On the Optimality of the Neighbor Joining Algorithm

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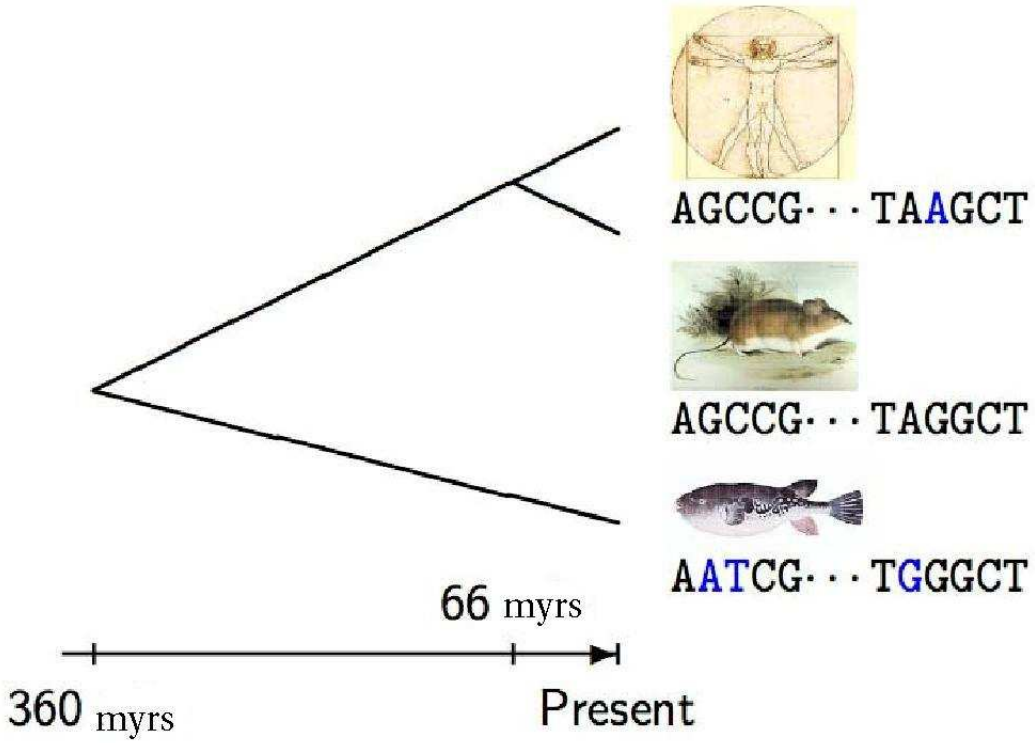
Phylogeny

Phylogenetic trees describe 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 rapidly changing species, such as HIV virus.

Constructing trees from sequence data

"Ten years ago most biologists would have agreed that all organisms evolved from a single ancestral cell that lived 3.5 billion or more years ago. More recent results, however, indicate that this family tree of life is far more complicated than was believed and may not have had a single root at all." (W. Ford Doolittle, (June 2000) *Scientific American*).

Since the proliferation of Darwinian evolutionary biology, many scientists have sought a coherent explanation from the evolution of life and have tried to reconstruct phylogenetic trees.

Methods to reconstruct a phylogenetic tree from DNA sequences include:

- **The maximum likelihood estimation (MLE) methods**: These describe evolution in terms of a discrete-state continuous-time Markov process. The substitution rate matrix can be estimated using the **expectation maximization (EM) algorithm**. (for eg. Dempster, Laird, and Rubin (1977), Felsenstein (1981)).

- **The Balanced Minimum Evolution (BME) method**: This is a **distance based method** and weighted Least Square method (the principle of Least Squares is a general method for estimating unknown parameters values so that error is minimized). It finds a closest additive metric from the given non-additive distance matrix with the smallest branch lengths (more biologically makes sense).

However

The MLE methods: An exhaustive search for the ML phylogenetic tree is computationally prohibitive for large data sets.

The BME method: This is an NP hard algorithm in terms of the number of taxa (Farach, Kannan, Warnow (1996), Rzhetsky and Nei (1993), Desper and Gascuel (2004)).

But there is a polynomial time algorithm to estimate the BME tree.

Neighbor-joining (NJ) method: This is the most popular distance based method. It computes a tree from all pair-wise distances obtained easily. (Saito and Nei (1987), Studier and Keppler (1988)).

Fact: The NJ algorithm is a greedy algorithm to find the BME tree (Gascuel and Steel (2006)).

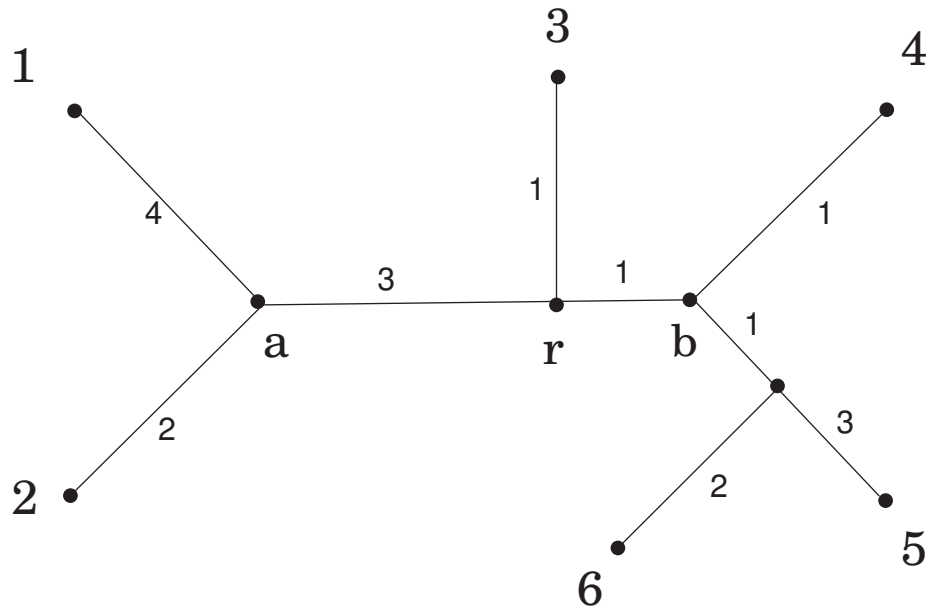
From this point of view, NJ is "optimal" whenever the NJ algorithm outputs the tree which minimizes the BME criterion.

Goal: We want to study the optimality of the NJ algorithm, (i.e., want to study how often the NJ returns the BME tree).

Plan: I will discuss NJ method today closely and then I will discuss BME method in the next lecture.

Distance Matrix

A **distance matrix** for a tree T is a matrix D whose entry D_{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 D for the example.

Definitions

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

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

Def. D 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, $D_{ij} =$ the sum of the edge weights along the path from i to j.

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

The NJ 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.

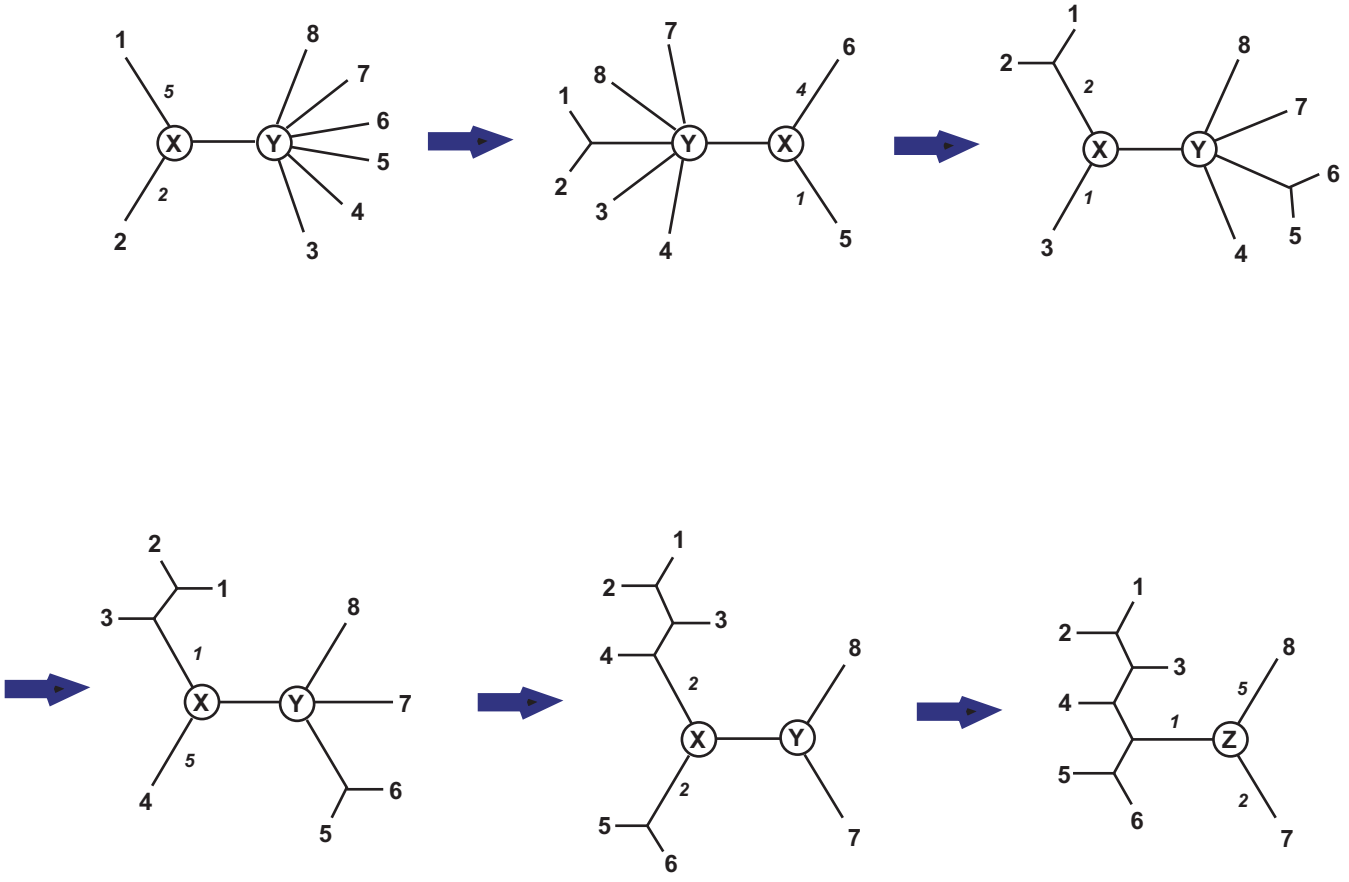
Thm. (Q-criterion) [Saitou-Nei, 1987 and Studier-Keppler, 1988]

Let $Q \in \mathbb{R}^{n \times n}$ such that $Q_{ij} = (n-2)D_{ij} - (r_i + r_j)$, where $r_i := \sum_{k=1}^{n} D_{ik}$. $\{i^*, j^*\}$ is a cherry in T if $Q_{i^*j^*}$ is a minimum for all $i \neq j$.

Neighbor Joining Method:

Input. A tree matric D. **Output.** An additive tree T.
Idea. Initialize a star-like tree. Then find a cherry $\{i, j\}$ and compute 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



The NJ is consistent, i.e., it returns the additive tree if the input distance matrix is tree metric.

However, we usually estimate all pairwise distances via MLE. Usually these distance matrices are not tree metric.

The NJ returns a tree topology which induces a tree metric that is hopefully close to the input.

Question: For which distance matrices will the NJ return a particular tree topology?

We look at the algorithm closely.....

Q-criterion

Go back to the previous example....

$$Q = \begin{array}{|c|c|c|c|c|c|} \hline 0 & -20 & -16 & -15 & -16 & -11 \\ \hline -20 & 0 & -14 & -13 & -14 & -9 \\ \hline -16 & -14 & 0 & -9 & -10 & -5 \\ \hline -15 & -13 & -9 & 0 & -9 & -4 \\ \hline -16 & -14 & -10 & -9 & 0 & -5 \\ \hline -11 & -9 & -5 & -4 & -5 & 0 \\ \hline \end{array}$$

The Q-criterion

For $n = 4$ by symmetry we have

$$\begin{aligned}
Q_{12} &= -D_{13} - D_{14} - D_{23} - D_{24} \\
Q_{13} &= -D_{12} - D_{14} - D_{23} - D_{34} \\
Q_{23} &= -D_{12} - D_{13} - D_{24} - D_{34} \\
Q_{14} &= -D_{12} - D_{13} - D_{24} - D_{34} \\
Q_{24} &= -D_{12} - D_{14} - D_{23} - D_{34} \\
Q_{34} &= -D_{13} - D_{14} - D_{23} - D_{24}
\end{aligned}$$

$$\begin{pmatrix} Q_{12} \\ Q_{13} \\ Q_{23} \\ Q_{14} \\ Q_{24} \\ Q_{34} \end{pmatrix} = \begin{pmatrix} 0 & -1 & -1 & -1 & -1 & 0 \\ -1 & 0 & -1 & -1 & 0 & -1 \\ -1 & -1 & 0 & 0 & -1 & -1 \\ -1 & -1 & 0 & 0 & -1 & -1 \\ -1 & 0 & -1 & -1 & 0 & -1 \\ 0 & -1 & -1 & -1 & -1 & 0 \end{pmatrix} \begin{pmatrix} D_{12} \\ D_{13} \\ D_{23} \\ D_{14} \\ D_{24} \\ D_{34} \end{pmatrix}.$$

In general...

Let $m = \binom{n}{2}$. Let $\mathbf{d} \in \mathbb{R}^m$ be a vector representation of D and $\mathbf{q} \in \mathbb{R}^m$ be a vector representation of Q. The Q-criterion is obtained from the input data by a linear transformation:

$$\mathbf{q} = \mathbf{A^{(n)}}\mathbf{d},$$

where the entries of the matrix $A^{(n)}$ are given by

$$\mathbf{A^{(n)}_{ab}} = \mathbf{A^{(n)}_{ij,kl}} = \begin{cases} n-4 & \text{if } a = b, \\ -1 & \text{if } a \neq b \text{ and } \{i,j\} \cap \{k,l\} \neq \emptyset, \\ 0 & \text{else,} \end{cases} .$$

The Q-criterion:

$$\text{find smallest } \mathbf{q_a} \text{ for } \mathbf{a = 1, \cdots, m} \text{ such that } \mathbf{q = A^{(n)}d}.$$

The first step in cherry picking

Note that the Q-criterion is a linear programming problem:

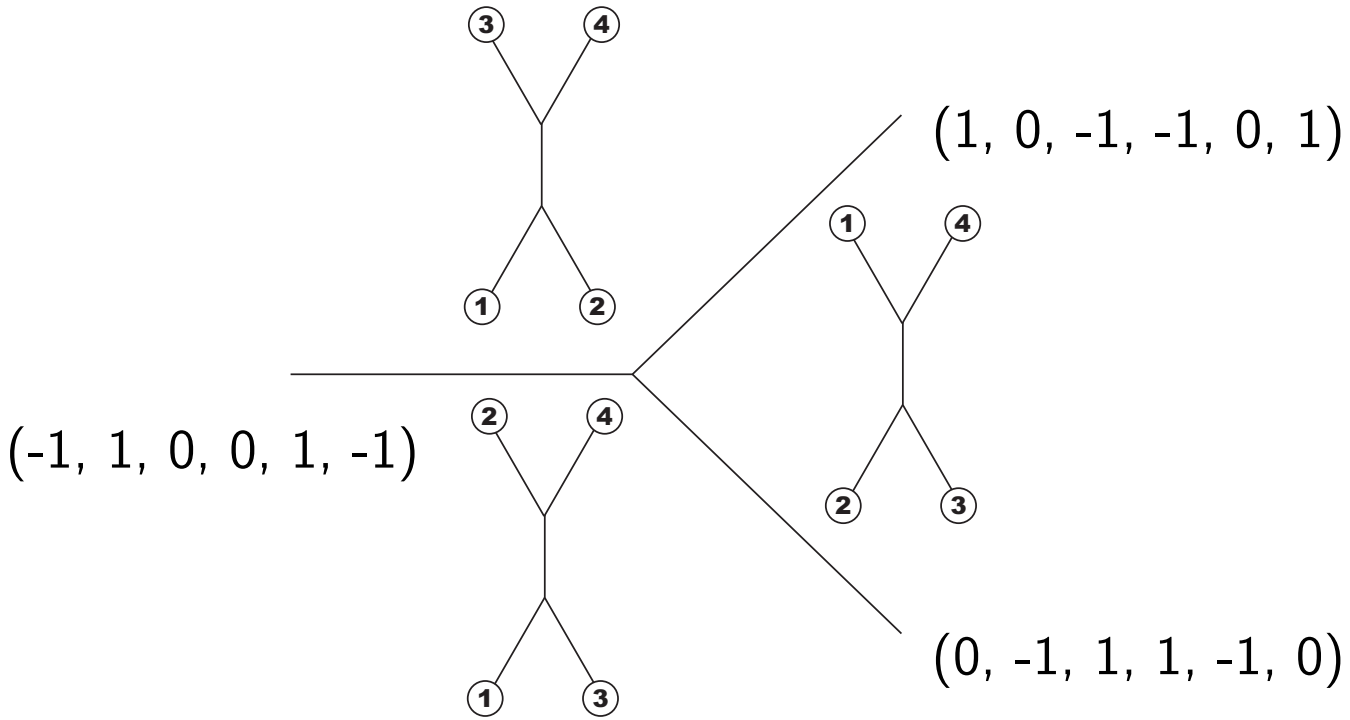
$$\min \mathbf{d} \cdot \mathbf{x} \text{ such that } \mathbf{x} \in \text{conv}\{\mathbf{Ae_1}, \ldots, \mathbf{Ae_m}\}.$$

Therefore the set cd_i of all *parameter* vectors $\mathbf{d}$ for which the NJ algorithm will select cherry i in the first step is the normal cone at Ae_i to the polytope

$$\mathbf{P_n^{nj}} := \text{conv}\{\mathbf{Ae_1}, \ldots, \mathbf{Ae_m}\}.$$

The **shifting lemma** implies that the affine dimension of the polytope P_n^{nj} is at most $m - n$.

Example for $n = 4$



Reducing the number of taxa

Suppose out of our n taxa $\{1, \ldots, n\}$, the first cherry to be picked is the $\binom{n}{2}$th cherry $\{n-1, n\}$, which we view as the new node number $n-1$.

The reduced pairwise distance matrix is one row and one column shorter than the original one. Explicitly,

$$\mathbf{d'_i} = \begin{cases} d_i & \text{for } 1 \leq i \leq \binom{n-2}{2} \\ \frac{1}{2}(d_i + d_{i+(n-2)} - d_m) & \text{for } \binom{n-2}{2} + 1 \leq i \leq \binom{n-1}{2} \end{cases}$$

We see that the reduced distance matrix depends linearly on the original one:

$$\mathbf{d}' = \mathbf{R}\mathbf{d},$$

with $R = (r_{ij}) \in \mathbb{R}^{(m-n+1)\times m}$, where

$$r_{ij} = \begin{cases} 1 & \text{for } 1 \leq i = j \leq \binom{n-2}{2} \\ 1/2 & \text{for } \binom{n-2}{2} + 1 \leq i \leq \binom{n-1}{2}, j = i \\ 1/2 & \text{for } \binom{n-2}{2} + 1 \leq i \leq \binom{n-1}{2}, j = i + n - 1 \\ -1/2 & \text{for } \binom{n-2}{2} + 1 \leq i \leq \binom{n-1}{2}, j = m \\ 0 & \text{else} \end{cases}$$

The process of picking cherries is repeated until there are only three taxa left, which are then joined to a single new node.

Note: Each tree topology is determined by a polyhedral cone (i.e., we add more constraints to the normal cone at a vertex of P_n^{nj}). We call these cones **NJ cones**.

The cone $C_{45,3}$

Since we can apply a permutation $\sigma \in S_5$ on taxa, without loss of generality, we suppose that the first cherry to be picked is the cherry with leaves 4 and 5. This is true for all input vectors $\mathbf{d}$ which satisfy

$$(\mathbf{h_{10,i}}, \mathbf{d}) \geq \mathbf{0} \text{ for } \mathbf{i} = \mathbf{1}, \ldots, \mathbf{9},$$

where the vector

$$\mathbf{h_{ij}^{(n)}} := -\mathbf{A^{(n)}}(\mathbf{e_i} - \mathbf{e_j}).$$

Then, the set of all input vectors $\mathbf{d}$ for which the first picked cherry is 4-5 and the second one is 1-2:

$$C_{45,3} :=$$
$$\{\mathbf{d} \mid (\mathbf{h}_{10,i}, \mathbf{d}) \geq 0 \text{ for } i = 1, \ldots, 9, \text{ and } (\mathbf{r}_1 - \mathbf{r}_2, \mathbf{d}) \geq 0, (\mathbf{r}_1 - \mathbf{r}_3, \mathbf{d}) \geq 0\}$$

where $\mathbf{r}_1$, $\mathbf{r}_2$ and $\mathbf{r}_3$ are the first three rows of $-A^{(4)}R^{(5)}$.

The NJ cones

For $n = 5$, there is only one unlabeled tree and there are 15 labeled trees. There are 30 cones in the 5-dimension (i.e. there are two cones per a lebeled tree).

- They do not form a fan.
- The union of cones $C_{12,3}$ and $C_{45,3}$ does not form a convex body (i.e. the union of two cones for one tree topology does not form a convex cone).

Example

$$D_1 = \begin{pmatrix} 0 & 0.056244 & 0.168744 & 0.506257 & 0.056256 \\ 0.056244 & 0 & 0.168755 & 0.056256 & 0.506245 \\ 0.168744 & 0.168755 & 0 & 0.056244 & 0.056256 \\ 0.506257 & 0.056256 & 0.056244 & 0 & 0.168744 \\ 0.056256 & 0.506245 & 0.056256 & 0.168744 & 0 \end{pmatrix} \text{ and}$$

$$D_2 = \begin{pmatrix} 0 & 0.168694 & 0.056194 & 0.506306 & 0.112556 \\ 0.168694 & 0 & 0.056307 & 0.056307 & 0.562445 \\ 0.056194 & 0.056307 & 0 & 0.168694 & 0.225056 \\ 0.506306 & 0.056307 & 0.168694 & 0 & 0.112444 \\ 0.112556 & 0.562445 & 0.225056 & 0.112444 & 0 \end{pmatrix}.$$

NJ algorithm returns the tree in Figure 1 from D_1 and D_2.

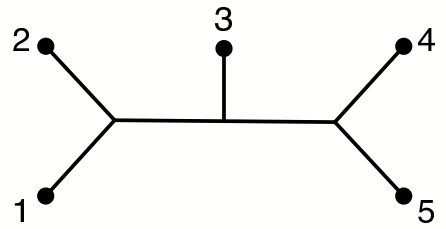


Figure 1: A tree with five leaves.

However, the NJ returns a different tree topology with $(D_1 + D_2)/2$.

For $n = 6$

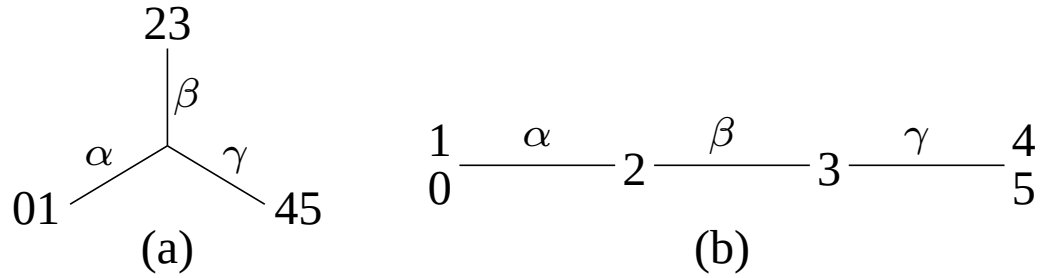


Figure 2: The two possible topologies for trees with six leaves, with edges connecting to leaves shrunk to zero.

There are three different classes of cones which cannot be mapped onto each other by the group action, C_I, C_{II}, C_{III}.

- **Type I**: $a, b, c, d, e, f \to a, b, c, d, (ef) \to a, b, (cd), (ef), \to$ Fig. 2(a)

- **Type II**: $a, b, c, d, e, f \to a, b, c, d, (ef) \to a, b, (cd), (ef)$
  $\to cd - a - b - ef$ (like Fig 2(b), but different labels)

- **Type III**: $a, b, c, d, e, f, \to a, b, c, d, (ef) \to a, b, c, (d(ef))$
  $\to ab - c - d - ef$ (exactly as in Fig 2(b))

	C_{I}	C_{II}	C_{III}
stabilizer	$\langle (12), (34), (56) \rangle$	$\langle (12), (56) \rangle$	$\langle (12), (56) \rangle$
size of stabilizer	8	4	4
number of cones	90	180	180
cones giving same labeled topology	6	2	2

Comparing NJ and BME cones

Neighbor-joining (NJ) method: This is the most popular distance based method. It computes a tree from all pair-wise distances obtained easily. (Saito and Nei (1987), Studier and Keppler (1988)).

Fact: The NJ algorithm is a greedy algorithm to find the BME tree (Gascuel and Steel (2006)).

From this point of view, NJ is "optimal" whenever the NJ algorithm outputs the tree which minimizes the BME criterion.

We studied the optimality of the NJ algorithm, (i.e., want to study how often the NJ returns the BME tree).

Issues with neighbor joining

- Neighbor joining is fast and consistent, but it isn't based on a model of speciation.
- Until recently, it hasn't been very clear what NJ is optimizing — if anything at all.
- Neighbor joining outputs a tree topology T iff the data lies in a union of cones. Unions of cones need not be convex.
- In fact neighbor joining is not convex: There are distance matrices D, D', such that NJ produces the same tree T_1 when run on input D or D', but NJ produces a different tree $T_2 \neq T_1$ when run on the input $(D + D')/2$

BME cones and NJ cones

- For each tree topology τ, we take the ratio the NJ cones and the BME cone by comparing the sperical volumes of intersections between the NJ cones and the unit sphare and between the BME cone and the unit sphare.

- A key requirement is the measurement of volumes of spherical polytopes in high dimension, which we obtain using a combination of traditional Monte Carlo methods and polyhedral algorithms.

- Our analysis reveals new insights into the performance of the NJ and BME algorithms for phylogenetic reconstruction.

Comparing NJ and BME cones

- As a supplement to our forthcoming paper, we are creating a catalog of frequencies of all possible types of pairs of NJ and BME trees, for up to 8 (or perhaps even more) taxa.

- Quick summary stats: Overall agreement between NJ and BME topologies is
  $100\%, 98\%, 90\%, 80\%, 65\%$ for $n = 4, 5, 6, 7, 8$ taxa.

- For $n \geq 7$ taxa, the ability of NJ to recover a BME caterpillar tree decreases much more quickly than for other BME tree topologies.

Future work

- We conjecture that the caterpillar tree is the most difficult BME tree for NJ to reproduce, as the number of taxa grows. Is this true? Why?

- In general, how does NJ's performance as a greedy BME heuristic depending on the topology of the BME tree?

- Rather than compare NJ and BME under a Gaussian distribution on $R^{\binom{n}{2}}$, one could use other distributions — namely $D = D_0 + \epsilon$, where D_0 are the true distances, and ϵ is either Gaussian or distributed according to the WLS in BME. This might still lead to some tractable and interesting computational geometry.

- Is there a combinatorial criterion (or at least sufficient conditions) for when two tree topologies form an edge on the BME polytope? Can this be used as a better way to move through tree space?

Thank you....