Maximum Likelihood Methods in Phylogenetics

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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**	

Introduction: ML on Coin Tossing

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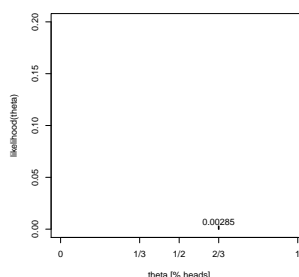

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Probability   **Likelihood**

$p(k$ heads in n tosses$|\theta) \quad \equiv \quad L(\theta|k$ heads in n tosses$)$

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Probability   **Likelihood**

$$\begin{aligned} p(k \text{ heads in } n \text{ tosses}|\theta) & \equiv L(\theta|k \text{ heads in } n \text{ tosses}) \\ & = \binom{n}{k}\theta^k(1-\theta)^{n-k} \end{aligned}$$

(here binomial distribution)

Introduction: ML on Coin Tossing (Estimate)

coint tossing: 7 heads, 13 tails

Three coin case

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

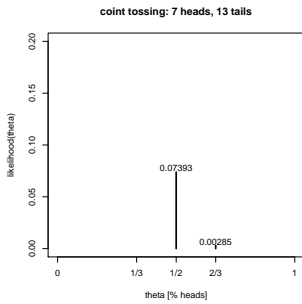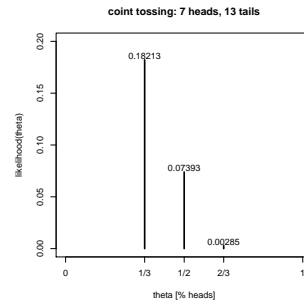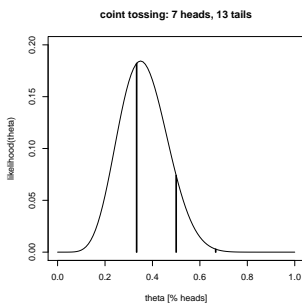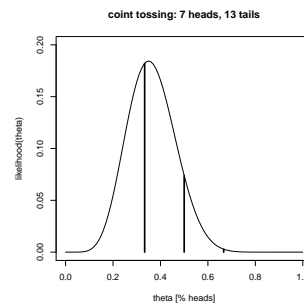for each coin $\theta \in \left\{\frac{1}{3}, \frac{1}{2}, \frac{2}{3}\right\}$

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For infinitely many coins
$\theta = (0...1)$

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For infinitely many coins
$\theta = (0...1)$

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

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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.

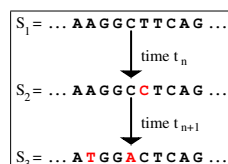
Modeling Evolution

- 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.

$S_1 = \ldots$ A A G G C T T C A G $\ldots$

        time t_n

$S_2 = \ldots$ A A G G C **C** T C A G $\ldots$

        time t_{n+1}

$S_3 = \ldots$ A **T** G G **A** C T C A G $\ldots$

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:
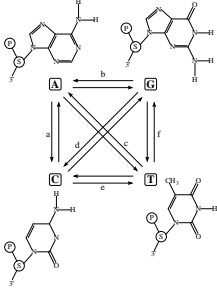Mutations in either direction are equally likely

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

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

$\ldots R$ and Π are combined into the instantaneous rate matrix Q

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

(where the row sums are zero).

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(where the row sums are zero).

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 $i \rightarrow j$ over a time t.

Relations between DNA models
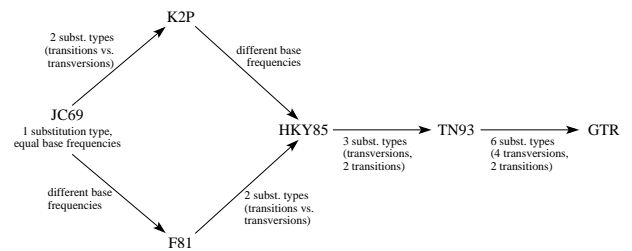
Protein Models

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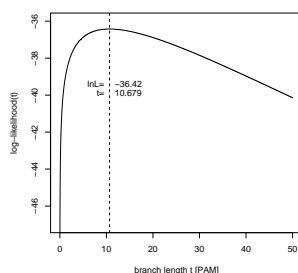
Computing ML Distances Using $P_{ij}(t)$

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

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

Likelihood surface for two sequences under JC69:

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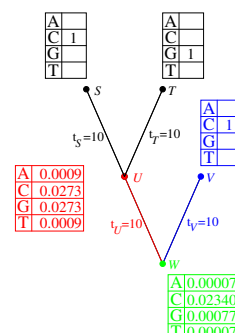
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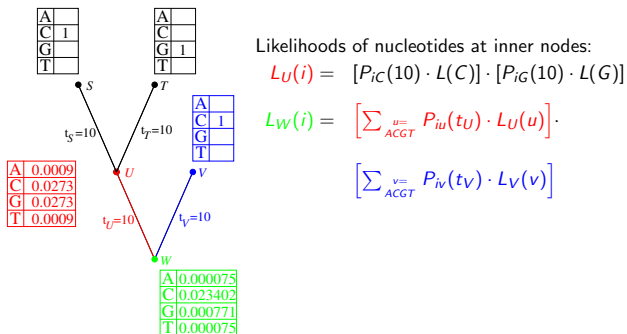Note: we do not compute the probability of the distance t but that of the data $D = \{s, s'\}$.

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

Likelihoods of nucleotides at inner nodes:
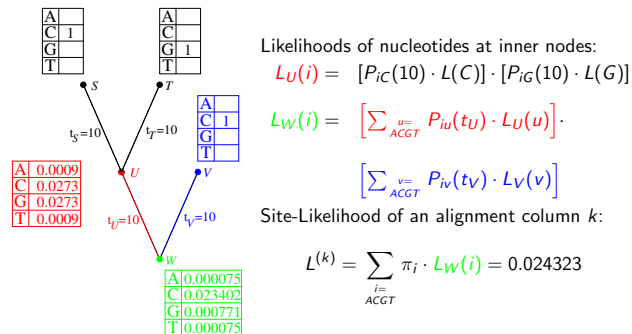$$L_U(i) = [P_{iC}(10) \cdot L(C)] \cdot [P_{iG}(10) \cdot L(G)]$$

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$$L_W(i) = \left[\sum_{ACGT}^{u=} P_{iu}(t_U) \cdot L_U(u) \right] \cdot$$

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

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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

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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.).
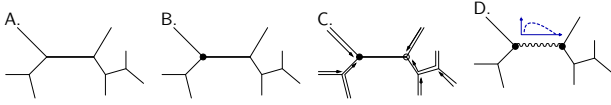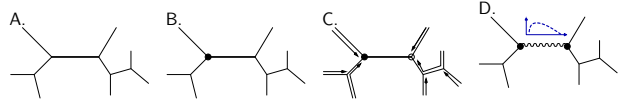
A.

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Repeat this for every branch until no better likelihood is gained.
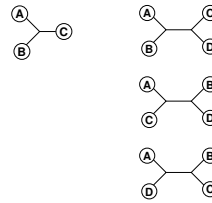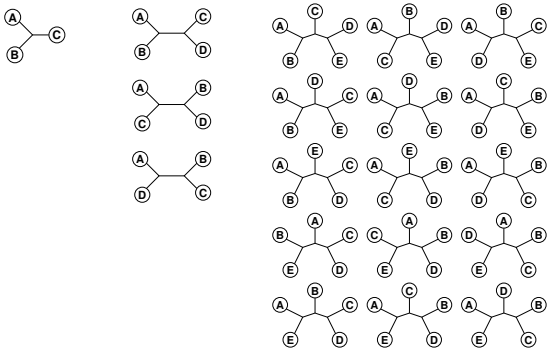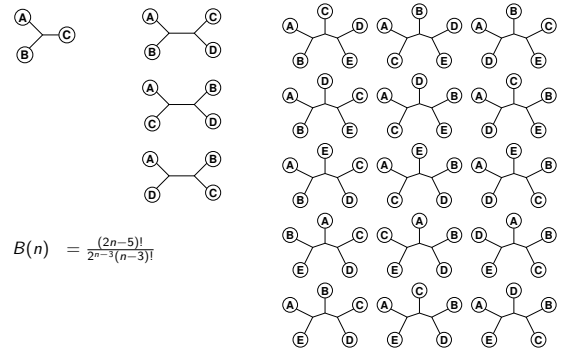
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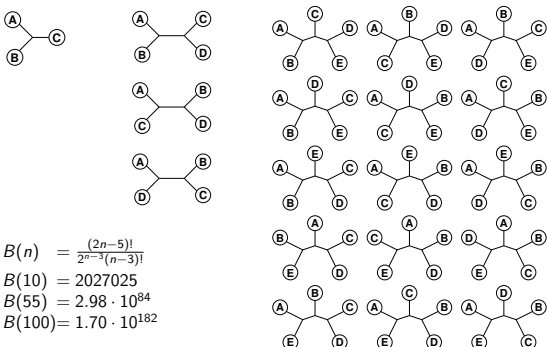
$$B(n) = \frac{(2n-5)!}{2^{n-3}(n-3)!}$$
$$B(10) = 2027025$$
$$B(55) = 2.98 \cdot 10^{84}$$
$$B(100) = 1.70 \cdot 10^{182}$$

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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Build up a tree: Stepwise Insertion

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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

Slide 1

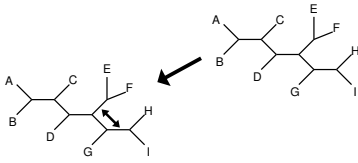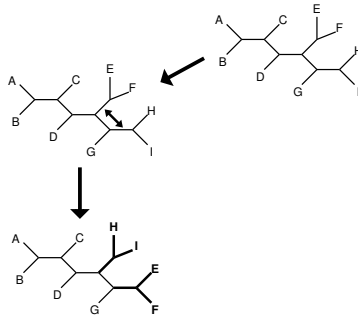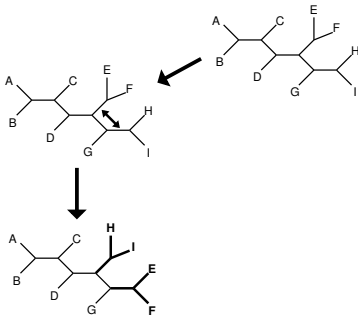## Tree Rearrangements

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Slide 2

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Slide 3

Tree Rearrangements

Nearest Neighbor Interchange

Possible NNI trees = O(n)

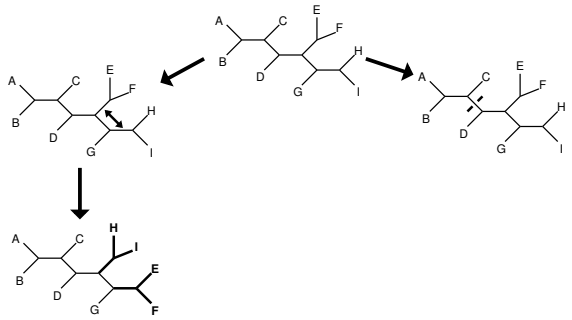Heiko A. Schmidt   Maximum Likelihood Methods in Phylogenetics

Slide 4

Tree Rearrangements

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Slide 5

Tree Rearrangements

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Slide 6

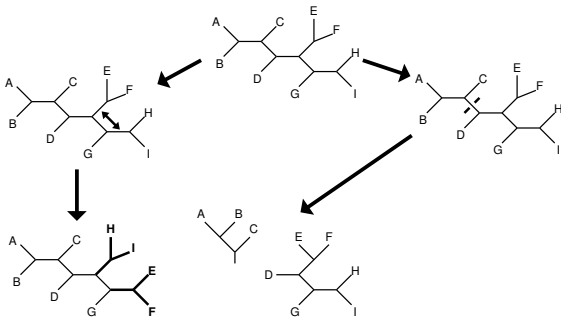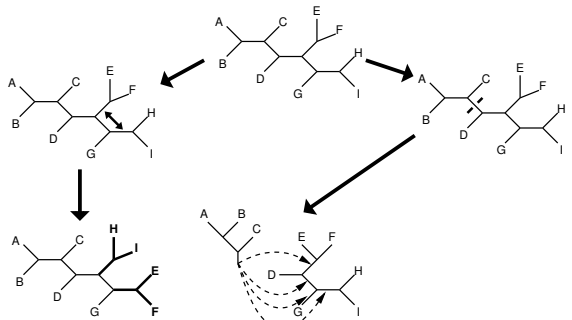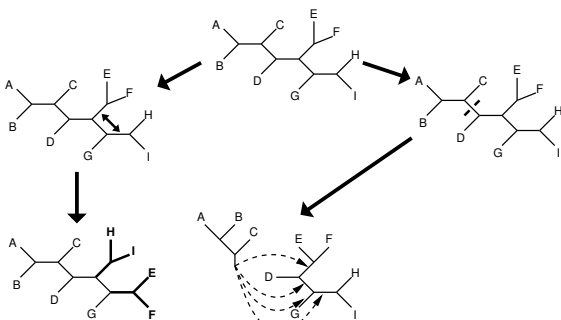## Tree Rearrangements

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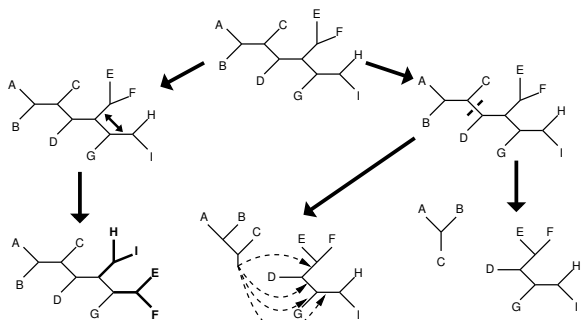Heiko A. Schmidt   Maximum Likelihood Methods in Phylogenetics

Slide 7

Tree Rearrangements

Nearest Neighbor Interchange   **subtree pruning + regrafting**

Possible NNI trees = O(n)   Possible SPR trees = O(n*n)

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Slide 8

Tree Rearrangements

Nearest Neighbor Interchange   **subtree pruning + regrafting**

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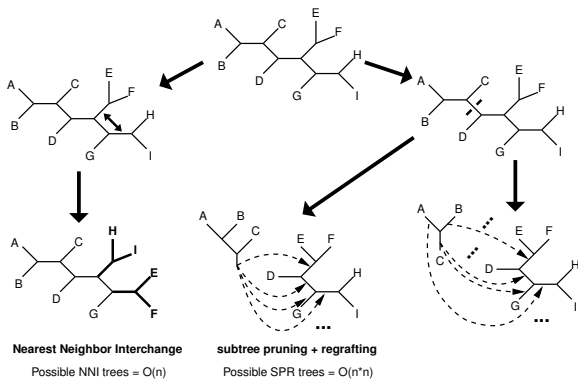Heiko A. Schmidt   Maximum Likelihood Methods in Phylogenetics

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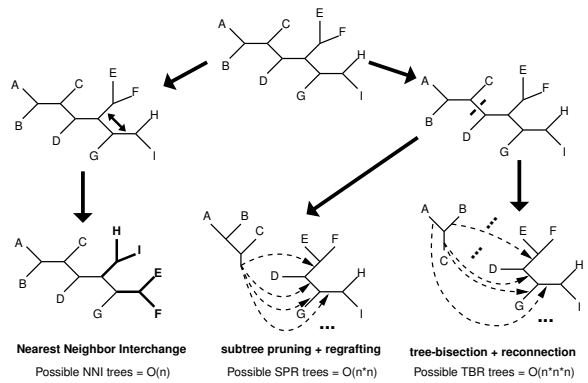
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Tree Rearrangements

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

- Build tree with stepwise insertion
- after each insertion optimize using NNI/local rearrangement (default, but user-adjustable gradually up to SPR; only fastDNAml)
- after the last insertion optimize using SPR/global rearrangement (in DNAML; in fastDNAml user-adjustable gradually down to NNI)
- repeat rearrangements until no better tree found.

ML programs: MOLPHY

- Build tree with star decomposition
- after the last insertion optimize using NNI/local rearrangement
- repeat rearrangements until no better tree found.

ML programs: (R)AxML family

- Descendant on fastDNAml, but . . .
- Starting with MP tree.
- Many smart algorithmic and numerical optimized ML computation.
- Uses *lazy rearrangements*, i.e., only the 3 insertion branches are optimized.
- (Several versions with slightly different algorithms, e.g., Simulated Annealing.)

ML programs: PHYML

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

ML programs: PHYML-SPR

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

ML programs: IQPNNI

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 until stop criterion is met.

ML programs: Genetic Algorithms (GARLI, MetaPIGA)

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

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.
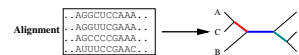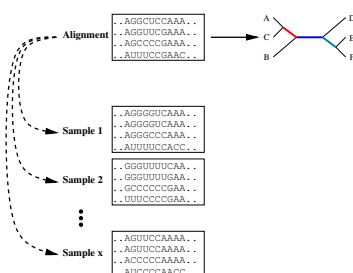
Branch Support

- 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

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Estimating Confidence: The Bootstrap
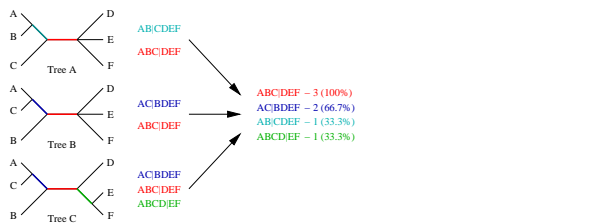
Summarizing Trees: Consensus Methods

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ABC|DEF − 3 (100%)
AC|BDEF − 2 (66.7%)
AB|CDEF − 1 (33.3%)
ABCD|EF − 1 (33.3%)

Summarizing Trees: Consensus Methods

strict consensus
ABC|DEF

ABC|DEF − 3 (100%)
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Summarizing Trees: Consensus Methods

strict consensus
ABC|DEF

semi−strict
ABC|DEF
ABCD|EF

majority−rule
AC|BDEF
ABC|DEF

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)

- 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:
- Usage:

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

  - 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)
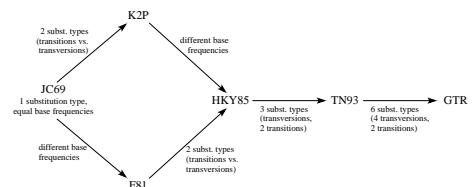
LRT – Likelihood Ratio Test (1)

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)