Maximum Likelihood Analysis of Phylogenetic Trees

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Phylogenetic Reconstruction Methods

- Input: A set of $n$ aligned sequences (genes, proteins) from $n$ species,
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- Tree reconstruction is still a challenge today.
- Many concrete questions are still unresolved (e.g. mammalian evolutionary tree).
- Most realistic formulations of the problem, which take errors into account, give rise to hard computational problems.
Popular Reconstruction Methods

• Distance based methods:
Popular Reconstruction Methods

- Distance based methods:
  - UPGMA
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  - Buneman trees.

Character Based Methods:
- Maximum Parsimony.
- Maximum Likelihood.

Additional Methods:
- Quartets Based.
- Disc Covering.
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Talk Outline

- Maximum likelihood (ML).
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- Computation complexity: Maximum likelihood vs. maximum parsimony (MP).
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- Existence of multiple maxima.
- Computation complexity: Maximum likelihood vs. maximum parsimony (MP).
- Ancestral maximum likelihood (AML) and its computational complexity.
Maximum Likelihood

• Input: A set of \( n \) observed sequences and an underlying substitution model.
Maximum Likelihood

- Input: A set of $n$ observed sequences and an underlying substitution model.
- Desired Output: The weighted tree $T$ that maximizes the likelihood of the data.

Likelihood of data: The conditional probability of producing the data, given the model parameters. Likelihood is a common optimization criterion in numerous settings, including phylogenetic (Felsenstein 1981).
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### Neyman 2–State Substitution Model

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<thead>
<tr>
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<tbody>
<tr>
<td>1</td>
<td>XXXXXXXXYYYY XXY XY YX XY X</td>
</tr>
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</tr>
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<td>3</td>
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</tr>
<tr>
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- Just **two** characters states, *X* and *Y*.  

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- Equal rates across sites.
- Every column induces a pattern.
- Remark: A simple model, yet very powerful.
Neyman 2–State Substitution Model

For each edge $e$ of a tree $T$, the edge weight $p_e$ represents the probability of having different states at the two ends of $e$. 
A Very Simple Example

Four species \((n = 4)\), just one site \((c = 1)\)

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Analyze the natural tree \((12)(34)\)

\((1)\) X

\((2)\) X

\((3)\) Y

\((4)\) Y
Computing the Likelihood

Each unknown state (?) can assume one of two possibilities, $X$ or $Y$. For example, the assignment

$\begin{align*}
(1) & \quad X \\
(2) & \quad X
\end{align*}$

contributes $(1 - p_1) \cdot (1 - p_2) \cdot p_{12} \cdot (1 - p_3) \cdot (1 - p_{123})$. The likelihood is the sum of this

$\begin{align*}
+ & \quad \text{three similar expressions} \ldots
\end{align*}$
Computing the Likelihood

- Last expression has the form
  \[ \sum_{\text{internal assignments}} \prod_{\text{edges}} m_{e,a,t} \]
  where each \( m_{e,a,t} \) is either \( pe \) or \( 1 - pe \), depending on the assignment \( a \), and input pattern \( t \) at two ends of the edge.
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- When the data has more than one column, we multiply the expressions to get the likelihood of the data, given the model parameters, \( L(\text{data}|\text{tree & edge weights}) \):
  \[ \prod_{\text{columns}} \sum_{\text{internal assignments}} \prod_{\text{edges}} m_{e,a,t} . \]
Three Likelihood Versions

- Big Likelihood: Given the sequence data, find a tree and edge weights that maximize $L(\text{data|tree & edge weights})$. 
- Small Likelihood: Given observed data & a tree, but not the edge weights, find the edge weights that maximize the likelihood. 
- Tiny Likelihood: Given observed data & a tree & edge weights, find the likelihood. Tiny likelihood can be efficiently computed using dynamic programming (Felsenstein, 1981).
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Hill Climbing and Small Likelihood

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• Typical approach to small likelihood, used in practice:
• Start at some initial point with edge weights $p$.
• Apply hill climbing on the likelihood function to reach a maximum.
The Likelihood Surface

• For hill climbing to be guaranteed to find the maximum, there must be a single *local and global maximum* in the parameter space.
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- (94–present): Hill climbing techniques still used. Steel’s counter example is considered too “biologically unrealistic” to warrant concern.
The Likelihood Surface (cont.)

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The Likelihood Surface (cont.)

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The Likelihood Surface (cont.)

- Rogers and Swofford (99): Simulation Study
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  - ...especially on the *correct* tree.
- Goal here: Investigate the problem *analytically* (joint work with Hendy, Holland, Penny).
Maximizing Likelihood on Trees

Tools used

• Hadamard conjugation (Hendy and Penny 93).
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- Analytical solution: very hard in general, even for four taxa.
- Employing computer algebra and algebraic geometry tools.
Example: Conservative Data, Two Very Different ML Trees

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- Phylogenetic trees under a molecular clock (MC): 
  - Rooted trees.
  - Equal distance from root to all leaves.

3 taxa
one rooted topology
MC-triplet

4 taxa
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MC-fork  MC-comb
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```
1  2
  |
  3
  |
  4
```

Maximum Likelihood Analysis of Phylogenetic Trees – p. 18
MC Trees, 4 Taxa

- Fork: Closed form ML solution.

Joint work with Snir and Khetan.
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- In both cases, ML solution is **unique**.
- Attaining solutions requires fairly heavy math and computer algebra tools.

Joint work with Snir and Khetan.
Small Likelihood & Multiple Maxima

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Small Likelihood & Multiple Maxima

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- Multiple ML points for general case imply small likelihood cannot be solved by hill climbing.
- Not clear if small likelihood has efficient (worst case) solutions.
Maximum Parsimony (MP)

- **Big Parsimony**: Given the sequence data, find a tree and assignment of sequences to internal nodes that minimizes the number of changes across all edges.
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Indeed, small parsimony has efficient algorithms (Fitch 1971, Sankoff and Cedergren 1983).
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- MP considered by practitioners easier than ML. Indeed *small parsimony* has efficient algorithms (Fitch 1971, Sankoff and Cedergren 1983).
Complexity: MP vs. ML

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Complexity: MP vs. ML

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- Big parsimony is NP hard (Day, Johnson and Sankoff, 1986).
- Big likelihood – unknown. Given the importance of ML, it would be nice to know more about its complexity than just “seems harder than MP”.
Ancestral Max. Likelihood (AML)

- A tree reconstruction method that is “in between” ML and MP.

The goal is to simultaneously find edge weights and assignment of sequences to internal nodes so that the likelihood of the data, given the tree parameters, is maximized. AML is widely used in evolutionary studies. Also termed joint reconstruction of ancestral sequences. AML computes the likelihood contribution resulting from best assignment to internal nodes, while “regular ML” sums up over all assignments.
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- **ACHLPW 2003**: Big AML is NP-hard.
Useful AML Observation

- Given sequence data, a tree, and assignment to internal nodes.
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- The edge weights that maximize the likelihood of the data equal $d_e/k$. Where $e$ equals the number of changes across edge, and $k$ is the common sequence length.
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- Where $d_e$ equals the number of changes across edge $e$, and $k$ is the common sequence length.
AML, Reformulated

Previous observation implies

- **Input:** A set $S$ of $n$ binary sequences, each of length
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- **Goal:** Find a tree $T$ with $n$ leaves, an assignment $p : E(T) \rightarrow [0, 1]$ of edge probabilities, and a labelling $\lambda : V(T) \rightarrow \{0, 1\}^k$ of the vertices such that

1. The labels of the leaves are exactly the sequences from $S$.
2. The sum of all "edge entropies" is minimized.
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     \[ \sum_{e \in E(T)} H \left( \frac{d_e}{k} \right) \] is minimized.
AML vs. MP

Optimization criteria

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- Can think of the two problems as attempting to minimize different edge weights (functions of $d_e$).
NP hardness of AML: Ideas

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- Analogy of AML and MP optimization criteria suggests using similar approach.
- Reduction from VC indeed identical.
- Proof substantially more involved as entropy $H(d_e/k)$ is not as “well behaved” as plain edge differences $d_e/k$. 
Conclusion and Open Problems

- Analytic solutions to additional ML problems with few taxa may be feasible, and may reveal additional properties of likelihood surface (e.g. number of local maxima).
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