Neighbor Joining with Subtree Weights

Ruriko Yoshida
Dept. of Mathematics Duke University

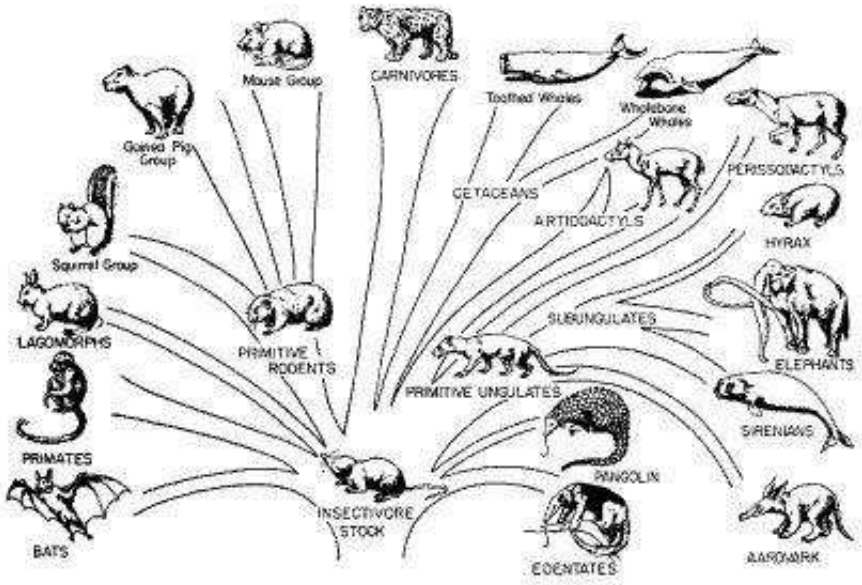
Joint work with Dan Levy and Lior Pachter

www.math.duke.edu/~ruriko

September 28th, 2004

Phylogeny

Phylogenetic trees illustrate the evolutionary relations among groups of organisms.



Why we care?

- We can analyze changes that have occurred in evolution of different species.
- Phylogenetic relations among different species help predict which species might have similar functions.
- We can predict changes occurring in rapid changing species, such as HIV virus.

Input Data for Phylogeny

- Numerical data
  - Distance between different species.
    Each branch length represents evolutional time along an edge of the tree.
    We can derive distances from DNA sequences.

- Discrete characters
  - Each character has finite number of states
    e.g. DNA $= \{A, T, C, G\}$.

Distance Based Methods

We reconstruct phylogenetic trees with distance based methods.

Input: Pair-wise distances from n many species.

Output: An unrooted edge weighted binary tree with n leaves.

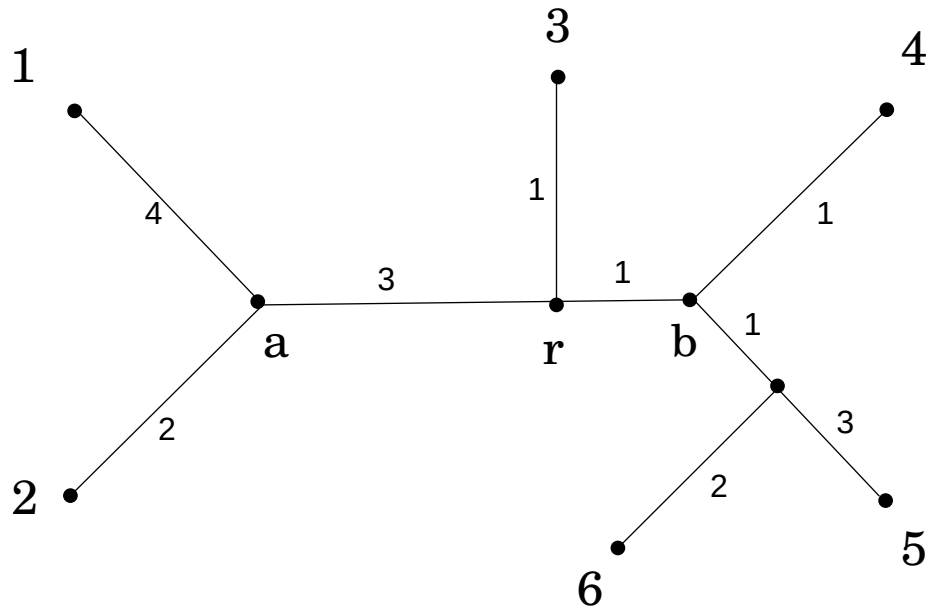
Distance based methods operate two steps:

1. Compute pair-wise distance between every pair of taxa.

2. With all pair-wise distances, compute tree topology and all branch length.

Distance Matrix

A distance matrix for a tree T is a matrix M whose entry M_{ij} stands for the mutation distance between i and j.



Distance Matrix

	1	2	3	4	5	6
1	0	6	8	9	12	11
2	6	0	6	7	10	9
3	8	6	0	3	6	5
4	9	7	3	0	5	4
5	12	10	6	5	0	5
6	11	9	5	4	5	0

Table 1: Distance matrix M for the example.

Let $D(ij)$ be a pairwise distance between i and j.

Definitions

Def. A distance matrix M is a **metric** iff M satisfies:

- Symmetric: $M_{ij} = M_{ji}$ and $M_{ii} = 0$.
- Triangle Inequality: $M_{ik} + M_{jk} \geq M_{ij}$.

Def. M is an **additive metric** iff there exists a tree T s.t.

- Every edge has a positive weight and every leaf is labeled by a distinct species in the given set.
- For every pair of i, j, $M_{ij} =$ the sum of the edge weights along the path from i to j.

Also we call such T an **additive tree**.

If we want to reconstruct an additive tree T from an additive metric M, we can do in polynomial time on n.

Problem:

- A distance matrix M obtained from an alignment of DNA sequences is a non-additive metric.

- If M is not additive, finding the nearest additive metric $\bar{M}$ is NP-hard (by Farach, Kannan, and Warnow).

We are interested in estimating the additive tree T of $\bar{M}$ in polynomial time.

Neighbor Joining Method

Def. We call a pair of two distinct leaves $\{i, j\}$ a **cherry** if there is exactly one intermediate node on the unique path between i and j.

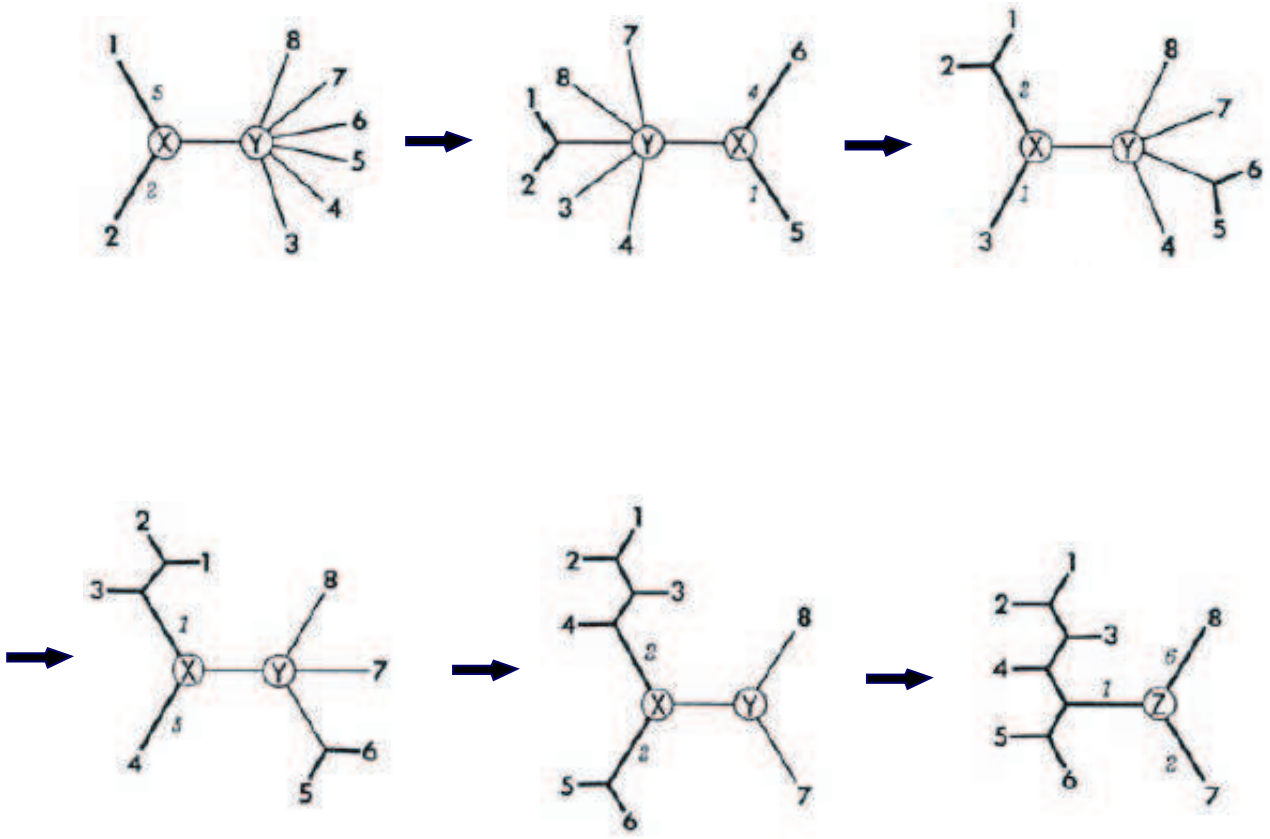
Thm. [Saitou-Nei and Studier-Keppler]

$\{i, j\}$ is a cherry if $A_{ij} = D(ij) - (r_i + r_j)/(n-2)$, where $r_i := \sum_{k=1}^{n} D(ik)$, is minimal.

Neighbor Joining Method:

Idea. Initialize a star-like tree. Then find a cherry $\{i, j\}$ and computing branch length from the interior node x to i and from x to j. Repeat this process recursively until we find all cherries.

Neighbor Joining Method



Advantages and Disadvantages

The most popular and widely used distance based method for reconstructing a phylogenetic tree.

Advantages:

- Fast (the time complexity of this algorithm is $O(n^3)$).
- Permits lineages with largely different branch lengths.

Disadvantages:

- Sequence information is reduced.
- Gives only one possible tree.

Neighbor Joining with Subtree Weights

- Extended the Neighbor Joining method with the weights of m-leaf subtrees.
- Increasing $2 \leq m \leq \frac{n+1}{2}$, reconstructed tree from our method gets closer to the additive tree of the nearest additive matric.
- If $m = 3$, the time complexity of our new method is $O(n^3)$, which is the same as the Neighbor Joining with pairwise distances and a tree reconstructed by our method is more accurate than the one with pairwise distances.

Note: If $m = 2$, then our method is the Neighbor Joining method with pairwise distances.

Notations and Definitions

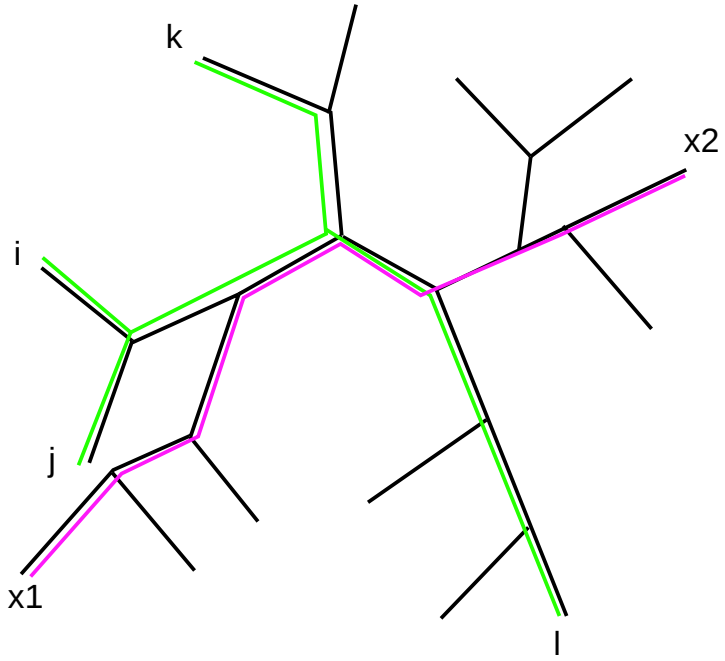
Notation. Let $[n]$ denote the set $\{1, 2, ..., n\}$ and $\binom{[n]}{m}$ denote the set of all m-element subsets of $[n]$.

Def. A *m-dissimilarity map* is a function $D : \binom{[n]}{m} \to \mathbb{R}_{\geq 0}$.

In the context of phylogenetic trees, the map $D(i_1, i_2, ..., i_m)$ may measure the weight of a subtree that spans the leaves $i_1, i_2, ..., i_m$.

Denote $D(i_1 i_2 \dots i_m) := D(i_1, i_2, ..., i_m)$.

Weights of Subtrees in T



$D(ijkl)$ is the total branch length of the subtree in green. Also $D(x_1x_2)$ is the total branch length of the subtree in pink and it is also a pairwise distance between x_1 and x_2.

Thm. [Levy, Pachter, Y.] Let D_m be an m-dissimilarity map on n leaves, $D_m : \binom{[n]}{m} \to \mathbb{R}_{\geq 0}$, and define

$$S(ij) := \sum_{X \in \binom{[n-i-j]}{m-2}} D_m(ijX).$$

If the weights D_m correspond to m-subtree weights of a tree T then $S(ij)$ is a tree metric.

Furthermore, if T' is the additive tree corresponding to this tree metric then T' and T have the same tree topology and there is an invertible linear map between their edge weights.

Note. This means that if we reconstruct T', then we can reconstruct T.

Computing edge weights on T

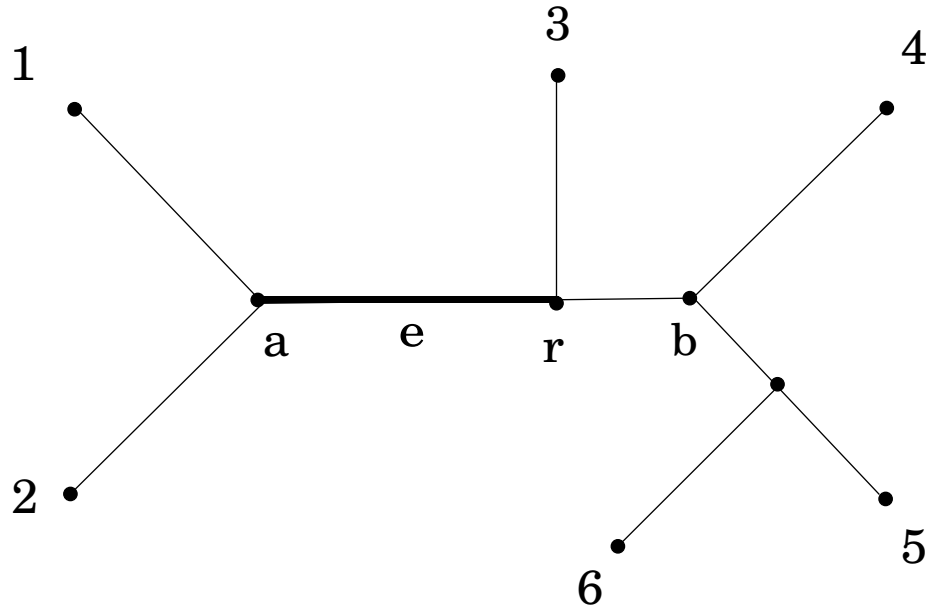
Lemma 1. [Levy, Pachter, Y.] If e is an internal edge of T (equivalently T'), then

$$w_{T'}(e) = \frac{1}{2}[\binom{|L_1(e)|-2}{m-2} + \binom{|L_2(e)|-2}{m-2}]w_T(e)$$

where $L_1(e)$ and $L_2(e)$ are the two leaf sets of $T - e$.

For an edge $e \in E(T)$ and a leaf i, $L_i(e)$ denotes the set of leaves in $T - e$ that are in the same connected component as i.

If $i = 3$, then $L_3(e) = \{3, 4, 5, 6\}$.



Lemma 2. [Levy, Pachter, Y.] Denote the edges adjacent to the leaves by $e_1, \ldots, e_n$.

Let $C_i = \sum_{e \in int(E(T))} \left(\binom{n-2}{m-2} - \binom{|L_i(e)|-2}{m-2} \right) w_T(e)$. Then

$$\begin{pmatrix} w_T(e_1) \\ \vdots \\ w_T(e_n) \end{pmatrix} = A^{-1} \begin{pmatrix} 2w_{T'}(e_1) - C_1 \\ \vdots \\ 2w_{T'}(e_n) - C_n \end{pmatrix},$$

where $A^{-1} = \frac{1}{2\binom{n-2}{m-2}} \left(\mathbf{I} - \frac{m-2}{(m-1)(n-2)} \mathbf{J} \right)$.

Neighbor Joining with Subtree Weights

Input: n many DNA sequences.

Output: A phylogenetic tree T with n leaves.

1. Compute all m-subtree weights via the maximum likelihood.
2. Compute $S(ij)$ for each pair of leaves i and j.
3. Apply Neighbor Joining method with a tree metric $S(ij)$ and obtain additive tree T'.
4. Using Lemma 1, obtain a weight of each internal edge of T.
5. Using Lemma 2, obtain a weight of each leaf edge of T.

Complexity

Lemma. [Levy, Pachter, Y.] If $m \geq 3$, the time complexity of this algorithm is $O(n^m)$, where n is the number of leaves of T and if $m = 2$, then the time complexity of this algorithm is $O(n^3)$.

Sketch of Proof: If $m \geq 3$, the computation of $S(ij)$ is $O(n^m)$ (both steps are trivially parallelizable). The subsequent neighbor-joining is $O(n^3)$ and edge weight reconstruction is $O(n^2)$. If $m = 2$, then the subsequent neighbor-joining is $O(n^3)$ which is greater than computing $S(ij)$. So, the time complexity is $O(n^3)$.

Note: The running time complexity of the algorithm is $O(n^3)$ for both $m = 2$ and $m = 3$.

Cherry Picking Theorem

Thm. [Levy, Pachter, Y.] Let T be a tree with n leaves and no nodes of degree 2 and let m be an integer satisfying $2 \leq m \leq n-2$. Let $D : \binom{[n]}{m} \to \mathbb{R}_{\geq 0}$ be the m-dissimilarity map corresponding to the weights of the subtrees of size m in T. If $Q_D(ij)$ is a minimal element of the matrix

$$Q_D(ij) = \left(\frac{n-2}{m-1}\right) \sum_{X \in \binom{[n-i-j]}{m-2}} D(ijX) - \sum_{X \in \binom{[n-i]}{m-1}} D(iX) - \sum_{X \in \binom{[n-j]}{m-1}} D(jX)$$

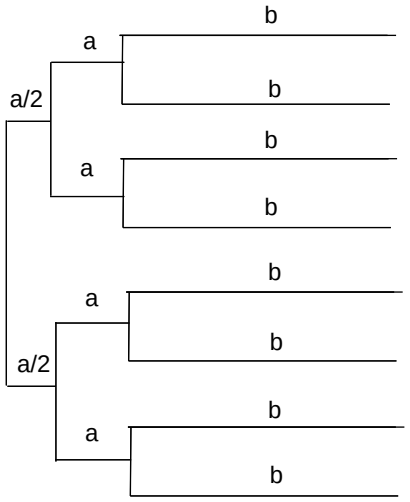
then $\{i, j\}$ is a cherry in the tree T.

Note. The theorem by Saitou-Nei and Studier-Keppler is a corollary from Cherry Picking Theorem.

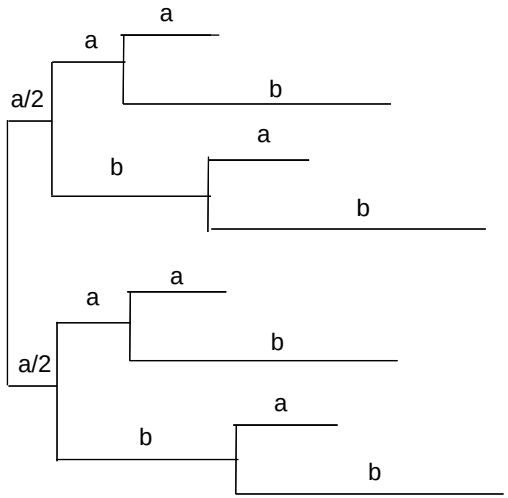
Simulation Results

Consider two tree models...

Modeled from Strimmer and von Haeseler.



T1



T2

We generate 500 replications with the Jukes-Cantor model via a software `evolver` from `PAML` package.

The number represents a percentage which we got the same tree topology.

l	a/b	m=2	m=3	m=4	fastDNAml
500	0.01/0.07	68.2	76.8	80.4	74.8
	0.02/0.19	54.2	61.2	73.6	55.6
	0.03/0.42	10.4	12.6	23.8	12.6
1000	0.01/0.07	94.2	96	97.4	96.6
	0.02/0.19	87.6	88.6	96.2	88
	0.03/0.42	33.4	35	52.4	33.6

Table 2: Success Rates for the model T_1.

l	a/b	m=2	m=3	m=4	fastDNAml
500	0.01/0.07	84.4	86	85.6	88.4
	0.02/0.19	68.2	72	73.2	88.4
	0.03/0.42	18.2	29.2	36.2	87.4
1000	0.01/0.07	95.6	97.8	97.4	99.4
	0.02/0.19	88.4	89.6	93.4	99.8
	0.03/0.42	40	48.2	57.6	96.6

Table 3: Success Rates for the model T_2.

Questions??

Paper and Software

The paper will be available soon at Arxiv

Software package `Shinrin` will be available soon.

Download at `http://bio.math.berkeley.edu/mjoin/`

Thank you...