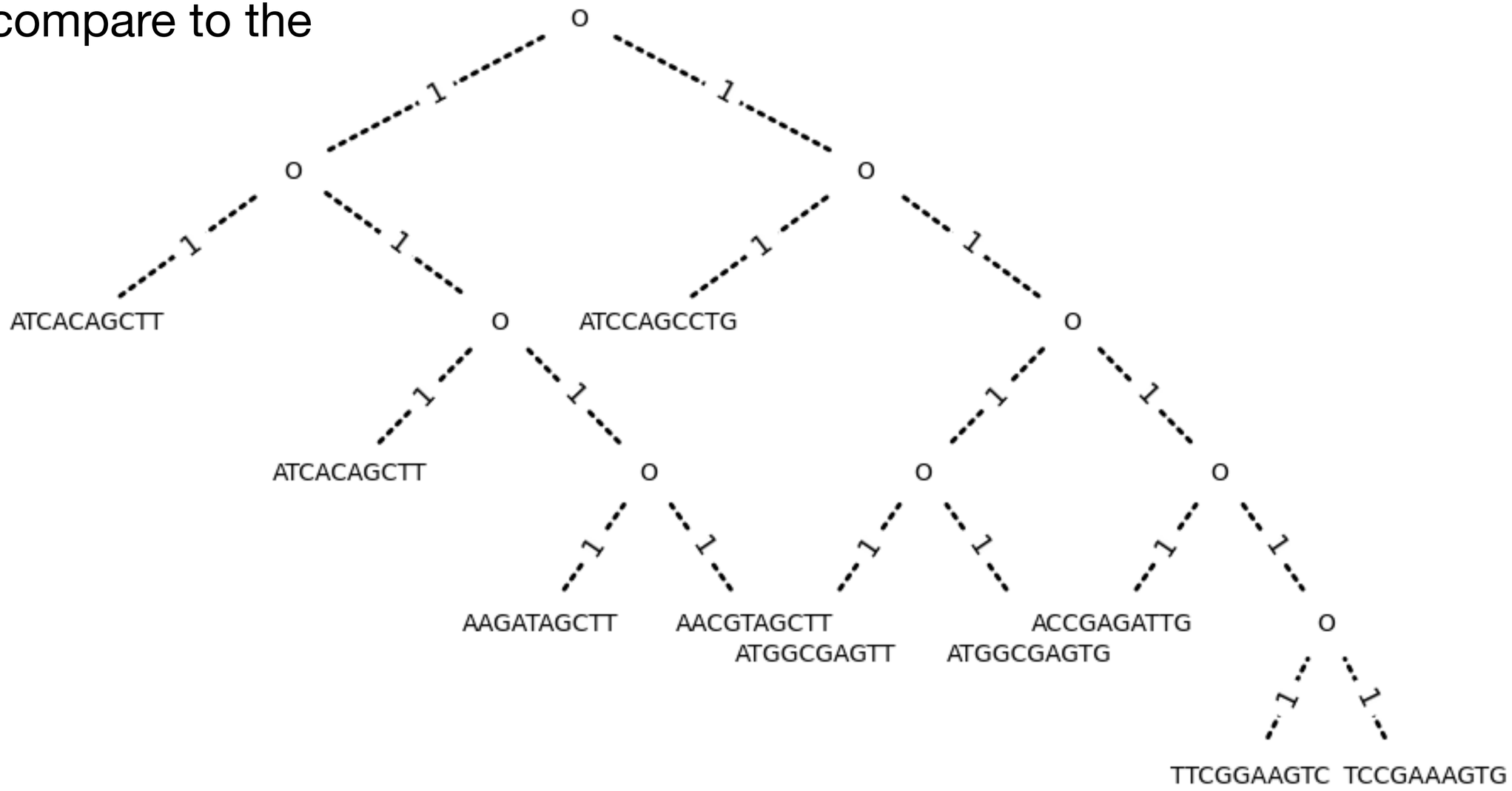

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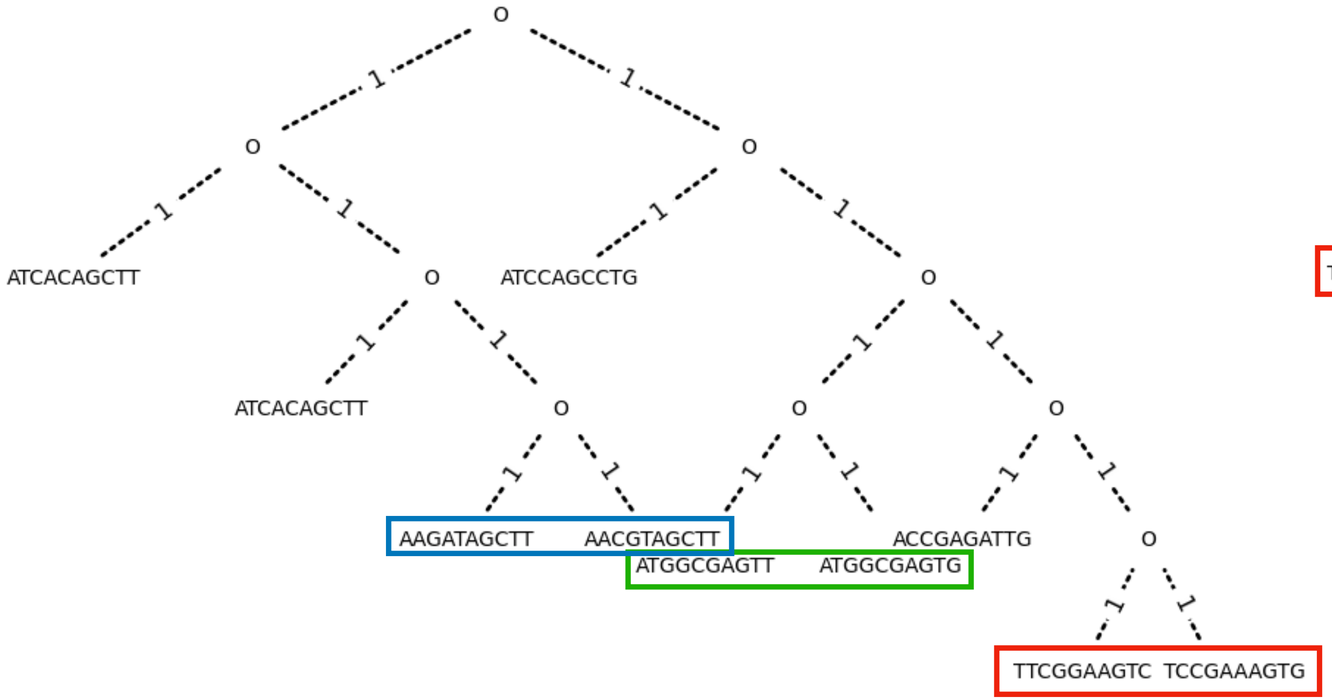

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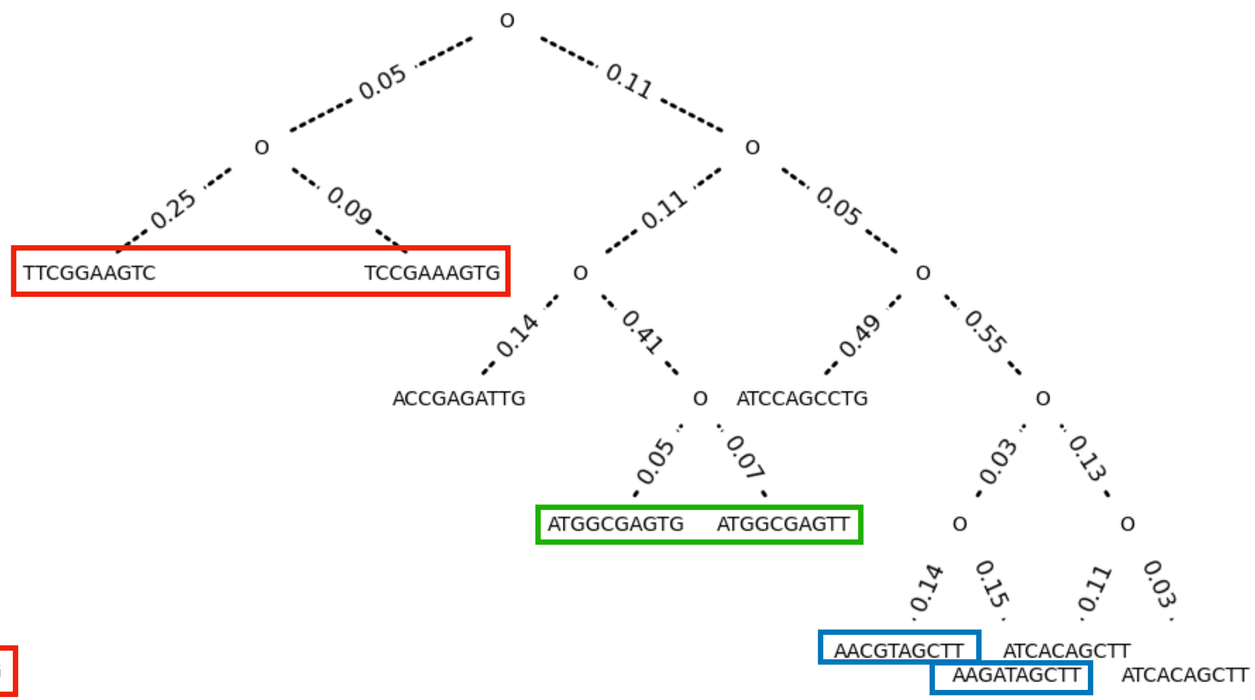

Ranking by $\log(P)$: 2596 out of 3797

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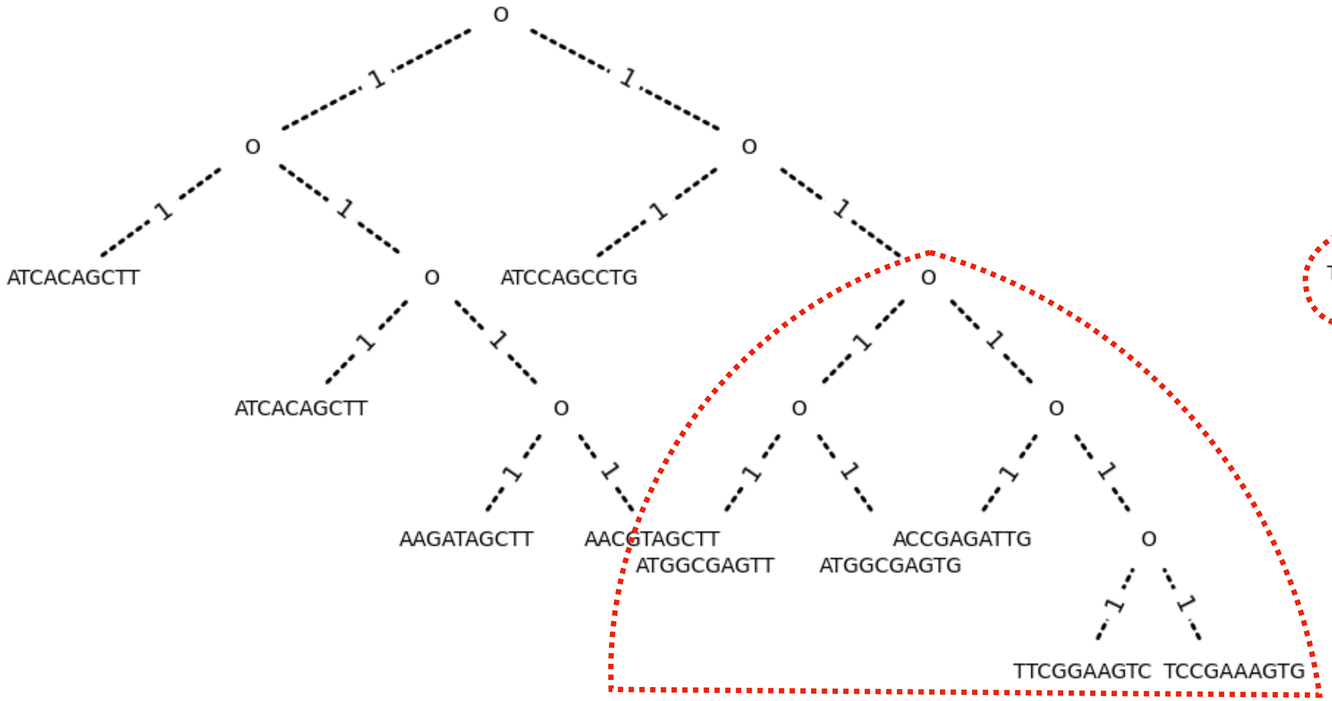
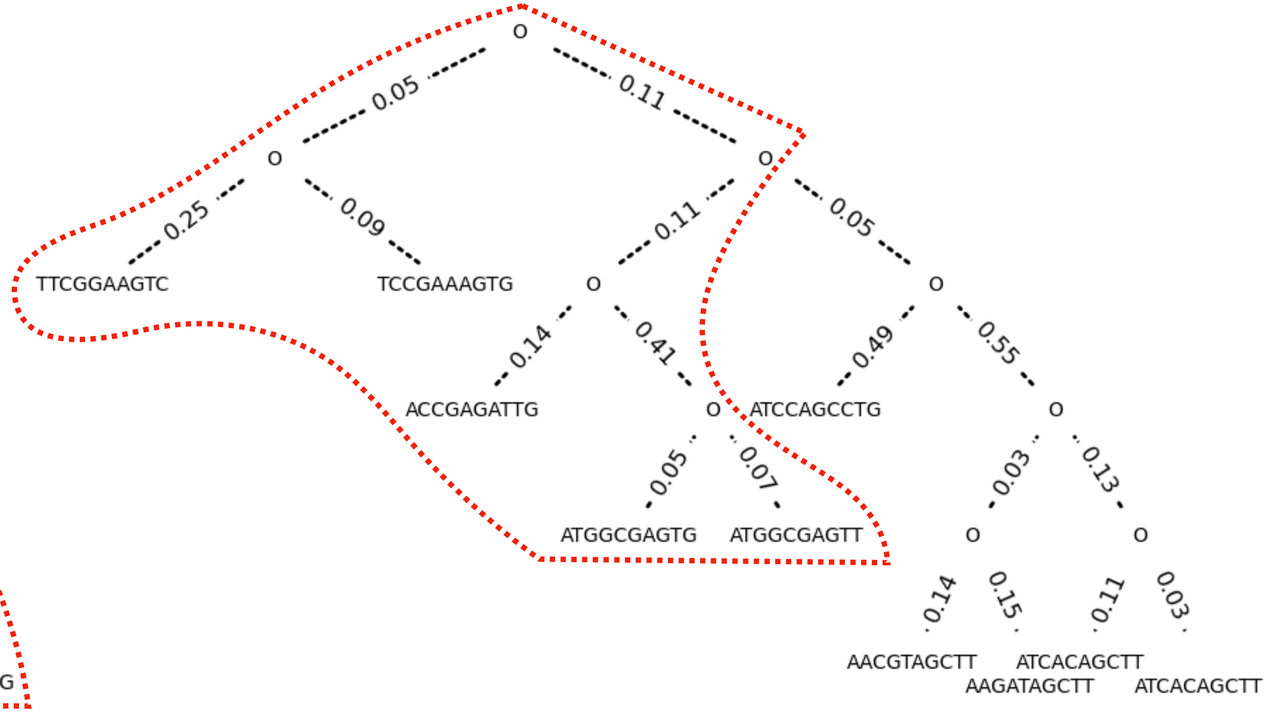


Original



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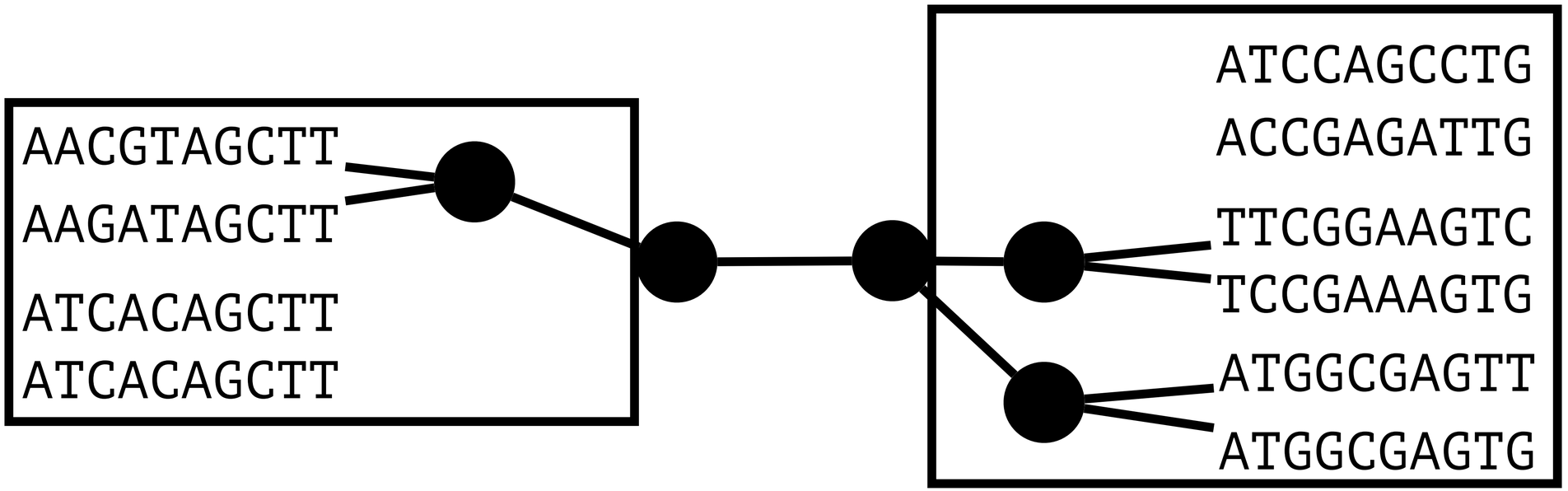
Consensus tree



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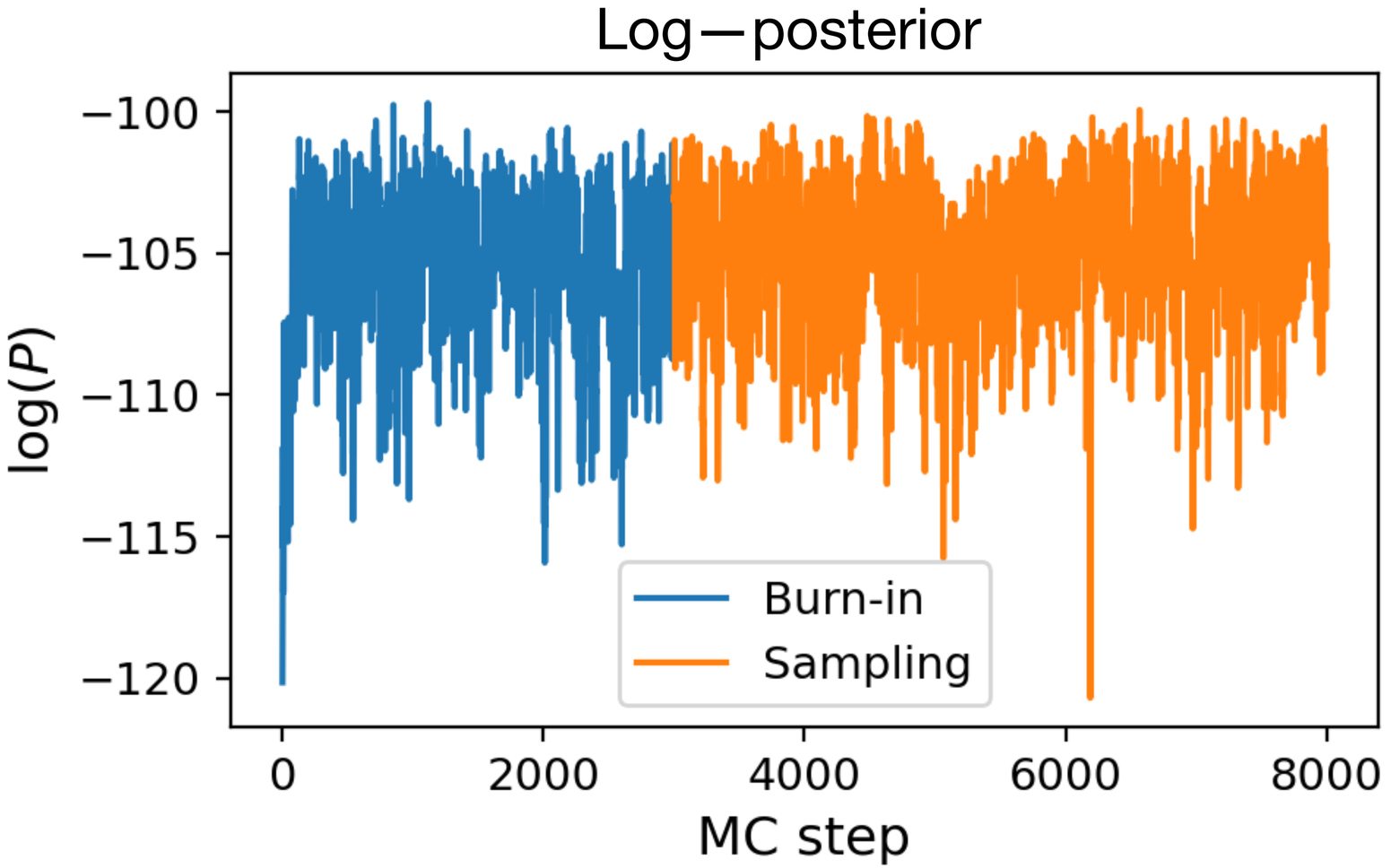

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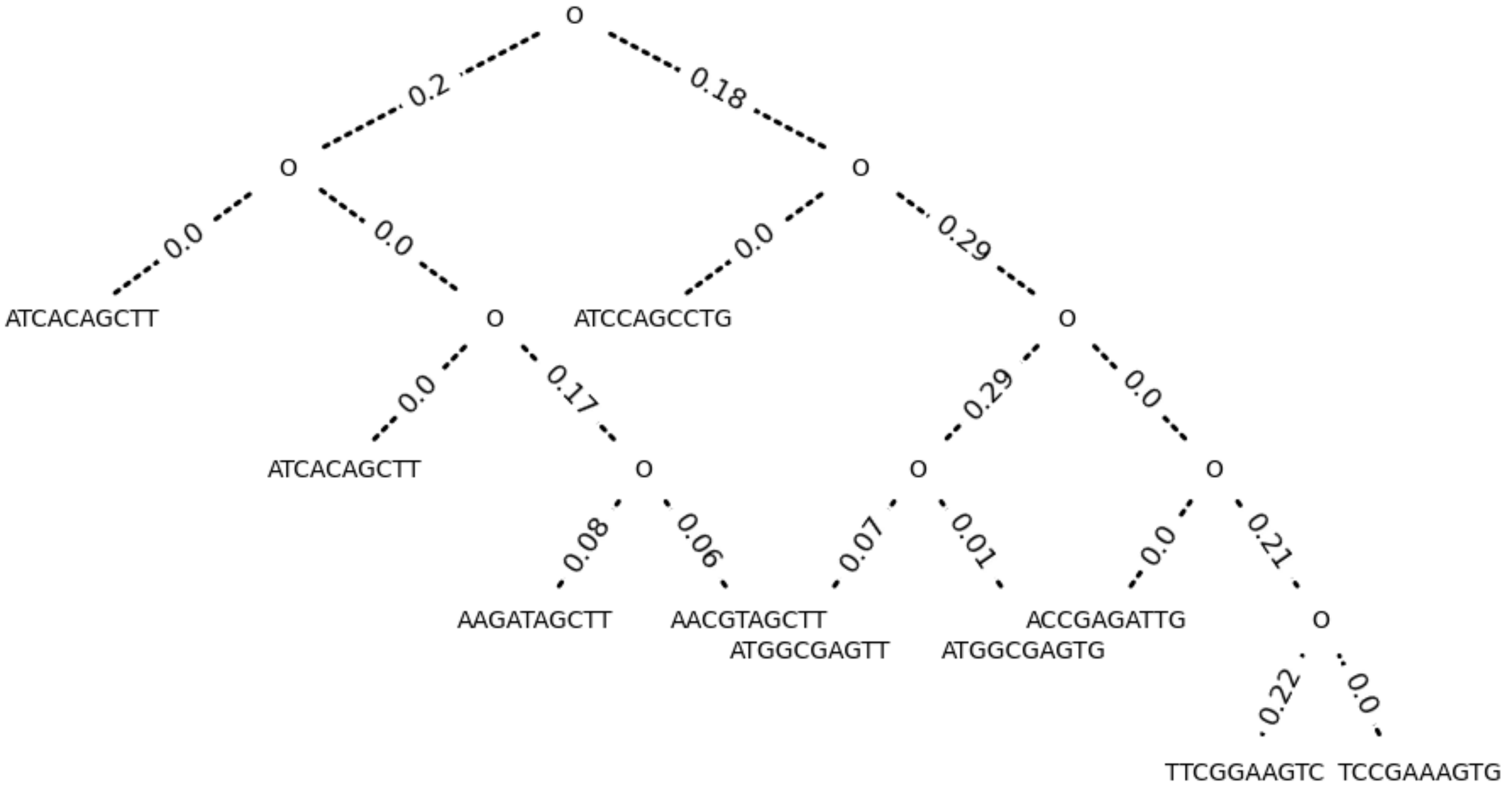

CONCLUSION

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Achieved goals

- Simulated phylogenetic data using the Jukes-Cantor sequence evolution model.
- Performed inference on the synthetic data using the Markov Chain Monte Carlo approach → able to partially reconstruct the original phylogenetic relationships.