The Search for the Tree of Life: A Location Problem in the Phylogenetic Tree Space

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Georg-August Universität Göttingen

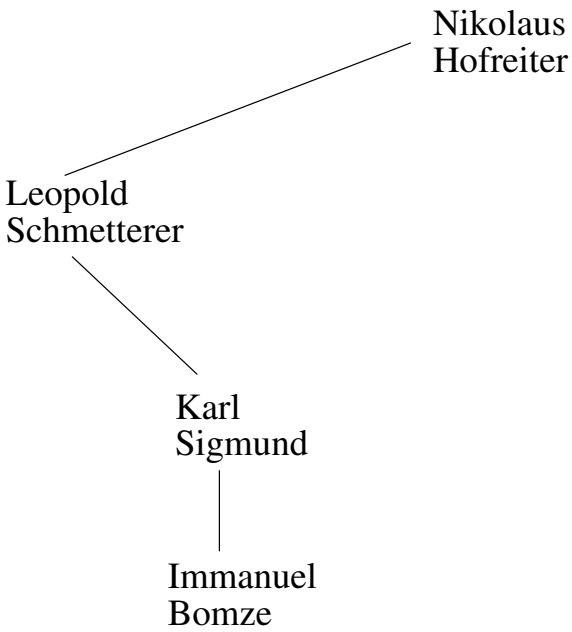
20. December 2018

The trees of this talk: phylogenetic trees

More interesting: Math genealogy

Immanuel
Bomze

More interesting: Math genealogy



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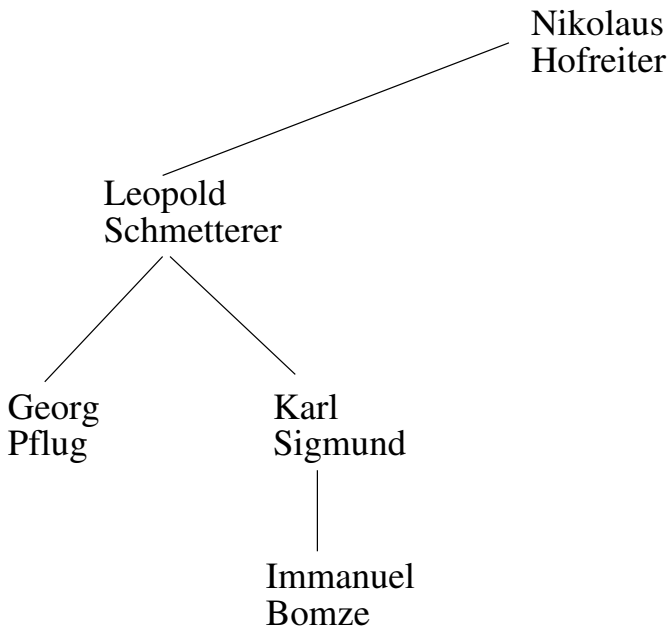

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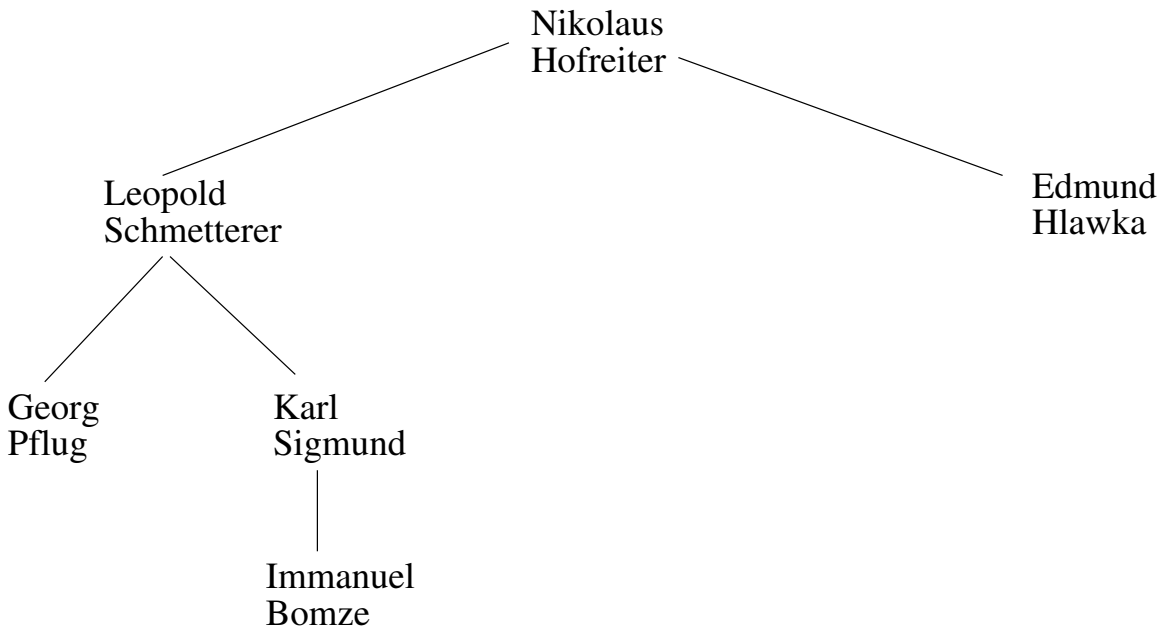

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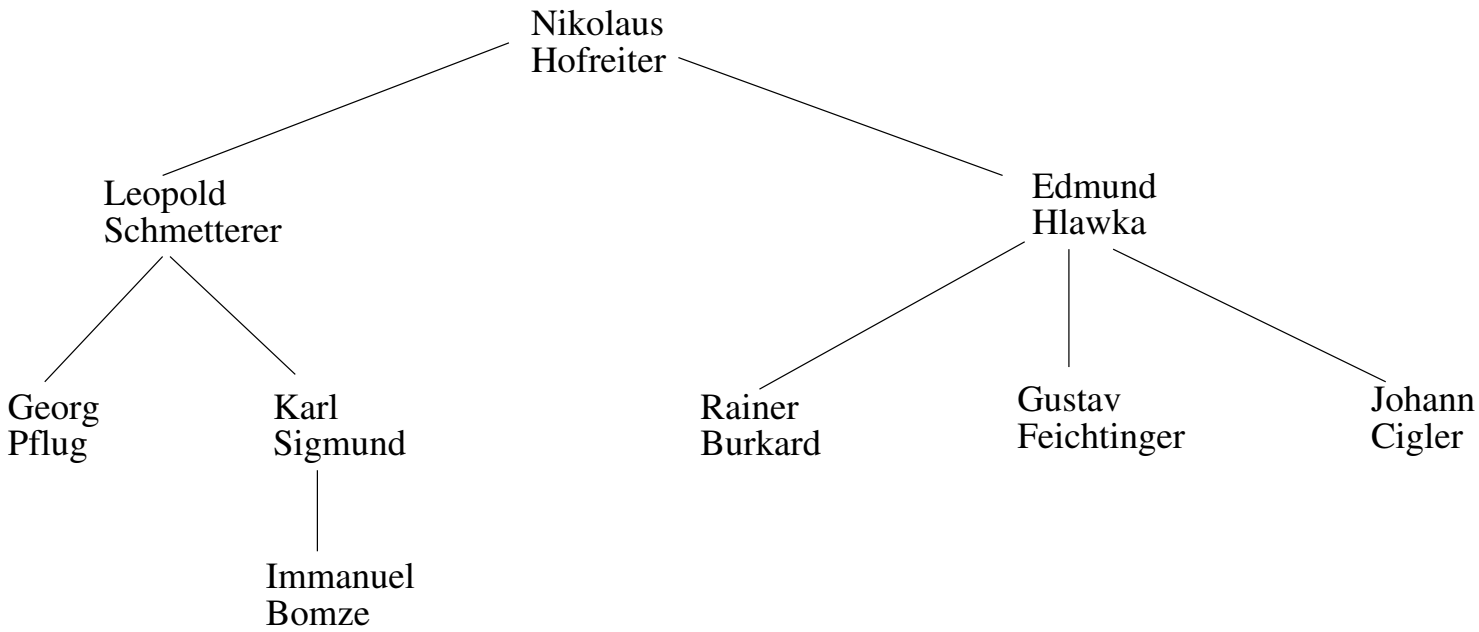

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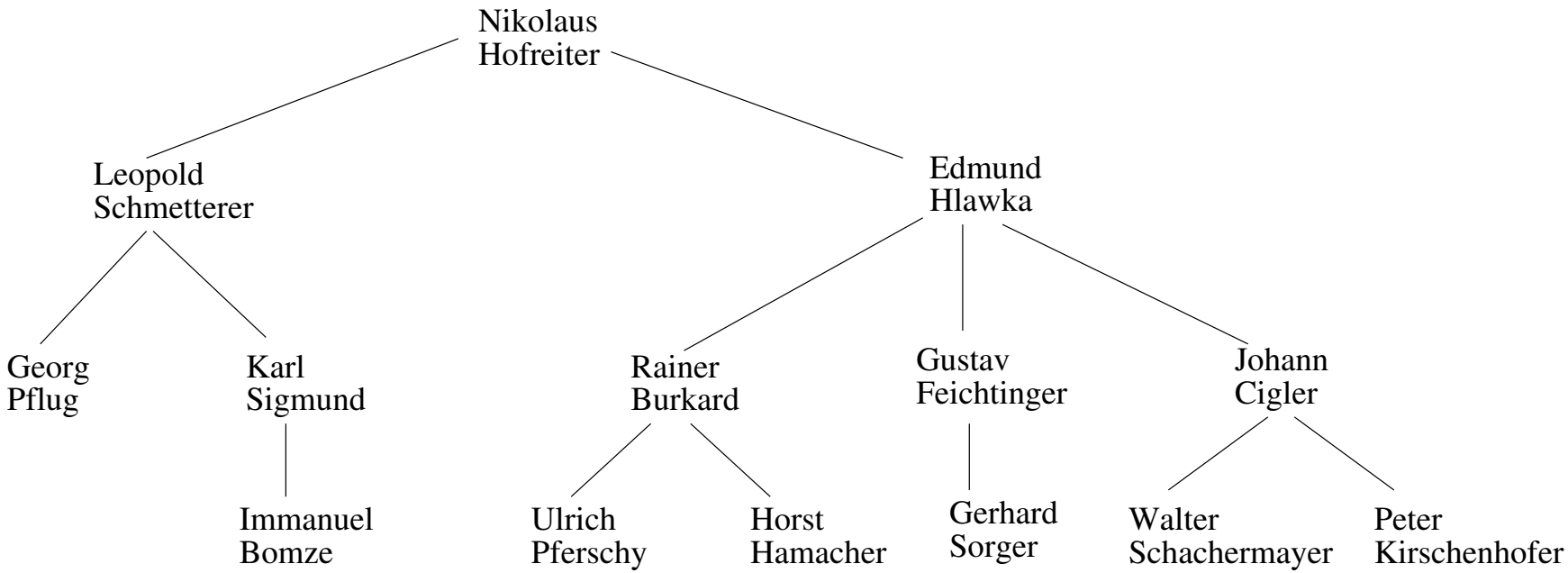

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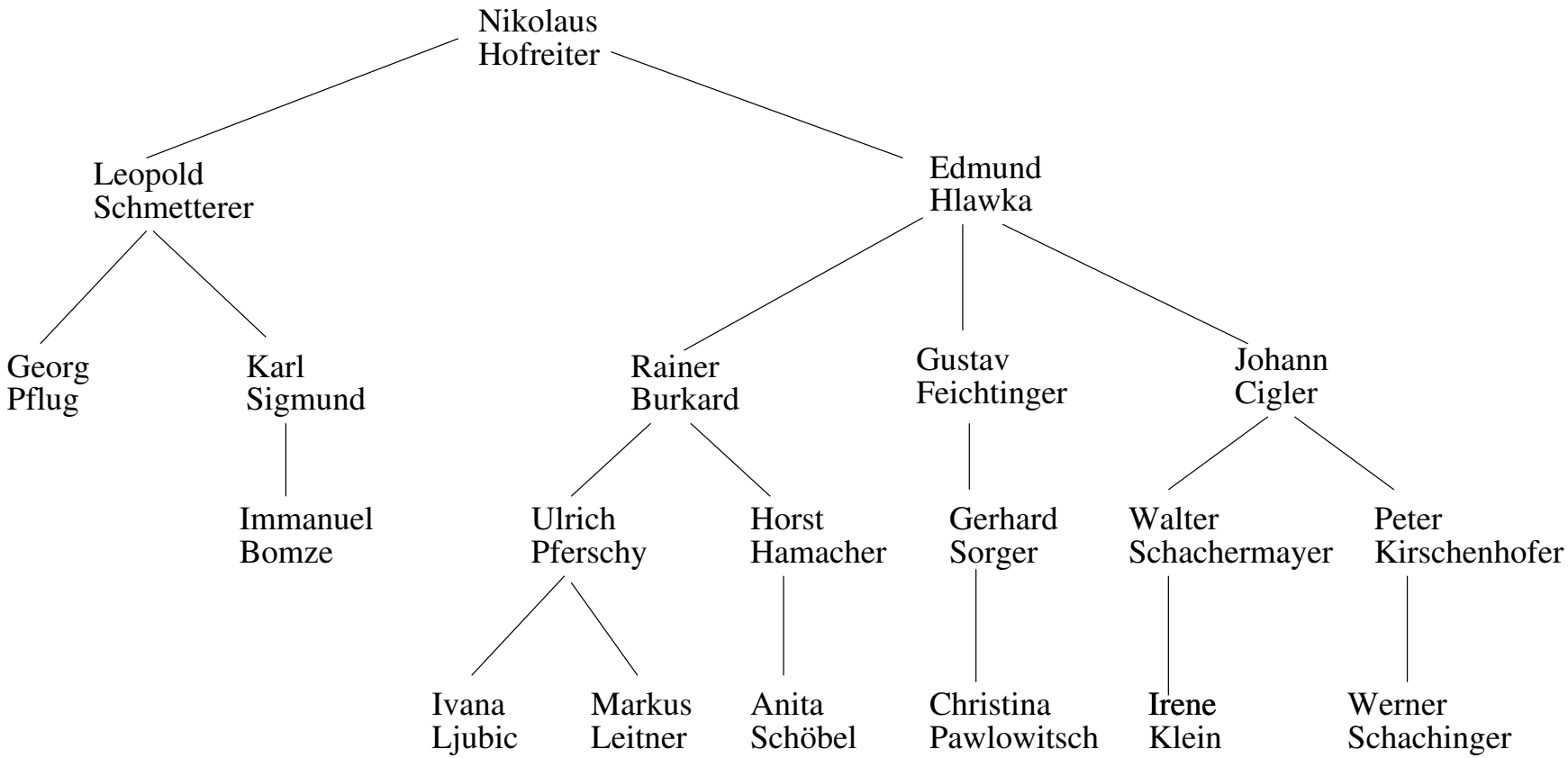

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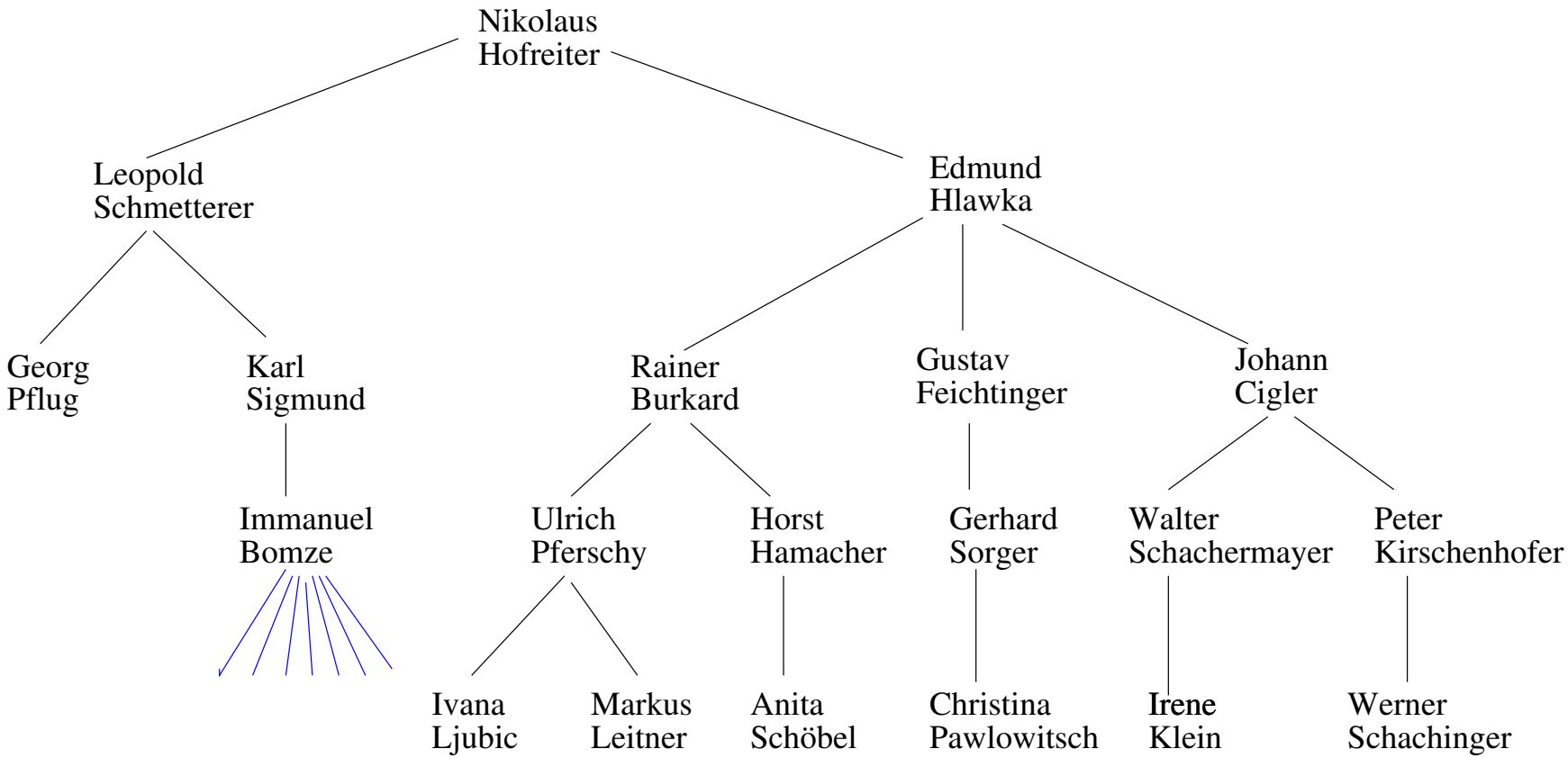

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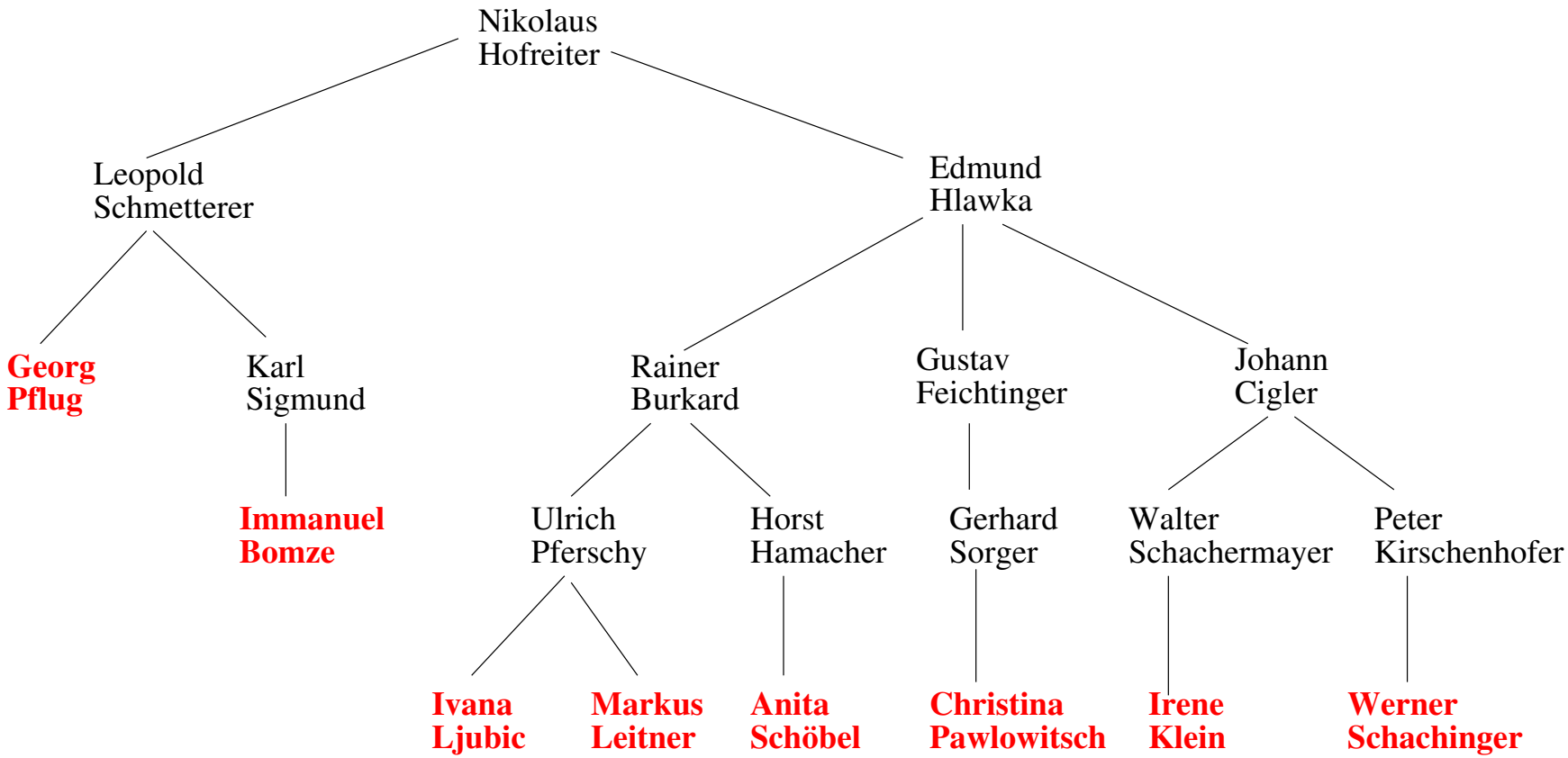

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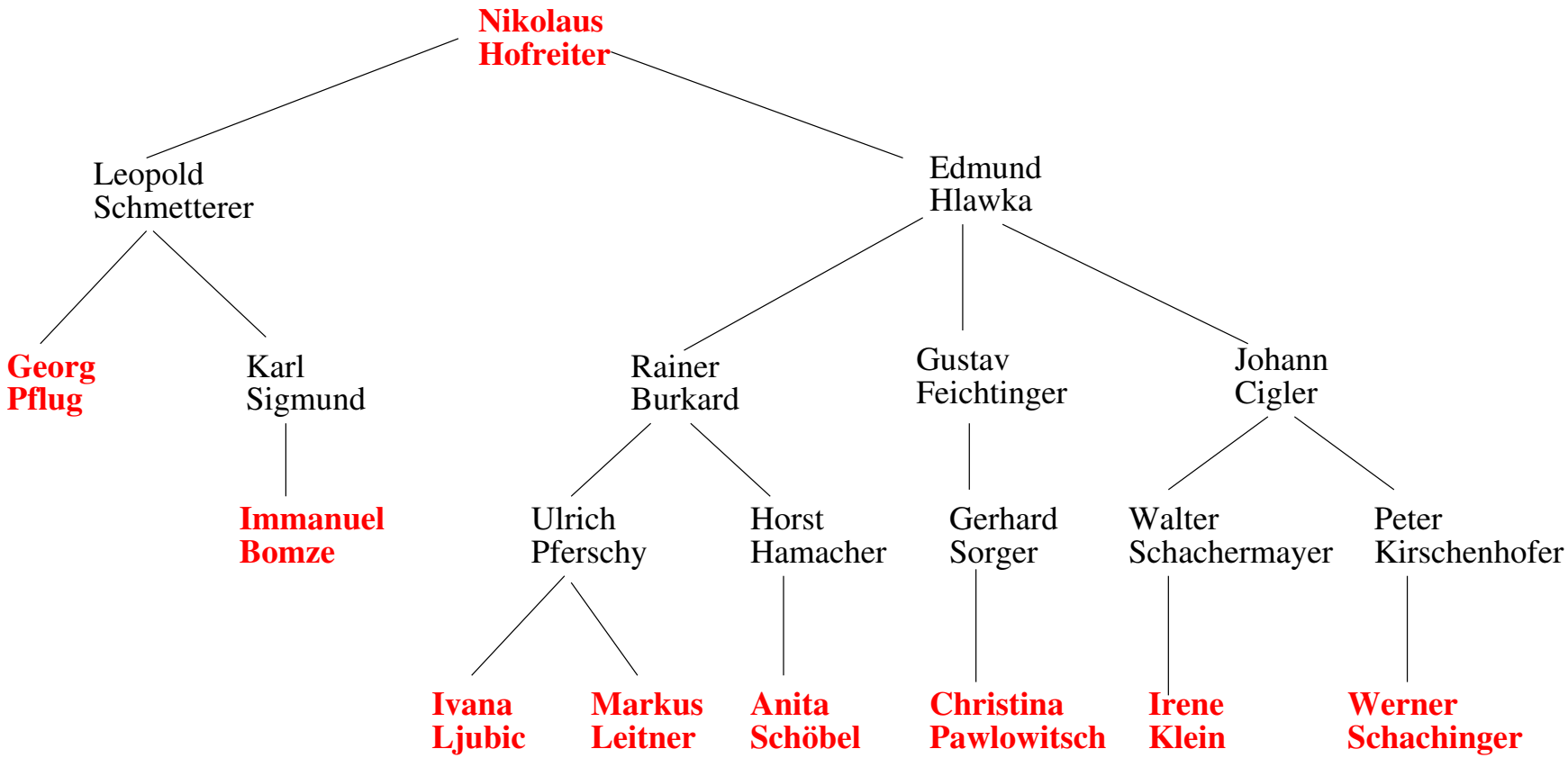

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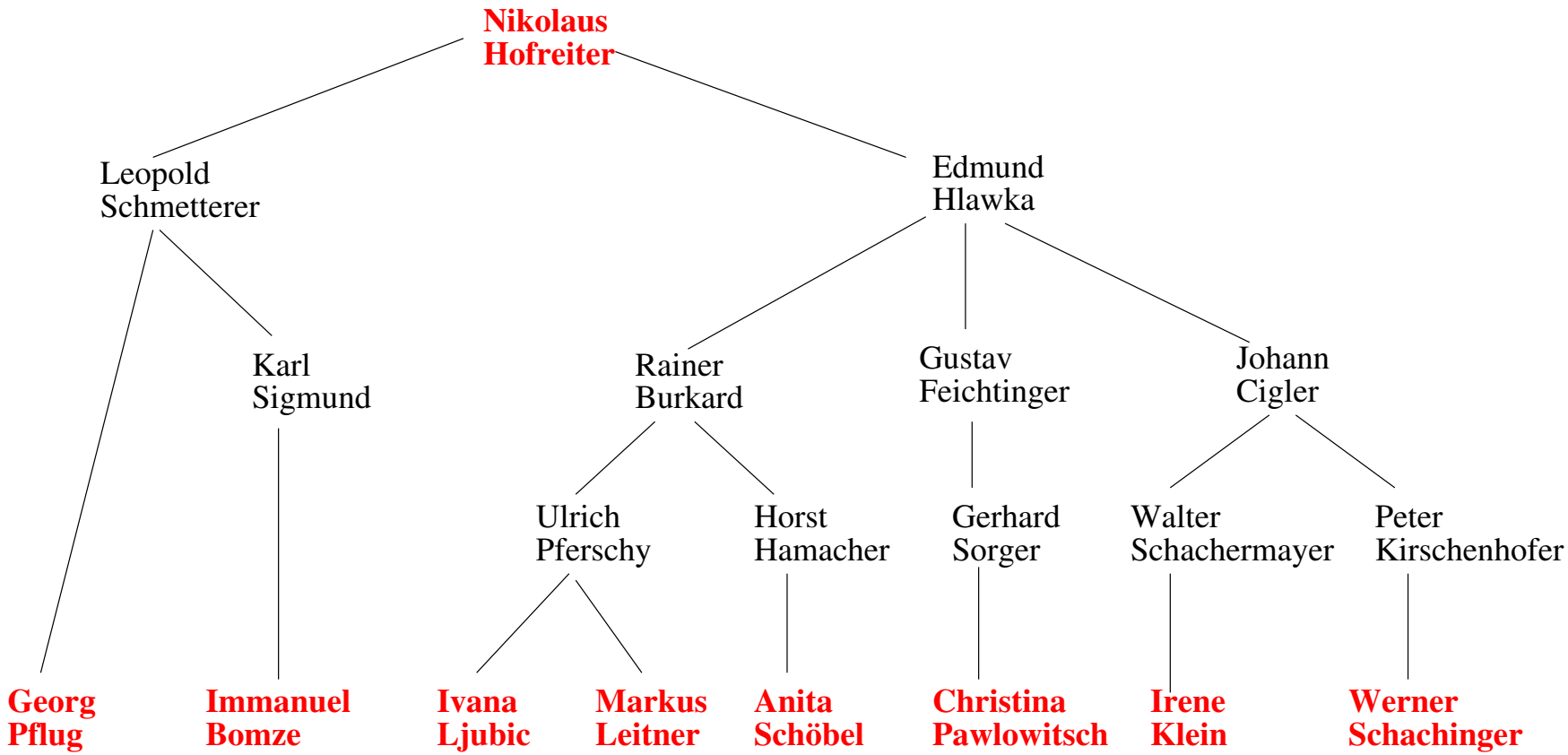

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Nikolaus Hofreiter

Georg Pflug | **Immanuel Bomze** | **Ivana Ljubic** | **Markus Leitner** | **Anita Schöbel** | **Christina Pawlowitsch** | **Irene Klein** | **Werner Schachinger**

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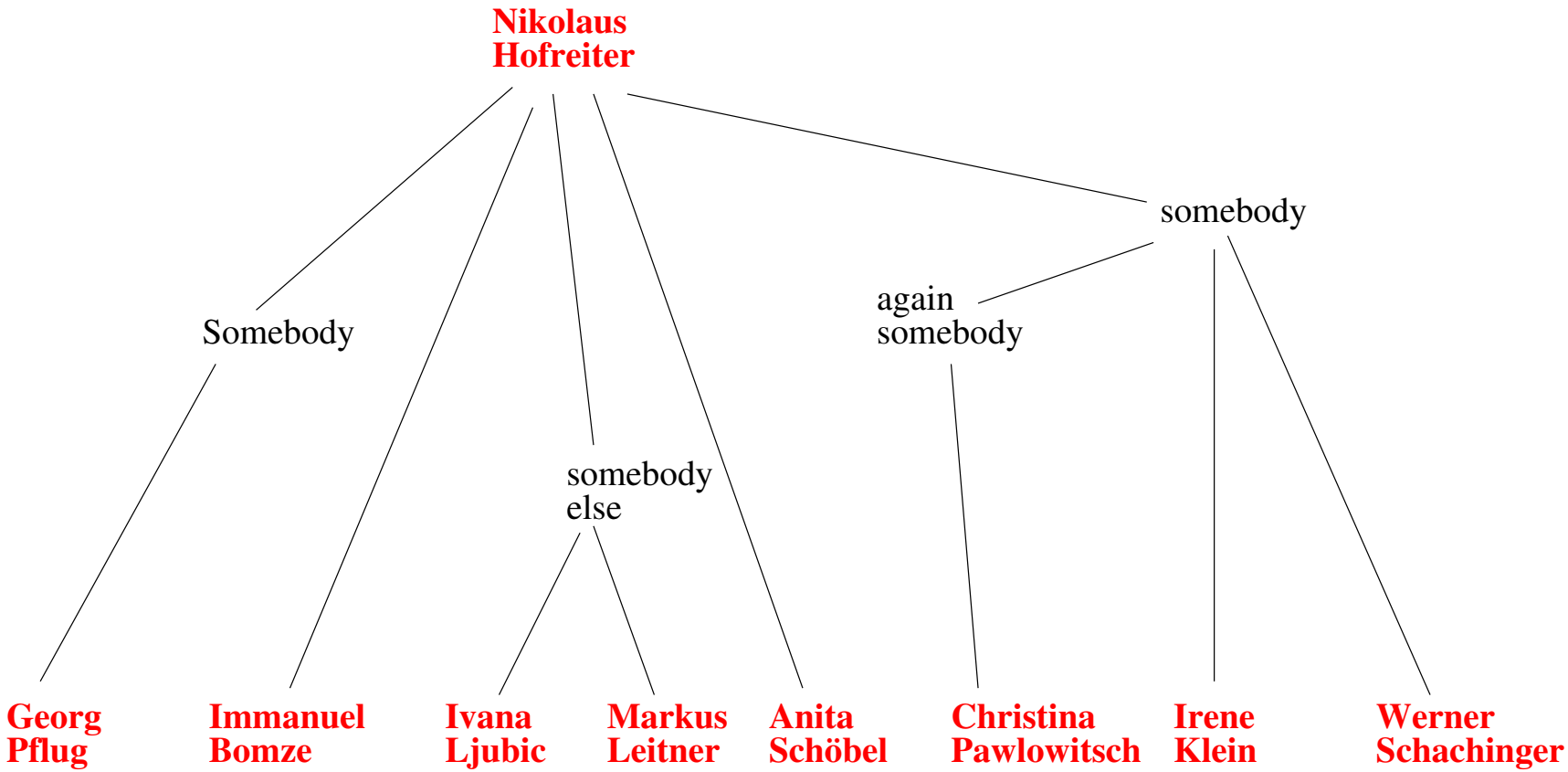

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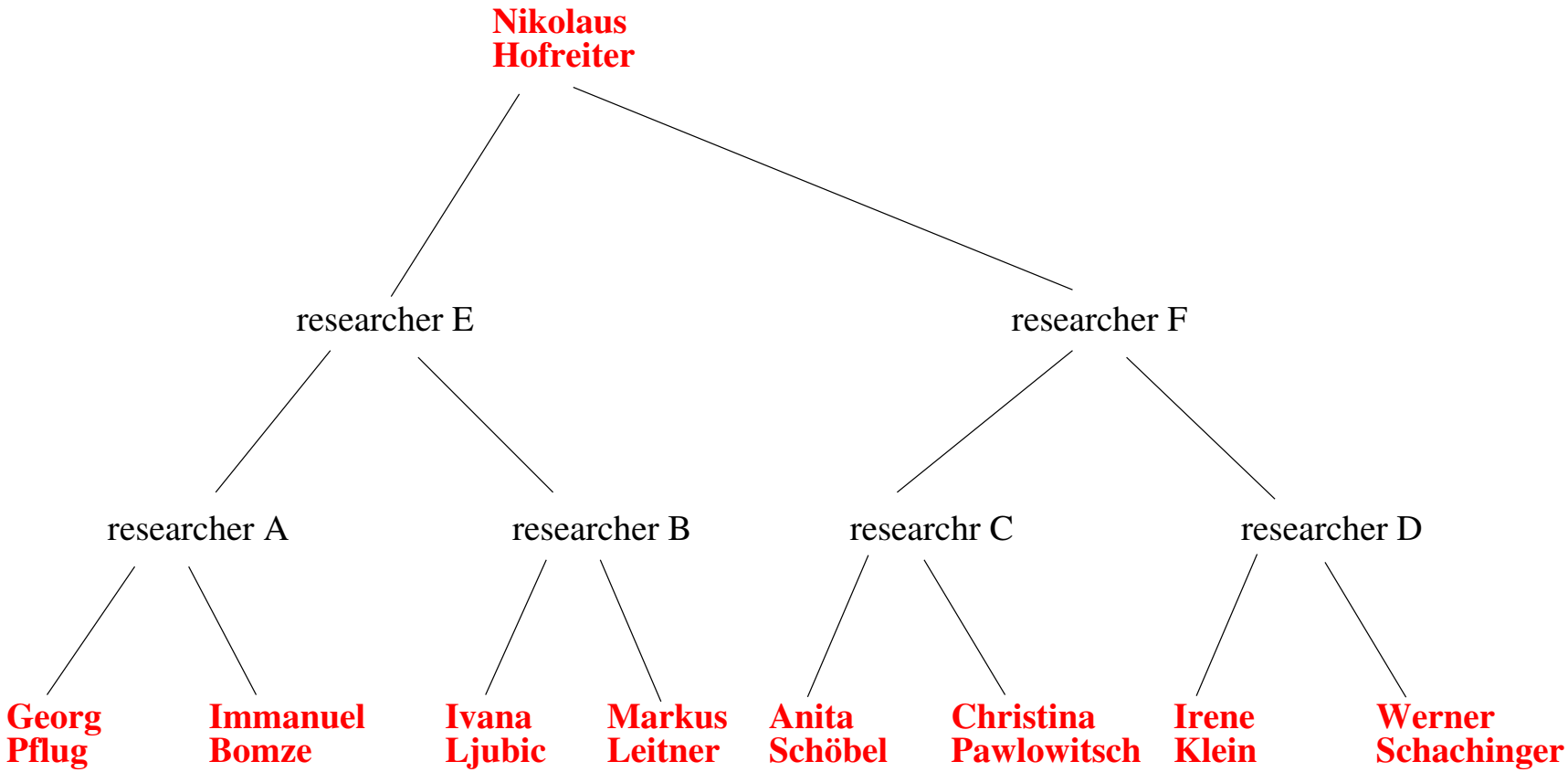

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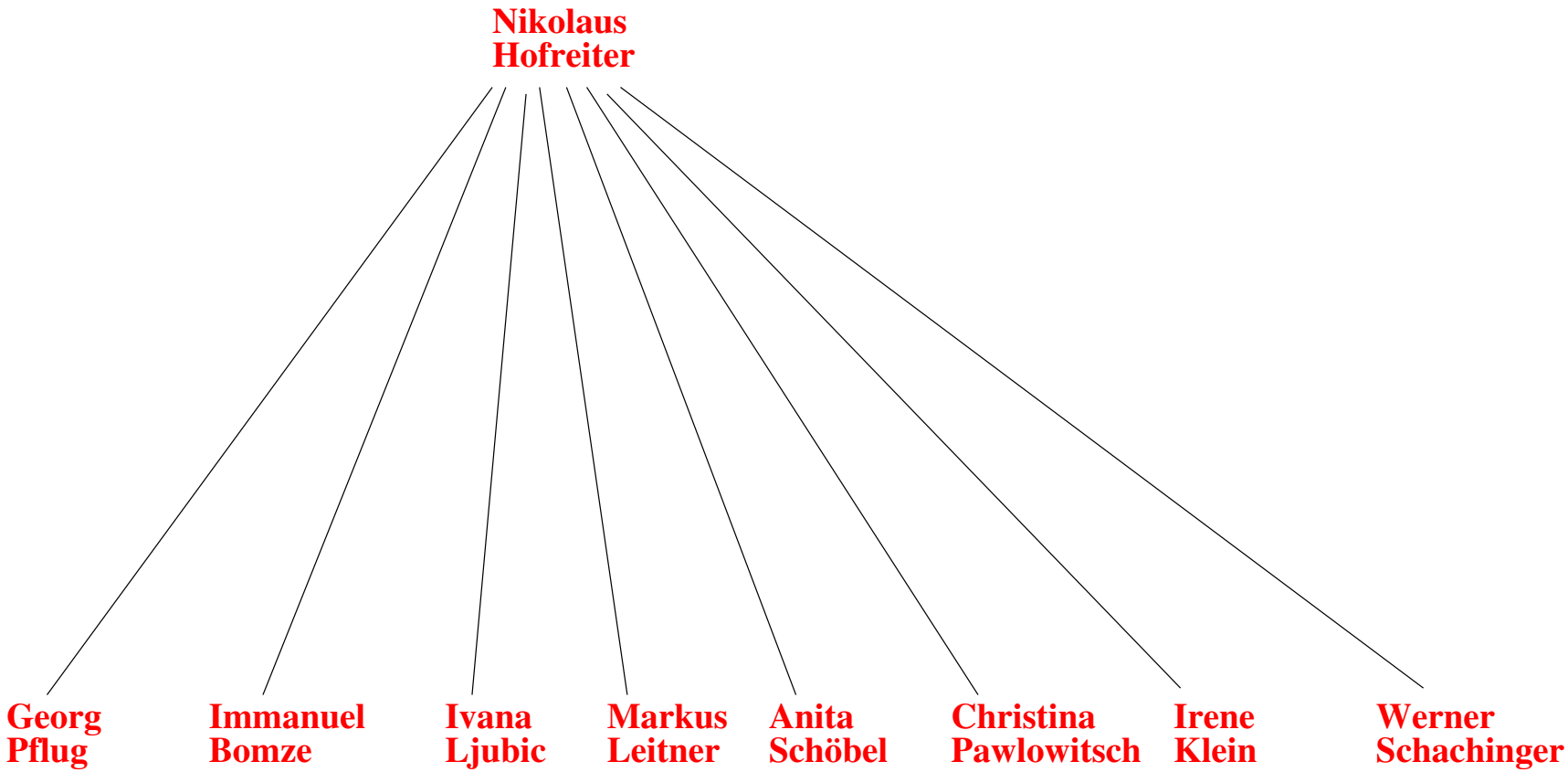

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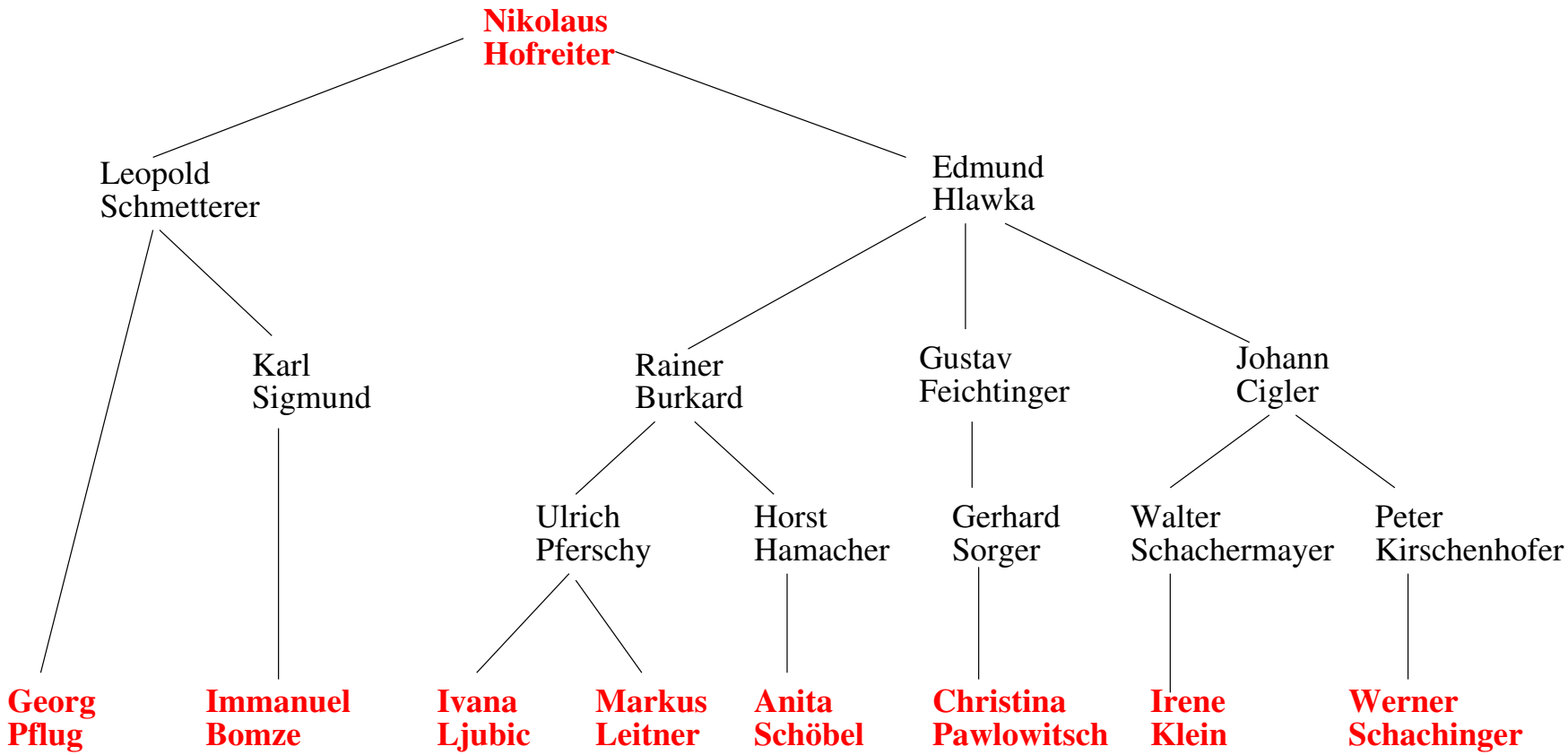

Contents

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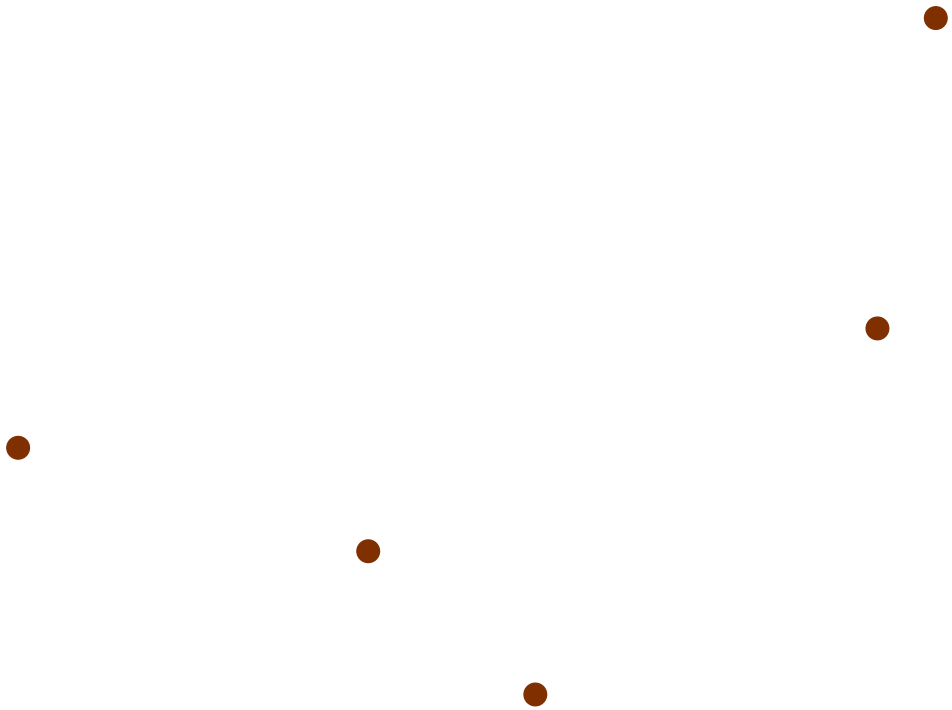
Euclidean location problems

Question: Given a set of L points in the plane, find the point that minimizes the sum of Euclidean distances to them.



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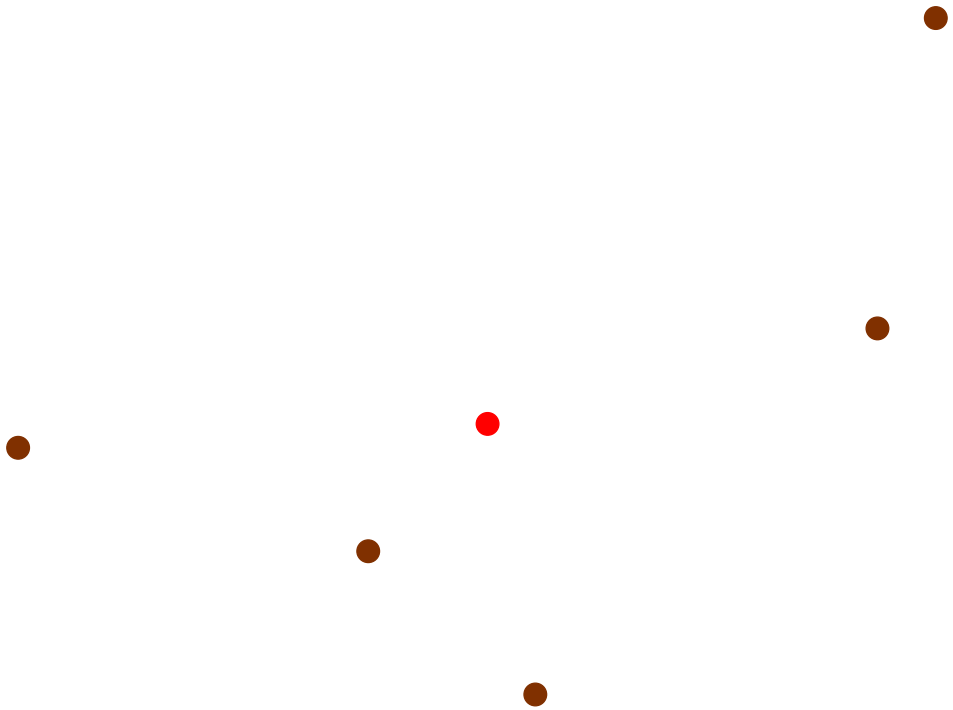

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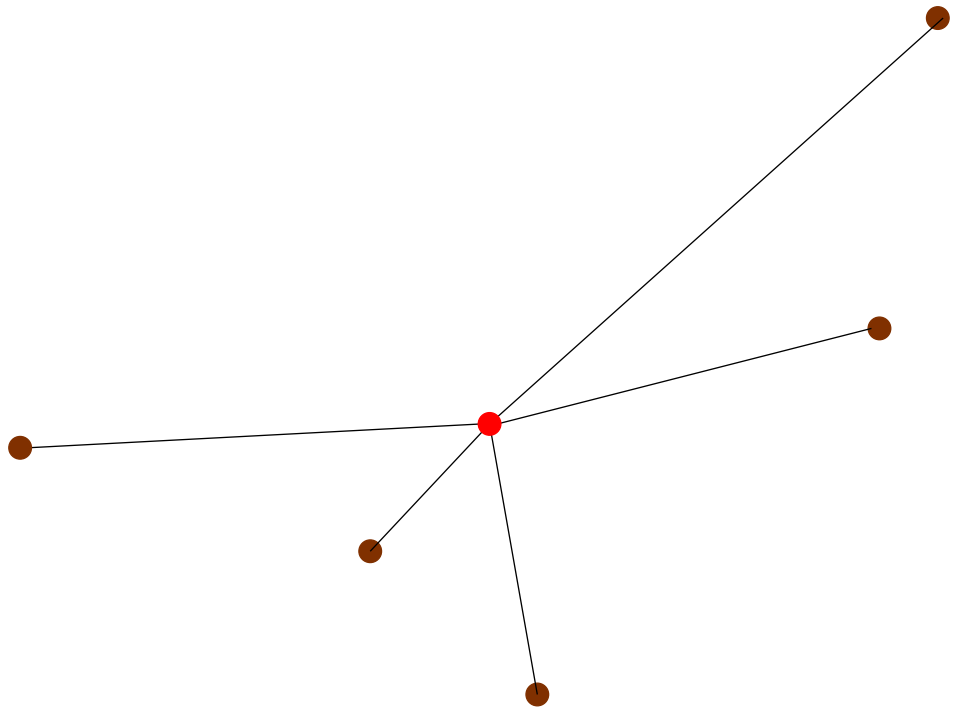

1-median Euclidean location problem
(Weber problem/ Fermat-Torricelli-problem)

The Tree Space

Is a metric space.

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- Elements of the space: All trees such that n given species are leaves of the tree.
- Distance: geodesic distance describing how quickly a tree can be transformed into another one.

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- Elements of the space: All trees such that n given species are leaves of the tree.
- Distance: geodesic distance describing how quickly a tree can be transformed into another one.

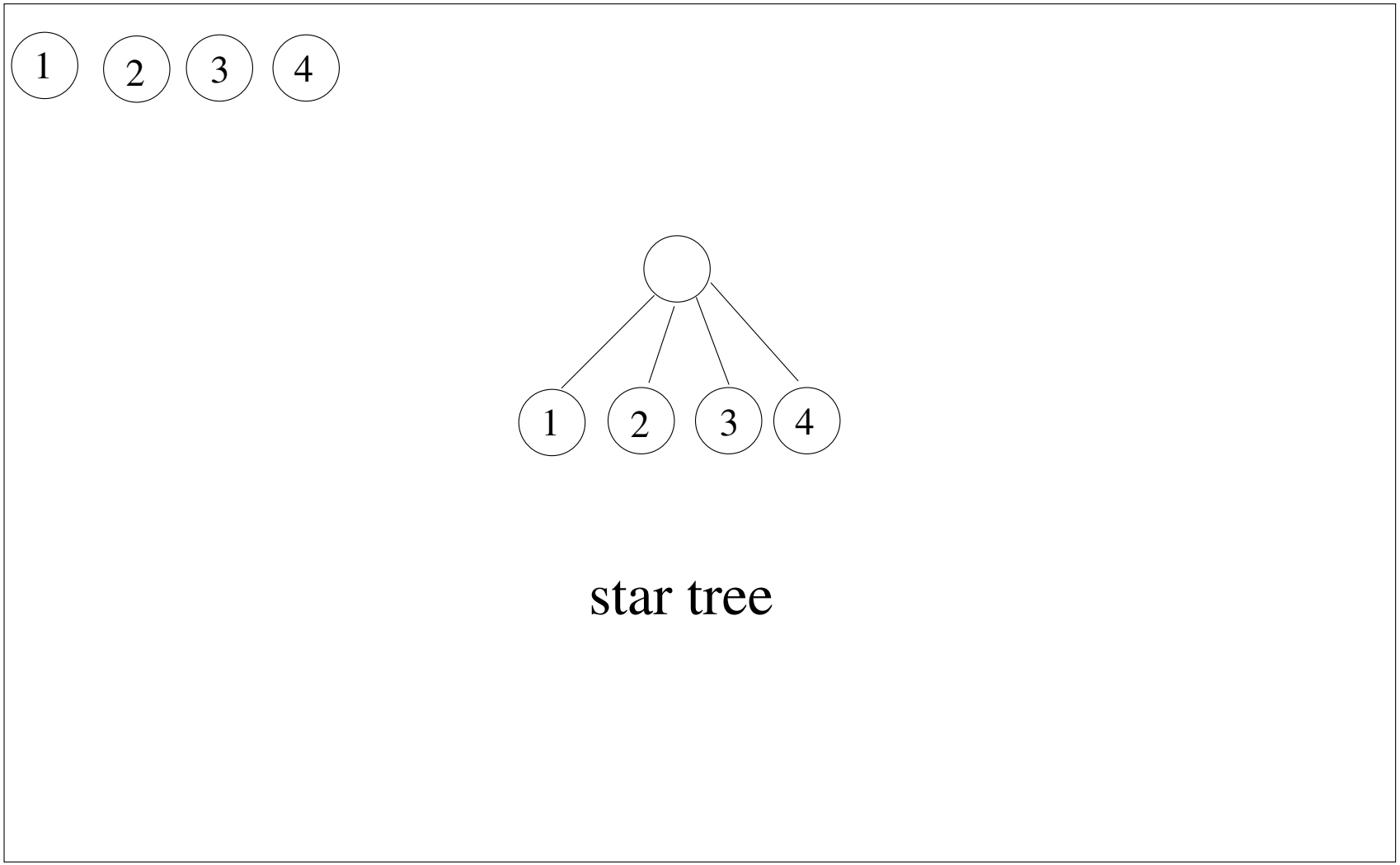
Question: Given a set of L such trees (estimated by biologists), find the *real* one.

Idea: The real one minimizes the geodesic distances to the estimated trees. We receive a

1-median location problem in the tree space.

Contents

Example: Phylogenetic Trees with four species



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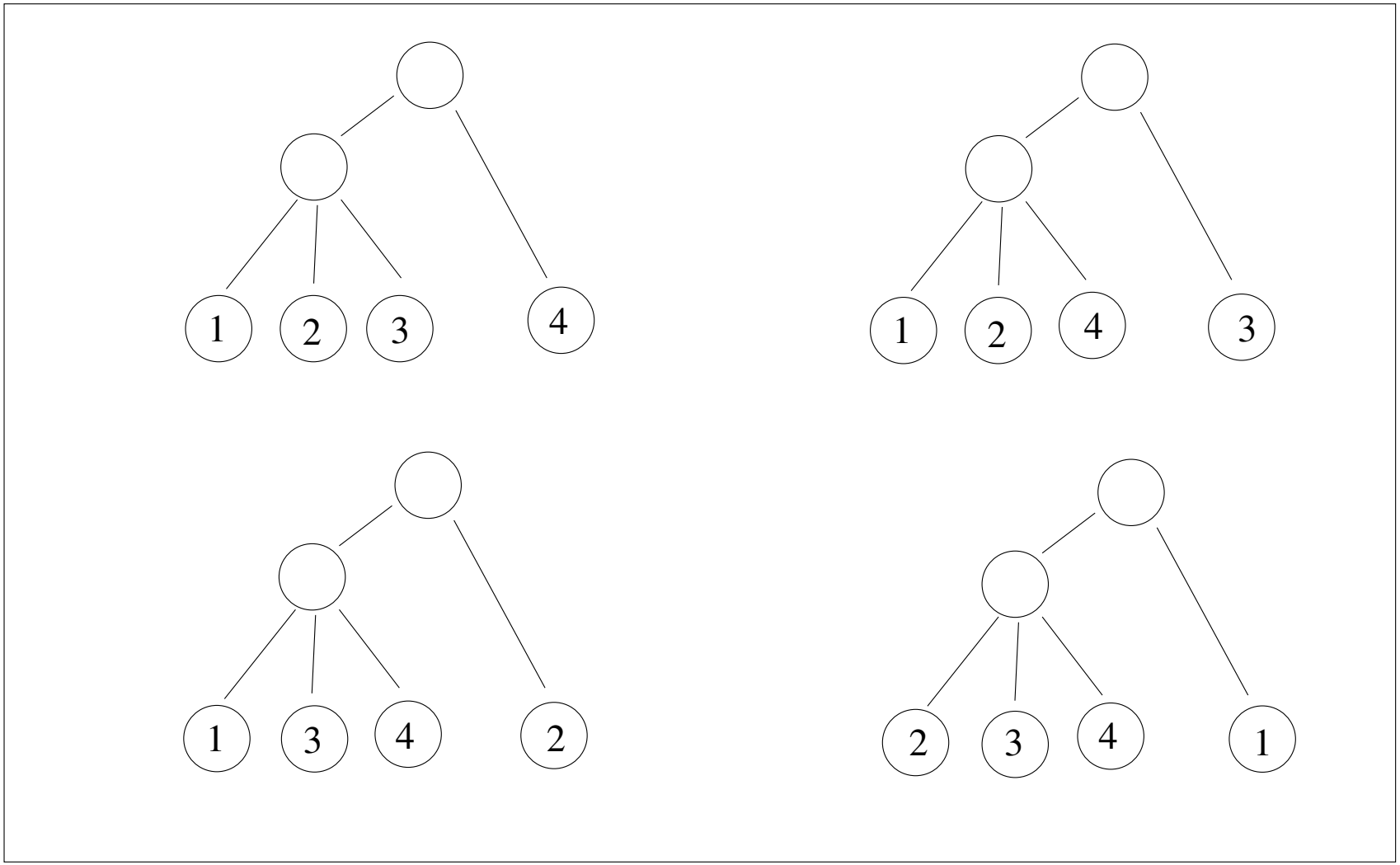

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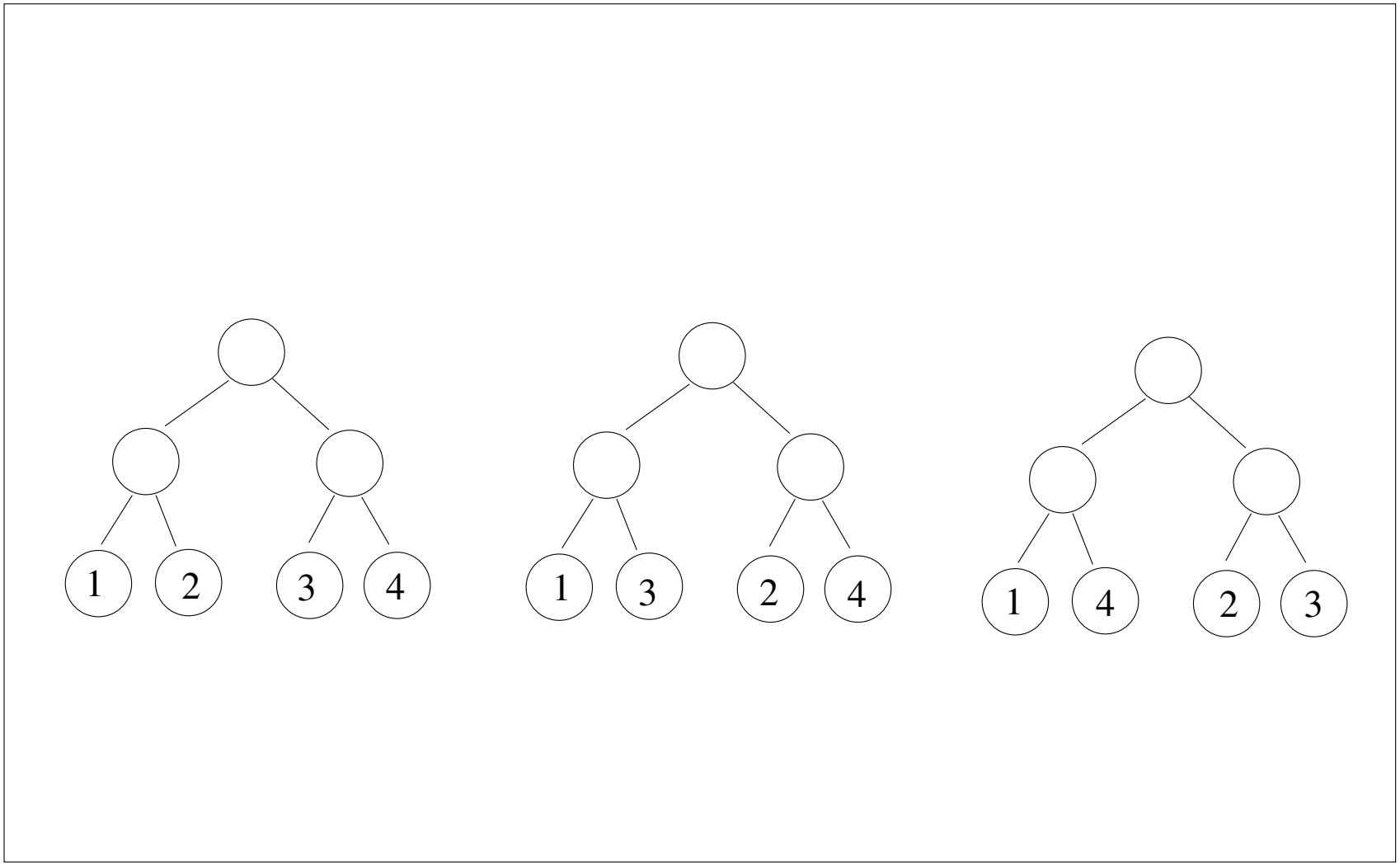

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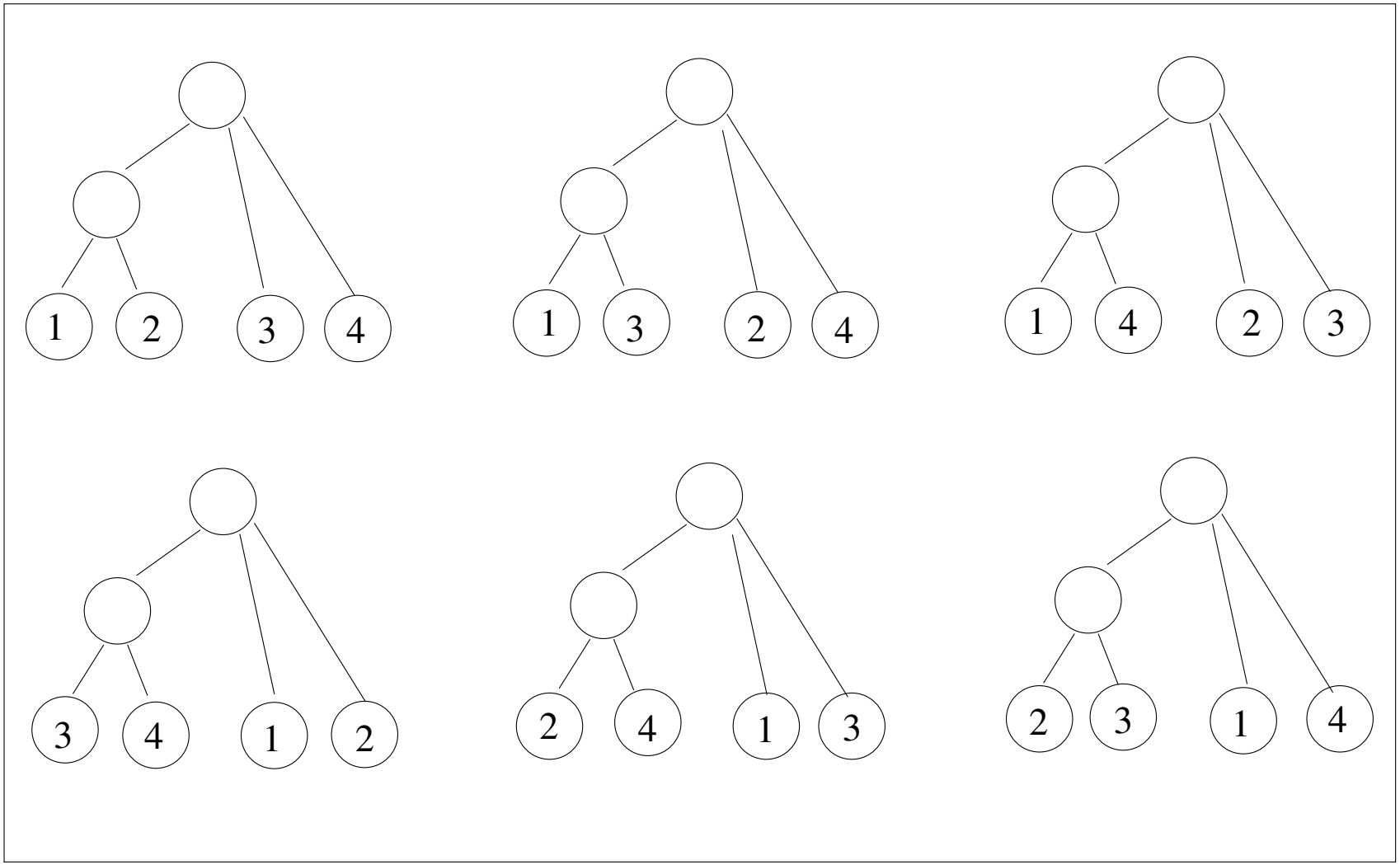

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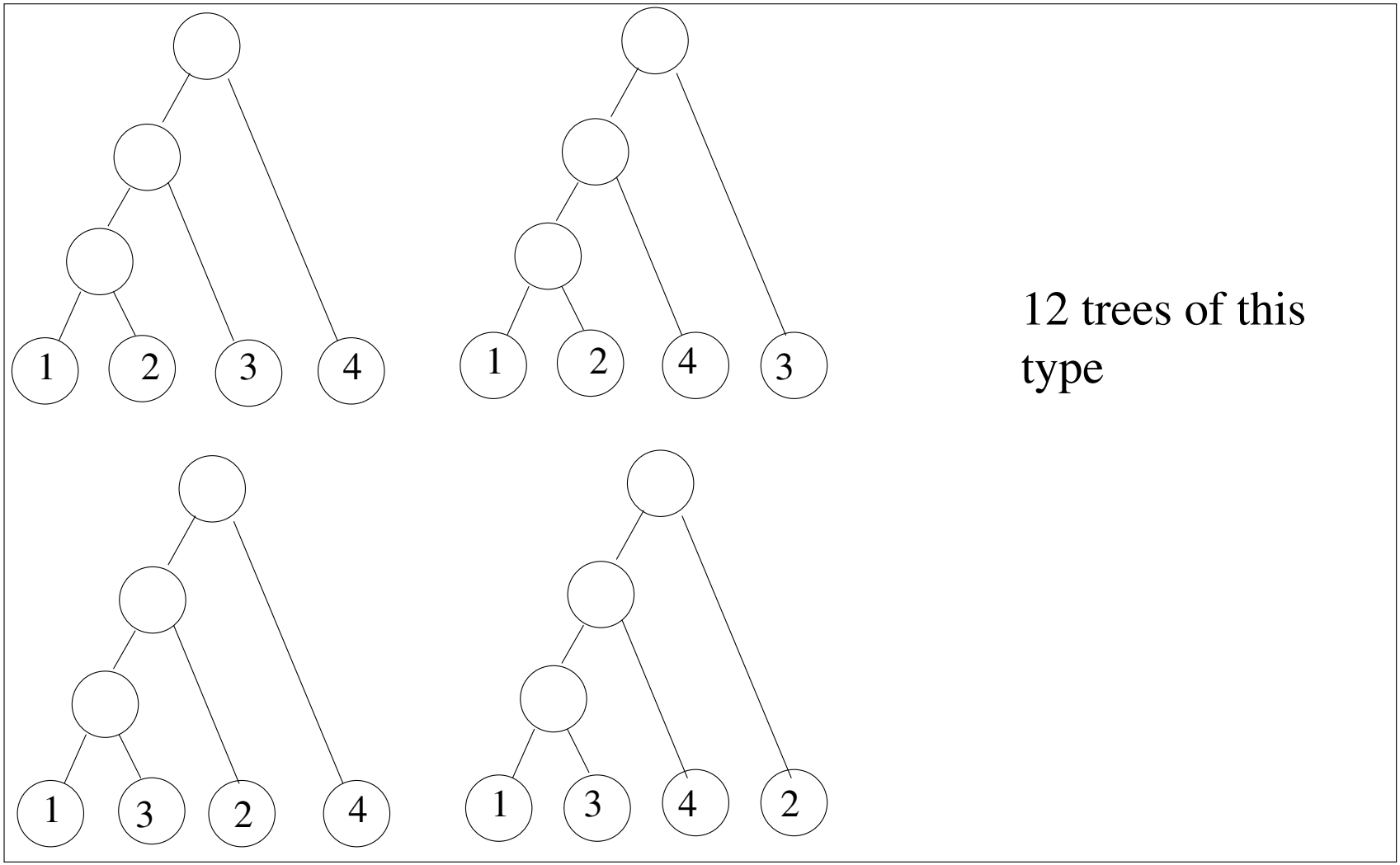

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The tree space for 4 species $\mathcal{T}_4$ consists of all these trees with all positive edge weights.

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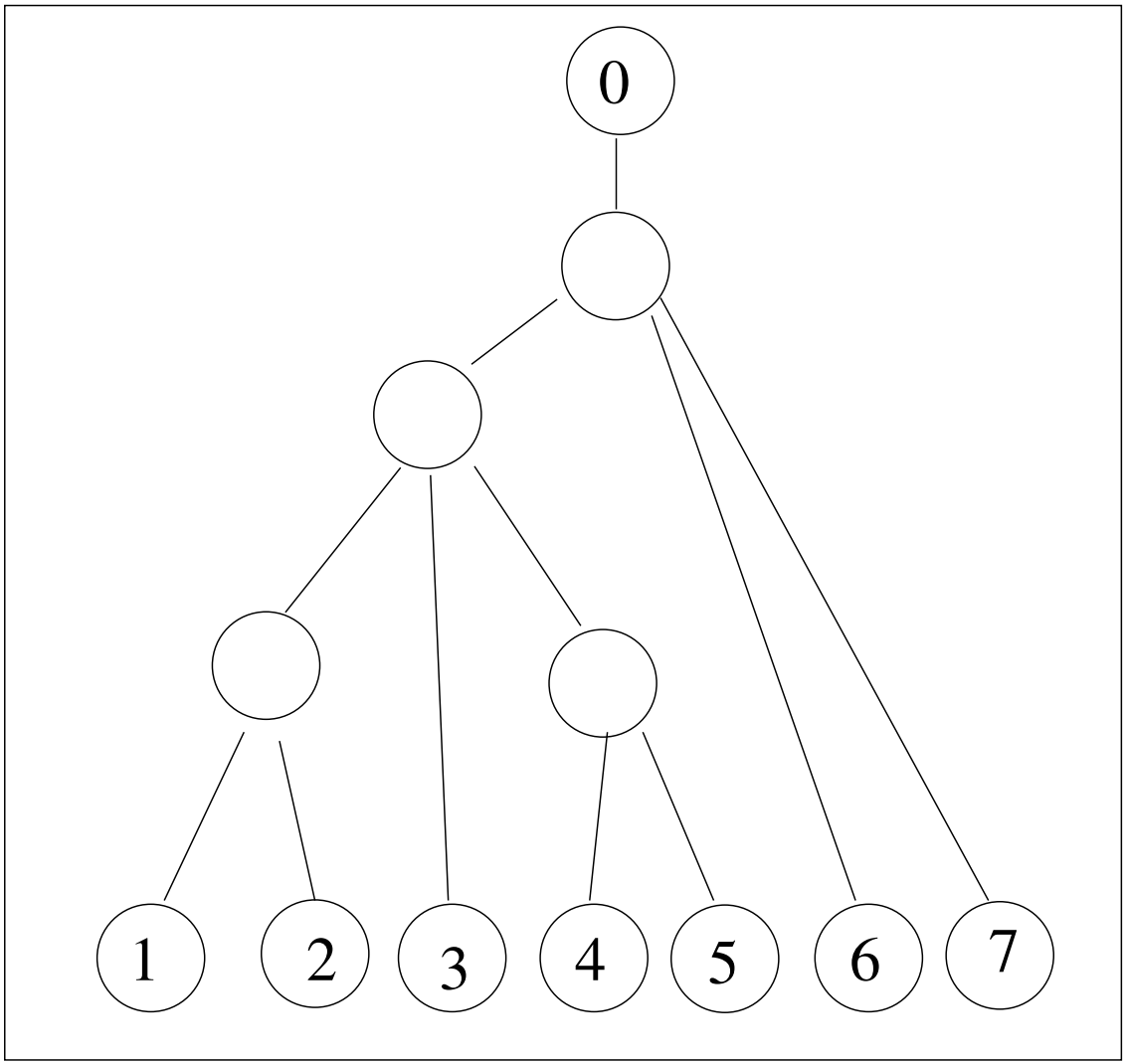
What is a mathematically sound description of these trees?

Each edge makes a partition of the leaves



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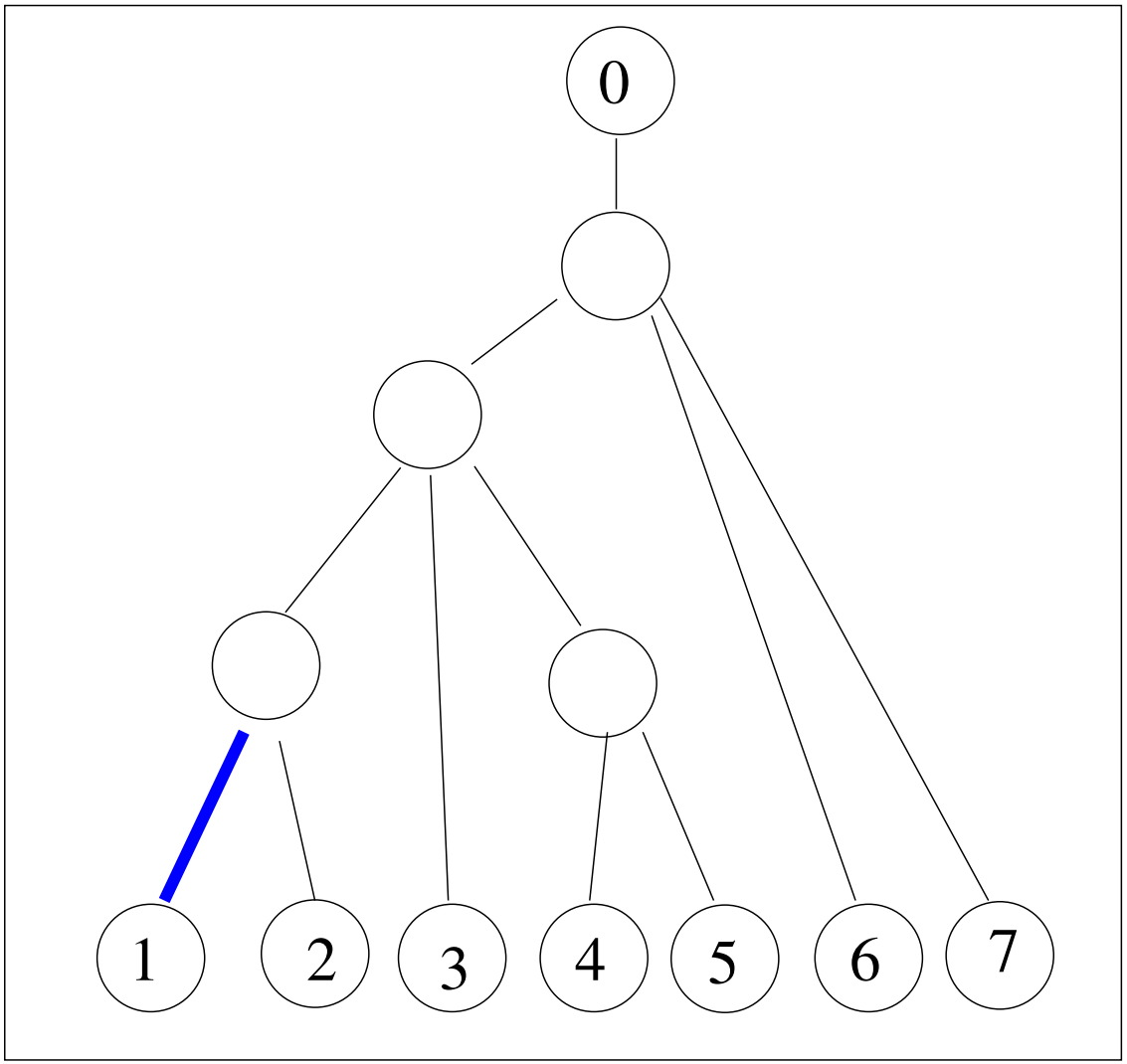

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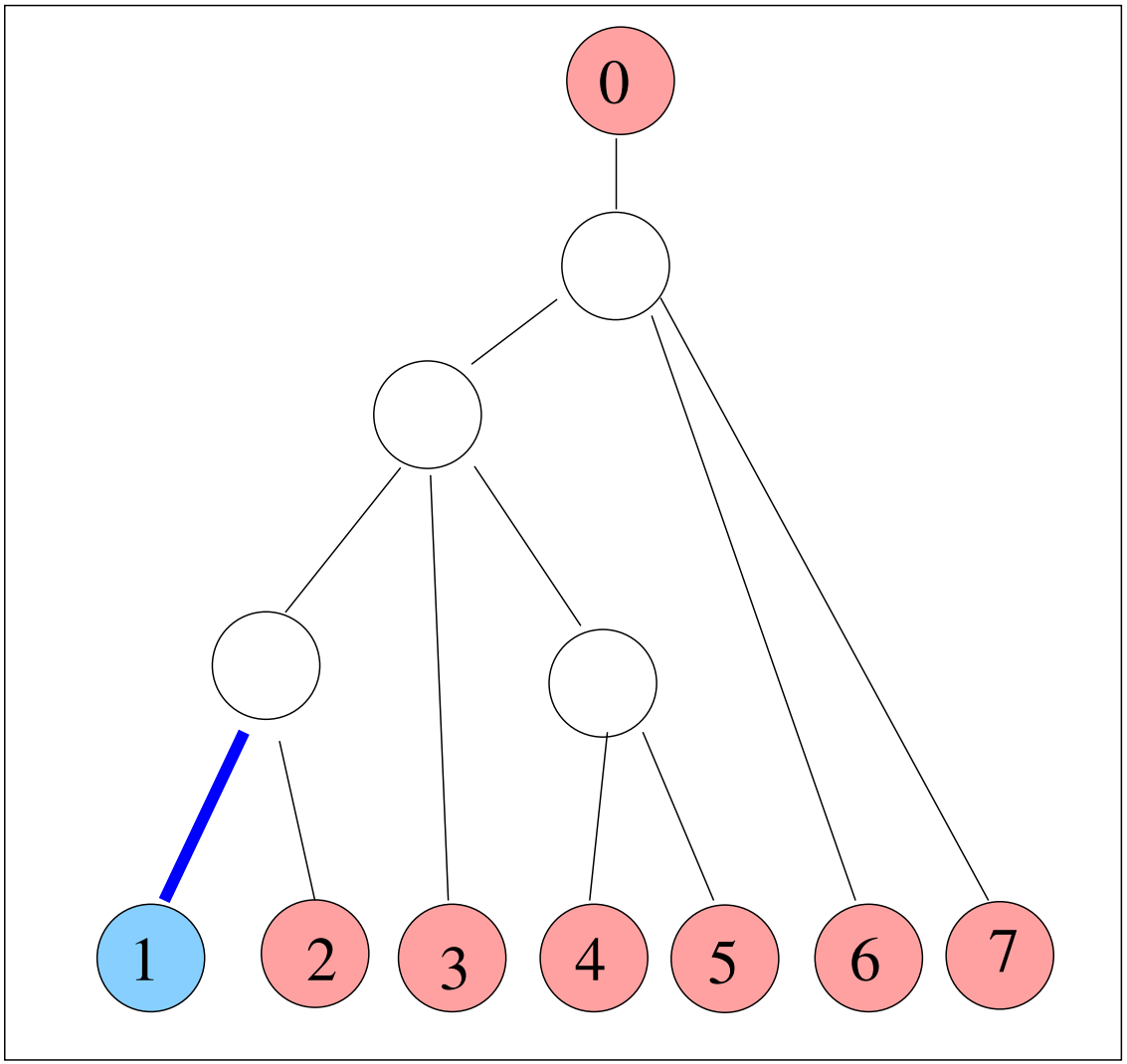

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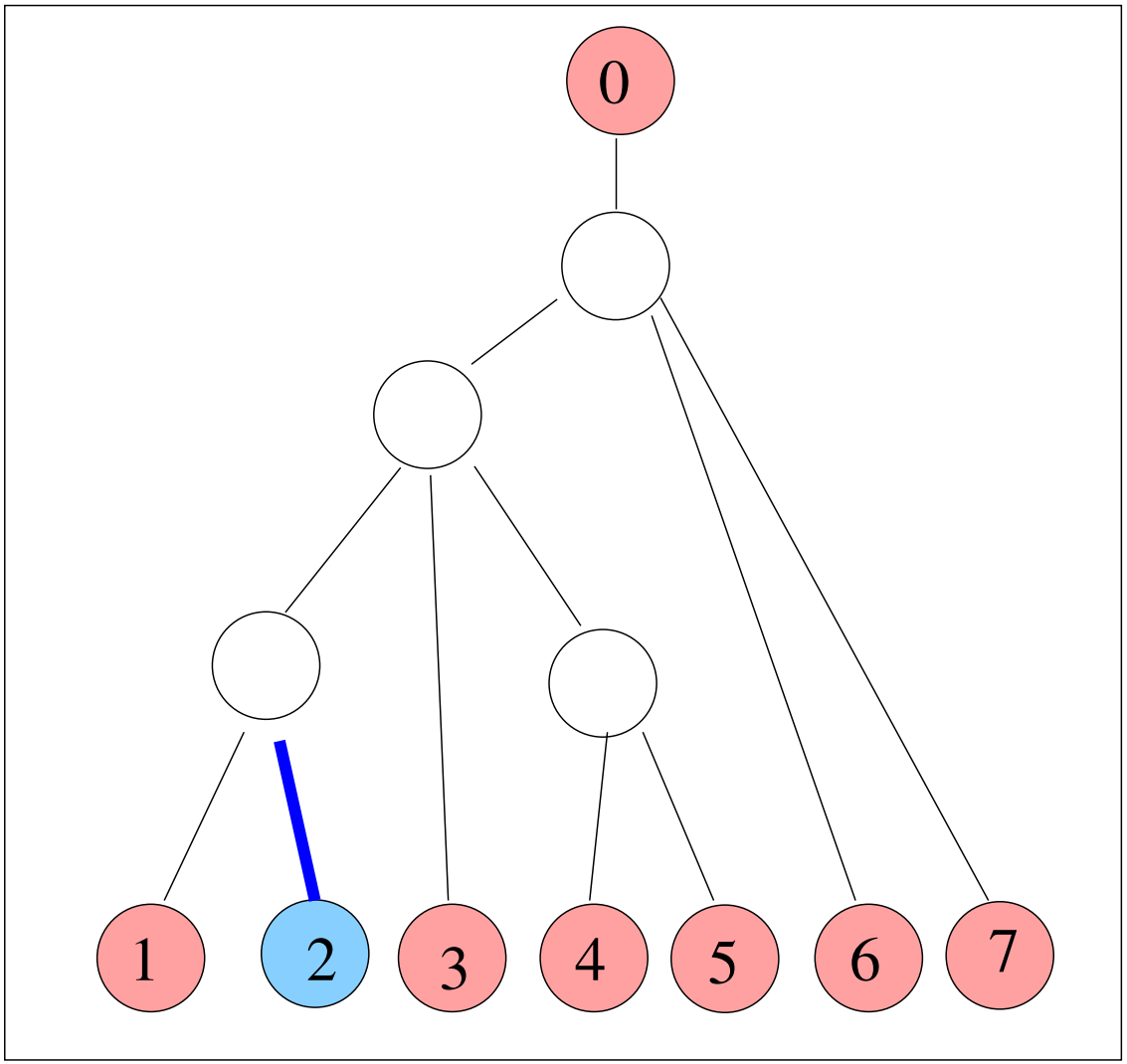

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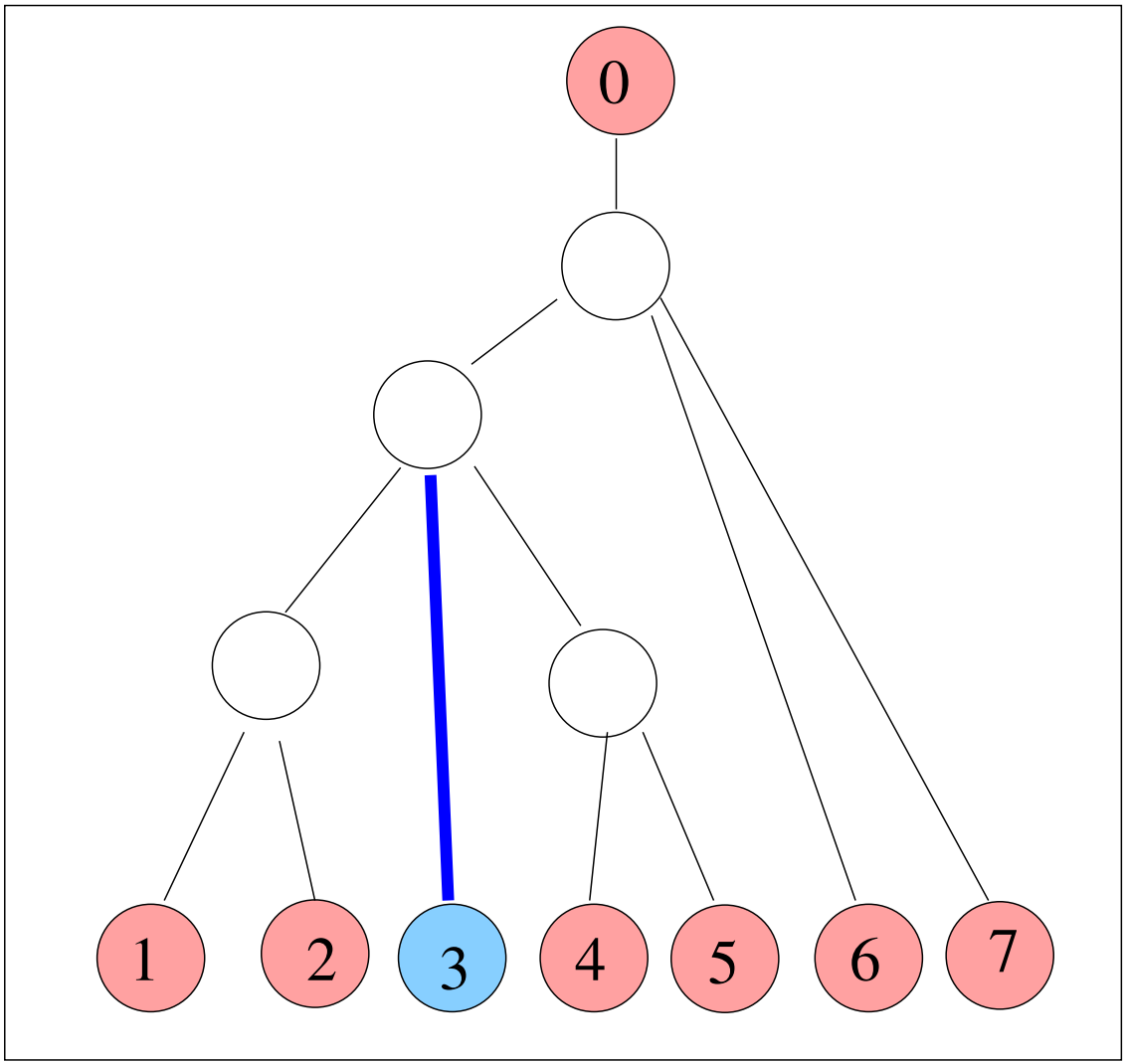

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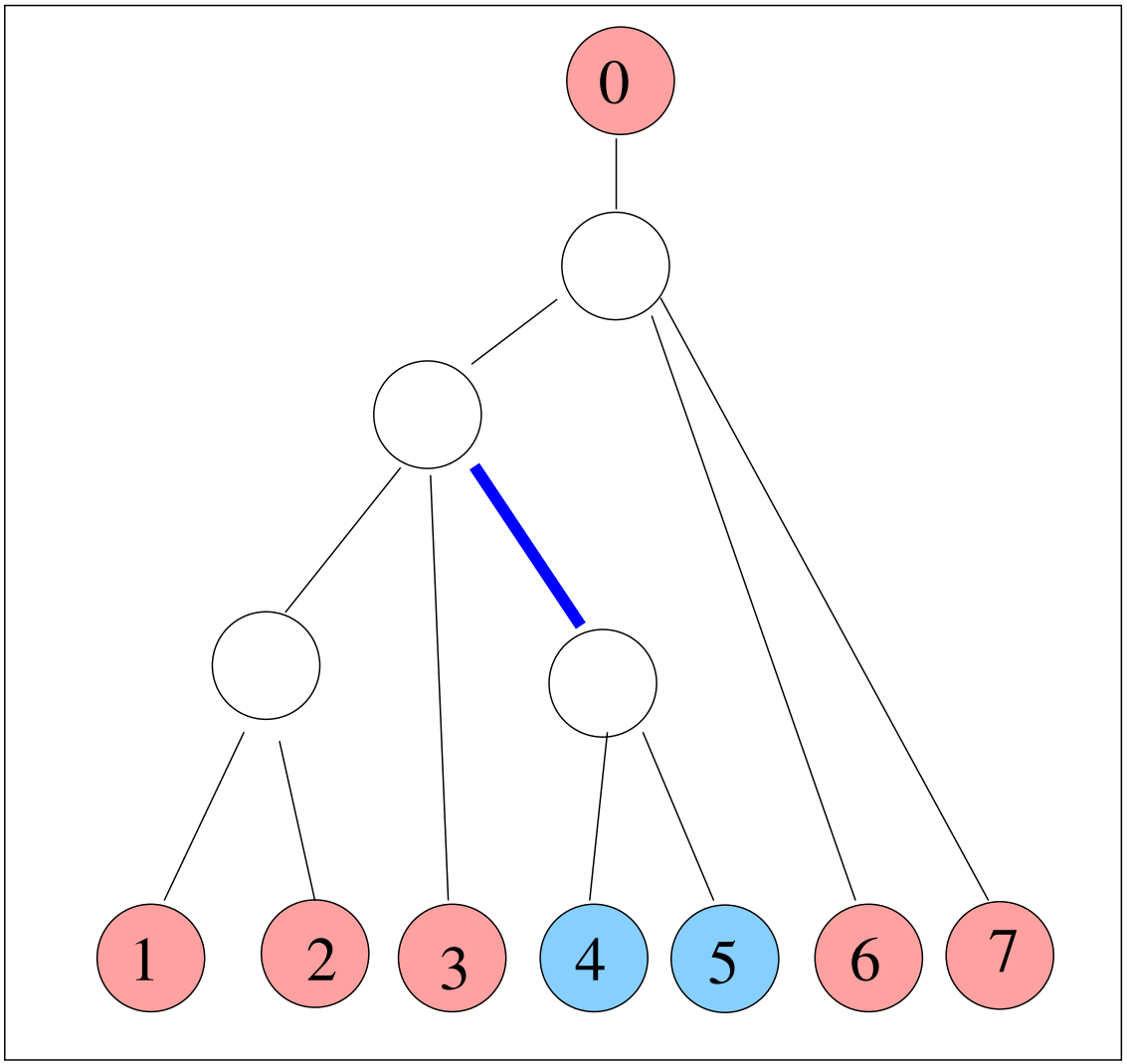

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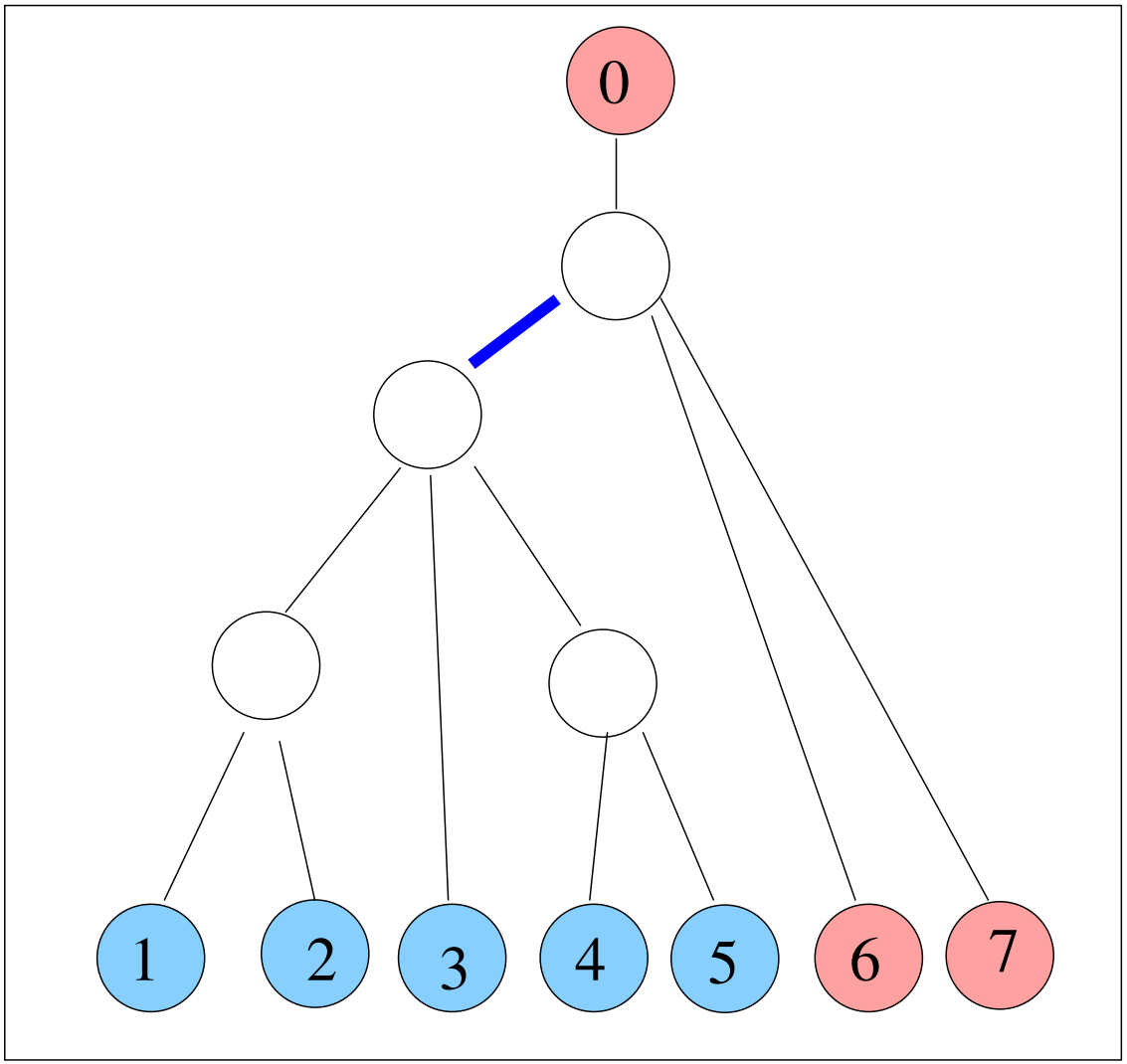
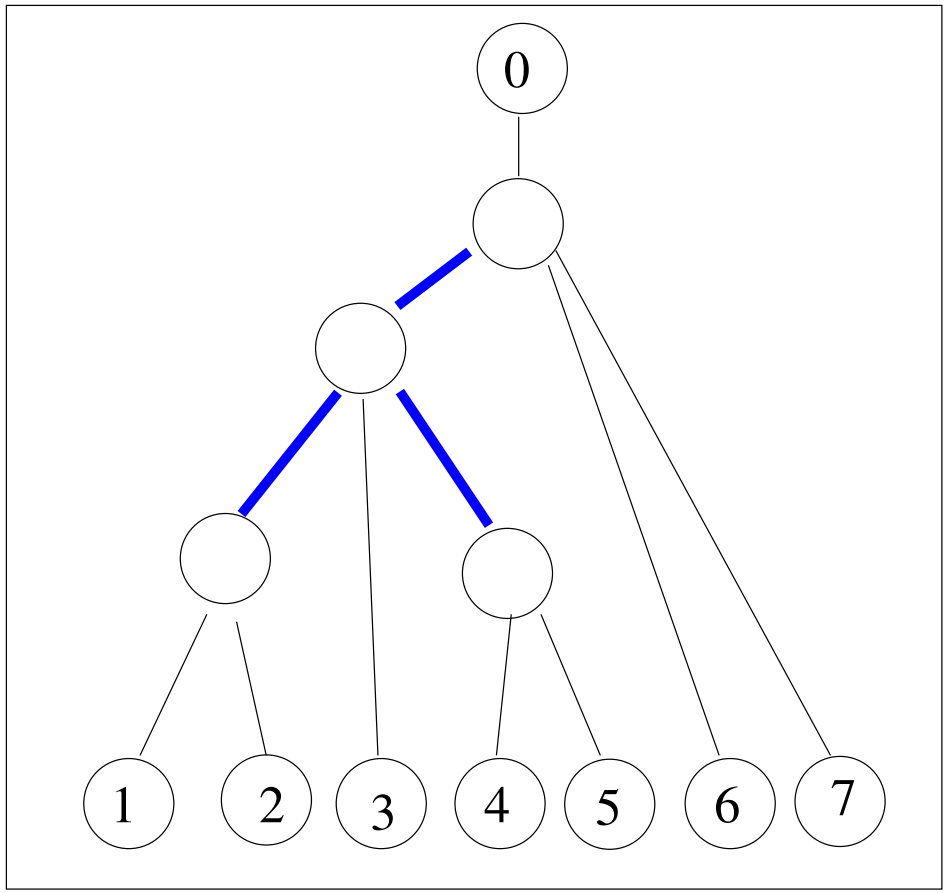


Describing the topology of a weighted tree

- Each edge gives a partition of the leaves.
- Only the *inner edges* (not connected to a leaf) are interesting.



Splits

Definition (Split)

A split of a set A of leaves is a partition $(A|A^C)$ of the leaves with $|A| \geq 2, |A^C| \geq 2$.

For n species there exist $N := 2^n - (n+2)$ possible splits.

Notation: $Split(T)$ denotes the splits of T defined by its inner edges.

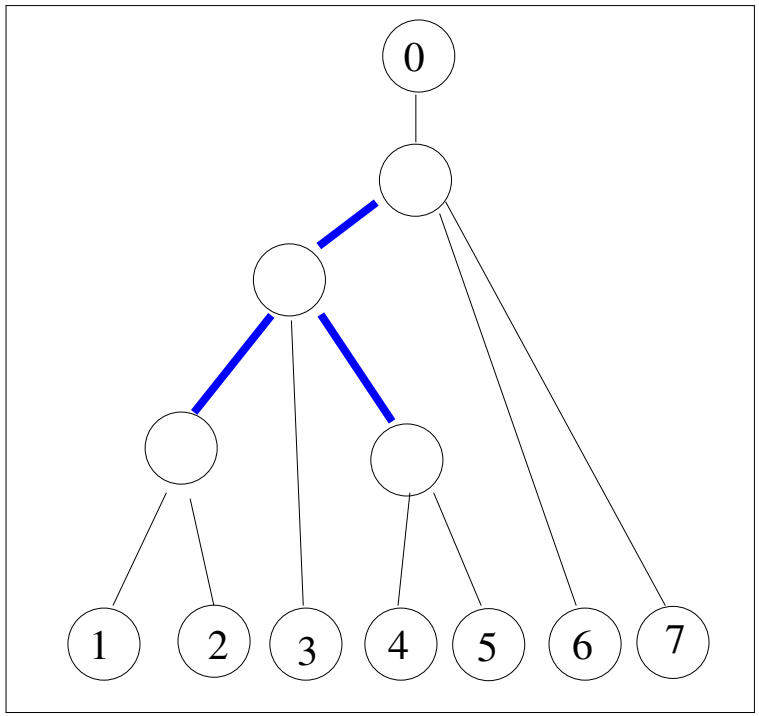
Theorem (Billera, Holmes and Vogtman (2001))

A tree is uniquely characterized by its splits and the weights on them.

Orthants

Definition

Two weighted trees T_1 and T_2 are in the same orthant if they have the same inner edges, i.e., the same topology.



For location theory: Embedding of the tree space

A tree can be represented by a vector in $x \in \mathbb{R}_+^N$ where x_s is length of the inner edge which belongs to split s.

$$\mathcal{T}_n \subseteq \mathbb{R}^N$$

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$$\mathcal{T}_n \subseteq \mathbb{R}^N$$

Question: Does every vector in $\mathbb{R}_+^N$ represent a tree?
No!
E.g.: $(\{1,2\}|\{3,4\})$ and $(\{1,3\}|\{2,4\})$ can not exist in the same tree.

Hence the tree space is only a (small) part of $\mathbb{R}^N$, consisting of many (low-dimensional) orthants.

E.g. $\mathcal{T}_4$

- is embedded in $\mathbb{R}^{10}$,
- consisting of a union of $\mathbb{R}^3$, $\mathbb{R}^2$ and $\mathbb{R}$-orthants.
- All orthants are connected through 0.

Contents

Case 1: Distance between trees in the same orthant

Definition

Let T_a, T_b be two trees in the same orthant. Then

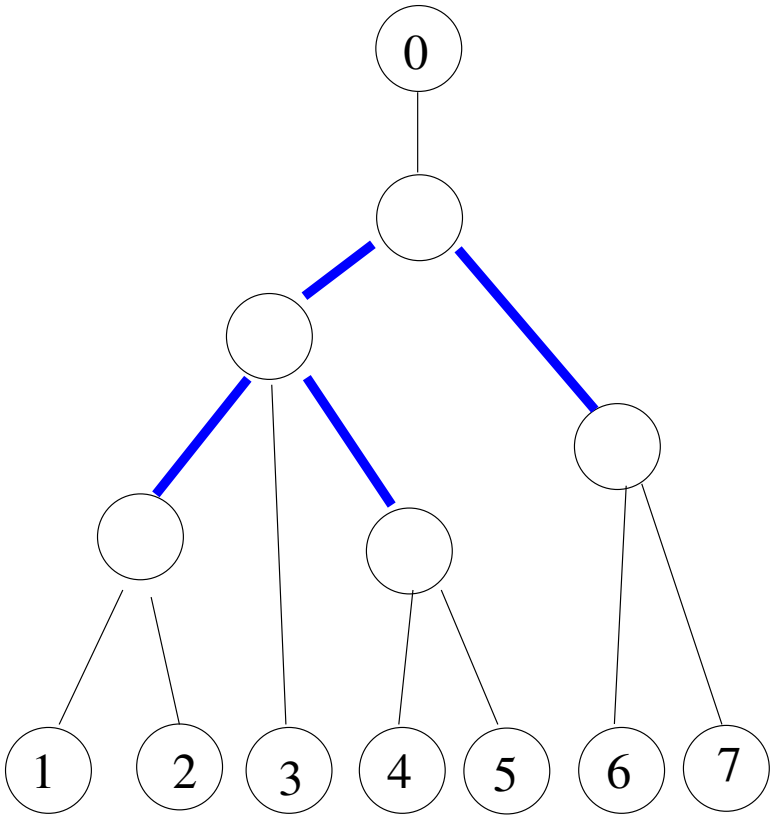
$$d(T_a, T_b) = \|T_a - T_b\|_2$$

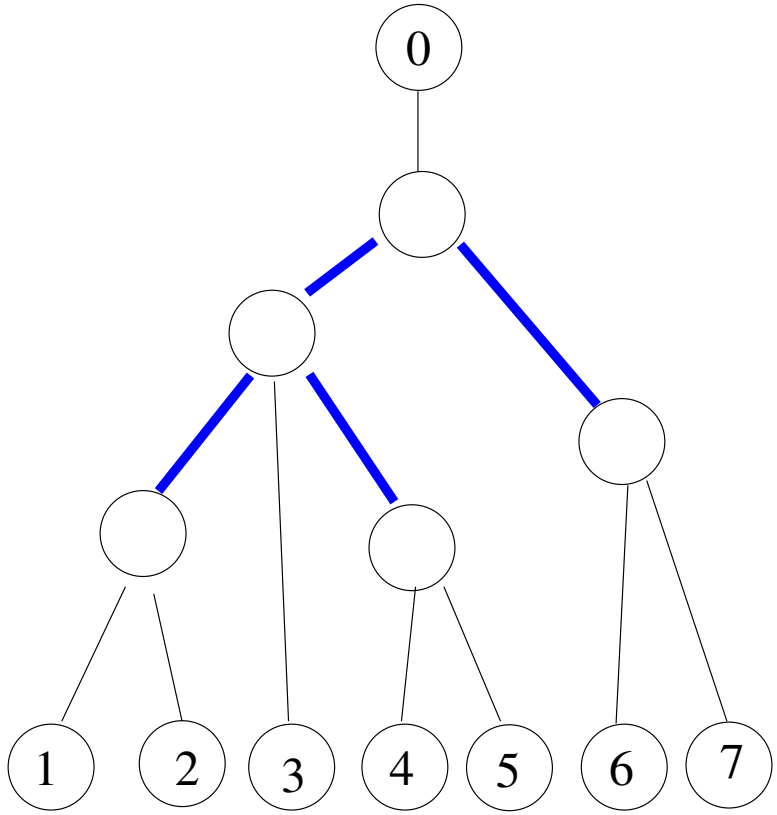
Case 2: Distance between trees in different orthants?

Trick: Edges with length zero make a tree belonging to several orthants!

Consequence: Paths in the tree space connecting different orthants.

Understanding topology and orthants





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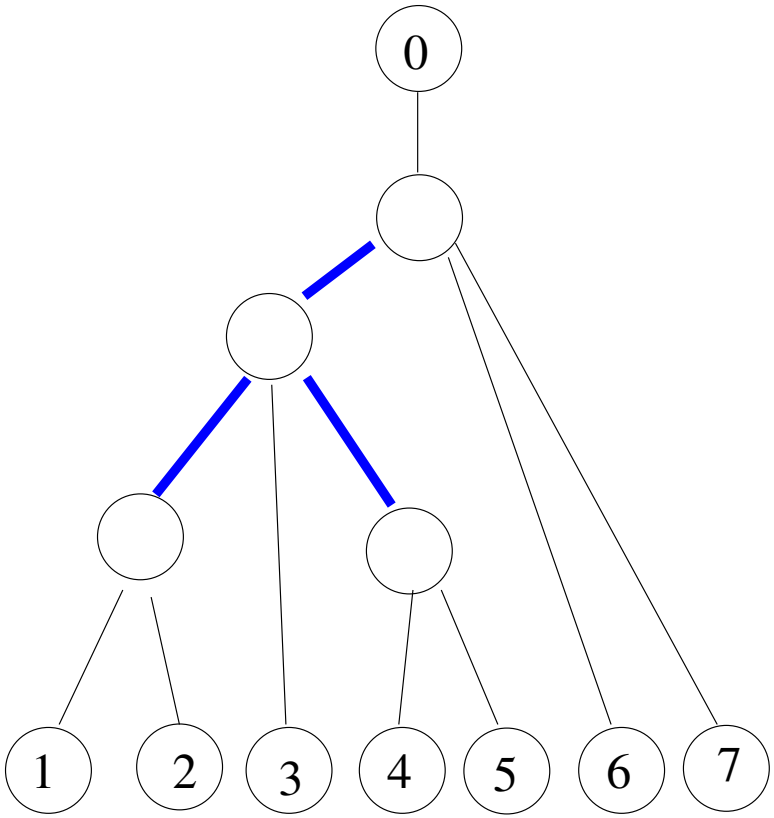

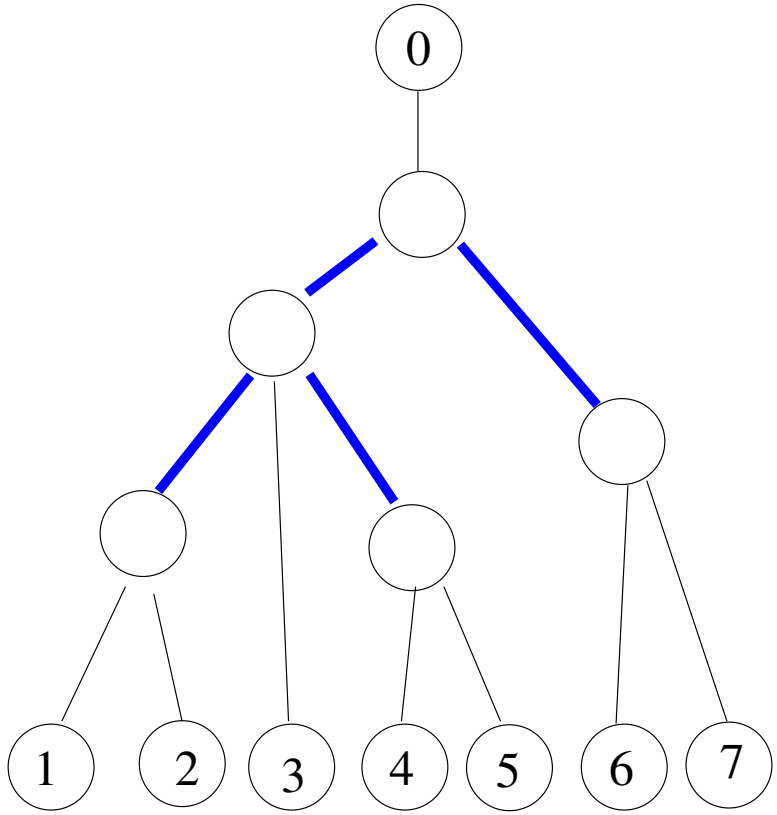

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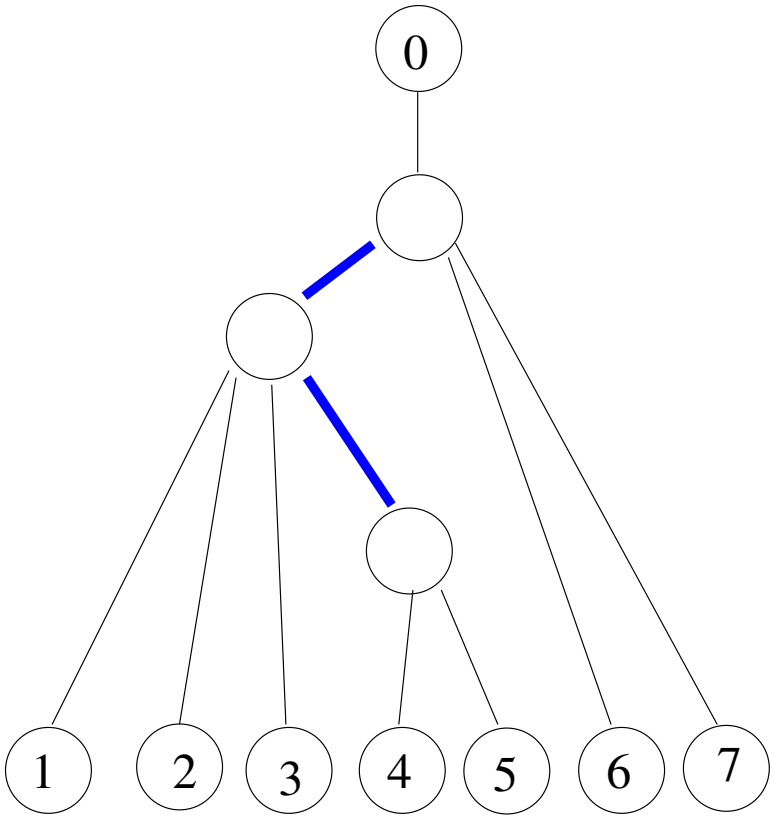

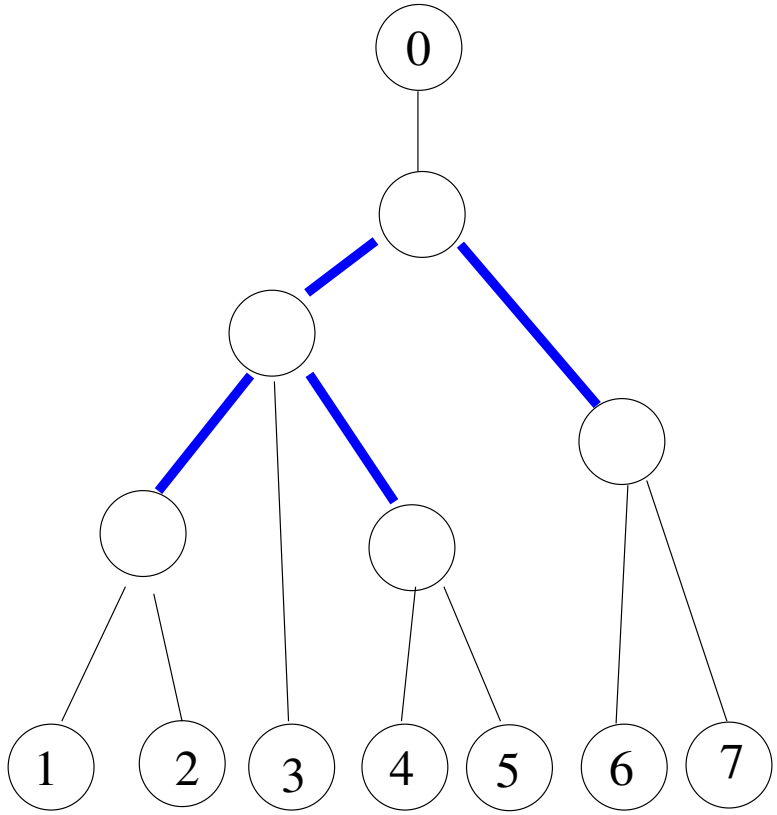

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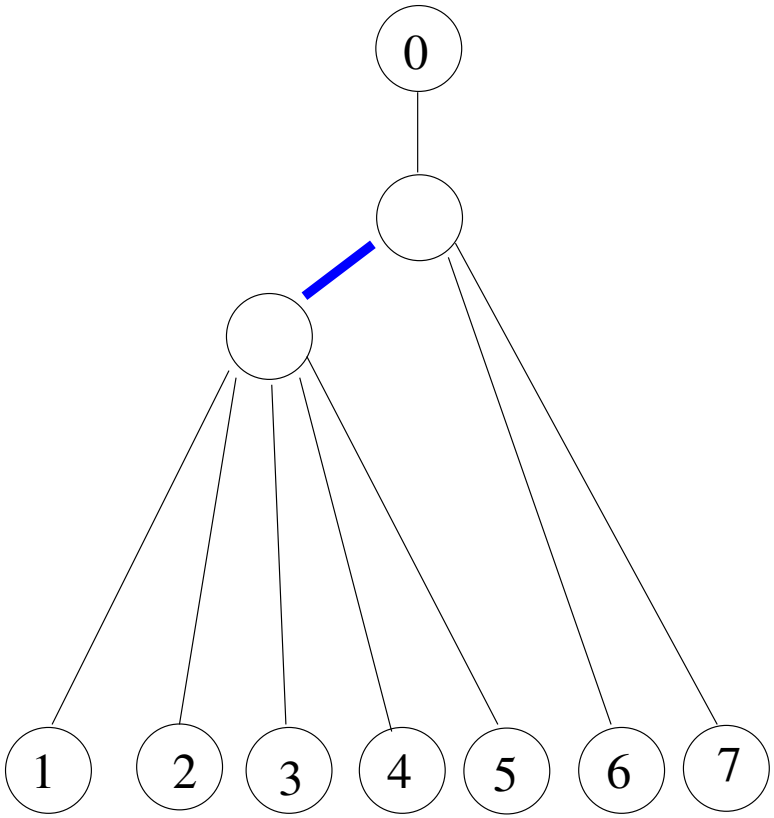

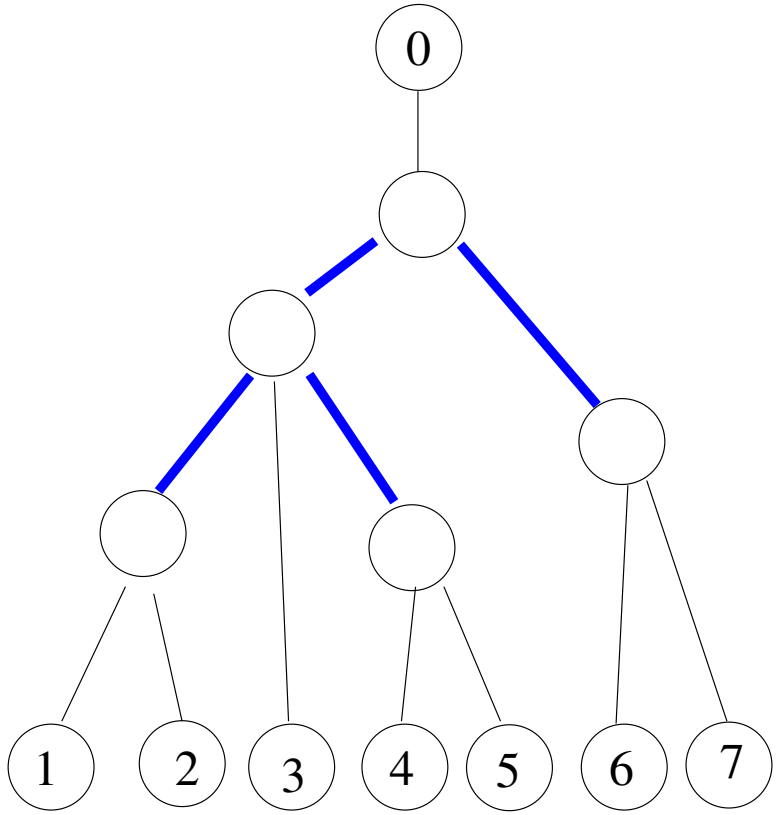

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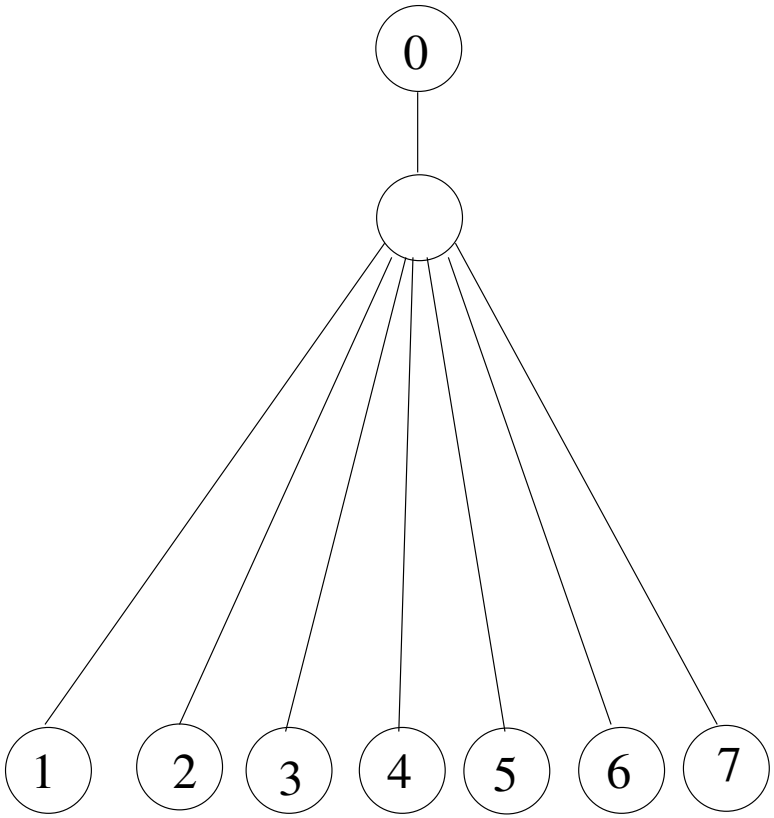

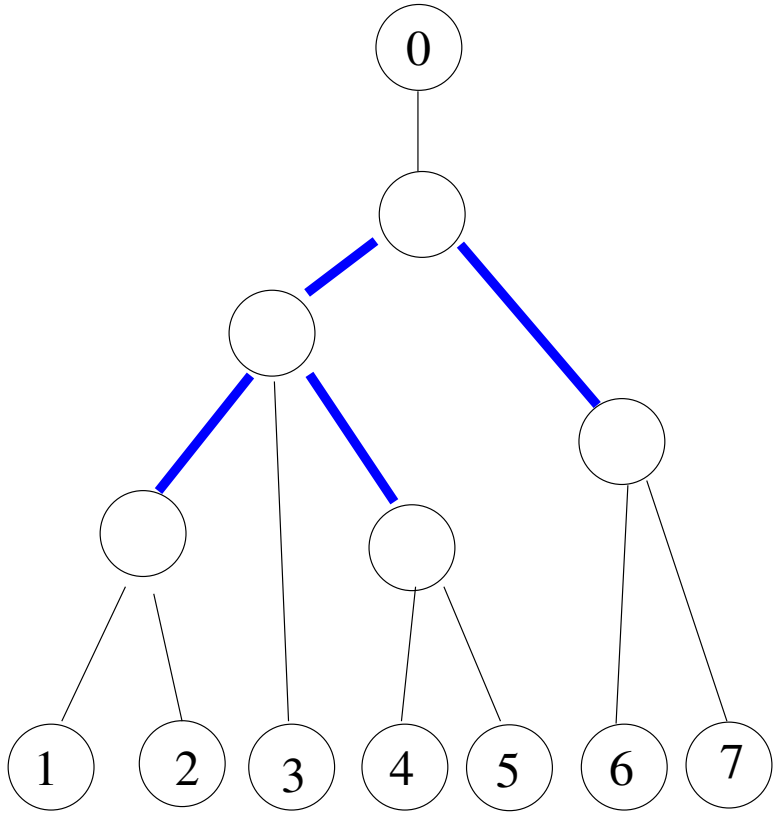

The geodesic distance

Definition

A sequence of trees $(T_1, T_2, \ldots, T_k)$ is a *path* in the tree space from T_1 to T_k if for each $i = 1, \ldots, k-1$ there exists an orthant $\mathcal{O}_i$ with $T_i, T_i + 1 \in \mathcal{O}_i$.

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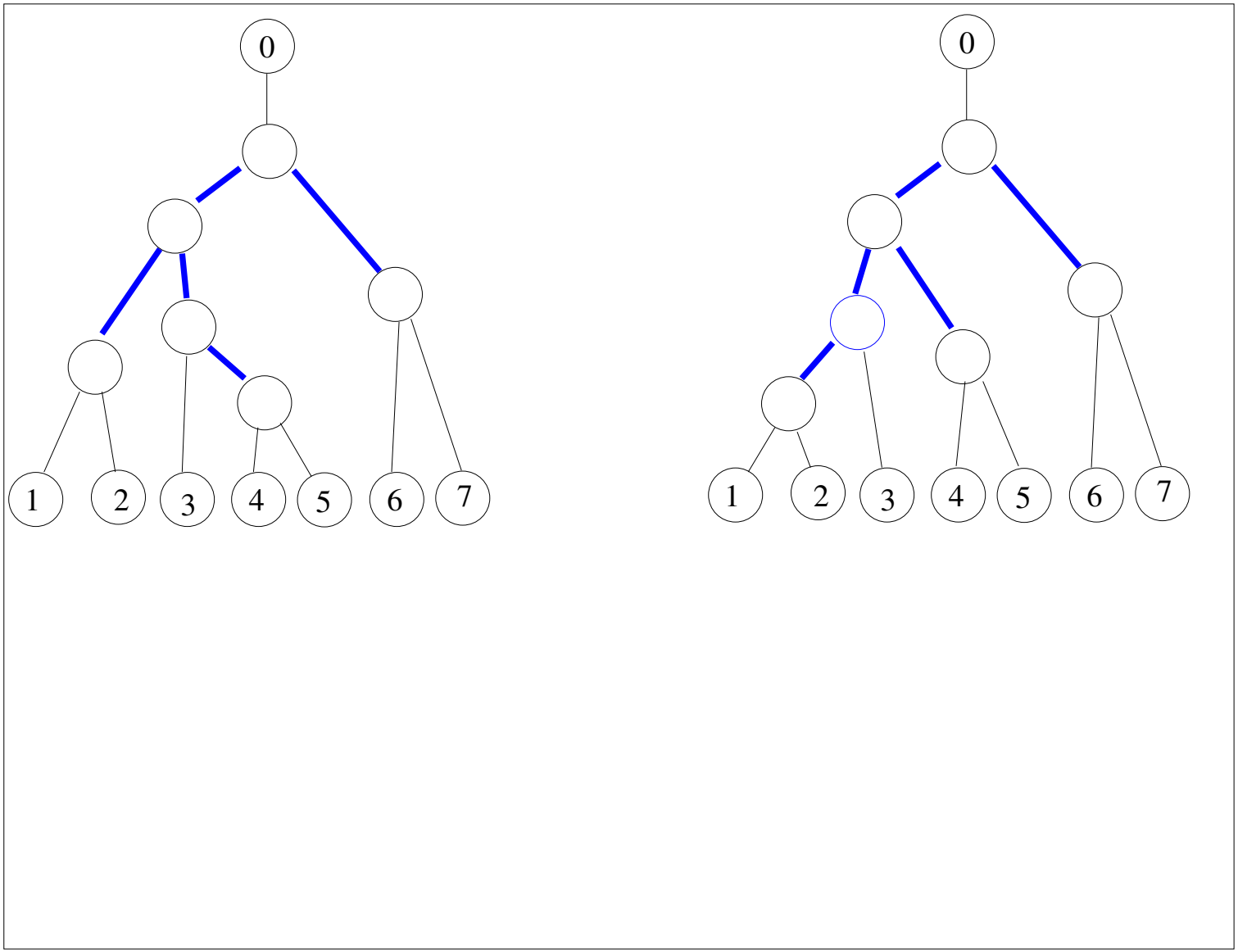
We finally get:

Definition (Geodesic distance)

$$d(T_a, T_b) = \inf \left\{ \sum_{i=1}^{k} \| T_i - T_{i+1} \|_2 : (T_1, \ldots, T_k) \text{ is a path from } T_a \text{ to } T_b \right\}$$

Existence guaranteed since the *star tree* belongs to all orthants.

Example



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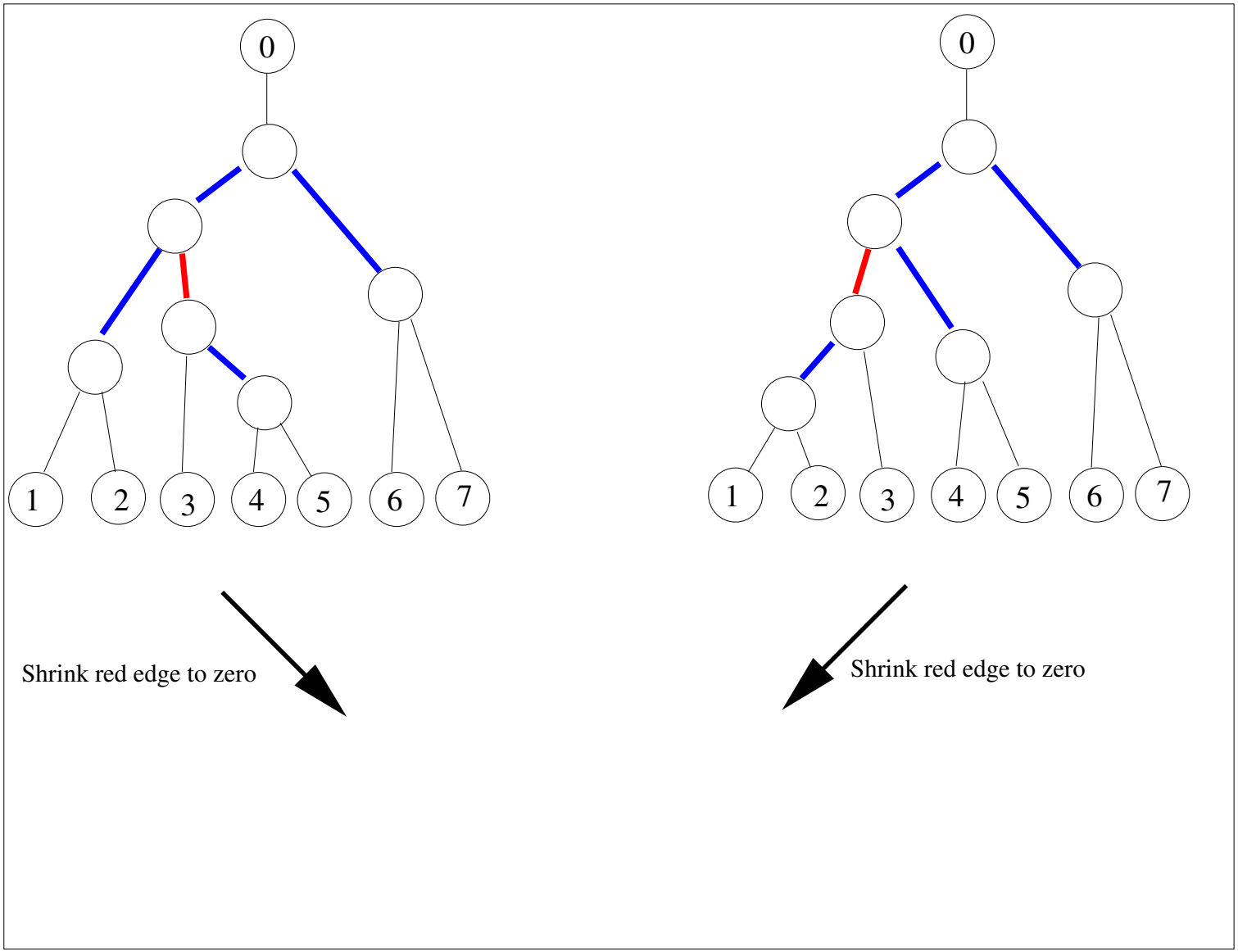
0
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Shrink red edge to zero
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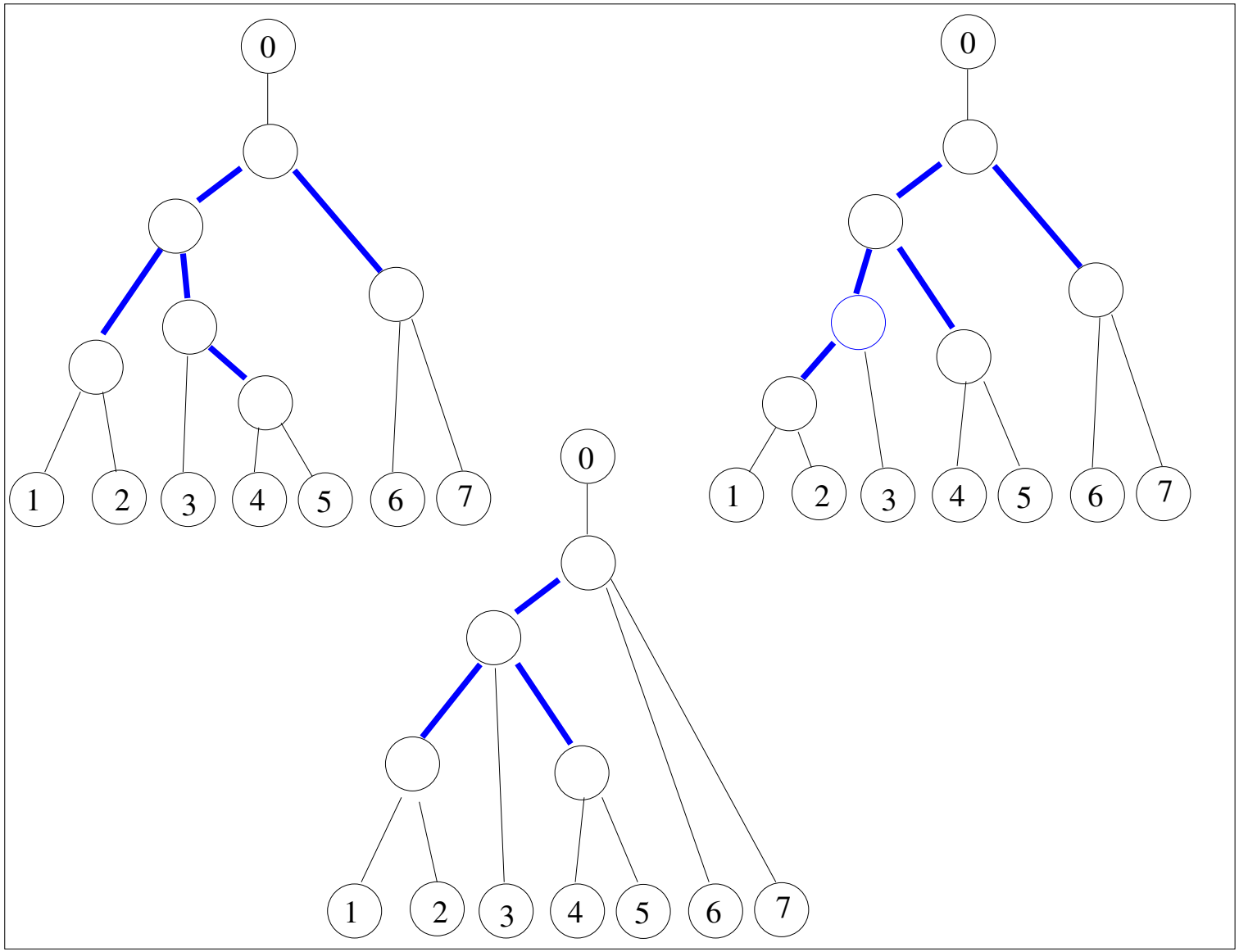

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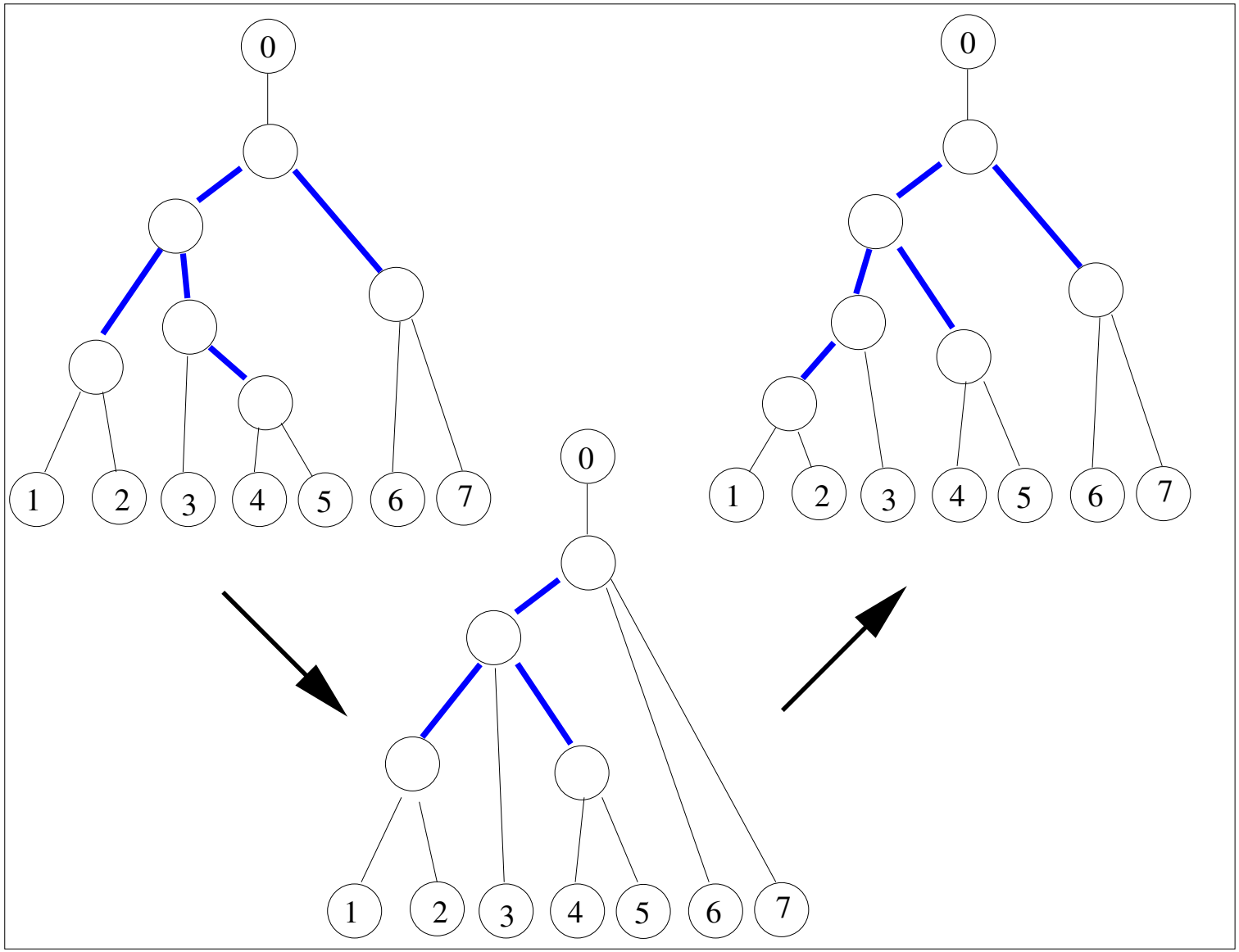

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Theorem (Billera, Holmes and Vogtman (2001))

The minimal path between two trees always exists and is unique.

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Theorem (Owen (2011))

The geodesic distance can be computed in polynomial time.

Contents

A median location problem in the tree space

Given a set of phylogenetic trees, find one tree which minimizes the sum of geodesic distances to these trees.

We hope:

This is a good approximation of the tree we want.

Idea

In every orthant the geodesic distance reduces to the Euclidean distance.

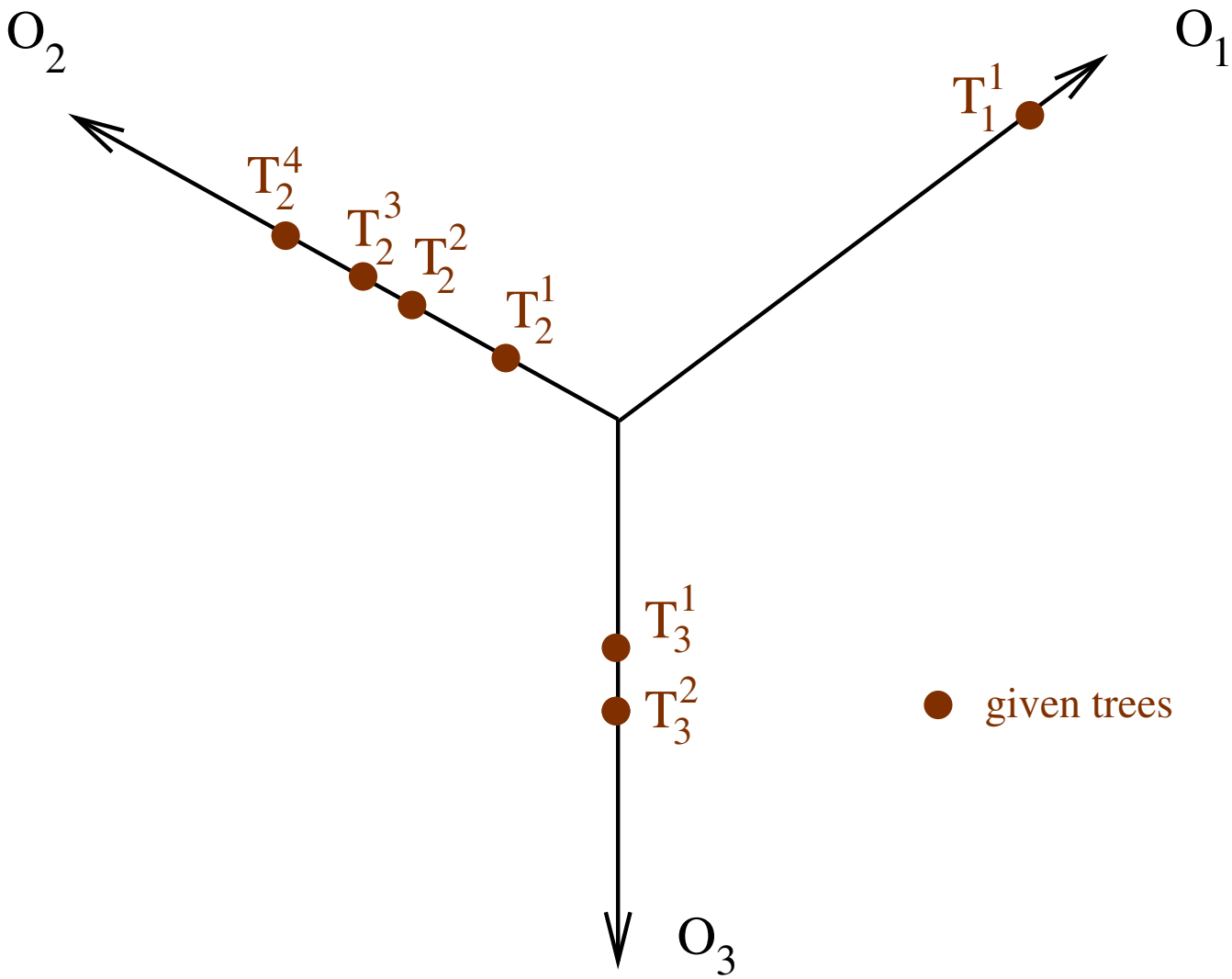
Can we use this?

Contents

Transformation to Euclidean location problems

- Problems in $\mathcal{T}_3$
- Problems in $\mathcal{T}_4$ if existing trees are in maximal two orthants
- Problems in $\mathcal{T}_n$ if existing trees are in maximal two orthants with special structure
- Problems in $\mathcal{T}_n$ if all existing trees are in completely incompatible orthants

Median Location problems in $\mathcal{T}_3$ (4 orthants, 3 splits)



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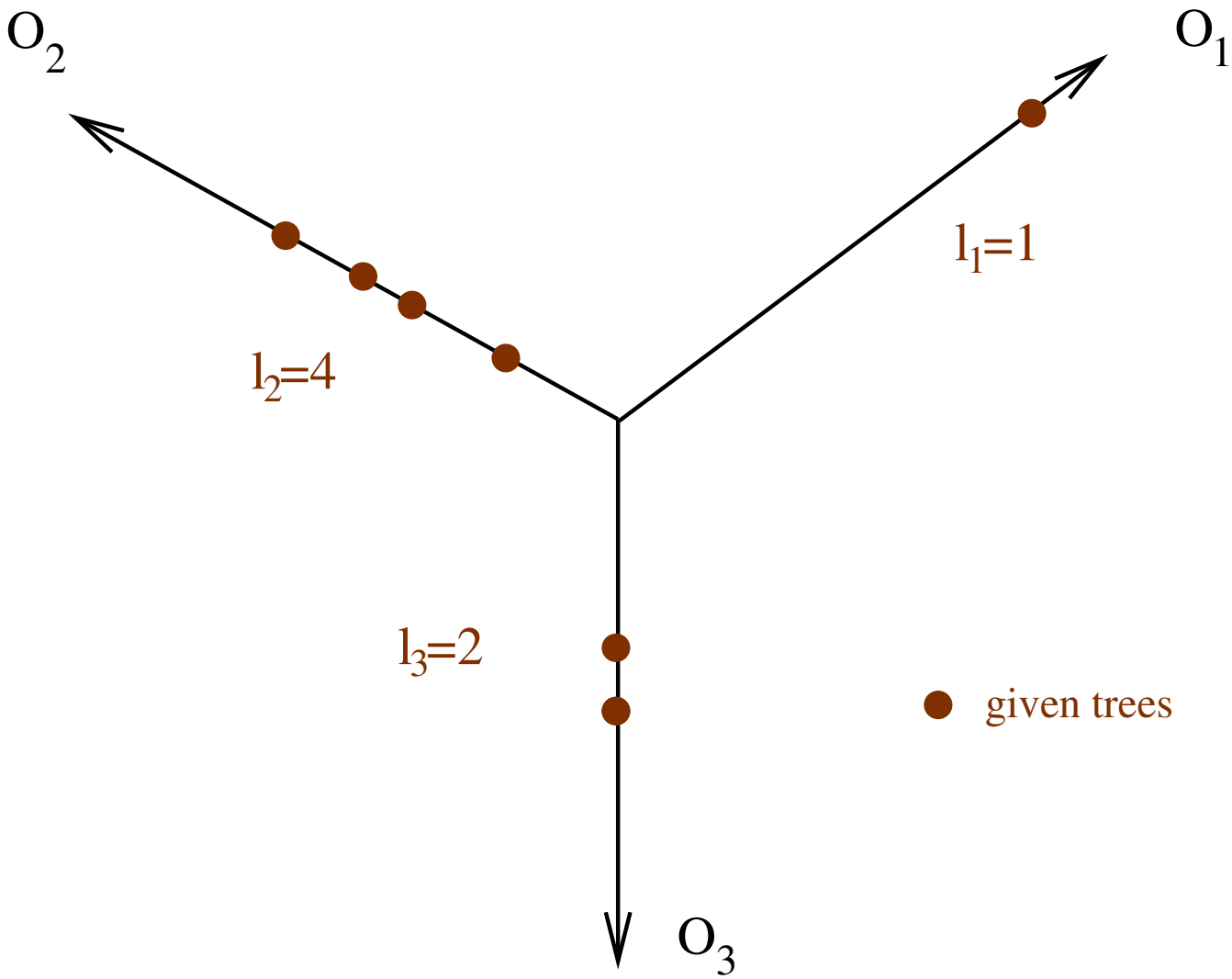

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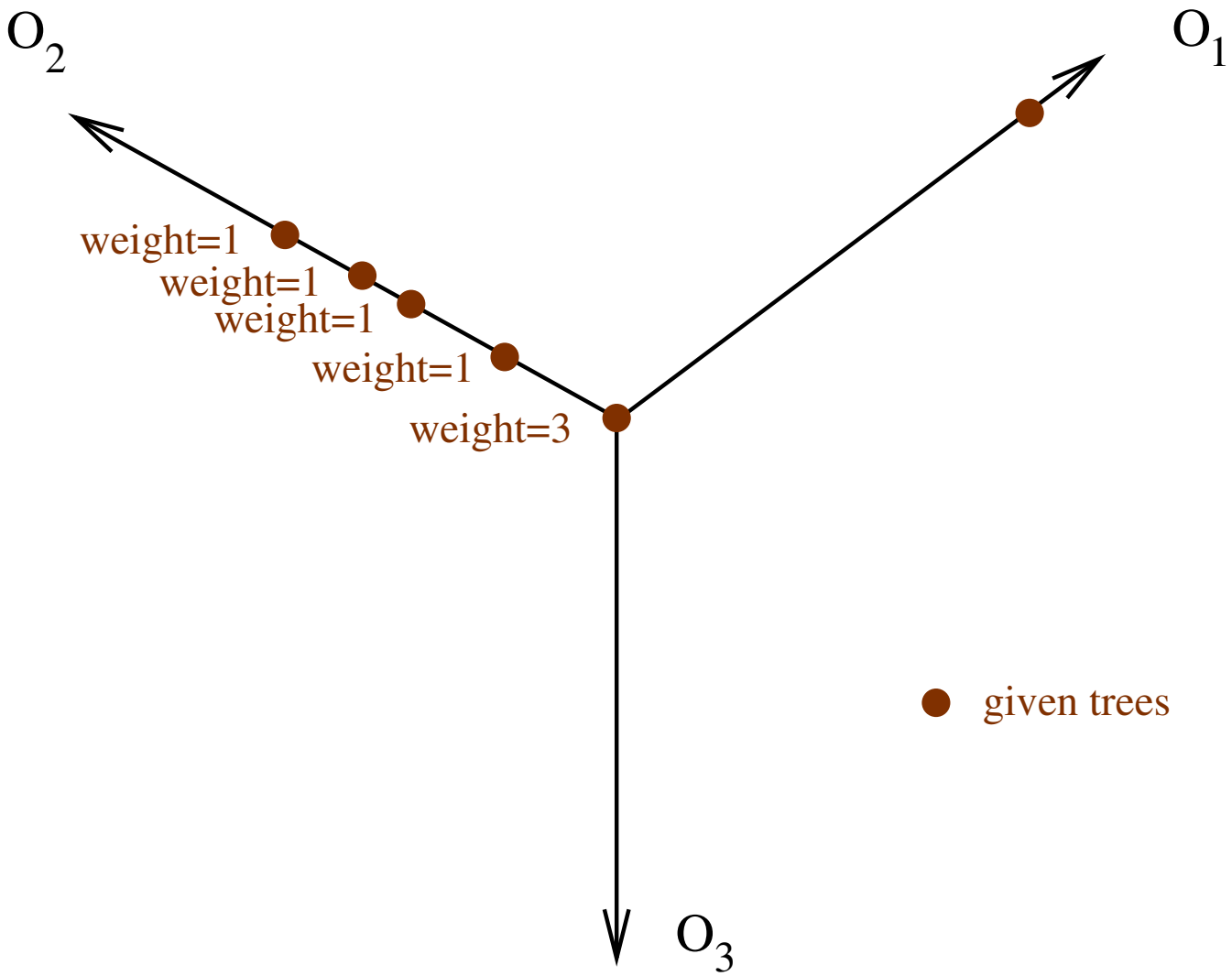

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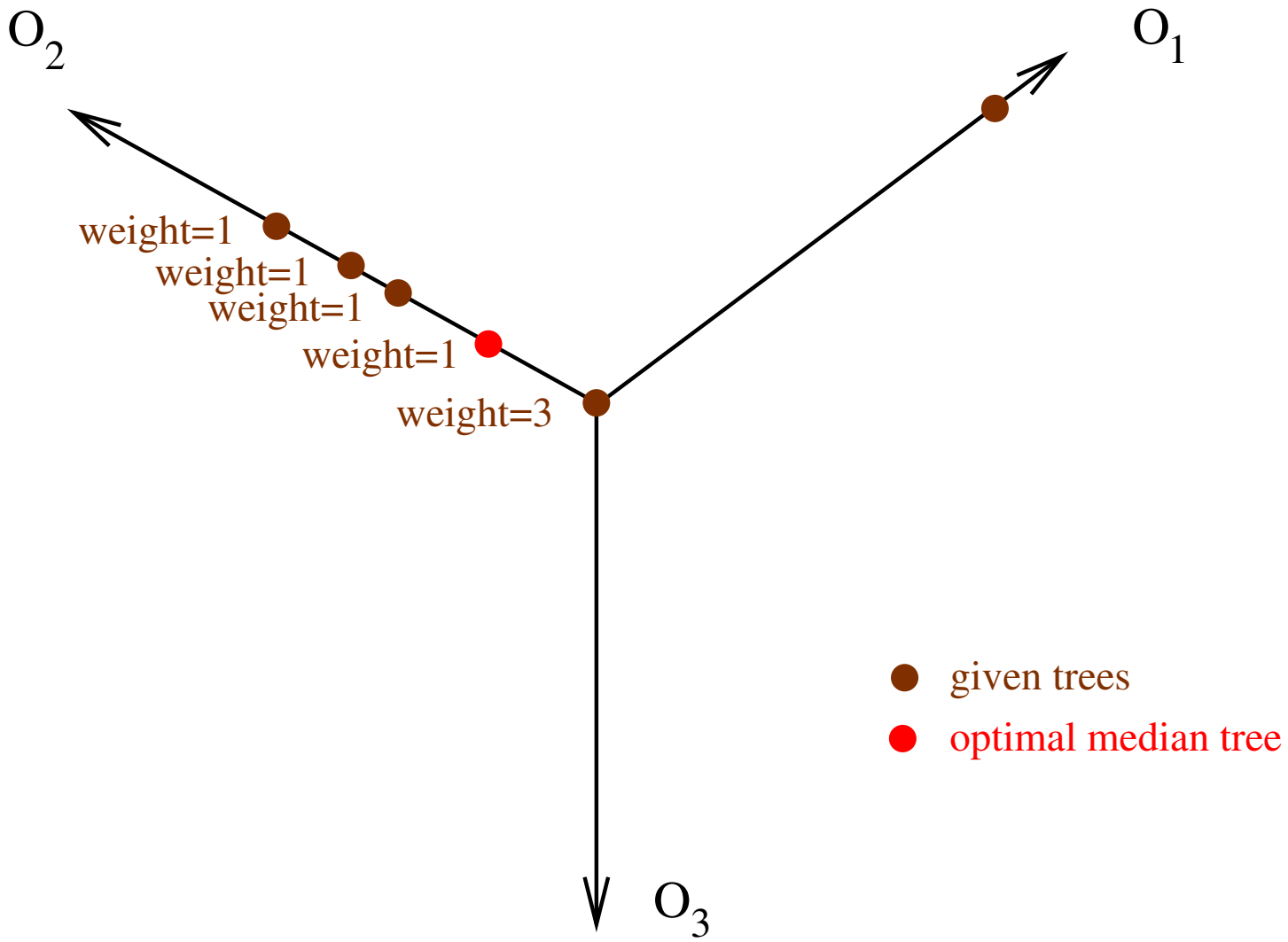


Transformation to Euclidean location problems

- Problems in $\mathcal{T}_3$
- Problems in $\mathcal{T}_4$ if existing trees are in maximal two orthants
- Problems in $\mathcal{T}_n$ if existing trees are in maximal two orthants with special structure
- Problems in $\mathcal{T}_n$ if all existing trees are in completely incompatible orthants

Transformation to Euclidean location problems

- Problems in $\mathcal{T}_3$
  $\rightarrow$ Network median location problem in small tree
- Problems in $\mathcal{T}_4$ if existing trees are in maximal two orthants
- Problems in $\mathcal{T}_n$ if existing trees are in maximal two orthants with special structure
- Problems in $\mathcal{T}_n$ if all existing trees are in completely incompatible orthants

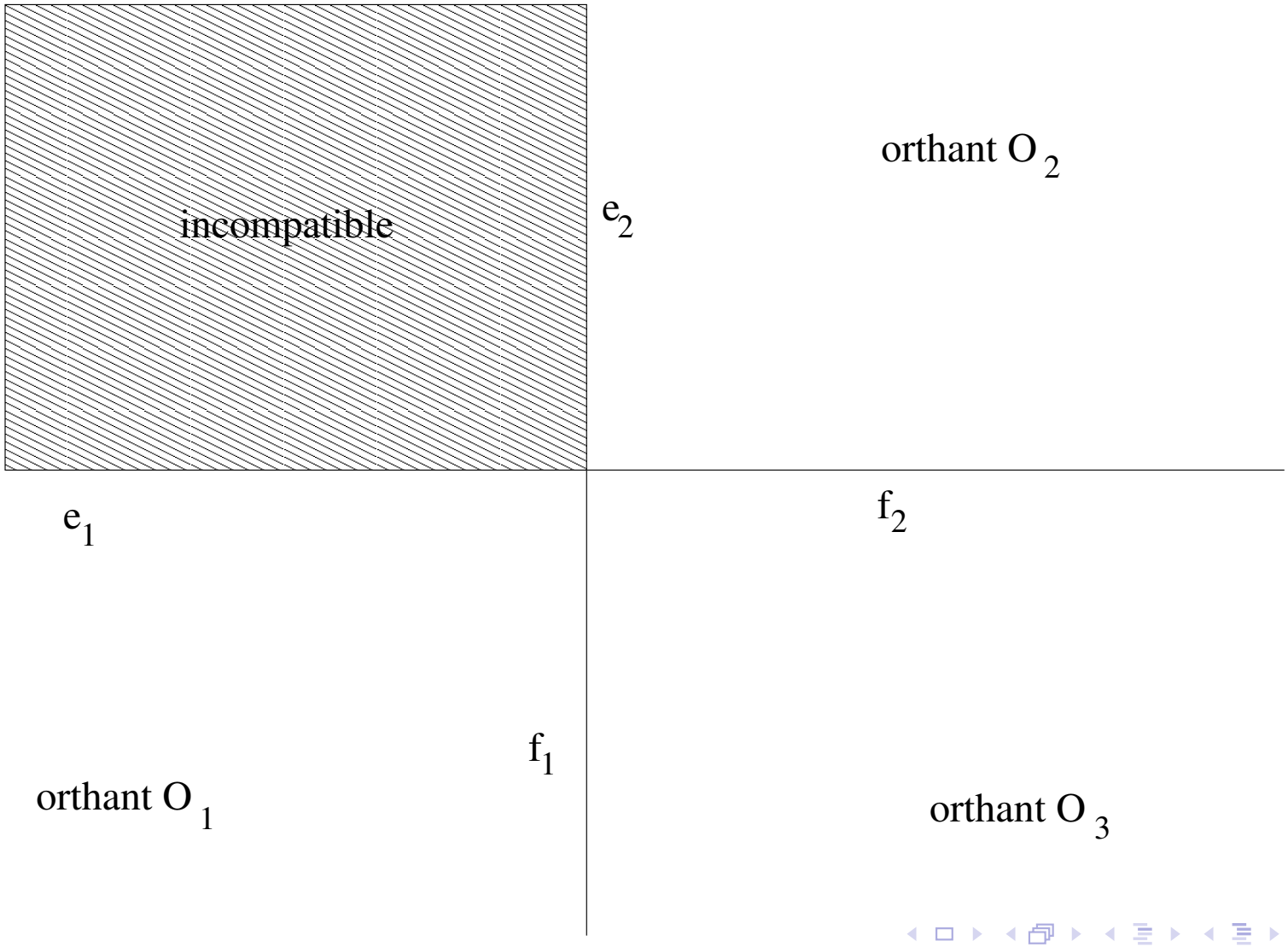
$\mathcal{T}_4$ with trees in maximal two orthants (26 orthants, 10 splits)

1. One common split: neighboring orthants
2. One pair of compatible splits
3. Completely incompatible orthants

Theorem

All three cases can be modeled and solved as planar location problems.

$\mathcal{T}_4$ with given trees in two orthants with exactly one compatible pair of splits



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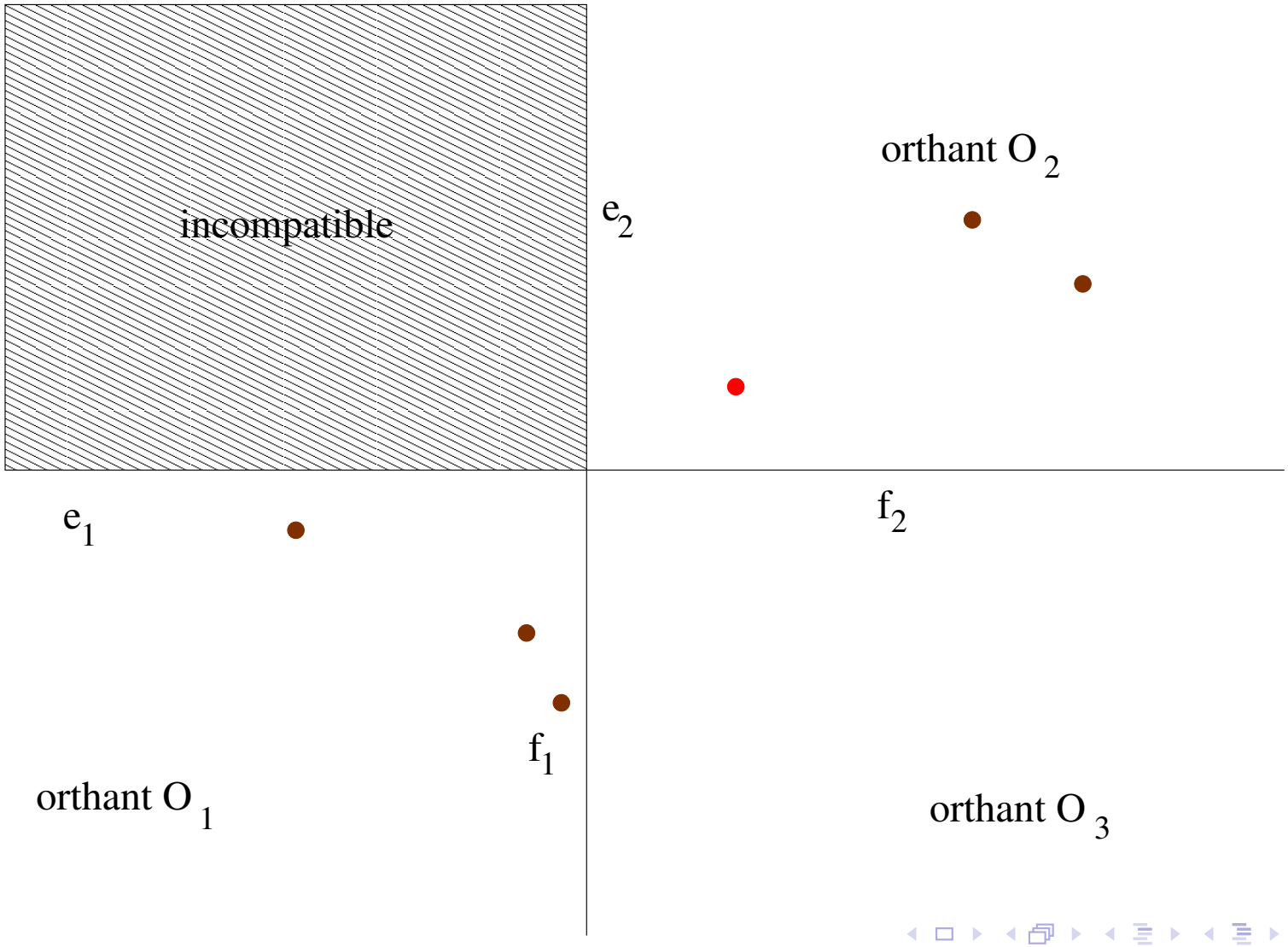

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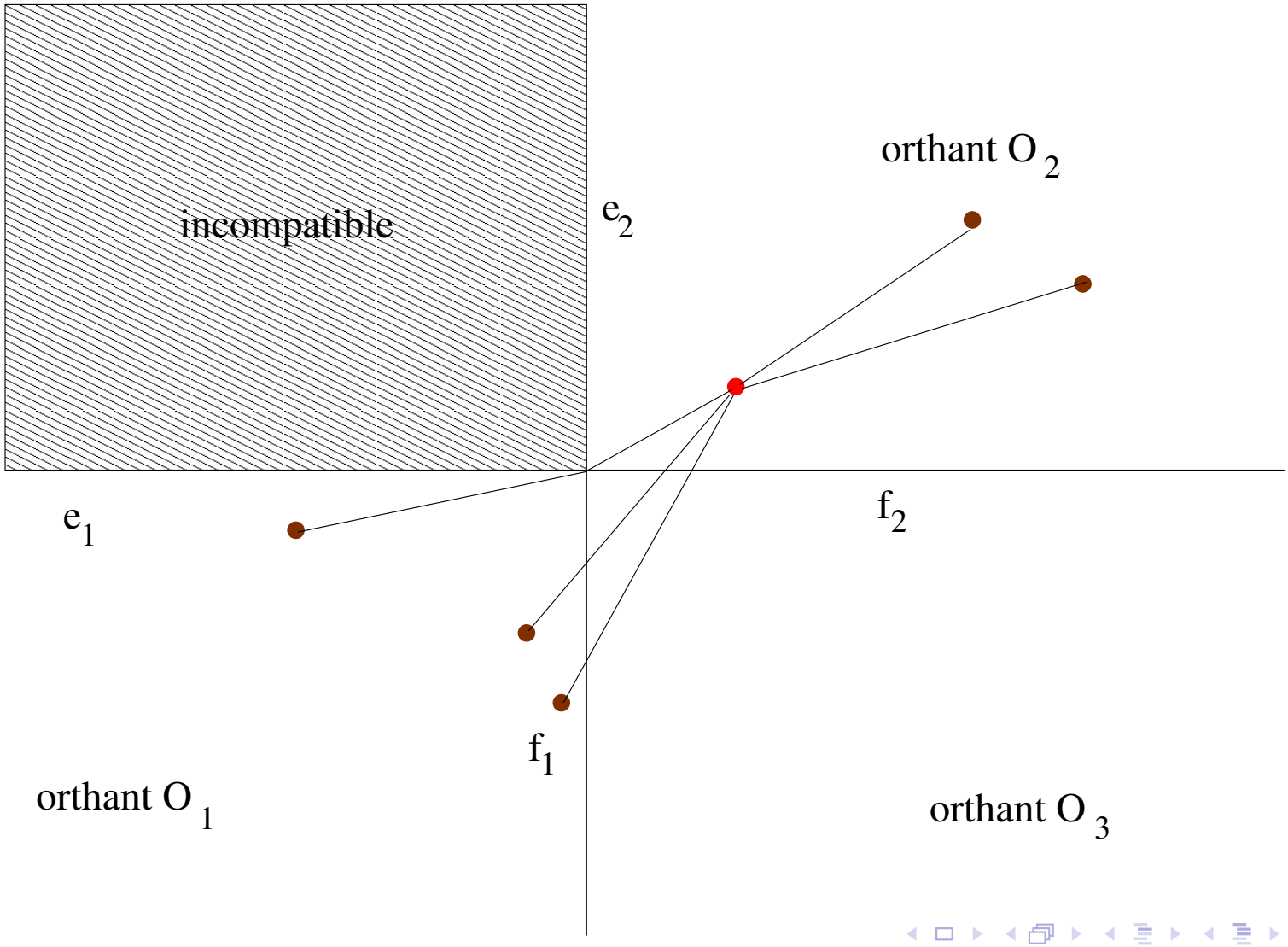

Transformation to Euclidean location problems

- Problems in $\mathcal{T}_3$
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- Problems in $\mathcal{T}_4$ if existing trees are in maximal two orthants
- Problems in $\mathcal{T}_n$ if existing trees are in maximal two orthants with special structure
- Problems in $\mathcal{T}_n$ if all existing trees are in completely incompatible orthants

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- Problems in $\mathcal{T}_3$
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- Problems in $\mathcal{T}_4$ if existing trees are in maximal two orthants
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- Problems in $\mathcal{T}_n$ if existing trees are in maximal two orthants with special structure
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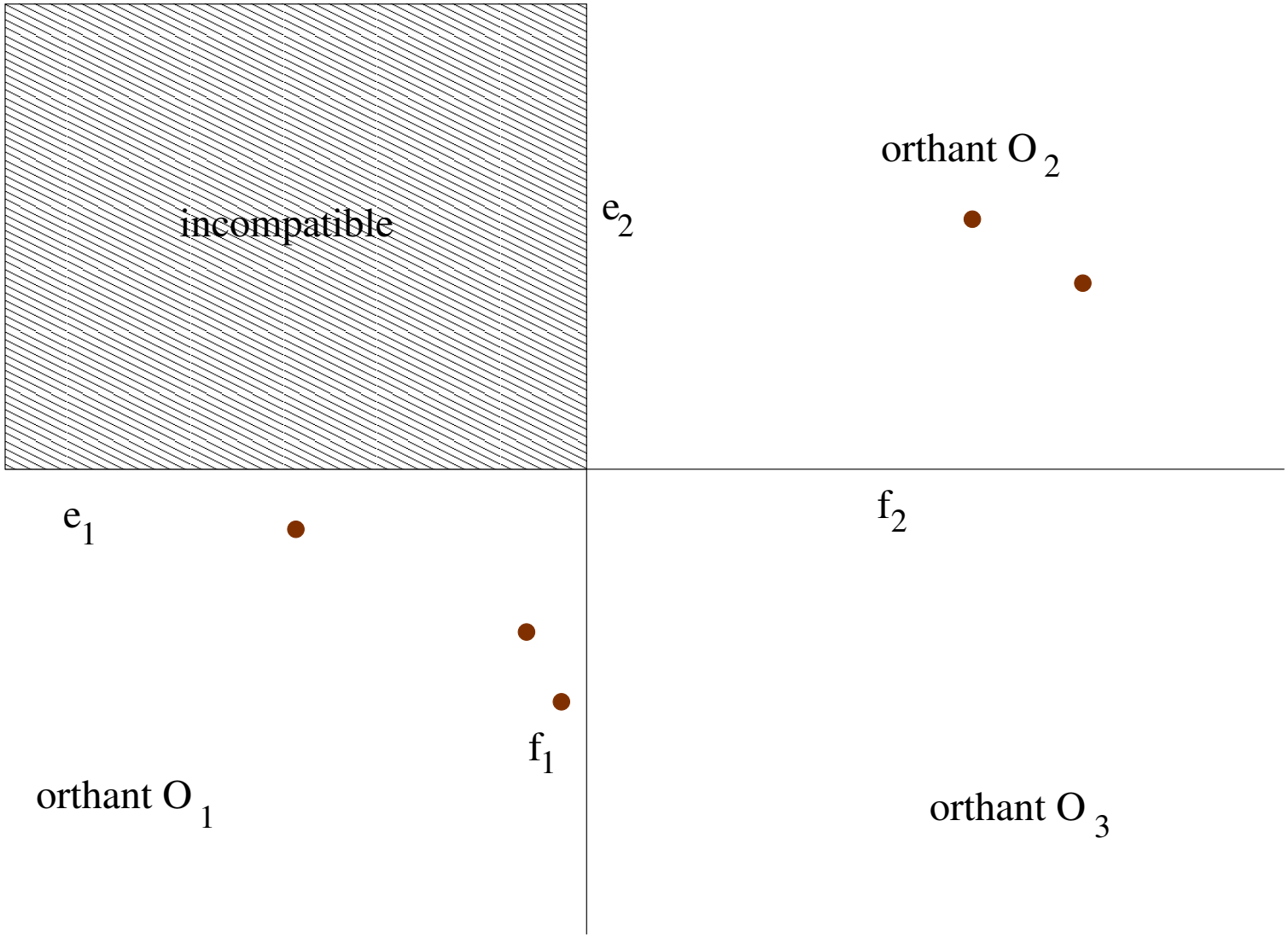
  $\rightarrow$ Euclidean median location problem with barriers
- Problems in $\mathcal{T}_n$ if all existing trees are in completely incompatible orthants
  $\rightarrow$ Euclidean median location problem with a gate point

Contents

Balance Point Algorithm



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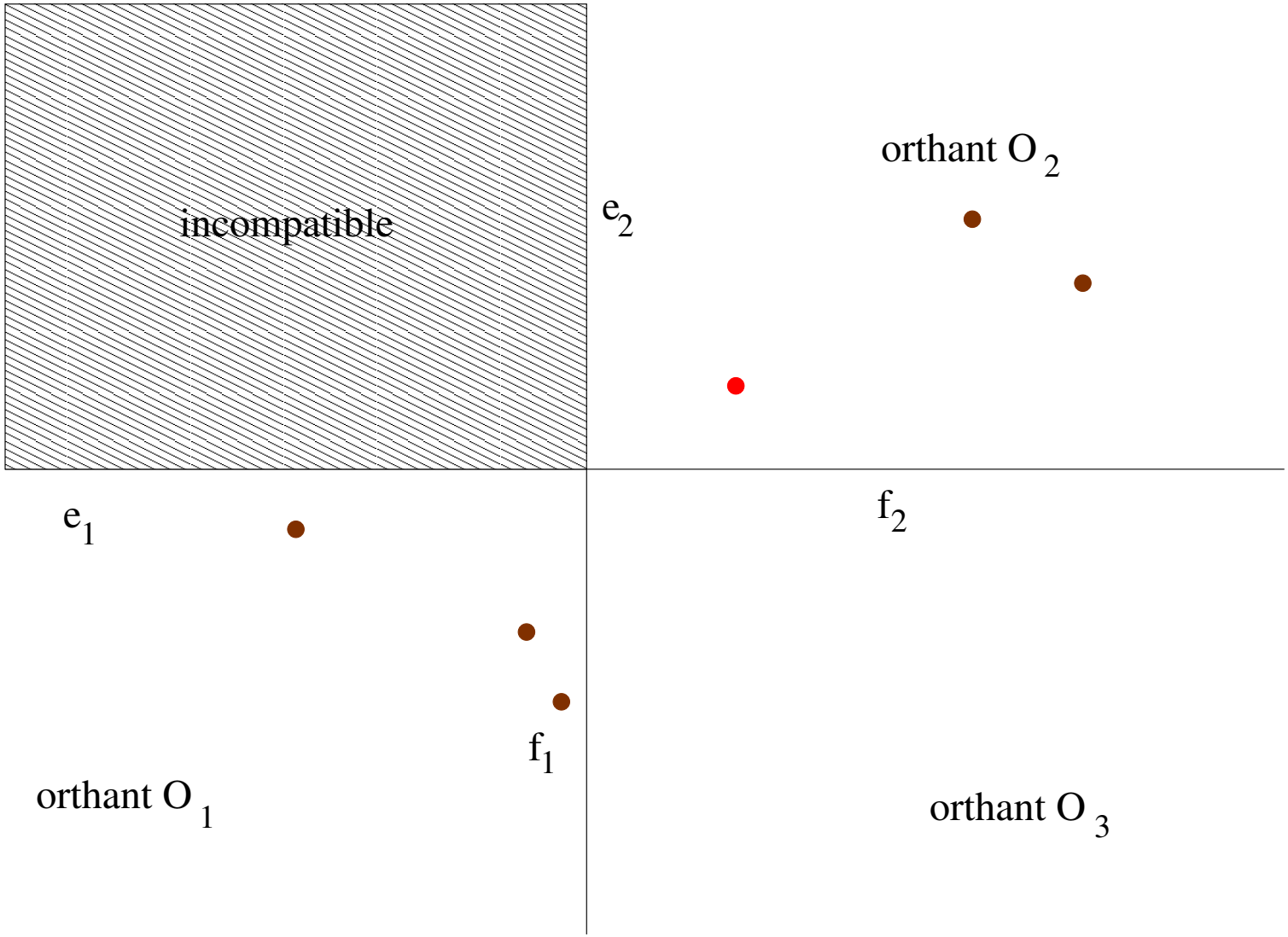

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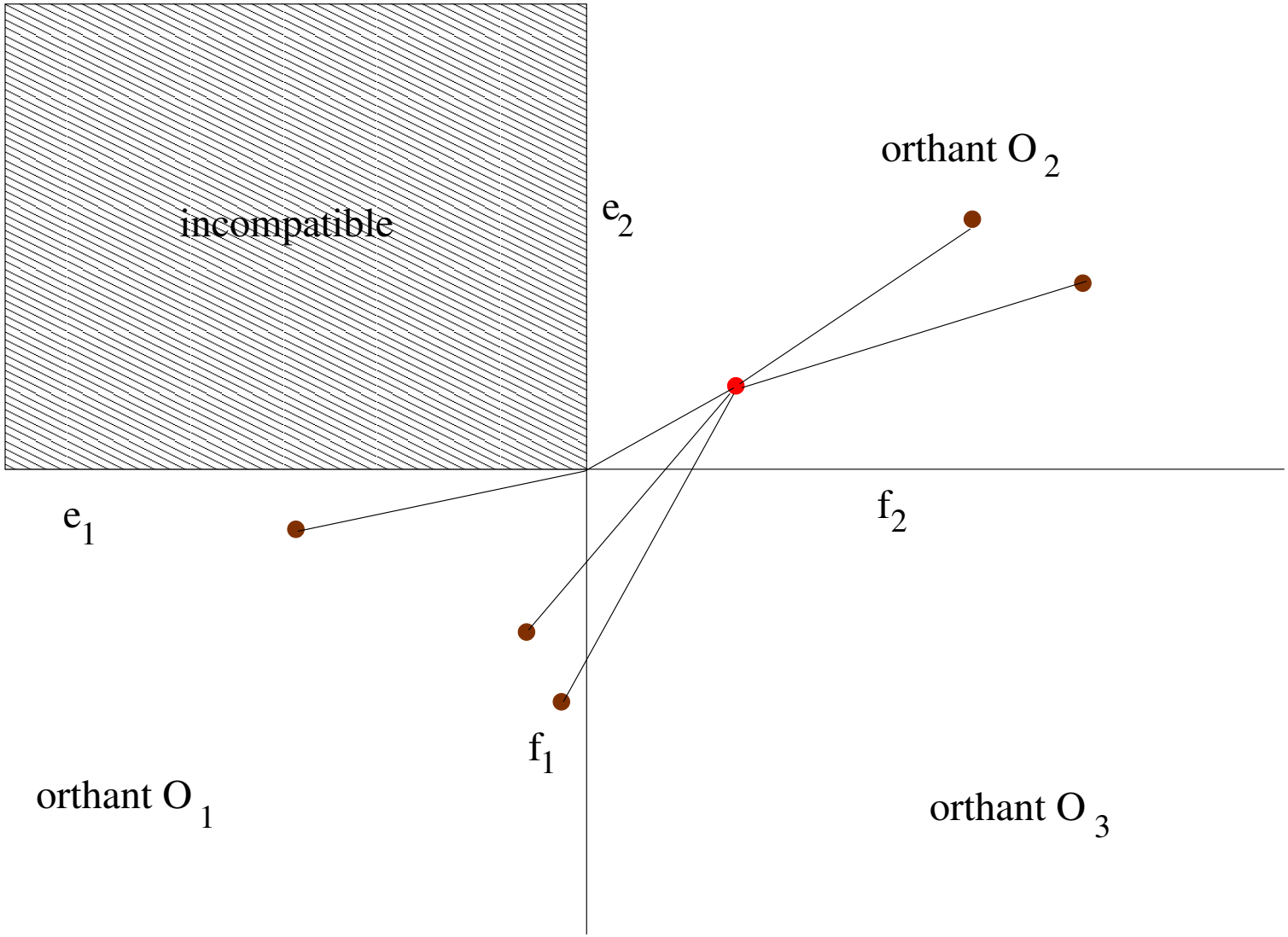

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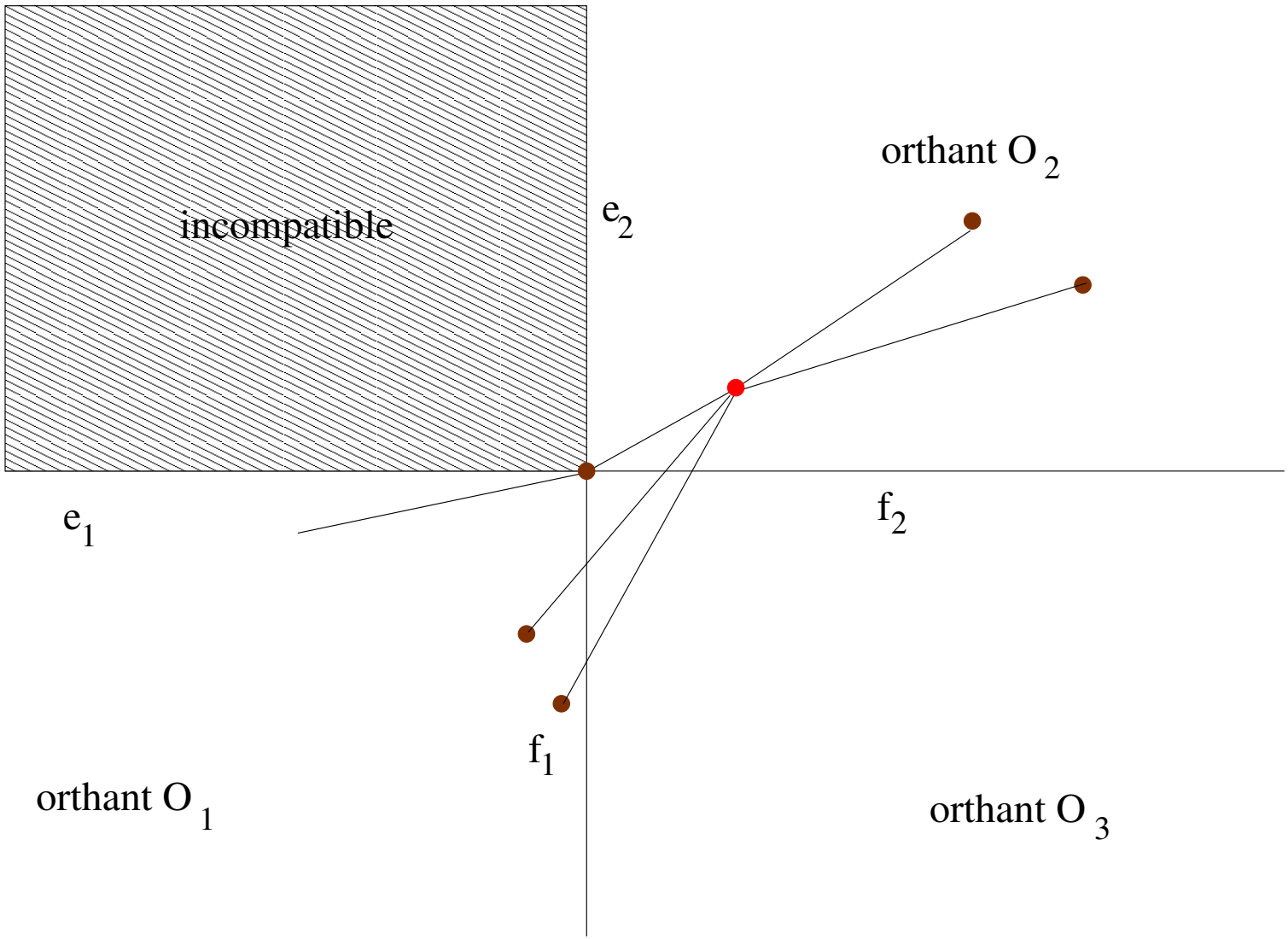

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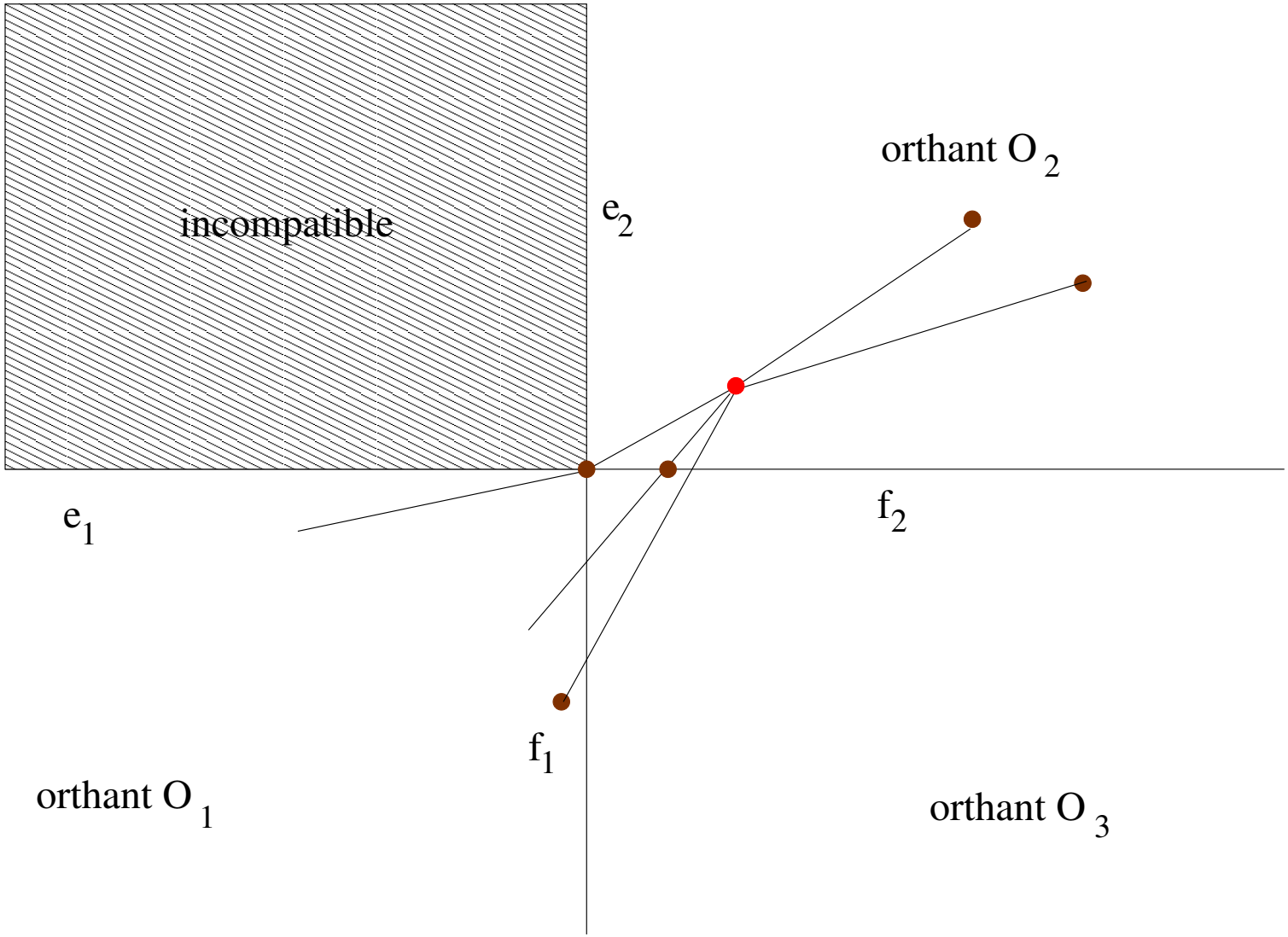

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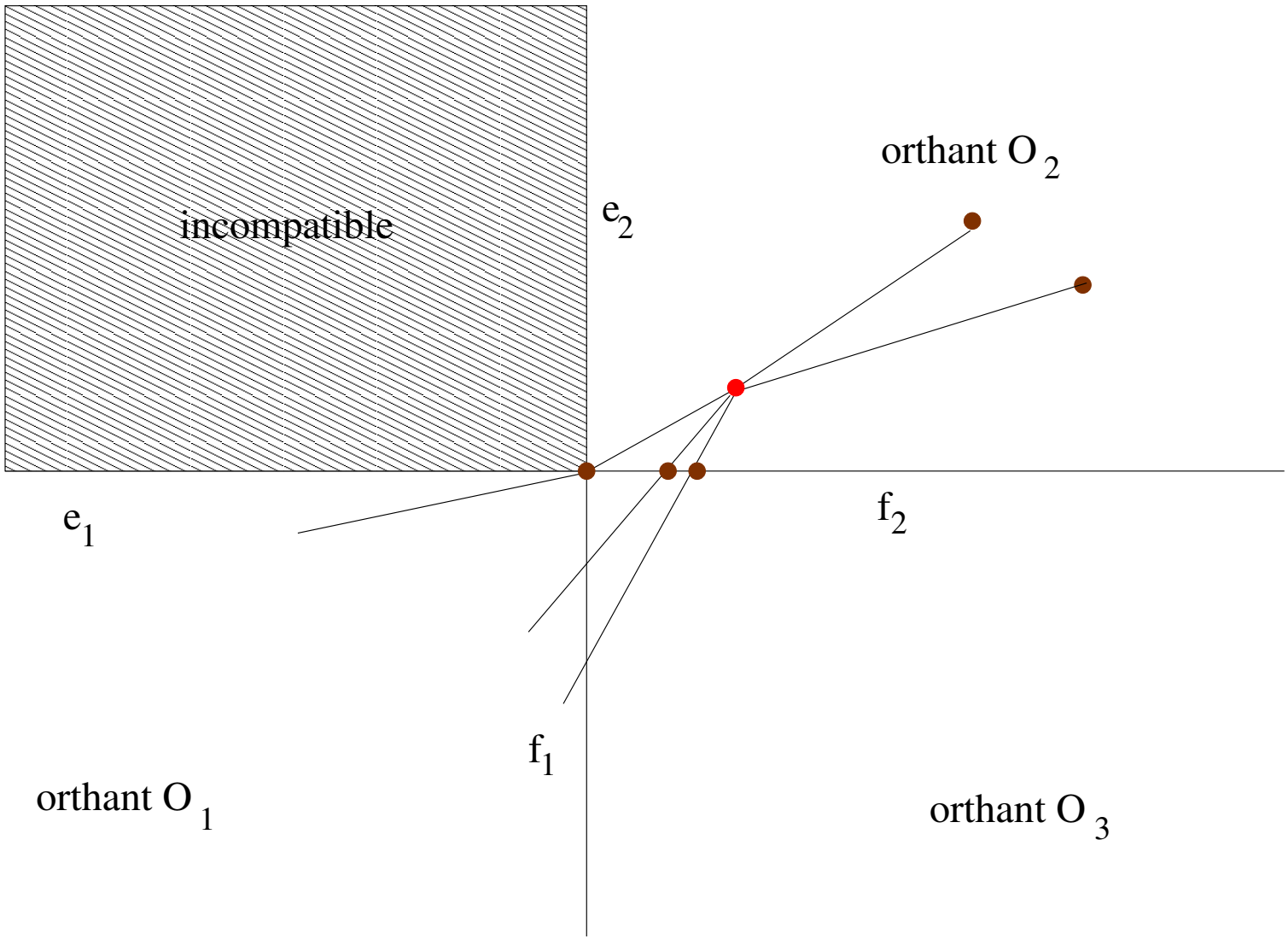

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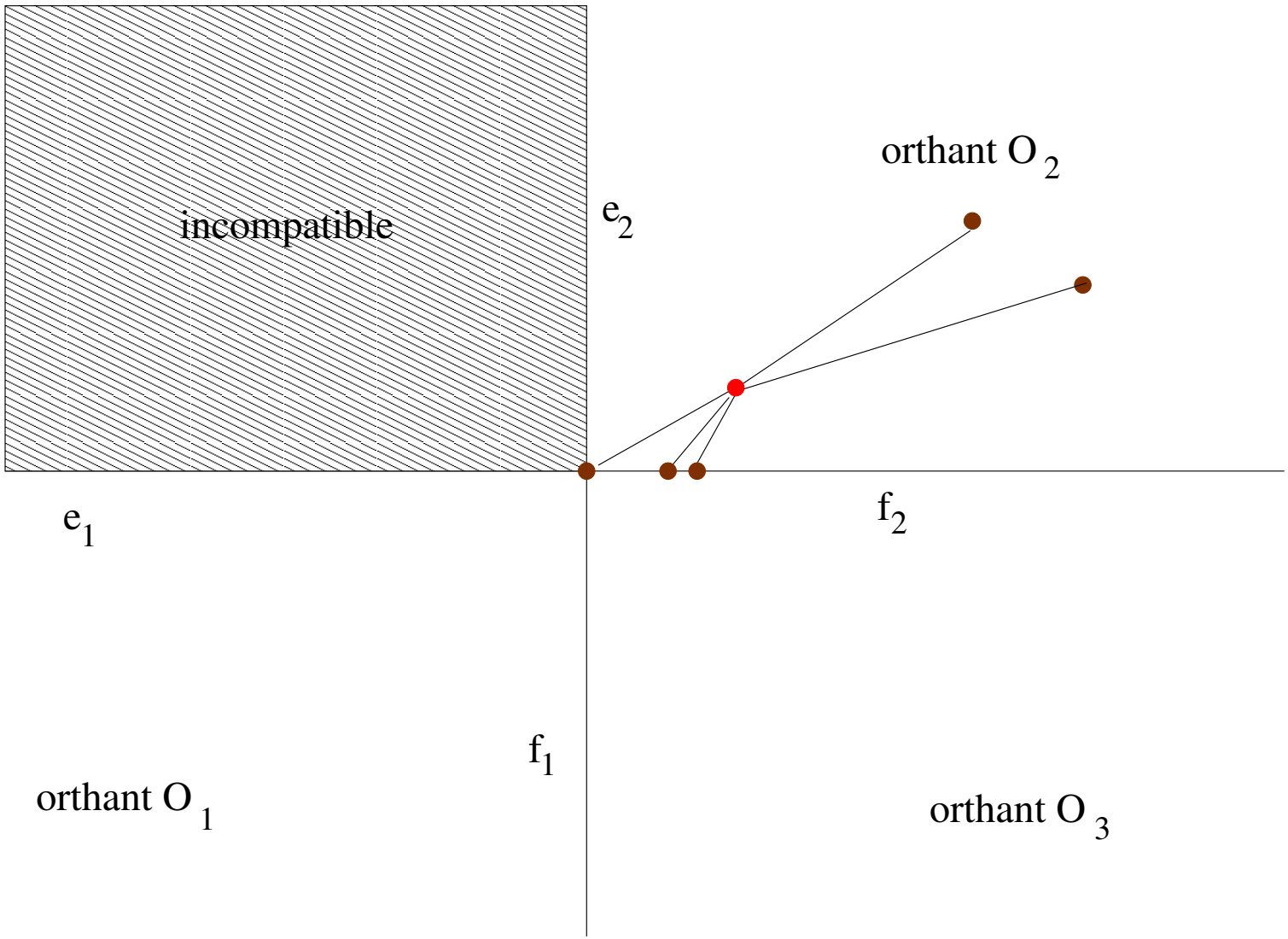

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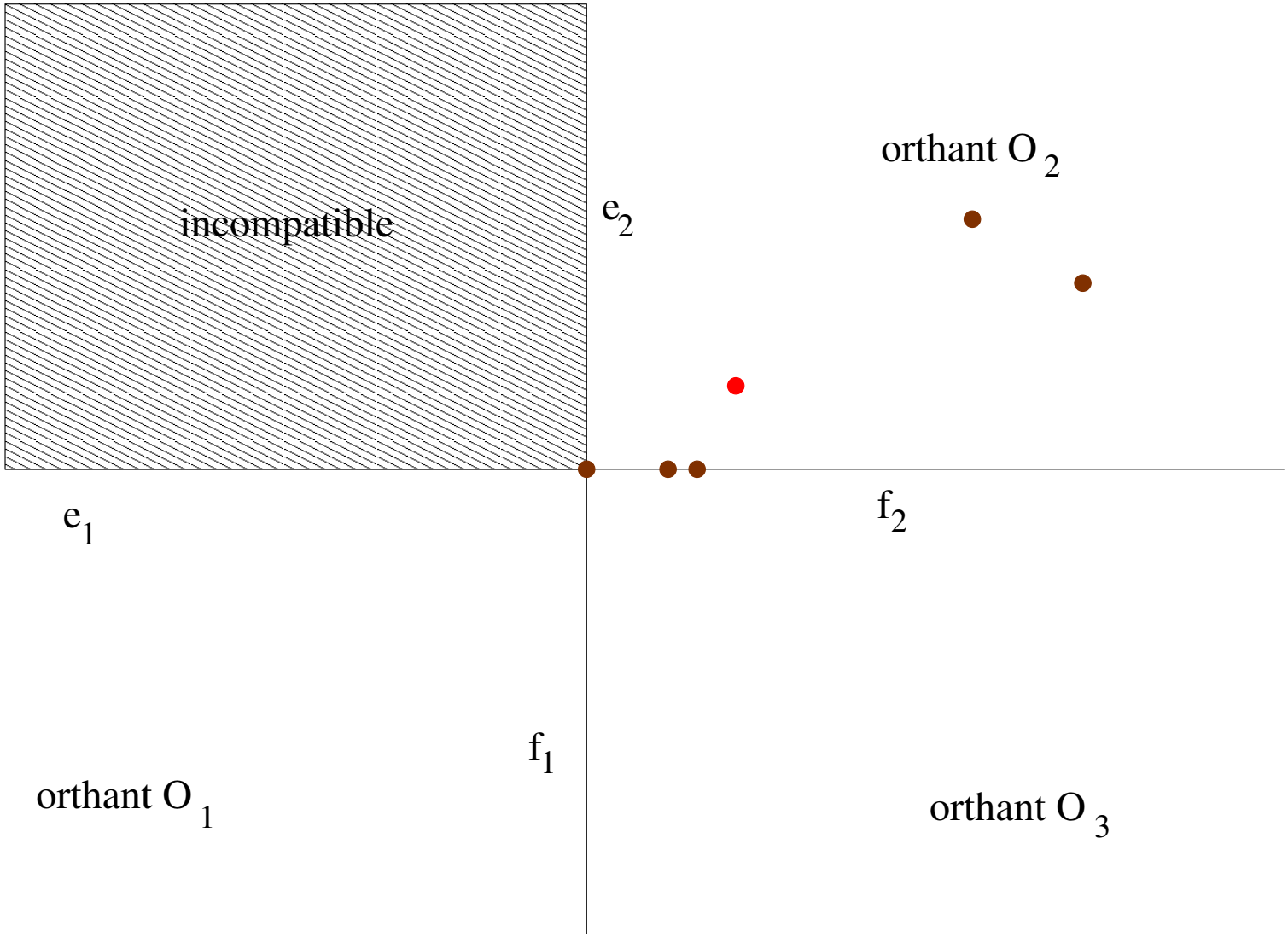

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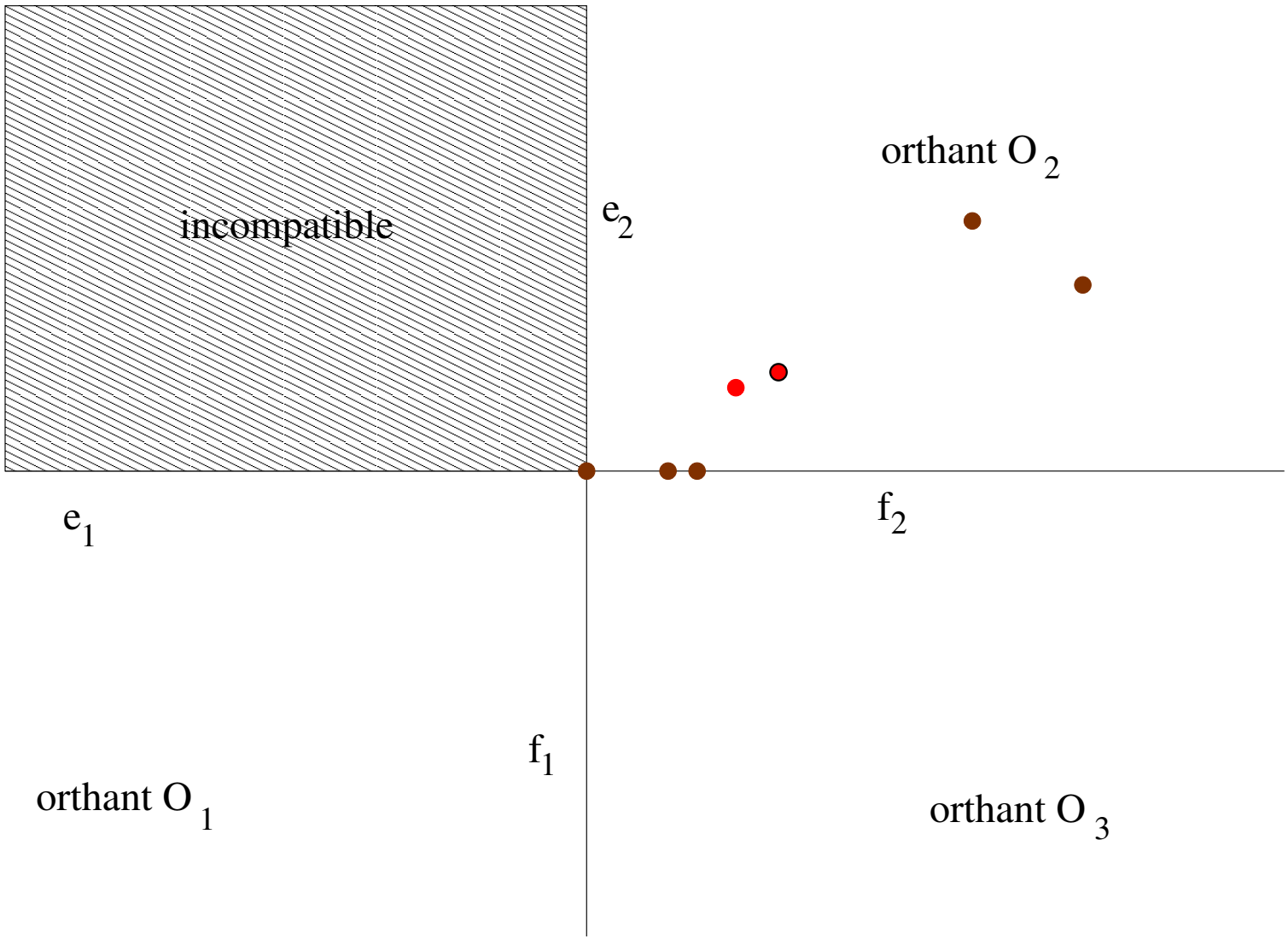

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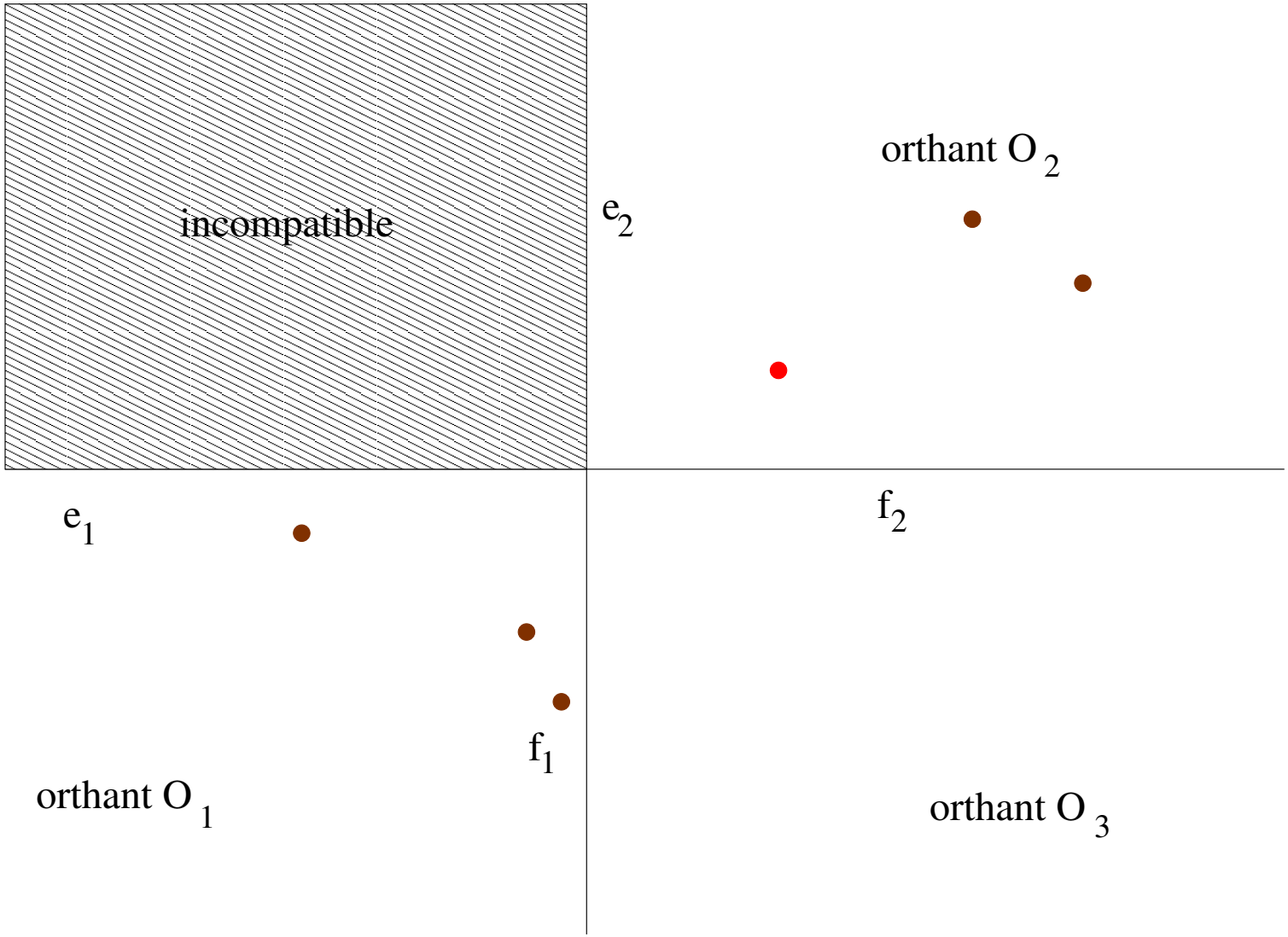

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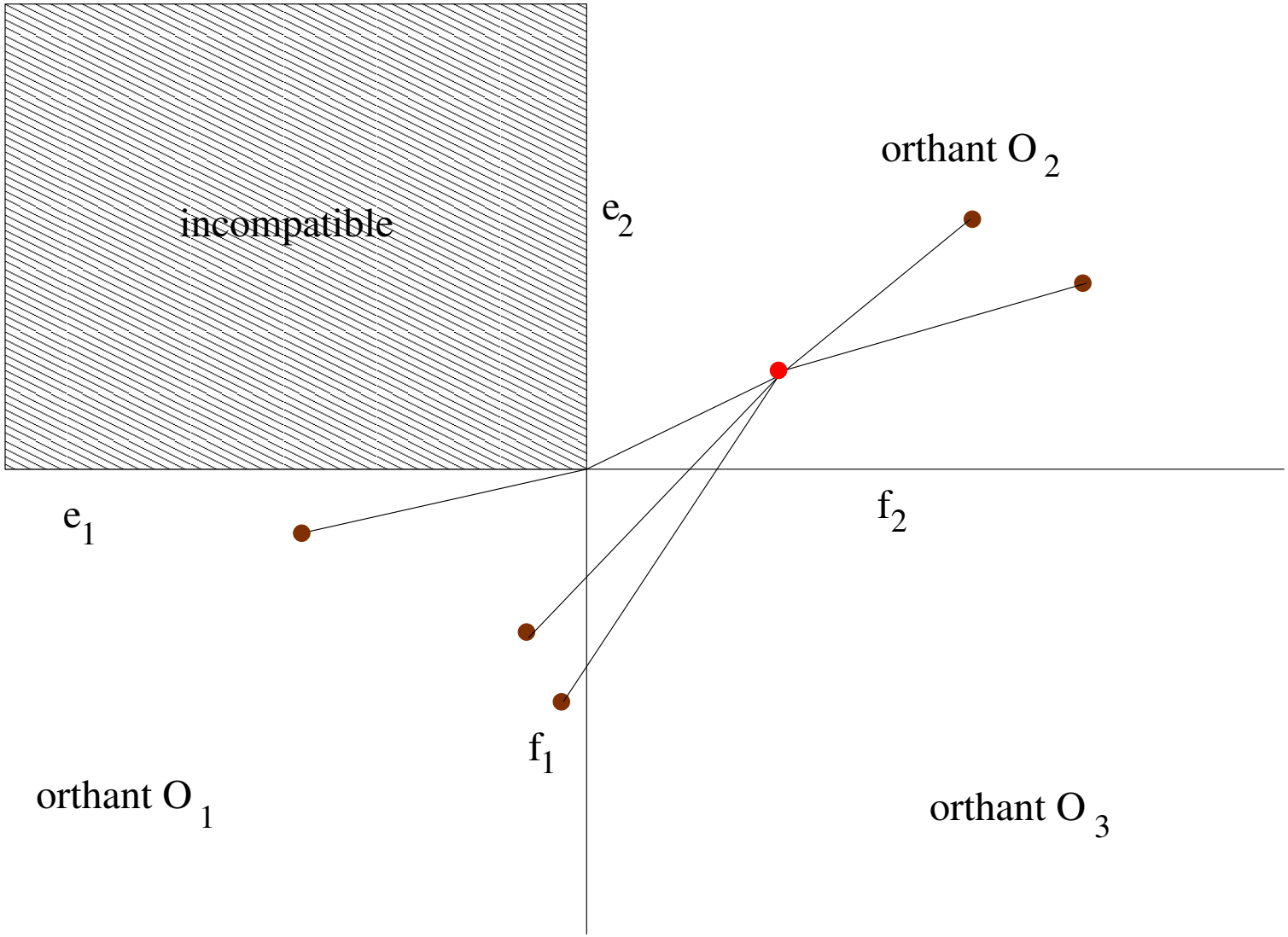

Balance Point Algorithm

2. For each orthant $\mathcal{O}$ do
3. *Inner Loop*
   1. Start with some tree T in the interior of $\mathcal{O}$.
   2. Compute geodesics from T to all other trees together with entry points into orthant $\mathcal{O}$.
   3. Solve location problem within the orthant and get new tree T.
   4. Goto step 2 until no improvement.
4. Take best solution.

Balance Point Algorithm

1. Remove orthants by bounds
2. For each remaining orthant $\mathcal{O}$ do
3. *Inner Loop*
   1. Start with some tree T in the interior of $\mathcal{O}$.
   2. Compute geodesics from T to all other trees together with entry points into orthant $\mathcal{O}$.
   3. Solve location problem within the orthant and get new tree T.
   4. Goto step 2 until no improvement.
4. Take best solution.

Bounds

$$d(T_a, T_b) = \inf \left\{ \sum_{i=1}^{k} \| T_i - T_{i+1} \|_2 : (T_1, \ldots, T_k) \text{ is a path from } T_a \text{ to } T_b \right\}$$

Lower bound for every orthant:

- Objective of Euclidean median problem in $\mathbb{R}^N$ is a lower bound
- . . . can be improved by using structure of orthants.

Bounds

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Lower bound for every orthant:

- Objective of Euclidean median problem in $\mathbb{R}^N$ is a lower bound
- . . . can be improved by using structure of orthants.

Global upper bound: Take the star tree

$$UB_{star} = \sum_{\text{existing trees } T} \| T \|$$

or any other feasible solution

Theoretical results

The balance point algorithm

- is a blockwise coordinate descent method
- improves the objective value in every step (or stays the same)
- both steps are convex
  (but convexity is tricky in the tree space!)
- both steps need not find unique solutions and may be non-differentiable
- STILL: convergence to an optimal solution is provable (under a few conditions)!
  $\rightarrow$ dissertation of Marco Botte, 2019

Numerical results

- The balance point algorithm works (many experiments in low dimensions) and a real-data case study (Apicomplexa, 252 existing trees, 8 species)
- The identified trees are what biologist expect.

Comparison with the proximal point method by Baćak (2014):

- The balance point algorithm converges much quicker when close to optimal solution. (Proximal point method is not monotone.)
- The proximal point method can identify a good orthant.
- Best: starting with the proximal point method and then switching to the new approach.

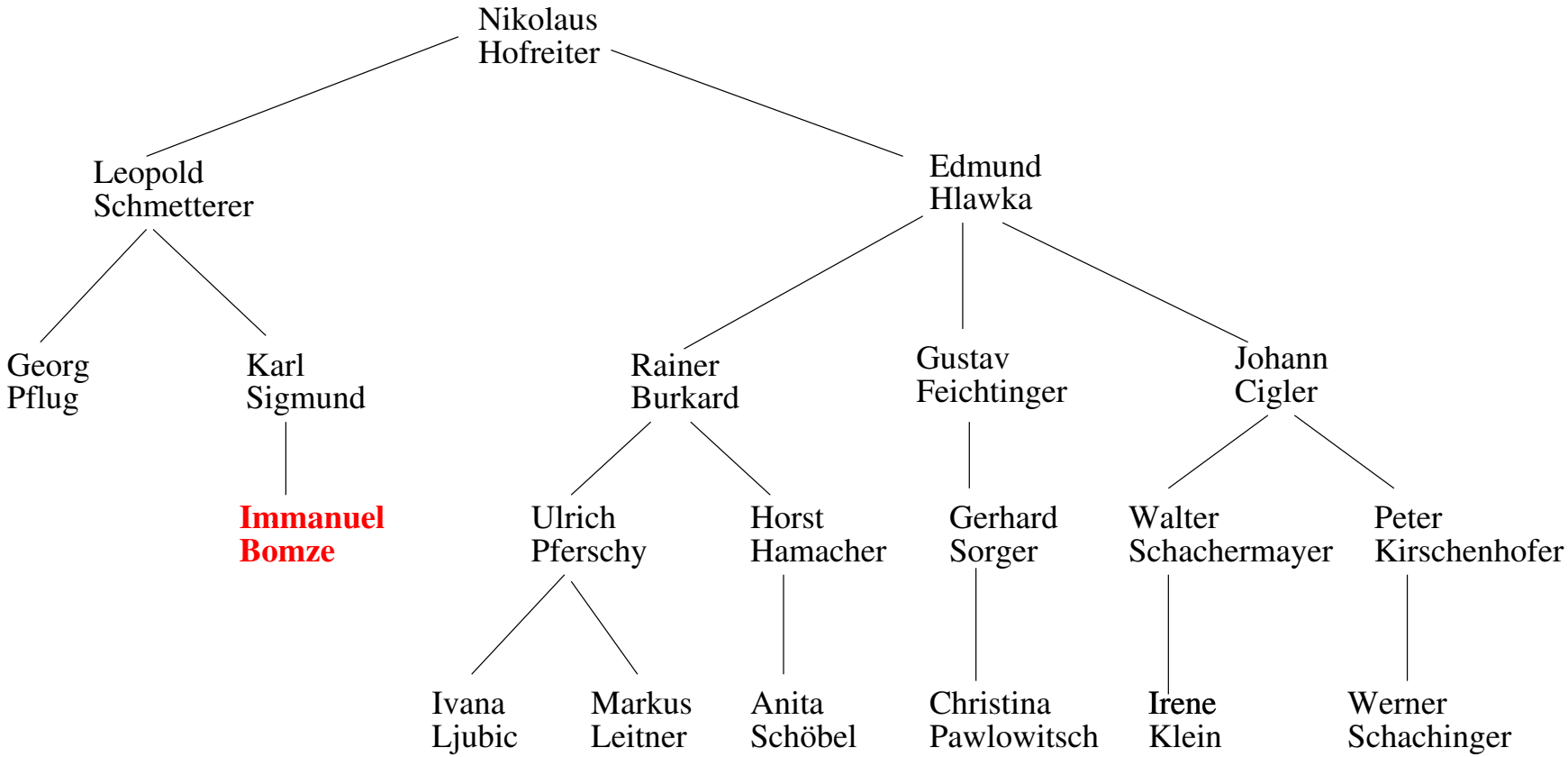
$\rightarrow$ dissertation of Marco Botte, 2019

Contents

Conclusion and Outlook

- What you could have seen:
  - Finding phylogenetic trees can be modeled as a location problem in an interesting metric space
  - Methods of location theory seem appropriate for solving the problem.
- What is still to come:
  - identify more cases which can be transferred to Euclidean location problems
  - work on (high-dimensional) Euclidean location problems with barriers
  - improve the balance point algorithm, e.g., better bounds
  - more case studies

Conclusion and Outlook



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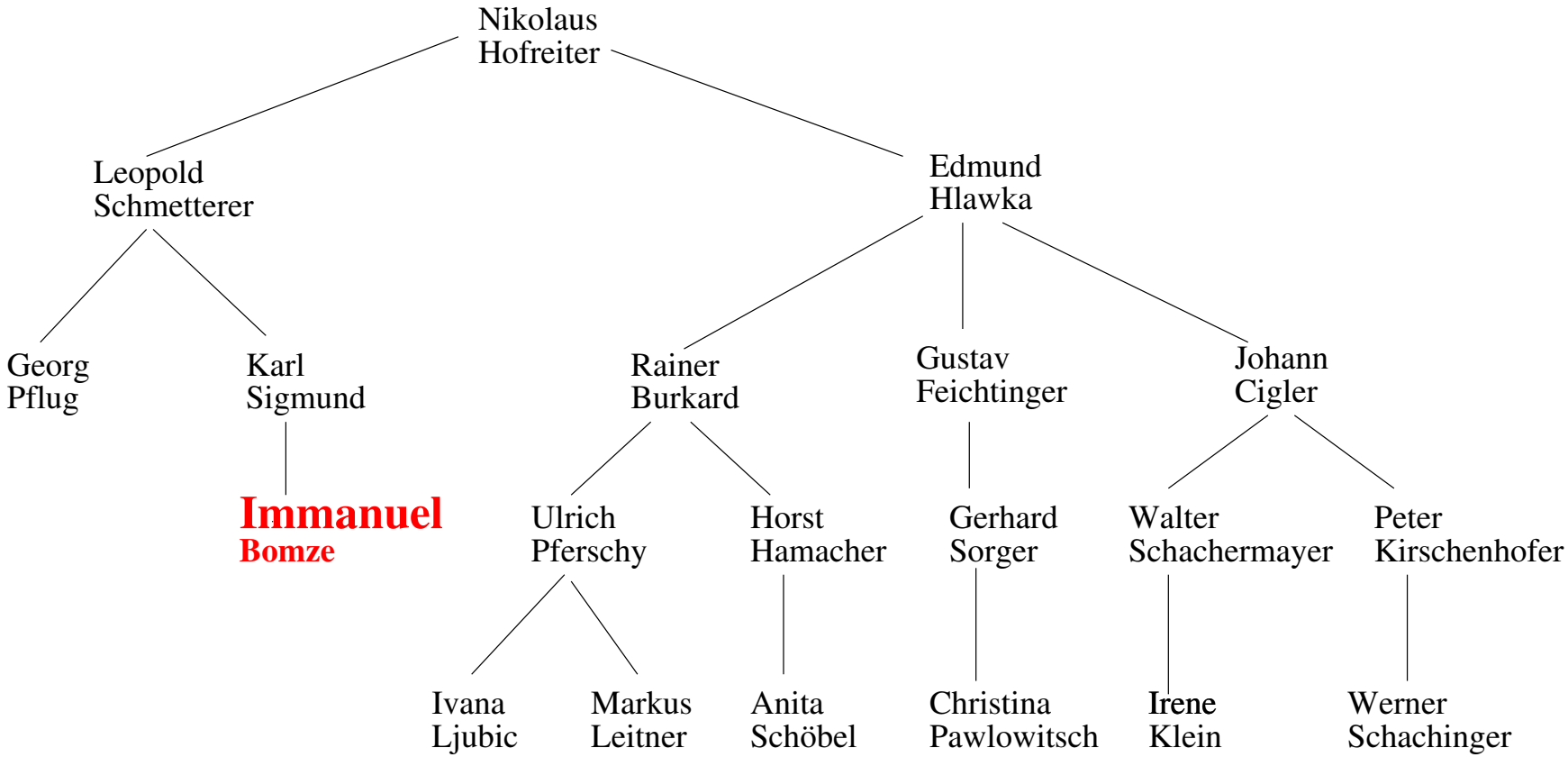

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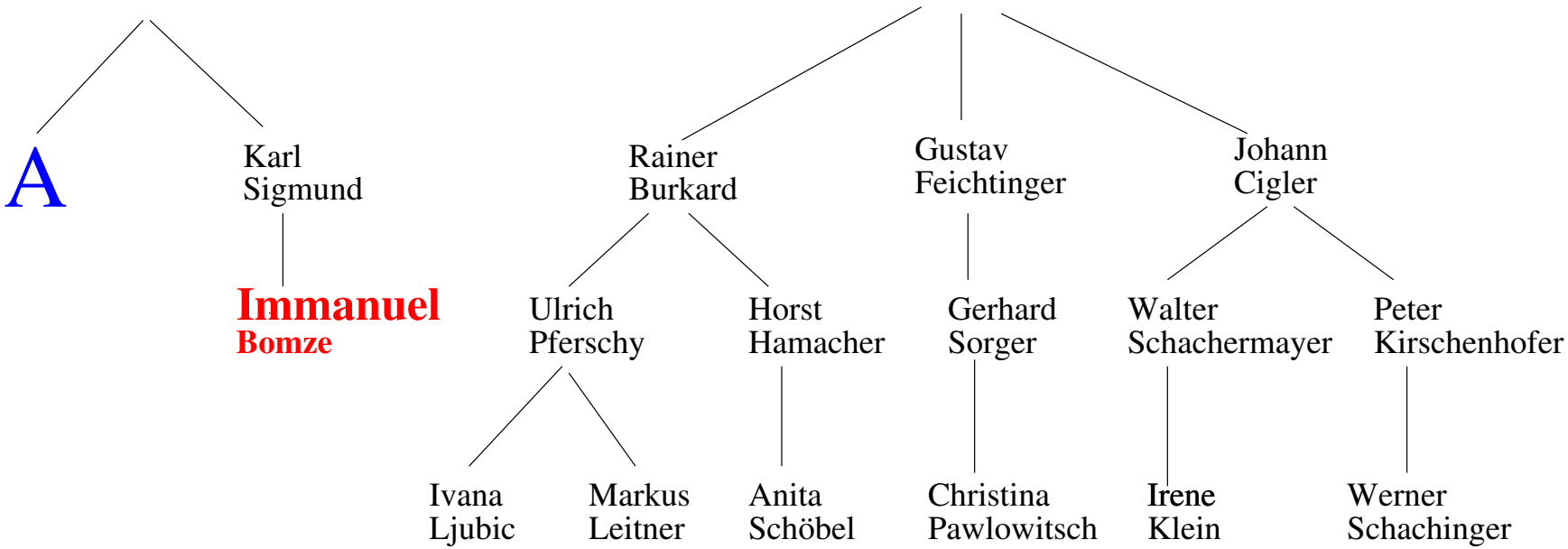

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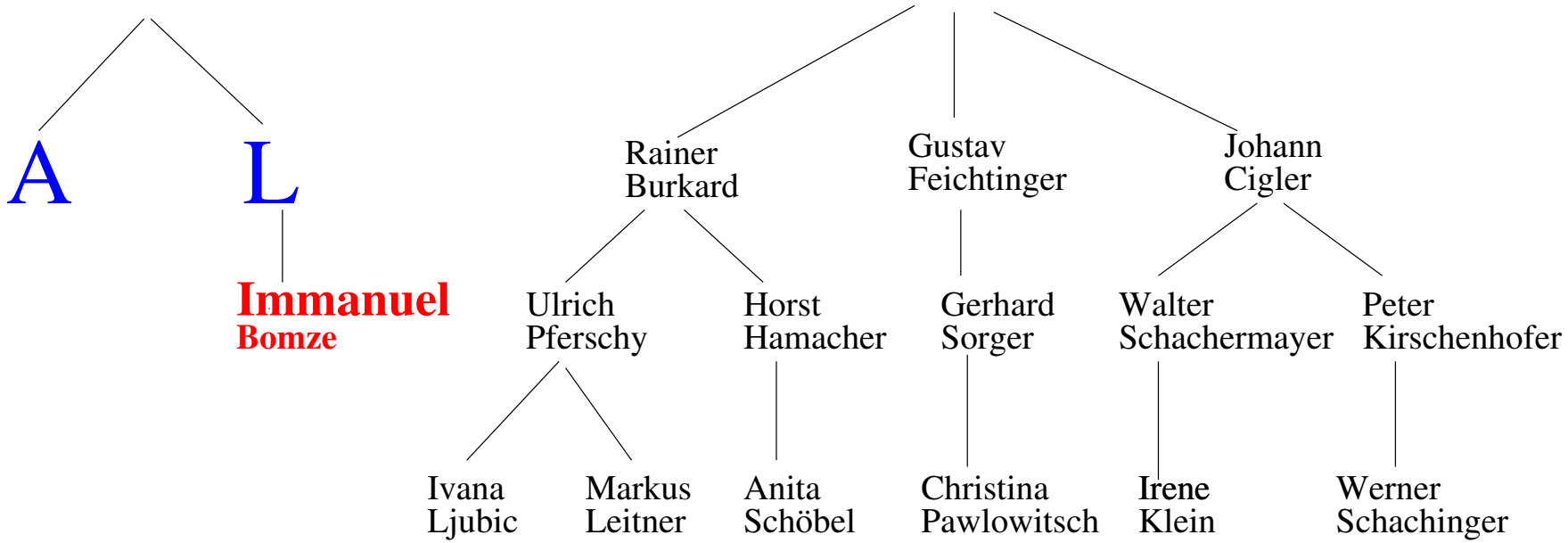

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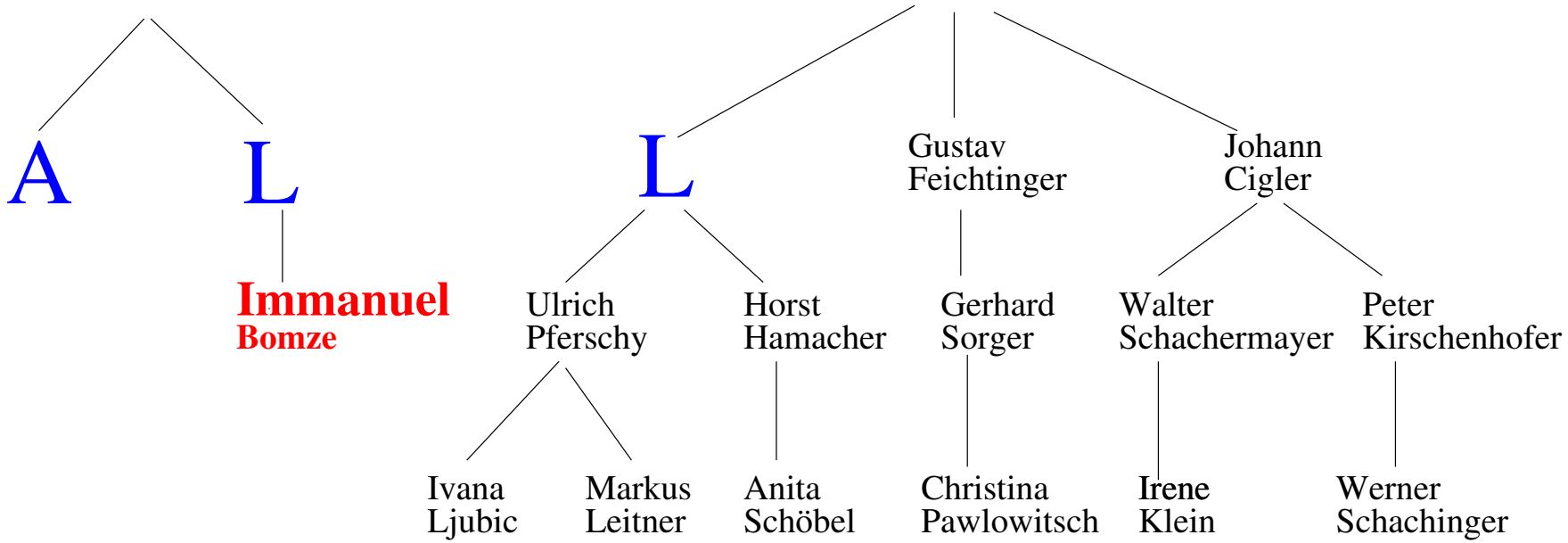

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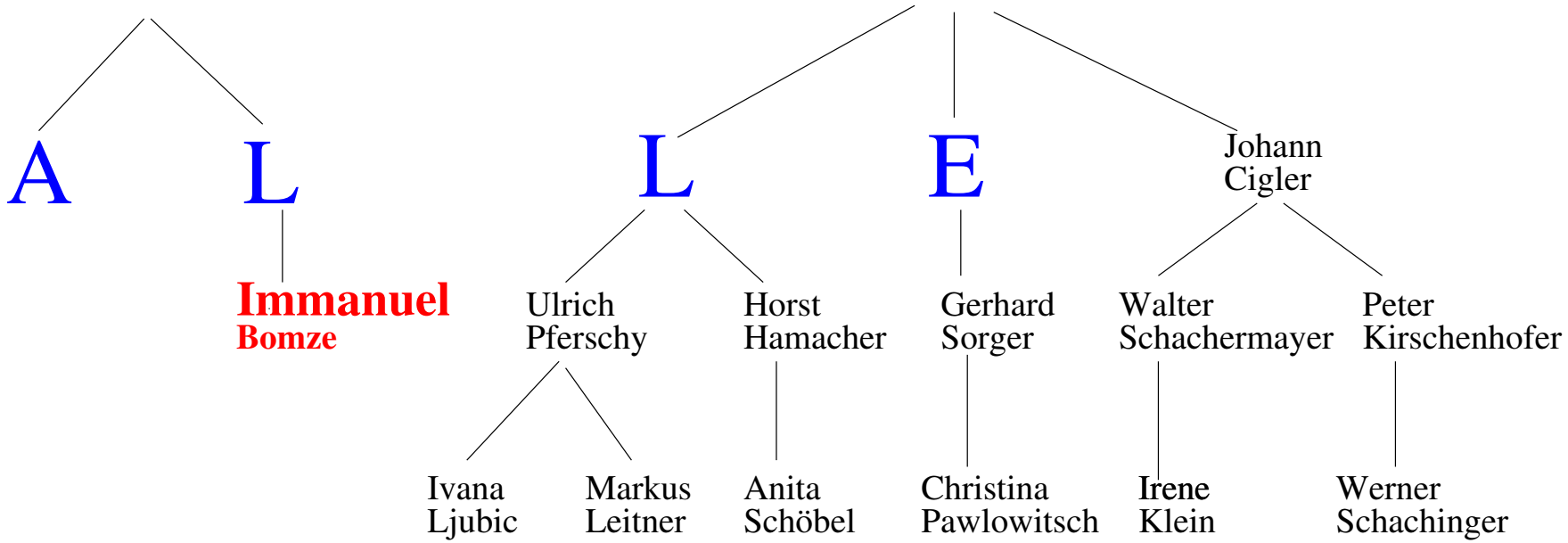

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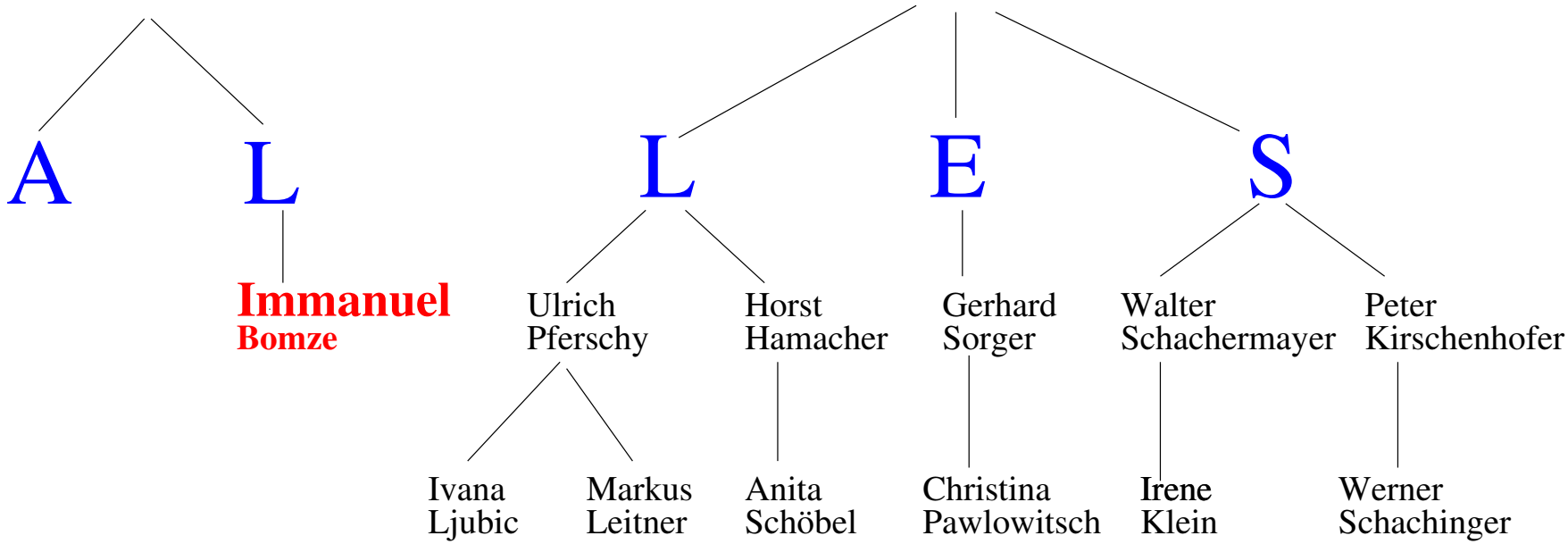

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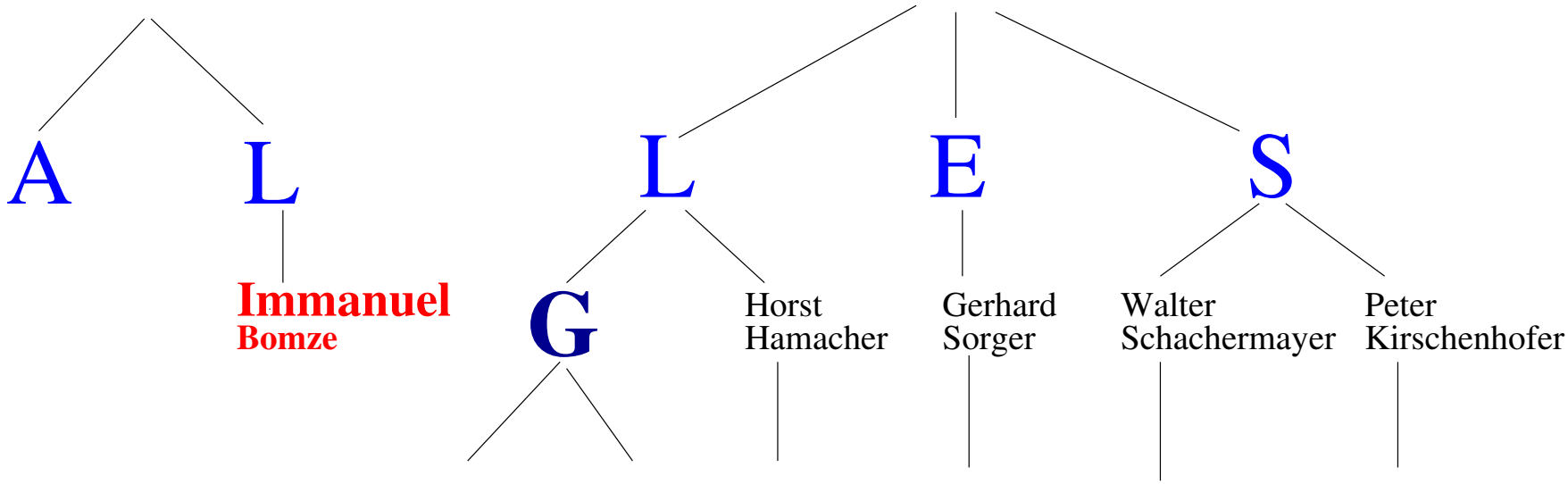

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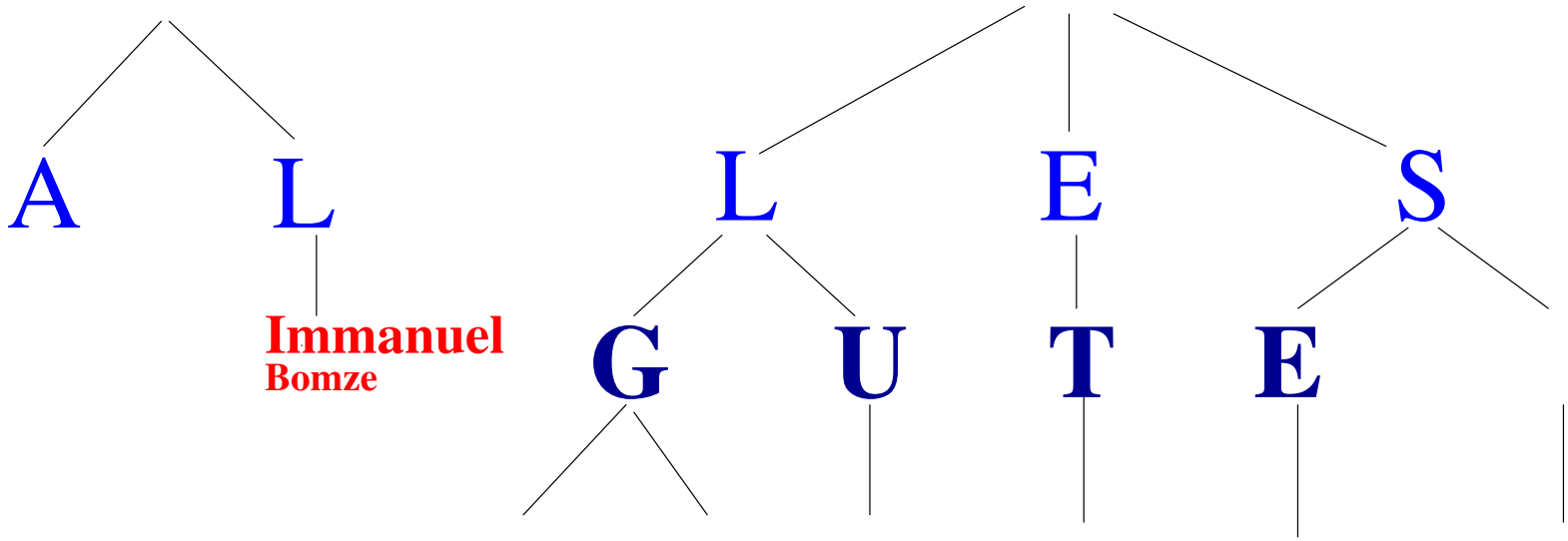

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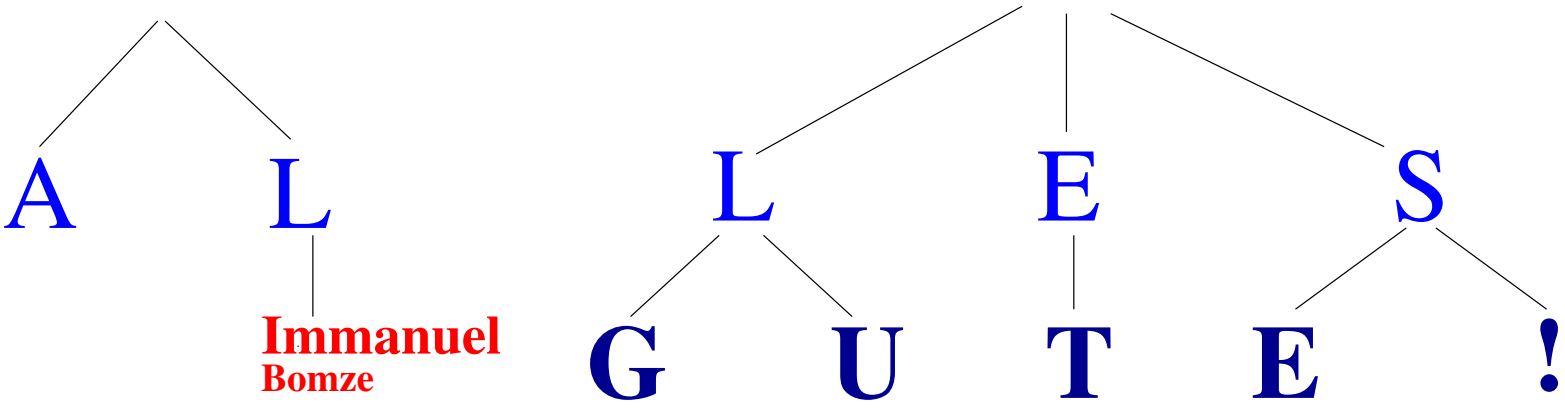

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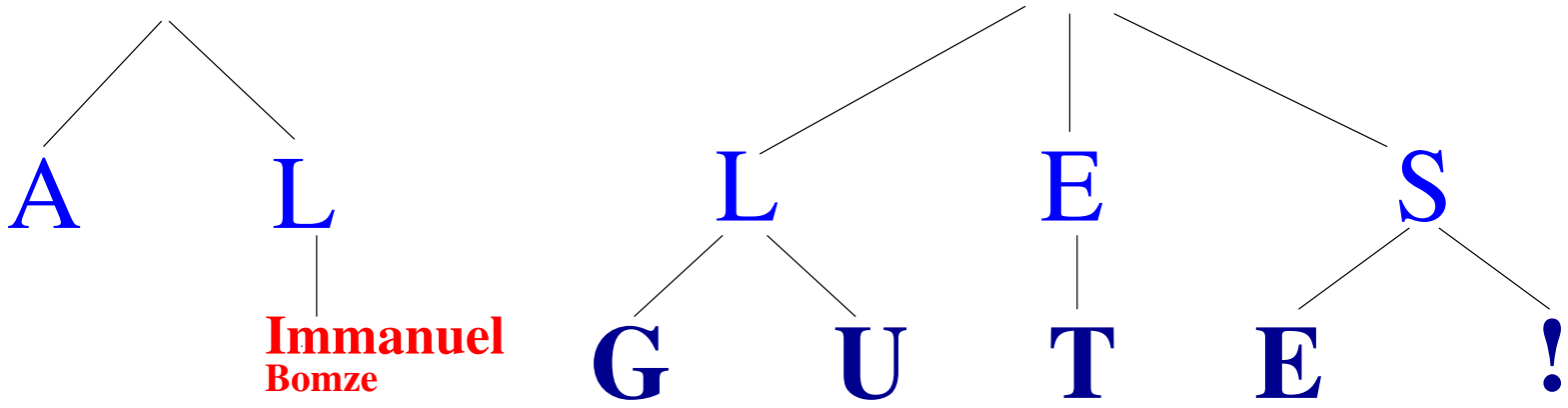

Thank you! Questions?