

# Phylogenetic reconstruction: criteria

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*How to find the best tree given my data?*

- **Need for a criterion/score**
- **Need for an algorithm to find/construct the tree**

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  - Maximum Parsimony
  - Minimum Evolution or least squares (distance methods)
  - Maximum Likelihood  $\sim P(D|M)$
  - Posterior Probability  $P(M|D)$
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- e.g.: try several topologies, (choose some branch lengths,) score the topologies, choose the one that has the best score

# Plan: Criteria for evaluating phylogenies

- Criteria for evaluating phylogenetic trees:
  - Parsimony
  - Distance methods
  - Maximum Likelihood
    - Using a Monte Carlo simulation
    - Using Felsenstein's pruning algorithm
  - Posterior probability (Bayesian approach)
- *Conventions:*
  - We're dealing with aligned sequence data
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# Parsimony

- “The principle that the most acceptable explanation of an occurrence, phenomenon, or event is the simplest, involving the fewest entities, assumptions, or changes. In phylogenetics, for example, the preferred tree showing evolutionary relationships between species, molecules, or other entities is the one that requires the least amount of evolutionary change, that is, maximum parsimony.”

## Maximum parsimony

- Has been advocated strongly by some against model-based approaches: many controversies (see “The Troubled Growth of Statistical Phylogenetics”, Felsenstein 2001)
- Edwards and Cavalli-Sforza (1963): the preferred evolutionary tree involves “the minimum net amount of evolution” = *Maximum parsimony tree*
- → For sequence data: find the phylogeny that involves the minimum number of substitutions
  - We need a way to count the minimum number of substitutions on a phylogeny = compute the **parsimony score** of a phylogenetic tree



How to compute the parsimony score?

***Alexis!***

---

# Conclusion on maximum parsimony

- Involves looking for the tree with the least amount of change
- Computing the parsimony score of a tree can be done with Fitch's algorithm
- Searching through topology space for the most parsimonious tree can be done with algorithms similar to those used for Maximum Likelihood reconstruction (see Alexis's talk)

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# Distance methods

- Distance-based approaches:
  - least squares methods,
  - Minimum evolution method,
  - Neighbor Joining.

# Minimum Evolution or least squares: distance methods

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*Sp1* ATGCGCT...

*Sp2* AGTCGCA...

*Sp3* AGGTGCA...

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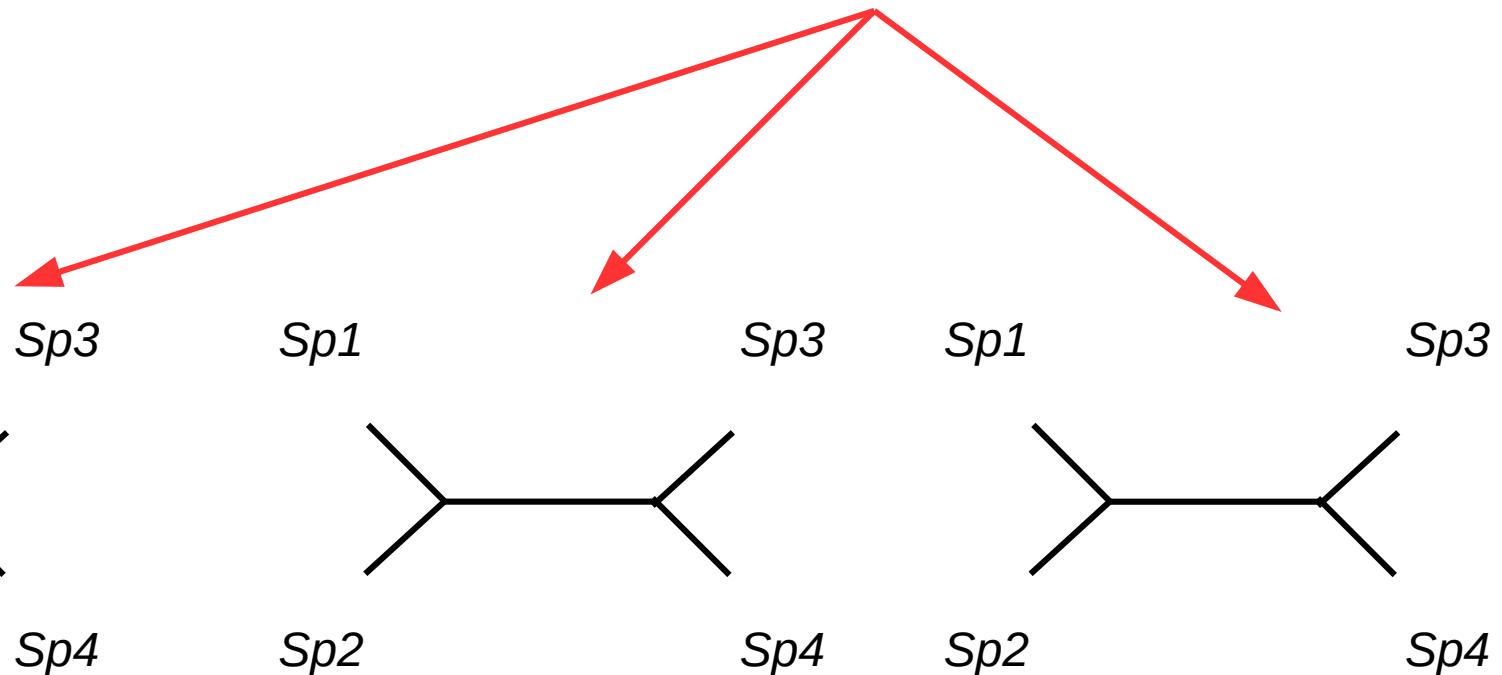
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Sp1

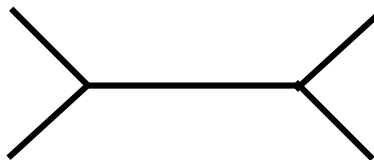
Sp3

Sp1

Sp3

Sp1

Sp3



Sp2

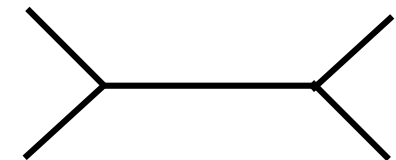
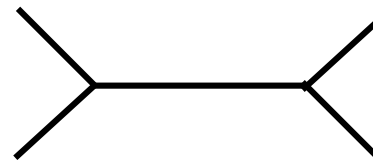
Sp4

Sp2

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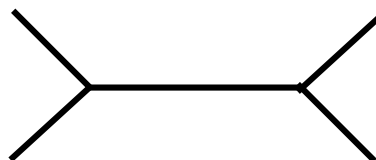
Sp3

Sp1

Sp3

Sp1

Sp3



Sp2

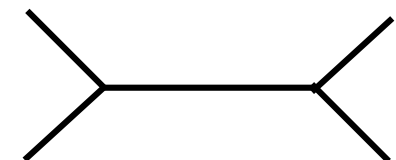
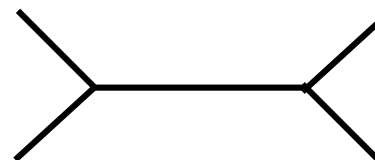
Sp4

Sp2

Sp4

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- Use a model of sequence evolution
  - $\rightarrow$  *cf. talk on models*
  - Advantages:
    - *Hidden substitutions are taken into account*
    - *Parameters of the model of substitution can be estimated in the Maximum Likelihood framework*

# Minimum Evolution or least squares: distance methods

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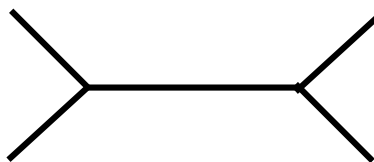
Sp3

Sp1

Sp3

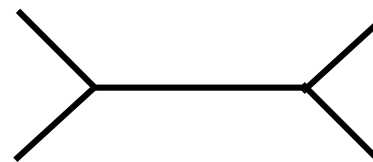
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Sp3



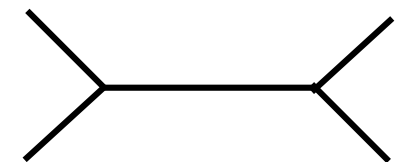
Sp2

Sp4



Sp2

Sp4

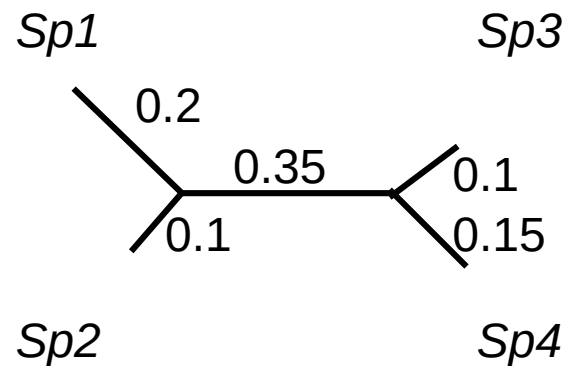


Sp2

Sp4

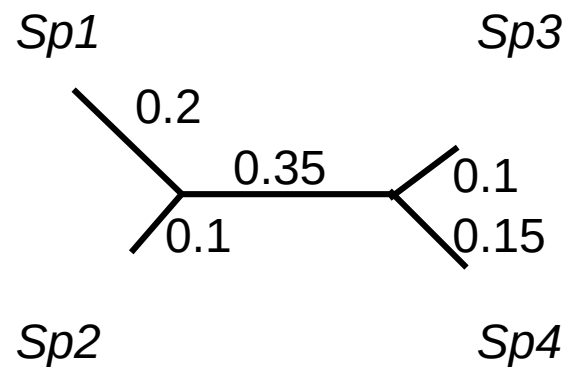
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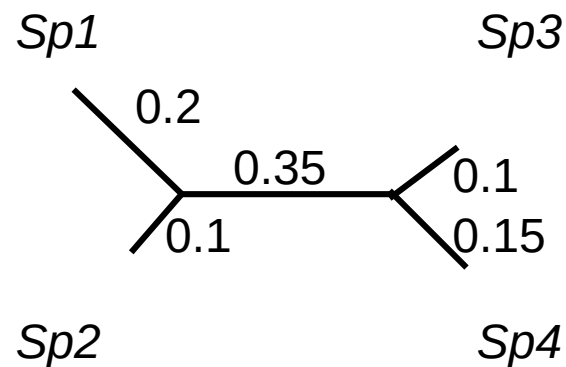


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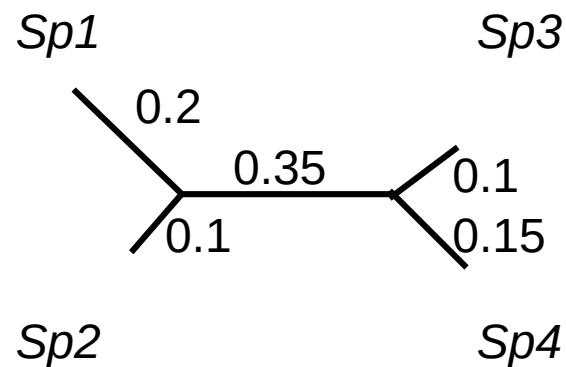
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$$\text{score}_{\text{ULS}} = (0-0)^2 + (0.3-0.1)^2 + (0.65-0.2)^2 + \dots$$

With ULS: Unweighted Least Squares  
(other criteria have been proposed)

# Computing the optimal distances on a given topology

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*But how can we pick branch lengths on the topology?*

ULS provides a mathematical way to find the optimal branch lengths on a given topology! This involves some simple matrix algebra (solving a set of linear equations).

# Searching for the best tree using Unweighted Least Squares

- We now know how to compute the ULS score of a tree topology. It involves:
  - Matrix algebra to find the best branch lengths
  - Computing the score<sub>ULS</sub> for that tree
- Given a set of tree topologies, we can compute the “best” tree topology according to the ULS criterion: it is the one with the lowest score<sub>ULS</sub>
- How to obtain a set of tree topologies to score is tackled later in the course (*see Alexis's talk*)

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- Motivation similar to parsimony
- **Hypothesis:** the true tree should be the shortest tree
- → Idea:
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  - Match pairwise distances onto each tree topology
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**ME: involves the patristic  
matrix, matrix algebra  
and summing branch  
lengths**

2

Sp1

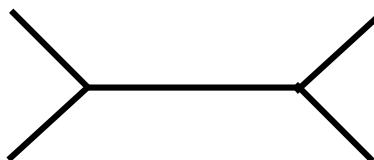
Sp3

Sp1

Sp3

Sp1

Sp3



Sp2

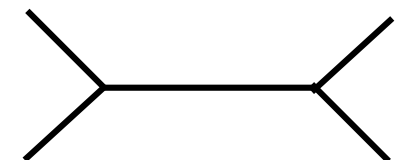
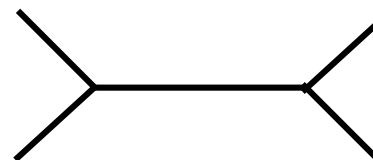
Sp4

Sp2

Sp4

Sp2

Sp4



# Minimum evolution criterion

- To obtain a Minimum Evolution tree, at some point we have to use Least Squares estimation to assign branch lengths to a tree topology
  - hybrid approach where two different criteria are mixed up
- However, Minimum evolution works pretty well in practice
- Neighbor-Joining (Saitou and Nei, 1987) is a famous heuristic algorithm for finding the Minimum Evolution tree (not seen in our course, but has been very widely used); see Gascuel and Steel, 2006 for a clear explanation

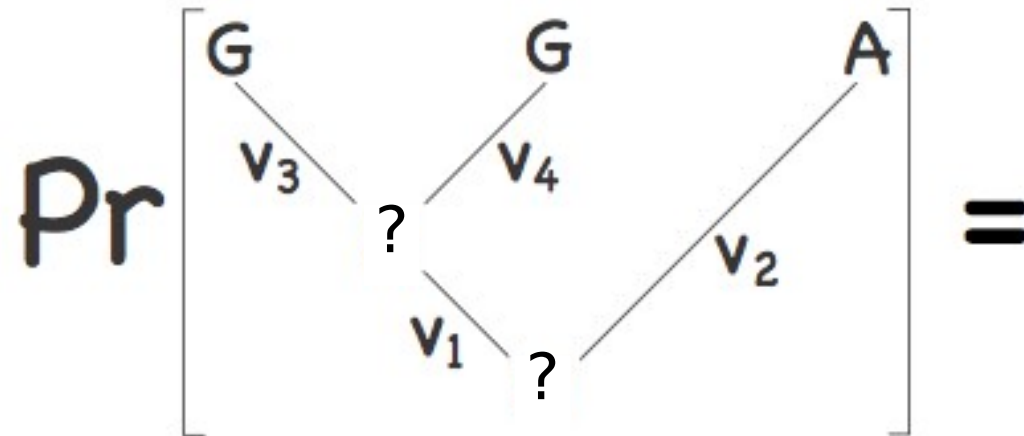
# Summary on distance methods

- Distance methods are the fastest phylogenetic methods available, notably thanks to Neighbor Joining and other algorithms to build a tree given a distance matrix (e.g. BioNJ, Weighbor, FastME...)
- Can be based on models of sequence evolution to compute pairwise distances
- Better than Maximum Parsimony when sequences are divergent, but less accurate than Maximum Likelihood or Bayesian Inference
- The main reason is that distance methods do not use the entire data matrix together, but look at it pair of sequences by pair of sequences

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# An Introduction to the Likelihood Function



$$\pi_i \times p_{ij}(v_1) \times p_{iA}(v_2) \times p_{jG}(v_3) \times p_{jG}(v_4)$$

$\pi_i$  Stationary frequencies

$p_{ij}(v)$  Transition probabilities

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**A model that has a high likelihood score on a data set is a model that has a high probability of simulating this data set.**

substitution-model parameters

The likelihood is a score that measures the fit of the model to the data, providing a basis for comparing different hypotheses/parameter values on the same data

# An Introduction to the Likelihood Function

OK, so what does likelihood *really* mean?

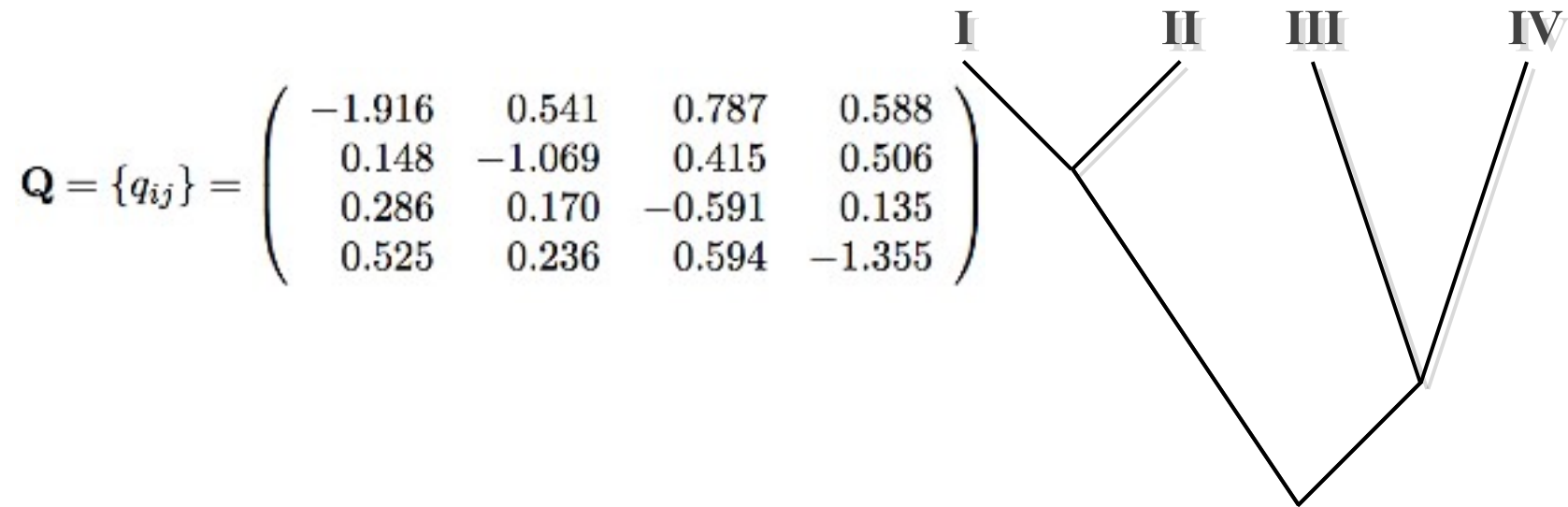
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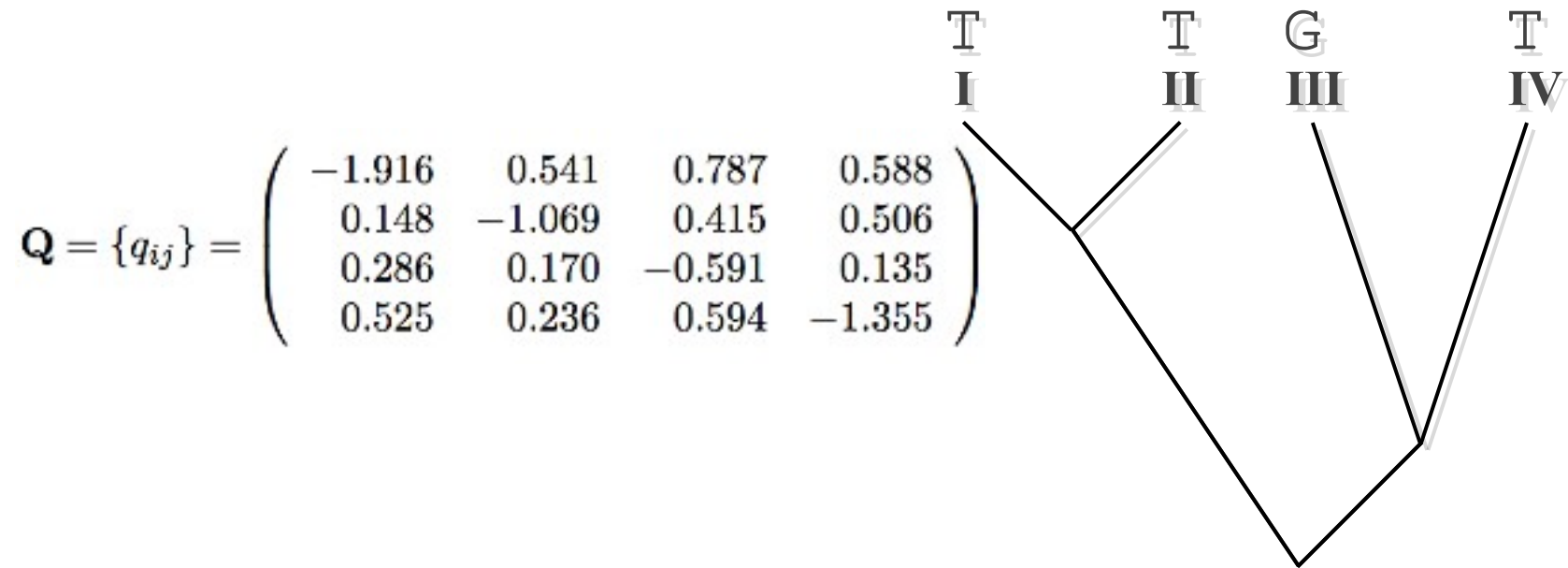
Imagine we have a fully specified phylogenetic model for four species:



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The four species have the following observed site pattern: TTGT

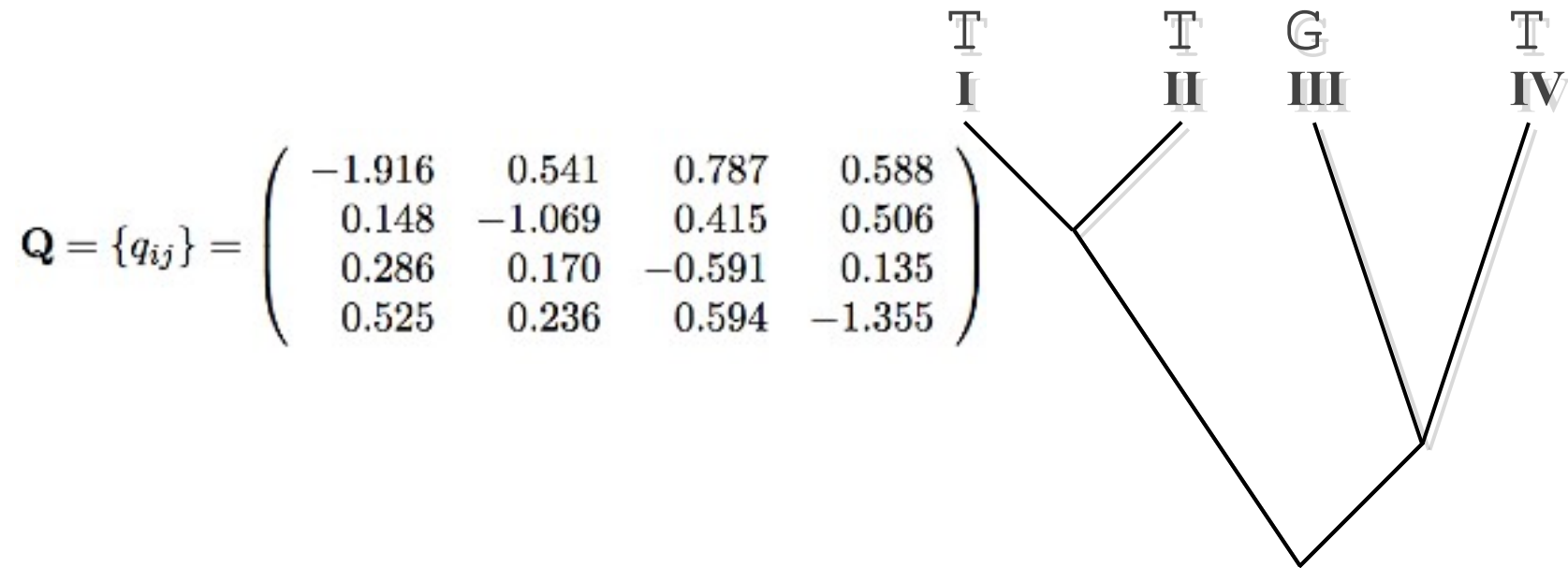


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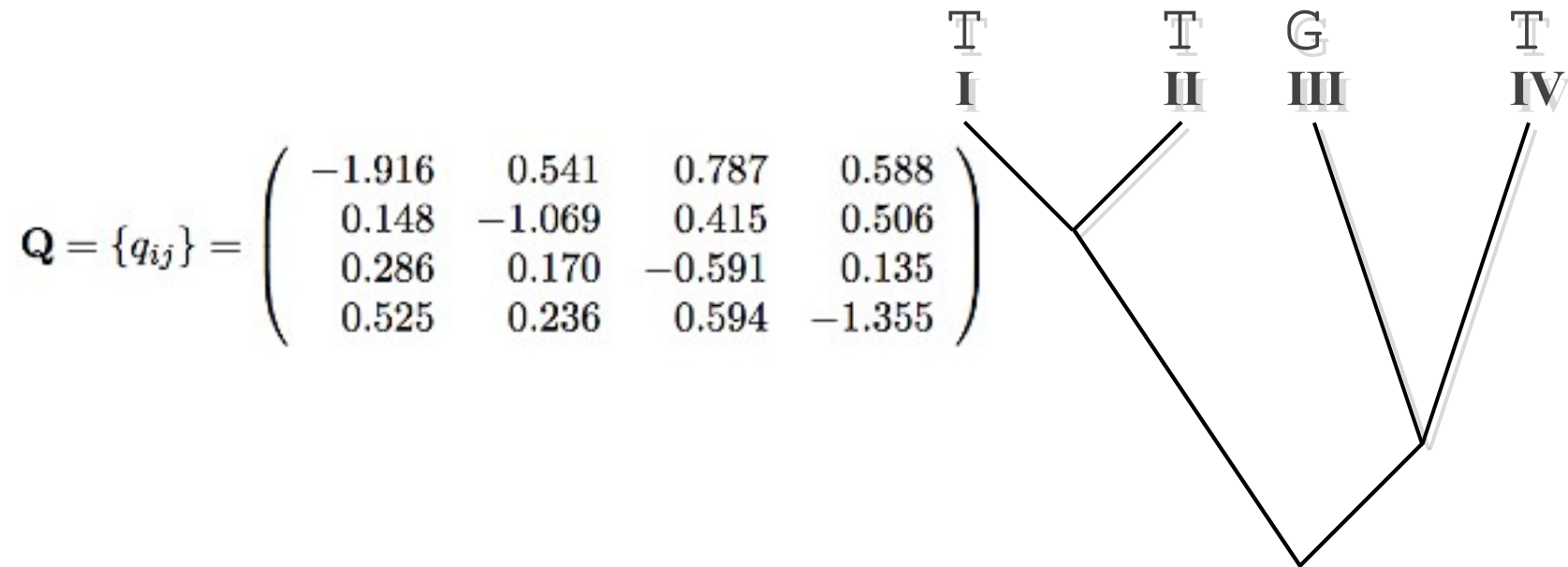


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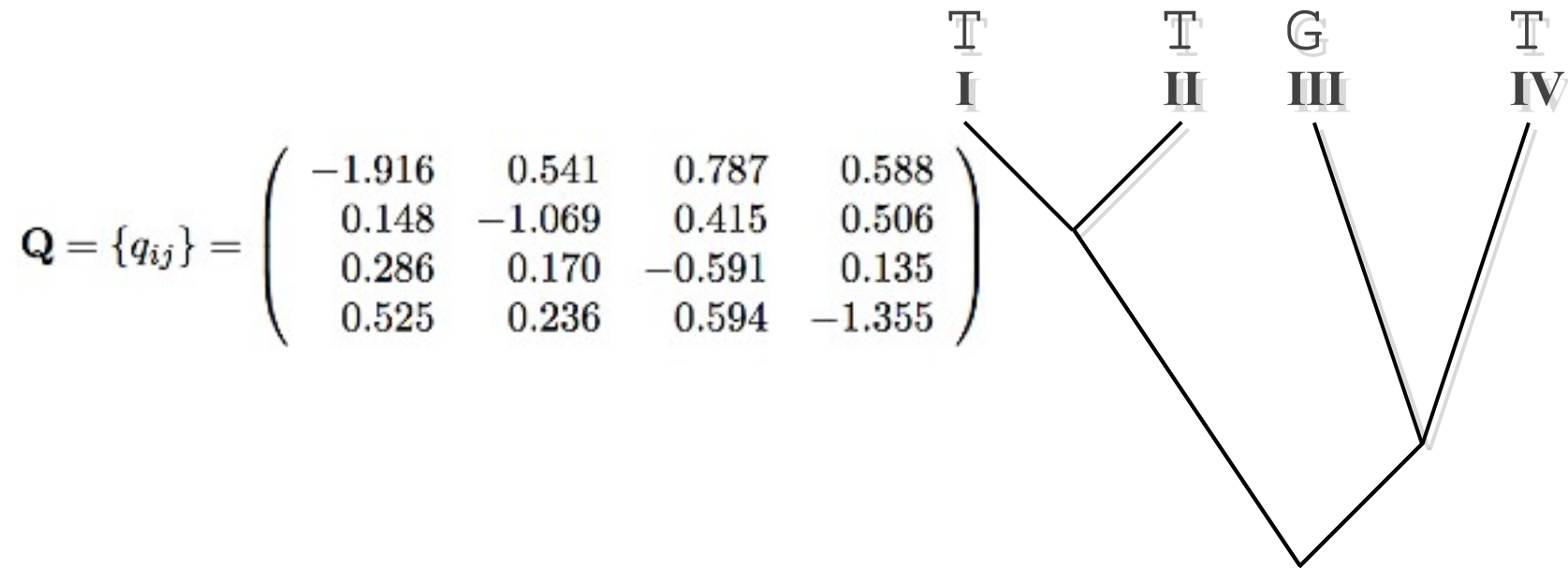
$$\mathbf{P}(100.0) = \begin{pmatrix} 0.138 & 0.188 & 0.495 & 0.179 \\ 0.138 & 0.188 & 0.495 & 0.179 \\ 0.138 & 0.188 & 0.495 & 0.179 \\ 0.138 & 0.188 & 0.495 & 0.179 \end{pmatrix}$$

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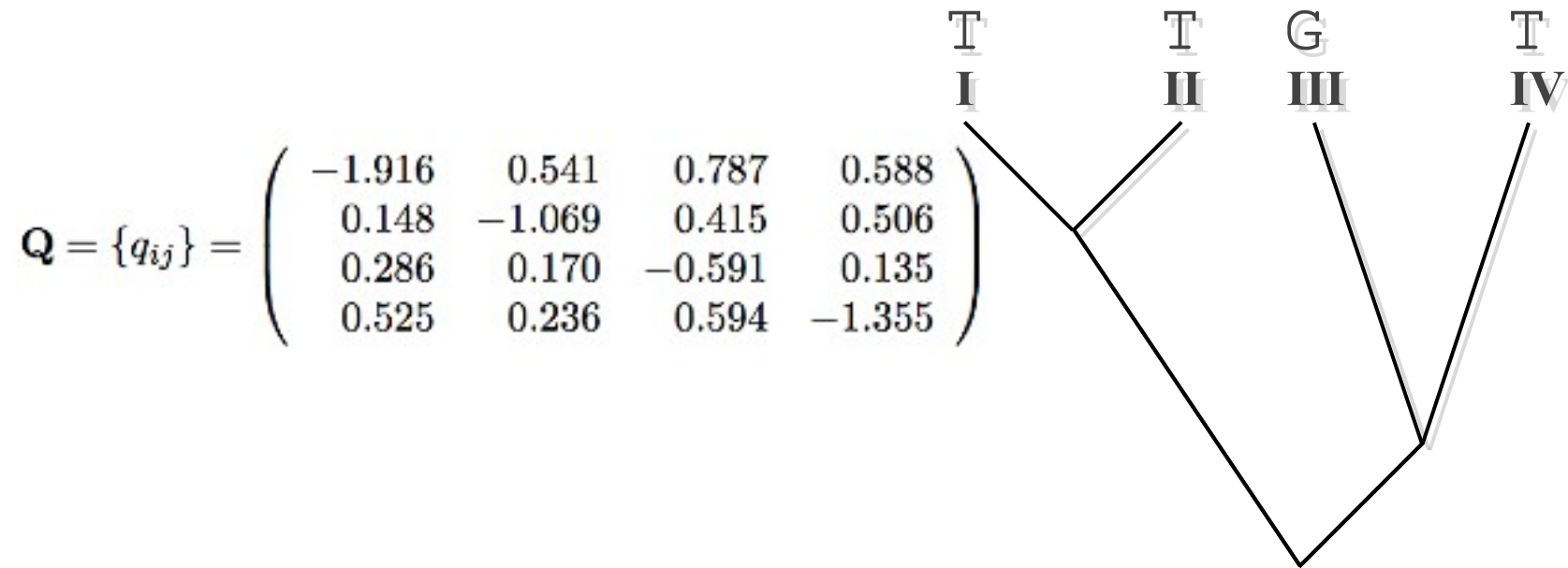
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$$\begin{array}{lll}
 A = 0.138 & 0 - 0.138 & = A \\
 C = 0.188 & 0.138 - 0.326 & = C \\
 G = 0.495 & 0.326 - 0.821 & = G \\
 T = 0.179 & 0.821 - 1 & = T
 \end{array}$$

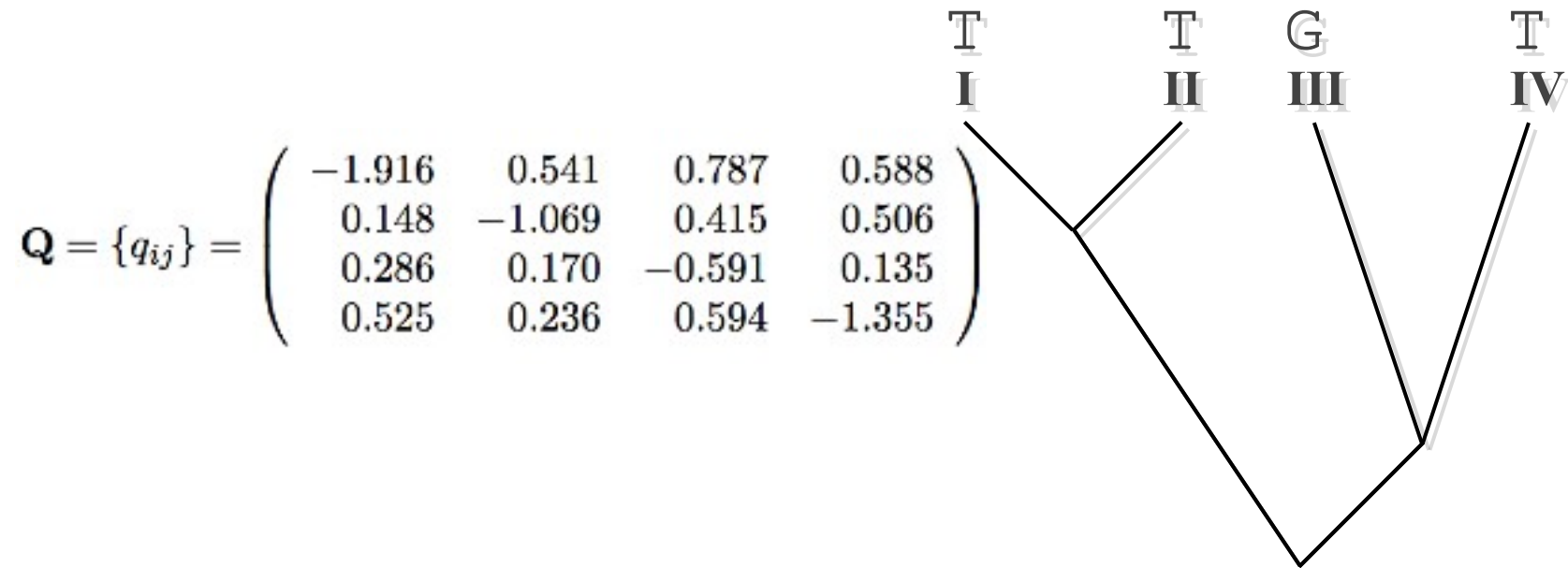


# An Introduction to the Likelihood Function

OK, so what does likelihood *really* mean?

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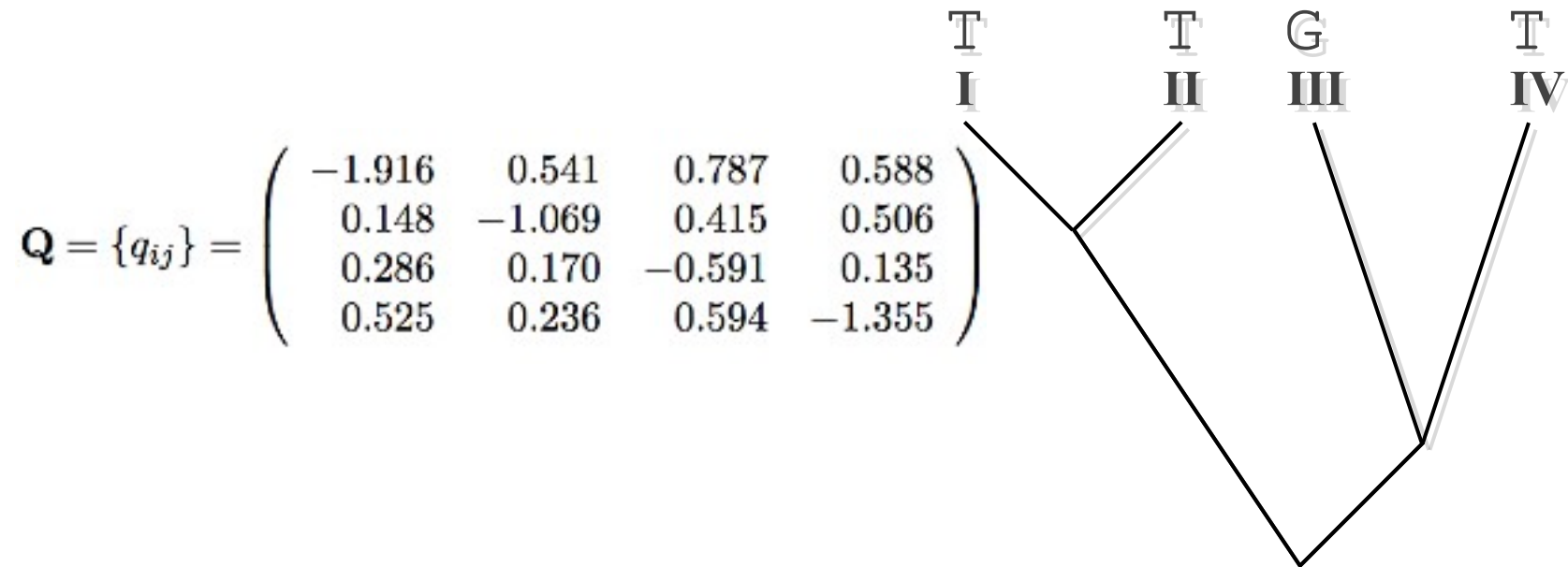
Pick a starting state at the root using `x~dnUniform(0,1)`

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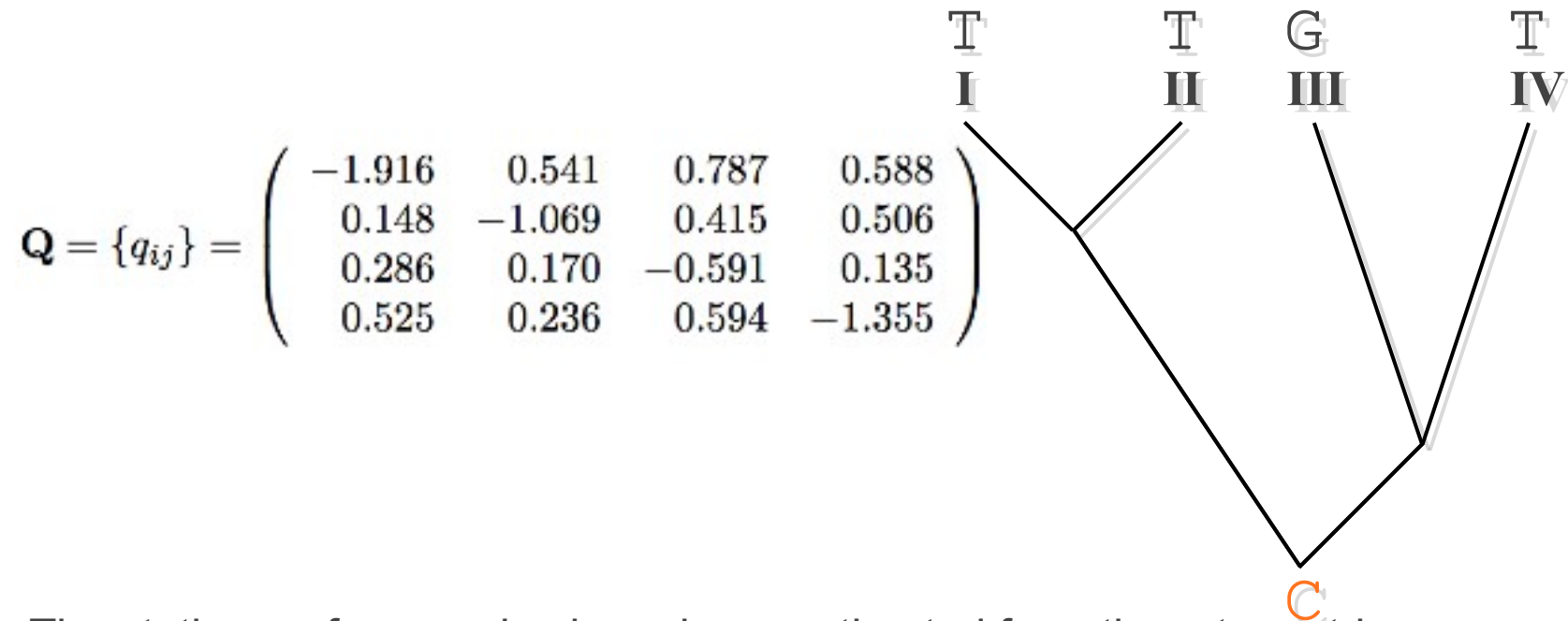
$x = 0.246$

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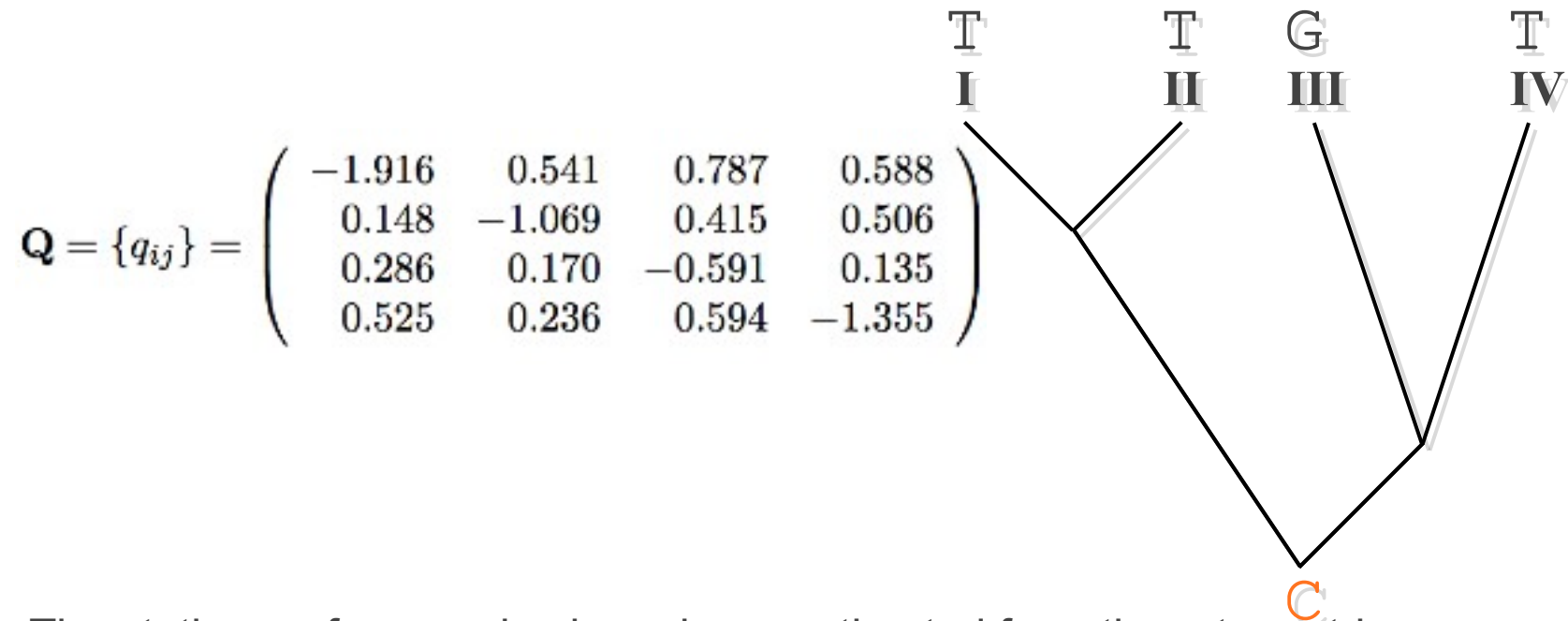
We randomly selected state C

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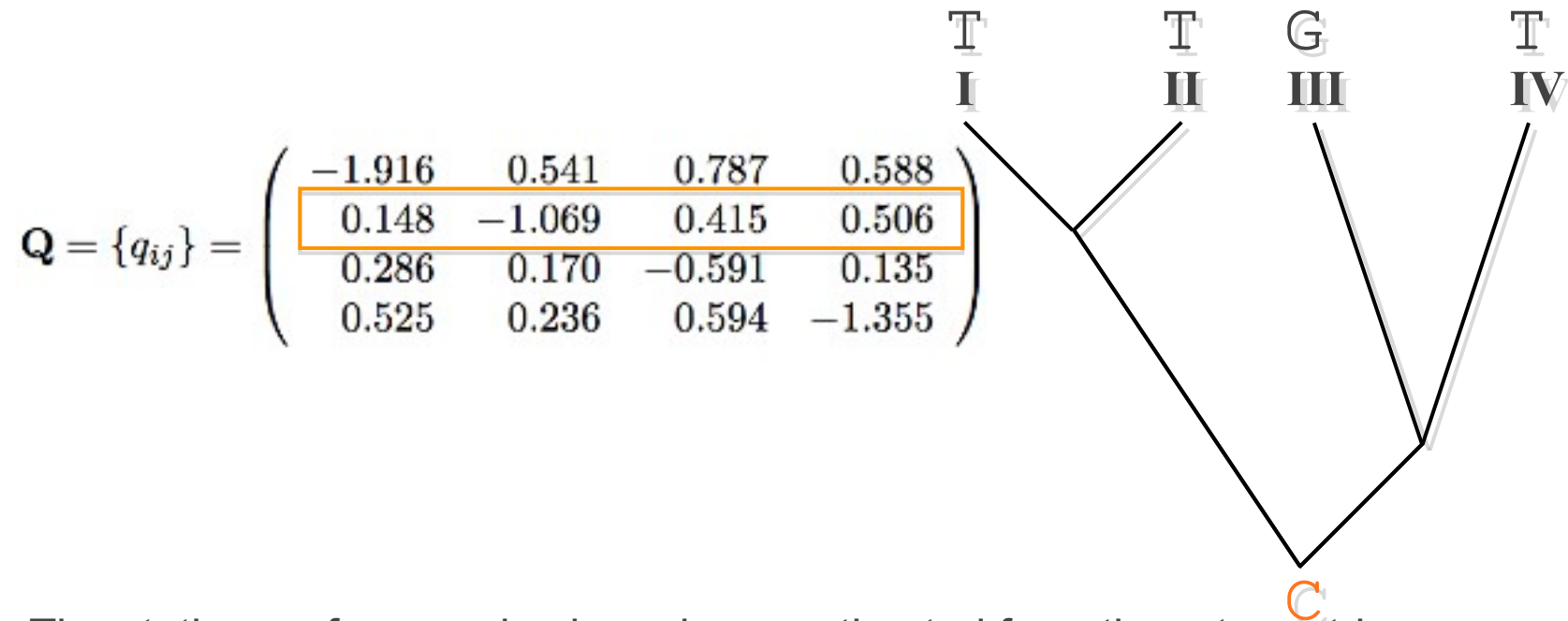
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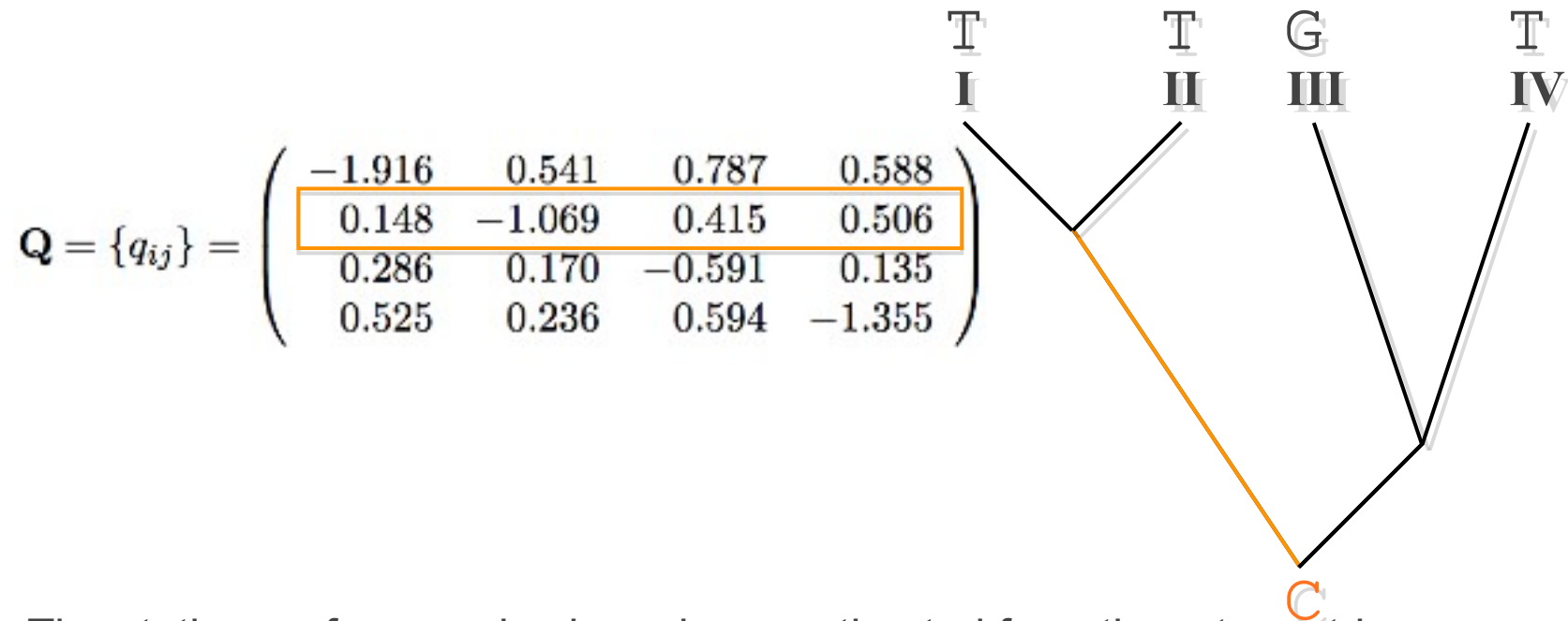
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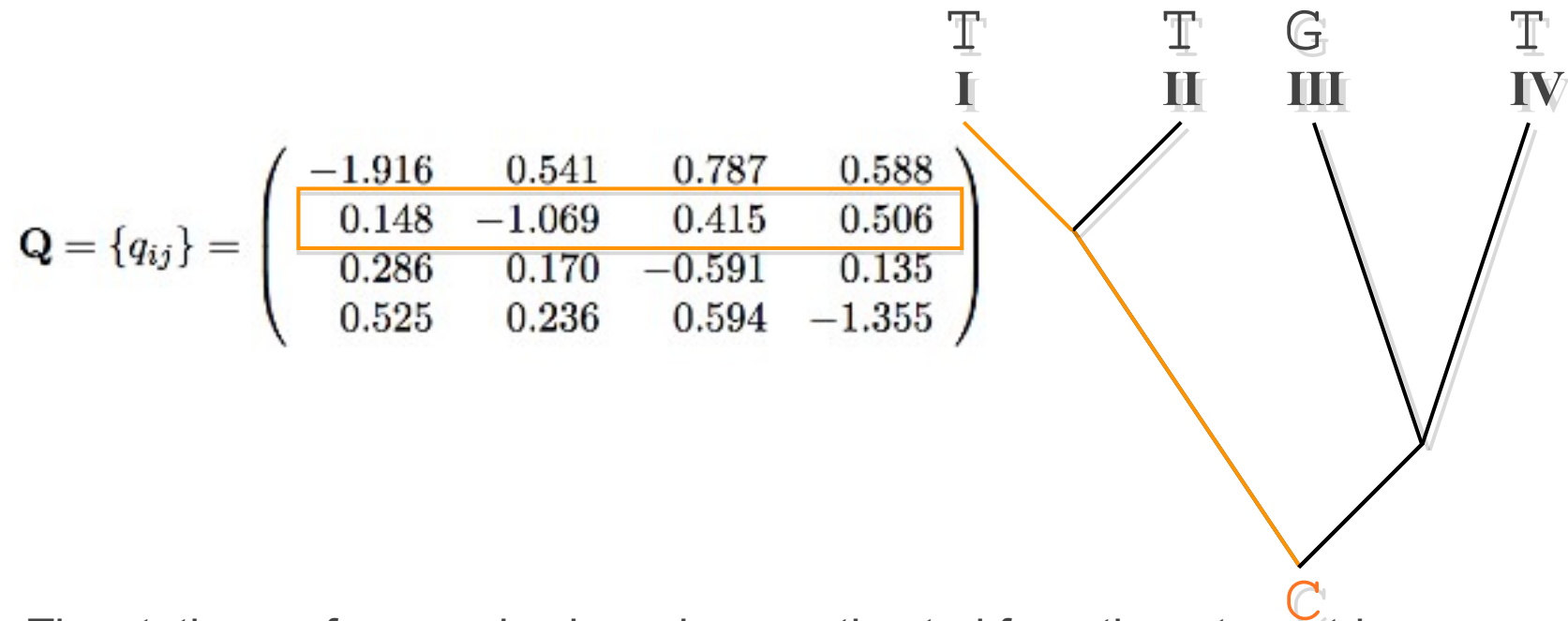
`u ~ dnExponential(1.069)`

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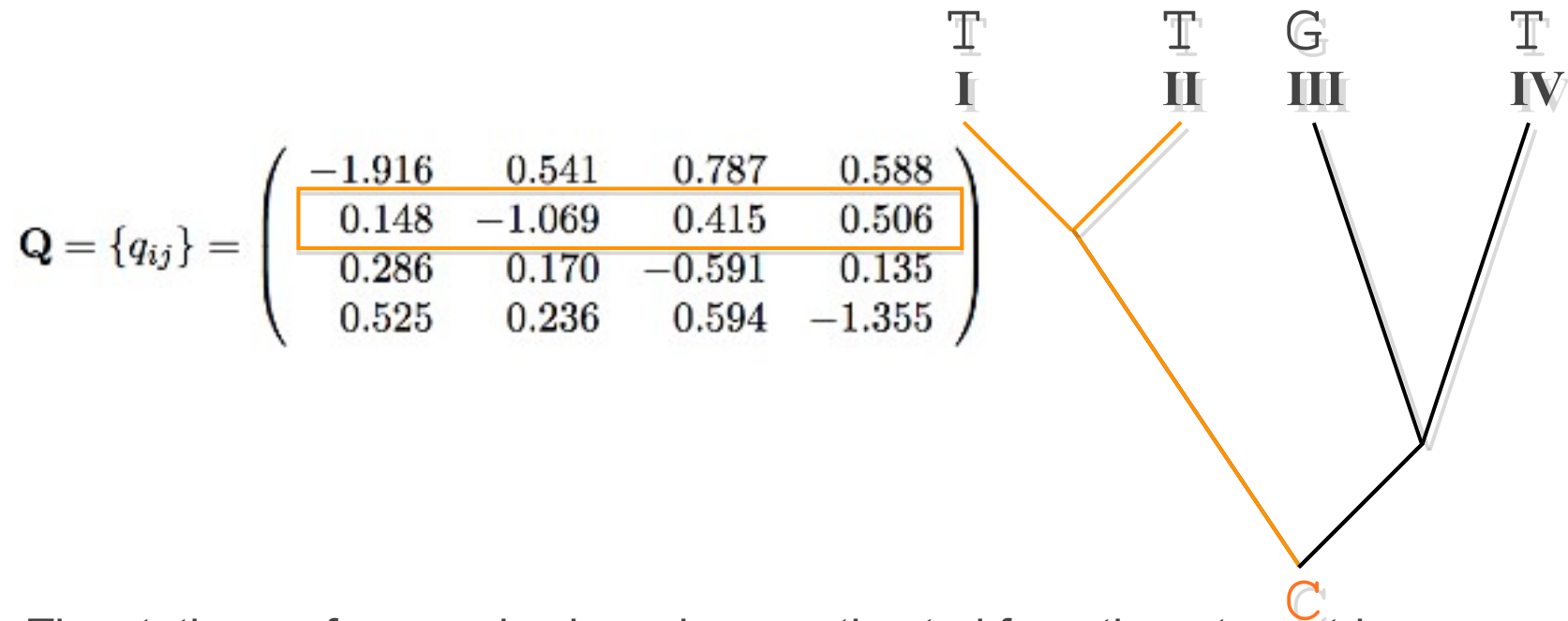
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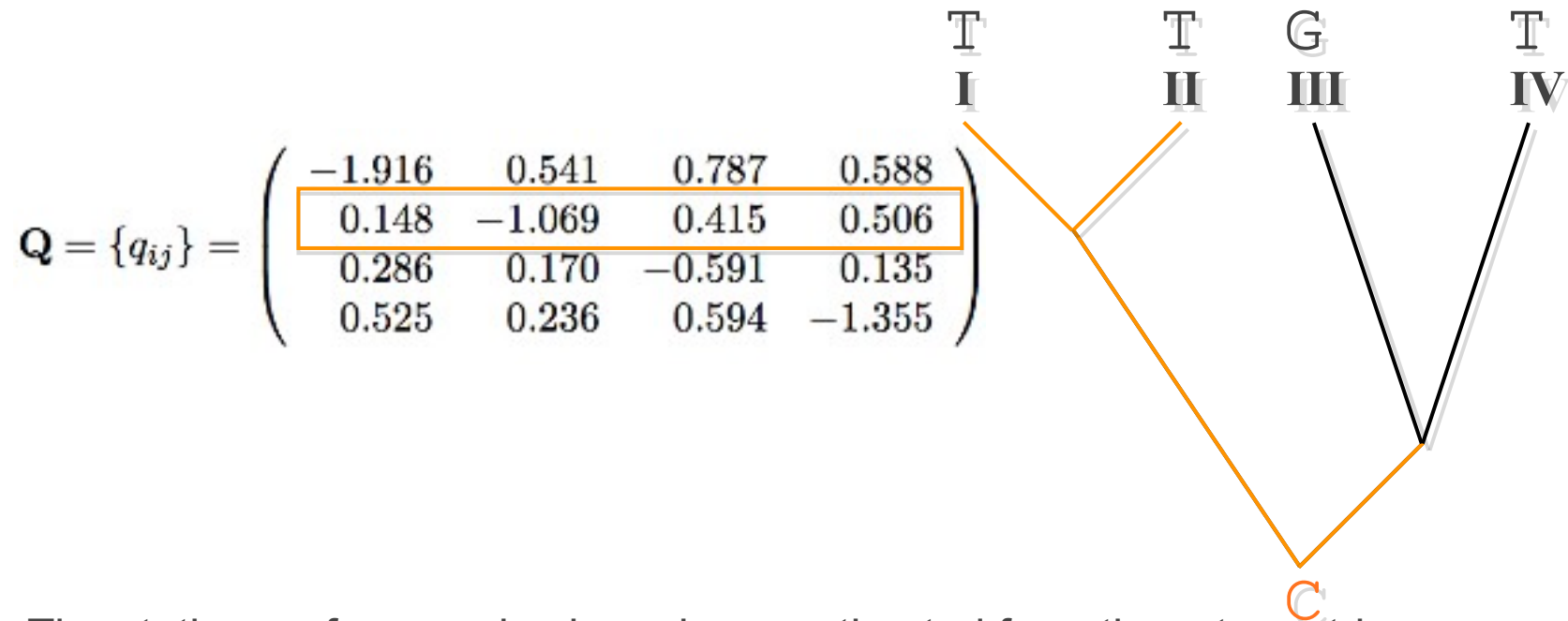


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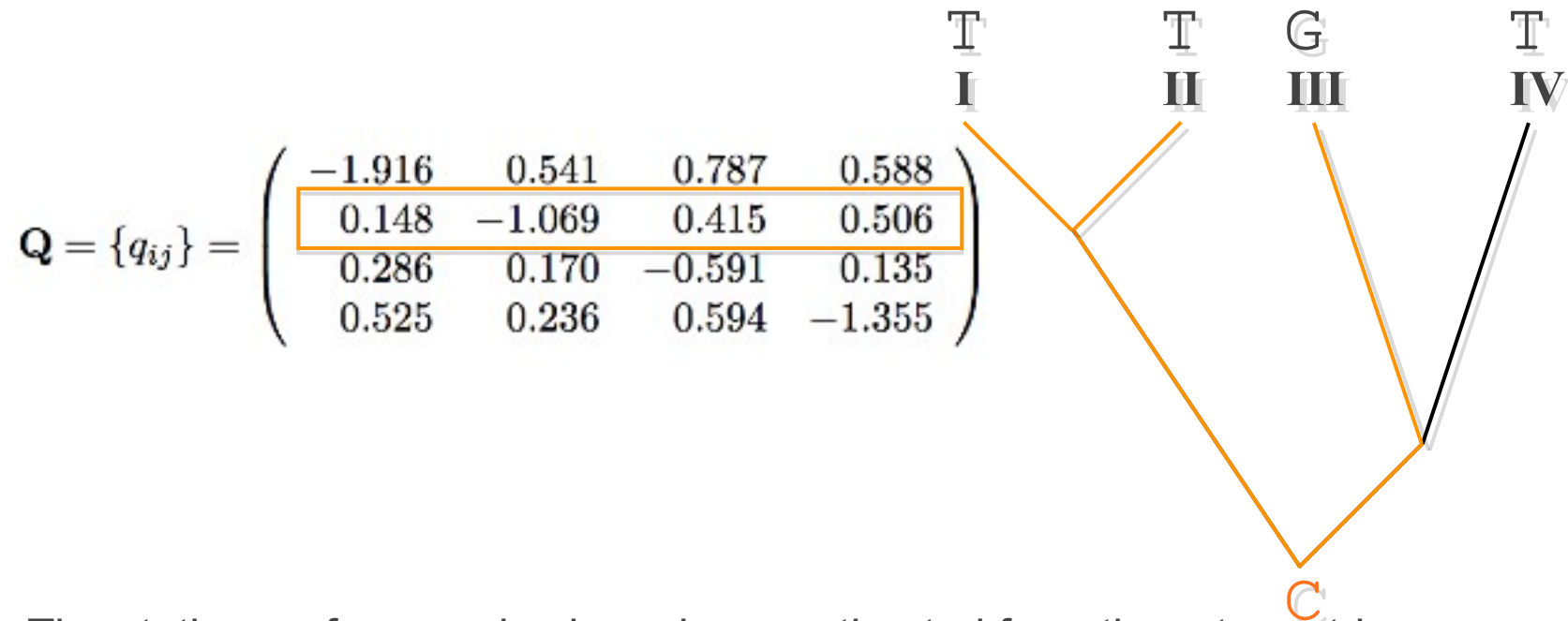
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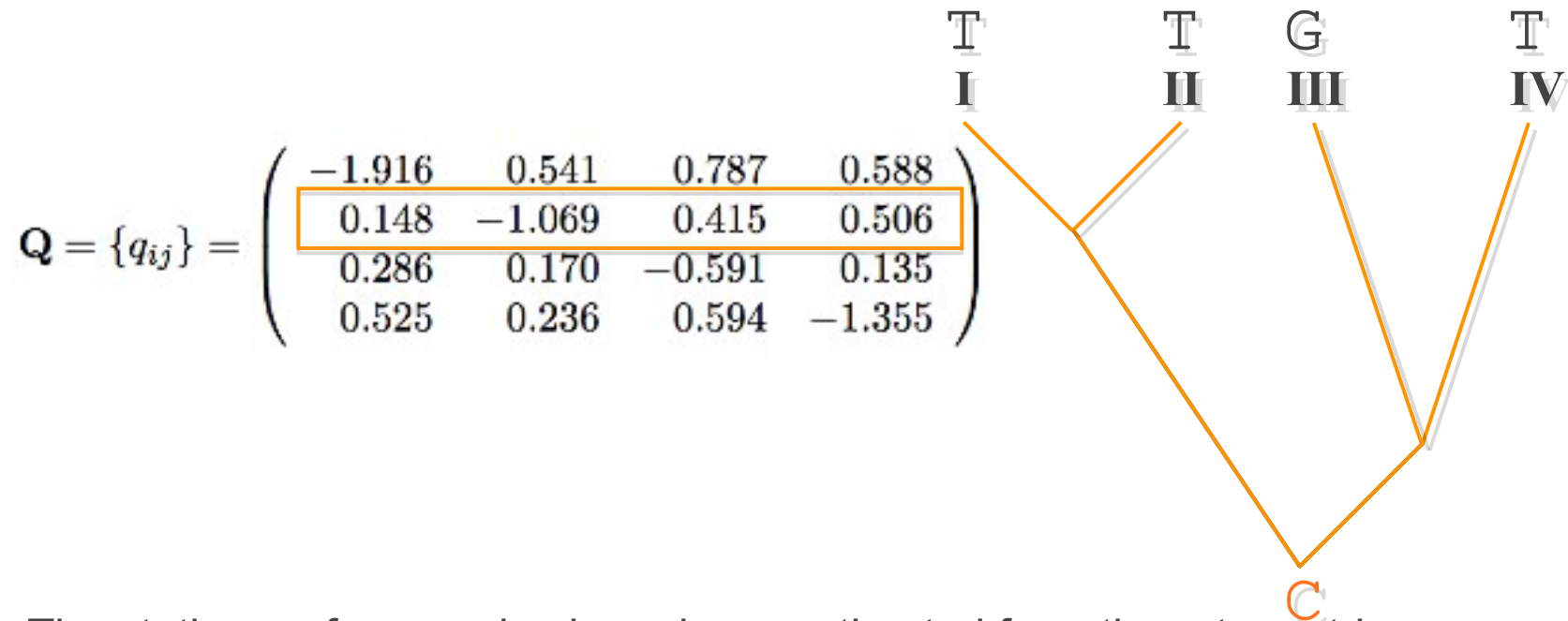
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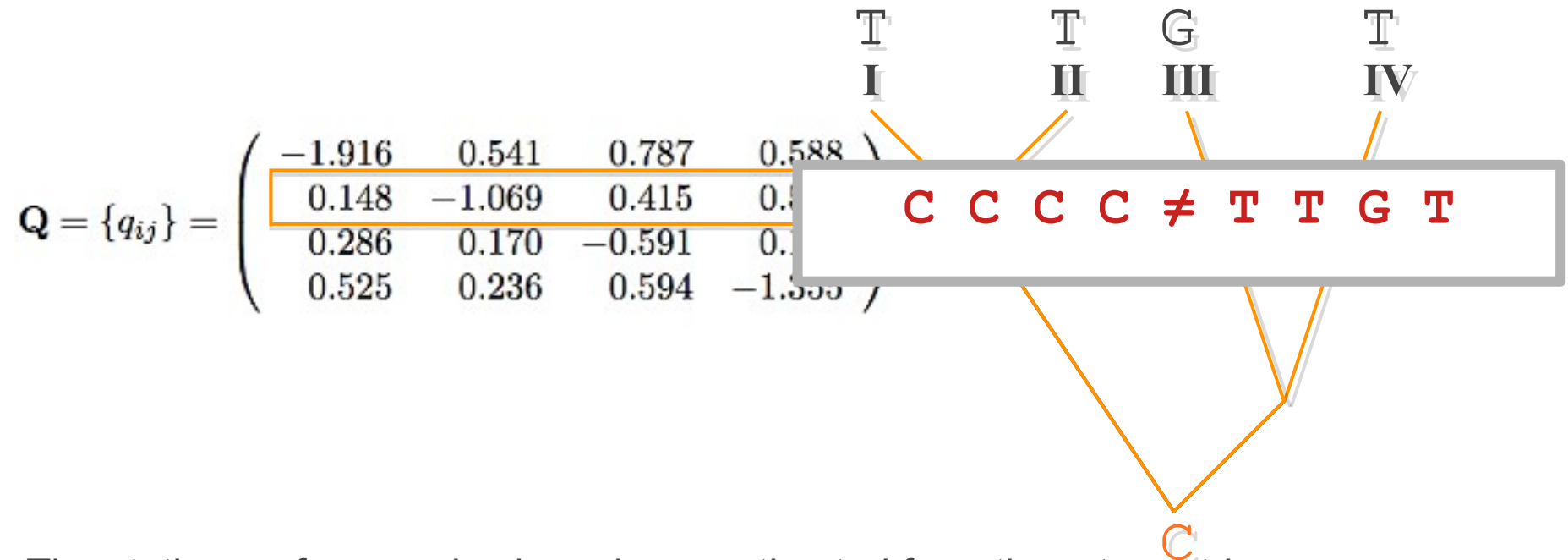
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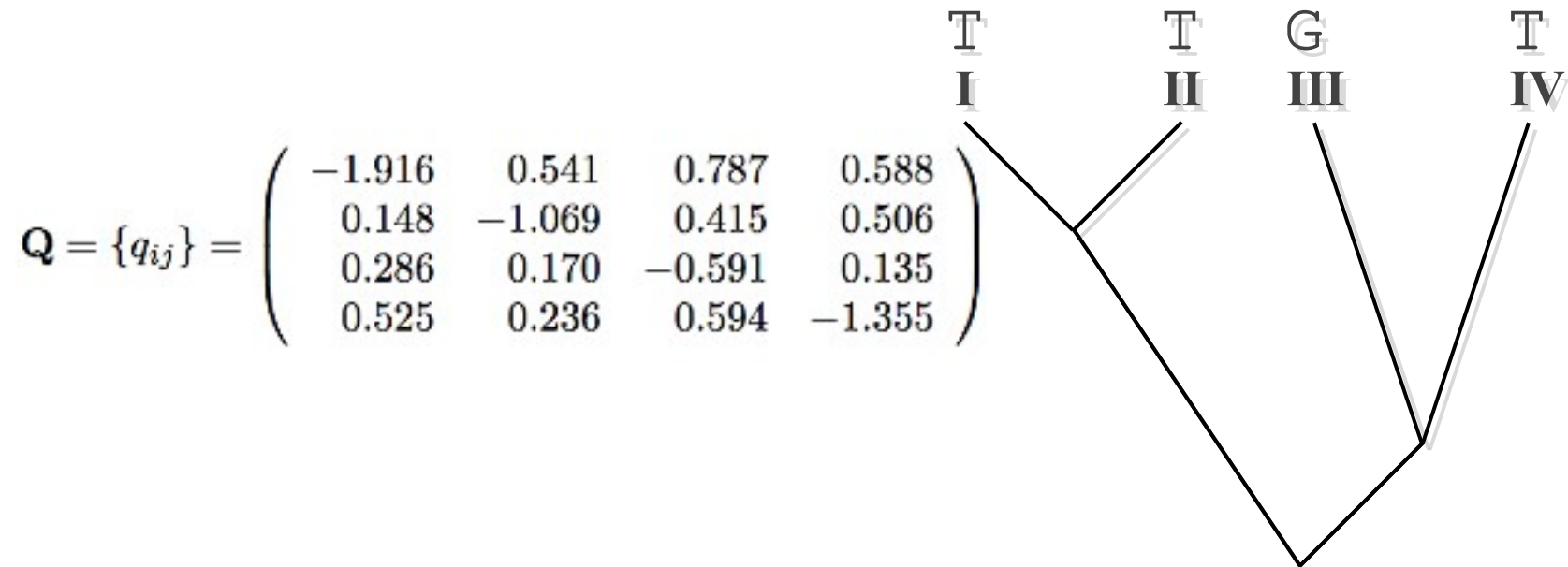
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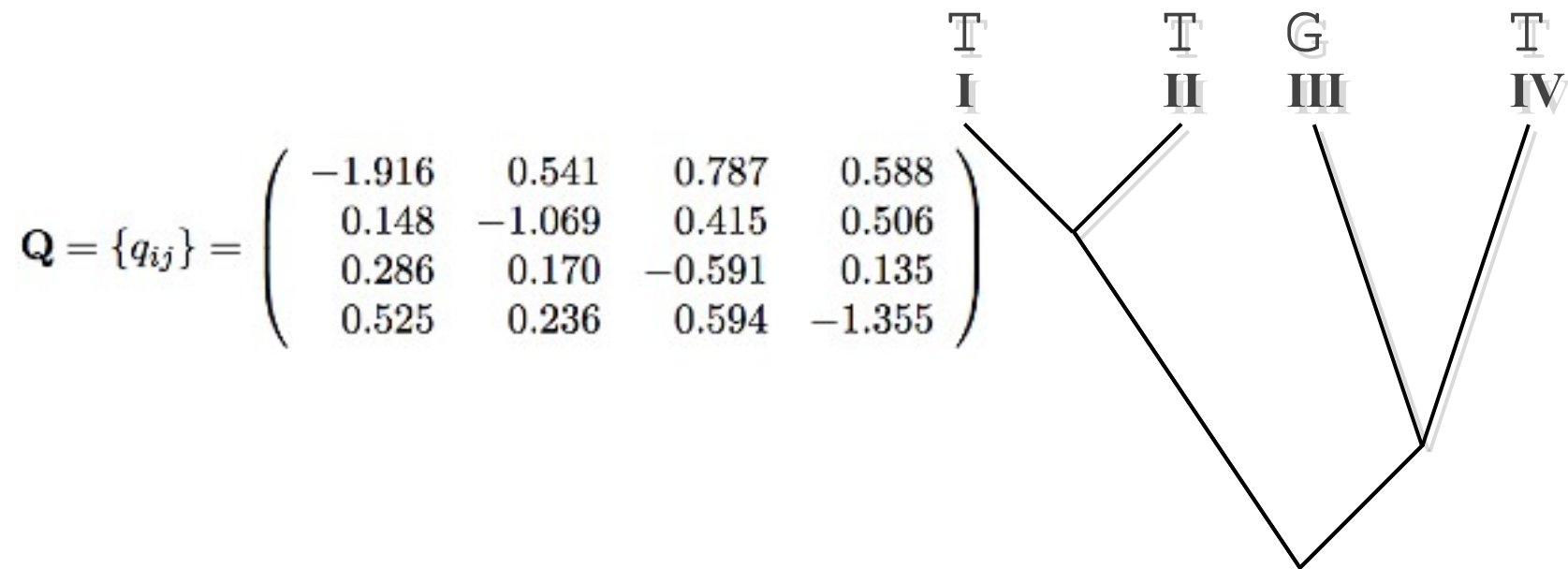
We repeat the simulation 100,000,000 times and record the frequency of outcomes that match the observed tip states.

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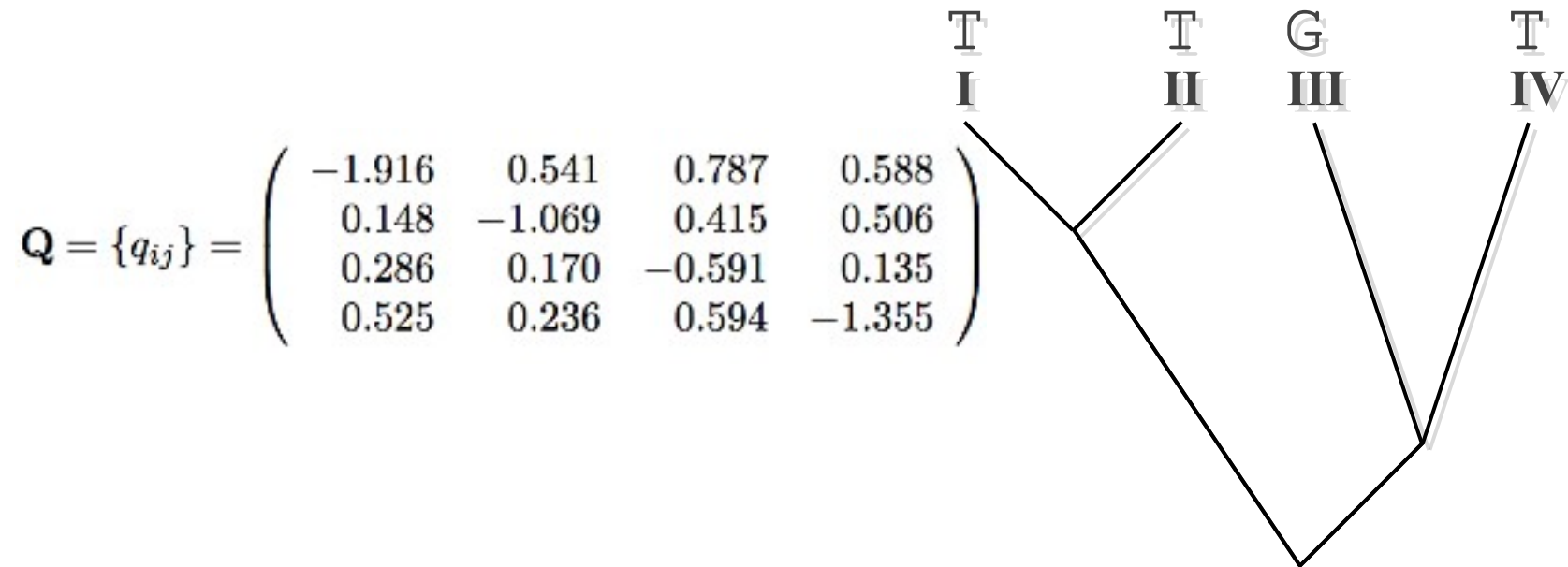
The observed site pattern, TTGT, is one of  $4^4 = 256$  possible site patterns.

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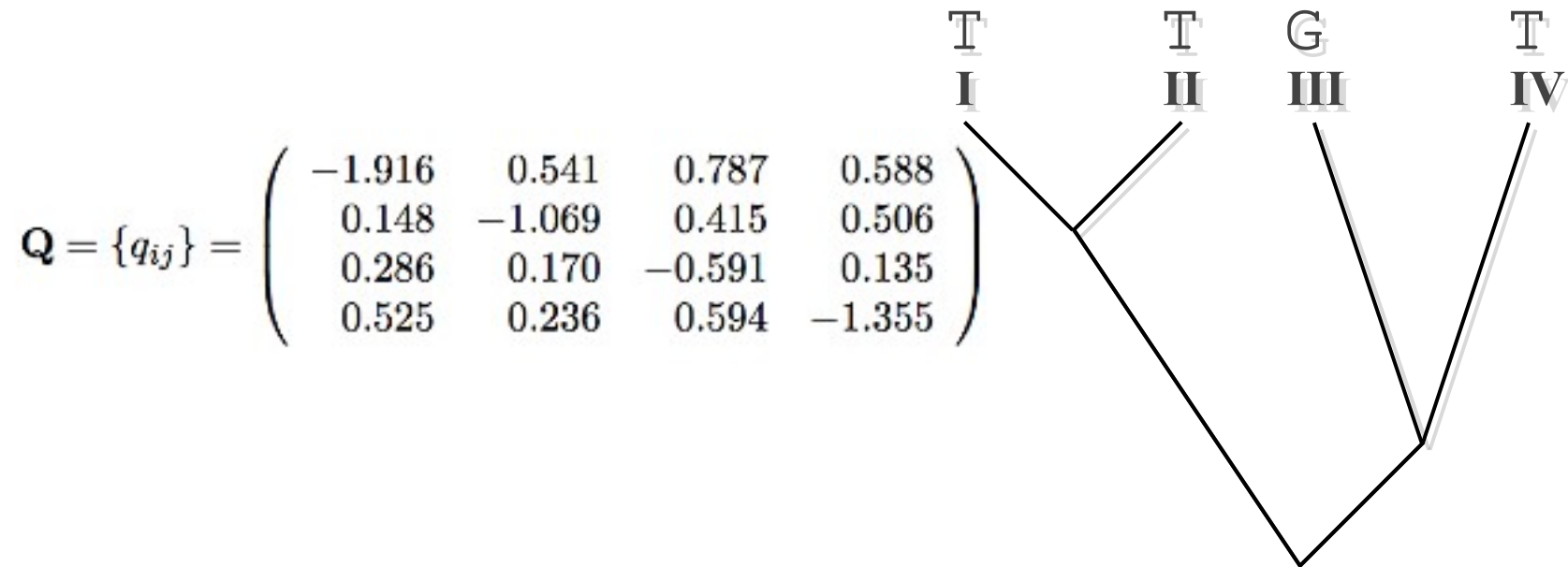
Of the 100,000,000 simulations, 850,358 realize the observed data (TTGT); the estimated probability of the observed data is therefore 0.00850358.

# An Introduction to the Likelihood Function

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Of the 100,000,000 simulations, 850,358 realize the observed data (TTGT);  
the estimated probability of the observed data is therefore 0.00850358.

The probability includes **all of the possible histories** that can give rise to the data.

Pattern	Number of Changes							
	0	1	2	3	4	5	6	7
TTGT	0.000000	0.881408	0.075358	0.037817	0.004725	0.000622	0.000062	0.000007

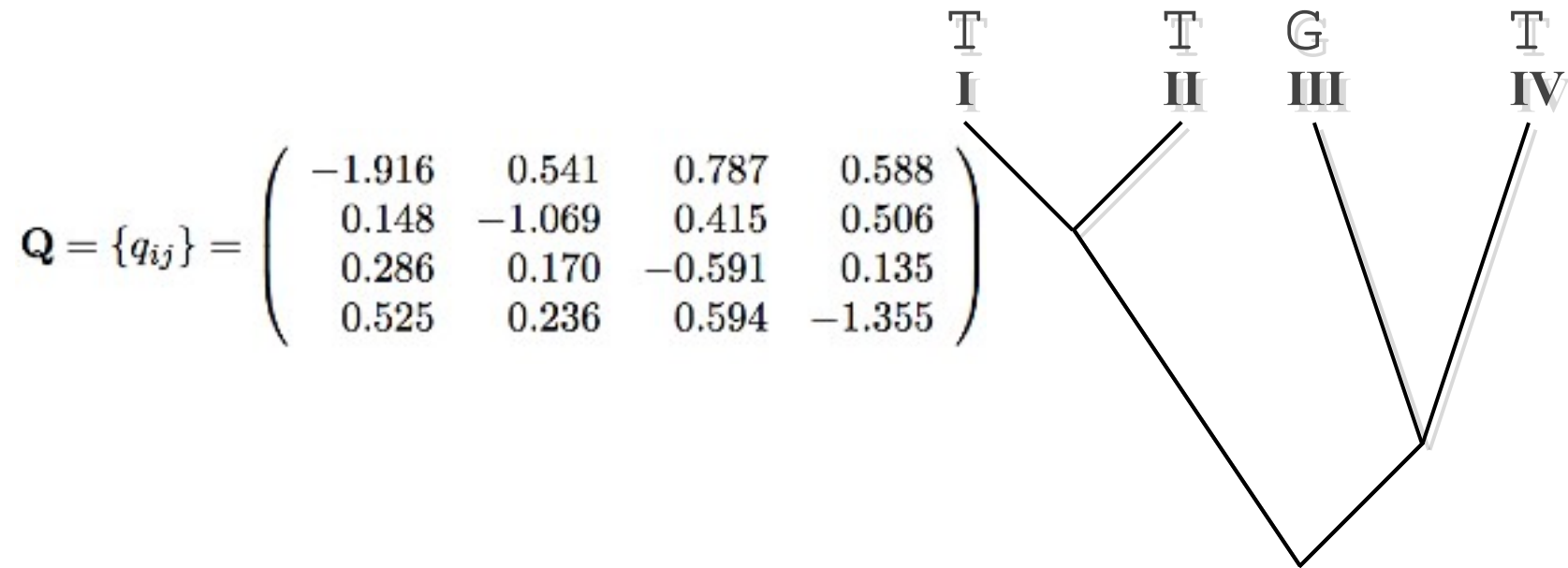


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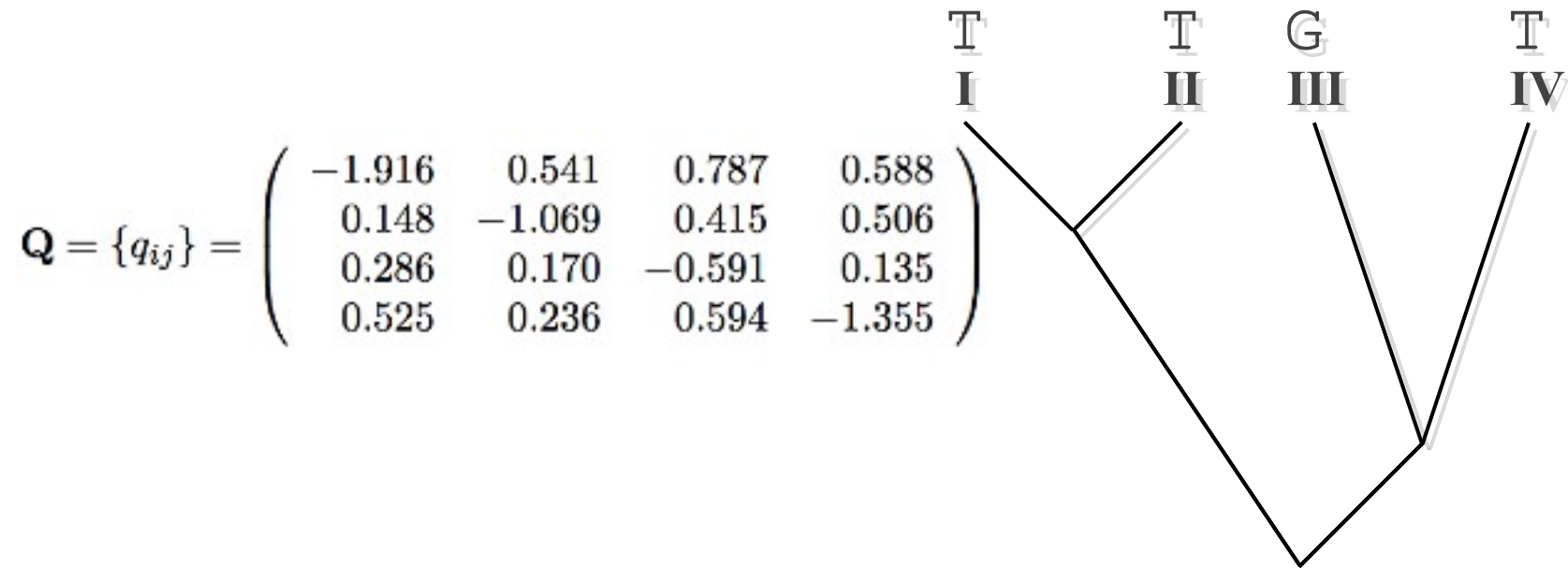
Using Monte Carlo simulation to estimate site likelihood is pedagogical, but too inefficient for the analysis of real data.

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Using Monte Carlo simulation to estimate site likelihood is pedagogical, but too inefficient for the analysis of real data.

*e.g.*, there are >1,000,000 possible site patterns for a tree with 10 species.

# Plan: Criteria for evaluating phylogenies

- Criteria for evaluating phylogenetic trees:
  - Parsimony
  - Distance methods
  - Maximum Likelihood
    - Using a Monte Carlo simulation
    - Using Felsenstein's pruning algorithm
  - Posterior probability (Bayesian approach)
- *Conventions:*
  - We're dealing with aligned sequence data
  - gaps are not taken into account

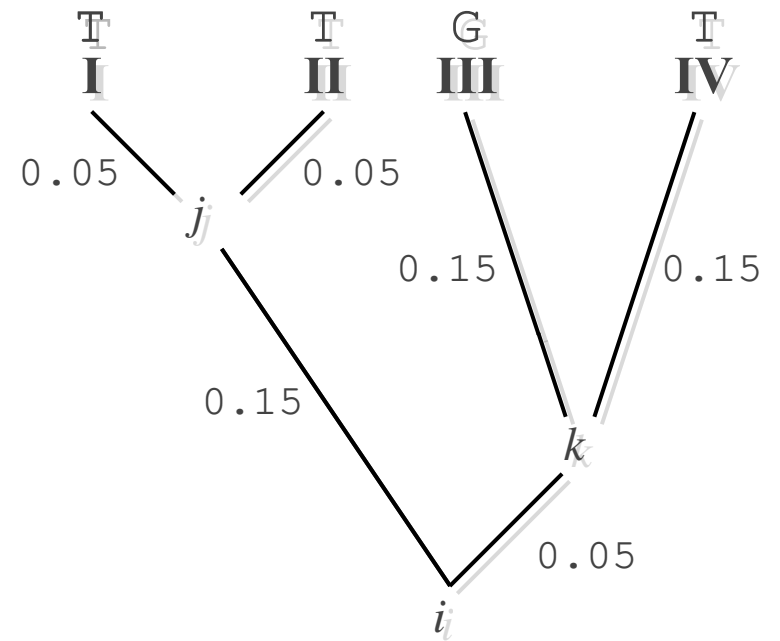
# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

Make the math mirror the tree to avoid redundant calculations.

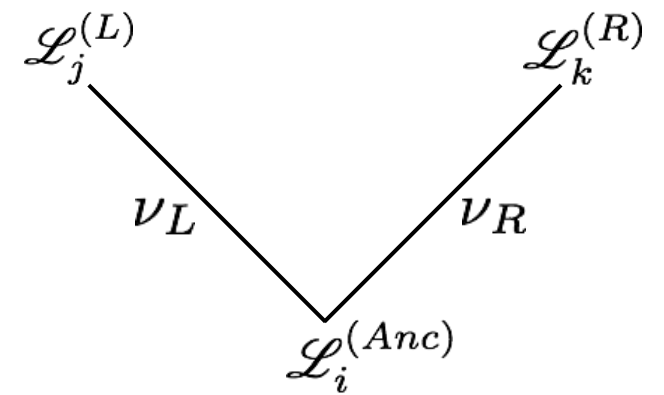
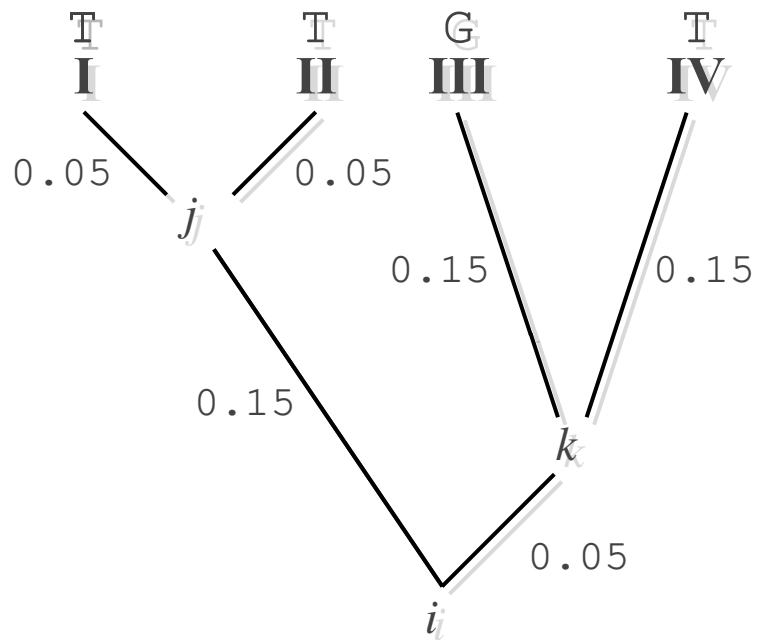


Joe Felsenstein (c.1981)



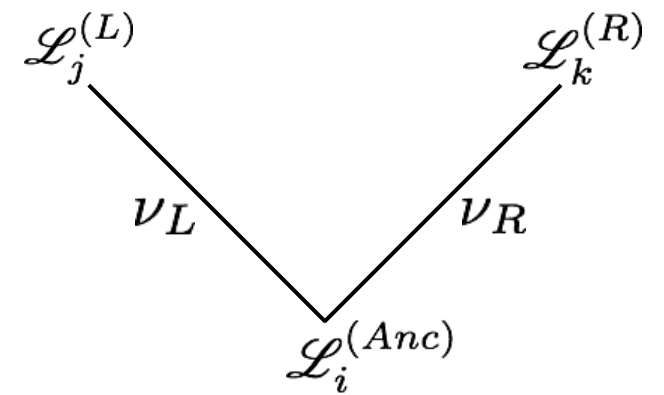
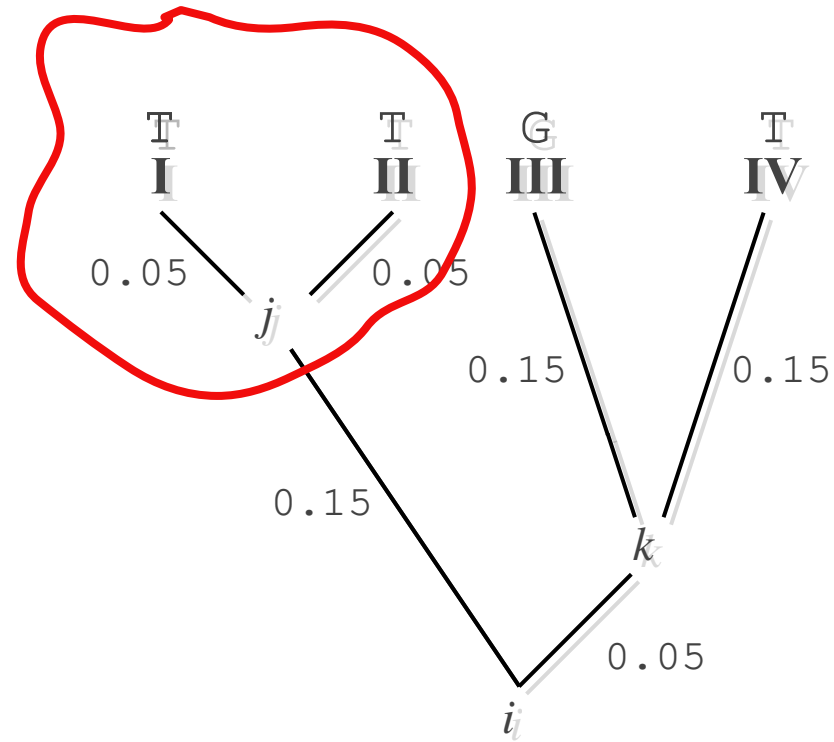
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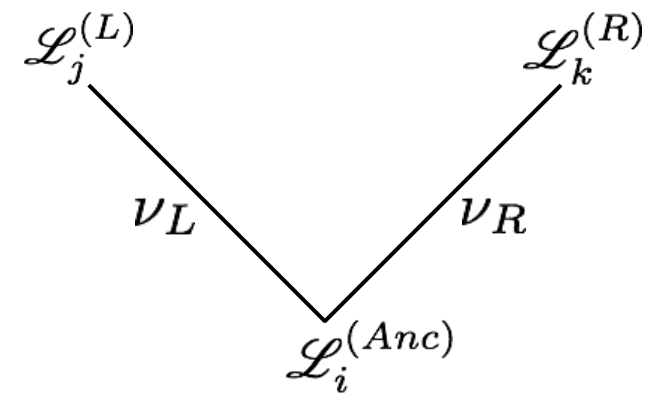
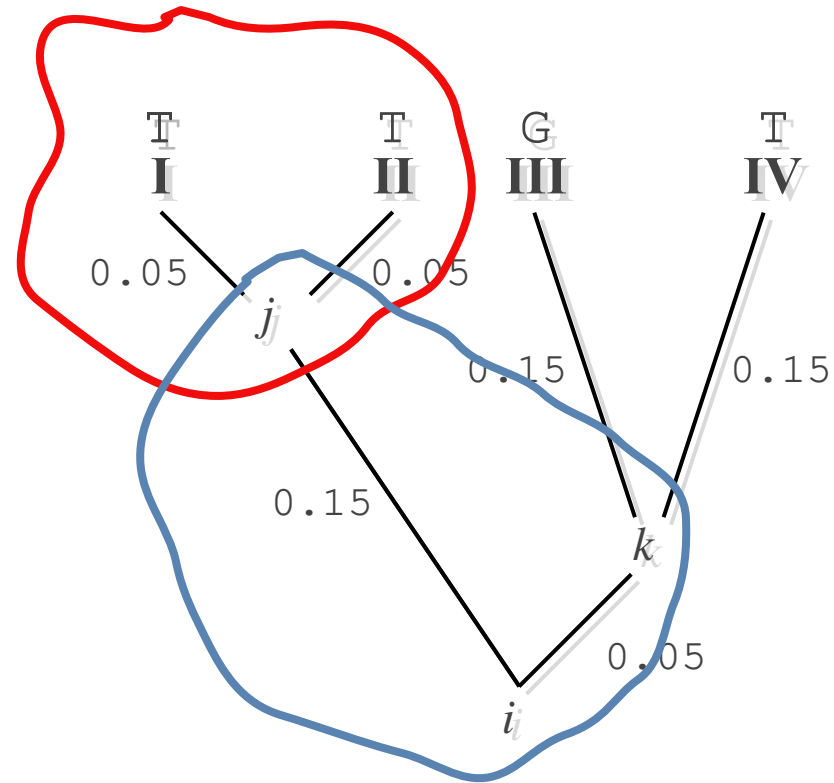
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# How Do We Calculate Site Likelihoods?

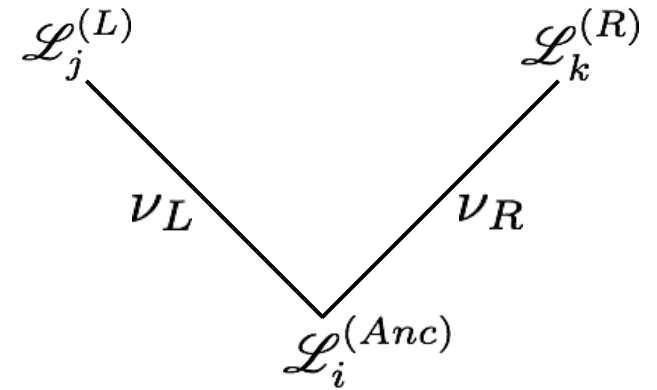
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# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

Evaluating the likelihood of a site involves the recursive calculation of *conditional likelihoods* from the tips of the tree to the root.



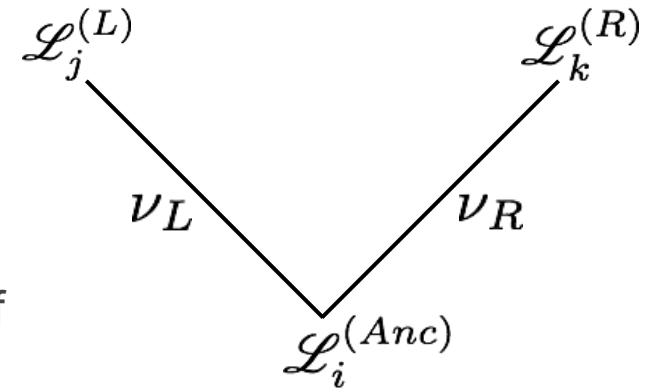


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Evaluating the likelihood of a site involves the recursive calculation of *conditional likelihoods* from the tips of the tree to the root.

The conditional likelihoods  $\mathcal{L}_i^{(Anc)}$  are the probabilities of the observations above some point in the tree (a local ancestral node, *Anc*), conditional on state  $i$  at that node.

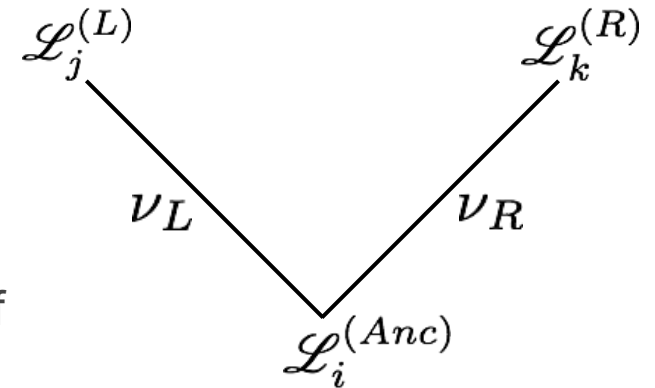


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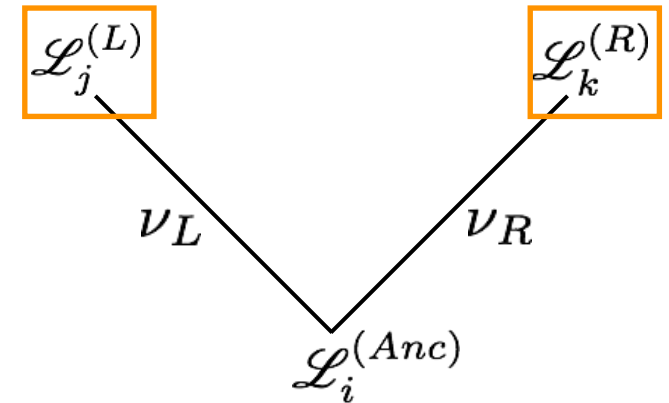


$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A,C,G,T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right) \times \left( \sum_{k \in (A,C,G,T)} p_{ik}(\nu_R) \mathcal{L}_k^{(R)} \right)$$

where  $i \in (A,C,G,T)$

# How Do We Calculate Site Likelihoods?

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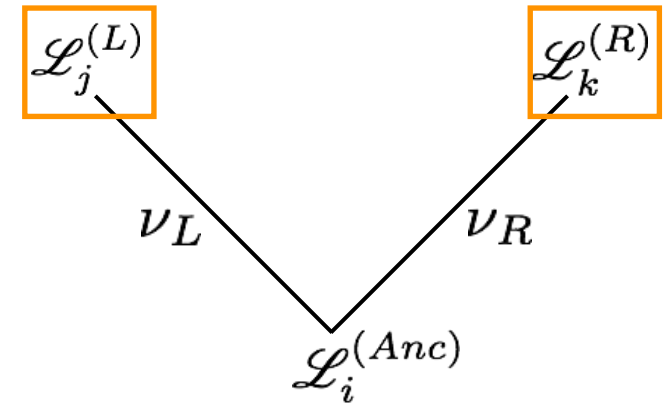


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These conditional likelihoods are the likelihoods of the observations above the end of each branch...

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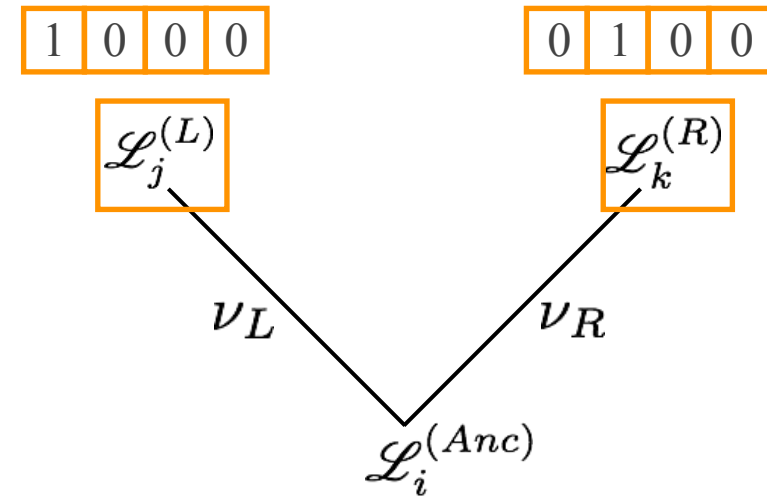


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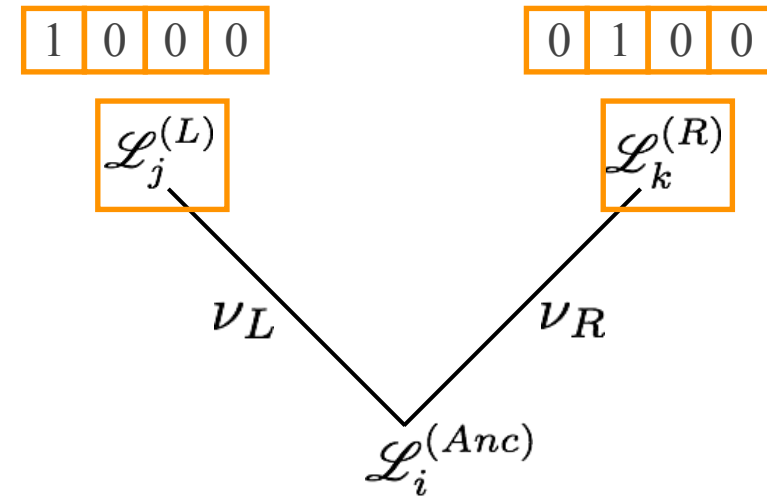
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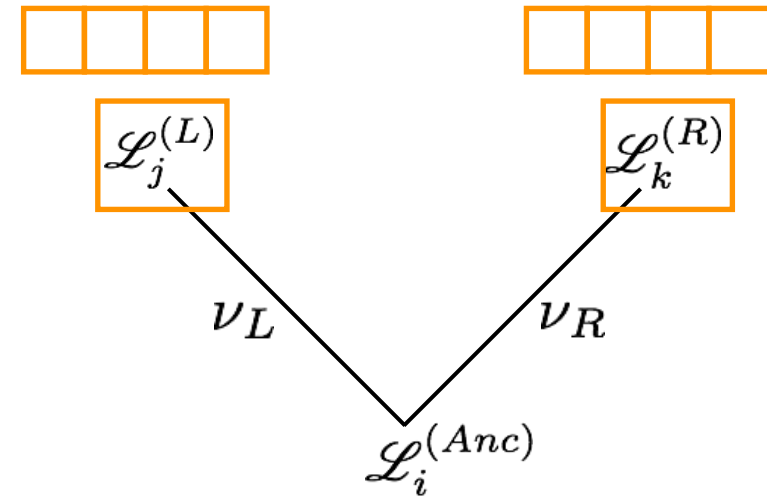
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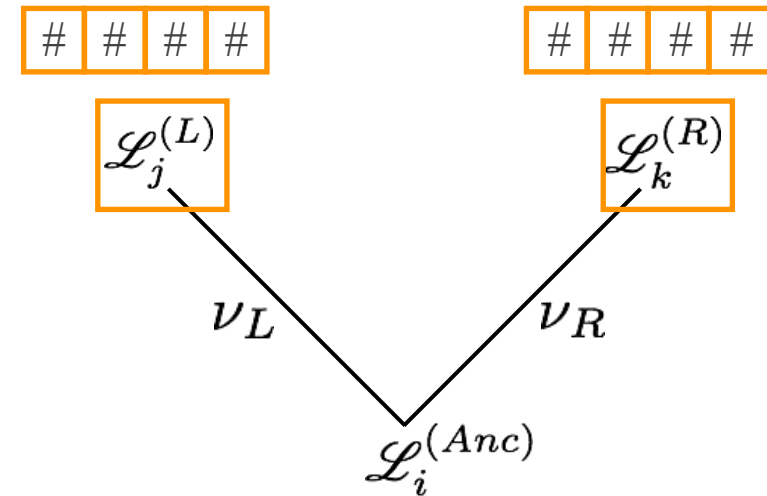
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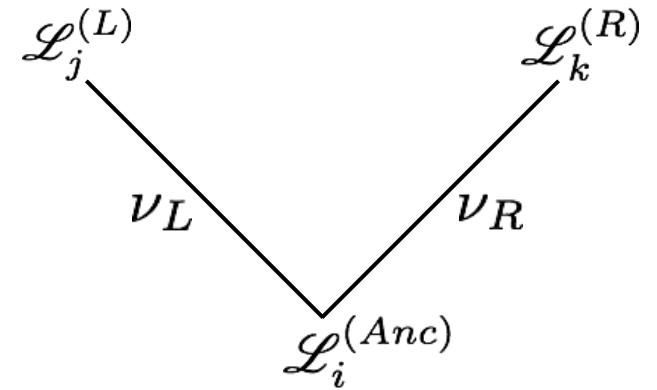
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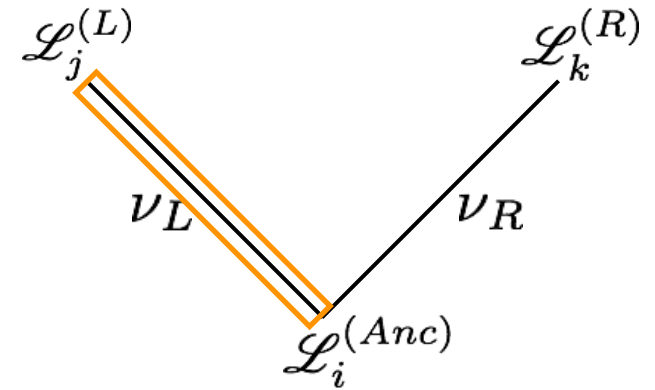


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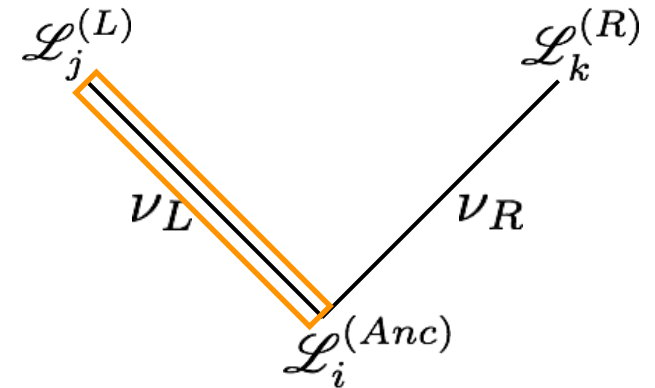
$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right)$$

Let's first focus on the left descendant branch.

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

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$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right)$$

for each possible  
end state sum...

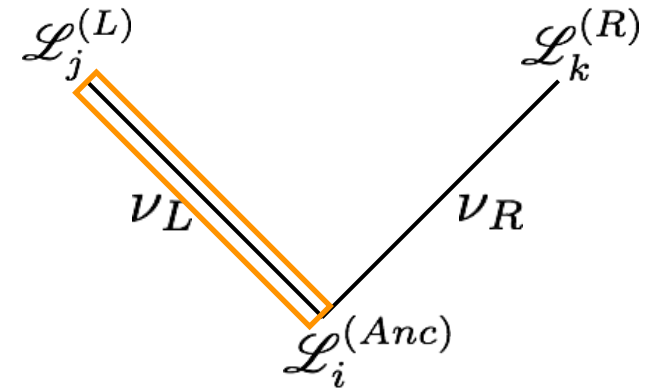
...the product of the  
transition probabilities  
of changes from  $i$  to  $j$   
over branch  $L$ ...

...and the conditional  
likelihood of each end  
state,  $j$ .

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## The Felsenstein Pruning Algorithm

So, *how* do we calculate the conditional likelihoods?



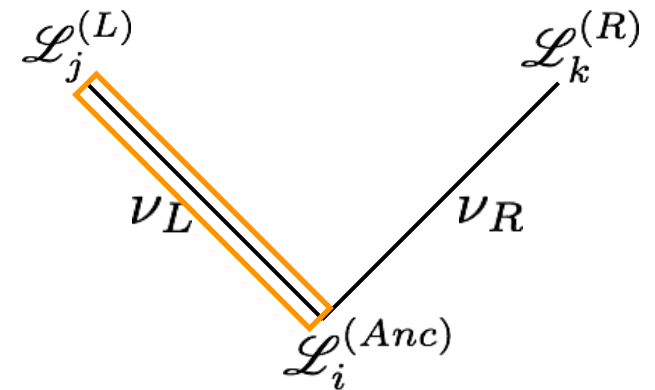
$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} \boxed{p_{ij}(\nu_L)} \mathcal{L}_j^{(L)} \right)$$

Recall that the transition probabilities,  $\mathbf{P}_{ij}(\nu_L)$ , of histories ending in state  $j$  that were initiated from state  $i$  and run over branch  $L$  are either approximated (by Monte Carlo simulation) or solved by exponentiating the product of the instantaneous-rate matrix,  $\mathbf{Q}$ , and branch length,  $\nu_L$

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

So, *how* do we calculate the conditional likelihoods?



$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} \boxed{p_{ij}(\nu_L)} \mathcal{L}_j^{(L)} \right) \quad \mathbf{Q} = q_{ij} = \begin{pmatrix} - & \mu a \pi_C & \mu b \pi_G & \mu c \pi_T \\ \mu a \pi_A & - & \mu d \pi_G & \mu e \pi_T \\ \mu b \pi_A & \mu d \pi_C & - & \mu f \pi_T \\ \mu c \pi_A & \mu e \pi_C & \mu f \pi_G & - \end{pmatrix}$$

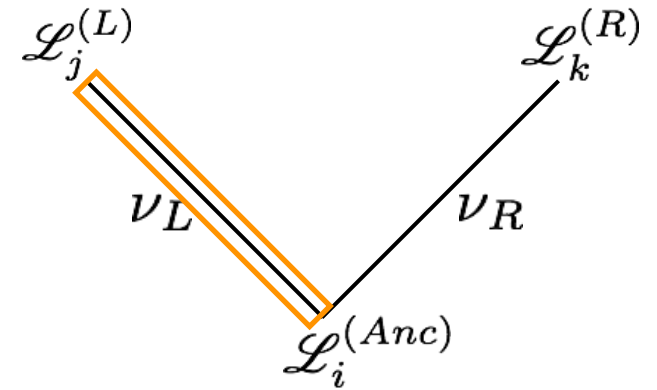
$$\mathbf{P}_{ij}(\nu) = e^{\mathbf{Q}\nu}$$

Recall that the transition probabilities,  $\mathbf{P}_{ij}(\nu_L)$ , of histories ending in state  $j$  that were initiated from state  $i$  and run over branch  $L$  are either approximated (by Monte Carlo simulation) or solved by exponentiating the product of the instantaneous-rate matrix,  $\mathbf{Q}$ , and branch length,  $\nu_L$

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

So, *how* do we calculate the conditional likelihoods?



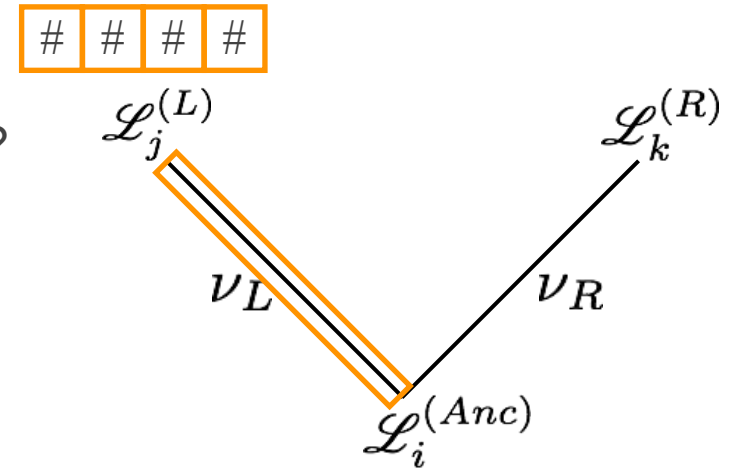
$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} \boxed{p_{ij}(\nu_L)} \mathcal{L}_j^{(L)} \right)$$

The probability that the process is in state  $j$  at the end of the branch, times...

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

So, *how* do we calculate the conditional likelihoods?



$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} \boxed{p_{ij}(\nu_L)} \boxed{\mathcal{L}_j^{(L)}} \right)$$

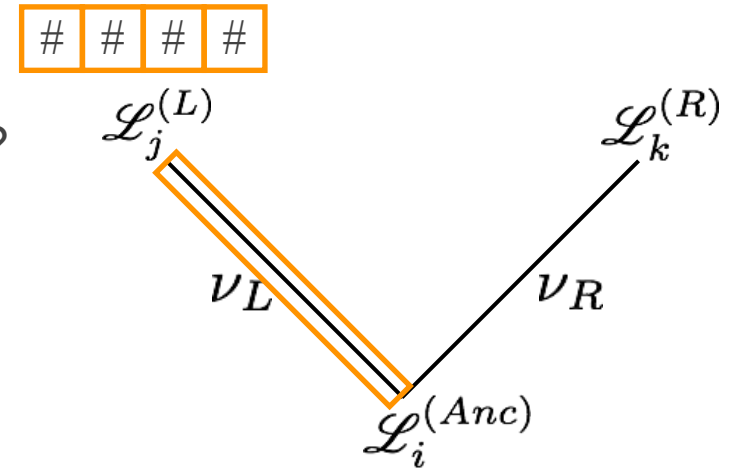
The probability that the process is in state  $j$  at the end of the branch, times...

...the probability of everything 'above' the end of the branch, conditional on state  $j$ .

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

So, *how* do we calculate the conditional likelihoods?



$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right)$$

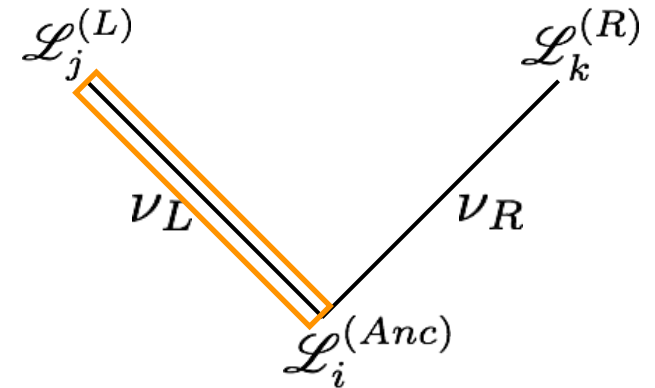
We iteratively compute this product for each of the four  $j$  end states, A,C,G,T...



# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

So, *how* do we calculate the conditional likelihoods?



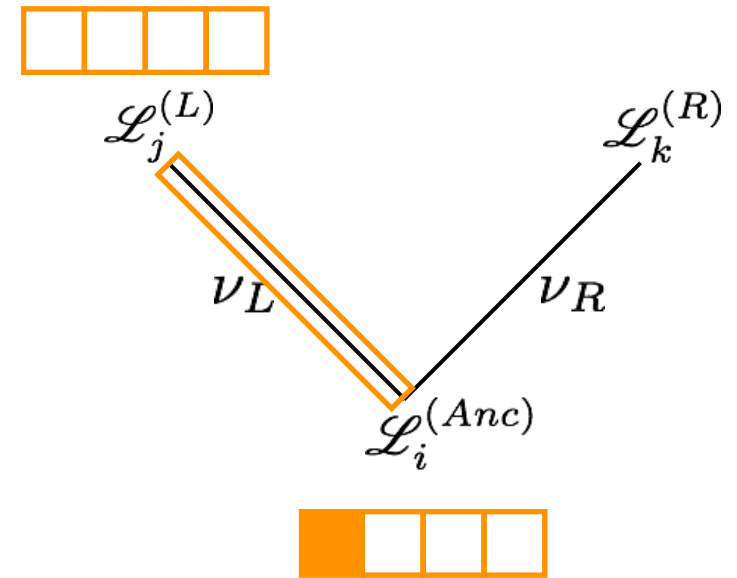
$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right)$$

We iteratively compute this product for each of the four  $j$  end states, A,C,G,T...  
...and then we sum these four terms because they are mutually exclusive.

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

First, set the start state,  $i$ , to  $i = A$



$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right)$$

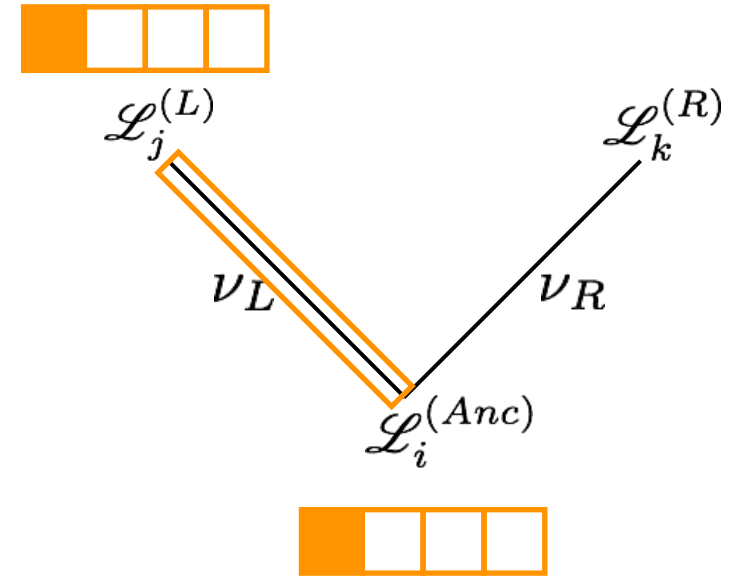
$$\mathcal{L}_A^{(Anc)} \xrightarrow{\nu_L} \mathcal{L}_A^{(L)}$$

The transition probabilities  $p_{AA}(\nu_L)$  over branch  $\nu_L$  are calculated by exponentiating the product of the instantaneous rate matrix,  $\mathbf{Q}$ , and branch length  $\nu_L$ .

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

First, set the start state,  $i$ , to  $i = A$   
and set the end state,  $j$ , to  $j = A$



$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right)$$

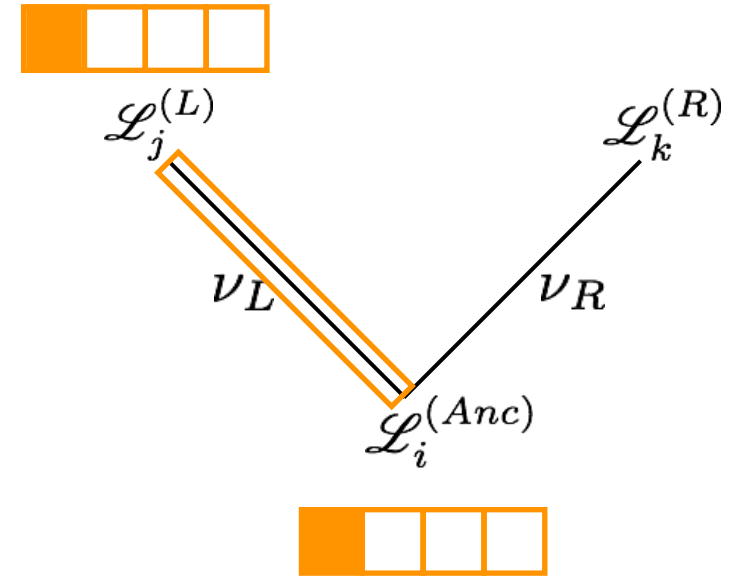
$$\mathcal{L}_A^{(Anc)} \xrightarrow[\nu_L]{\quad} \mathcal{L}_A^{(L)}$$

The transition probabilities  $p_{AA}(\nu_L)$  over branch  $\nu_L$  are calculated by exponentiating the product of the instantaneous rate matrix,  $\mathbf{Q}$ , and branch length  $\nu_L$ .

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

First, set the start state,  $i$ , to  $i = A$   
 and set the end state,  $j$ , to  $j = A$   
 next set the end state,  $j$ , to  $j = C$ ...



$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right)$$

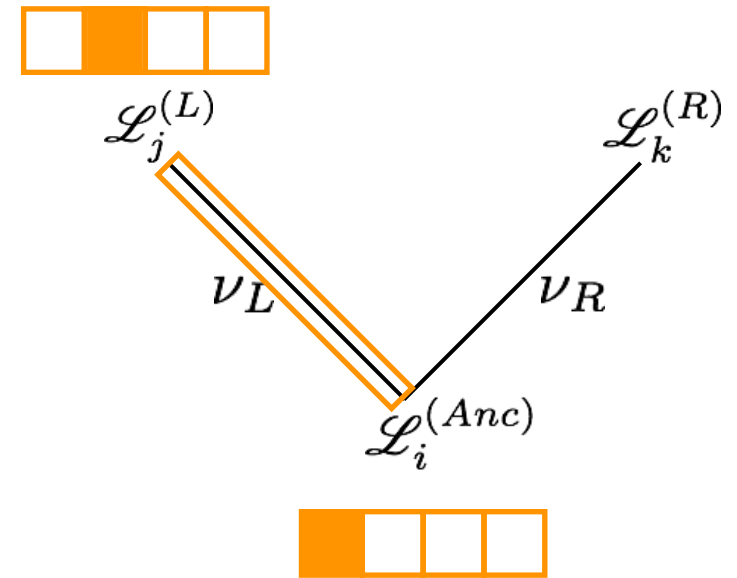
$\mathcal{L}_A^{(Anc)} \xrightarrow{\nu_L} \mathcal{L}_C^{(Anc)}$

Then we do the same thing for end state  $j = C$ ...

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

First, set the start state,  $i$ , to  $i = A$   
 and set the end state,  $j$ , to  $j = A$   
 next set the end state,  $j$ , to  $j = C$   
 then set the end state,  $j$ , to  $j = G \dots$



$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right)$$

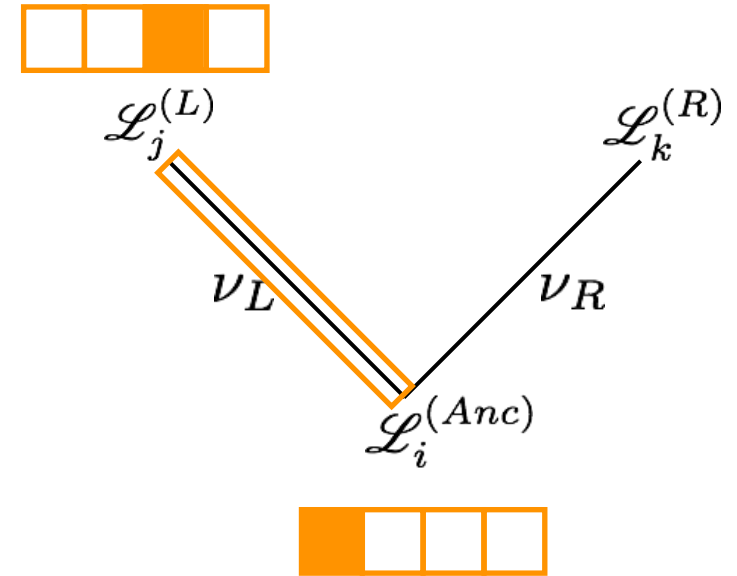
$\mathcal{L}_A^{(Anc)} \xrightarrow{\nu_L} \mathcal{L}_G^{(Anc)}$

Then we do the same thing for end state  $j = G \dots$

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

First, set the start state,  $i$ , to  $i = A$   
 and set the end state,  $j$ , to  $j = A$   
 next set the end state,  $j$ , to  $j = C$   
 then set the end state,  $j$ , to  $j = G$   
 then set the end state,  $j$ , to  $j = T$



$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right)$$

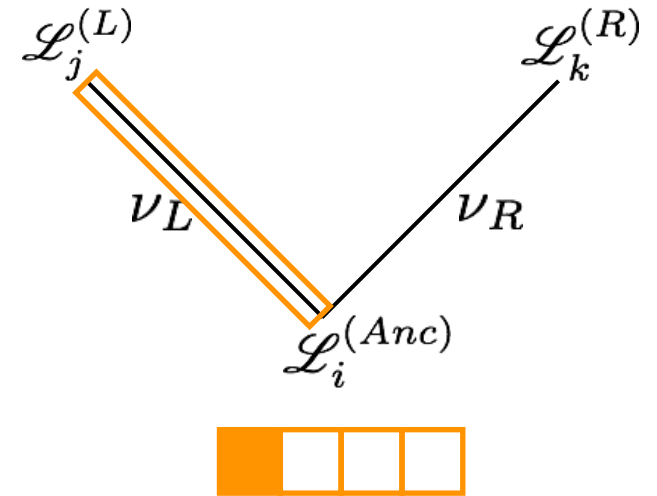
$$\mathcal{L}_A^{(Anc)} \xrightarrow{\nu_L} \mathcal{L}_T^{(Anc)}$$

Finally, we do the same thing for end state  $j = T$

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

Next, we sum the fractional likelihoods for each of the four end states  $j = \{A, C, G, T\} \dots$



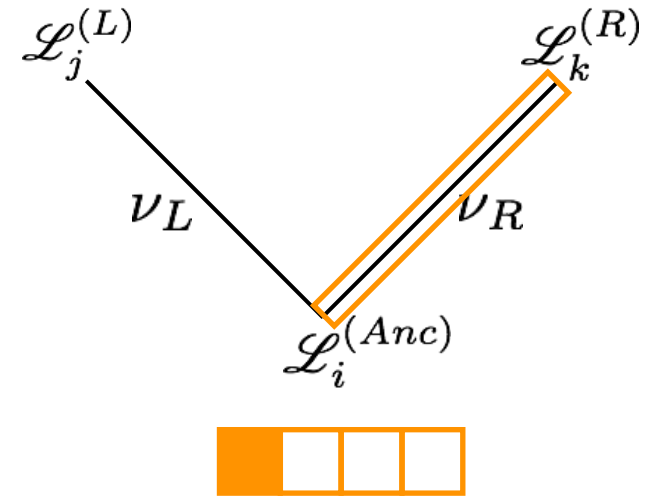
$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right)$$

Then we sum the fractional likelihoods for each of the four end states  $j = \{A, C, G, T\} \dots$

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

Next, we repeat the process for the right branch,  $\nu_R$ .



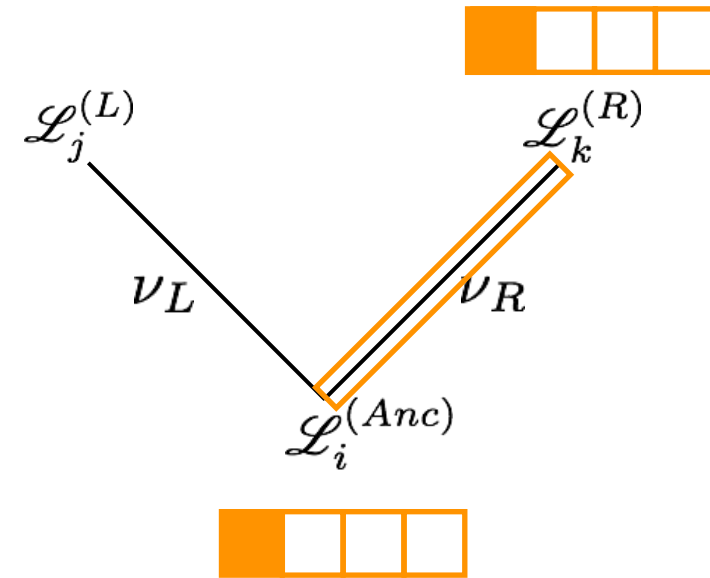
$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right) \times \left( \sum_{k \in (A, C, G, T)} p_{ik}(\nu_R) \mathcal{L}_k^{(R)} \right)$$



# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

Next, we repeat the process for the right branch,  $\nu_R$ .

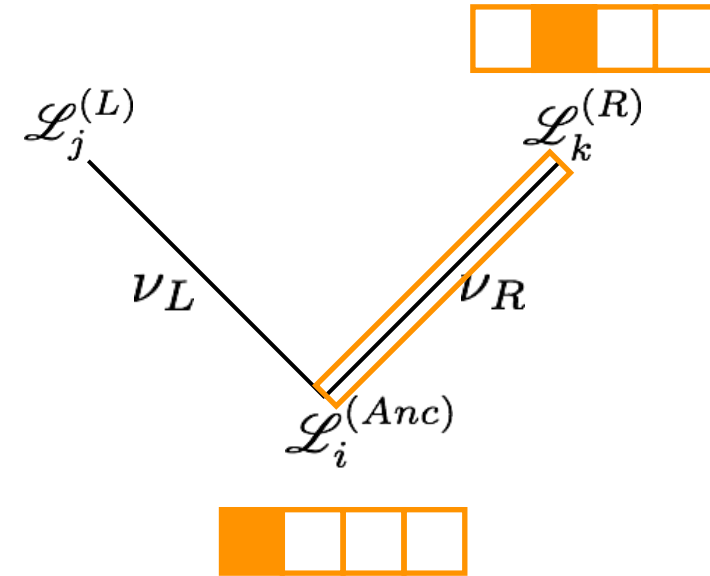


$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right) \times \left( \sum_{k \in (A, C, G, T)} p_{ik}(\nu_R) \mathcal{L}_k^{(R)} \right)$$

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

Next, we repeat the process for the right branch,  $\nu_R$ .

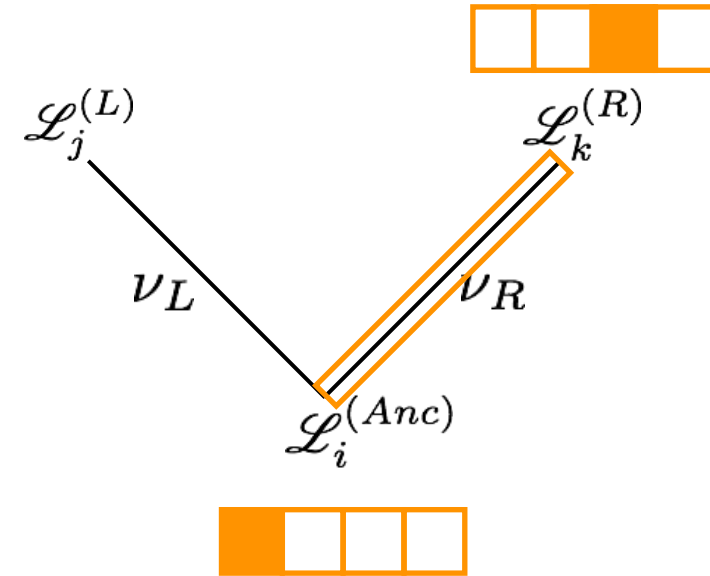


$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right) \times \left( \sum_{k \in (A, C, G, T)} p_{ik}(\nu_R) \mathcal{L}_k^{(R)} \right)$$

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

Next, we repeat the process for the right branch,  $\nu_R$ .

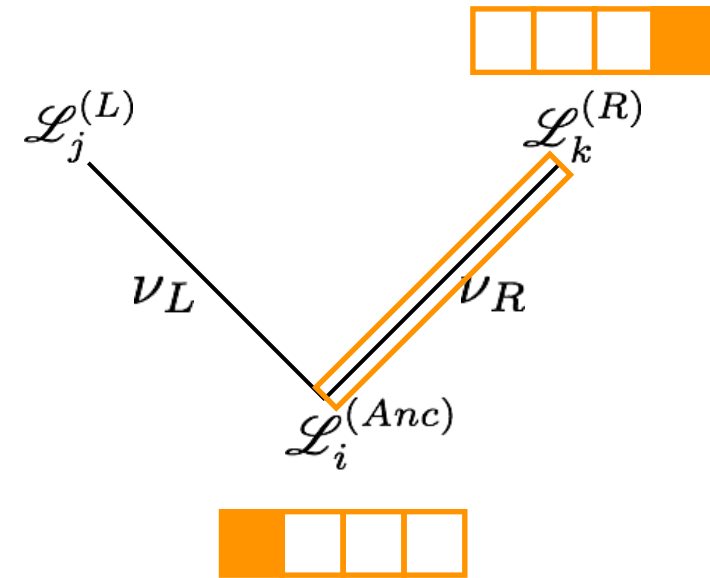


$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right) \times \left( \sum_{k \in (A, C, G, T)} p_{ik}(\nu_R) \mathcal{L}_k^{(R)} \right)$$

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

Next, we repeat the process for the right branch,  $\nu_R$ .

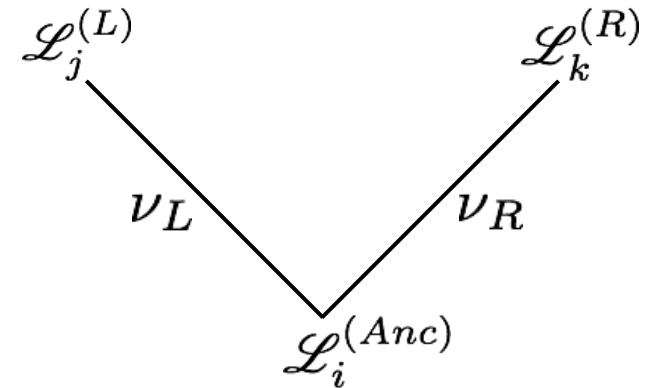


$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right) \times \left( \sum_{k \in (A, C, G, T)} p_{ik}(\nu_R) \mathcal{L}_k^{(R)} \right)$$

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

Finally, we calculate  $\mathcal{L}_i^{(Anc)}$  as the product of the conditional likelihoods of the two descendant branches, which makes explicit the assumption that substitutions along these two lineages are independent.

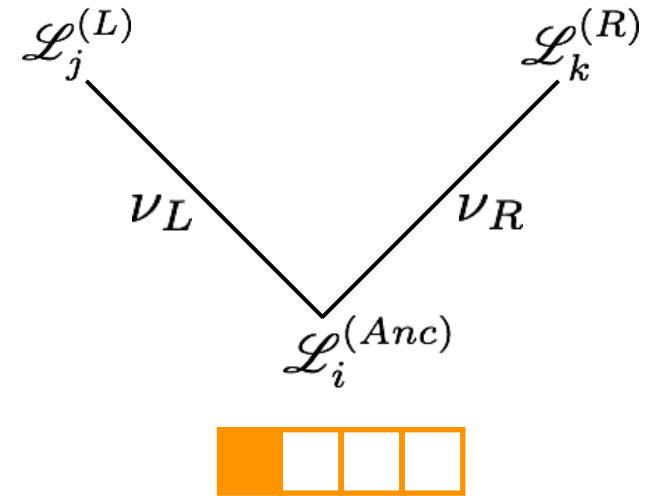


$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right) \times \left( \sum_{k \in (A, C, G, T)} p_{ik}(\nu_R) \mathcal{L}_k^{(R)} \right)$$

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

Now we have computed  $\mathcal{L}_A^{(Anc)}$  ...

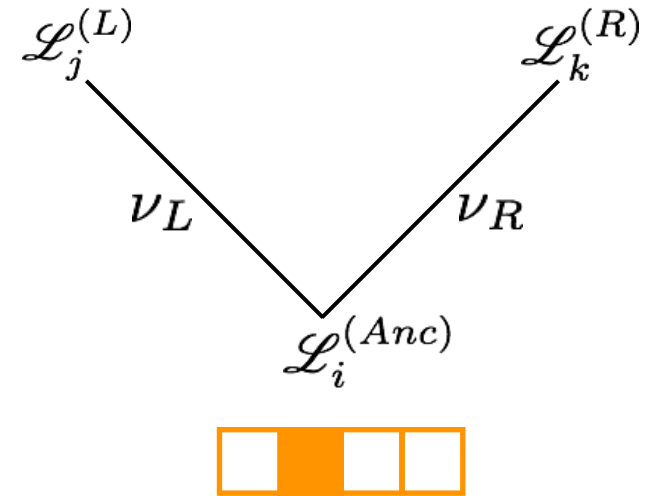


$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right) \times \left( \sum_{k \in (A, C, G, T)} p_{ik}(\nu_R) \mathcal{L}_k^{(R)} \right)$$

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

So, now we need to repeat the entire process  
for  $i = C$  to compute  $\mathcal{L}_C^{(Anc)}$  ...

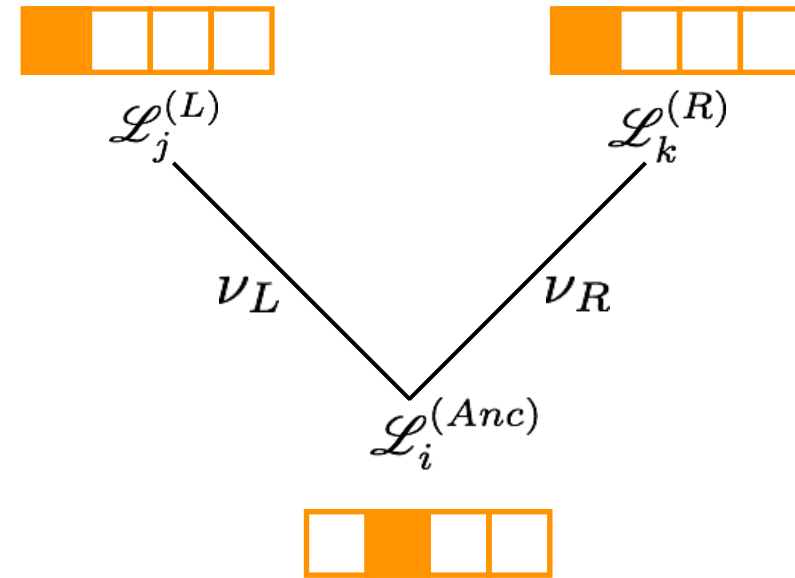


$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right) \times \left( \sum_{k \in (A, C, G, T)} p_{ik}(\nu_R) \mathcal{L}_k^{(R)} \right)$$

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

So, now we need to repeat the entire process  
for  $i = C$  to compute  $\mathcal{L}_C^{(Anc)}$  ...



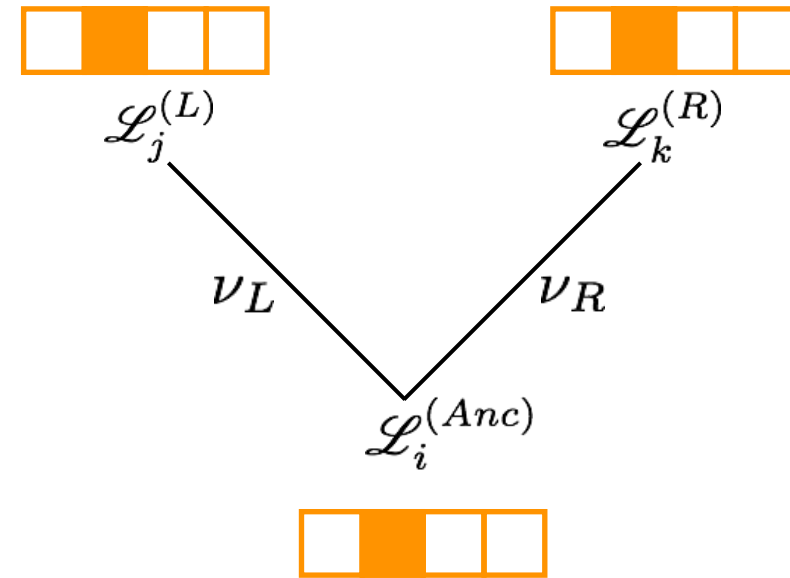
$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right) \times \left( \sum_{k \in (A, C, G, T)} p_{ik}(\nu_R) \mathcal{L}_k^{(R)} \right)$$



# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

So, now we need to repeat the entire process  
for  $i = C$  to compute  $\mathcal{L}_C^{(Anc)}$  ...

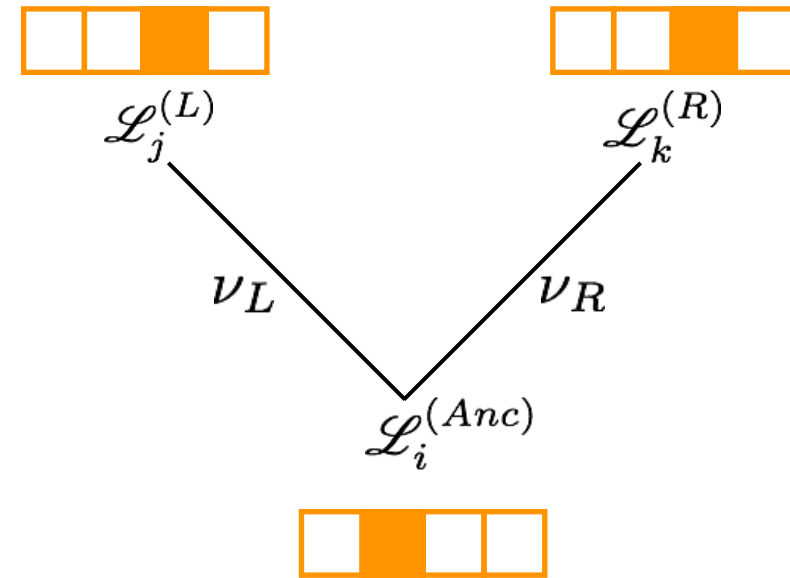


$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right) \times \left( \sum_{k \in (A, C, G, T)} p_{ik}(\nu_R) \mathcal{L}_k^{(R)} \right)$$

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

So, now we need to repeat the entire process  
for  $i = C$  to compute  $\mathcal{L}_C^{(Anc)}$  ...

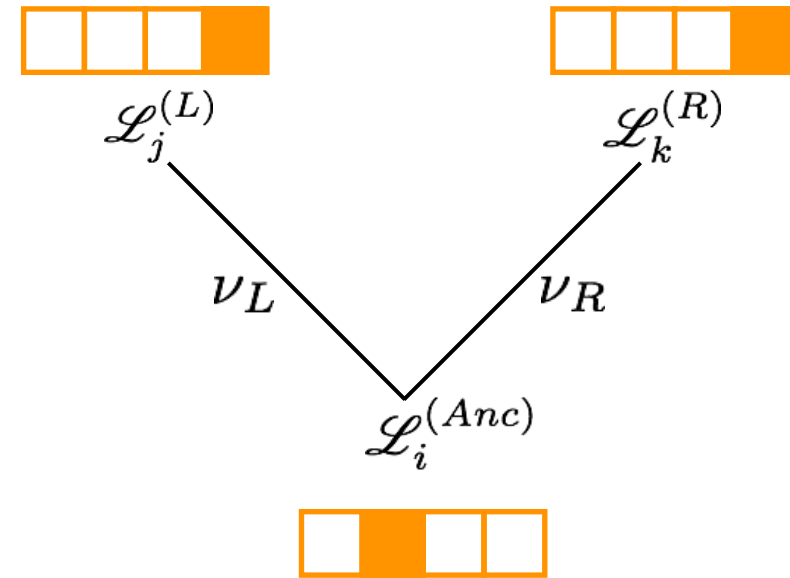


$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right) \times \left( \sum_{k \in (A, C, G, T)} p_{ik}(\nu_R) \mathcal{L}_k^{(R)} \right)$$

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

So, now we need to repeat the entire process  
for  $i = C$  to compute  $\mathcal{L}_C^{(Anc)}$  ...

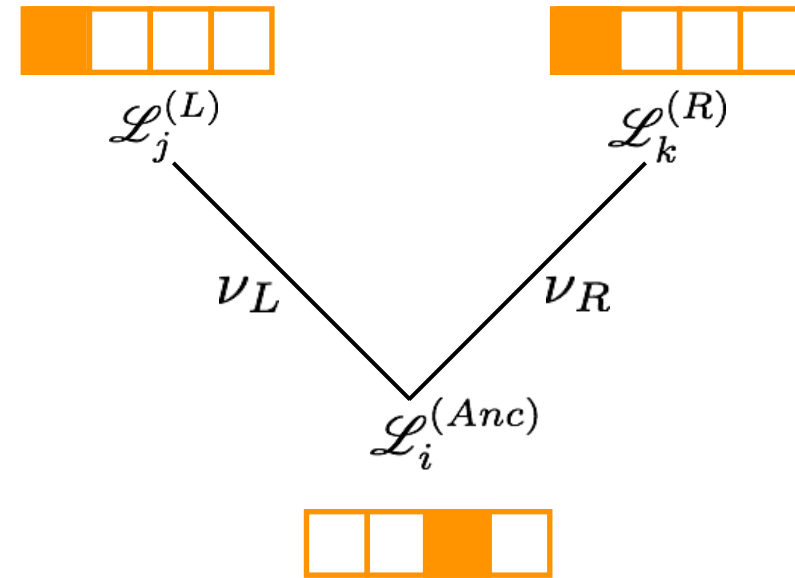


$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right) \times \left( \sum_{k \in (A, C, G, T)} p_{ik}(\nu_R) \mathcal{L}_k^{(R)} \right)$$

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

So, now we need to repeat the entire process  
 for  $i = C$  to compute  $\mathcal{L}_C^{(Anc)}$   
 for  $i = G$  to compute  $\mathcal{L}_G^{(Anc)}$  ...

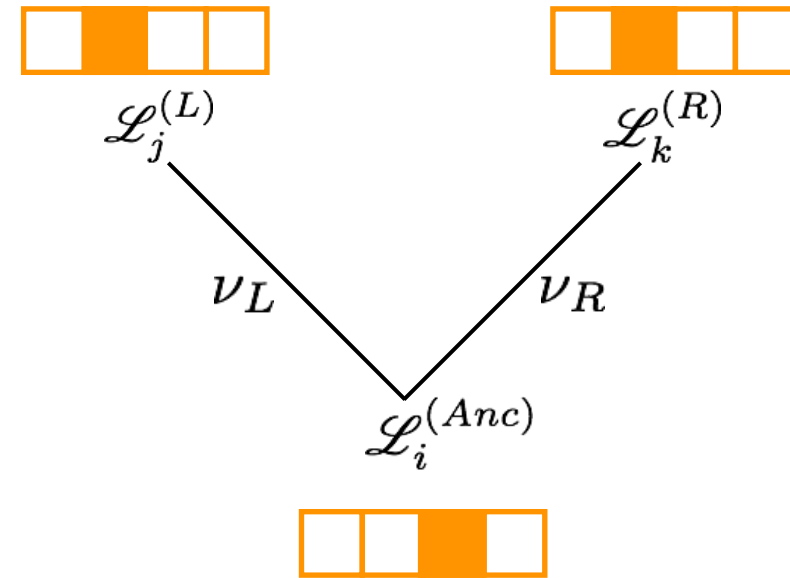


$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right) \times \left( \sum_{k \in (A, C, G, T)} p_{ik}(\nu_R) \mathcal{L}_k^{(R)} \right)$$

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

So, now we need to repeat the entire process  
for  $i = C$  to compute  $\mathcal{L}_C^{(Anc)}$   
for  $i = G$  to compute  $\mathcal{L}_G^{(Anc)}$  ...

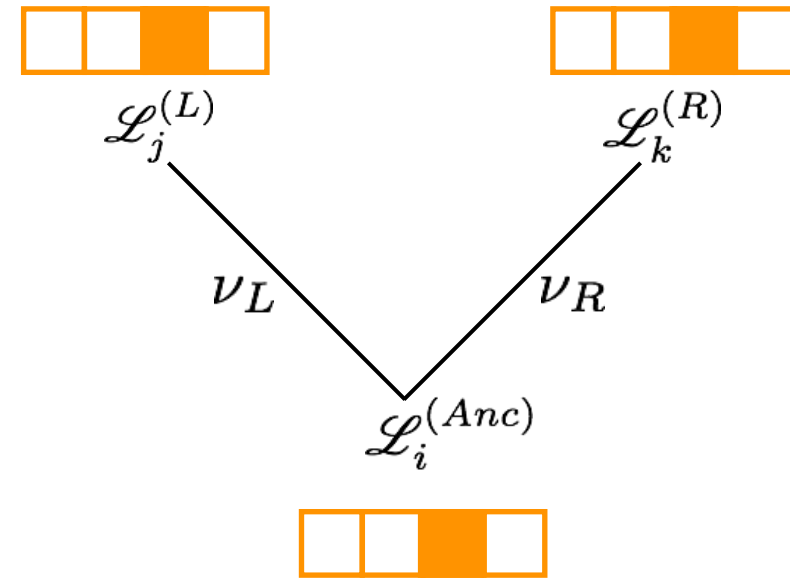


$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right) \times \left( \sum_{k \in (A, C, G, T)} p_{ik}(\nu_R) \mathcal{L}_k^{(R)} \right)$$

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

So, now we need to repeat the entire process  
for  $i = C$  to compute  $\mathcal{L}_C^{(Anc)}$   
for  $i = G$  to compute  $\mathcal{L}_G^{(Anc)}$  ...

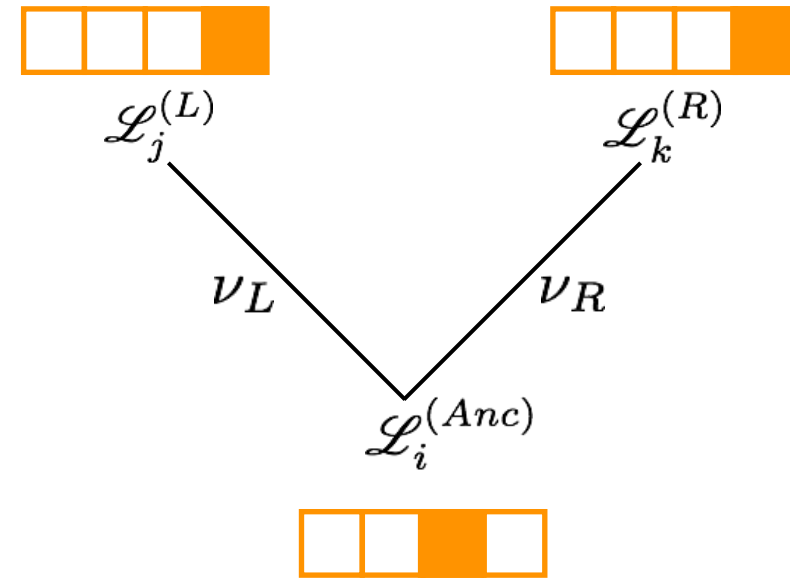


$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right) \times \left( \sum_{k \in (A, C, G, T)} p_{ik}(\nu_R) \mathcal{L}_k^{(R)} \right)$$

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

So, now we need to repeat the entire process  
 for  $i = C$  to compute  $\mathcal{L}_C^{(Anc)}$   
 for  $i = G$  to compute  $\mathcal{L}_G^{(Anc)}$  ...

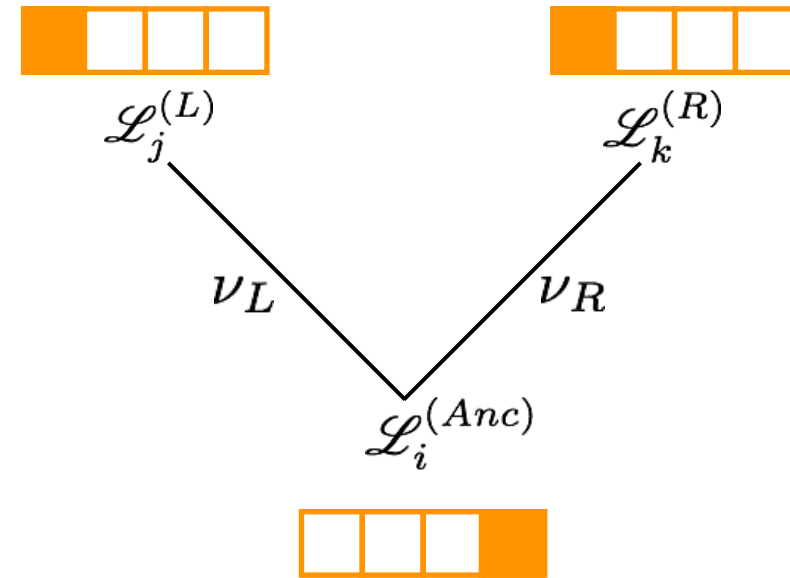


$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right) \times \left( \sum_{k \in (A, C, G, T)} p_{ik}(\nu_R) \mathcal{L}_k^{(R)} \right)$$

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

So, now we need to repeat the entire process  
 for  $i = C$  to compute  $\mathcal{L}_C^{(Anc)}$   
 for  $i = G$  to compute  $\mathcal{L}_G^{(Anc)}$   
 and finally for  $i = T$  to compute  $\mathcal{L}_T^{(Anc)}$  ...



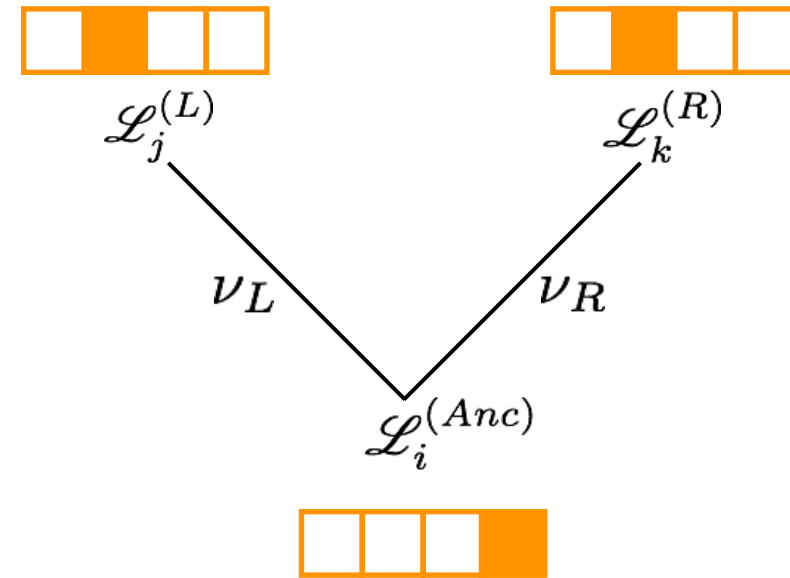
$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right) \times \left( \sum_{k \in (A, C, G, T)} p_{ik}(\nu_R) \mathcal{L}_k^{(R)} \right)$$



# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

So, now we need to repeat the entire process  
 for  $i = C$  to compute  $\mathcal{L}_C^{(Anc)}$   
 for  $i = G$  to compute  $\mathcal{L}_G^{(Anc)}$   
 and finally for  $i = T$  to compute  $\mathcal{L}_T^{(Anc)}$  ...

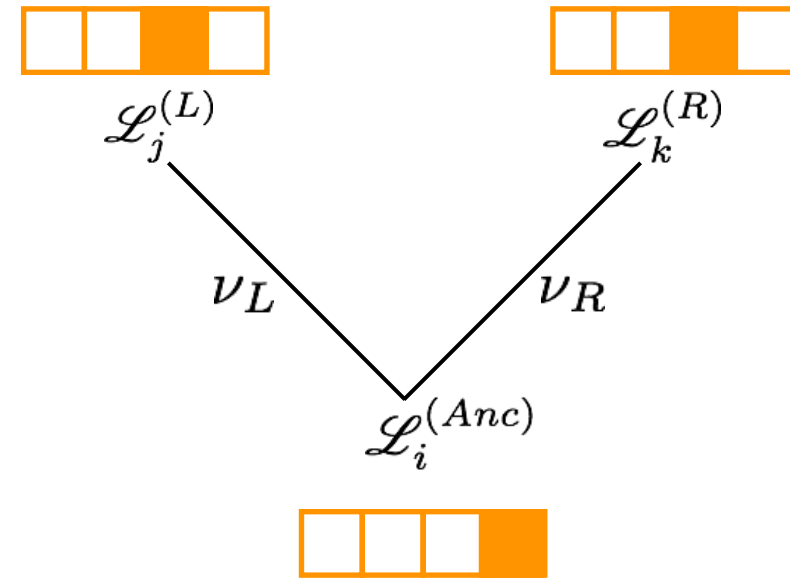


$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right) \times \left( \sum_{k \in (A, C, G, T)} p_{ik}(\nu_R) \mathcal{L}_k^{(R)} \right)$$

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

So, now we need to repeat the entire process  
 for  $i = C$  to compute  $\mathcal{L}_C^{(Anc)}$   
 for  $i = G$  to compute  $\mathcal{L}_G^{(Anc)}$   
 and finally for  $i = T$  to compute  $\mathcal{L}_T^{(Anc)}$  ...

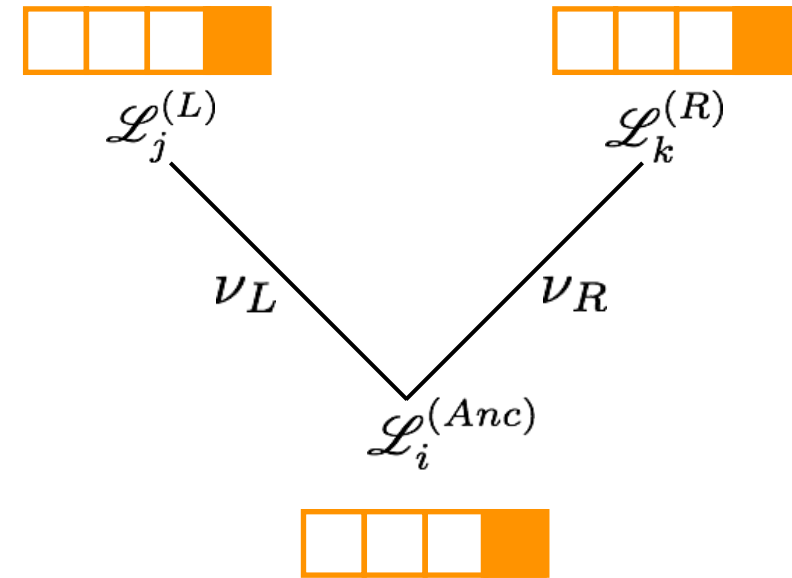


$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right) \times \left( \sum_{k \in (A, C, G, T)} p_{ik}(\nu_R) \mathcal{L}_k^{(R)} \right)$$

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

So, now we need to repeat the entire process  
 for  $i = C$  to compute  $\mathcal{L}_C^{(Anc)}$   
 for  $i = G$  to compute  $\mathcal{L}_G^{(Anc)}$   
 and finally for  $i = T$  to compute  $\mathcal{L}_T^{(Anc)}$  ...

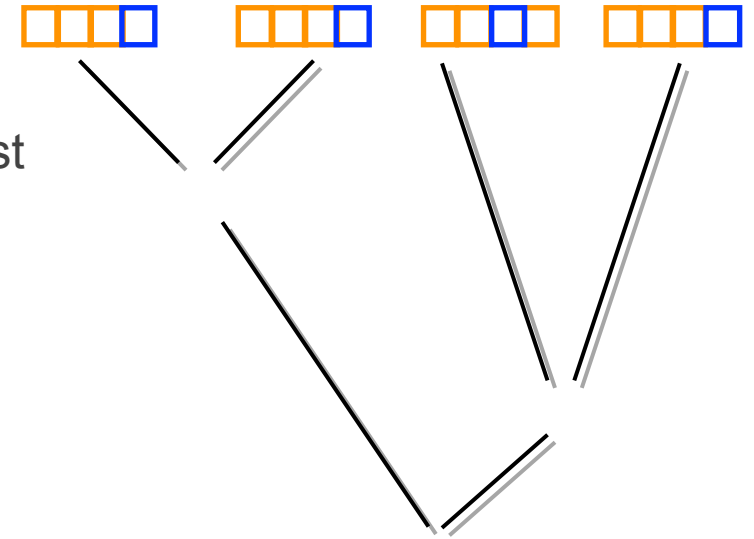


$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right) \times \left( \sum_{k \in (A, C, G, T)} p_{ik}(\nu_R) \mathcal{L}_k^{(R)} \right)$$

# How Do We Calculate Site Likelihoods?

## The Felsenstein Pruning Algorithm

Then we need to repeat the entire process for each of the more inclusive nodes toward the root, where the conditional likelihoods of the tips are first recorded...

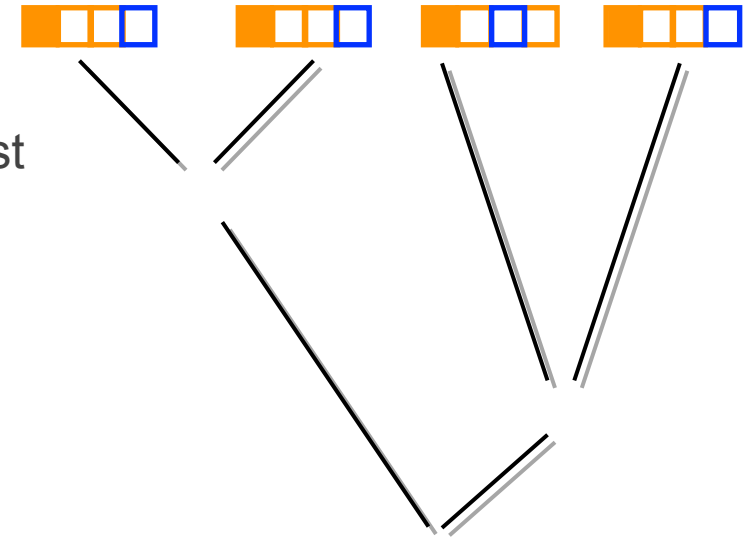


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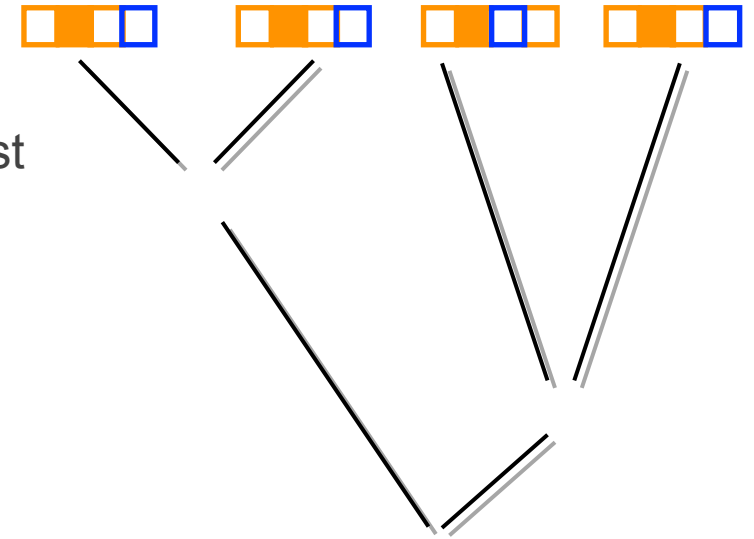


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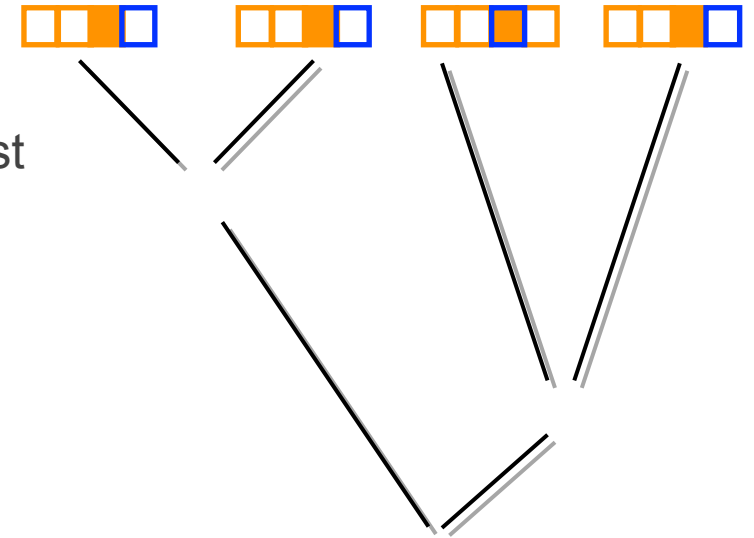


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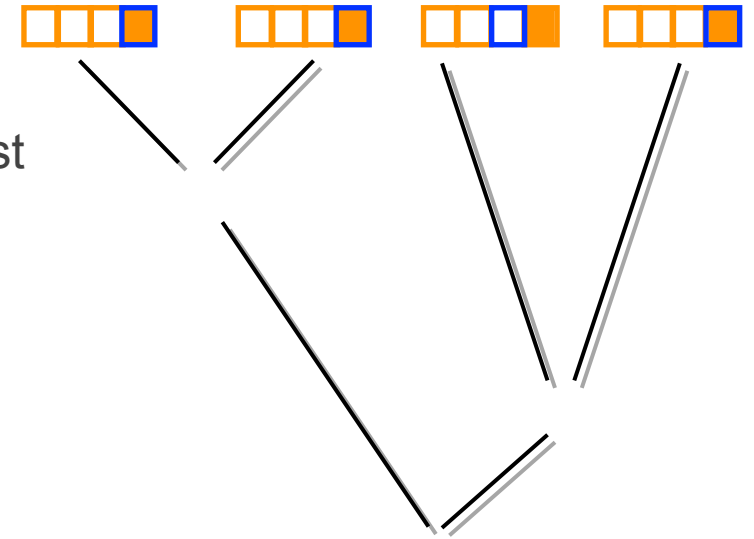


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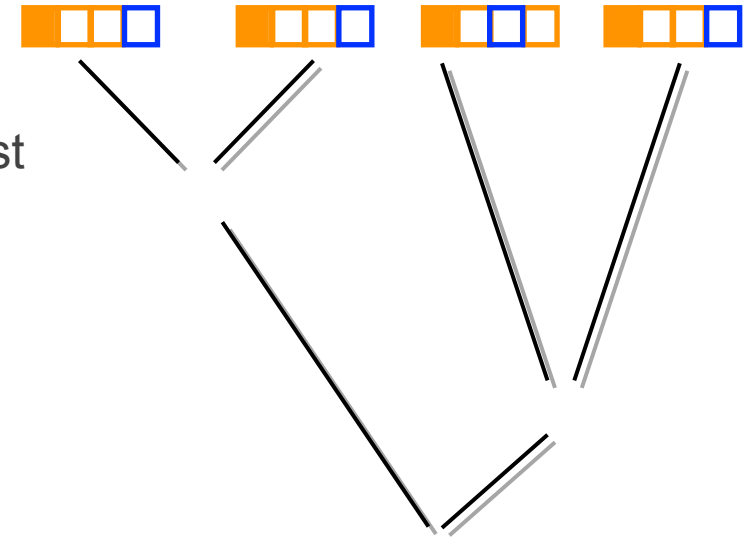
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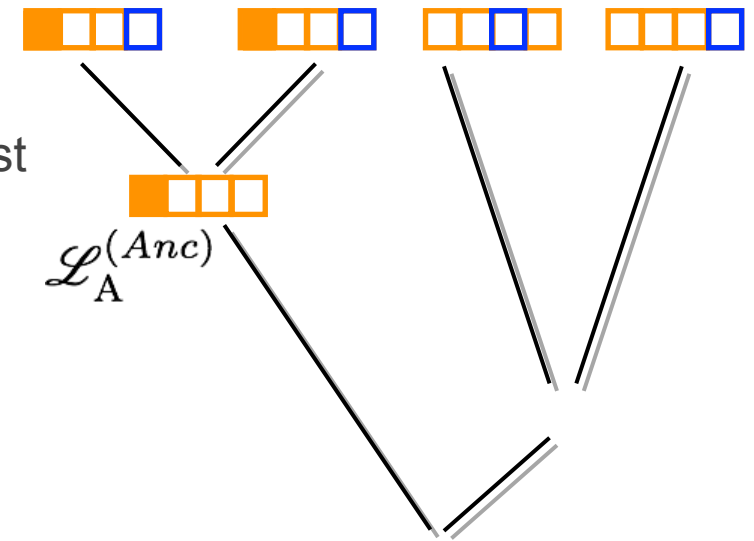


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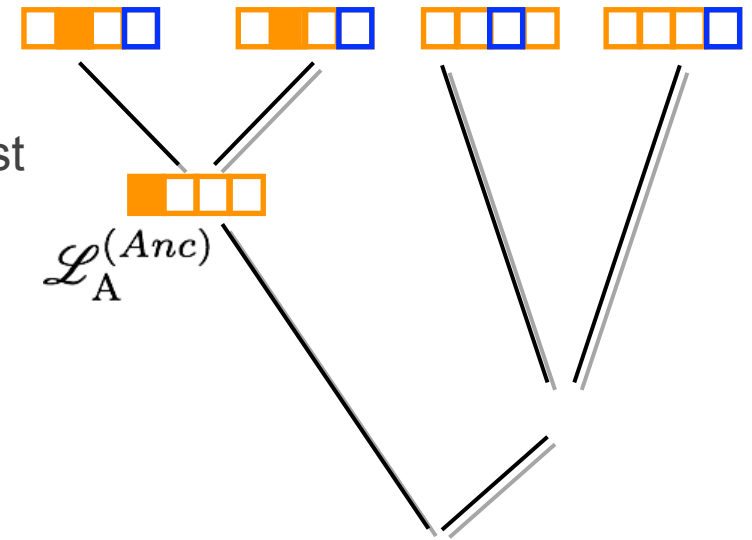


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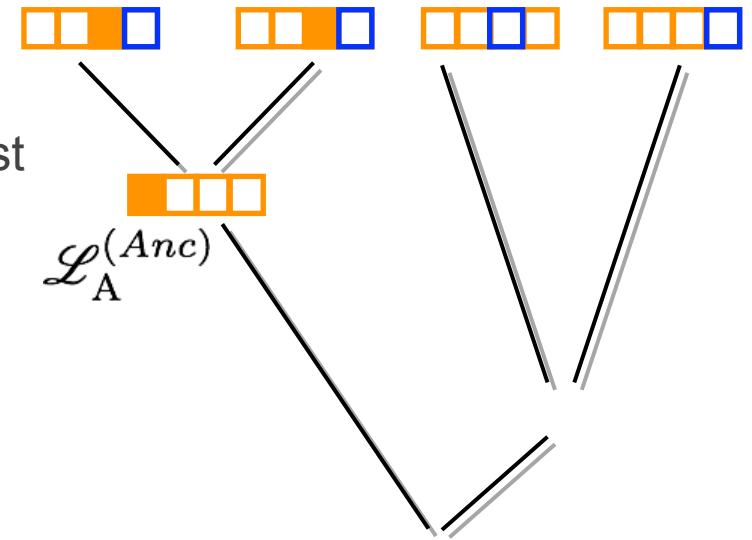
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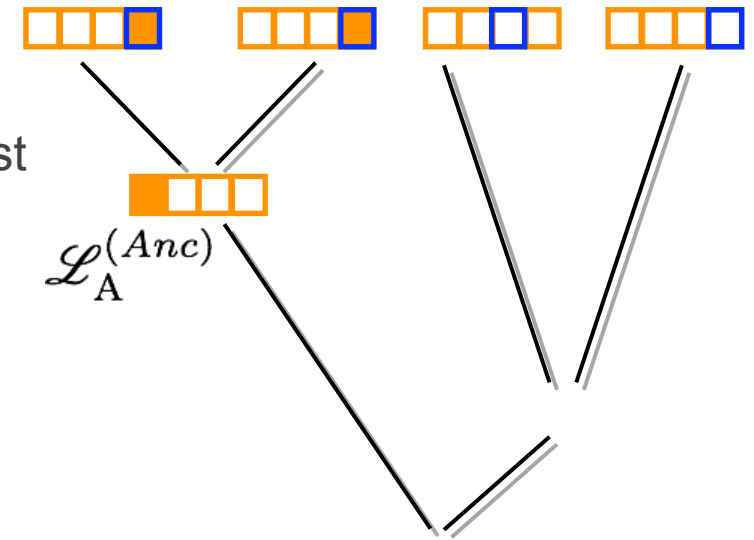
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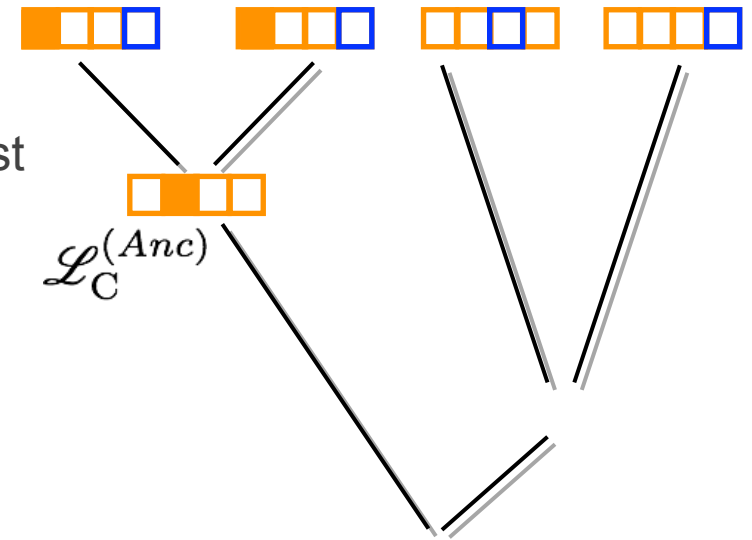
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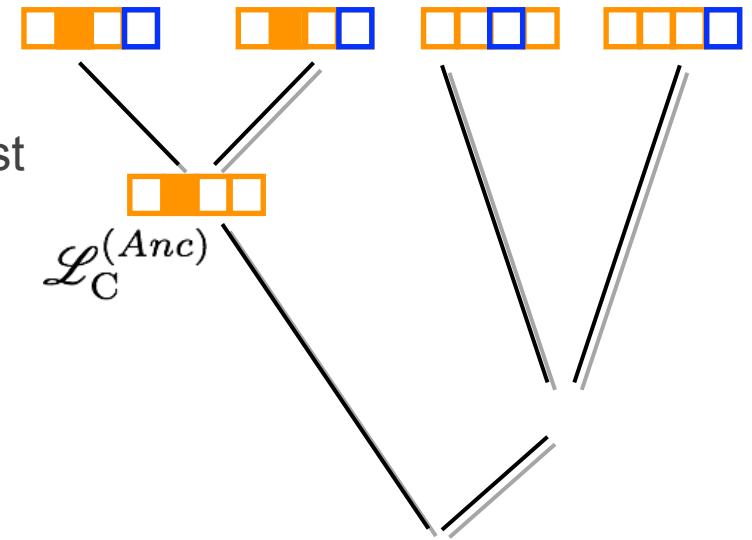
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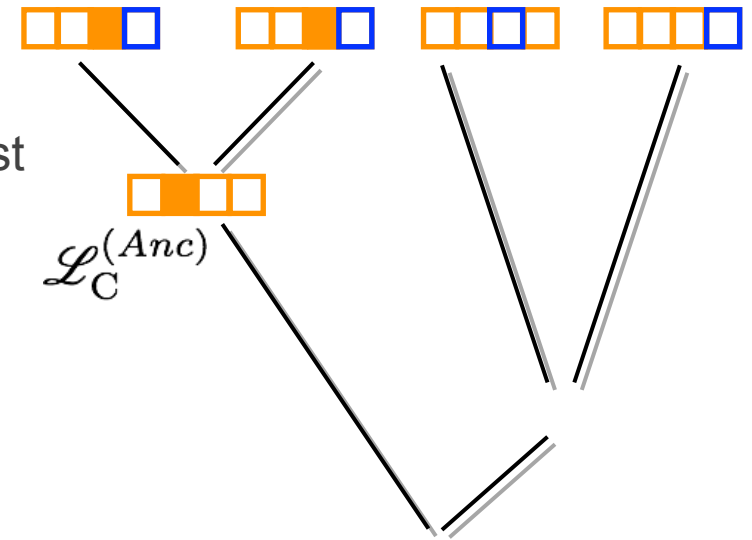
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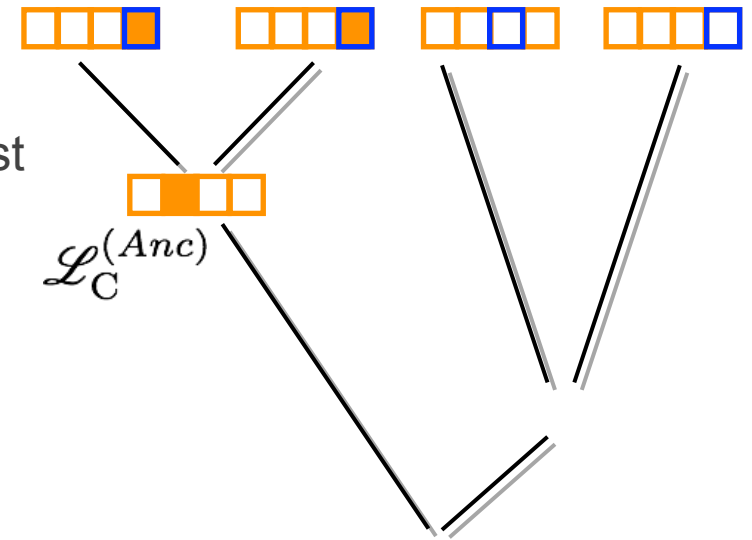


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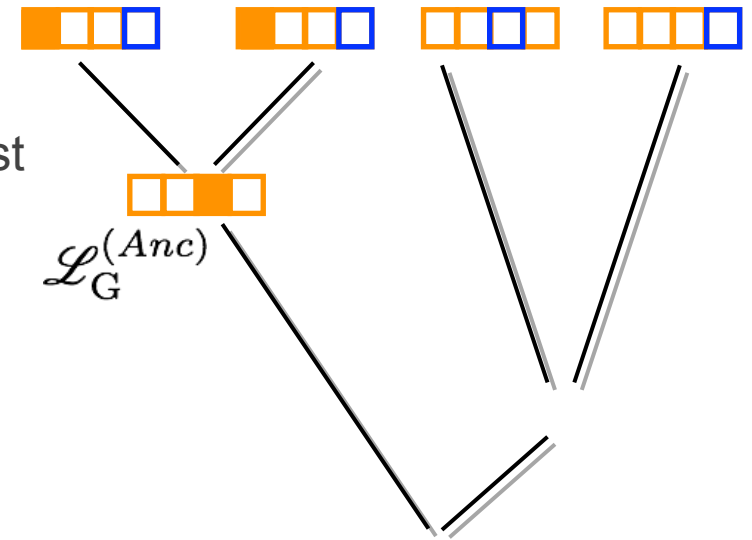
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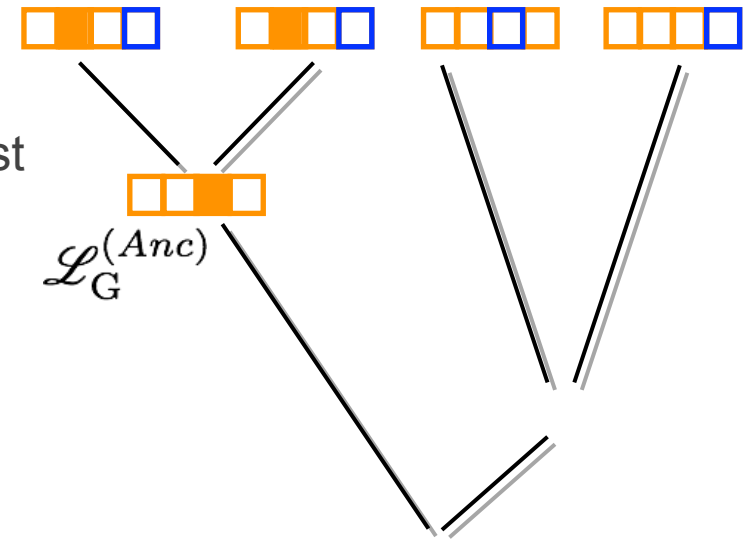
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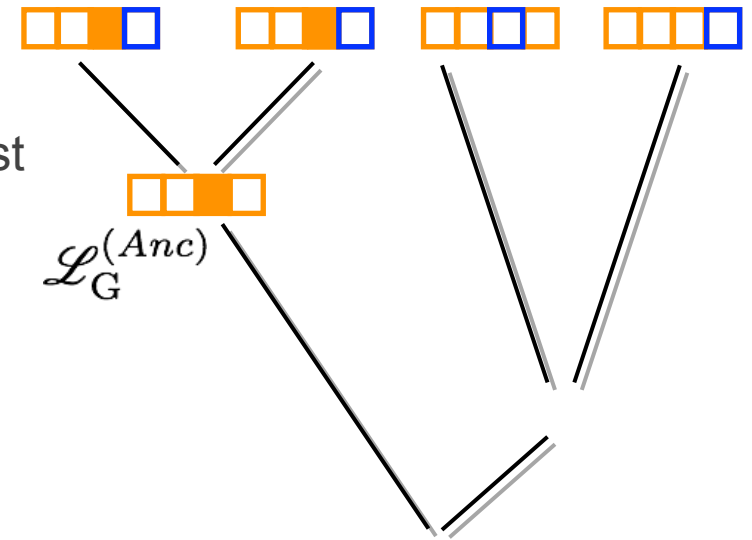
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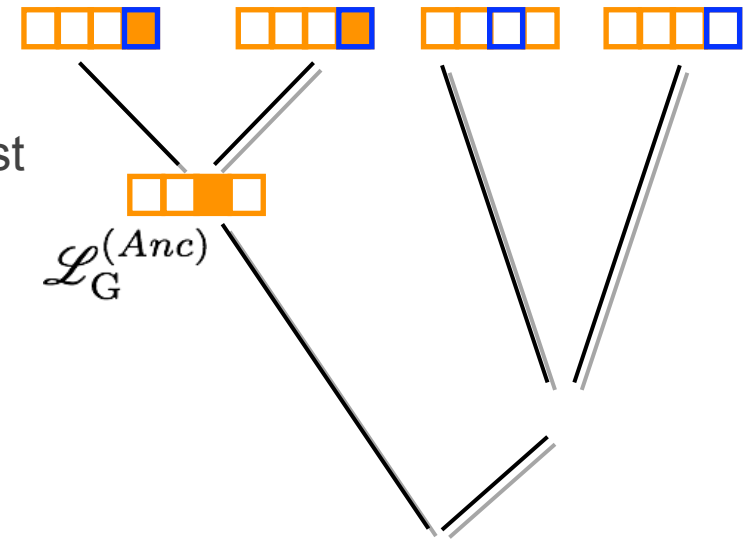
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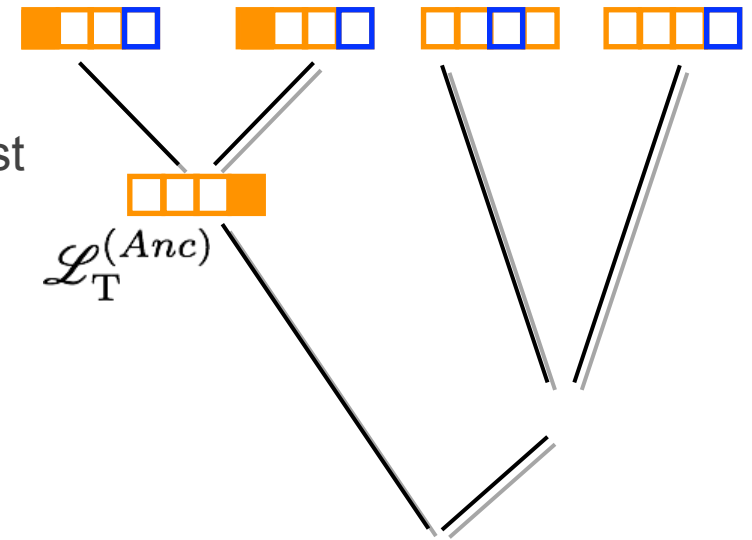
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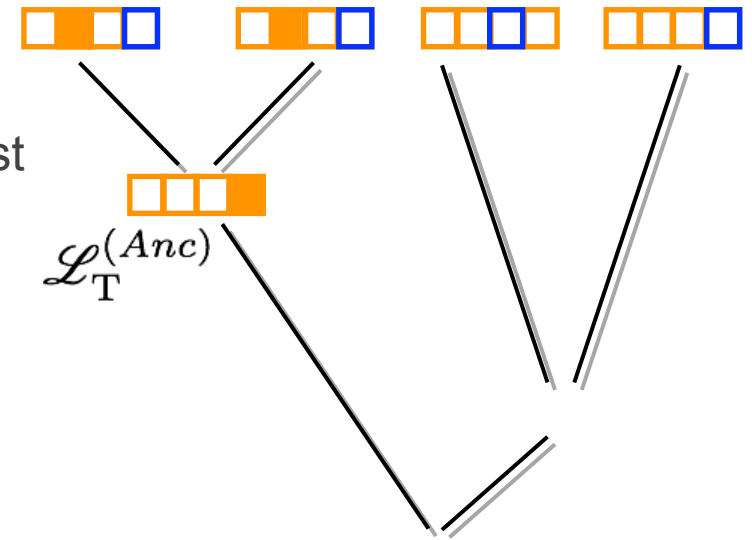
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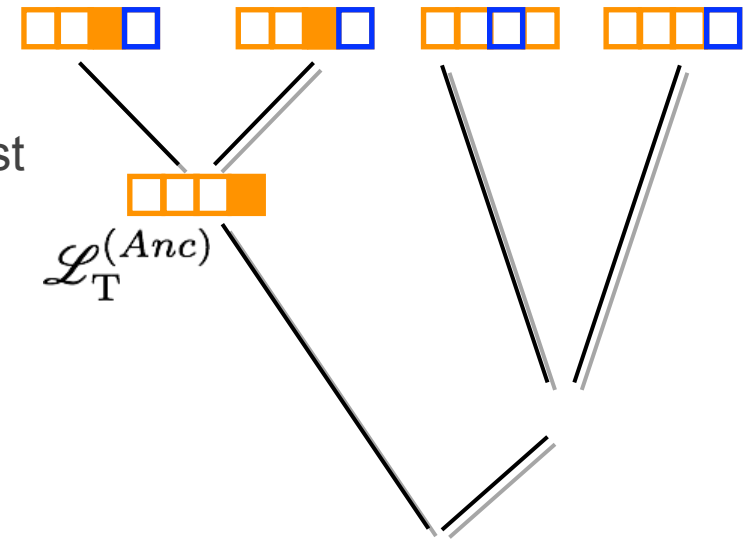
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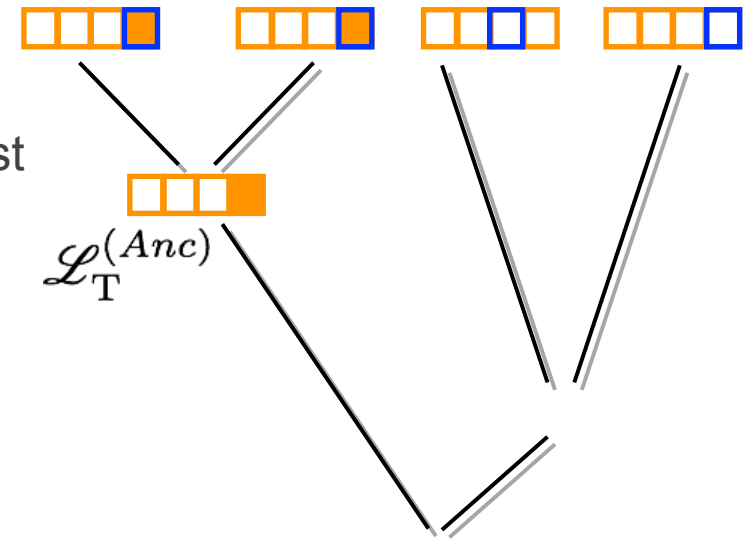


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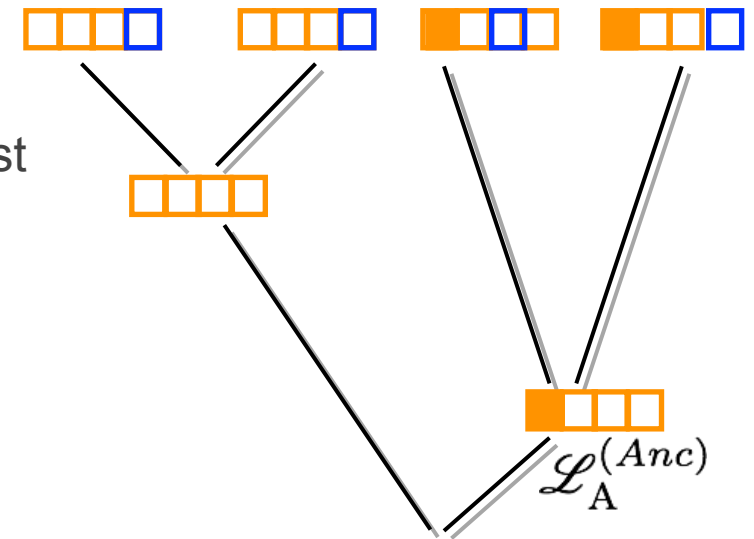


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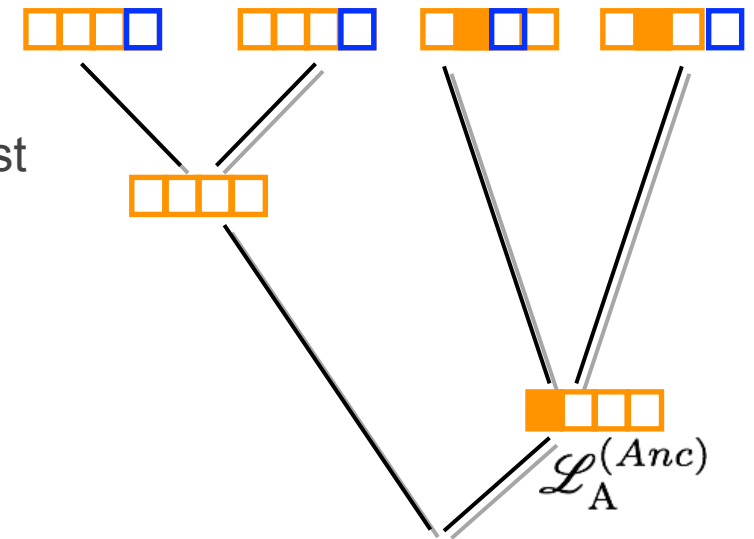


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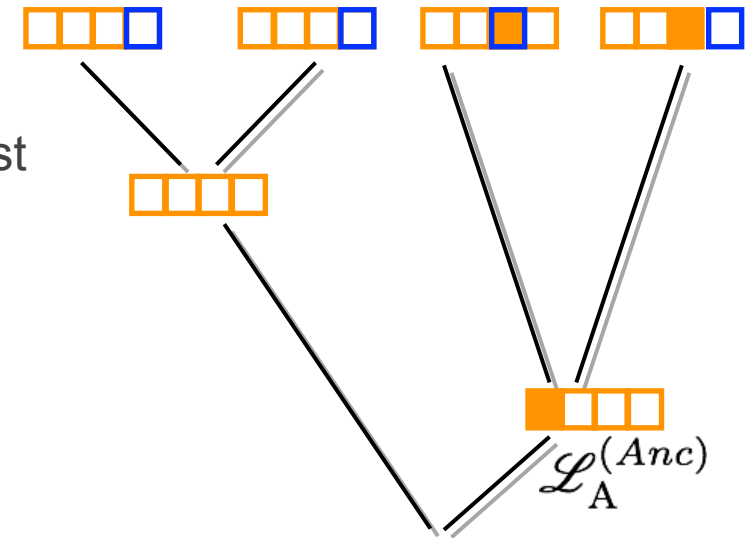


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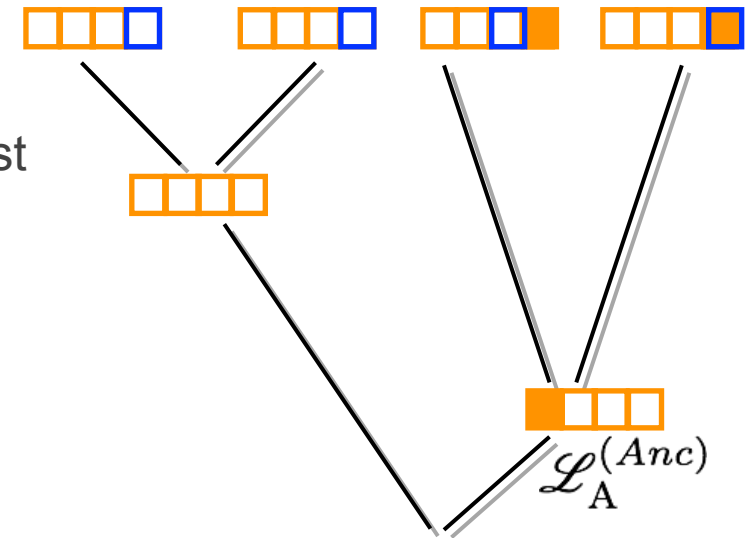


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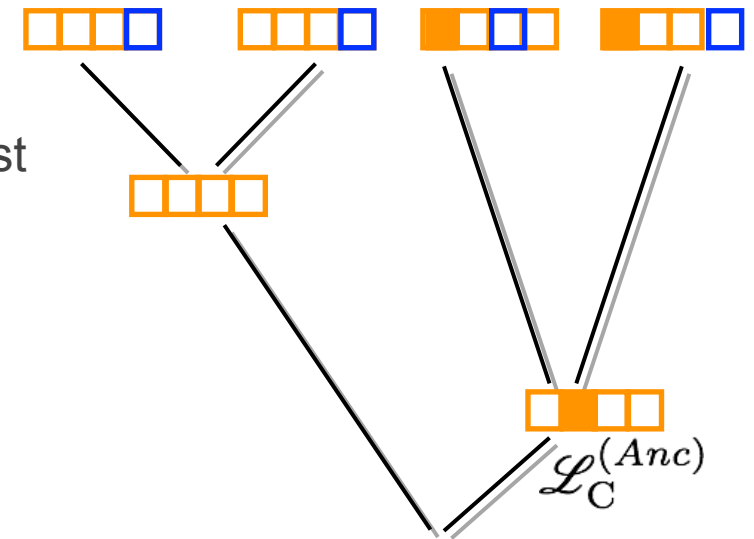


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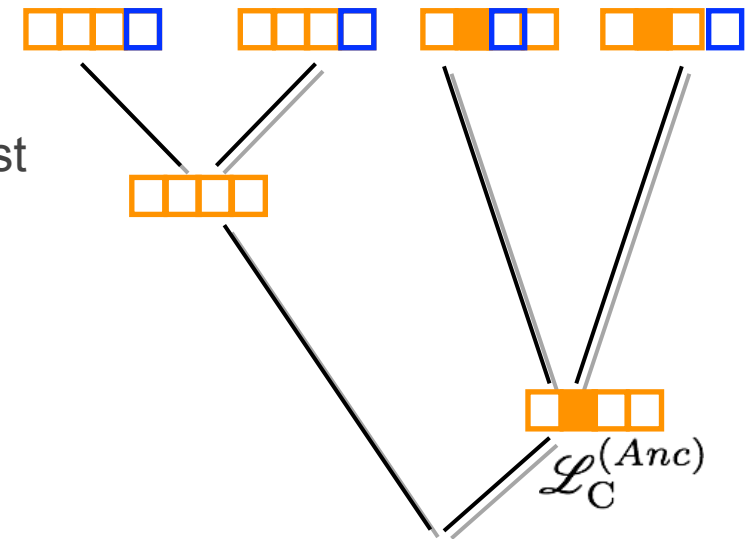


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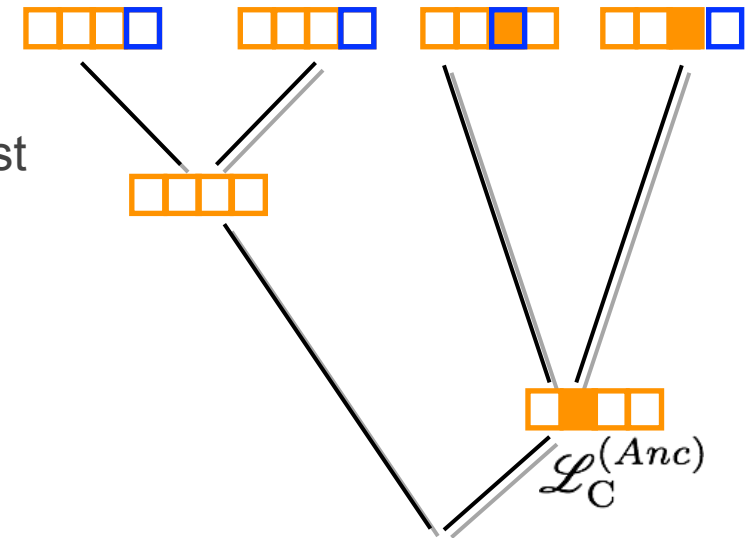


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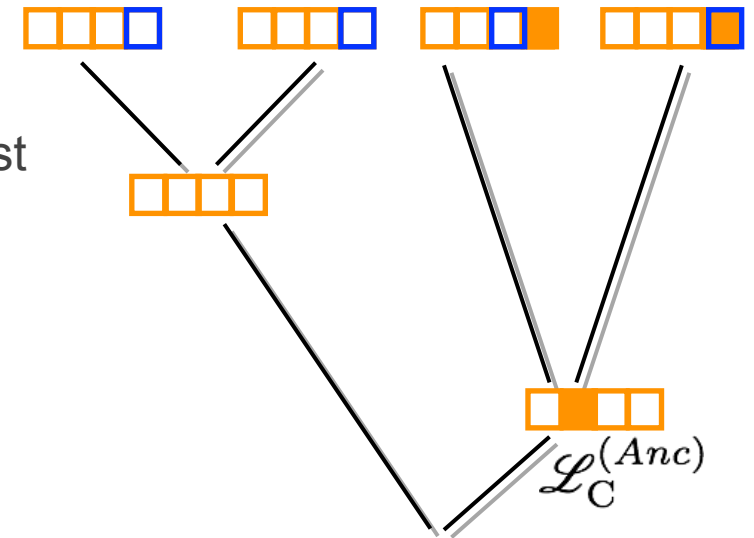
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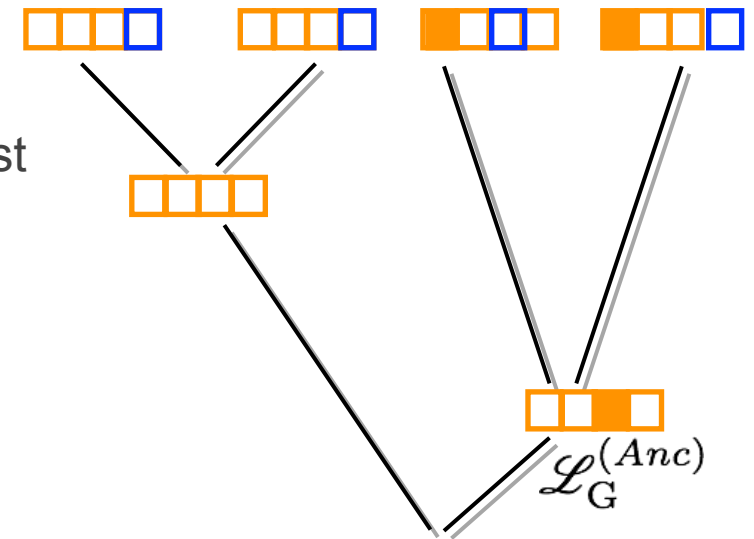


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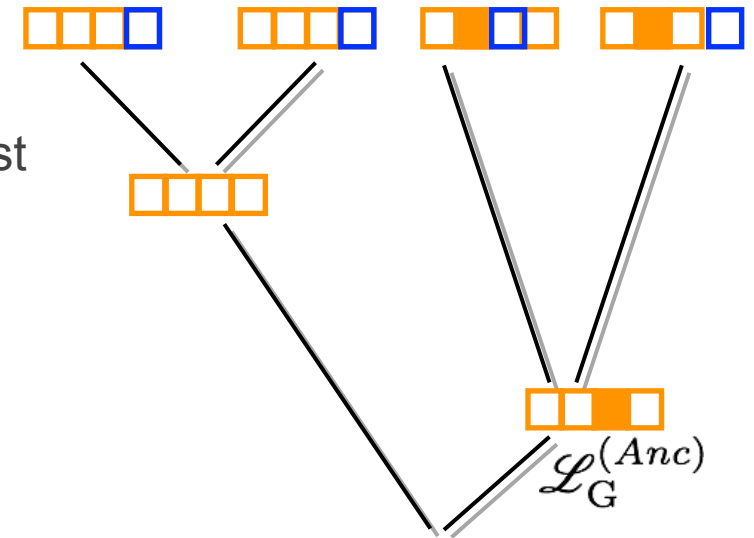


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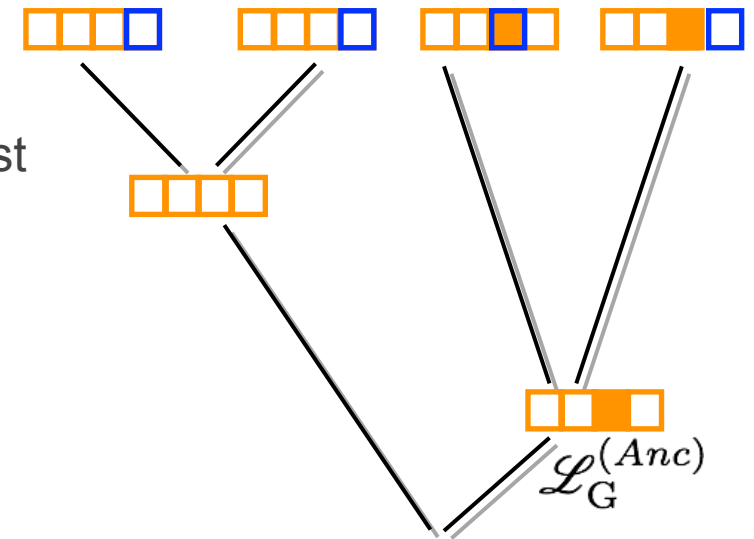


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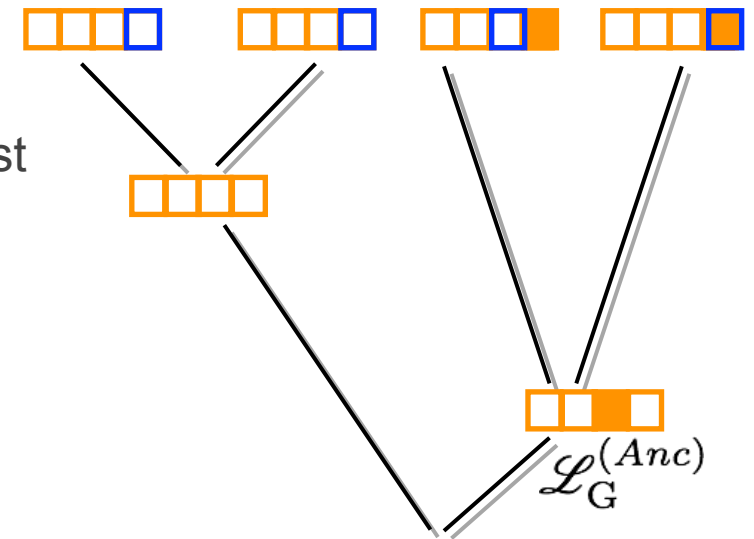


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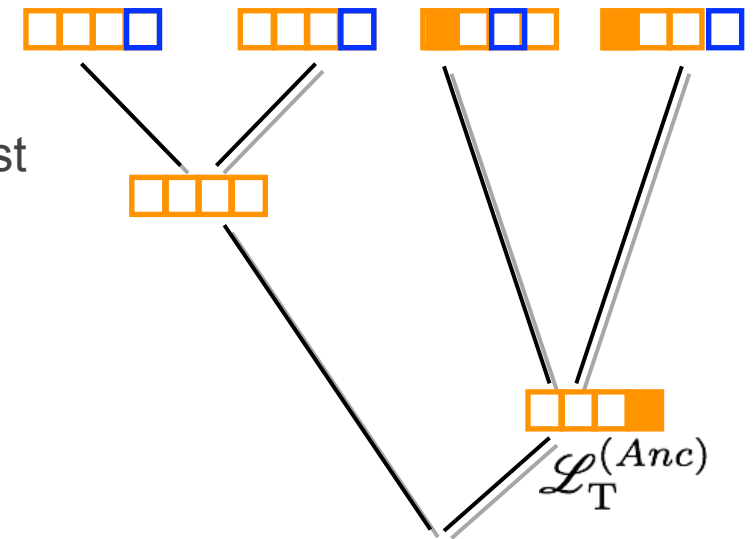


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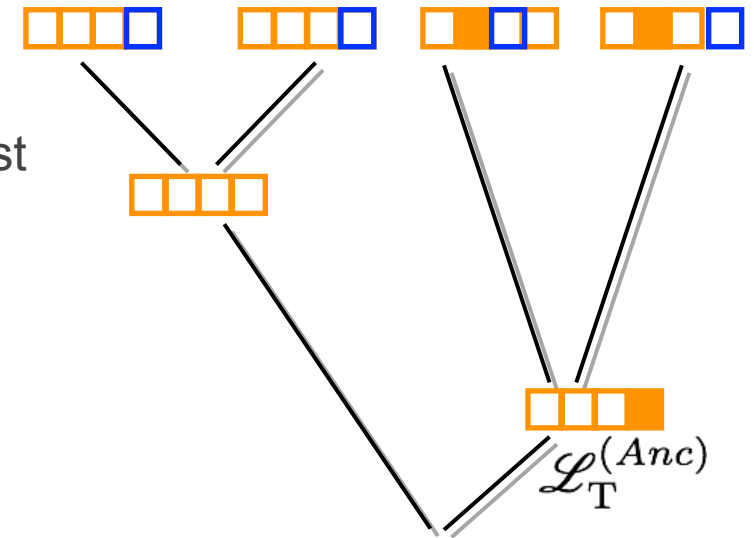


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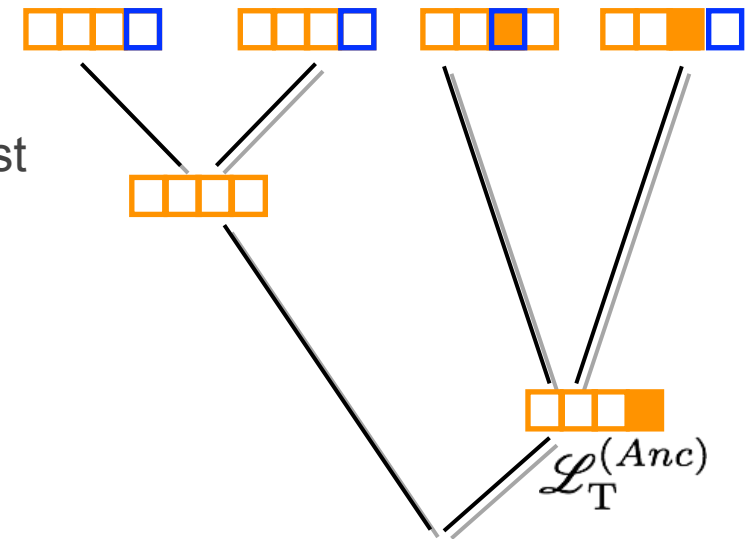


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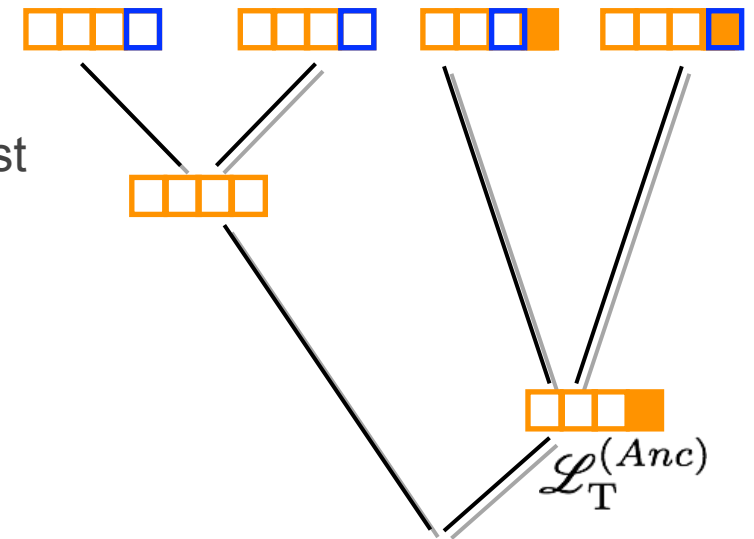
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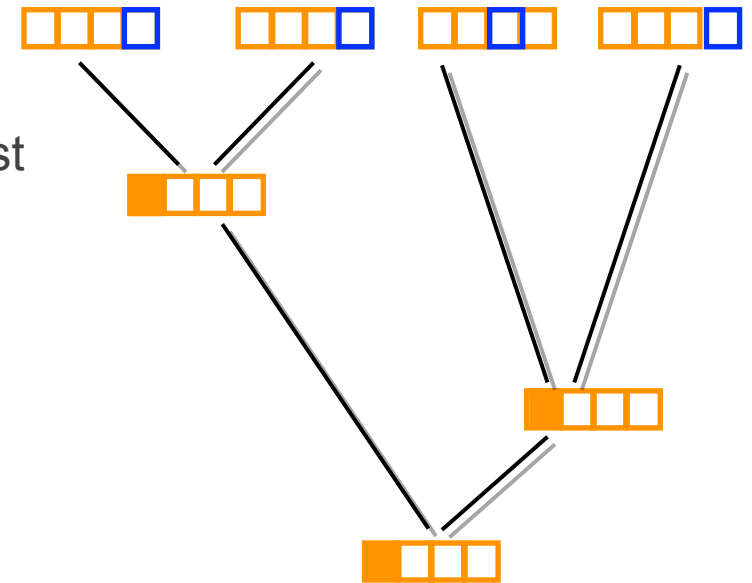


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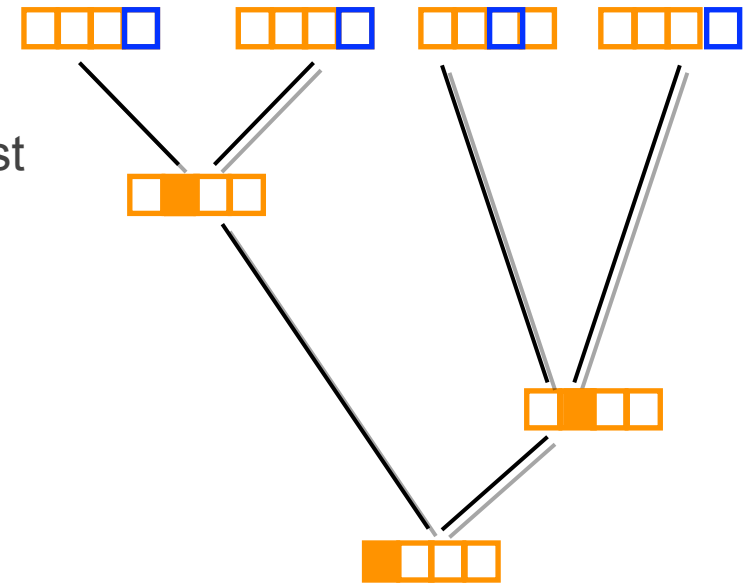


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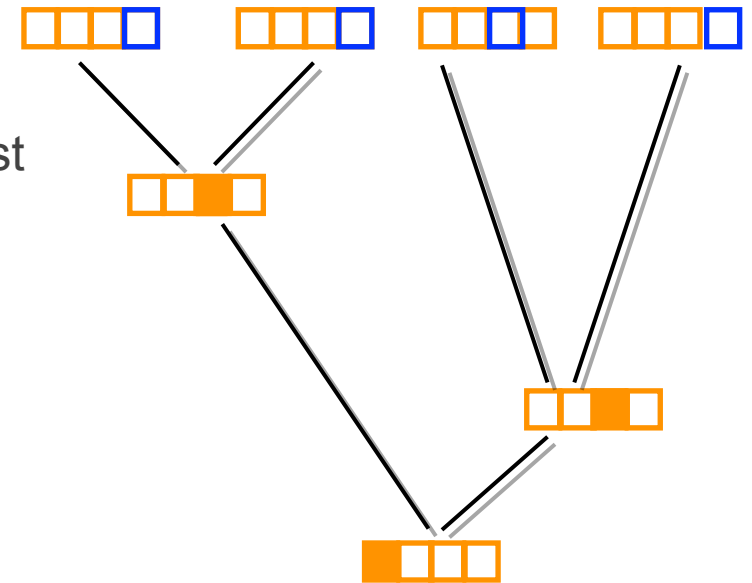
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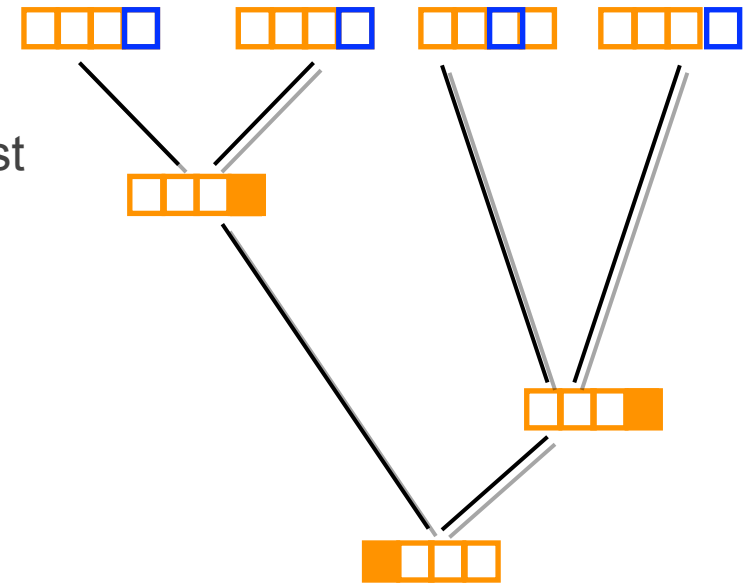
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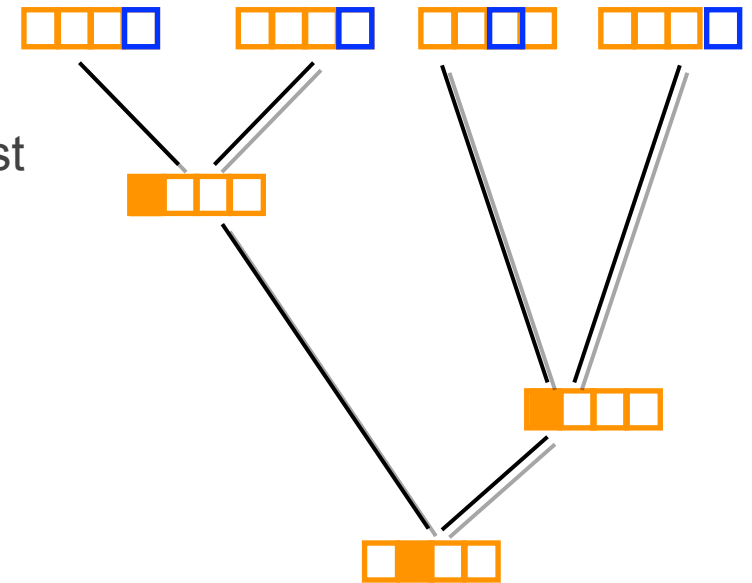
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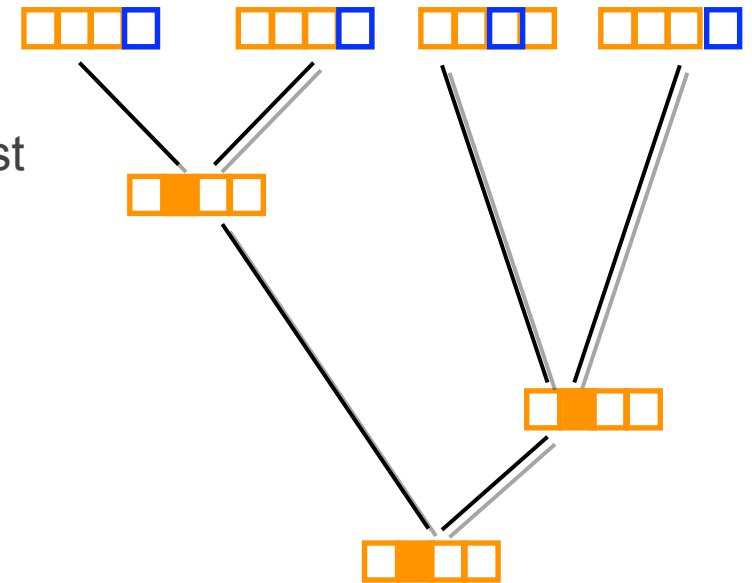
$$\mathcal{L}_A^{(root)}$$

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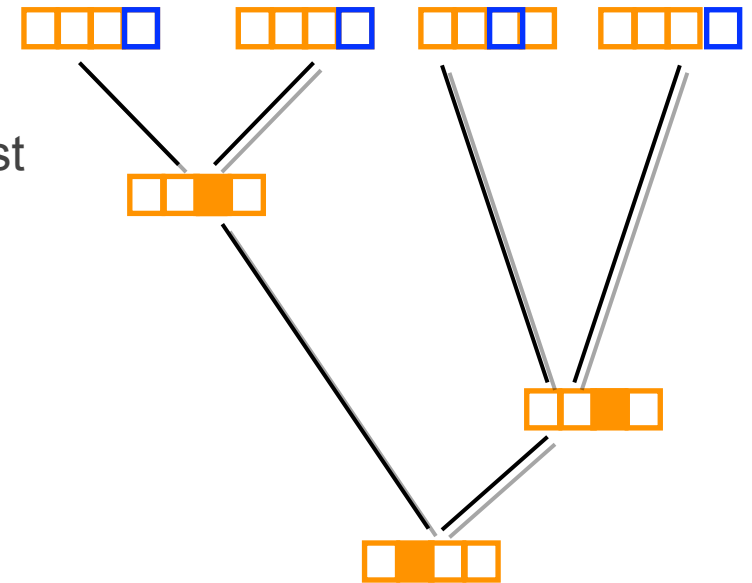
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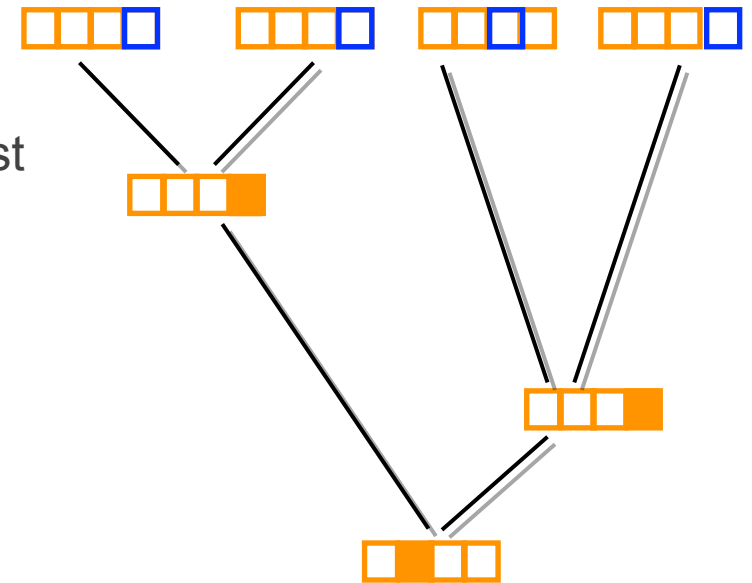
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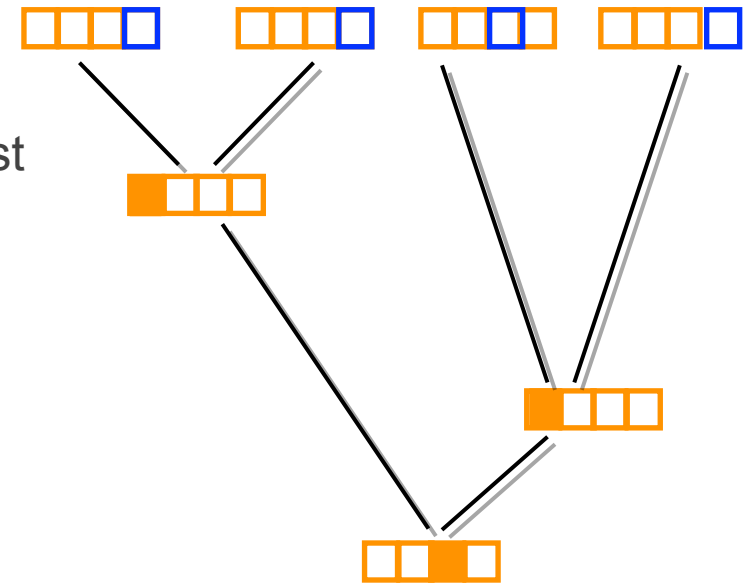
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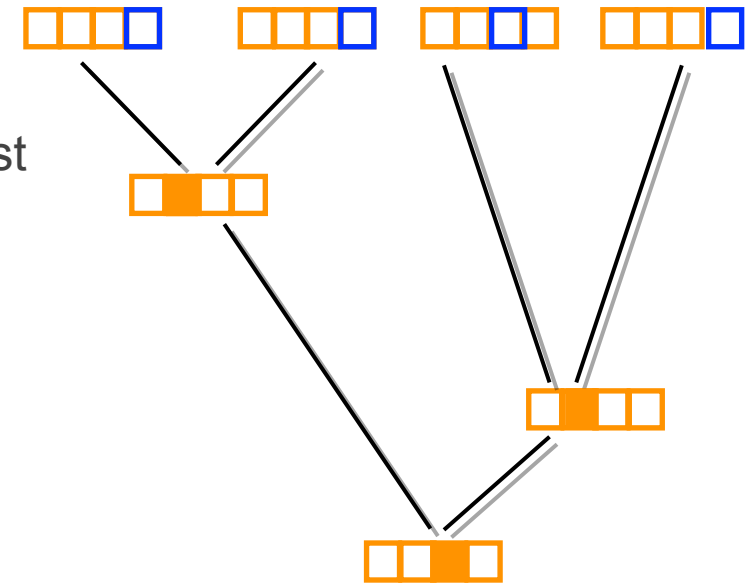
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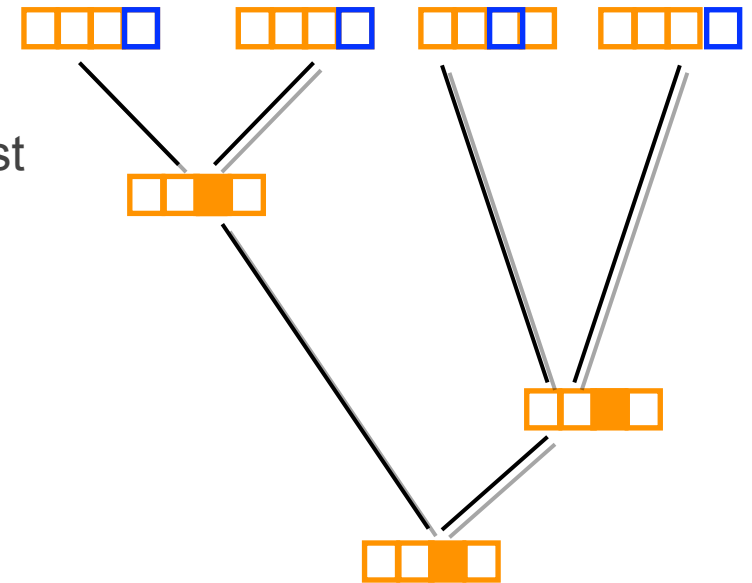
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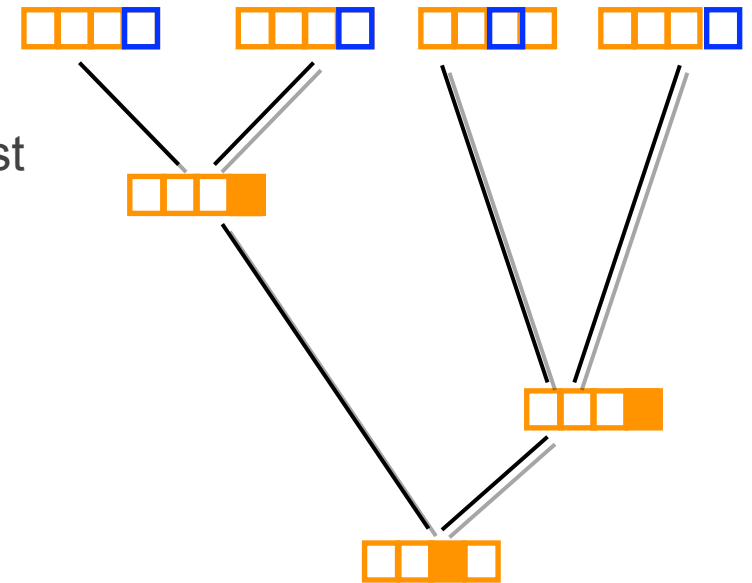
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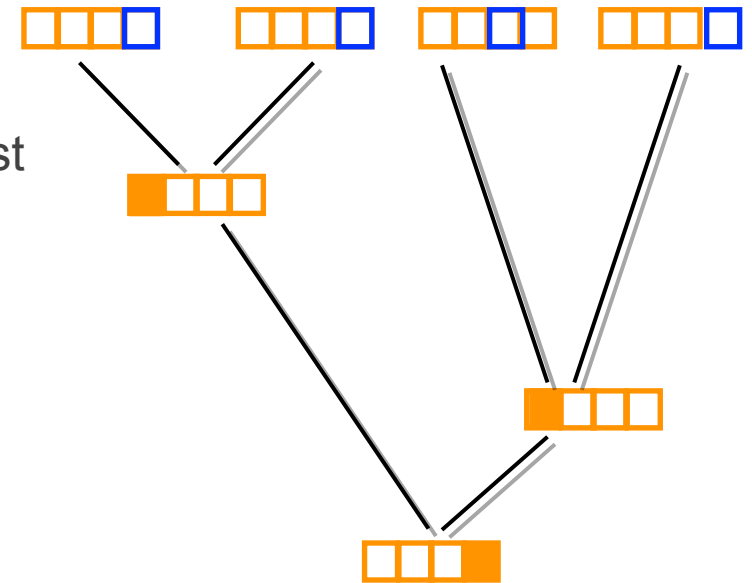
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$\mathcal{L}_A^{(root)}$

$\mathcal{L}_C^{(root)}$

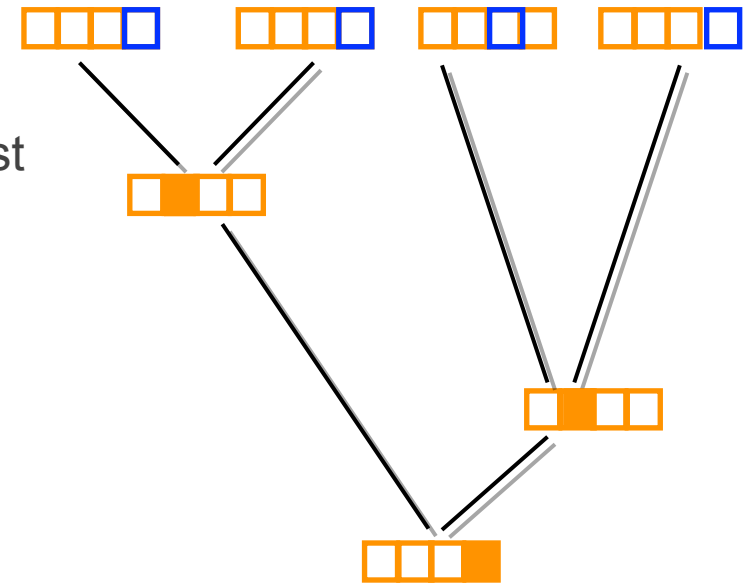
$\mathcal{L}_G^{(root)}$

$\mathcal{L}_T^{(root)}$

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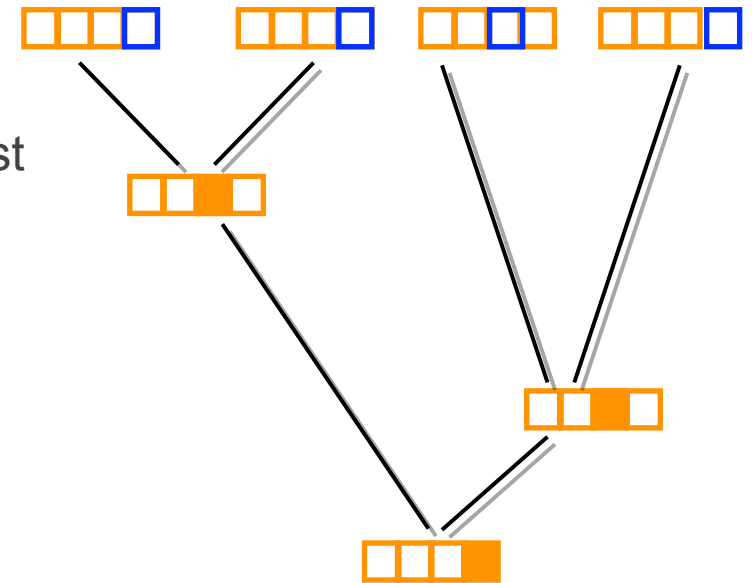
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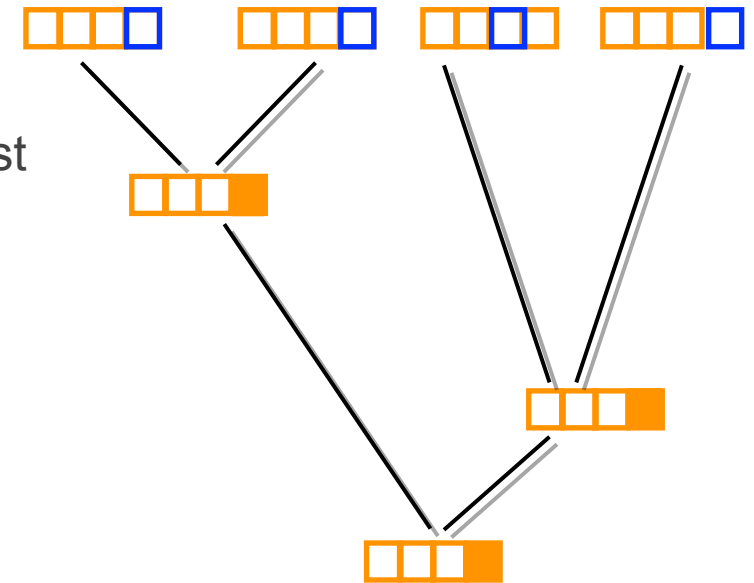
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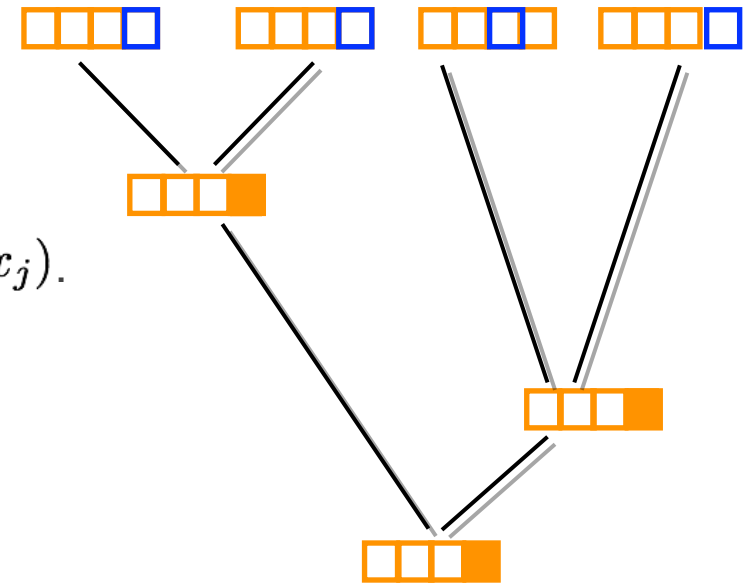
$$\mathcal{L}_G^{(root)}$$

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## The Felsenstein Pruning Algorithm

Upon reaching the root of the tree, the conditional likelihood of each state is 'weighted' by the prior probability (stationary frequency) of the corresponding state,  $\pi_j$ , to give the unconditional probability of the  $j^{th}$  site,  $\mathbf{P}(x_j)$ .



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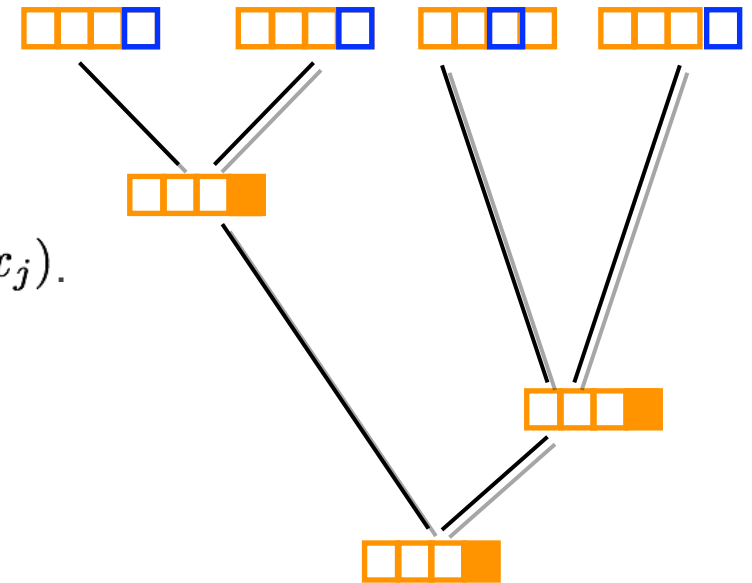
$$\mathcal{L}_T^{(root)}$$

The probability of everything in the tree above the root, given that the process is in state A...

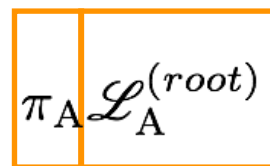
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$\mathcal{L}_C^{(root)}$

$\mathcal{L}_G^{(root)}$

$\mathcal{L}_T^{(root)}$

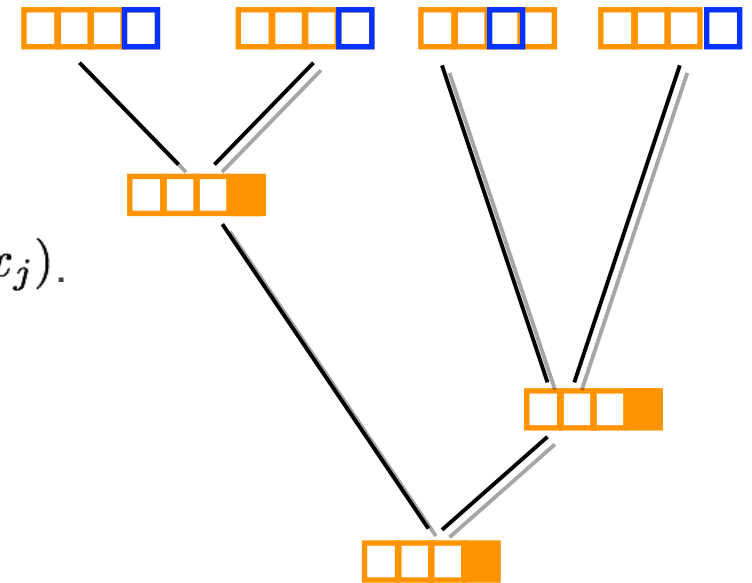
The probability of everything in the tree above the root, *given* that the process is in state A,...

...times the probability that the process *was* in state A at the root.

# How Do We Calculate Site Likelihoods?

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$$\pi_A \mathcal{L}_A^{(root)}$$



$$\pi_C \mathcal{L}_C^{(root)}$$

$$\mathcal{L}_G^{(root)}$$

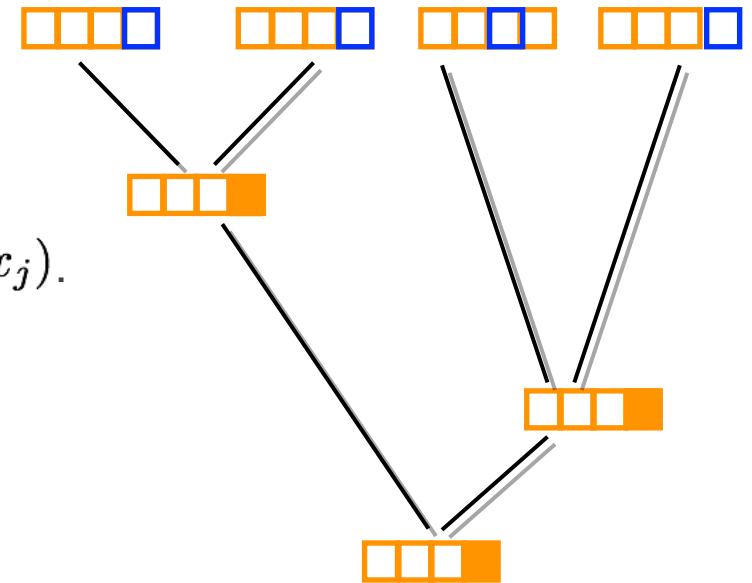
$$\mathcal{L}_T^{(root)}$$

We compute a similar product for the other three states, C...

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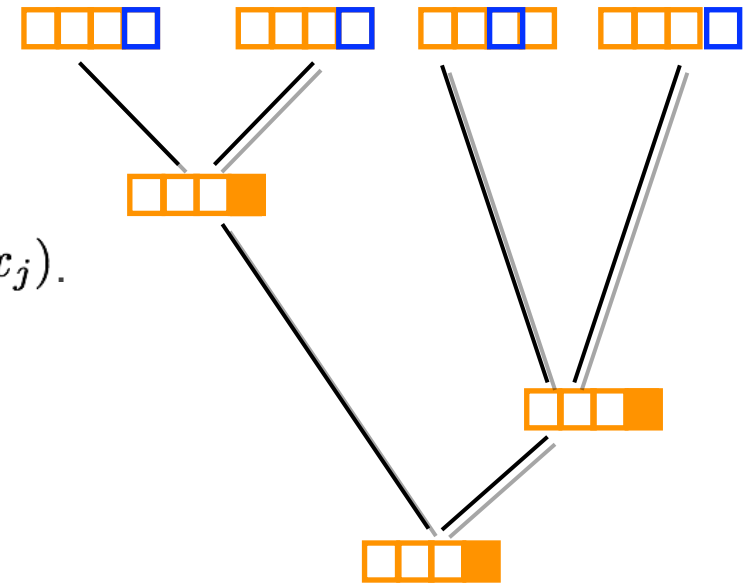
$$\pi_A \mathcal{L}_A^{(root)} \quad \pi_C \mathcal{L}_C^{(root)} \quad \boxed{\pi_G \mathcal{L}_G^{(root)}} \quad \mathcal{L}_T^{(root)}$$

We compute a similar product for the other three states, C, G...

# How Do We Calculate Site Likelihoods?

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$$\pi_A \mathcal{L}_A^{(root)} \quad \pi_C \mathcal{L}_C^{(root)} \quad \pi_G \mathcal{L}_G^{(root)} \quad \boxed{\pi_T \mathcal{L}_T^{(root)}}$$

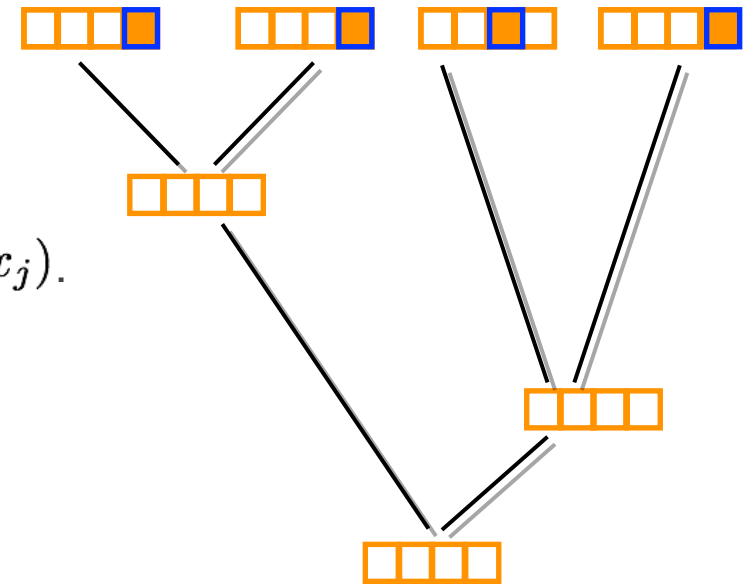


We compute a similar product for the other three states, C, G, and T...

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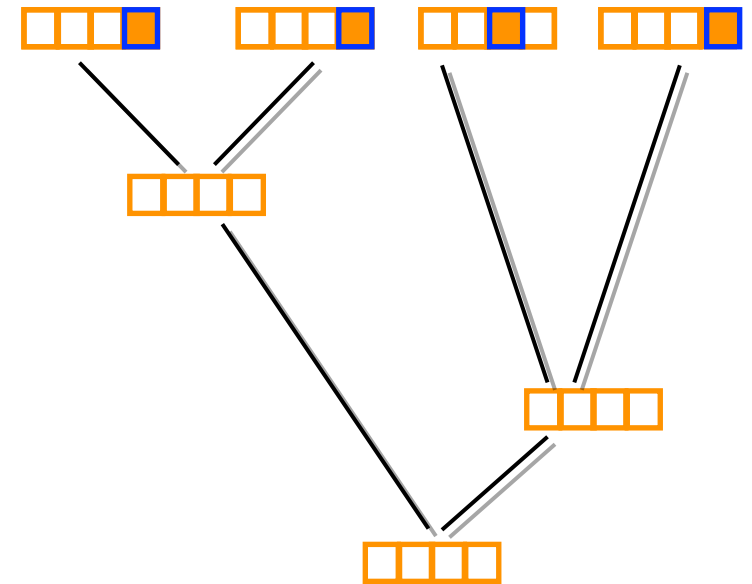
$$\mathbf{P}(\text{TTGT}) = \pi_A \mathcal{L}_A^{(root)} + \pi_C \mathcal{L}_C^{(root)} + \pi_G \mathcal{L}_G^{(root)} + \pi_T \mathcal{L}_T^{(root)}$$

...and then sum the four terms because these root states are mutually exclusive.

# How Do We Calculate Site Likelihoods?

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$$\mathcal{L}_i^{(Anc)} = \left( \sum_{j \in (A, C, G, T)} p_{ij}(\nu_L) \mathcal{L}_j^{(L)} \right) \times \left( \sum_{k \in (A, C, G, T)} p_{ik}(\nu_R) \mathcal{L}_k^{(R)} \right)$$

$$\mathbf{P}(\text{TTGT}) = \pi_A \mathcal{L}_A^{(root)} + \pi_C \mathcal{L}_C^{(root)} + \pi_G \mathcal{L}_G^{(root)} + \pi_T \mathcal{L}_T^{(root)}$$

→ We have computed the likelihood of site pattern TTGT using Felsenstein's pruning algorithm!



# Calculating the Likelihood of several sites

Calculating the likelihood of an alignment assumes independence of sites

We generally assume that the substitution process is independent across sites, which allows us to combine their probabilities as the product of the  $N$  site likelihoods.

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$$L(\tau, \nu, \Theta) \propto f(\mathbf{X} \mid \tau, \nu, \Theta) = \prod_{i=1}^N f(x_i \mid \tau, \nu, \Theta)$$

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$$L(\tau, \nu, \Theta) \propto f(\mathbf{X} \mid \tau, \nu, \Theta) = \prod_{i=1}^N f(x_i \mid \tau, \nu, \Theta)$$

That is, we compute the likelihood for each site in the alignment (one site at a time) and then combine them as a product

# Calculating the Likelihood of several sites

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Although this is a convenient assumption, it is not very biologically realistic.

More complex models can relax it, cf Jeff Thorne's talk.

# Plan: Criteria for evaluating phylogenies

- Criteria for evaluating phylogenetic trees:
  - Parsimony
  - Distance methods
  - Maximum Likelihood
    - Using a Monte Carlo simulation
    - Using Felsenstein's pruning algorithm
  - Posterior probability (Bayesian approach)
- *Conventions:*
  - We're dealing with aligned sequence data
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# Problems when relying on the maximum

So far, we have presented all methods for phylogenetic reconstruction as attempting to find the best tree according to some criterion.

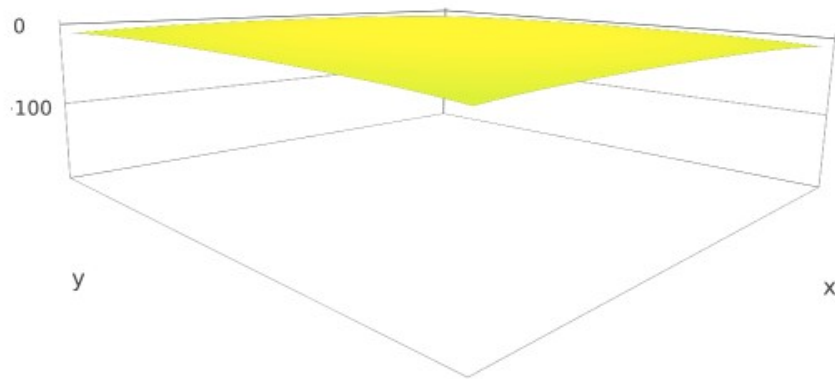
This optimization approach has some drawbacks.

Let's see two examples.

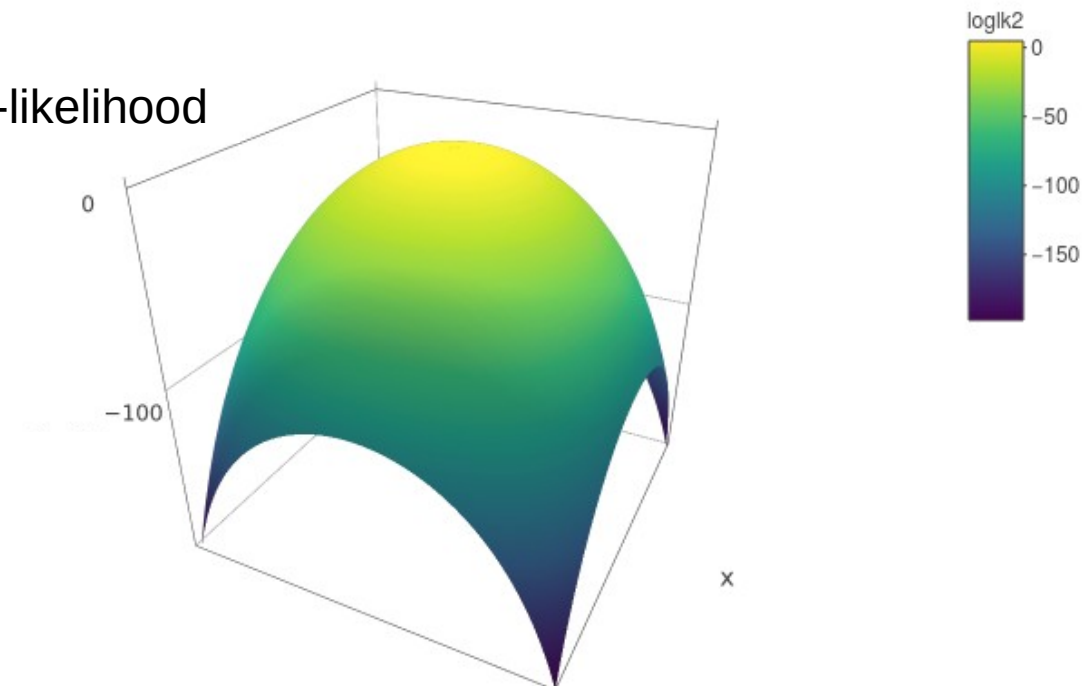
# Problems when relying on the maximum

**Ex. A:** likelihood surface for a simple model with two parameters:

Log-likelihood

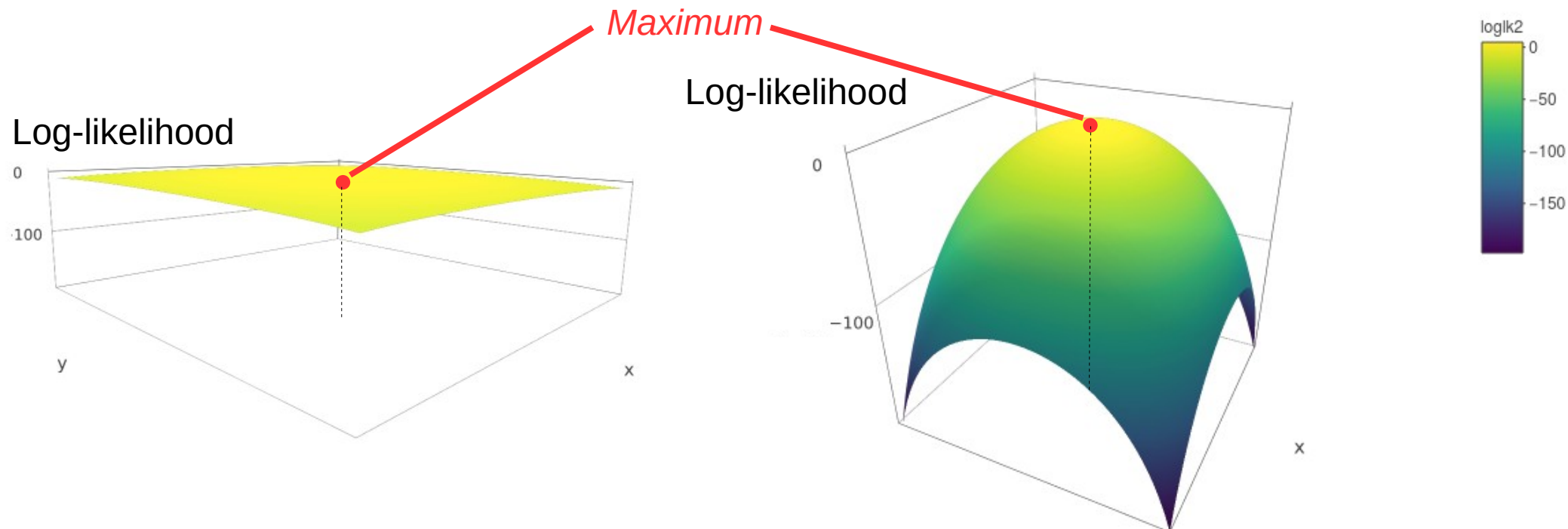


Log-likelihood



# Problems when relying on the maximum

**Ex. A:** likelihood surface for a simple model with two parameters:





# Problems when relying on the maximum

**Ex. B :** Given an alignment, 9 trees have very similar likelihoods and are much more likely than all the other ones.

Taking the most likely tree only provides knowledge about *1* of those 9 almost equi-likely trees.

→ It would be better to take into account all 9 of them!

# Optimizing, integrating, sampling

- **Optimizing:** Looking for the topology and all other parameter values that are most likely
- **Integrating:** visiting all topologies and parameter values according to their probability

Pros :

- If we are interested only in the topology, we integrate over all “nuisance” parameters
- One gets confidence intervals for free
- **Sampling:** like integrating, but we do not attempt to be exhaustive in our exploration of parameter values

# Likelihood vs Bayesian approach for sampling

Likelihood :  $P(D|M, \theta)$

We want to sample parameter values  $\theta$  of model  $M$ .

How can we know that the 9 sets of parameter values  $\theta$  we have sampled are much more likely than all other  $\theta$ , without sampling everything?

$$\sum_{\theta} P(D|M, \theta) \neq 1 \quad \rightarrow \text{NOT a probability distribution.}$$

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*Posterior probability*

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# Bayesian inference

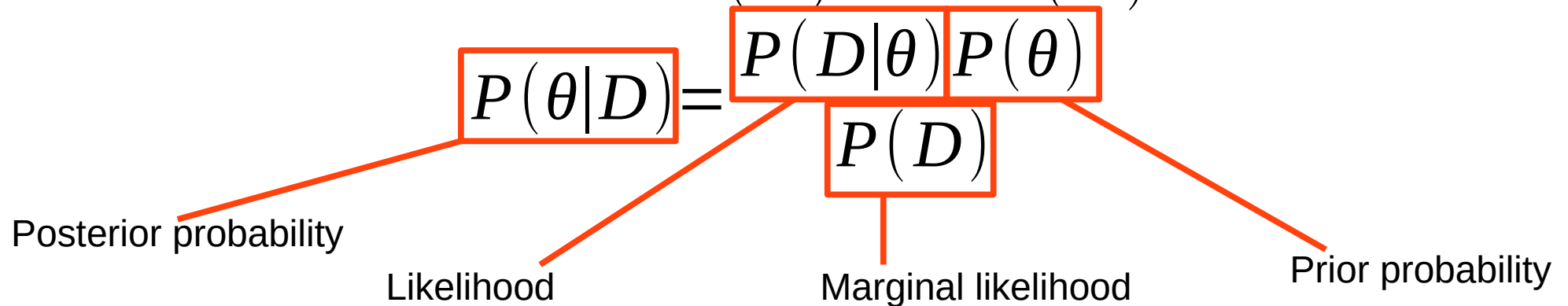
Bayes theorem:

$$P(\theta|D) = \frac{P(\theta \wedge D)}{P(D)} = \frac{P(D \wedge \theta)}{P(D)}$$
$$P(\theta|D) = \frac{P(D|\theta)P(\theta)}{P(D)}$$

# Bayesian inference

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# Bayesian phylogenetics

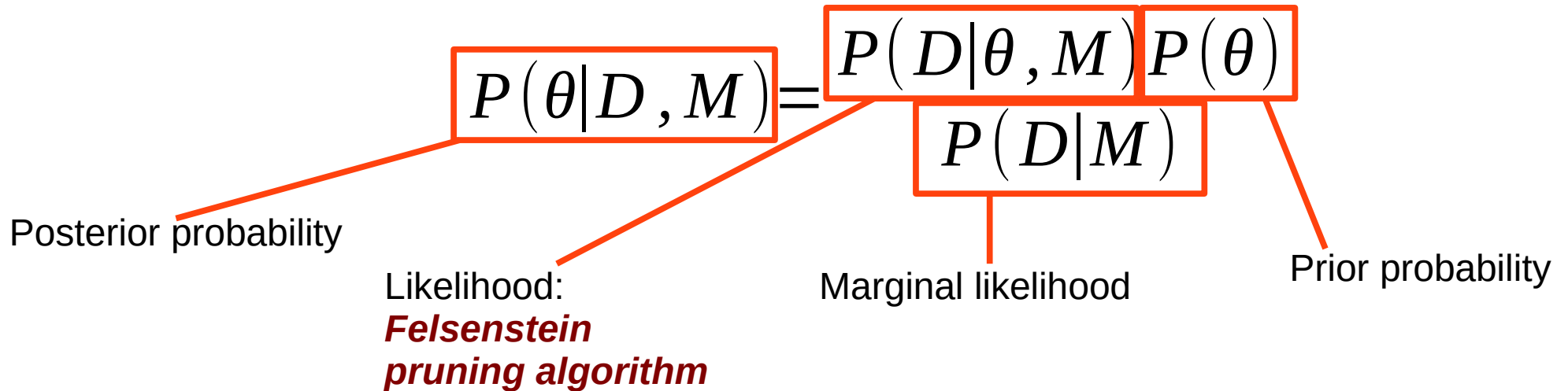
The diagram shows the equation for Bayesian phylogenetics:  $P(\theta|D, M) = \frac{P(D|\theta, M)P(\theta)}{P(D|M)}$ . Each term is enclosed in a red box. Red lines connect the boxes to their respective labels: 'Posterior probability' for  $P(\theta|D, M)$ , 'Likelihood' for  $P(D|\theta, M)$ , 'Marginal likelihood' for  $P(D|M)$ , and 'Prior probability' for  $P(\theta)$ .

$$P(\theta|D, M) = \frac{P(D|\theta, M)P(\theta)}{P(D|M)}$$

Posterior probability      Likelihood      Marginal likelihood      Prior probability

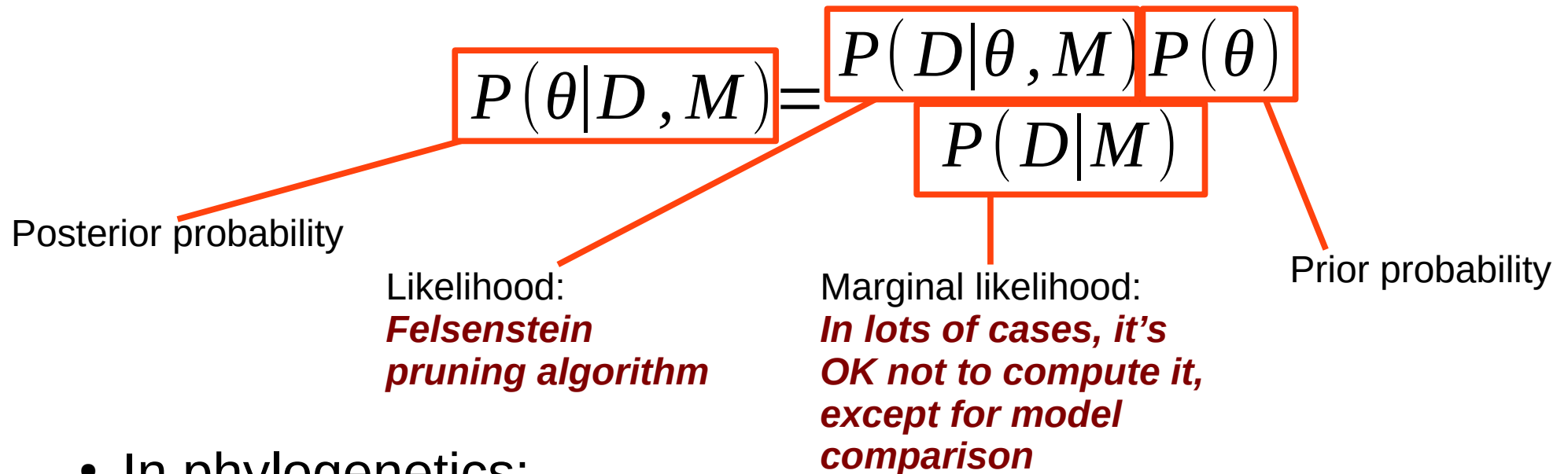
- In phylogenetics:
  - D: aligned sequence data
  - M: the model can be very complicated, but usually contains:
    - Topology
    - Branch lengths
    - Rate matrix
    - Etc...
  - $\theta$ : the values of the parameters above

# Bayesian phylogenetics



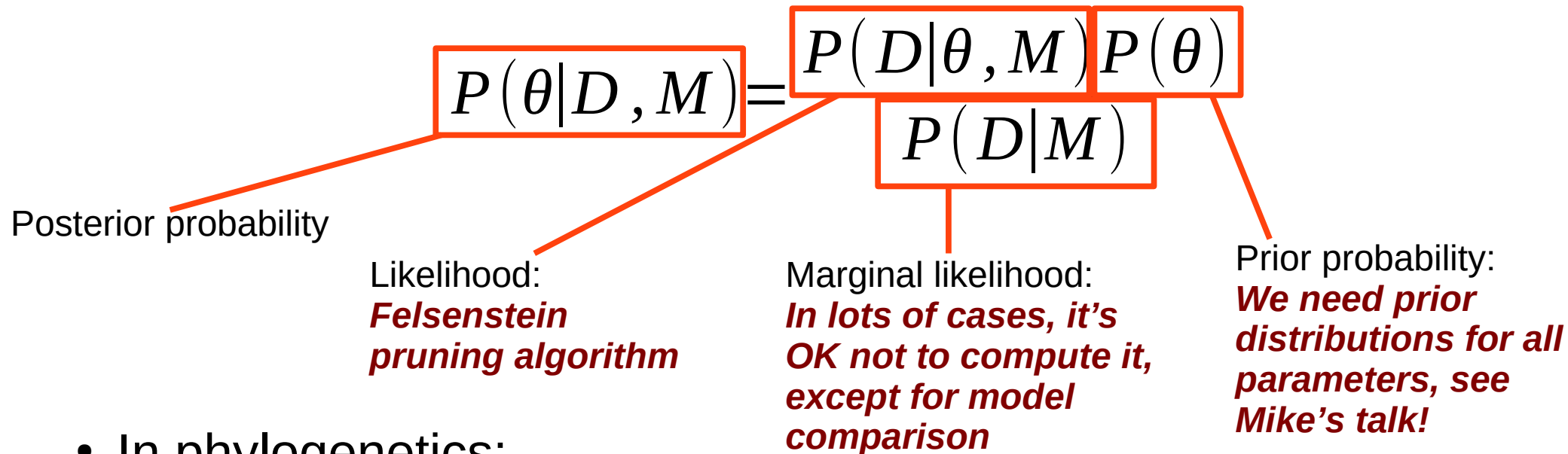
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# Bayesian phylogenetics



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# Conclusion

- One can perform inference according to the posterior probability of a probabilistic model
- That's what Bayesian inference is about
- It combines the likelihood with priors on parameter values
- In phylogenetics, the likelihood is typically computed thanks to Felsenstein's pruning algorithm (1981)
- Then priors need to be defined for:
  - Topologies and branch lengths / chronograms
  - Rates
  - Other parameters... (cf Mike)
- When parameters are independent, to compute the prior of all parameter values, one only needs to compute the product over individual parameter priors

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***Optimization algorithms  
(Alexis)***

***Bayesian inference and  
MCMC  
(Mike)***