Maximum Likelihood Methods in Molecular Phylogeny

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Main Types of Phylogenetic Methods

Data	Method	Evaluation Criterion
Characters (Alignment)	**Maximum Parsimony**	Parsimony
	Statistical Approaches: Likelihood, Bayesian	Evolutionary Models
Distances	**Distance Methods**	Evolutionary Models

Introduction: ML on Coin Tossing

Given a box with 3 coins of different fairness $\left(\frac{1}{3}, \frac{1}{2}, \frac{2}{3} \text{ heads}\right)$

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Probability

$$p(k \text{ heads in } n \text{ tosses}|\theta)$$

Aim: The ML approach seaches for that parameter set θ for the generating process which maximizes the probability of our given data.

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	Probability		**Likelihood**
$p(k \text{ heads in } n \text{ tosses}\|\theta)$	$\equiv$	$L(\theta\|k \text{ heads in } n \text{ tosses})$	
	$=$	$\binom{n}{k}\theta^k(1-\theta)^{n-k}$	
		(here binomial distribution)	

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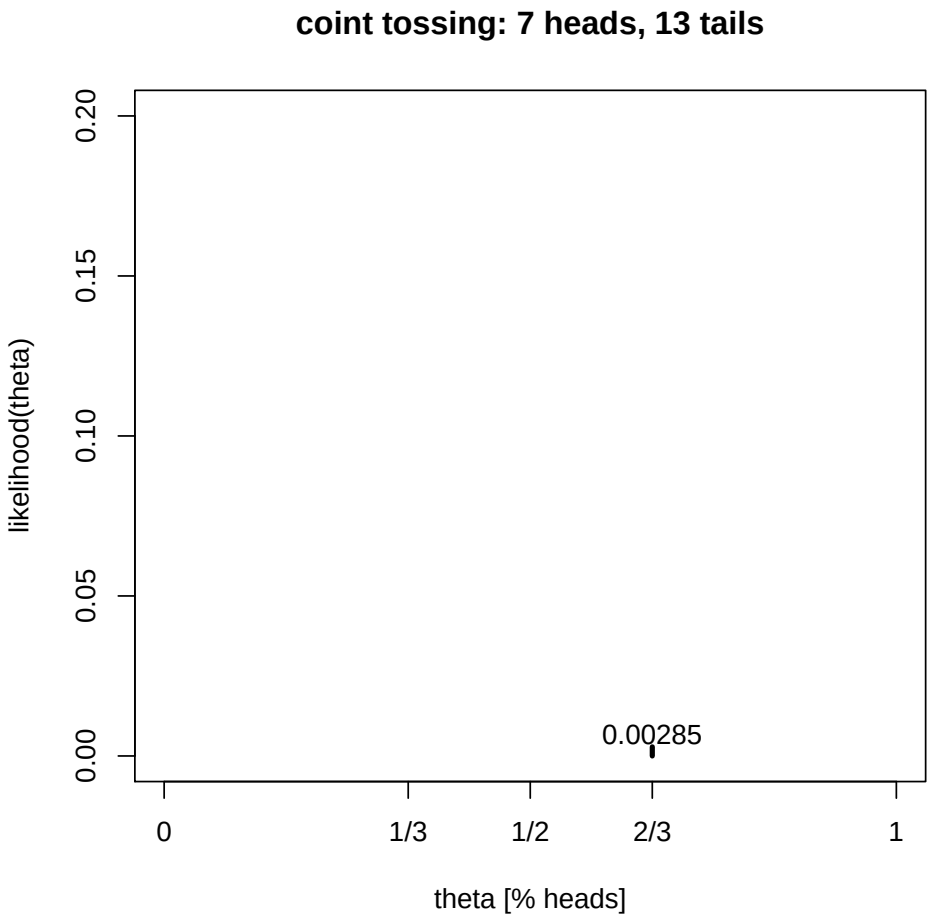

Three coin case

$$L(\theta|7 \text{ heads in } 20) = \binom{20}{7}\theta^7(1-\theta)^{13}$$

for each coin $\theta \in \left\{\frac{1}{3}, \frac{1}{2}, \frac{2}{3}\right\}$

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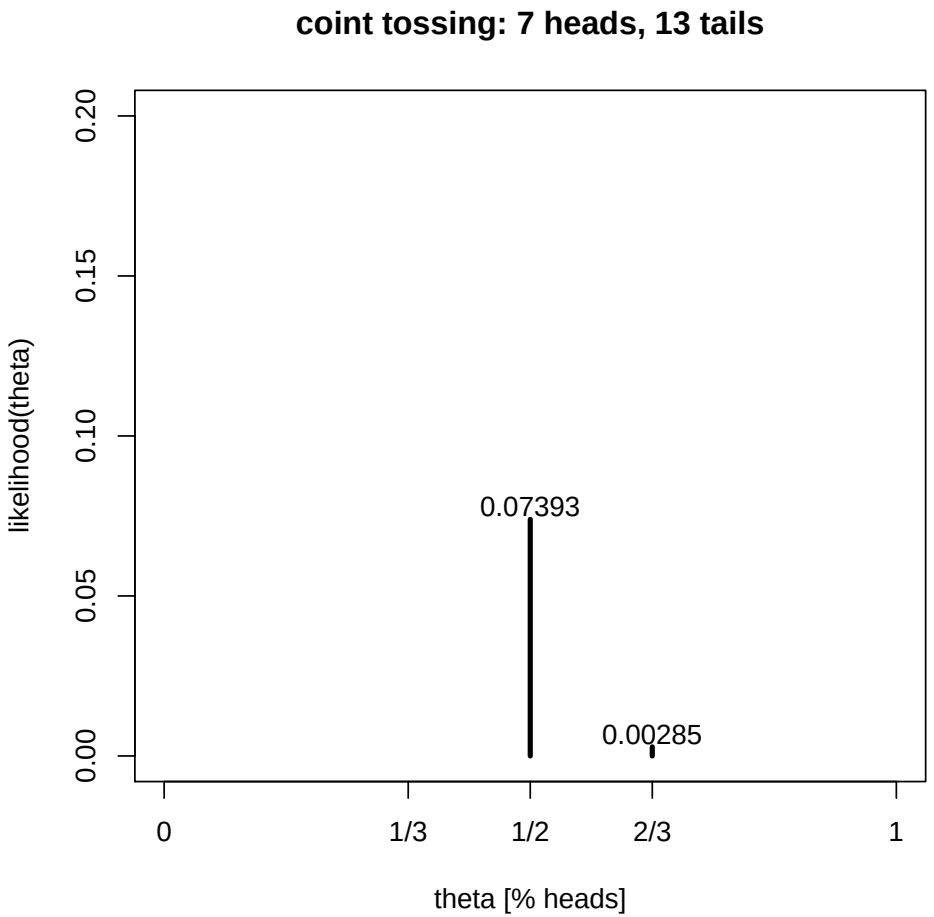

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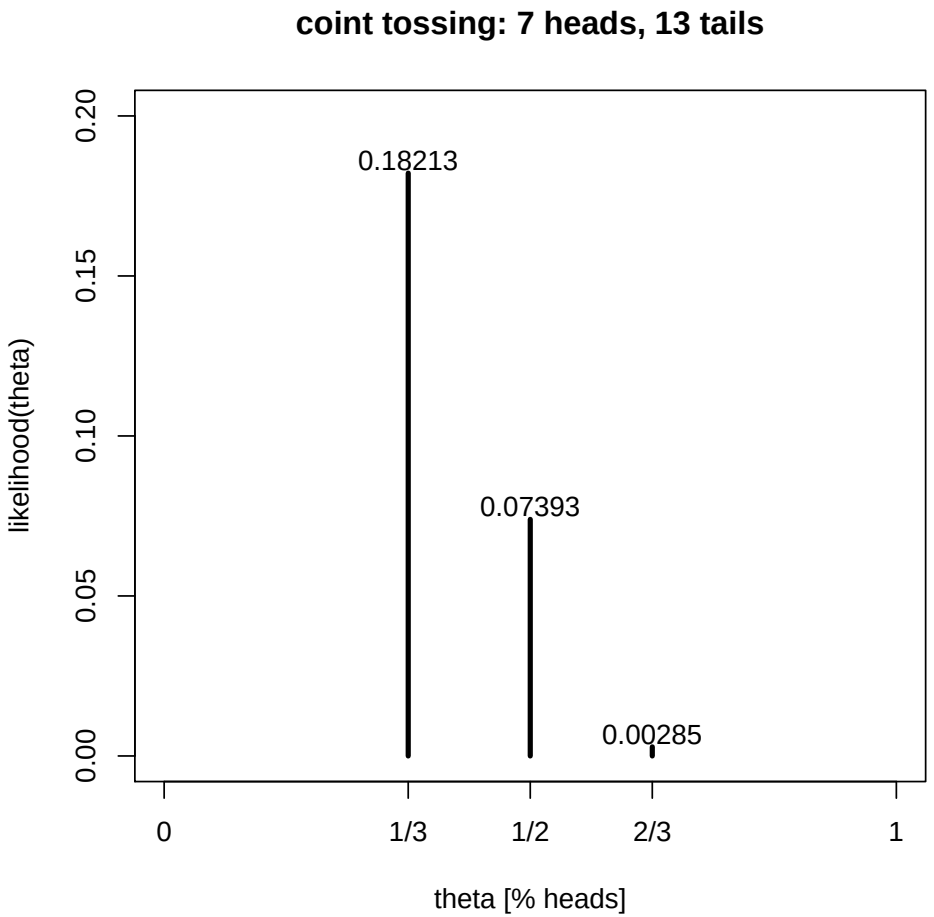

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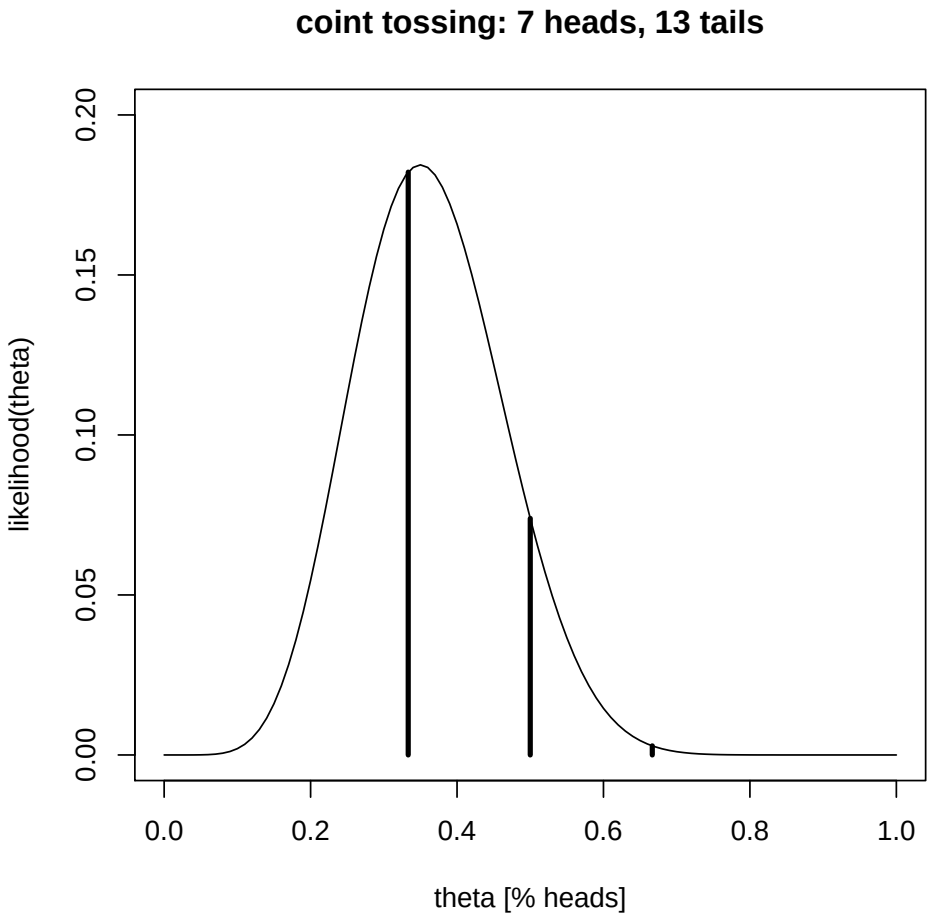

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For infinitely many coins
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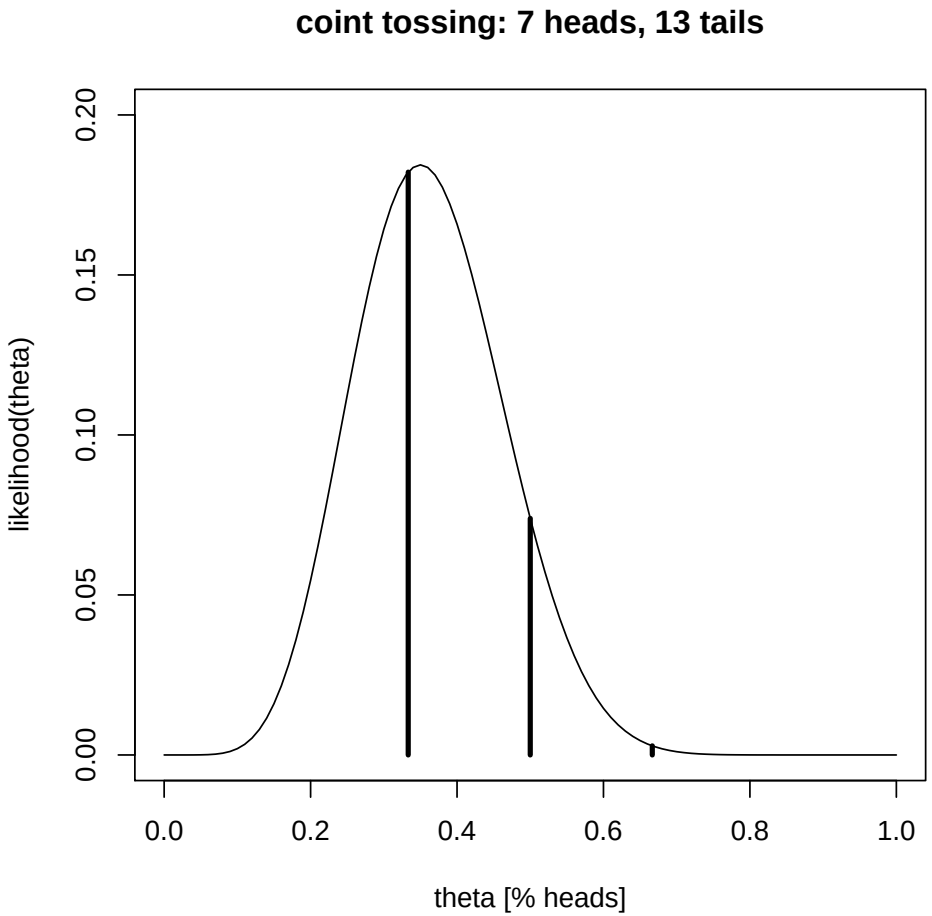

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ML estimate: $L(\hat{\theta}) = 0.1844$ where coin shows $\hat{\theta} = 0.35$ heads

From Coins to Phylogenies?

While the coin tossing example might look easy, in phylogenetic analysis, the parameter (set) θ comprises:

- evolutionary model
- its parameters
- tree topology
- its branch lengths

That means, a high dimensional optimization problem.
Hence, some parameters are often estimated/set separately.

Modeling Evolution

- Evolution is usually modeled as a

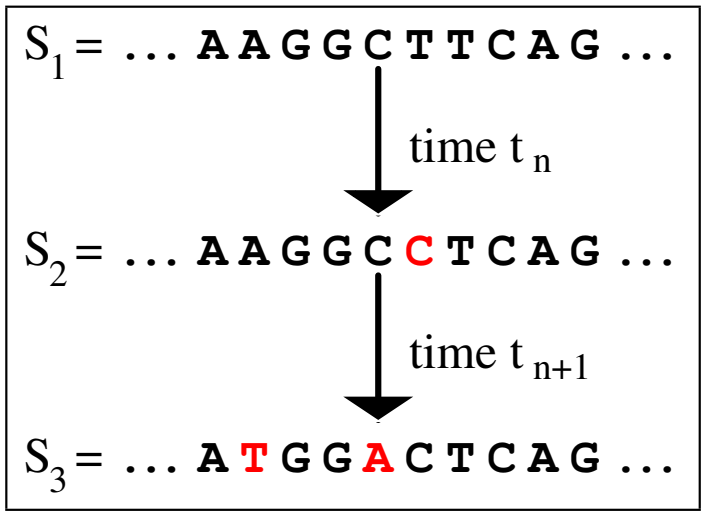
  stationary, time-reversible Markov process.

- What does that mean?

Assumptions on Evolution

Markov Process

The (evolutionary) process evolves without memory, i.e. sequence S_2 mutates to S_3 during time t_{n+1} independent of state of S_1.



Assumptions on Evolution

Stationary:
The overall character frequencies π_j of the nucleotides or amino acids are in an equilibrium and remain constant.

Time-Reversible:
Mutations in either direction are equally likely

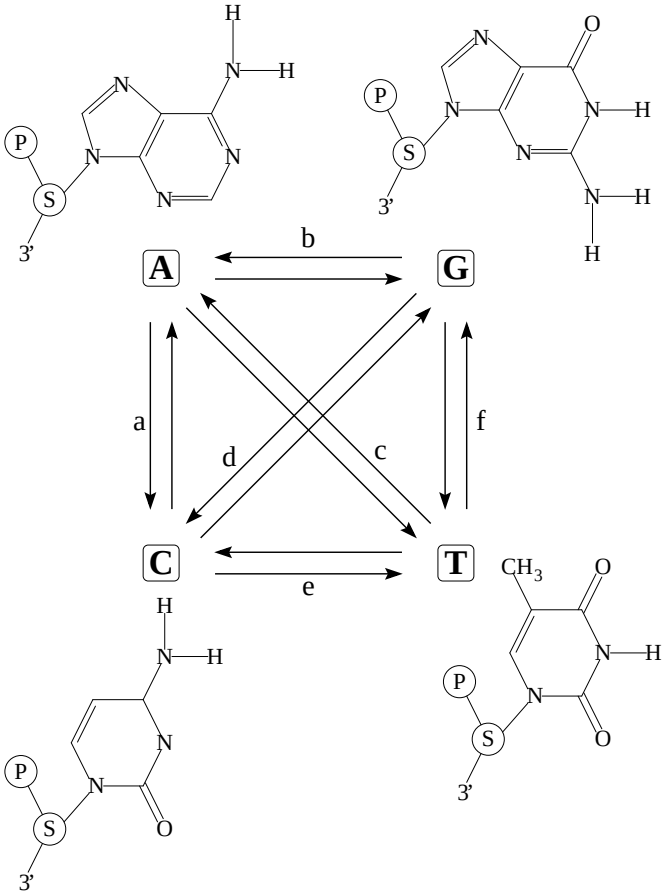
$$\pi_i \cdot P_{ij}(t) = P_{ji}(t) \cdot \pi_j$$

This means a mutation is as likely as its back mutation.

$$P(i \rightarrow j) = P(i \leftarrow j) \qquad \text{(JC69)}$$

Substitution Models

Evolutionary models are often described using a substitution rate matrix R and character frequencies Π. Here, 4×4 matrix for DNA models:



$$R = \begin{pmatrix} A & C & G & T \\ - & a & b & c \\ a & - & d & e \\ b & d & - & f \\ c & e & f & - \end{pmatrix}$$

$$\Pi = (\pi_A, \pi_C, \pi_G, \pi_T)$$

From Substitution rates to probabilities

. . . R and Π are combined into the instantaneous rate matrix Q

$$Q = \begin{pmatrix} \bullet_A & a\pi_C & b\pi_G & c\pi_T \\ a\pi_A & \bullet_C & d\pi_G & e\pi_T \\ b\pi_A & d\pi_C & \bullet_G & f\pi_T \\ c\pi_A & e\pi_C & f\pi_G & \bullet_T \end{pmatrix} \qquad \begin{aligned} \bullet_A &= -(a\pi_C + b\pi_G + c\pi_T) \\ \bullet_C &= -(a\pi_A + d\pi_G + e\pi_T) \\ \bullet_G &= -(b\pi_A + d\pi_C + f\pi_T) \\ \bullet_T &= -(c\pi_A + e\pi_C + f\pi_G) \end{aligned}$$

(where the row sums are zero).

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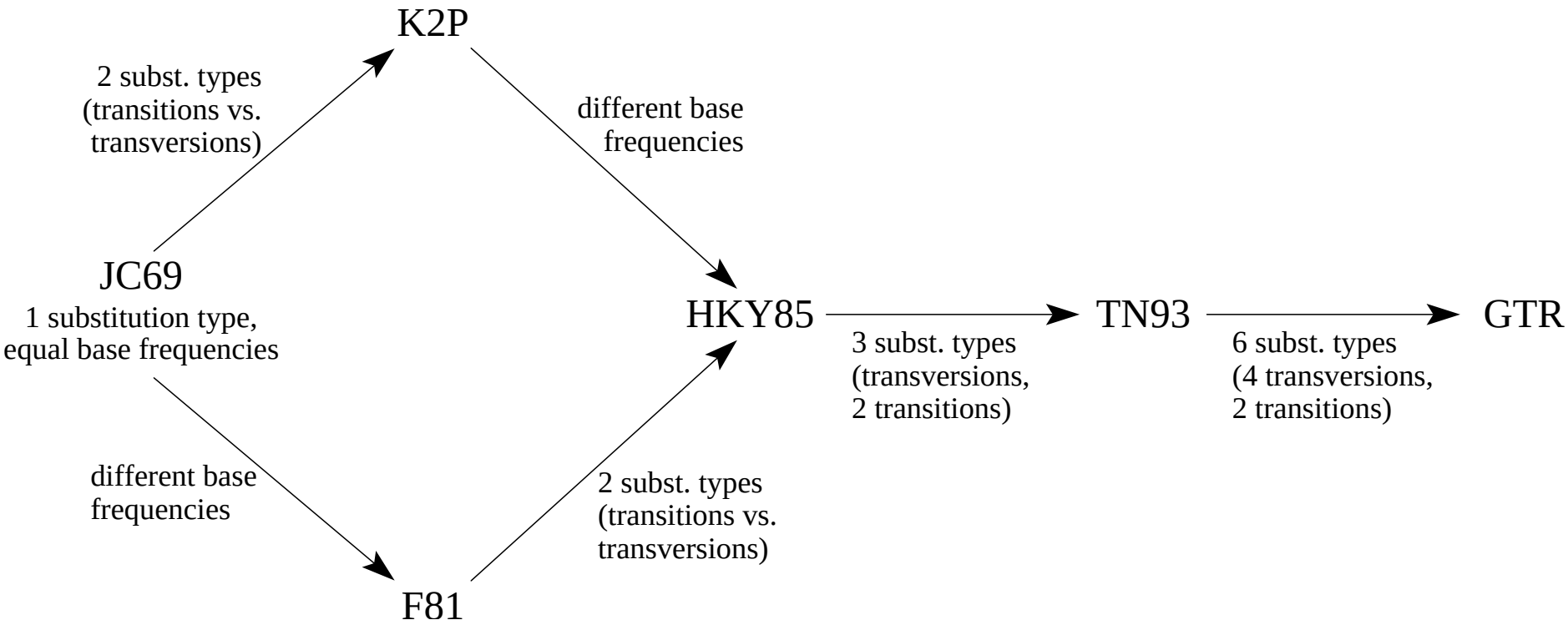
Given now the instantaneous rate matrix Q, we can compute a substitution probability matrix P

$$P(t) = e^{Qt}$$

With this matrix P we can compute the probability $P_{ij}(t)$ of a change $i \longrightarrow j$ over a time t.

Relations between DNA models



Protein Models

Generally this is the same for protein sequences, but with 20×20 matrices. Some protein models are:

- Poisson model ("JC69" for proteins)
- Dayhoff (Dayhoff *et al.*, 1978)
- JTT (Jones *et al.*, 1992)
- mtREV (Adachi & Hasegawa, 1996)
- cpREV (Adachi *et al.*, 2000)
- VT (Müller & Vingron, 2000)
- WAG (Whelan & Goldman, 2000)
- BLOSUM 62 (Henikoff & Henikoff, 1992)

Computing ML Distances Using $\mathbf{P_{ij}(t)}$

The Likelihood of sequence s evolving to s' in time t:

$$L(t|s \rightarrow s') = \prod_{i=1}^{m} \Big(\Pi(s_i) \cdot P_{s_i s'_i}(t) \Big)$$

Likelihood surface for two sequences under JC69:

GATCCTGAGAGAAATAAAC
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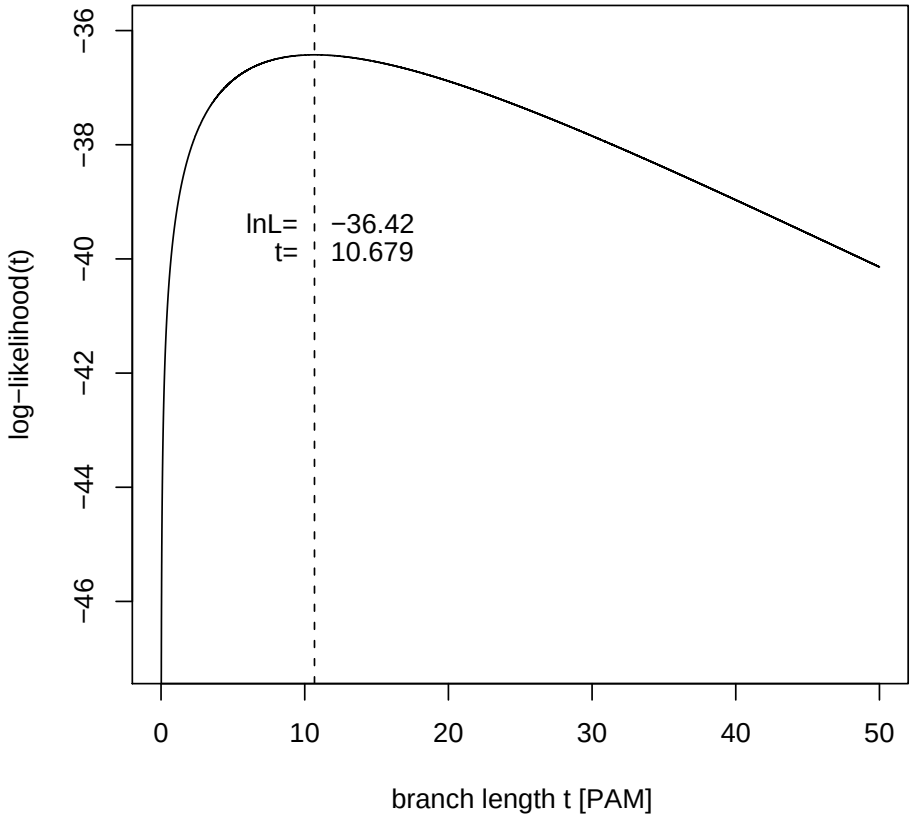
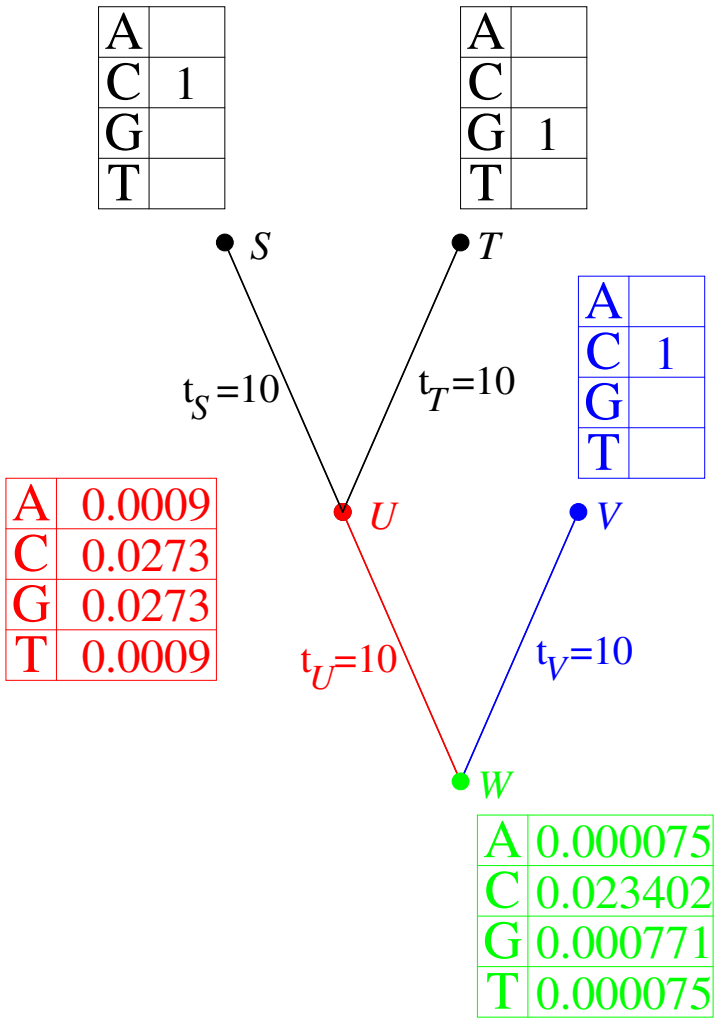
Note: we do not compute the probability of the distance t but that of the data $D = \{s, s'\}$.



Likelihoods of Trees (Single column $\begin{matrix} C \\ G \\ C \end{matrix}$, given tree)



Likelihoods of nucleotides at inner nodes:

$$L_U(i) = [P_{iC}(10) \cdot L(C)] \cdot [P_{iG}(10) \cdot L(G)]$$

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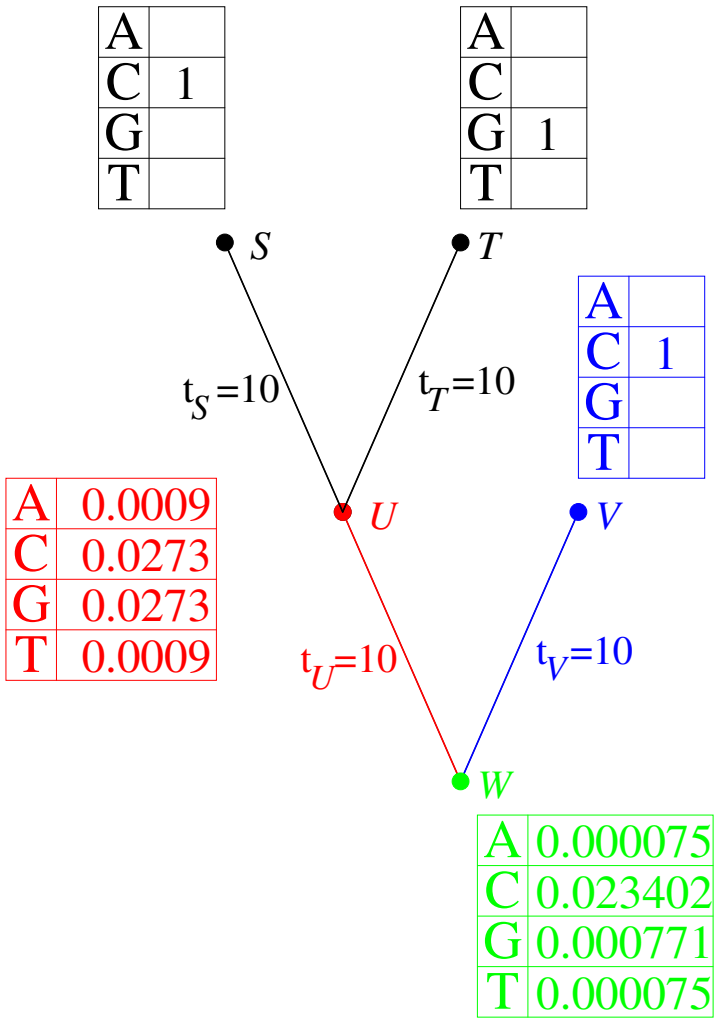

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$$\left[\sum_{\substack{v= \\ ACGT}} P_{iv}(t_V) \cdot L_V(v)\right]$$

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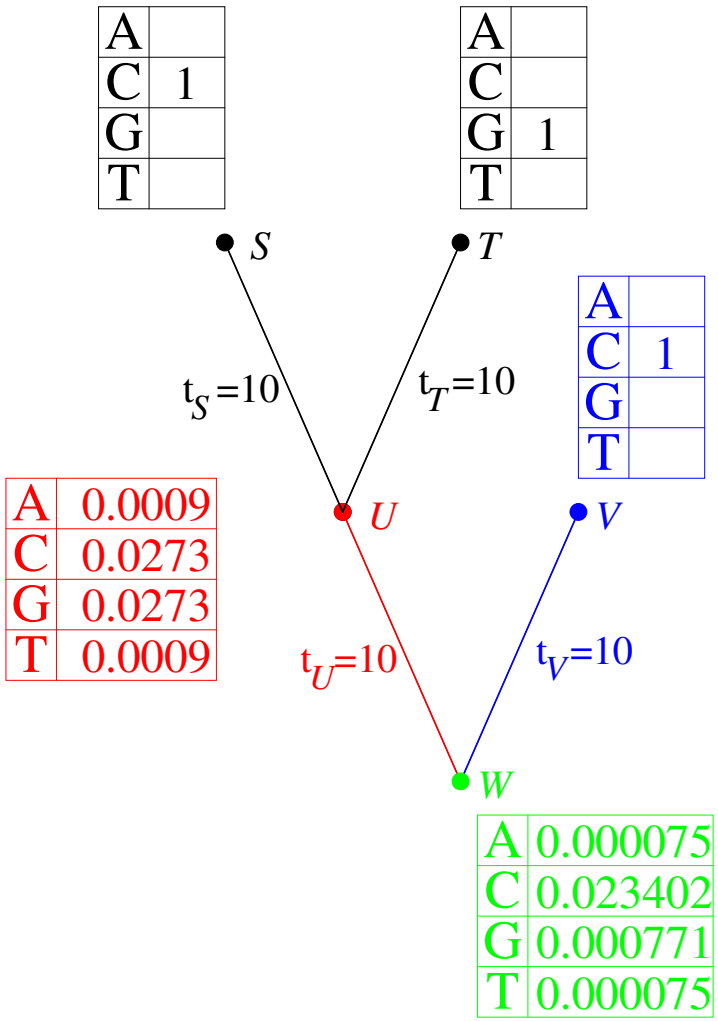

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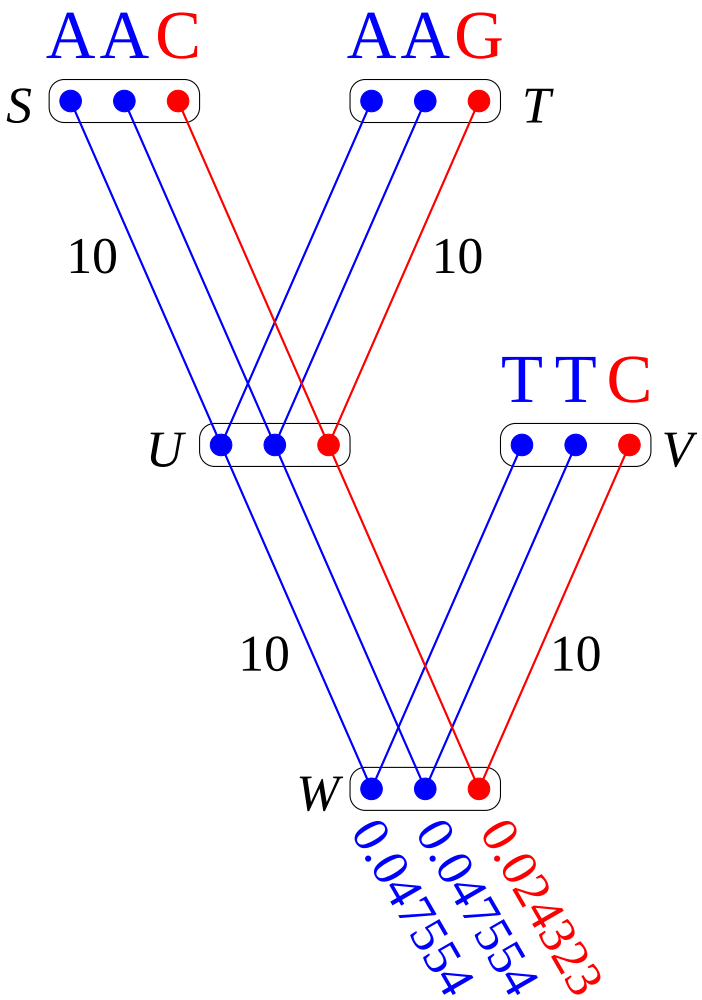
Site-Likelihood of an alignment column k:

$$L^{(k)} = \sum_{\substack{i= \\ ACGT}} \pi_i \cdot L_W(i) = 0.024323$$

Likelihoods of Trees (multiple columns)



Considering this tree with $n = 3$ sequences of length $m = 3$ the tree likelihood of this tree is

$$\mathcal{L}(T) = \prod_{k=1}^{m} L^{(k)}$$

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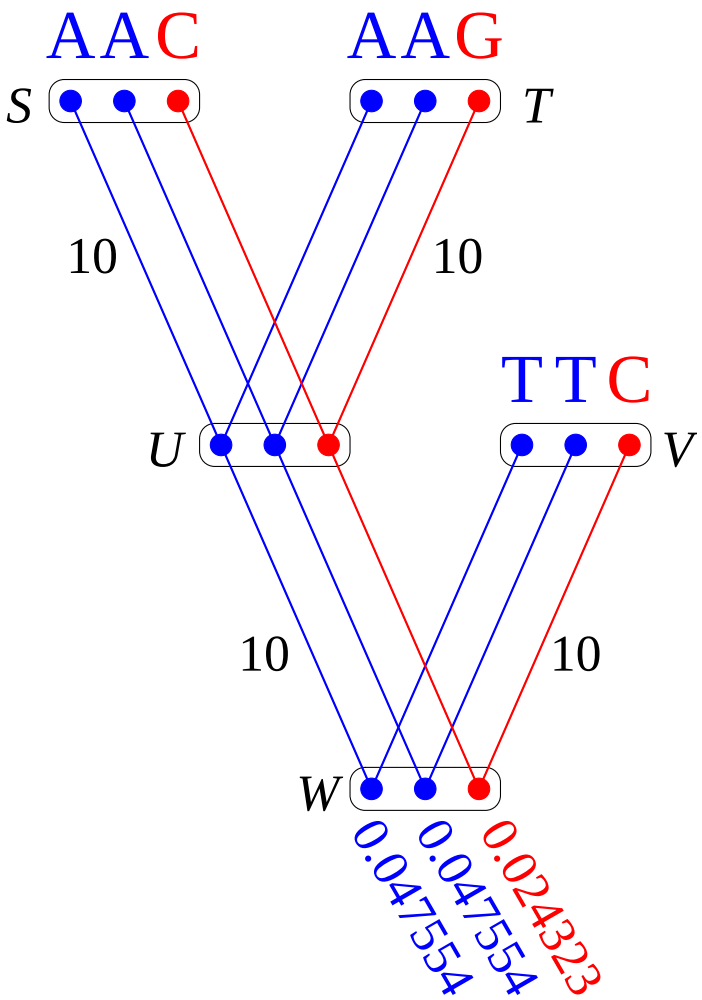

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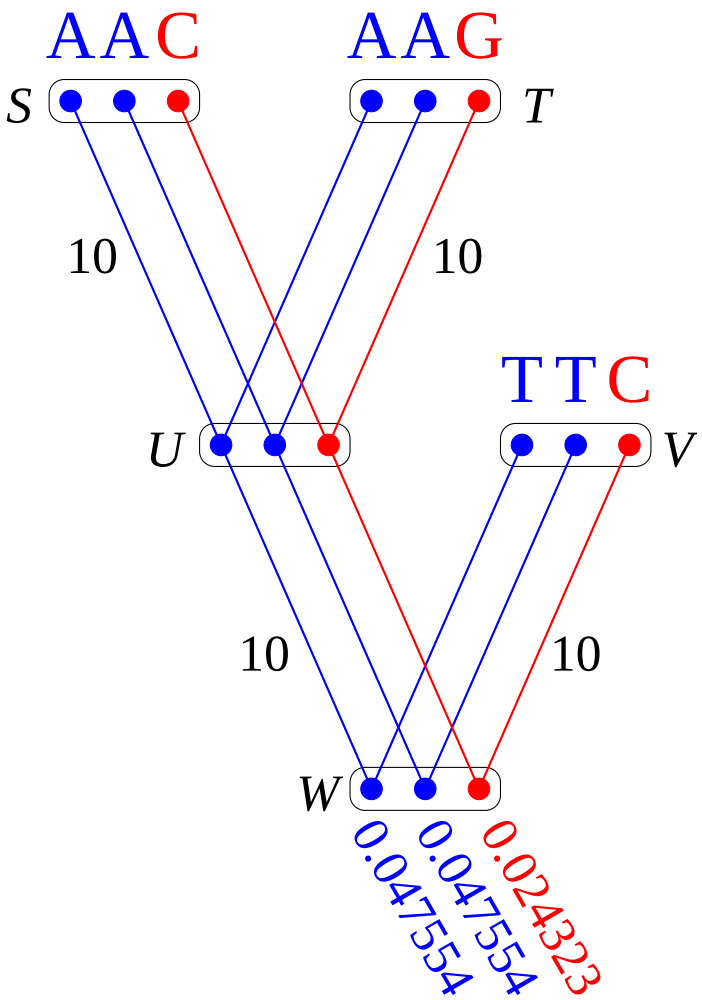

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or the log-likelihood

$$\ln \mathcal{L}(T) = \sum_{k=1}^{m} \ln L^{(k)} = -9.80811$$

Adjusting Branch Lengths Step-By-Step

To compute optimal branch lengths do the following. Initialize the branch lengths.
Choose a branch (A.). Move the virtual root to an adjacent node (B.).
Compute all partial likelihoods recursively (C.). Adjust the branch length to maximize the likelihood value (D.).

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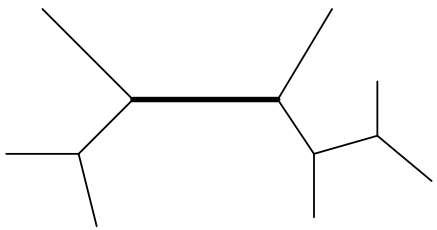

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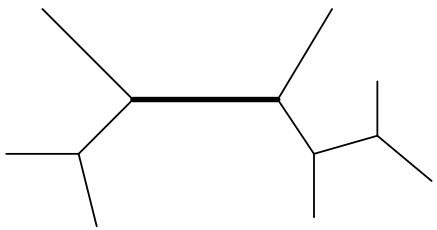

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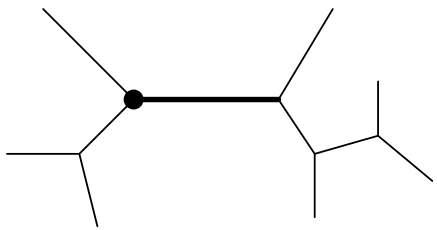

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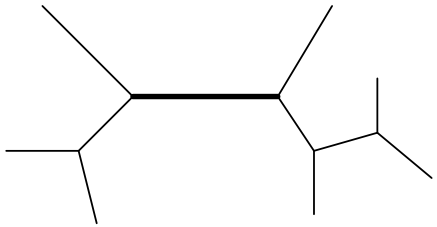

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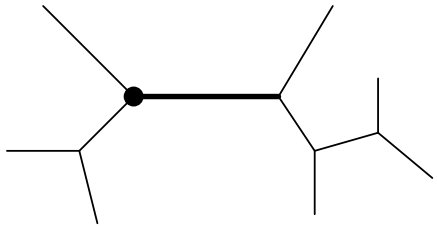

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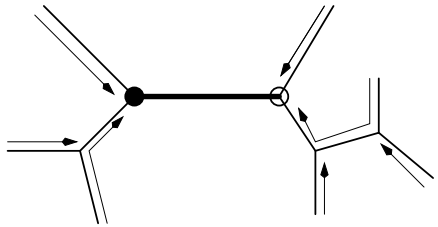

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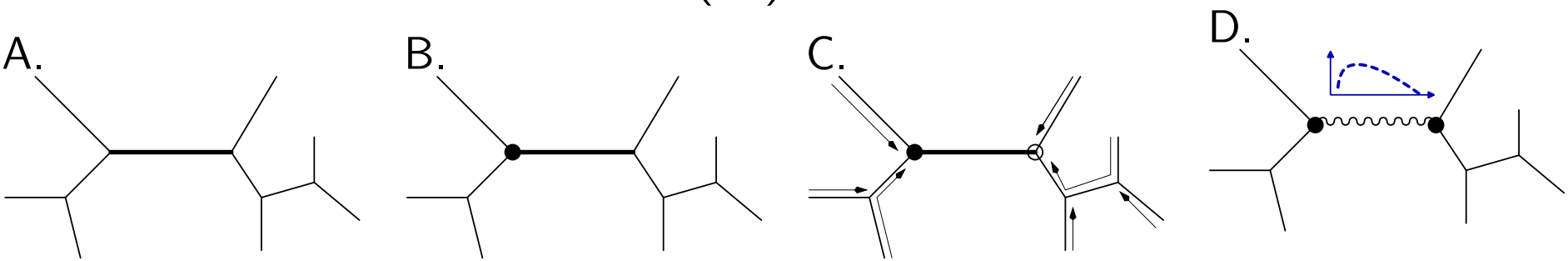

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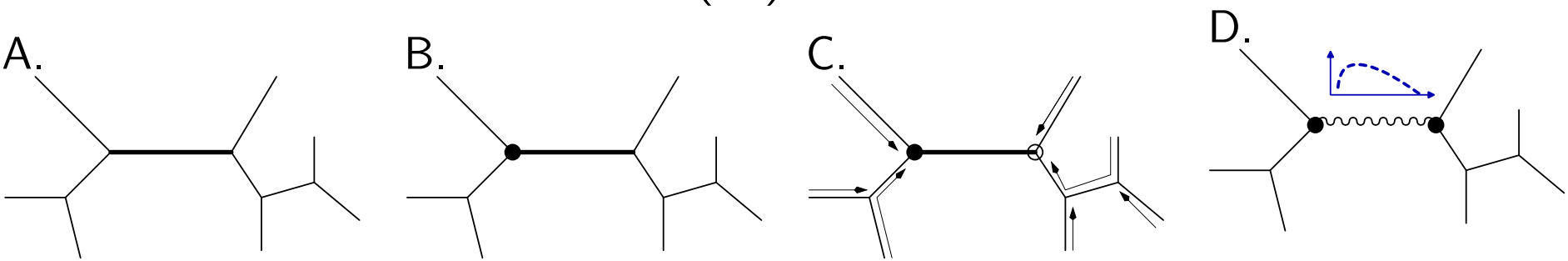
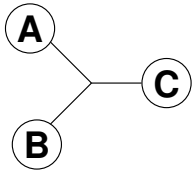


Repeat this for every branch until no better likelihood is gained.

Number of Trees to Examine...



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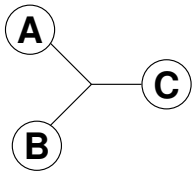

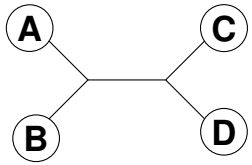

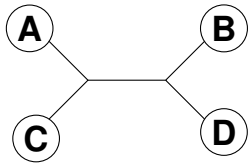

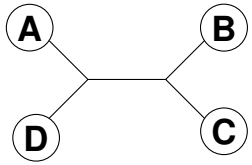

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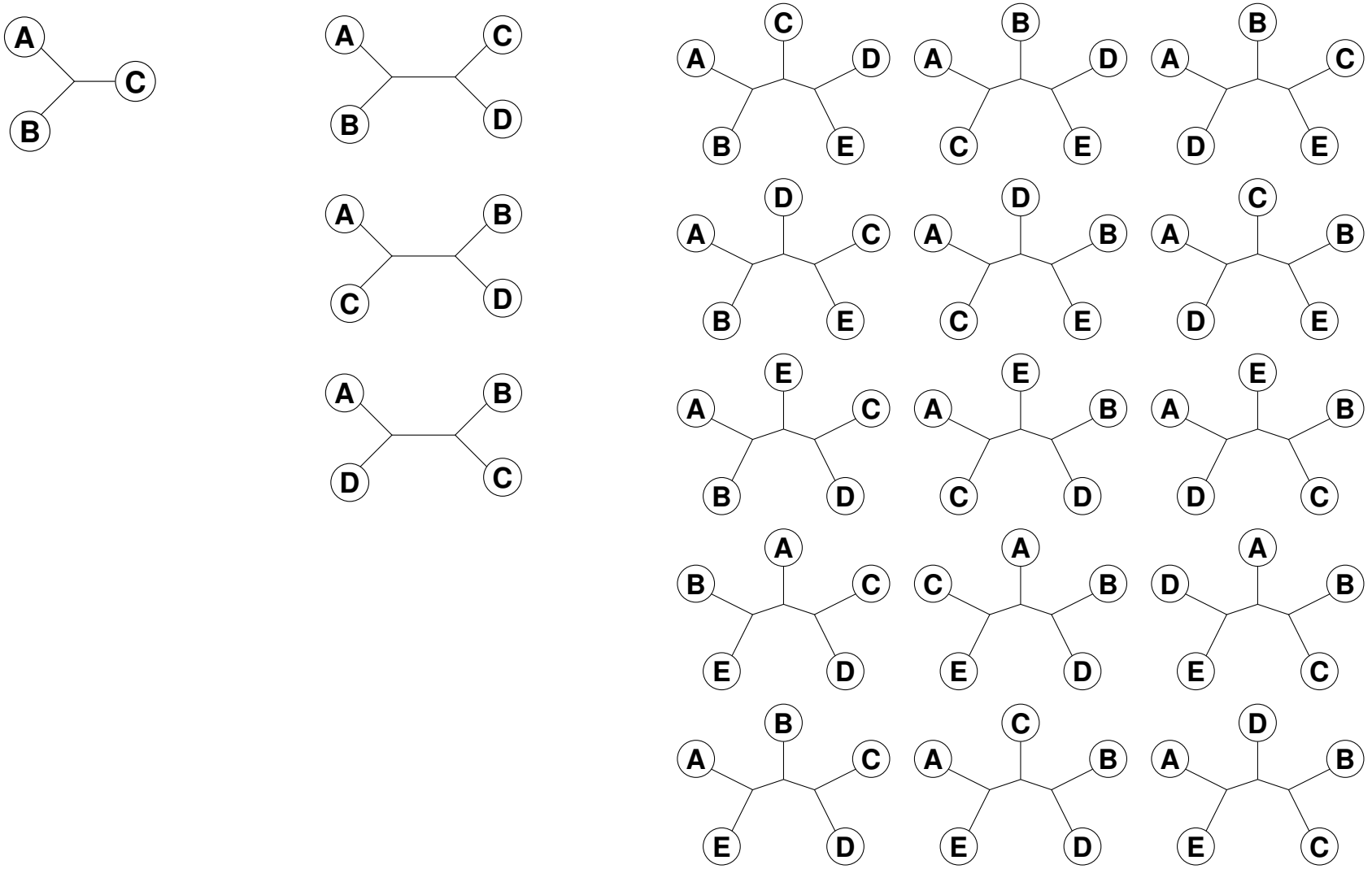

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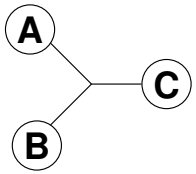
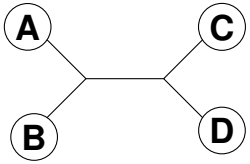
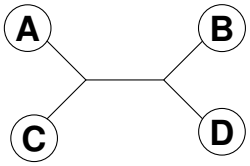
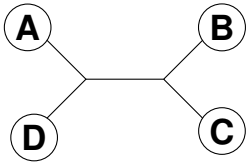
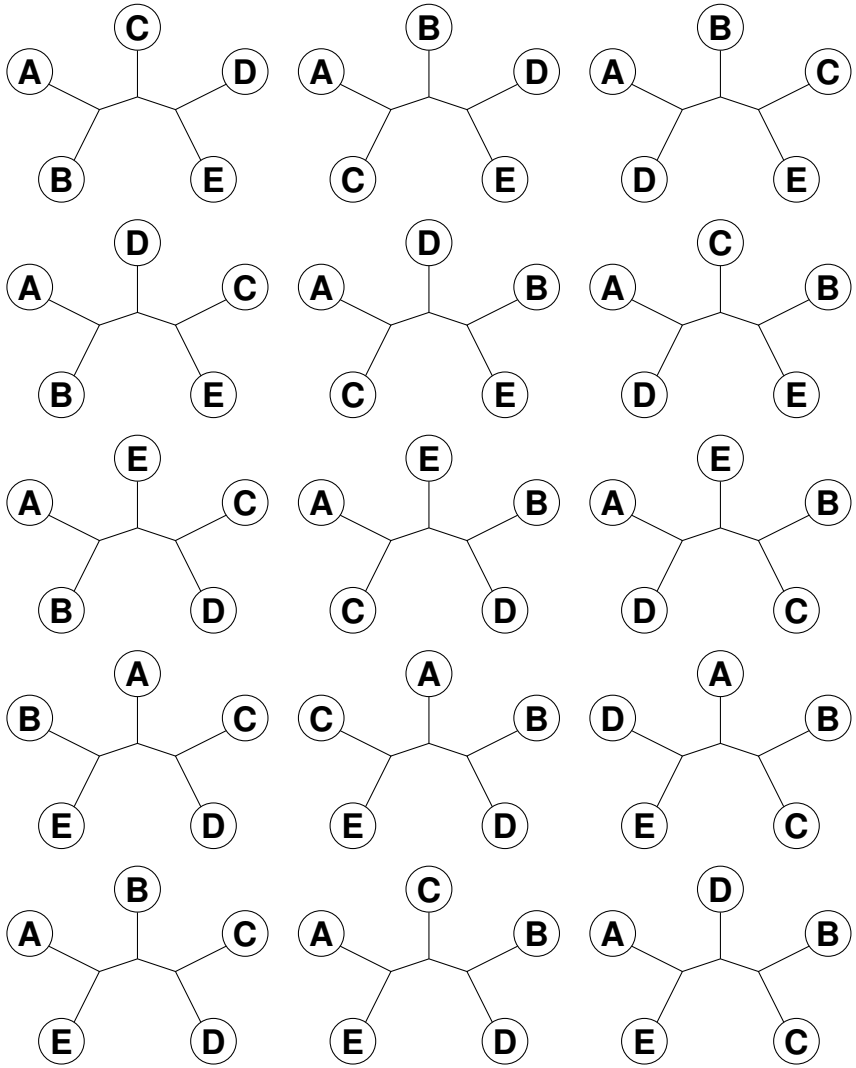




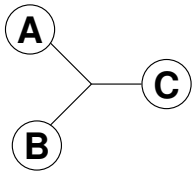


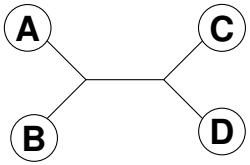


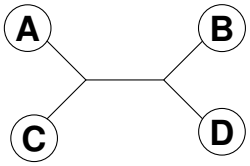
$$B(n) = \frac{(2n-5)!}{2^{n-3}(n-3)!}$$

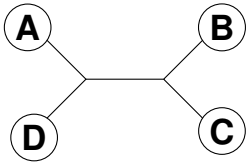


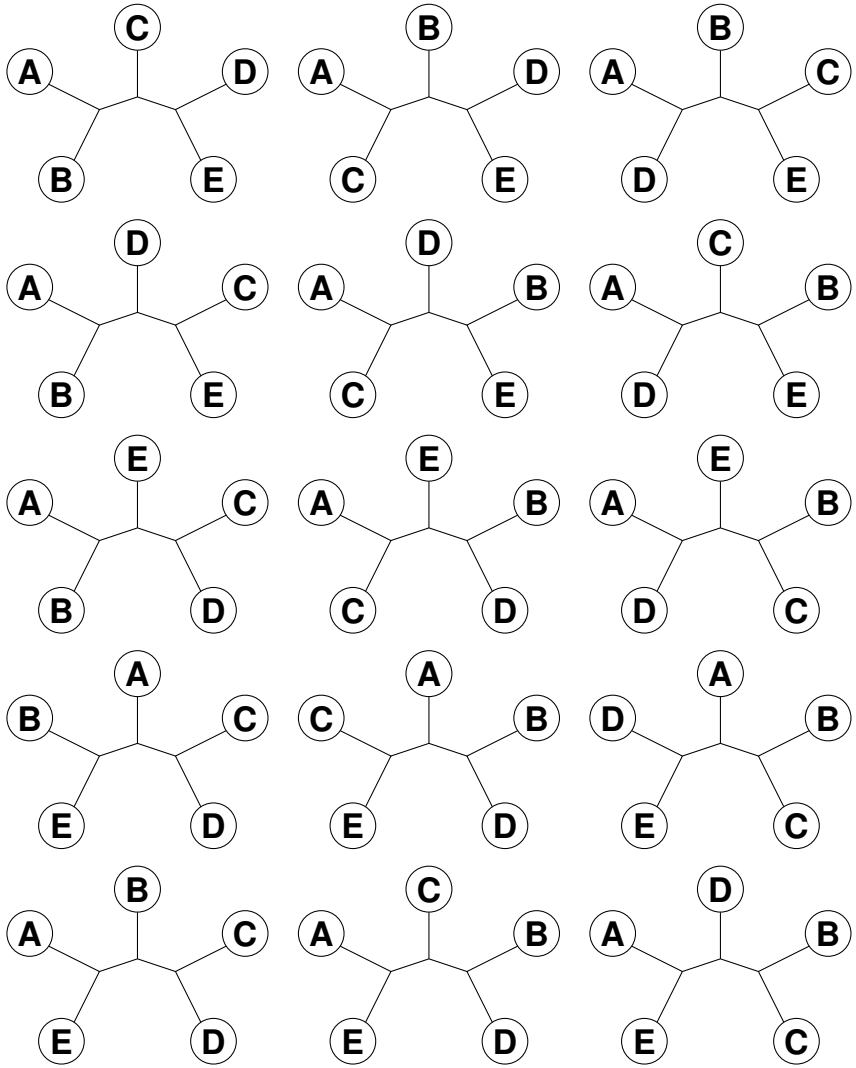
Number of Trees to Examine...











$$B(n) = \frac{(2n-5)!}{2^{n-3}(n-3)!}$$

$$B(10) = 2027025$$

$$B(55) = 2.98 \cdot 10^{84}$$

$$B(100) = 1.70 \cdot 10^{182}$$

Finding the ML Tree

Exhaustive Search: guarantees to find the optimal tree, because all trees are evaluated, but not feasible for more than 10-12 taxa.

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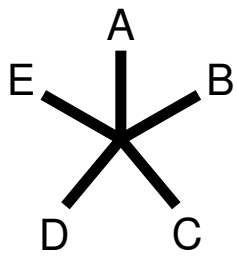
Branch and Bound: guarantees to find the optimal tree, without searching certain parts of the tree space – can run on more sequences, but often not for current-day datasets.

Heuristics: cannot guarantee to find the optimal tree, but are at least able to analyze large datasets.

Build up a tree: Star Decomposition



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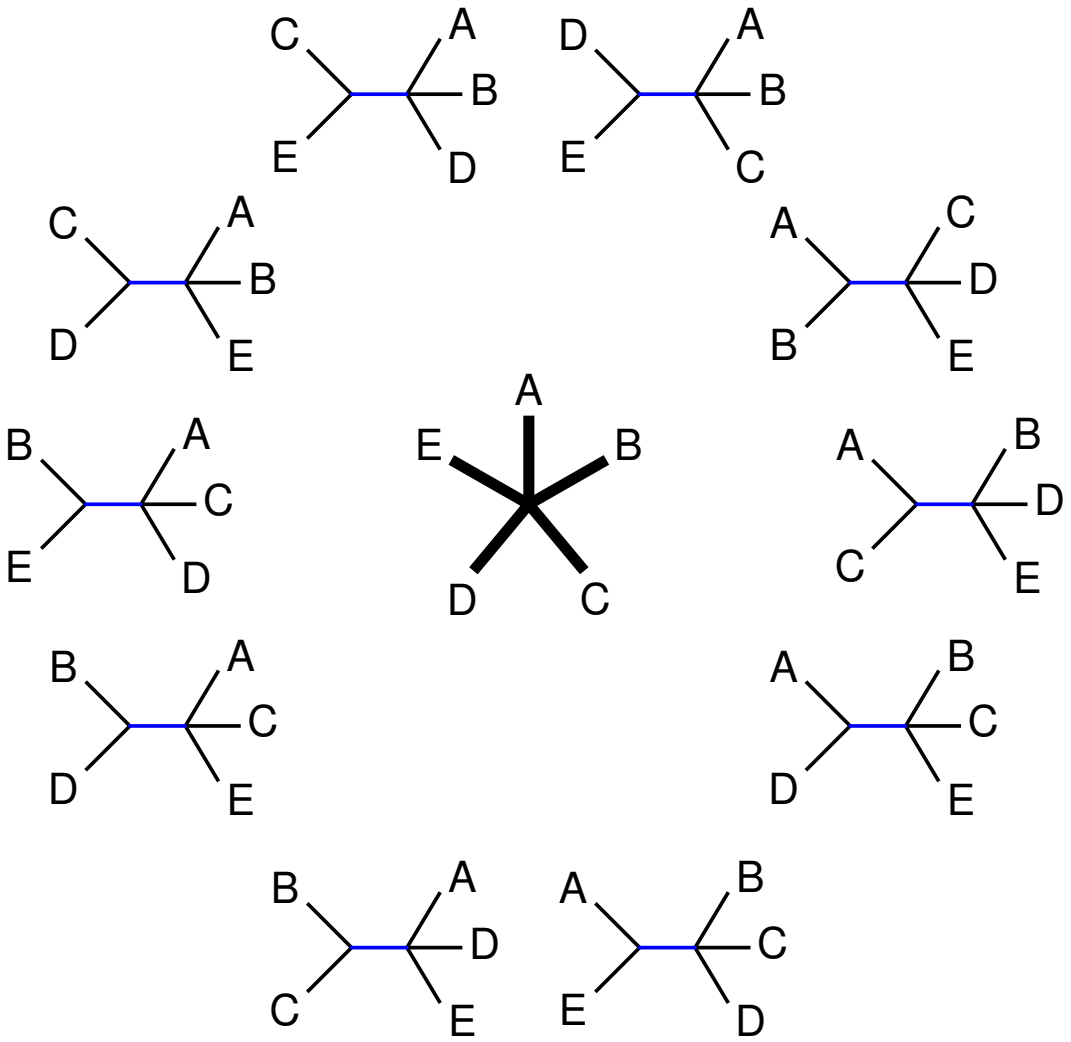

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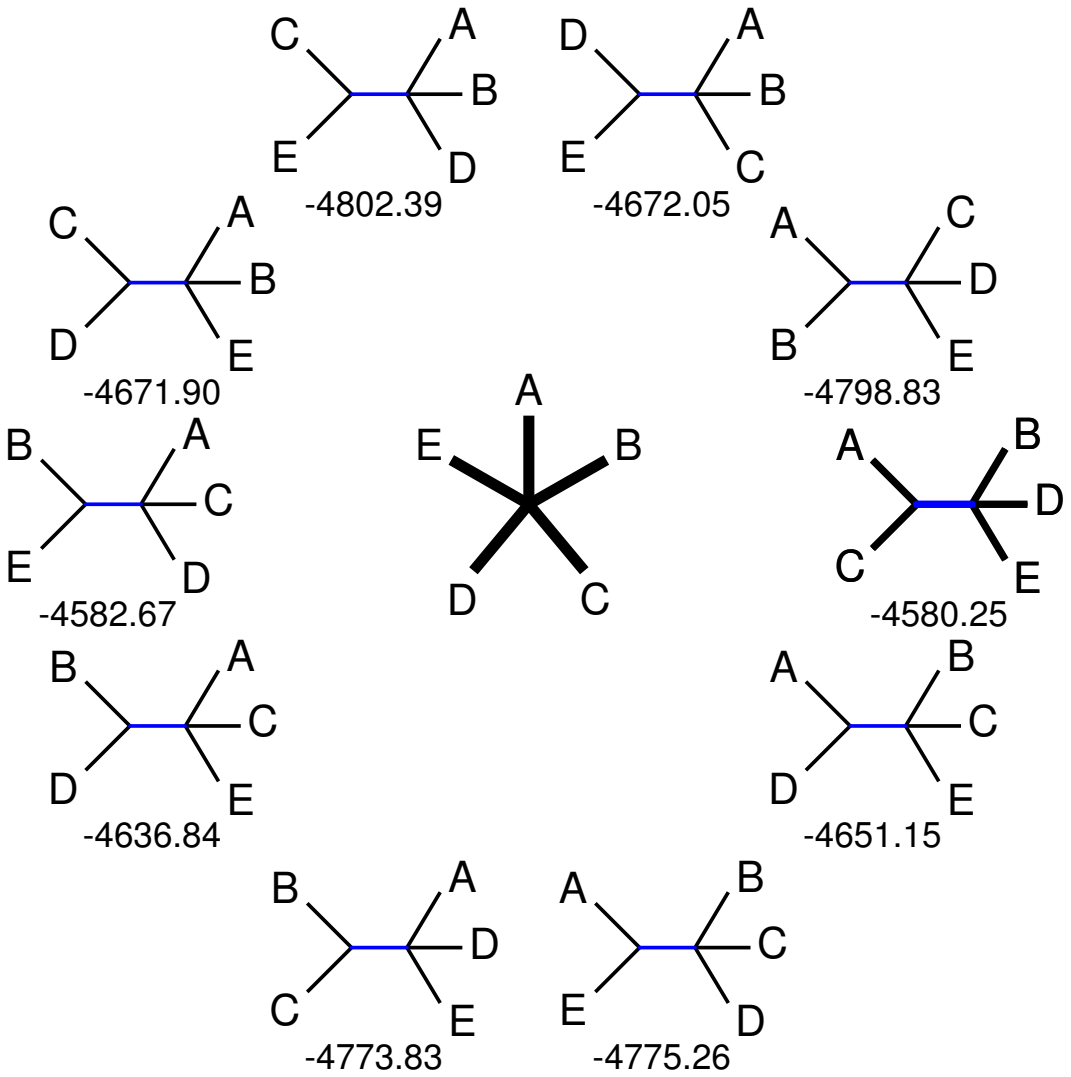

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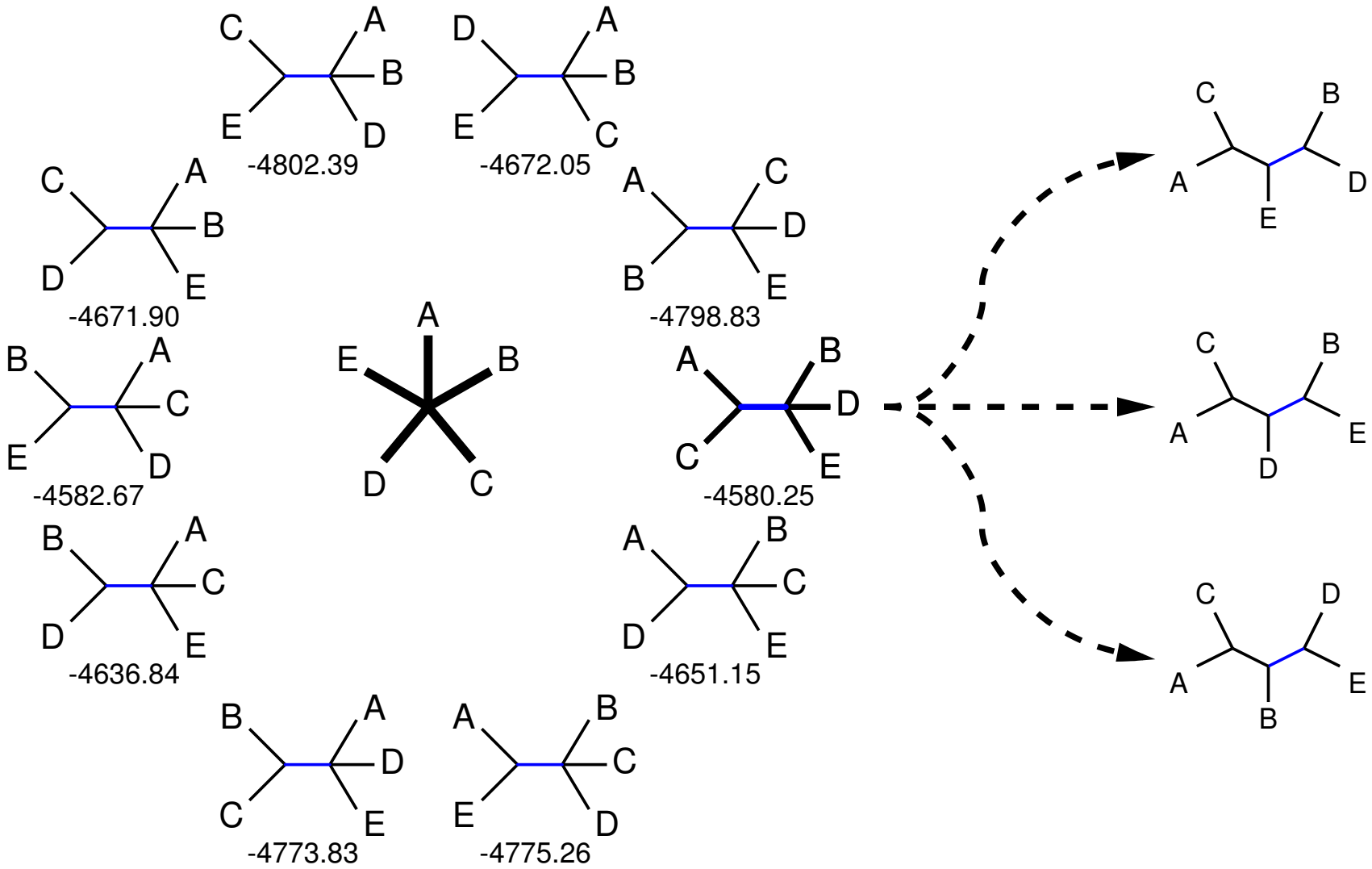

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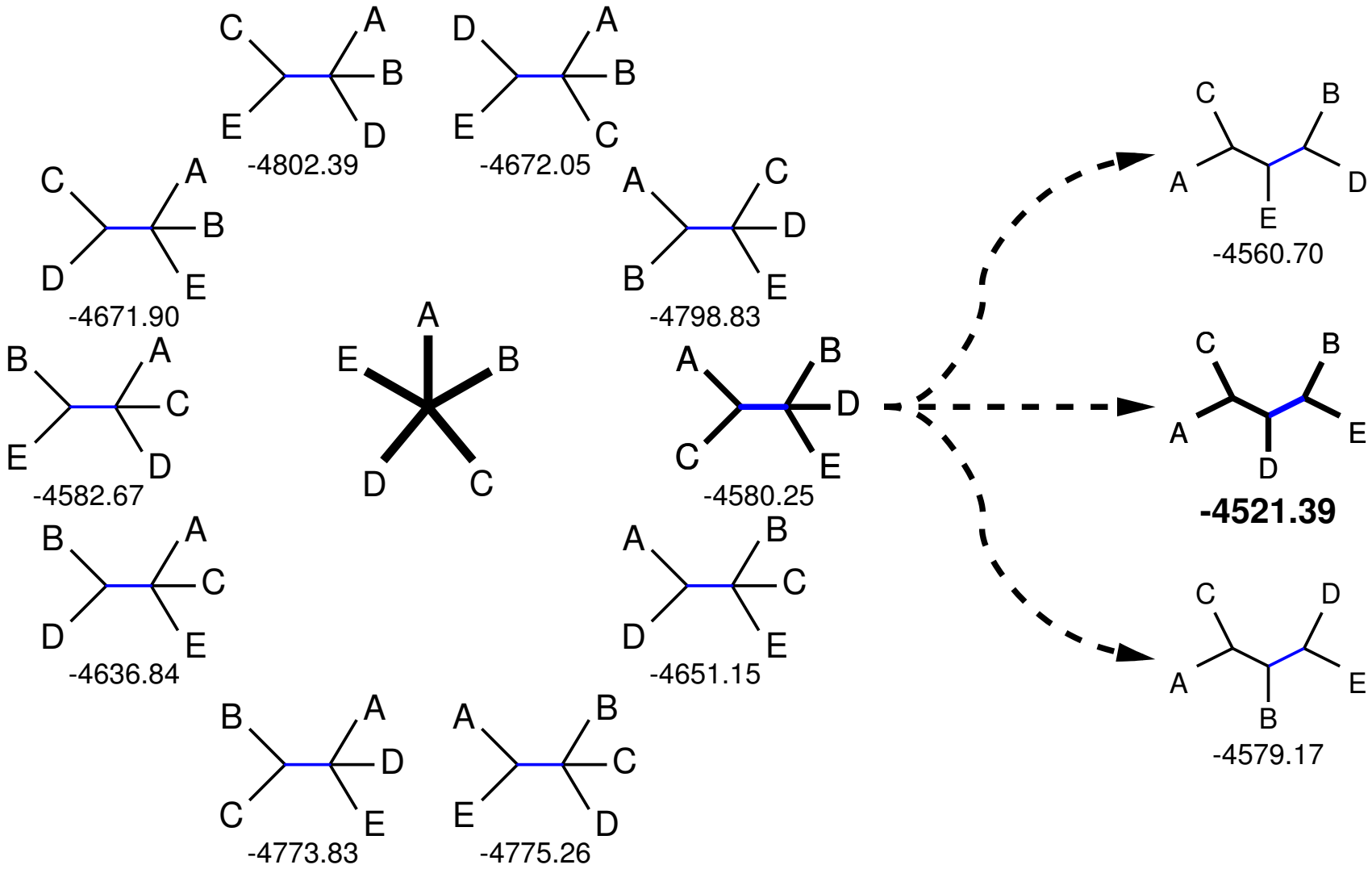
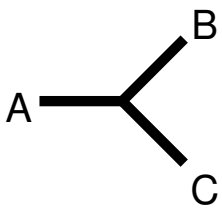


Build up a tree: Stepwise Insertion



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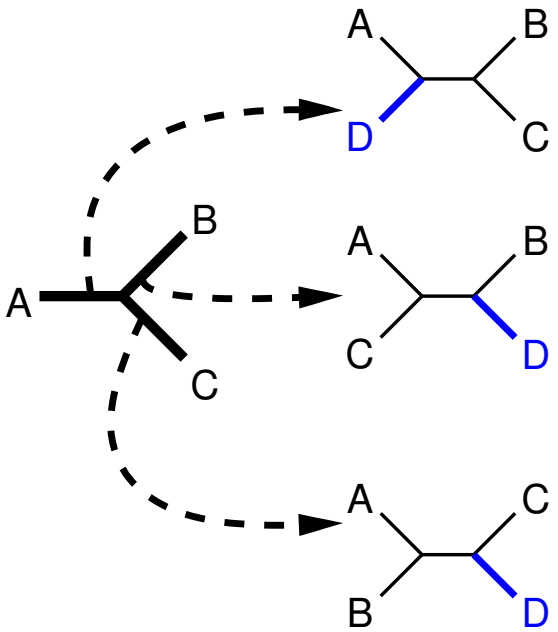

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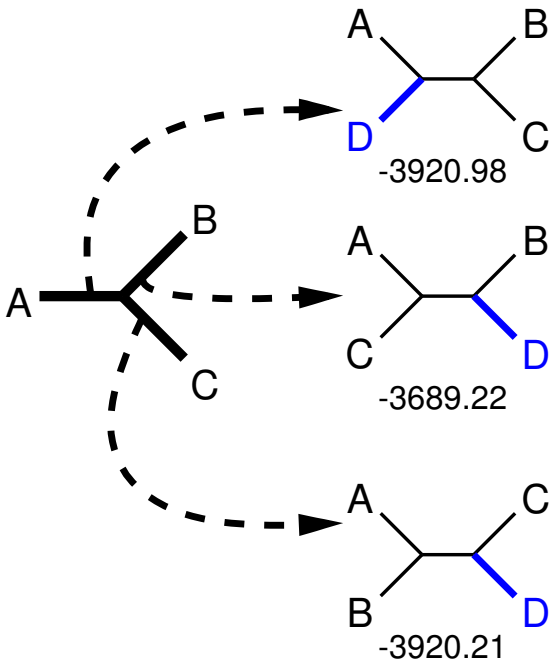

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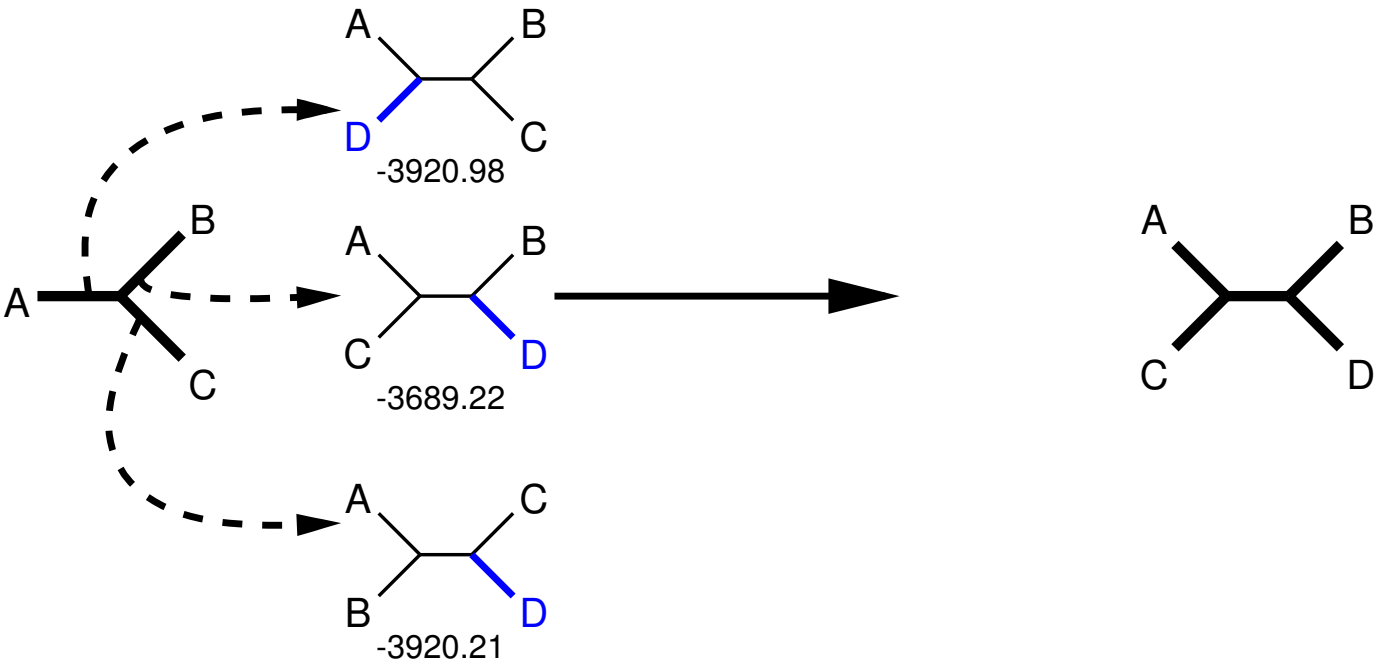

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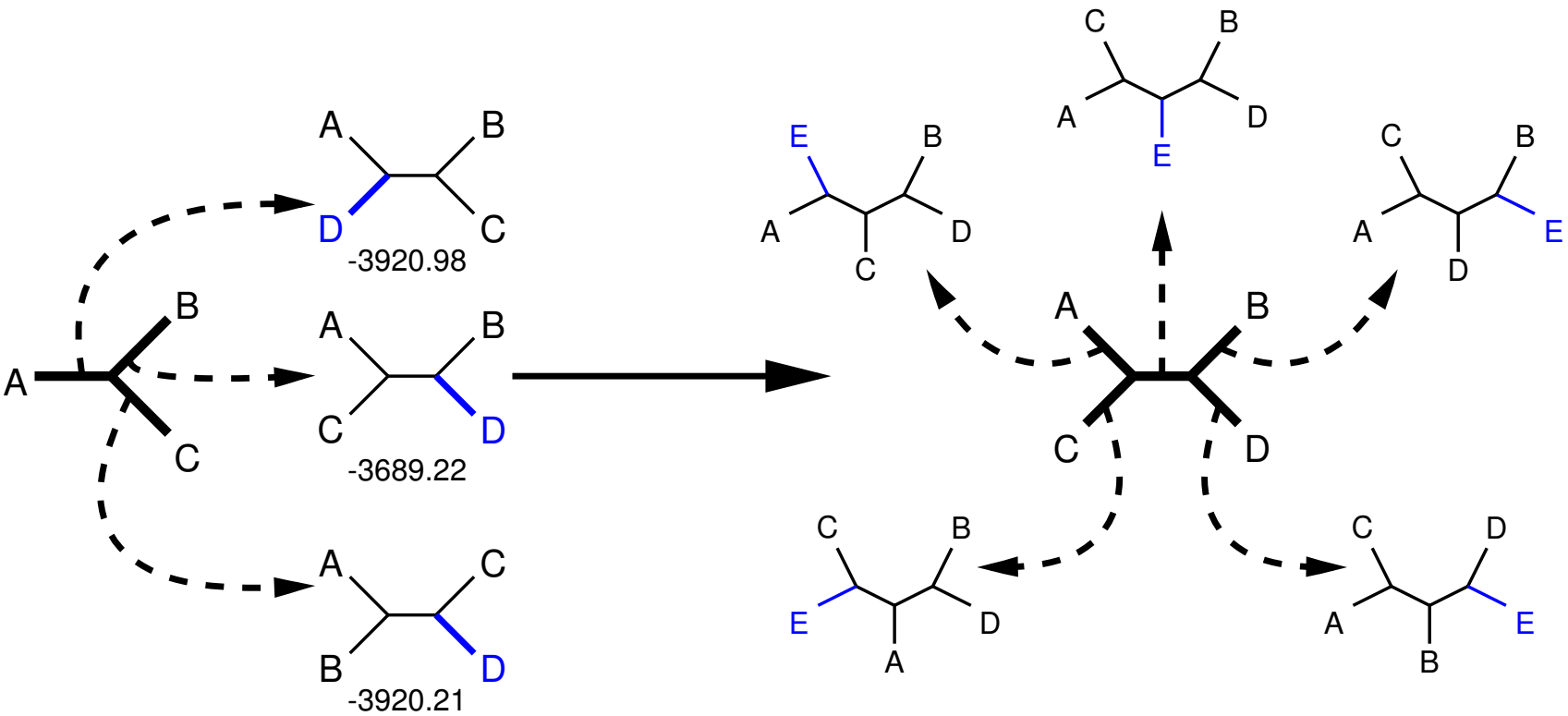

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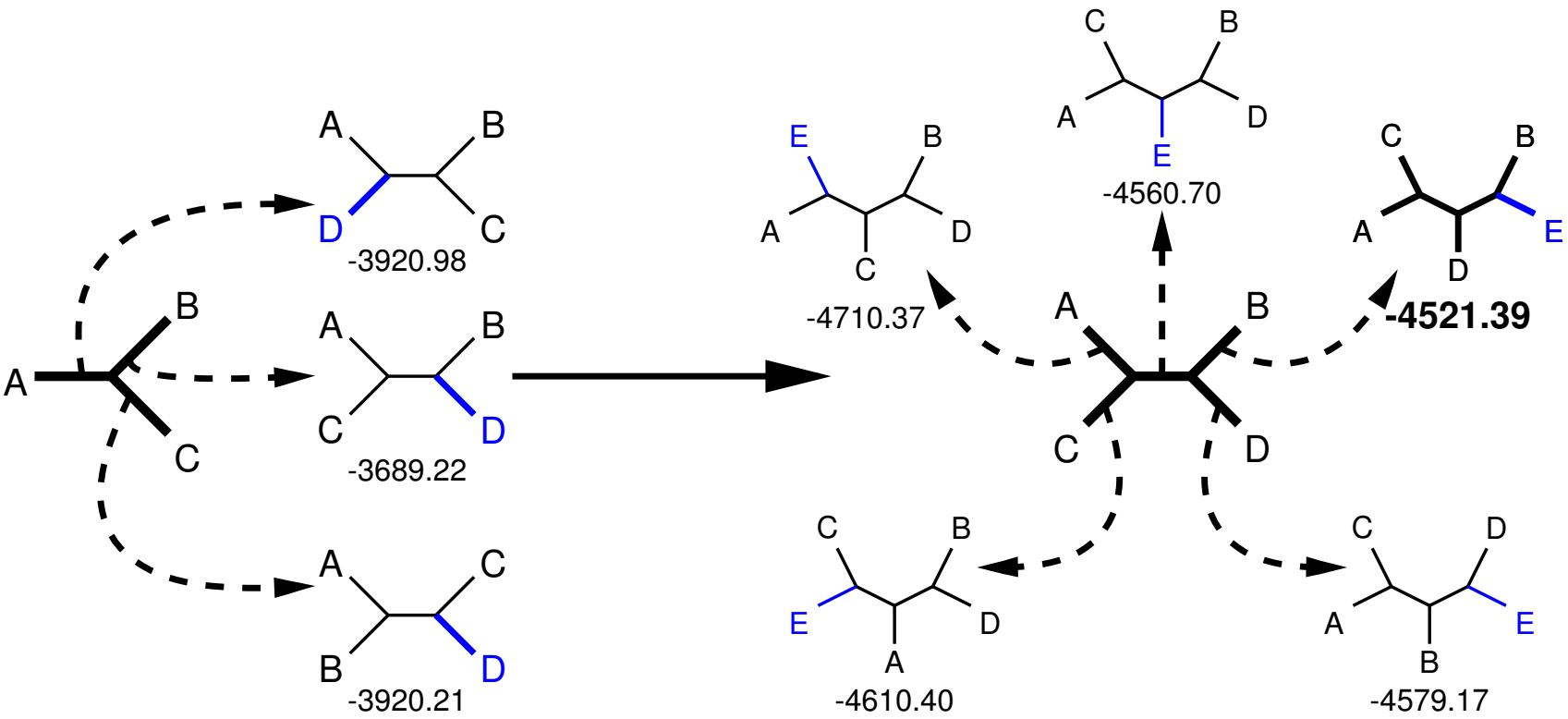
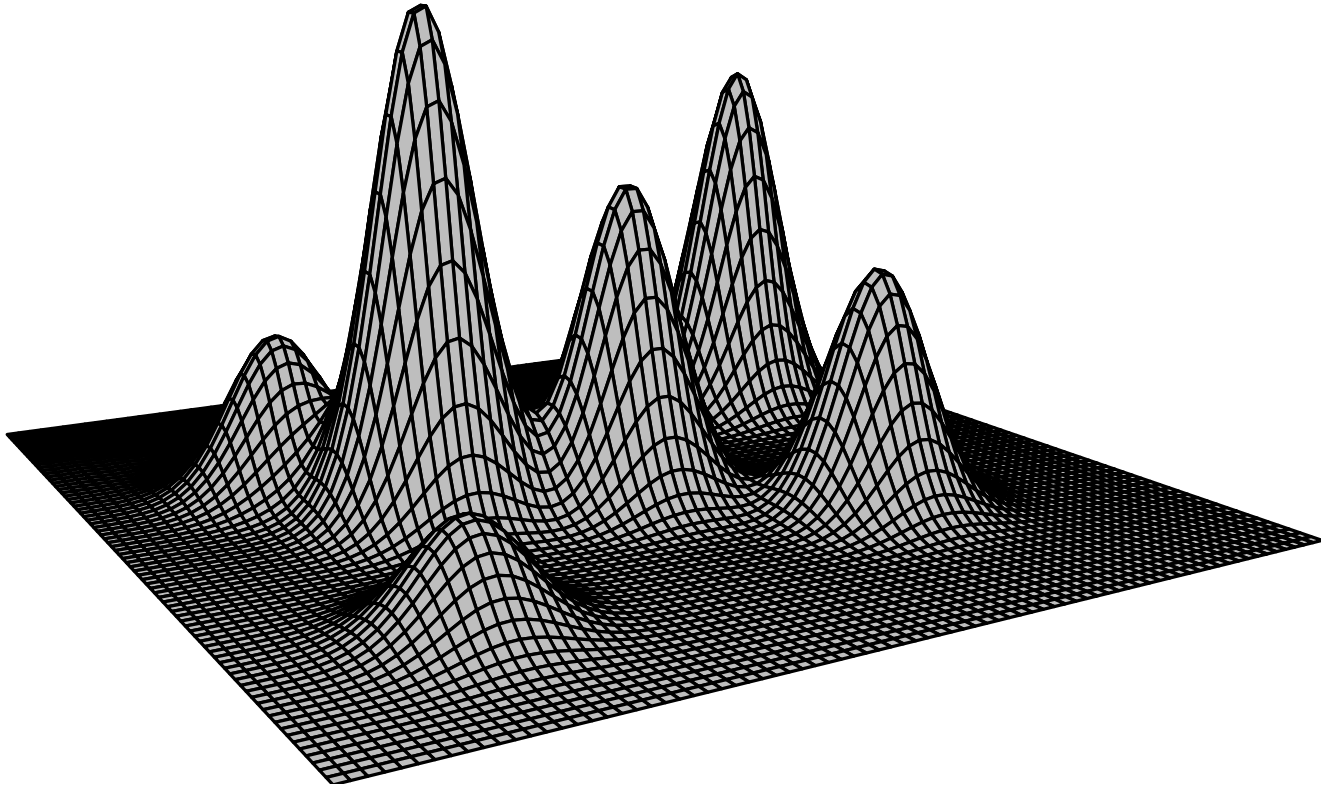


Local Maxima

What if we have multiple maxima in the likelihood surface?



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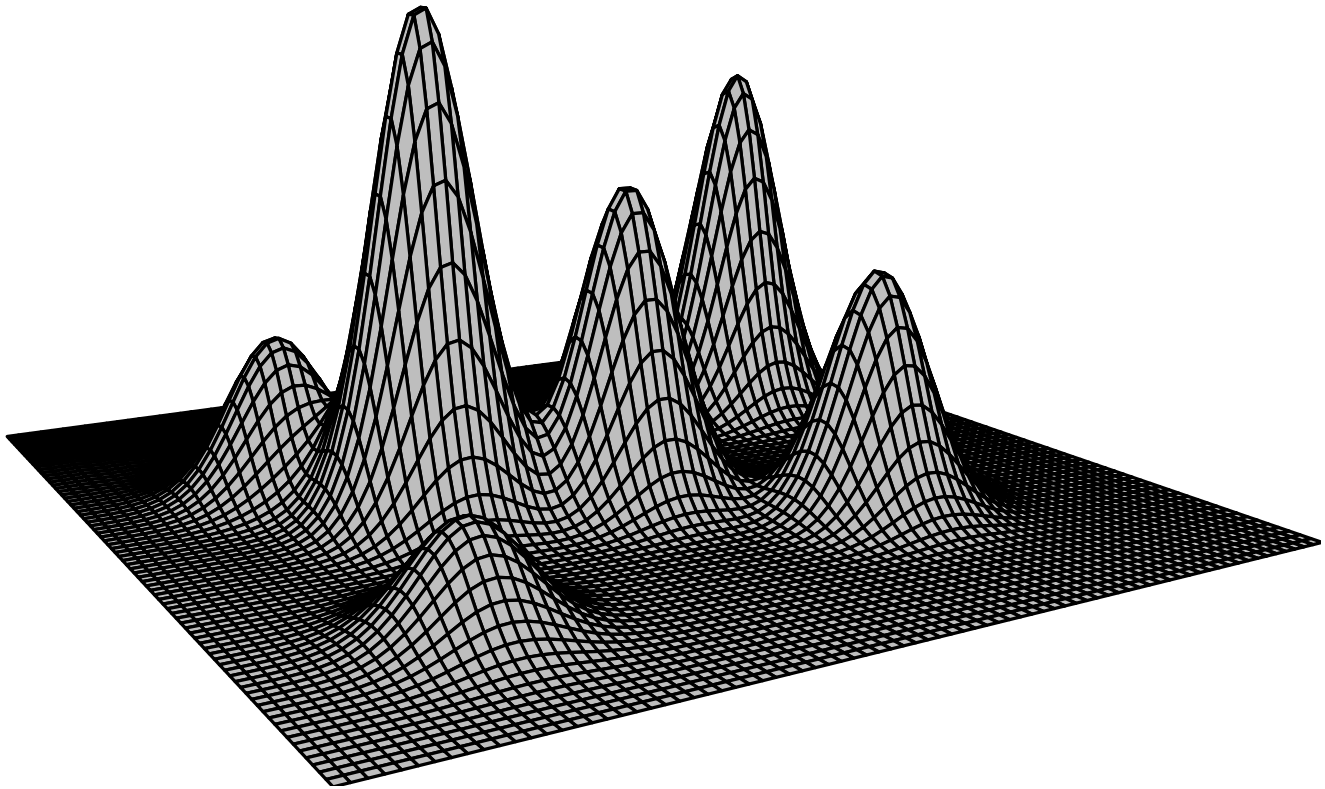
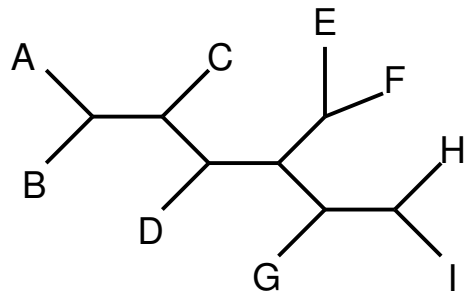
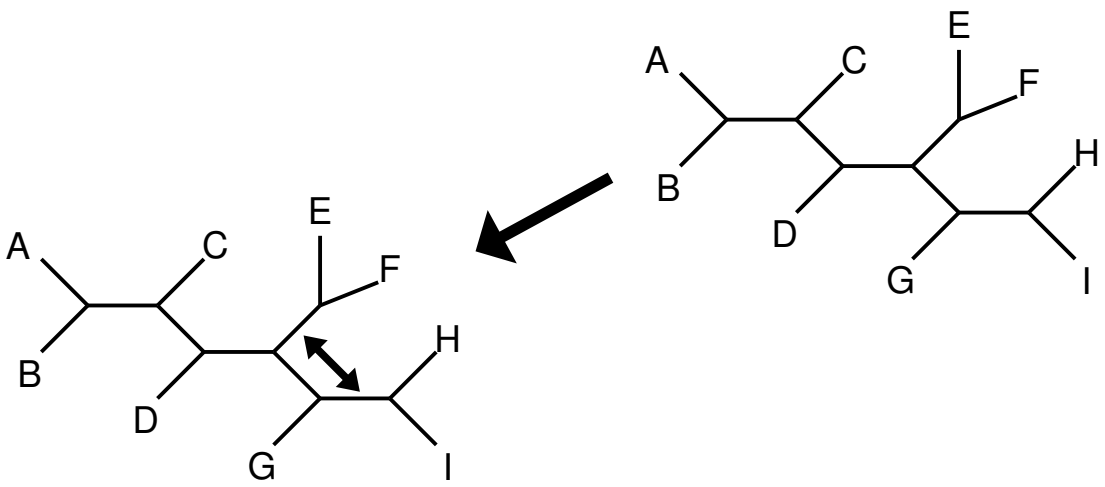


Tree rearrangements to escape local maxima.

Tree Rearrangements: Scanning a Tree's Neighborhood



Tree Rearrangements: Scanning a Tree's Neighborhood



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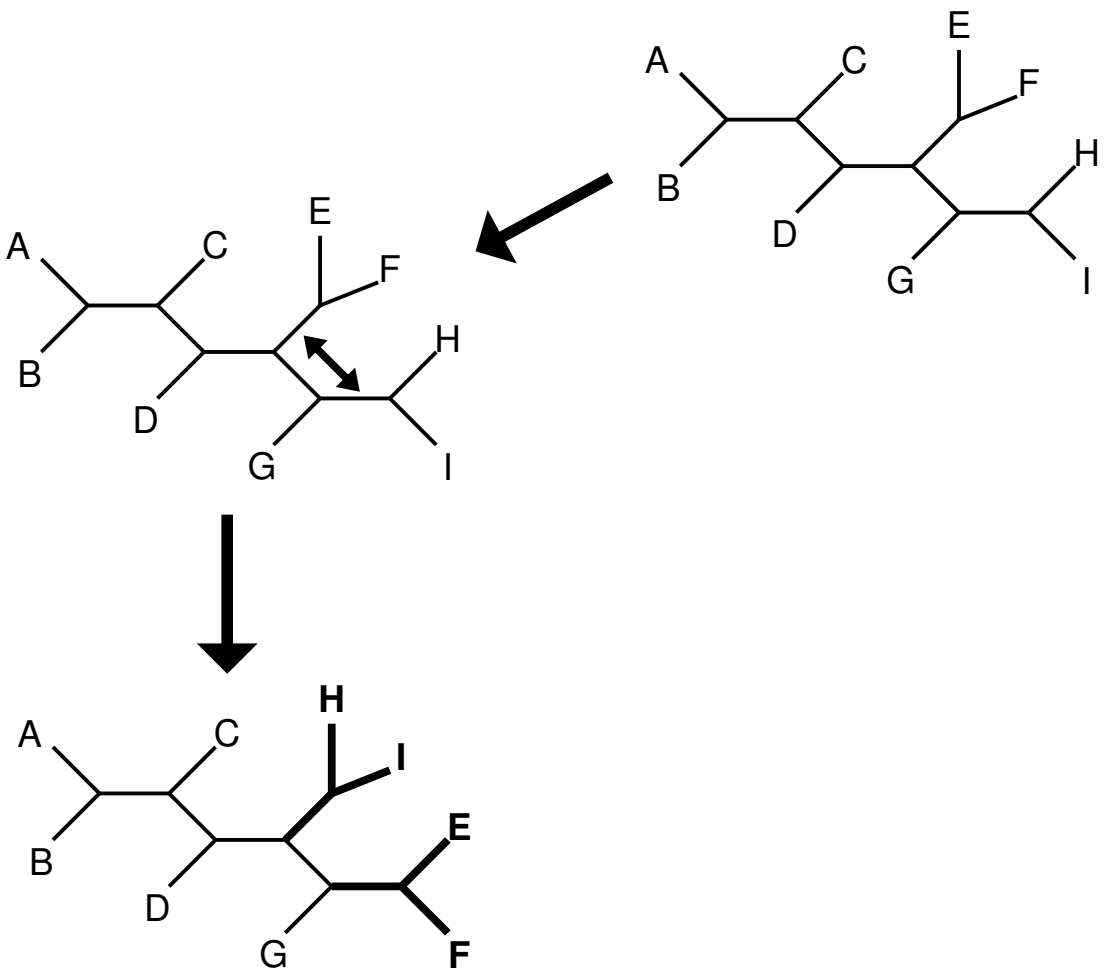

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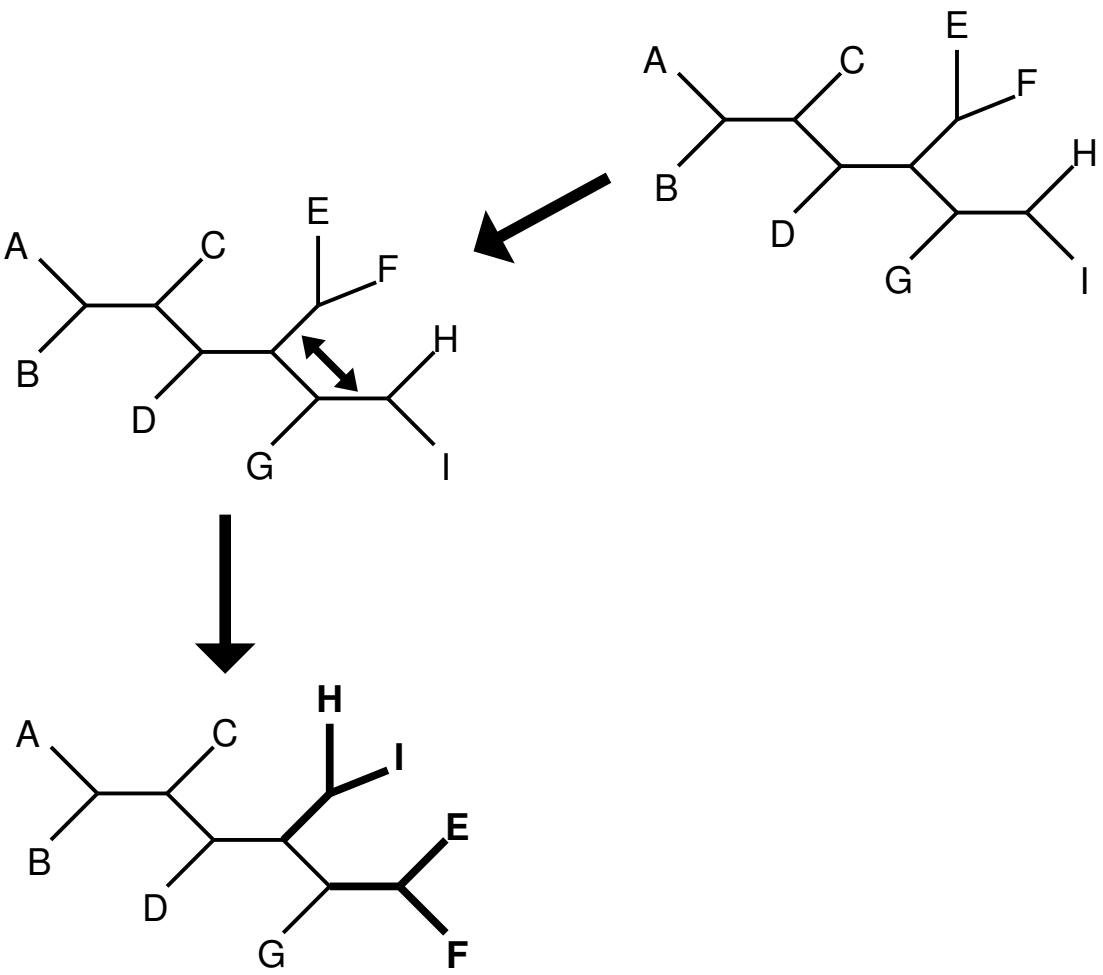
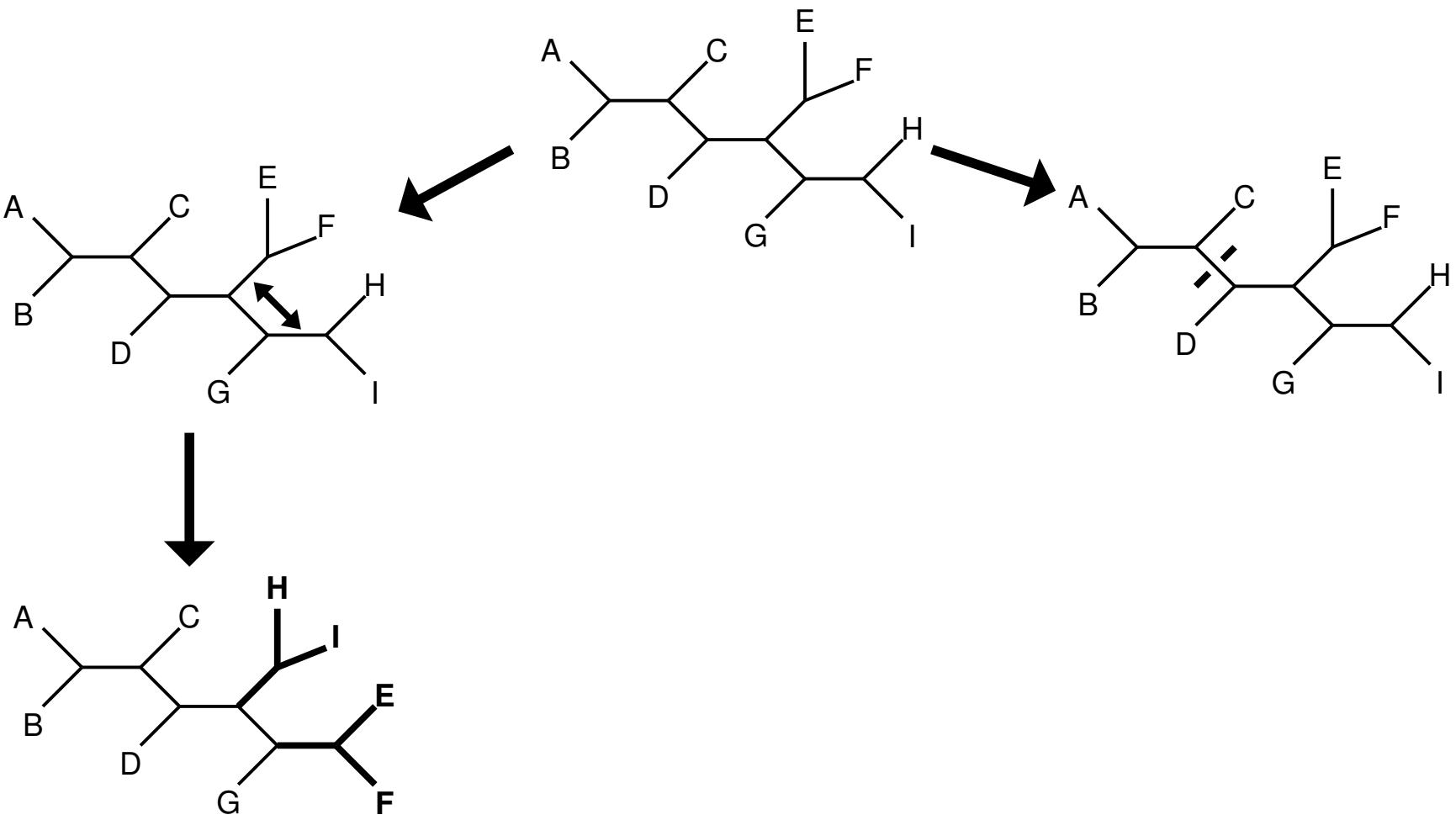


Nearest Neighbor Interchange

Possible NNI trees = O(n)

Tree Rearrangements: Scanning a Tree's Neighborhood



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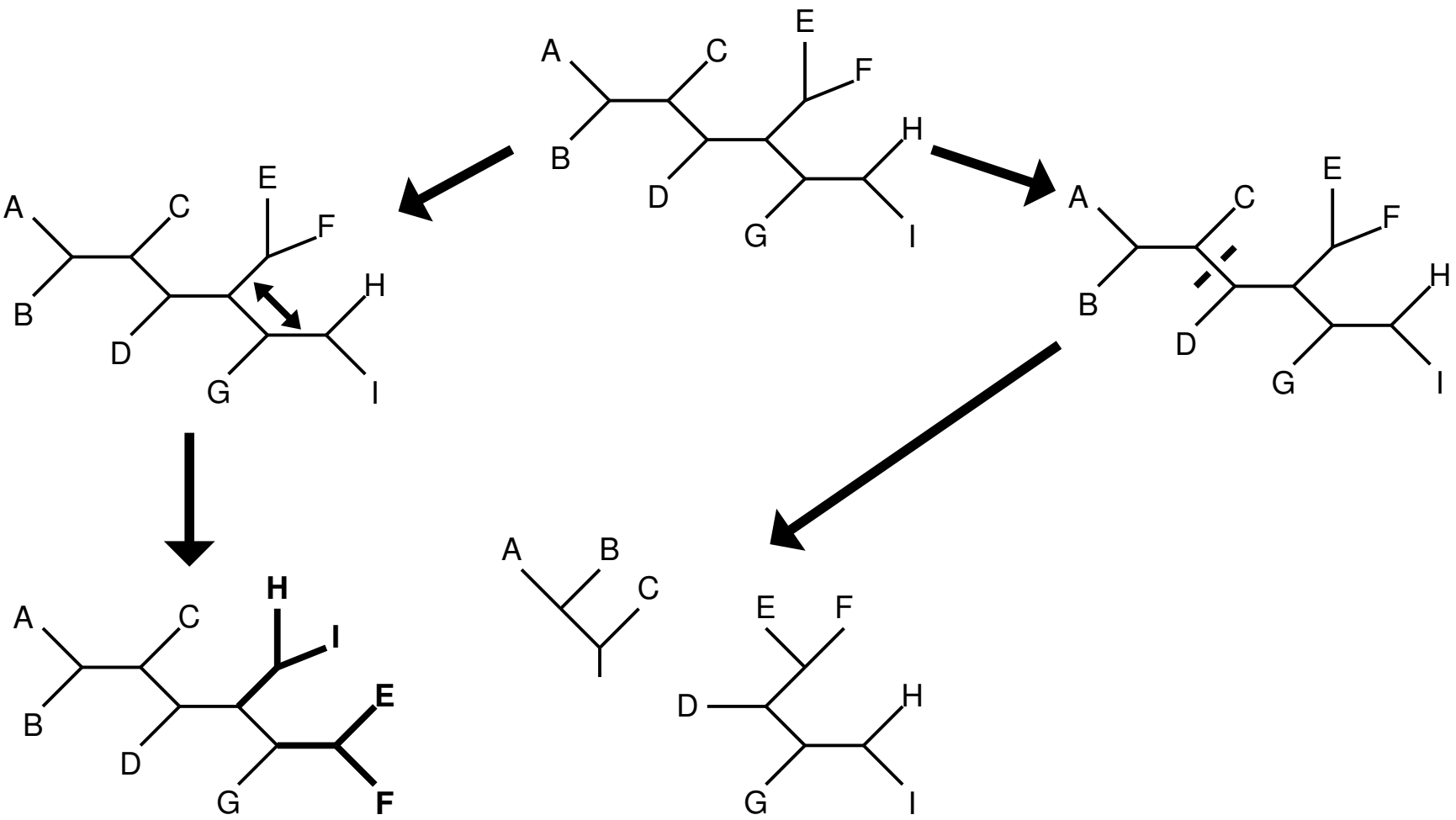

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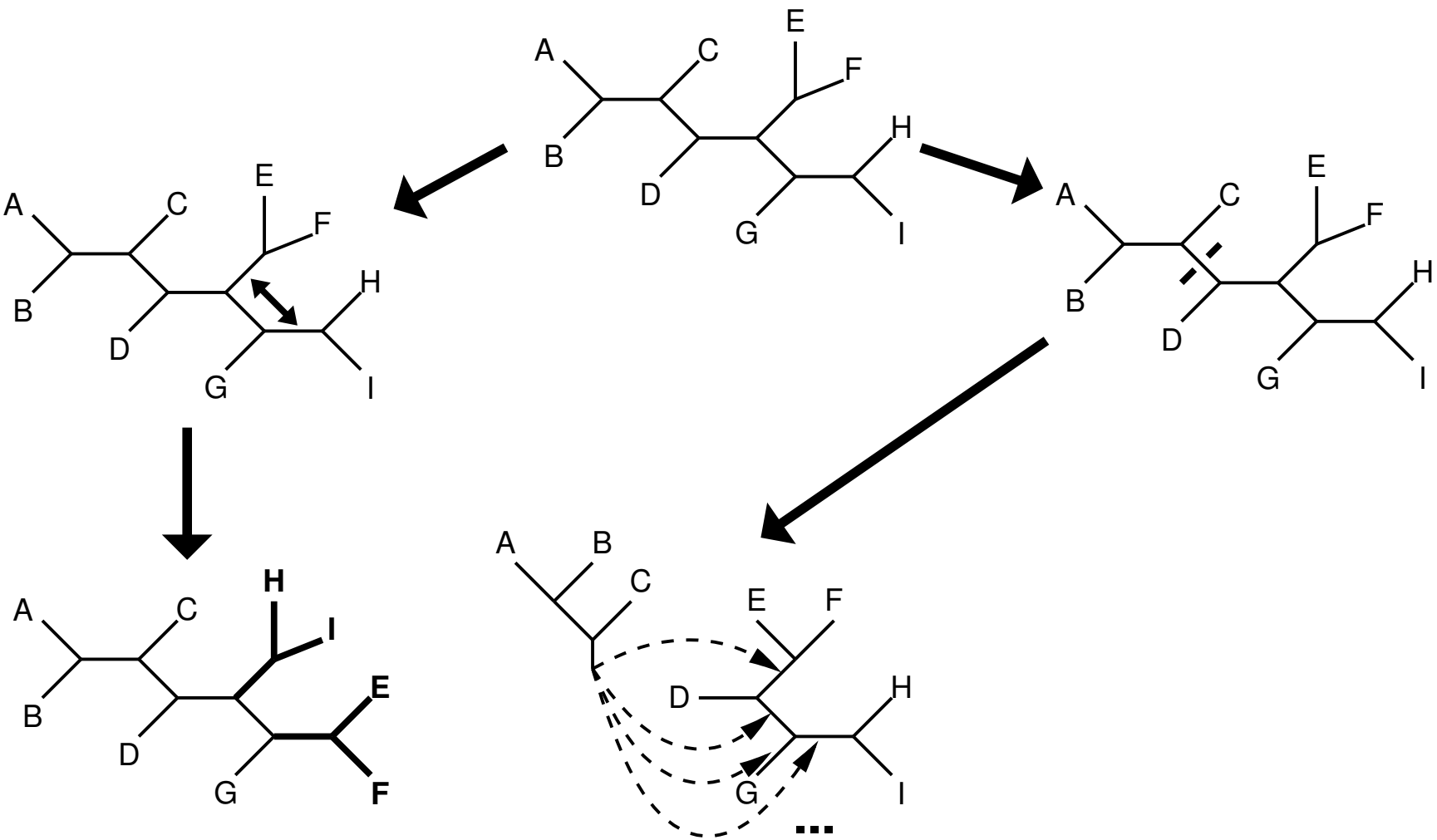

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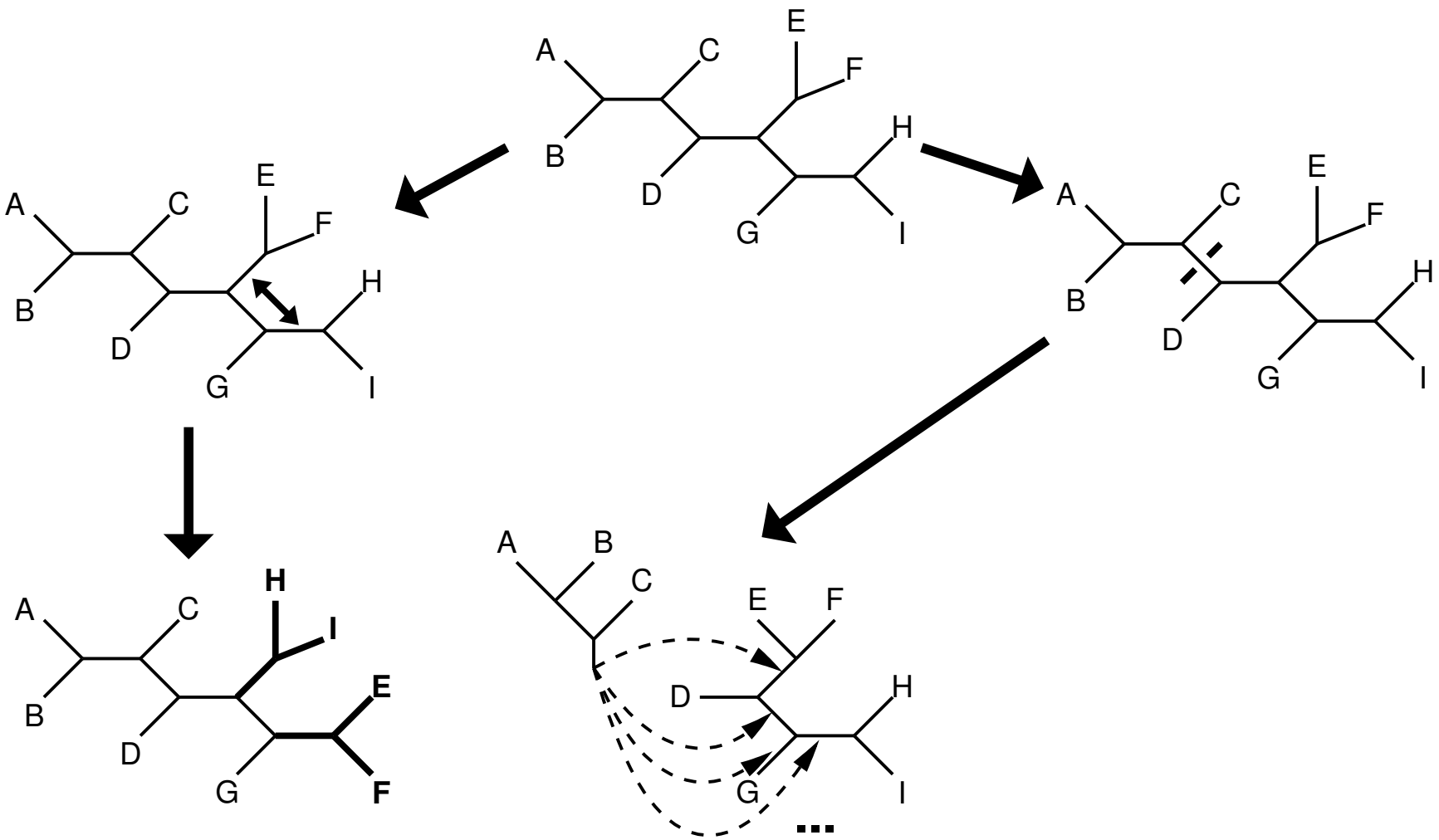


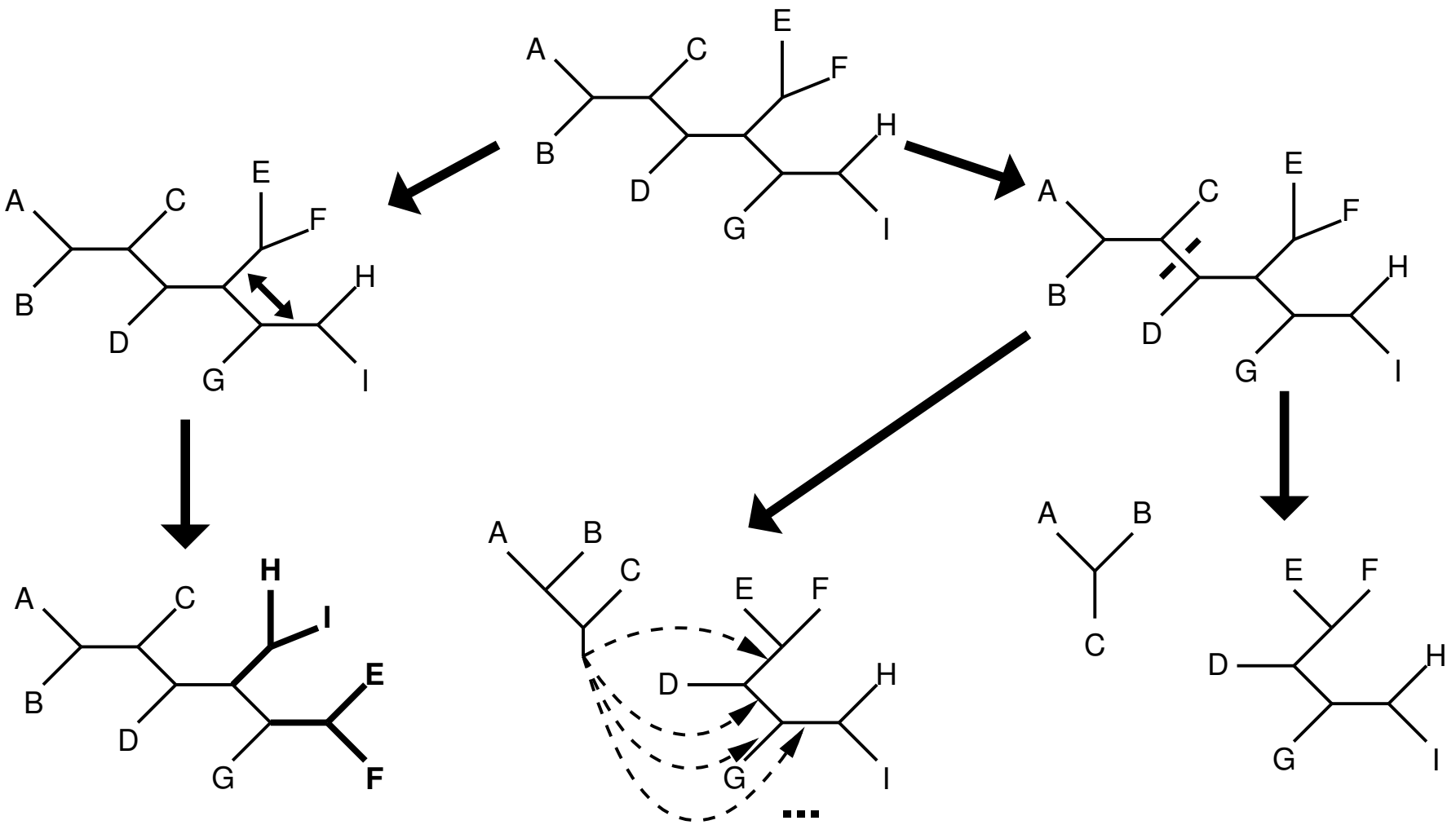
Nearest Neighbor Interchange

Possible NNI trees = O(n)

subtree pruning + regrafting

Possible SPR trees = O(n*n)

Tree Rearrangements: Scanning a Tree's Neighborhood



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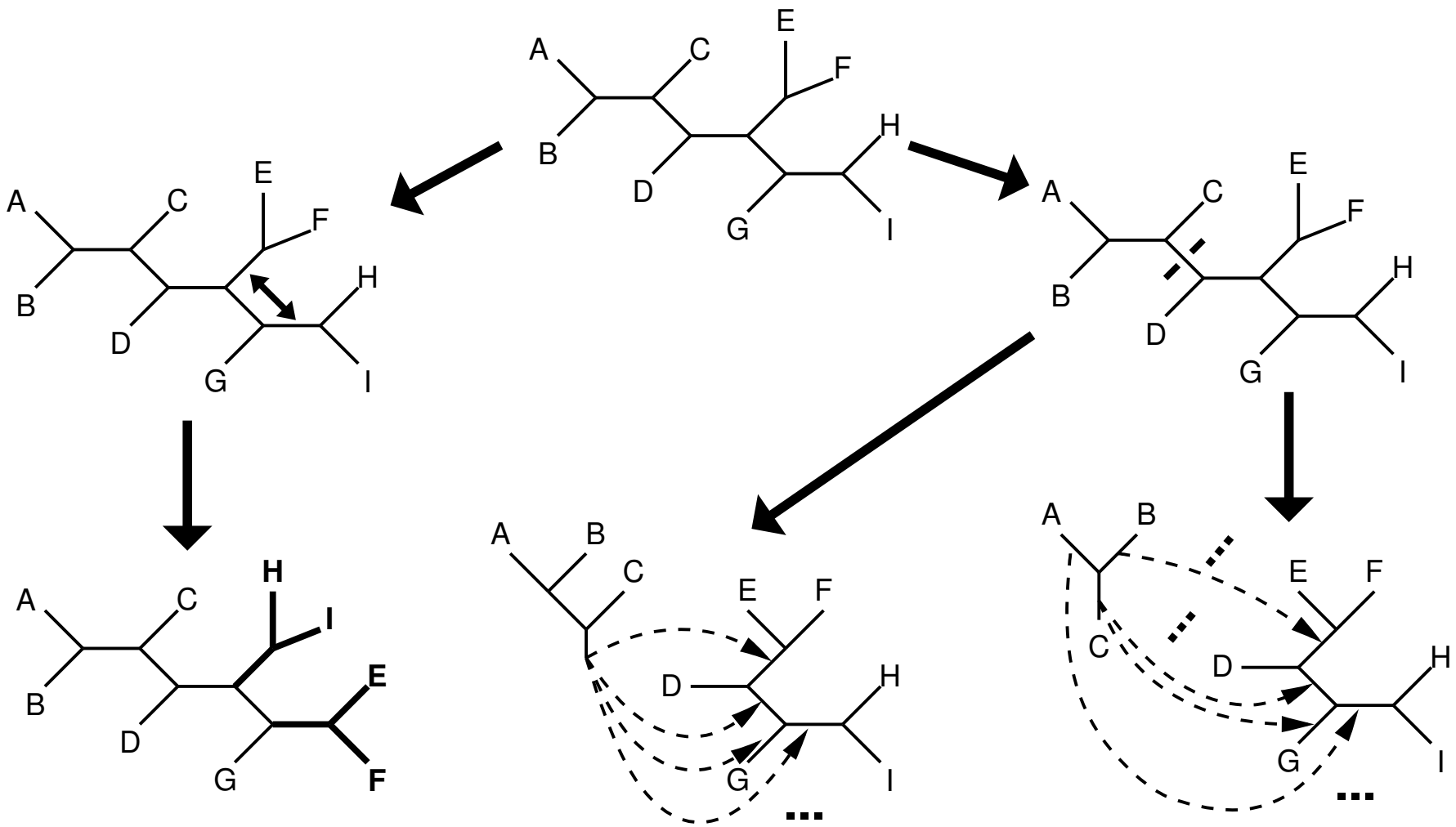

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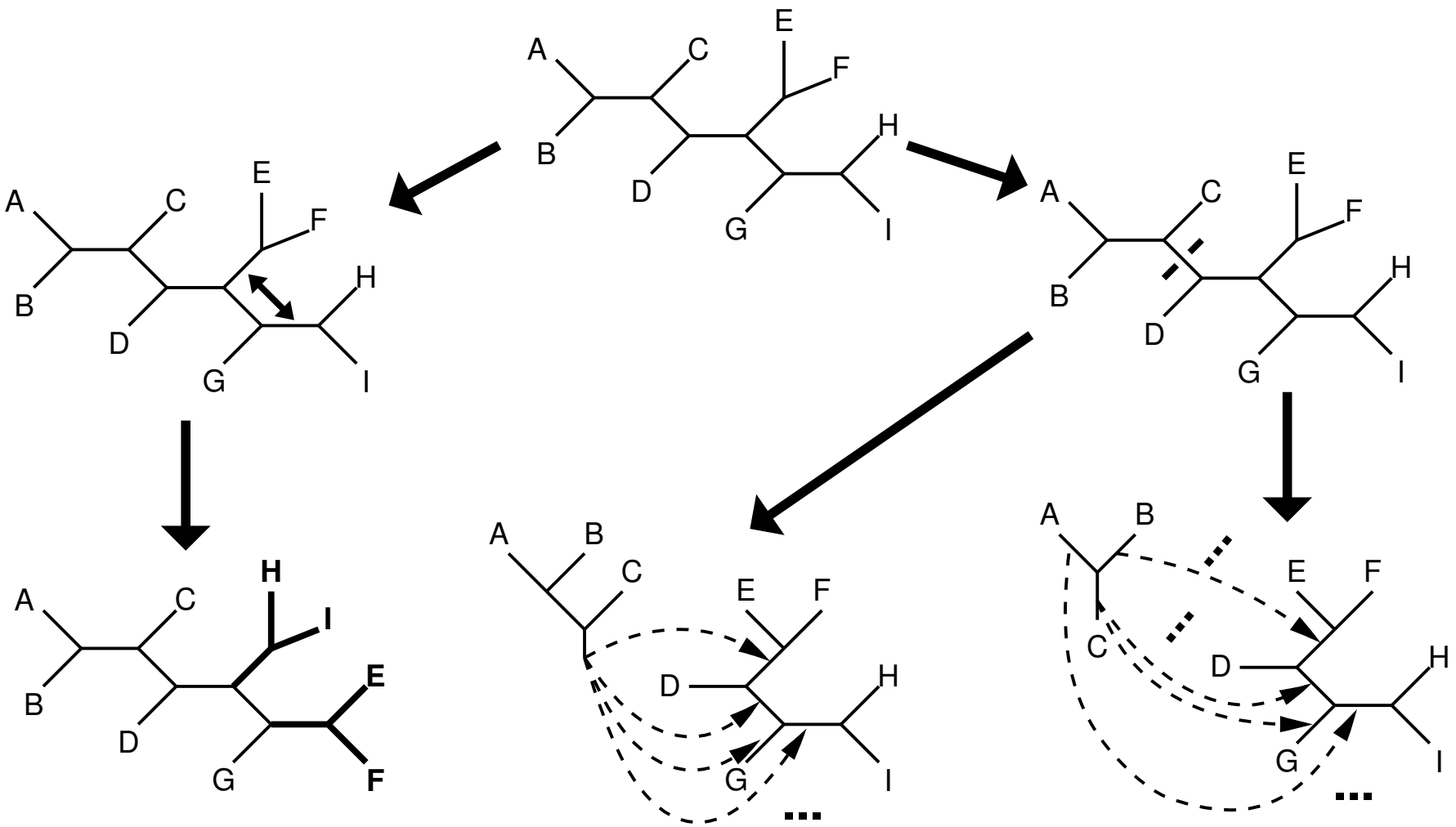

Nearest Neighbor Interchange

Possible NNI trees = O(n)

subtree pruning + regrafting

Possible SPR trees = O(n*n)

tree-bisection + reconnection

Possible TBR trees = O(n*n*n)

ML programs: DNAML (PHYLIP), fastDNAml

Concept: Stepwise insertion + NNI/SPR

1. Build tree with stepwise insertion
   (a) after each insertion optimize using NNI/local rearrangement (default, but user-adjustable gradually up to SPR; only fastDNAml)
   (b) repeat (a) rearrangements until no better tree found.

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2. after the last insertion optimize using SPR/global rearrangement (in DNAML; in fastDNAml user-adjustable gradually down to NNI)
3. repeat (2) rearrangements until no better tree found.

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Concept: Stepwise insertion + NNI/SPR

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2. after the last insertion optimize using SPR/global rearrangement (in DNAML; in fastDNAml user-adjustable gradually down to NNI)
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Pro: Evaluating large neighborhood with SPR.

Con: Slow.

ML programs: DNAML (PHYLIP), fastDNAml

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Pro: Evaluating large neighborhood with SPR.

Con: Slow.

Note: To save time, in other methods steps (1) and (2) are usually substituted by swiftly computed trees (e.g., BioNJ).

ML programs: MOLPHY

Concept: Star decomposition + NNI

1. Build tree with star decomposition
2. after the last insertion optimize using NNI/local rearrangement
3. repeat rearrangements (2) until no better tree found.

Con: Slow, not maintained anymore.

ML programs: MOLPHY

Concept: Star decomposition + NNI

1. Build tree with star decomposition
2. after the last insertion optimize using NNI/local rearrangement
3. repeat rearrangements (2) until no better tree found.

Con: Slow, not maintained anymore.

ML programs: RAxML

Concept: MP tree + LSR

Descendant on fastDNAml, but ...

1. Starting with MP tree.
2. Uses *lazy subtree rearrangements* (only the 3 insertion branches are optimized), collecting candidates.
3. Candidates are evaluated.
4. Iterating (2)-(4).

ML programs: RAxML

Concept: MP tree + LSR

Descendant on fastDNAml, but ...

1. Starting with MP tree.
2. Uses *lazy subtree rearrangements* (only the 3 insertion branches are optimized), collecting candidates.
3. Candidates are evaluated.
4. Iterating (2)-(4).

Pro: Fast,
smart algorithmic and numerical optimized ML computation.

Con: Only few trees fully evaluated trees.

ML programs: PHYML

Concept: BioNJ tree + fastNNI

1. Start with BioNJ tree.
2. Do fastNNIs to optimize trees, i.e., evaluate all NNIs simultaneously and then merge all best ones which are non-conflicting.
3. Repeat (1) until no better tree found anymore.

ML programs: PHYML

Concept: BioNJ tree + fastNNI

1. Start with BioNJ tree.
2. Do fastNNIs to optimize trees, i.e., evaluate all NNIs simultaneously and then merge all best ones which are non-conflicting.
3. Repeat (1) until no better tree found anymore.

Pro: Fast

Con: Prone to get stuck on local optima due to NNI-only.
(SPR-based version PhyML-SPR has not been released yet.)

ML programs: PHYML-SPR

1. Start with BioNJ tree.
2. Evaluate SPR by fast non-ML criterion to find best candidates.
3. Evaluate the candidate(s) more rigorously with ML and fastNNI.
4. Repeat until no better tree found anymore.

Pro: less prone to get stuck on local optima.

Con: software not released yet.

ML programs: IQPNNI

Concept: BioNJ tree + randomization + fastNNI

1. Start with BioNJ tree.
2. Do fastNNIs to optimize trees, i.e., evaluate all NNIs simultaneously and then accept all best ones which are non-conflicting. (after first round, identical to PHYML).
3. Remove randomly a certain amount of taxa and re-insert them by a fast and rough quartet-based method. (some randomization)
4. Repeat (2)-(3) until stop criterion is met.

ML programs: IQPNNI

Concept: BioNJ tree + randomization + fastNNI

1. Start with BioNJ tree.
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3. Remove randomly a certain amount of taxa and re-insert them by a fast and rough quartet-based method. (some randomization)
4. Repeat (2)-(3) until stop criterion is met.

Pro: Can evade local optima,
offers automatic stopping criterion,
hints when search didn't run enough,
numerically optimized ML computation,
offers codon models

Con: slower than PhyML/RAxML

ML programs: Genetic Algorithms (GARLI, MetaPIGA)

1. Start with some (random) tree.
2. View tree topology, branch lengths, and model parameter as part of a 'genome'.
3. Evolve the 'genome' by mutating (slightly changing) its parts.
4. Accept or reject new tree topologies from a pool of suggested trees according to their likelihood.
5. Iterate (3) and (4)

ML programs: Simulated Annealing

- Start with some (random) tree.
- Start a '*hot chain*' to suggest tree topologies (being far away).
- Accept proposals according to their likelihood.
- Cool down the chain, until the suggestions end up in some (local) optimum.

How reliable is the reconstructed tree:

- Usually programs deliver a single tree, but without confidence values for the subtrees.
- How can we assess reliability for the subtree?

Quartet Puzzling

The Quartet Puzzling algorithm implemented in the TREE-PUZZLE program is a three step procedure:

maximum-likelihood step: compute ML trees for all quartets of an alignment.

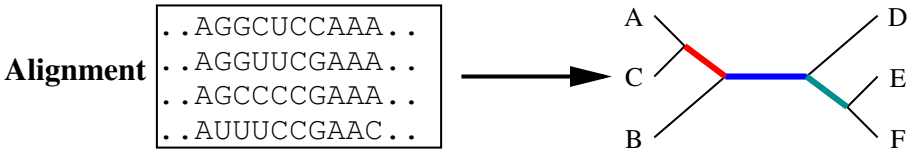
puzzling step: compose intermediate tree from quartet trees (this is done multiple times).

consensus step: construct a majority rule consensus tree from the intermediate trees and evaluate the branch lengths.

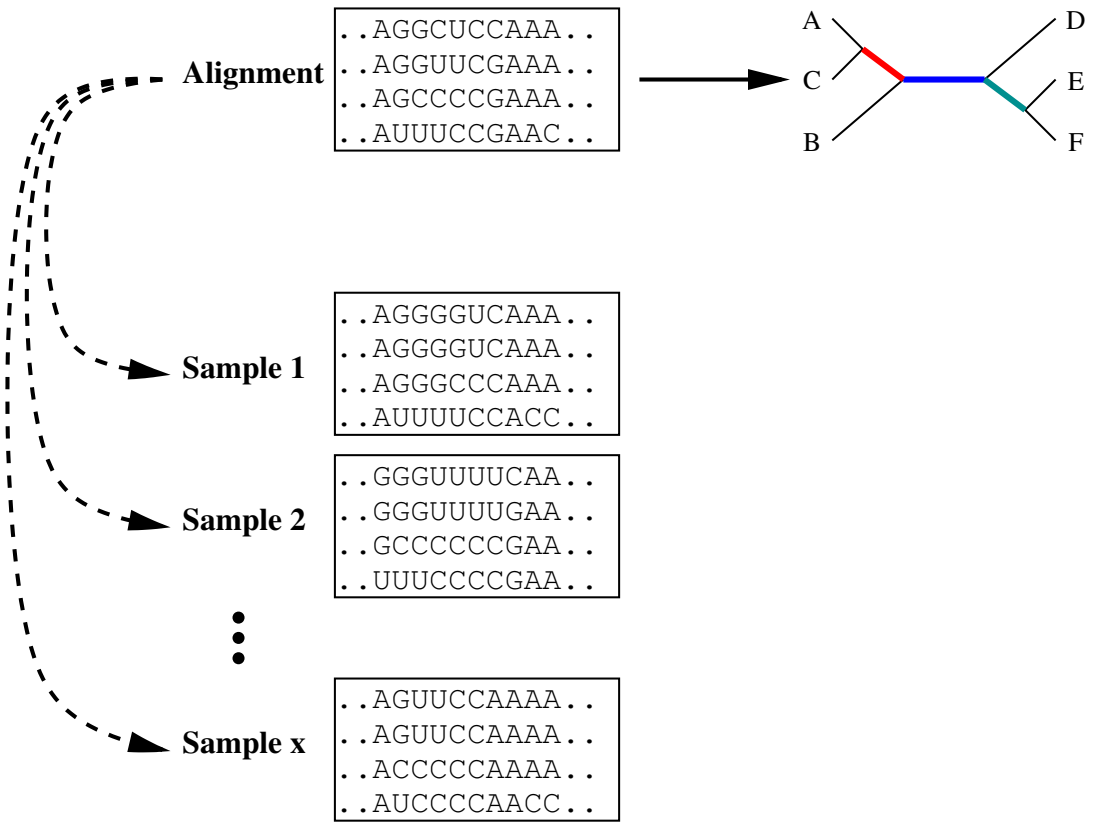
Branch Support

- We can now reconstruct ML trees, but how comparable are the likelihoods, how reliable the groupings?
- Branch reliability can be checked, support values computed using:
  - Randomizing input orders in stepwise insertions (TREE-PUZZLE).
  - Jackknifing alignment columns + consensus.
  - Bootstrapping alignment columns + consensus.
  - Trees from Bayesian MCMC sampling + consensus.

Estimating Confidence: The Bootstrap



Estimating Confidence: The Bootstrap



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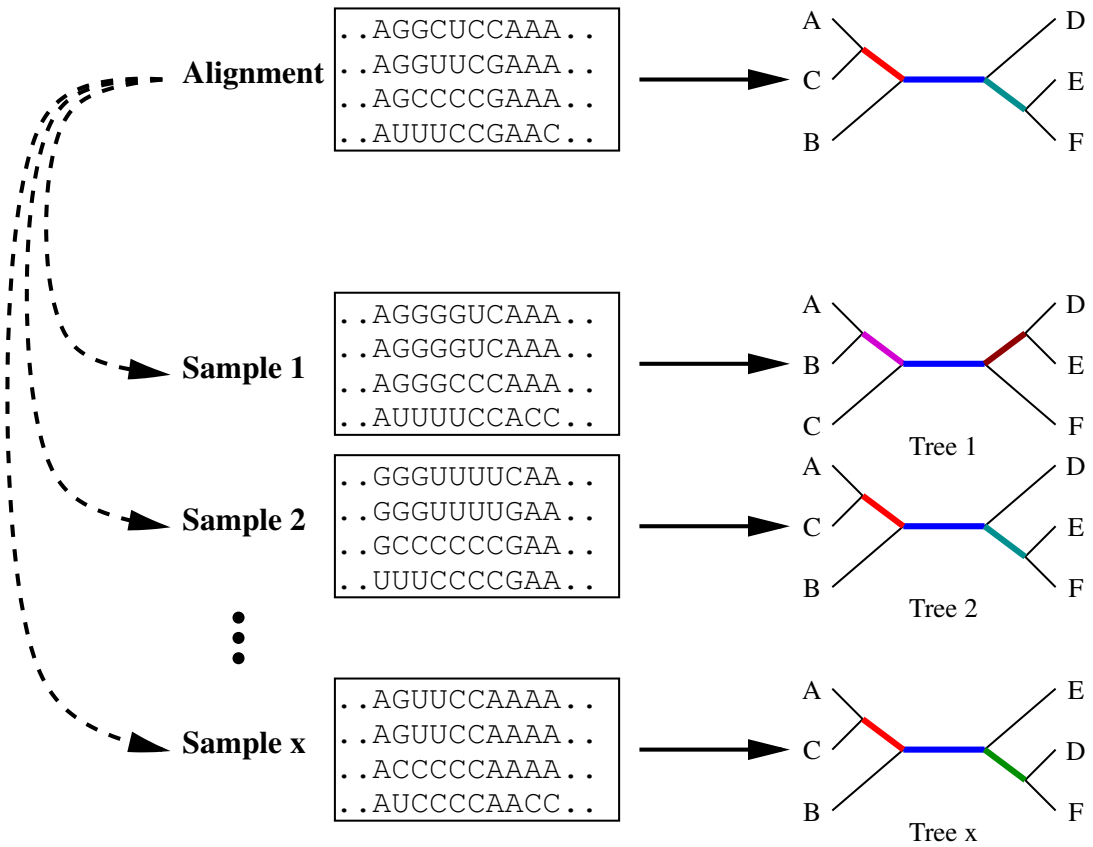

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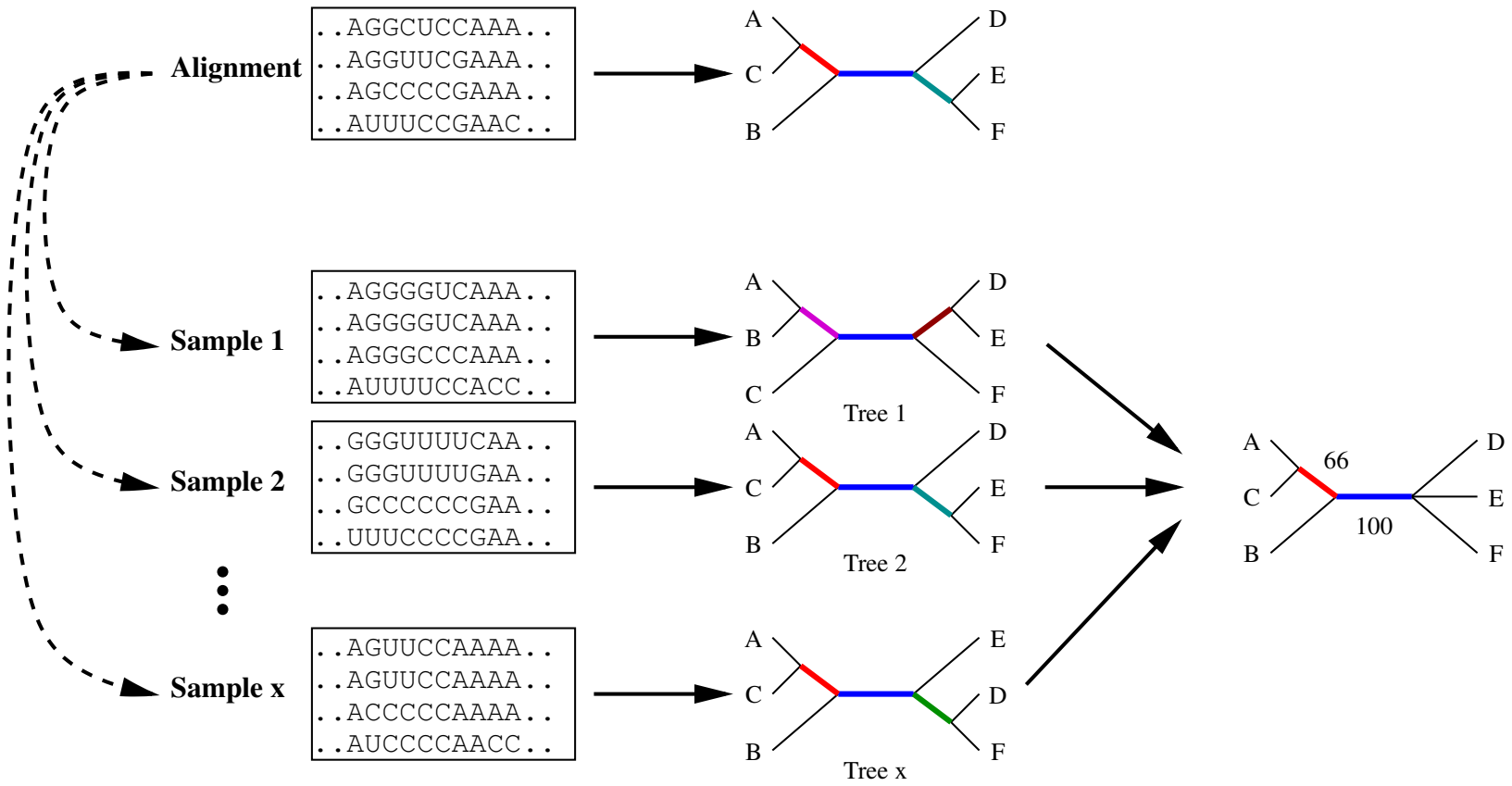
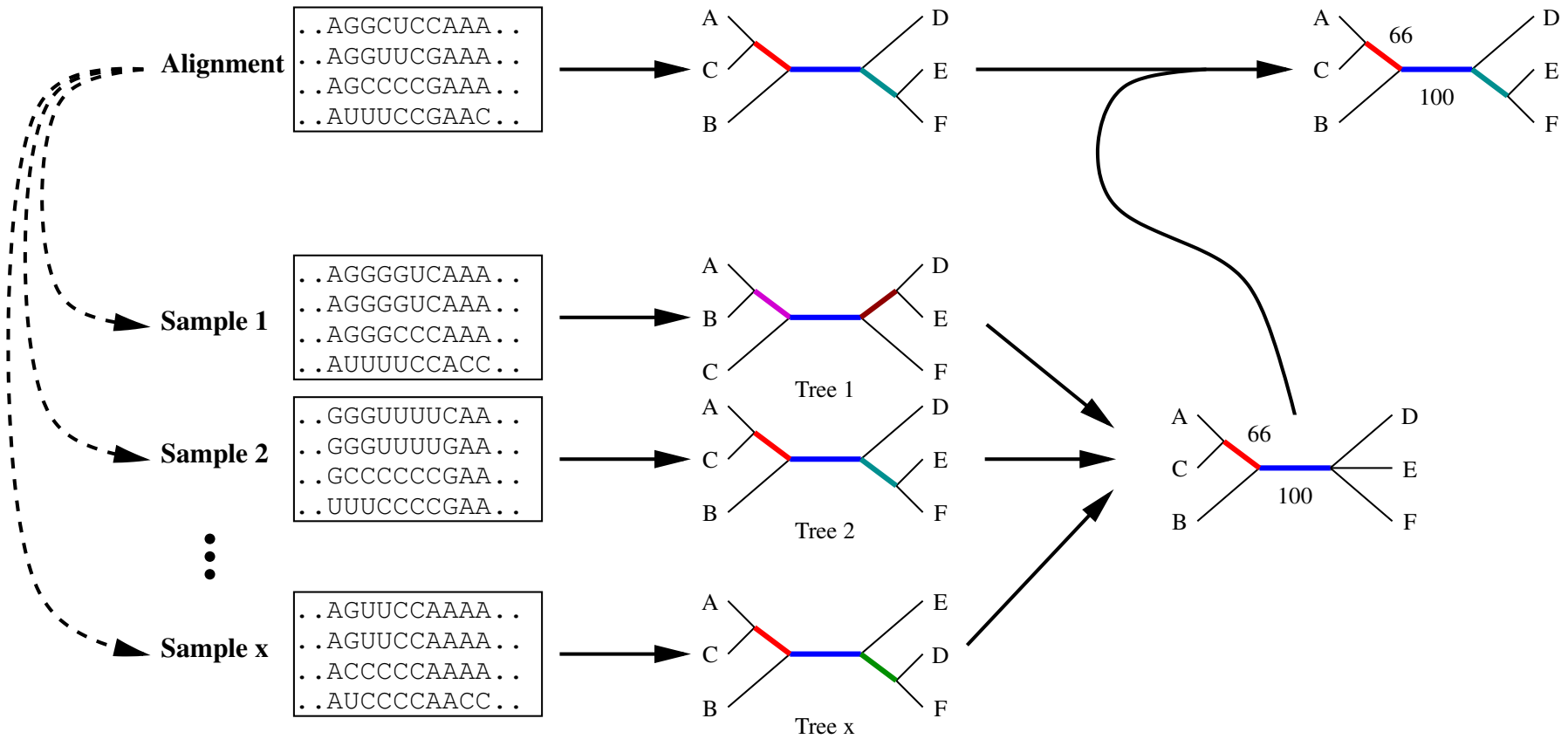
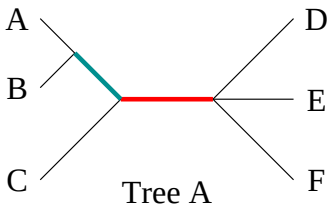


Estimating Confidence: The Bootstrap



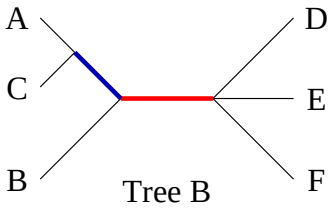
Summarizing Trees: Consensus Methods



Tree A

AB|CDEF

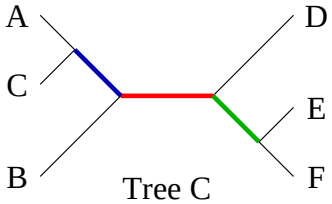
ABC|DEF



Tree B

AC|BDEF

ABC|DEF



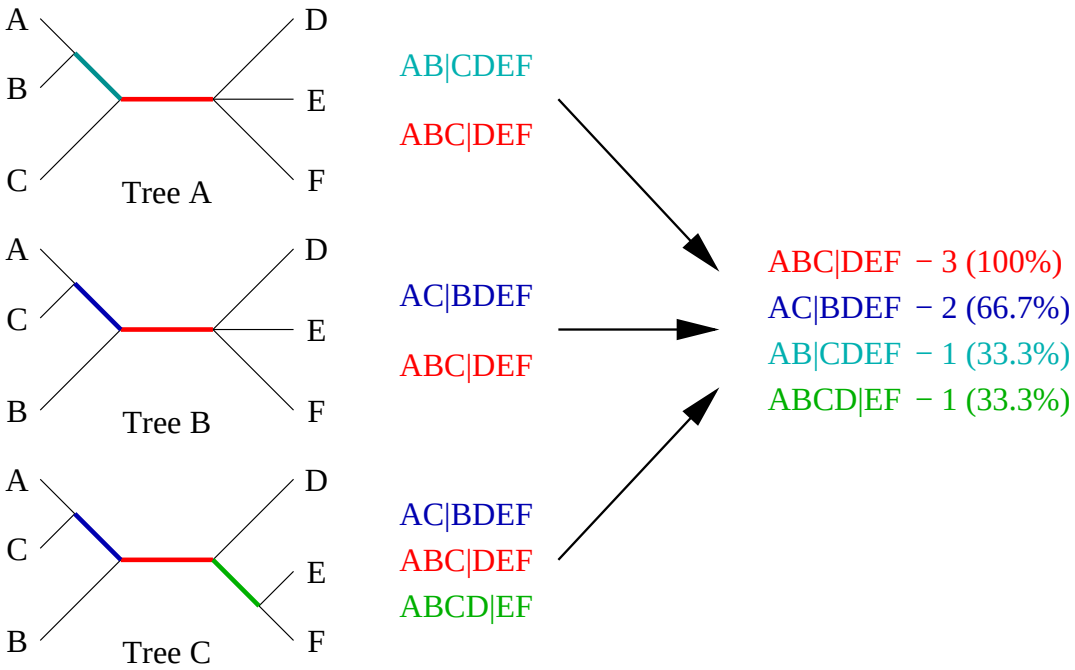
Tree C

AC|BDEF

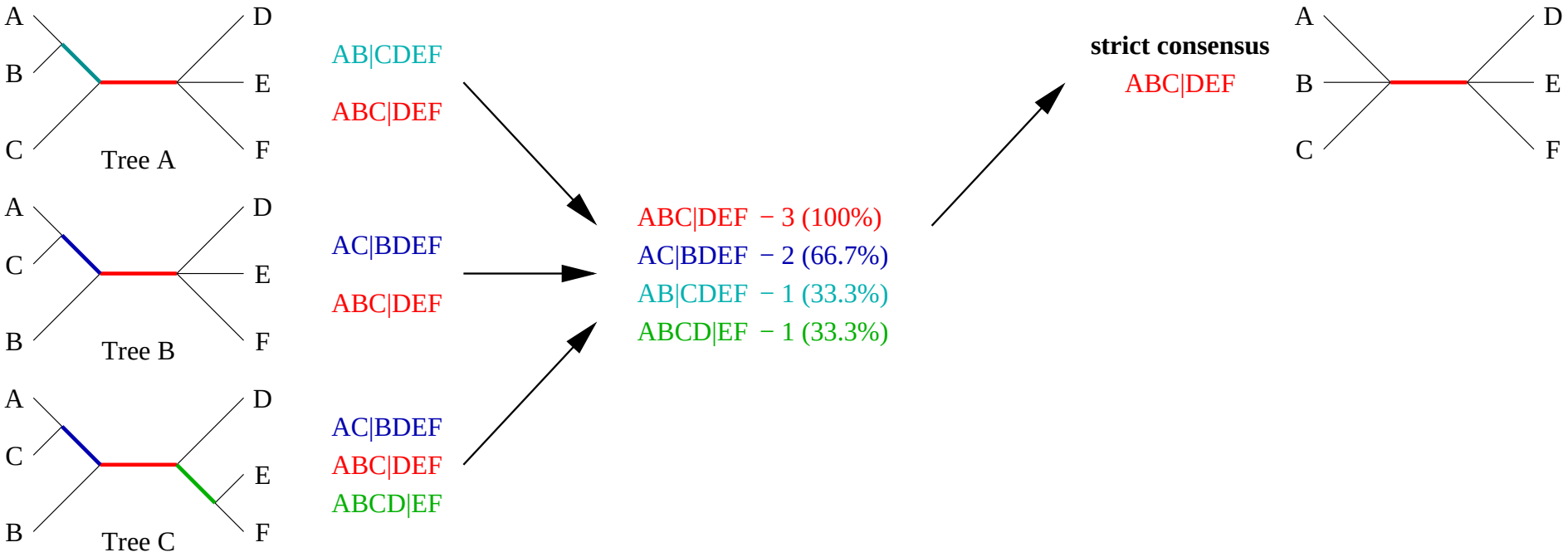
ABC|DEF

ABCD|EF

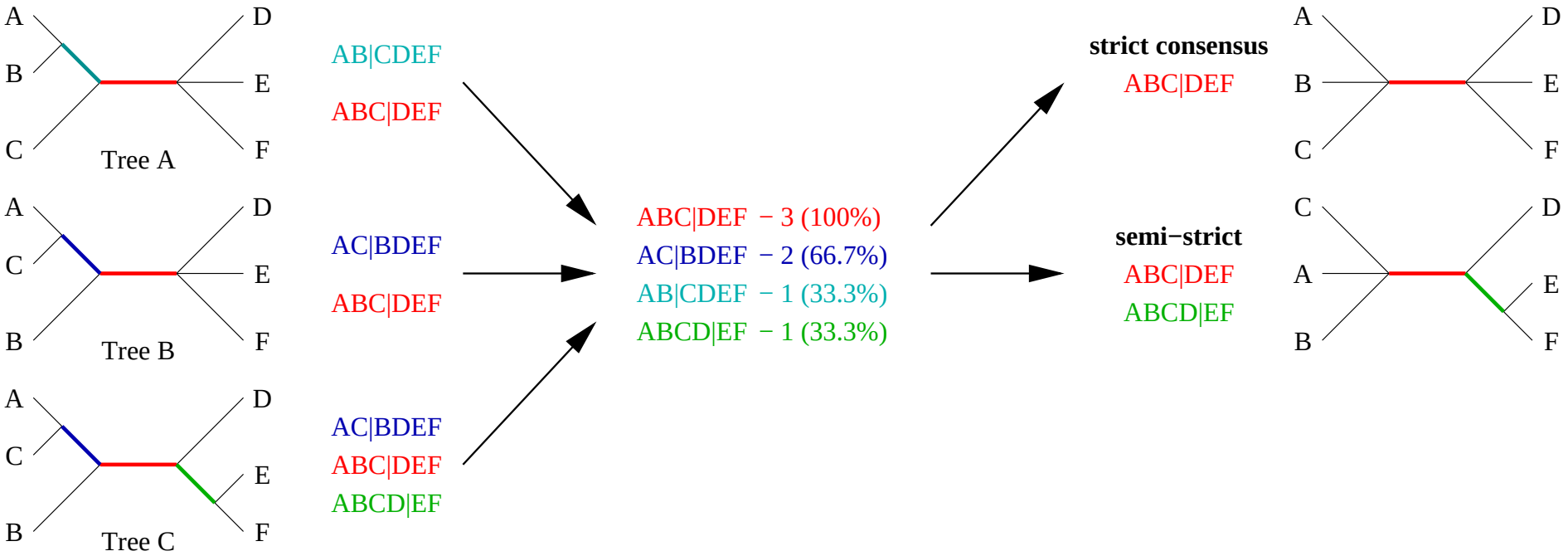
Summarizing Trees: Consensus Methods



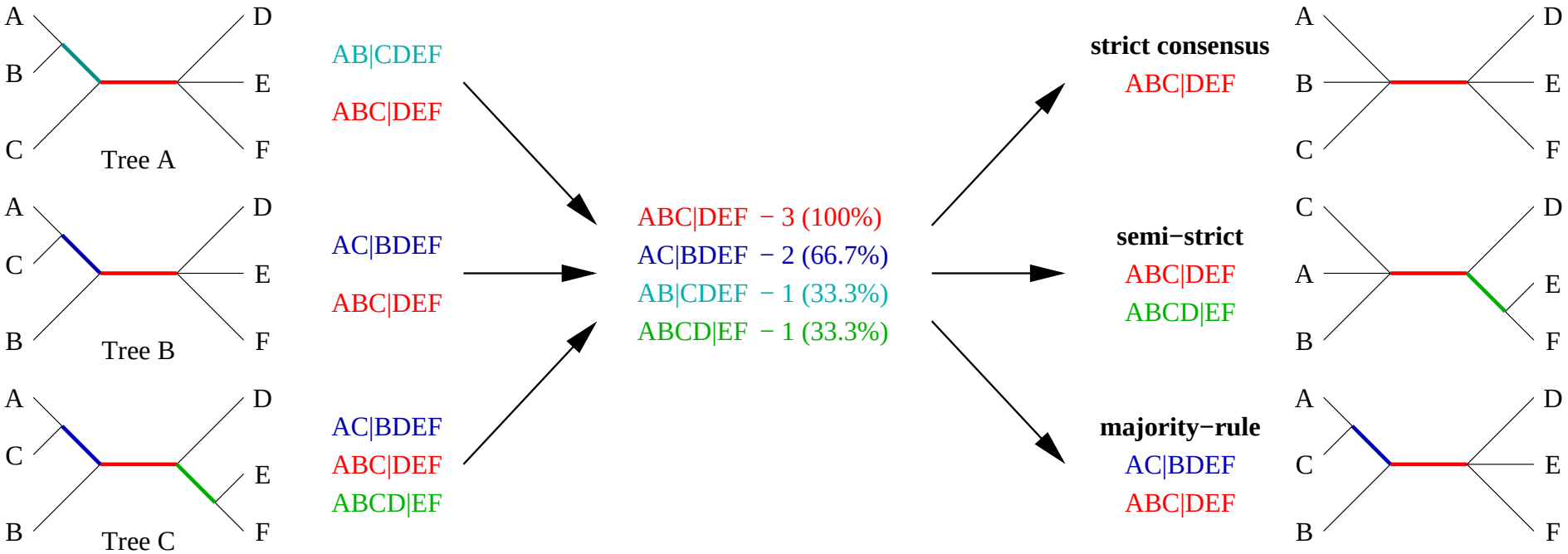
Summarizing Trees: Consensus Methods



Summarizing Trees: Consensus Methods



Summarizing Trees: Consensus Methods



Overview over Likelihood-based Analyses

- Comparing hypothesis with Likelihood-Ratio-Test (=LRT)
  - different models of evolution (ModelTest)
  - testing molecular clock assumption and root position (TREE-PUZZLE)
- Parameter estimation (TREE-PUZZLE, PAUP, ModelTest, . . .)
- Testing for phylogenetic content (TREE-PUZZLE)
- Comparing/testing different tree topologies with Kishino-Hasegawa test, Shimodaira-Hasegawa test (TREE-PUZZLE), SOWH-test, ELW
- Constructing confidence sets on posterior likelihoods (MrBayes)

Posterior Probabilities and Empirical Bayes

- Problem: How different are likelihoods? Just from the value of likelihoods one often cannot tell whether they are significantly different.

Posterior Probabilities and Empirical Bayes

- Problem: How different are likelihoods? Just from the value of likelihoods one often cannot tell whether they are significantly different.
- Normalization: Posterior probabilities are computed:

$$p_i = \frac{L_1}{\sum_n L_n}$$

- Usage:
  - Which sites along an alignment support a tree most?
  - Are there sites/partitions not supporting a tree?
  - Which model of evolution (e.g. dependent, independent) is supported by which site/partition? (PAML)
  - Is a site fast/medium/slowly evolving? (PAML, TREE-PUZZLE)
  - Constructing confidence sets on posterior tree likelihoods (MrBayes)

LRT – Likelihood Ratio Test (1)

The Likelihood function offers a natural way of comparing nested evolutionary hypothesis using the Likelihood Ratio (LR) statistics:

$$\Delta = 2(\ln L_1 - \ln L_0)$$

- L_1 maximum likelihood under the more parameter-rich, complex model (alternative hypothesis, H_A)
- L_0 maximum likelihood under the less parameter-rich simple model (Null-hypothesis, H_0)

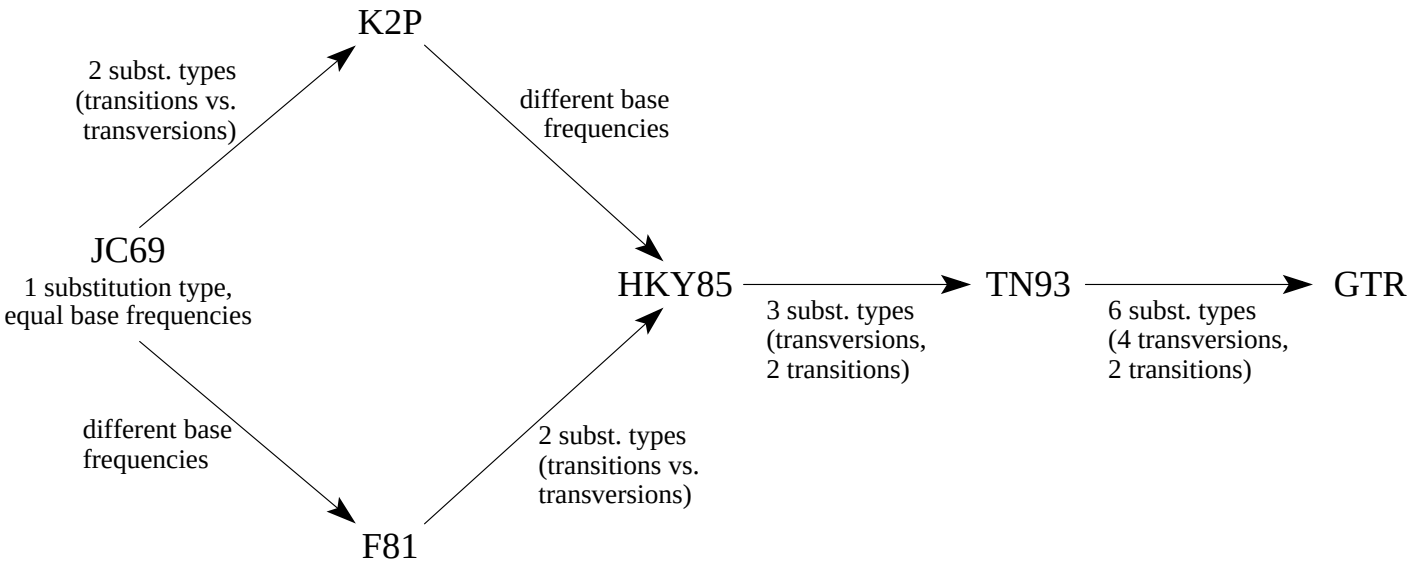
If the models are nested, i.e., H_0 is a special case of H_A and the Null-hypothesis (H0) is correct, Δ is asymptotically χ^2-distributed with the number of degrees of freedom equal to the difference in number of free parameters between the two models.

LRT – Likelihood Ratio Test (2)

- If the LRT is significant (i.e., $p < 0.05$ or $p < 0.01$): the use of the additional parameters in the alternative model H_A increases the likelihood significantly.
- If Δ is close to zero, that is, $p > 0.05$: the alternative hypothesis H_A does not fit the data significantly better than H_0, that means using the additional parameters of H_A does not explain the data better.
- Only nested models can be tested:
  One model (H_0, Null-model, constraint model) is nested in another model (H_A, alternative, unconstraint model) if the model H_0 can be produced by restricting parameters in model H_A.

LRT – Typical cases of nested models

- Different levels of evolutionary models:



- *rate-homogeneous models* (H_0) are nested in *rate-heterogeneous models* (H_A)
- A tree assuming *molecular clock* (H_0) are nested its *non-clock* version (H_A)

Exercises:

the exercises can be found at

`http://www.cibiv.at/~hschmidt/VEME/ML`