Computing medians and means of phylogenetic trees

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Contents of the talk

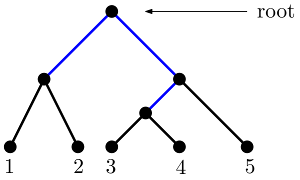
n-trees

Definition

A *metric n-tree* is a tree (connected graph with no circuit) with

- a distinguished vertex called *root*,
- n vertices called *leaves* that are labeled $1, \ldots, n$,
- leaf and inner edges of positive length.

5-tree



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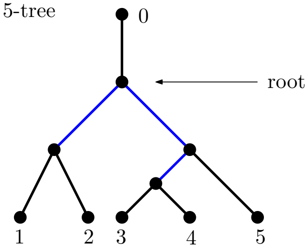

Need for a space of trees

We would like to

- measure distances between a given pair of trees,
- compute medians and means of a given set of trees.

We hence need a space of trees.

Construction due to **Billera, Holmes, and Vogtmann** in 2001:

BHV Tree space: a metric space whose points are trees.

(Metric space means we can measure distances.)

Moreover, tree space is an **Hadamard space** (i.e. it is nice).

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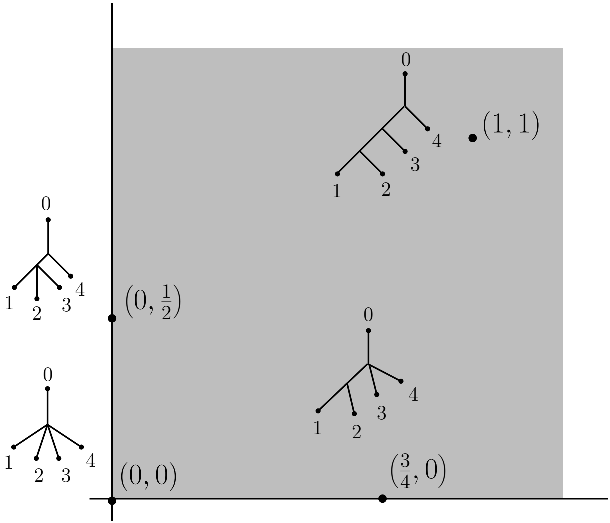
Orthant representation of a 4-tree



A piece of tree space $\mathcal{T}_4$

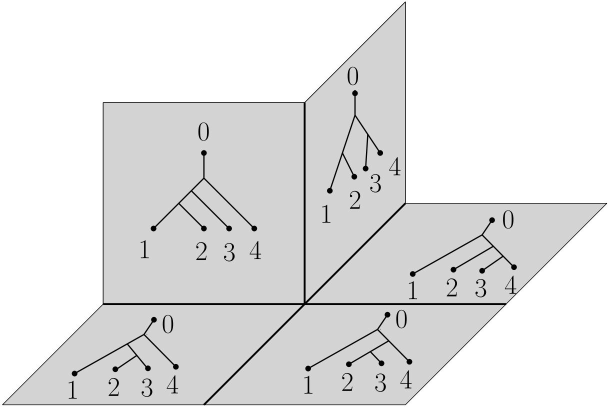


Figure : 5 out of 15 orthants of $\mathcal{T}_4$

Tree space

It is easy to define a metric in $\mathcal{T}_n$ – induced by Euclidean distances.

(Hence we are able to measure distances.)

Geodesics are piecewise linear (broken line segments).

(Geodesic = shortest path between a given pair of points.)

Theorem (Billera, Holmes, Vogtmann)

Tree space $\mathcal{T}_n$ is an Hadamard space.

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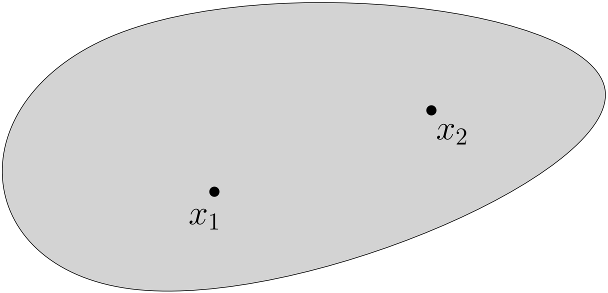

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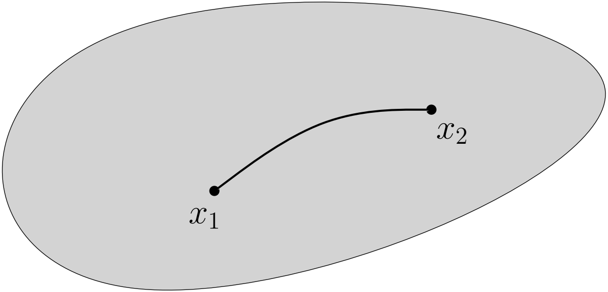

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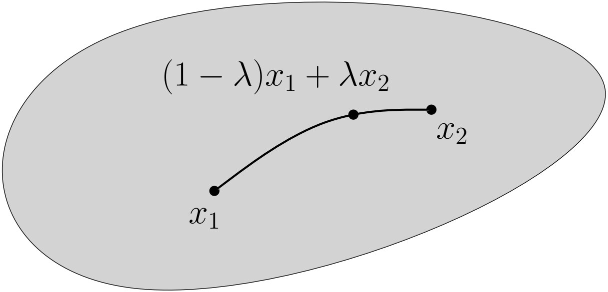
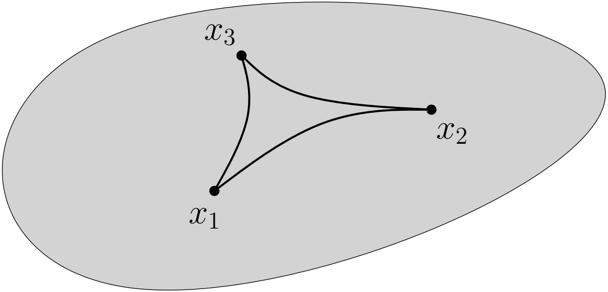


Definition of nonpositive curvature



The Fréchet mean

The arithmetic mean of $x_1, \ldots, x_K \in \mathbb{R}^m$ is defined as

$$\Xi\left(x_1, \ldots, x_K\right) := \frac{x_1 + \cdots + x_K}{K} = \frac{K-1}{K} \Xi\left(x_1, \ldots, x_{K-1}\right) + \frac{1}{K} x_K .$$

We cannot directly extend this into tree space.

Theorem (Methode der kleinsten Quadrate, Gauss, 1809)

The arithmetic mean is the unique vector in $\mathbb{R}^m$ such that

$$\sum_{k=1}^{K} d\left(\Xi, x_k\right)^2 = \min_{y \in \mathbb{R}^m} \sum_{k=1}^{K} d\left(y, x_k\right)^2 .$$

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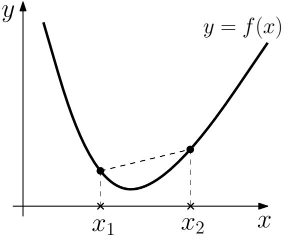
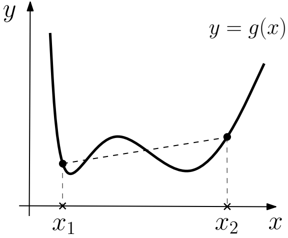
Convexity in tree space

Definition (Convex function)

A function $f : \mathcal{T}_n \to (-\infty, \infty]$ is *convex* if $f \circ \gamma$ is a convex function for any geodesic $\gamma : [0, 1] \to \mathcal{T}_n$.





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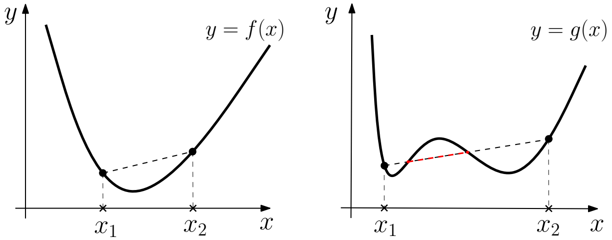

Definition of the Fréchet mean

Let $T_1, \ldots, T_K \in \mathcal{T}_n$. The function

$$\xi(S) := \sum_{k=1}^{K} d\left(S, T_k\right)^2$$

is (strongly) convex and continuous. (**By nonpositive curvature.**)

Theorem

1. *There exists a unique minimizer $\Xi \in \mathcal{T}_n$ of the function ξ.*
2. *The function $\Xi = \Xi\left(T_1, \ldots, T_K\right)$ is Lipschitz.*

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Probabilistic interpretation of the mean

Let $T_1, \ldots, T_K \in \mathcal{T}_n$. Denote the probability measure

$$\pi := \frac{1}{K} \sum_{k=1}^{K} \delta_{T_k}.$$

We can consider a random variable $Y : \Omega \to \mathcal{T}_n$ with distr. π.

If each of the values $T_1, \ldots, T_K$ occurs with probability $\frac{1}{K}$, then

$$\mathbb{E}Y := \operatorname*{arg\,min}_{S \in \mathcal{T}_n} \frac{1}{K} \sum_{k=1}^{K} d\left(S, T_k\right)^2 = \Xi\left(T_1, \ldots, T_K\right)$$

is the expectation of Y. (Also called the barycenter of π.)

The law of large numbers

Given a sequence of random variables Y_i with values in $\mathcal{T}_n$, we define $S_1 := Y_1$, and

$$S_{i+1} := \frac{i}{i+1} S_i + \frac{1}{i+1} Y_{i+1},$$

Theorem (The law of large numbers, Sturm 2003)

Let (Y_i) be a sequence i.i.d. according to π. Then

$$S_i \to \Xi\left(T_1, \ldots, T_K\right), \quad \text{as } i \to \infty,$$

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Geometric median

Let $T_1, \ldots, T_K \in \mathcal{T}_n$. Then

$$\psi(S) := \sum_{k=1}^{K} d\left(S, T_k\right)$$

is convex and continuous on $\mathcal{T}_n$.

($=$ the *Fermat-Weber problem* for optimal facility location)

Theorem

1. *There exists a minimizer $\Psi \in \mathcal{T}_n$ of the function ψ.*
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Let $x_1, \ldots, x_K \in \mathbb{R}^m$ and

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No explicit formula for a minimizer, only approximation algorithms, e.g. Weiszfeld's algorithm. (Compare with means.)

In $\mathbb{R}$ it coincides with the usual definition of a median:

$$\Pr(Y \leq \mu) \geq \frac{1}{2} \quad \text{and} \quad \Pr(Y \geq \mu) \geq \frac{1}{2},$$

where $Y : \mathbb{R} \to \mathbb{R}$ is a random variable. Then μ is a median of Y.

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Assume f attains its minimum. How to **compute** a minimizer?

Algorithm (Proximal point algorithm)

Choose $S_0 \in \mathcal{T}_n$ and set

$$S_{i+1} := \arg\min_{T \in \mathcal{T}_n} \left[f(T) + \frac{1}{2\lambda_i} d(T, S_i)^2 \right],$$

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The sequence S_i converges to a minimizer of f.

This is a classical optimization method in $\mathbb{R}^m$.

Works also in Hadamard spaces (M.B. 2011)

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Splitting proximal point algorithm

Let $f_1, \ldots, f_K$ be convex continuous and consider

$$f(T) := \sum_{k=1}^{K} f_k(T), \qquad T \in \mathcal{T}_n.$$

Example (Median and mean)

$$\psi(T) := \sum_{k=1}^{K} d\left(T, T_k\right), \qquad \xi(T) := \sum_{k=1}^{K} d\left(T, T_k\right)^2.$$

Key idea: use the PPA for $f_1, \ldots, f_K$ in a cyclic or random order.

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Splitting proximal point algorithm (for mean)

Hence instead of computing (the usual PPA)

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where T_k chosen by a selection rule (cyclic/random).

This is a **one-dimensional** problem!

$\implies$ S_{i+1} is a convex combination of T_k and S_i.

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Computing the mean: Cyclic order version

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The sequence S_i converges to the mean of $T_1, \ldots, T_K$.

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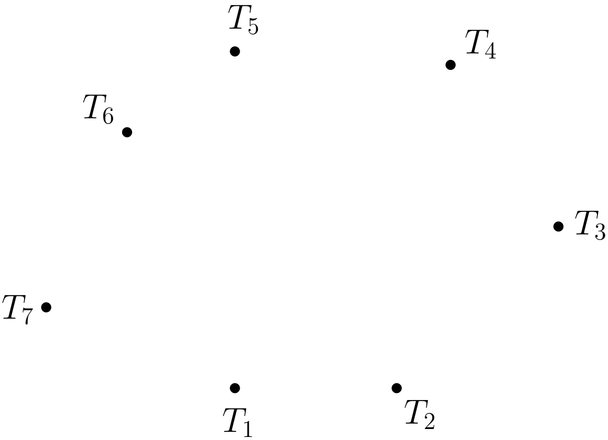

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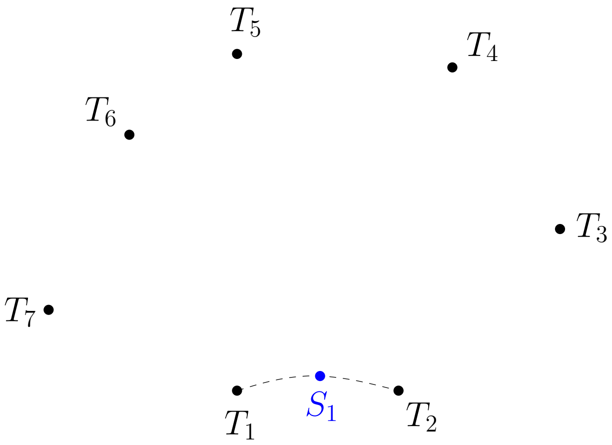

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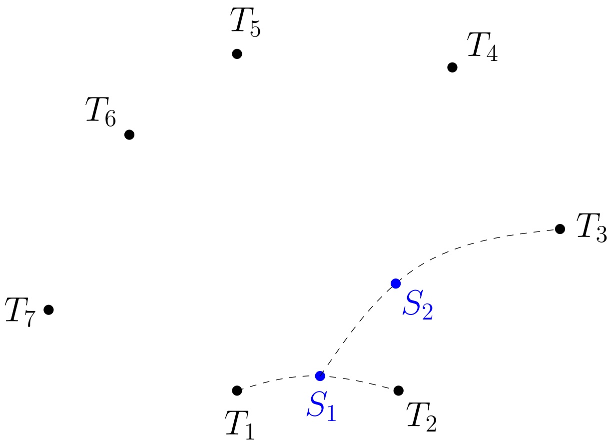

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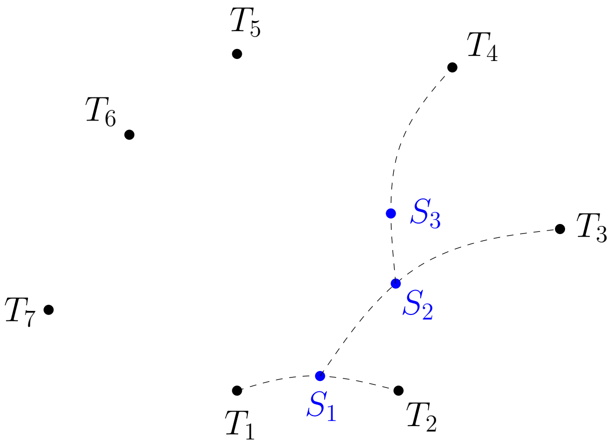

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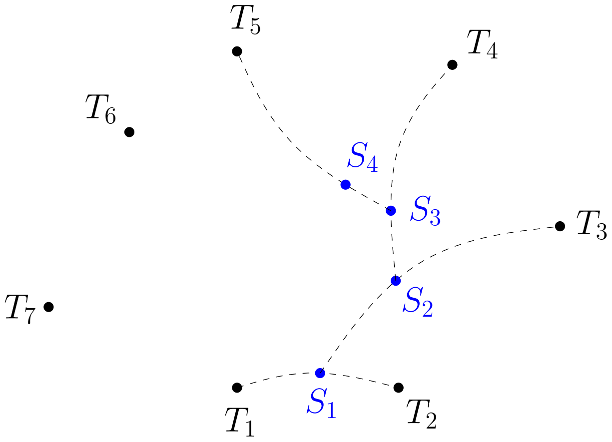

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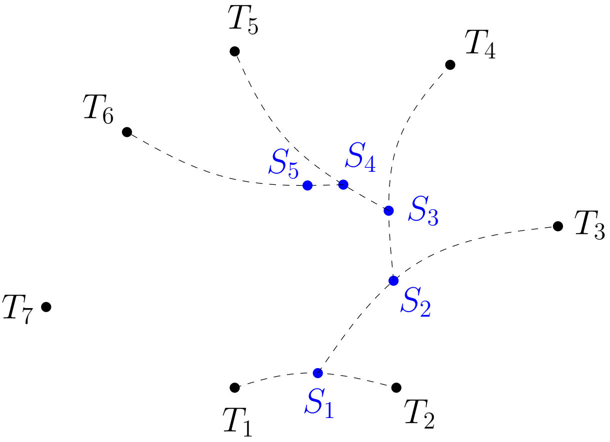

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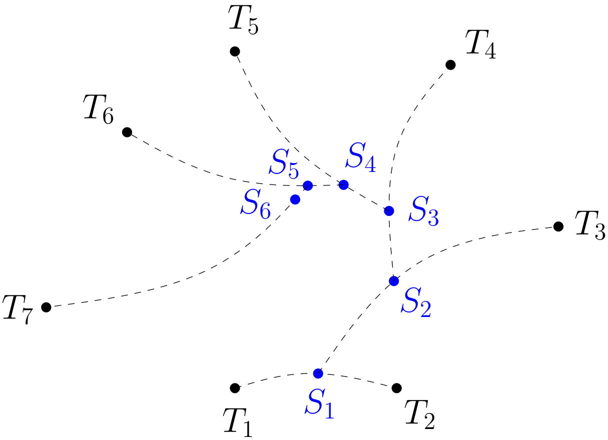

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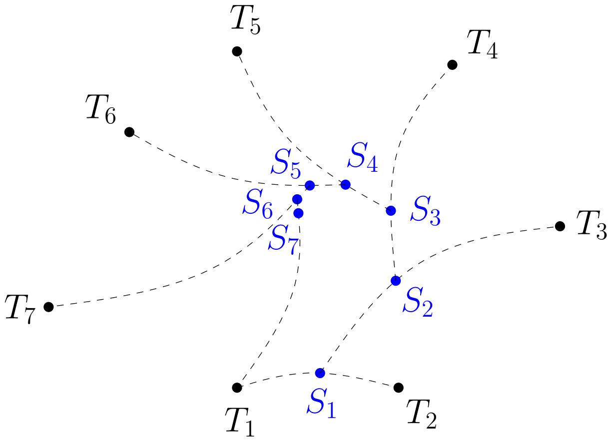

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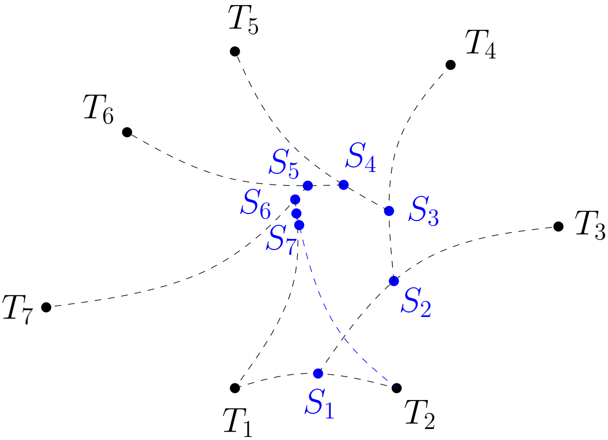

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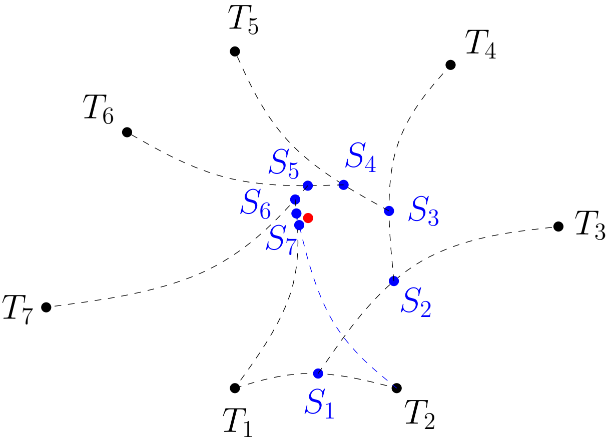

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Statistical model (see Philipp Benner's poster for details)

We start with multiple sequence alignments $\rightsquigarrow$

Posterior distribution is defined:

- first on each orthant $\mathcal{O}_i$ of tree space (fixed tree topology) $\implies \mu_i$
- posterior distribution on the whole tree space $\mathcal{T}_n$:

$$\mu := \sum_{i=1}^{(2n-3)!!} w_i \mu_i.$$

Difficulties:

- the weights w_i require to compute a complicated integral
- the number of orthants (tree topologies) is **big:** $(2n-3)!!$

Statistical model (see Philipp Benner's poster for details)

We start with multiple sequence alignments $\rightsquigarrow$

Posterior distribution is defined:

- first on each orthant $\mathcal{O}_i$ of tree space (fixed tree topology) $\Longrightarrow \mu_i$
- posterior distribution on the whole tree space $\mathcal{T}_n$:

$$\mu := \sum_{i=1}^{(2n-3)!!} w_i \mu_i .$$

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Statistical model - continued

We'll therefore give point estimates of posterior distribution μ:

- median:

$$\operatorname*{arg\,min}_{S\in\mathcal{T}_n} \int_{\mathcal{T}_n} d(S,T)\ \mathrm{d}\mu(T)$$

- mean:

$$\operatorname*{arg\,min}_{S\in\mathcal{T}_n} \int_{\mathcal{T}_n} d(S,T)^2\ \mathrm{d}\mu(T)$$

Markov chain Monte Carlo (MCMC) methods yield samples of posterior distribution:

$\rightsquigarrow T_1,\ldots,T_K \in \mathcal{T}_n$ $\qquad \rightsquigarrow \pi := \frac{1}{K}\sum_{k=1}^{K}\delta_{T_k}$ $\qquad (\pi \approx \mu)$

Median and mean of π are computed with the above algorithms.

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Real data experiments (see Philipp Benner's poster)

We used ribosomal subunit rRNA sequence alignment:

- number of species: 12
- number of trees: $20,000$
- number of iterations: 10^7

Conclusion:

- computations took less than 5 minutes
- very good speed of convergence (no theory though)
- random-order versions seem to be better

More computational studies certainly **needed** in the future!

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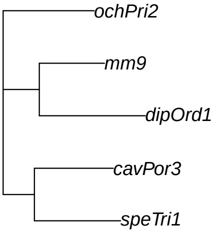
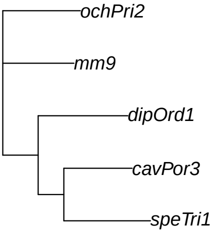
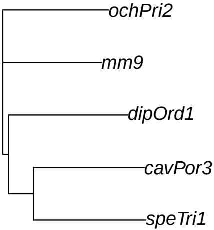
Real data experiments - continued







Summary:

- The BHV Tree space has nice geometrical properties.
- ... it is rather "big", but that doesn't seem to be an issue.
- The median and mean are well-defined and behave nicely.
- One can compute distances in polynomial time.
- There are rigorous approximation algorithms for medians and means.
- We used all that in phylogenetic inference and **would like to hear your opinion!**

References

- **M. Bacak:** *Computing medians and means in Hadamard spaces.* Preprint, arXiv:1210.2145.
- **P. Benner, M. Bacak:** *Computing the posterior expectation of phylogenetic trees.* Preprint, arXiv:1305.3692.
- **L. Billera, S. Holmes, K. Vogtmann:** *Geometry of the space of phylogenetic trees.* Adv. in Appl. Math., 2001.
- **E. Miller, M. Owen, S. Provan:** *Averaging metric phylogenetic trees.* Preprint, arXiv:1211.7046v1.
- **M. Owen, S. Provan:** *A fast algorithm for computing geodesic distances in tree space.* IEEE/ACM Trans. Computational Biology and Bioinformatics, 2011.

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