

Statistical stuff: models, methods, and performance issues

CS 394C

September 16, 2013

Today's Class

- Phylogeny as statistical estimation problem
- Stochastic models of evolution
- Distance-based estimation

Phylogeny estimation as a statistical inverse problem

Estimation of evolutionary trees as a statistical inverse problem

- We can consider characters as properties that evolve down trees.
- We observe the character states at the leaves, but the internal nodes of the tree also have states.
- The challenge is to estimate the tree from the properties of the taxa at the leaves. This is enabled by characterizing the evolutionary process as accurately as we can.

Performance criteria

- Running time.
- Space.
- Statistical performance issues (e.g., statistical consistency and sequence length requirements)
- “Topological accuracy” with respect to the underlying *true tree*. Typically studied in simulation.
- Accuracy with respect to a mathematical score (e.g. tree length or likelihood score) on real data.

Statistical models

- Simple example: coin tosses.
- Suppose your coin has probability p of turning up heads, and you want to estimate p . How do you do this?

Estimating p

- Toss coin repeatedly
- Let your estimate q be the fraction of the time you get a head
- Obvious observation: q will approach p as the number of coin tosses increases
- This algorithm is a *statistically consistent* estimator of p . That is, your error $|q-p|$ goes to 0 (with high probability) as the number of coin tosses increases.

Another estimation problem

- Suppose your coin is biased either towards heads or tails (so that p is not $1/2$).
- How do you determine which type of coin you have?
- Same algorithm, but say “heads” if $q > 1/2$, and “tails” if $q < 1/2$. For large enough number of coin tosses, ***your answer will be correct with high probability.***

Markov models of character evolution down trees

- The character might be binary, indicating absence or presence of some property at each node in the tree.
- The character might be multi-state, taking on one of a specific set of possible states. Typical examples in biology: the nucleotide in a particular position within a multiple sequence alignment.
- A probabilistic model of character evolution describes a random process by which a character changes state on each edge of the tree. Thus it consists of a tree T and associated parameters that determine these probabilities.
- The “Markov” property assumes that the state a character attains at a node v is determined only by the state at the immediate ancestor of v , and not also by states before then.

Binary characters

- Simplest type of character: presence (1) or absence (0).
- How do we model the presence or absence of a property?

Simplest model of binary character evolution: **Cavender-Farris**

- For each edge **e**, there is a probability **p(e)** of the property “changing state” (going from 0 to 1, or vice-versa), with $0 < p(e) < 0.5$ (to ensure that CF trees are identifiable).
- Every position evolves under the same process, independently of the others.

Statistical models of evolution

- Instead of directly estimating the tree, we try to estimate the process itself.
- For example, we try to estimate the probability that two leaves will have different states for a random character.

Cavender-Farris pattern probabilities

- Let x and y denote nodes in the tree, and p_{xy} denote the probability that x and y exhibit different states.
- Theorem: Let p_i be the substitution probability for edge e_i , and let x and y be connected by path $e_1e_2e_3\dots e_k$. Then
$$1-2p_{xy} = (1-2p_1)(1-2p_2)\dots(1-2p_k)$$

And then take logarithms

- The theorem gave us:

$$1-2p_{xy} = (1-2p_1)(1-2p_2)\dots(1-2p_k)$$

- If we take logarithms, we obtain

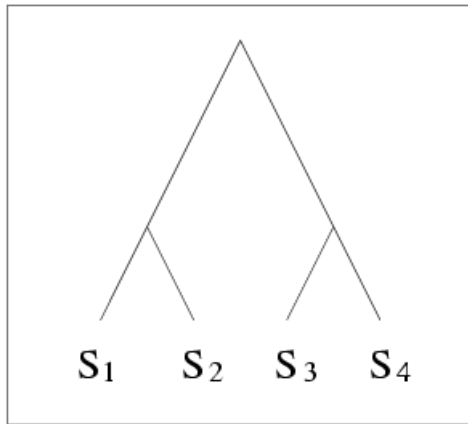
$$\ln(1-2p_{xy}) = \ln(1-2p_1) + \ln(1-2p_2) + \dots + \ln(1-2p_k)$$

- Since these probabilities lie between 0 and 0.5, these logarithms are all negative. So let's multiply by -1 to get positive numbers.

An additive matrix!

- Consider a matrix $D(x,y) = -\ln(1-2p_{xy})$
- This matrix is additive!
- Can we estimate this additive matrix from what we observe at the leaves of the tree?
- Key issue: how to estimate p_{xy} .
- (Recall how to estimate the probability of a head...)

Distance-based Methods

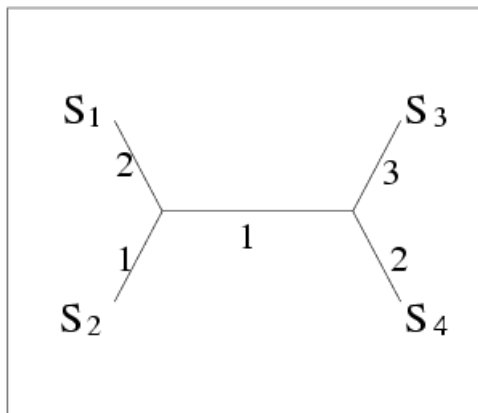


TRUE TREE

S₁ ACAATTAGAAC
S₂ ACCCTTAGAAC
S₃ ACCATTCCAAC
S₄ ACCAGACCAAC

DNA SEQUENCES

STATISTICAL
ESTIMATION
OF PAIRWISE
DISTANCES



INFERRED TREE

METHODS
SUCH AS
NEIGHBOR
JOINING

	S ₁	S ₂	S ₃	S ₄
S ₁	0	3	6	5
S ₂		0	5	4
S ₃			0	5
S ₄				0

DISTANCE MATRIX

Estimating CF distances

- Consider
$$d_{ij} = -1/2 \ln(1 - 2H(i,j)/k),$$
where k is the number of characters, and $H(i,j)$ is the Hamming distance between sequences s_i and s_j .
- Theorem: as k increases,
$$d_{ij} \text{ converges to } D_{ij} = -1/2 \ln(1 - 2p_{ij}),$$
which is an additive matrix.

CF tree estimation

- Step 1: Compute Hamming distances
- Step 2: Correct the Hamming distances, using the CF distance calculation
- Step 3: Use distance-based method (neighbor joining, naïve quartet method, etc.)

Four Point Method

- Task: Given 4x4 dissimilarity matrix, compute a tree on four leaves
- Solution: Compute the three pairwise sums, and take the split $ij|kl$ that gives the minimum!
- When is this guaranteed accurate?

Error tolerance for FPM

- Suppose every pairwise distance is estimated well enough (within $f/2$, for f the minimum length of any edge).
- Then the Four Point Method returns the correct tree (i.e., $ij+kl$ remains the minimum)

Naïve Quartet Method

- Compute the tree on each quartet using the four-point condition
- Merge them into a tree on the entire set if they are compatible:
 - Find a sibling pair A,B
 - Recurse on $S-\{A\}$
 - If $S-\{A\}$ has a tree T, insert A into T by making A a sibling to B, and return the tree

Error tolerance for NQM

- Suppose every pairwise distance is estimated well enough (within $f/2$, for f the minimum length of any edge).
- Then the Four Point Method returns the correct tree on every quartet.
- And so all quartet trees are compatible, and NQM returns the true tree.

In other words:

- The NQM method is statistically consistent methods for estimating Cavender-Farris trees!
- Plus it is polynomial time!

DNA substitution models

- Every edge has a substitution probability
- The model also allows 4x4 substitution matrices on the edges:
 - Simplest model: Jukes-Cantor (JC) assumes that all substitutions are equiprobable
 - General Time Reversible (GTR) Model: one 4x4 substitution matrix for all edges
 - General Markov (GM) model: different 4x4 matrices allowed on each edge

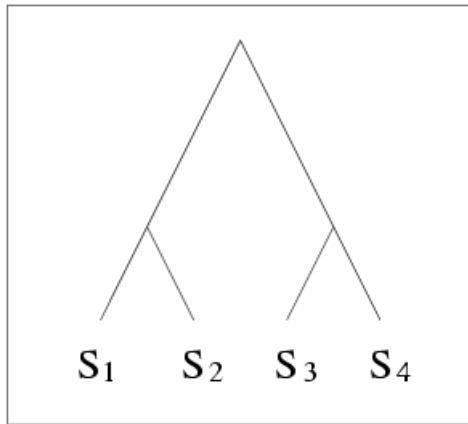
Jukes-Cantor DNA model

- Character states are A,C,T,G (nucleotides).
- All substitutions have equal probability.
- On each edge e , there is a value $p(e)$ indicating the probability of change from one nucleotide to another on the edge, with $0 < p(e) < 0.75$ (to ensure that JC trees are identifiable).
- The state (nucleotide) at the root is random (all nucleotides occur with equal probability).
- All the positions in the sequence evolve identically and independently.

Jukes-Cantor distances

- $D_{ij} = -3/4 \ln(1 - 4/3 H(i,j)/k)$ where k is the sequence length
- These distances converge to an additive matrix, just as with Cavender-Farris distances

Distance-based Methods

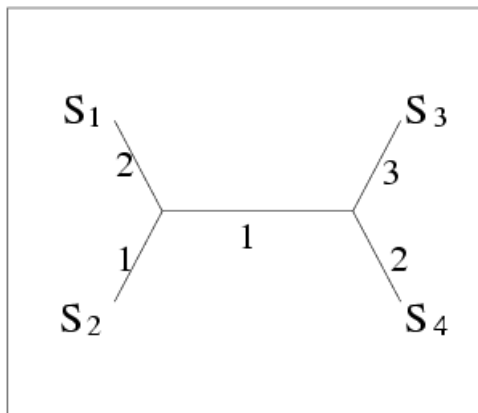


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S ₂		0	5	4
S ₃			0	5
S ₄				0

DISTANCE MATRIX

Other statistically consistent methods

- Maximum Likelihood
- Bayesian MCMC methods
- Distance-based methods (like Neighbor Joining and the Naïve Quartet Method)

But not maximum parsimony, not maximum compatibility, and not UPGMA (a distance-based method)

UPGMA

While $|S| > 2$:

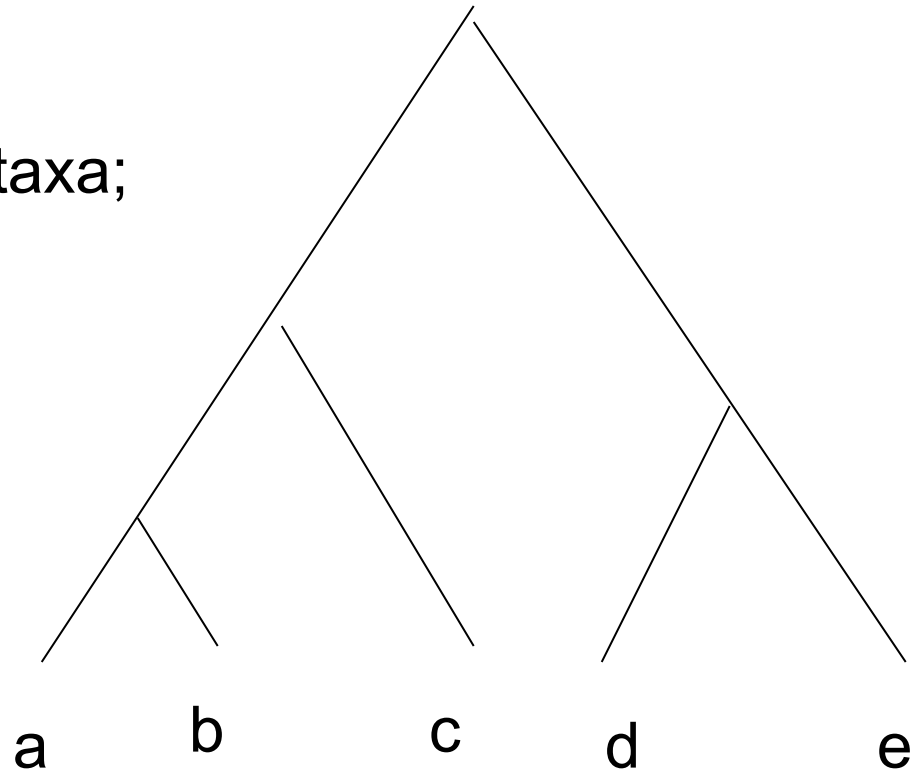
find pair x, y of closest taxa;

delete x

Recurse on $S - \{x\}$

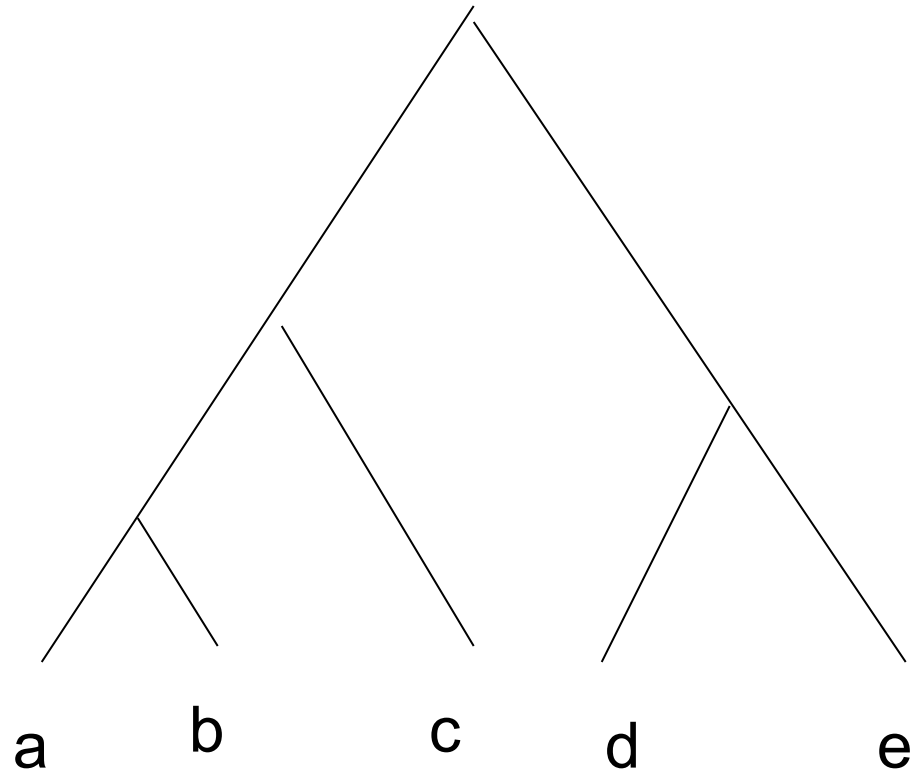
Insert y as sibling to x

Return tree



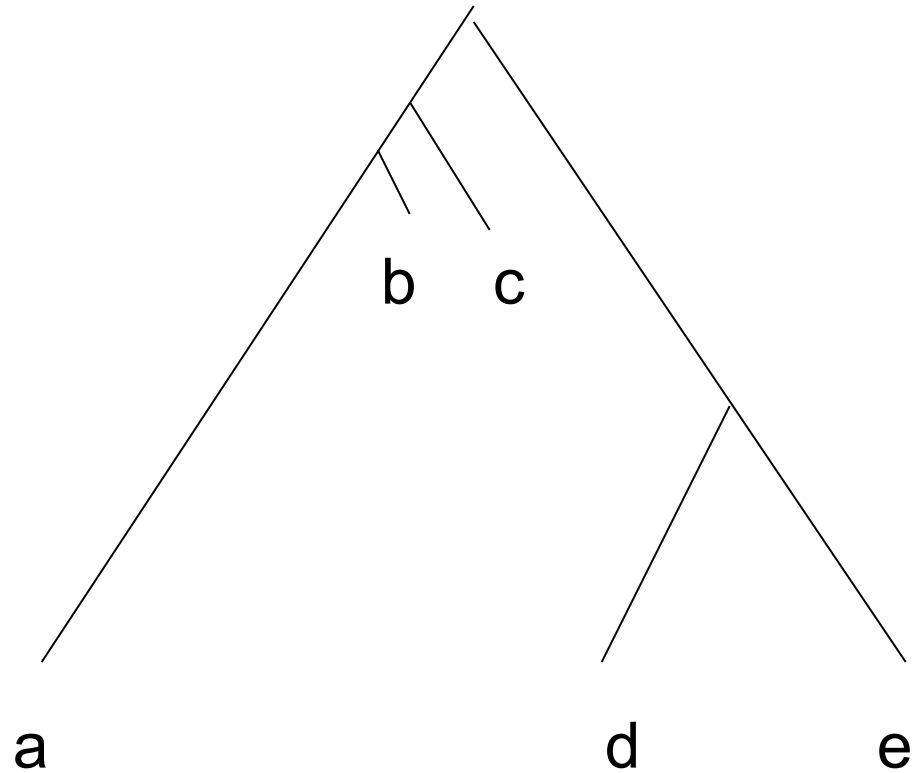
UPGMA

Works when
evolution is
“clocklike”



UPGMA

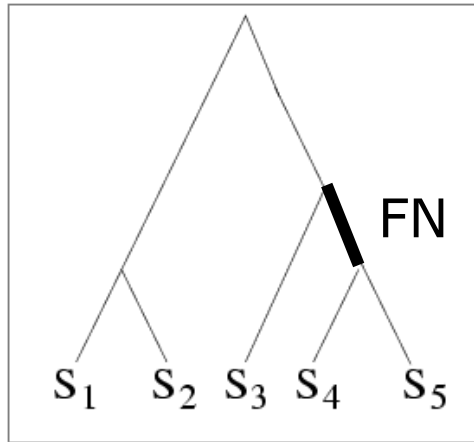
Fails to produce true tree if evolution deviates too much from a clock!



Better distance-based methods

- Neighbor Joining
- Minimum Evolution
- Weighted Neighbor Joining
- Bio-NJ
- DCM-NJ
- And others

Quantifying Error



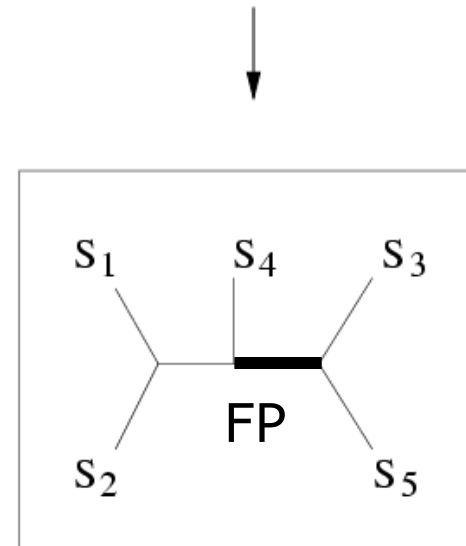
TRUE TREE

S ₁	ACAATTAGAAC
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S ₄	ACCAGACCAAC
S ₅	ACCAGACCGGA

DNA SEQUENCES

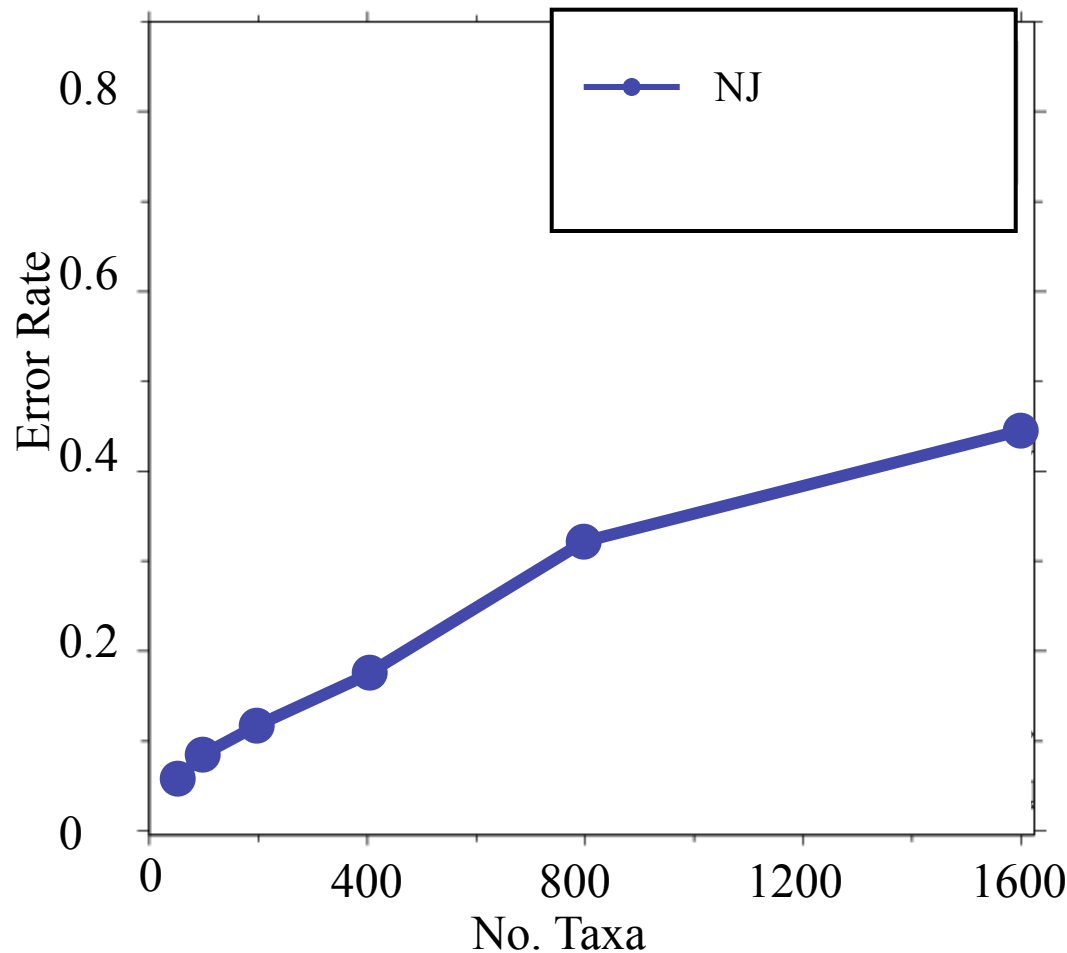
FN: false negative
(missing edge)
FP: false positive
(incorrect edge)

50% error rate



INFERRED TREE

Neighbor joining has poor performance on large diameter trees *[Nakhleh et al. ISMB 2001]*



Simulation study

based upon fixed edge lengths, K2P model of evolution, sequence lengths fixed to 1000 nucleotides.

Error rates reflect proportion of incorrect edges in inferred trees.

Statistical Methods of Phylogeny Estimation

- Many statistical models for biomolecular sequence evolution (Jukes-Cantor, K2P, HKY, GTR, GM, plus lots more)
- Maximum Likelihood and Bayesian Estimation are the two basic statistical approaches to phylogeny estimation
- MrBayes is the most popular Bayesian methods (but there are others)
- RAxML and GARLI are the most accurate ML methods for large datasets, but there are others
- Issues: running time, memory, and models...

Maximum Likelihood

- Input: sequence data S ,
- Output: the model tree (tree T and parameters θ) s.t. $\Pr(S|T, \theta)$ is maximized.

NP-hard.

Important in practice.

Good heuristics!

But what does it mean?

Computing the probability of the data

- Given a model tree (with all the parameters set) and character data at the leaves, you can compute the probability of the data.
- Small trees can be done by hand.
- Large examples are computationally intensive - but still **polynomial** time (using an algorithmic trick).

Cavender-Farris model calculations

- Consider an unrooted tree with topology $((a,b),(c,d))$ with $p(e)=0.1$ for all edges.
- What is the probability of all leaves having state 0?

We show the brute-force technique.

Brute-force calculation

Let E and F be the two internal nodes in the tree $((A,B), (C,D))$.

Then $\Pr(A=B=C=D=0) =$

- $\Pr(A=B=C=D=0|E=F=0) +$
- $\Pr(A=B=C=D=0|E=1, F=0) +$
- $\Pr(A=B=C=D=0|E=0, F=1) +$
- $\Pr(A=B=C=D=0|E=F=1)$

The notation “ $\Pr(X|Y)$ ” denotes the probability of X given Y .

Calculation, cont.

Technique:

- Set one leaf to be the root
- Set the internal nodes to have some specific assignment of states (e.g., all 1)
- Compute the probability of that specific pattern
- Add up all the values you get, across all the ways of assigning states to internal nodes

Calculation, cont.

Calculating $\Pr(A=B=C=D=0|E=F=0)$

- There are 5 edges, and thus no change on any edge.
- Since $p(e)=0.1$, then the probability of no change is 0.9. So the probability of this pattern, given that the root is a particular leaf and has value 0, is $(0.9)^5$.
- Then we multiply by 0.5 (the probability of the root A having state 0).
- So the probability is $(0.5) \times (0.9)^5$.

Maximum likelihood under Cavender-Farris

- Given a set S of binary sequences, find the Cavender-Farris model tree (tree topology and edge parameters) that maximizes the probability of producing the input data S .

ML, if solved exactly, is statistically consistent under Cavender-Farris (and under the DNA sequence models, and more complex models as well).

The problem is that **ML is hard to solve.**

“Solving ML”

- Technique 1: compute the probability of the data under each model tree, and return the best solution.
- Problem: Exponentially many trees on n sequences, and infinitely many ways of setting the parameters on each of these trees!

“Solving ML”

- Technique 2: For each of the tree topologies, find the best parameter settings.
- Problem: Exponentially many trees on n sequences, and calculating the best setting of the parameters on any given tree is hard!

Even so, there are hill-climbing heuristics for both of these calculations (finding parameter settings, and finding trees).

Bayesian analyses

- Algorithm is a **random walk** through space of all possible model trees (trees with substitution matrices on edges, etc.).
- From your current model tree, you perturb the tree topology and numerical parameters to obtain a new model tree.
- Compute the probability of the data (character states at the leaves) for the new model tree.
 - If the probability increases, accept the new model tree.
 - If the probability is lower, then accept with some probability (that depends upon the algorithm design and the new probability).
- Run for a long time...

Bayesian estimation

After the random walk has been run for a very long time...

- Gather a random sample of the trees you visit
- Return:
 - Statistics about the random sample (e.g., how many trees have a particular bipartition), OR
 - Consensus tree of the random sample, OR
 - The tree that is visited most frequently

Bayesian methods, if run *long enough*, are statistically consistent methods (the tree that appears the most often will be the true tree with high probability).

MrBayes is standard software for Bayesian analyses in biology.

Phylogeny estimation statistical issues

- Is the phylogeny estimation method statistically consistent under the given model?
- How much data does the method need need to produce a correct tree?
- Is the method robust to model violations?
- *Is the character evolution model reasonable?*