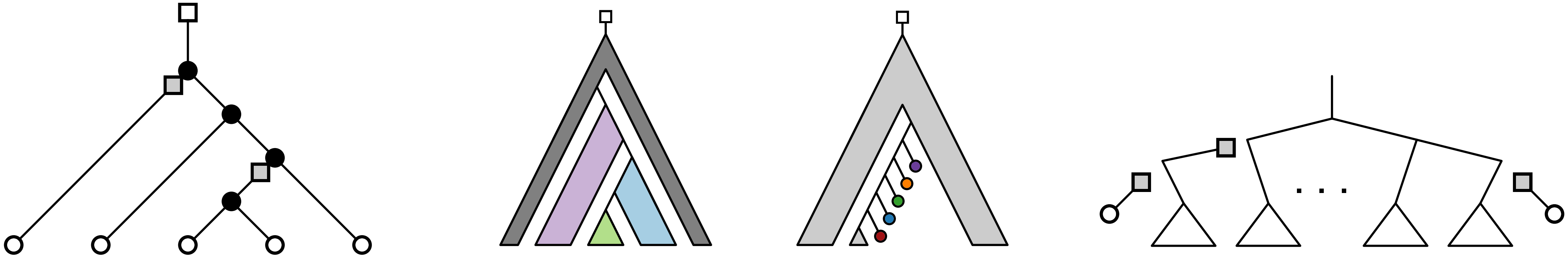
Julius-Maximilians-
UNIVERSITÄT
WÜRZBURG

Advanced Algorithms

Rearrangement Distance of Phylogenetic Trees

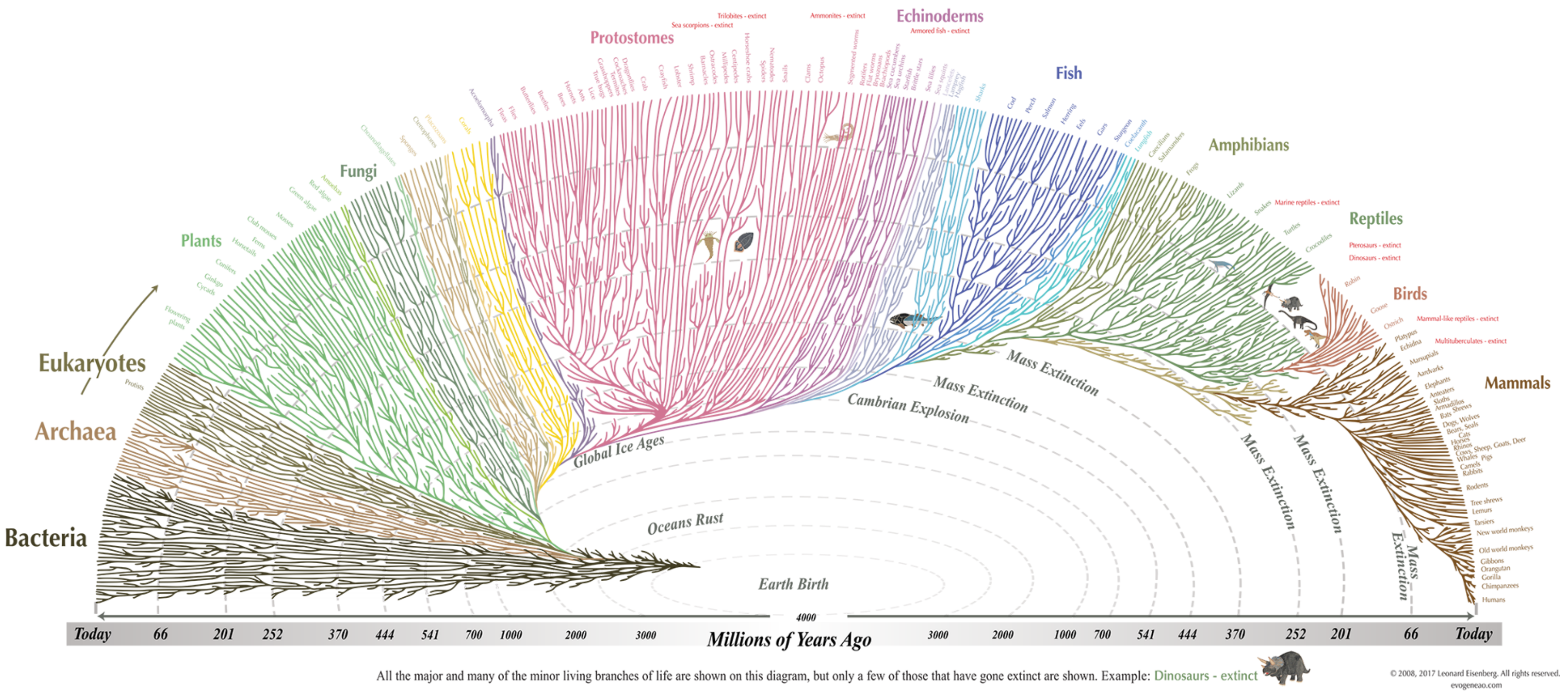
Kernelization, FPT, Approximation Algorithm

Johannes Zink · WS22



Phylogenetic Trees

... represent the evolutionary history of a set of taxa.



All the major and many of the minor living branches of life are shown on this diagram, but only a few of those that have gone extinct are shown. Example: Dinosaurs - extinct

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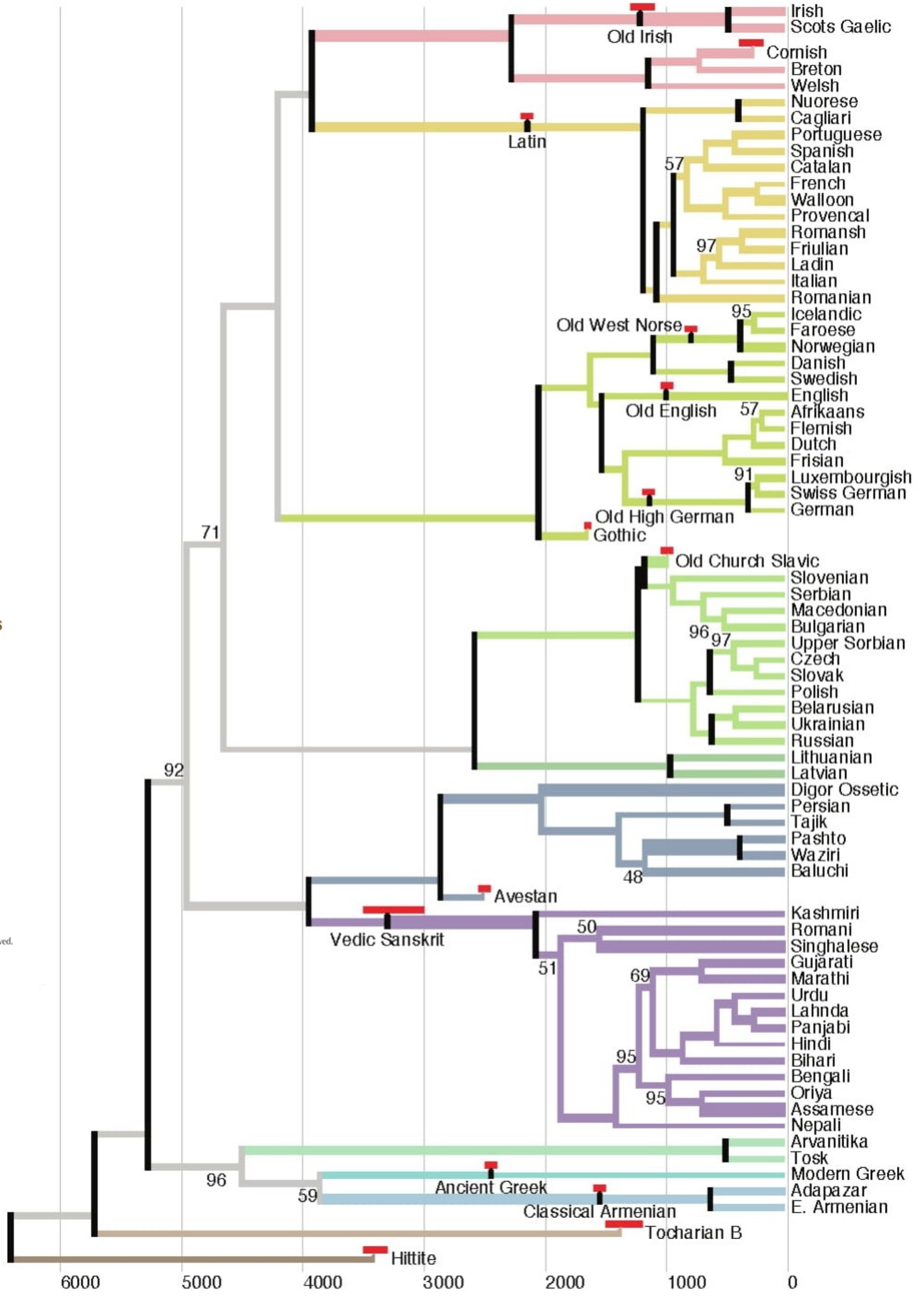
evogeneao.com

Tree of Life
www.evogeneao.com
(2017)



Phylogenetic tree of the Indo-European languages by Chang & Chundra (2015)

Phylogenetic Trees

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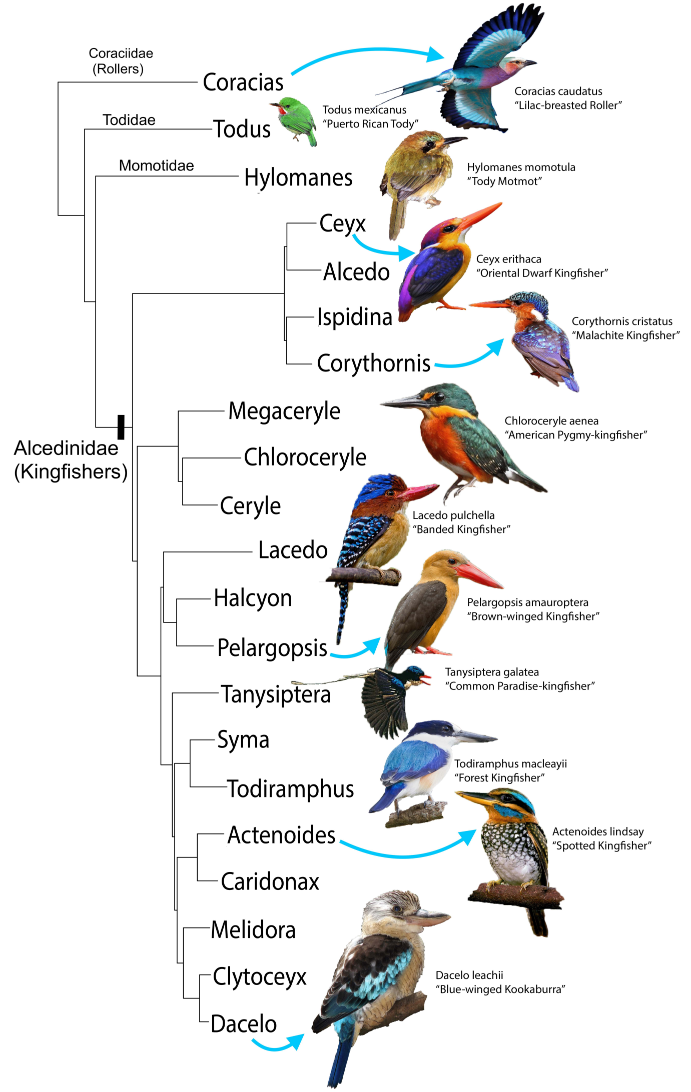


Kingfishers (German: *Eisvögel*)
by McCullough et al. (2016)

Properties (in the biological sense):

- Leaves are labelled with taxa.
- Each taxon represents a species, population, individual organism, gene, chromosome, . . .
- Edge length represents an amount of time passed or a genetic distance.
- Inference methods compute a phylogenetic tree based on some model and data.

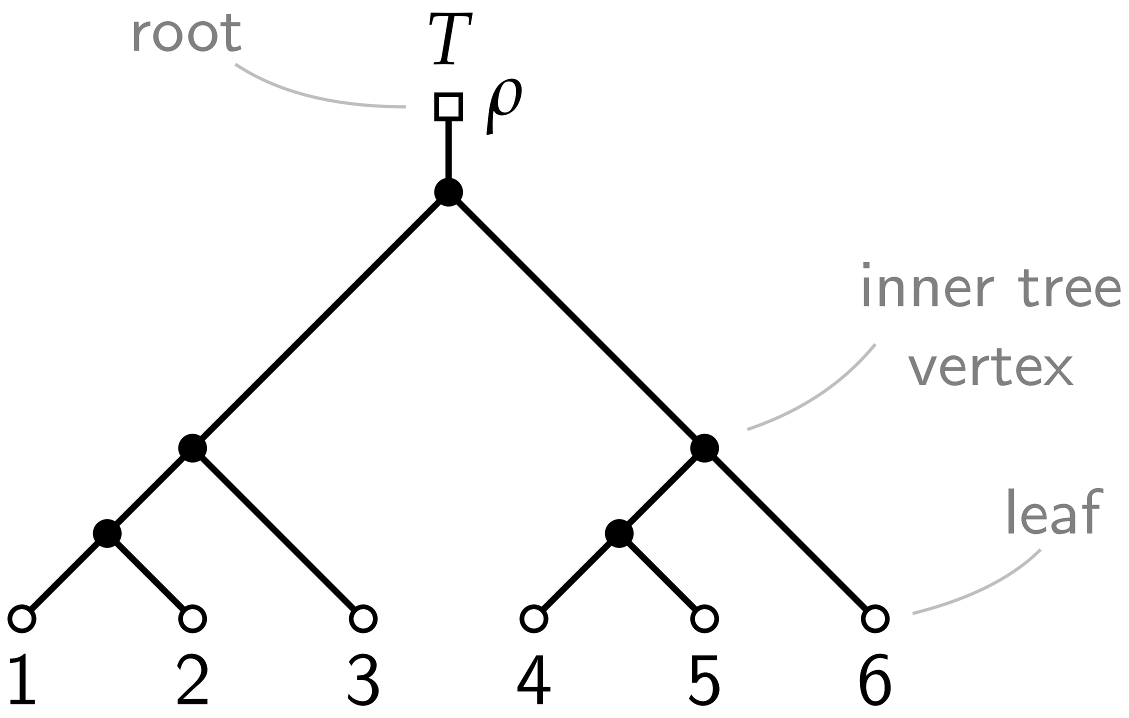
Phylogenetic Trees

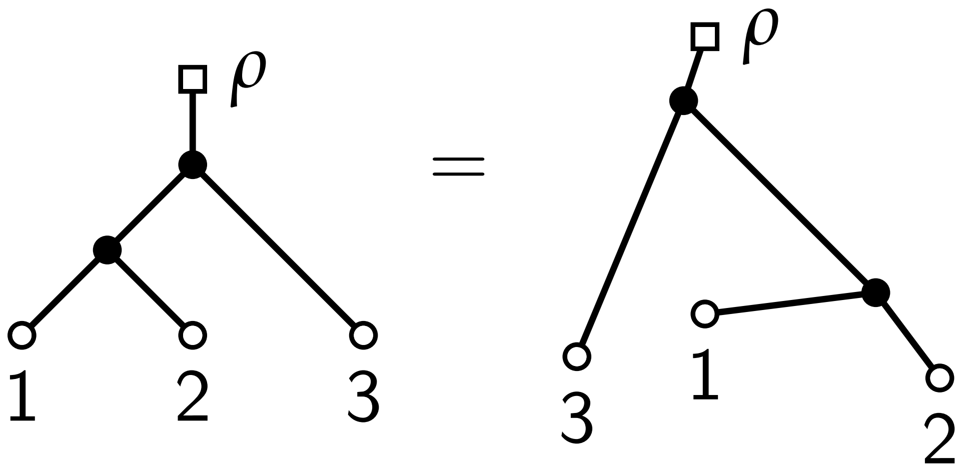
Let $X = \{1, 2, 3, \dots, n\}$.
A **(rooted, binary) phylogenetic tree** T is a rooted tree with the following properties:

- The unique **root** is labeled ρ and has outdegree 1.
- The leaves are bijectively labeled by X.
- All other vertices have indegree 1 and outdegree 2 (i.e., it is a *binary* tree).

Remarks. Here, in our definition

- vertices have **no heights** and
- the order of the children of a vertex does not matter.





Problem

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We want tc
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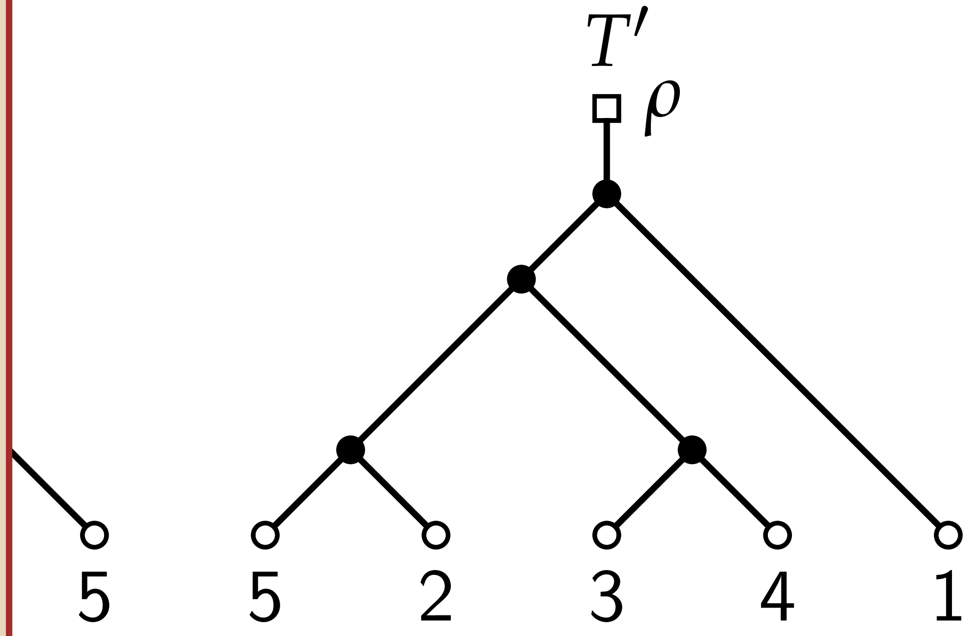
How?

Defintion:
A *metric* d is a function of two parameters such that:

- $d(x, x) = 0$ (no distance to itself)
- $d(x, y) > 0$ for $x \neq y$ (positive)
- $d(x, y) = d(y, x)$ (symmetric)
- $d(x, z) \leq d(x, y) + d(y, z)$ (triangle inequality holds)



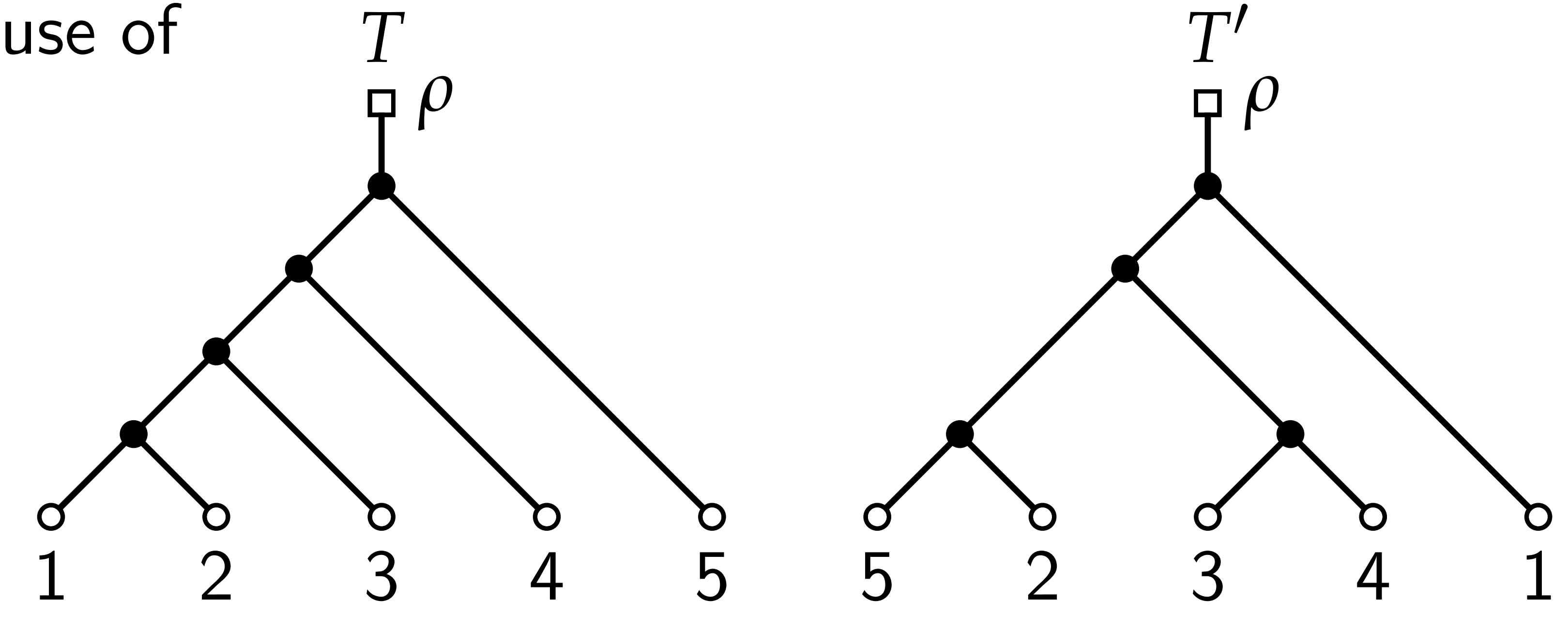
Goal.
Define a **metric** that specifies how similar two phylogenetic trees on the same set X are and devise algorithms to compute it.

Problem

For the same taxa, we may infer **different** phylogenetic trees because of the use of

- different inference methods,
- different models, or
- different data.

We want to be able to **compare** different phylogenetic trees. How?

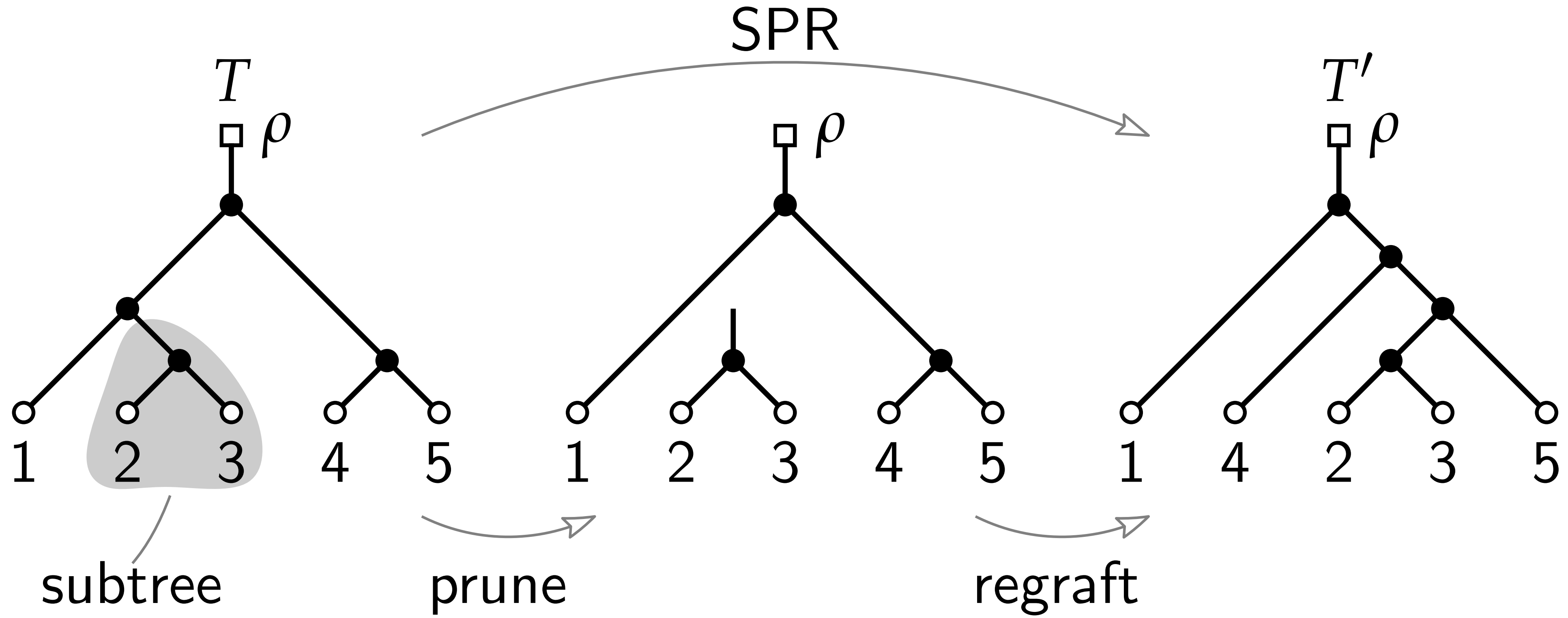


Goal.
Define a **metric** that specifies how similar two phylogenetic trees on the same set X are and devise algorithms to compute it.

Idea.
Count the number of **rearrangement operations** that are necessary to transform T into T'.

Subtree Prune & Regraft (SPR)

An **SPR** operation transforms one phylogenetic tree into another one.

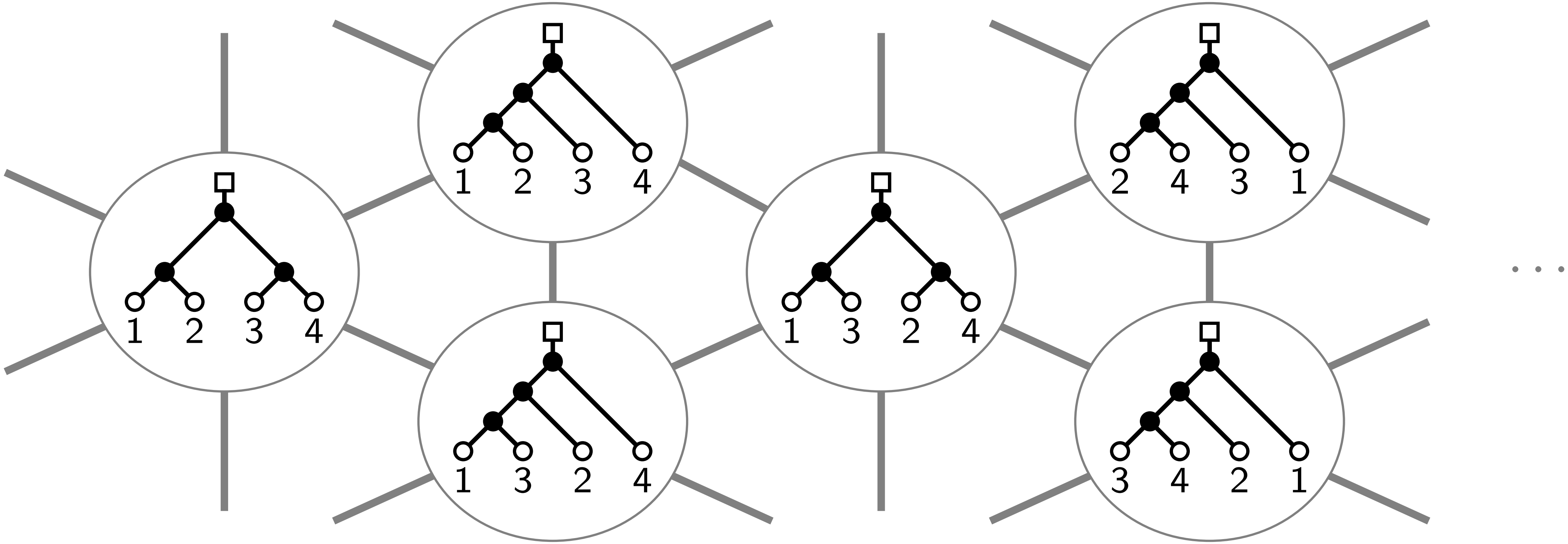


- Note that an SPR operation is reversible.

SPR-Graph

The SPR operations induce the **SPR-graph** $G = (V, E)$ for a set X:

- $V = \{T \mid T$ is a phylogenetic tree on X$\}$
- $E = \{\{T, T'\} \mid T$ can be transformed into T' with a single SPR operation$\}$



SPR-Distance

The **SPR-distance** $\mathsf{d}_{\mathsf{SPR}}(T, T')$ of T and T' is defined as the distance of T and T' in the SPR-graph G.

Lemma 1.
The SPR-graph G is connected.

Lemma 2.
The SPR-distance is a metric.

Proof. G is connected and undirected.
All properties of a metric follow. □

Defintion:
A *metric* d is a function of two parameters such that:

- $d(x, x) = 0$ (no distance to itself) ✓ trivial
- $d(x, y) > 0$ for $x \neq y$ (positive) ✓ shortest path exists because G is connected
- $d(x, y) = d(y, x)$ (symmetric) ✓ all paths can be reversed bc. G is undirected
- $d(x, z) \leq d(x, y) + d(y, z)$ (triangle inequality holds) ✓ the triangle inequality holds because we can compose the path $x \rightsquigarrow z$ by $x \rightsquigarrow y \rightsquigarrow z$

SPR-Distance

The **SPR-distance** $\mathsf{d}_{\mathsf{SPR}}(T, T')$ of T and T' is defined as the distance of T and T' in the SPR-graph G.

Lemma 1.
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Proof exercise

Goal.
Compute the SPR-distance $\mathsf{d}_{\mathsf{SPR}}(T, T')$.

Lemma 2.
The SPR-distance is a metric.

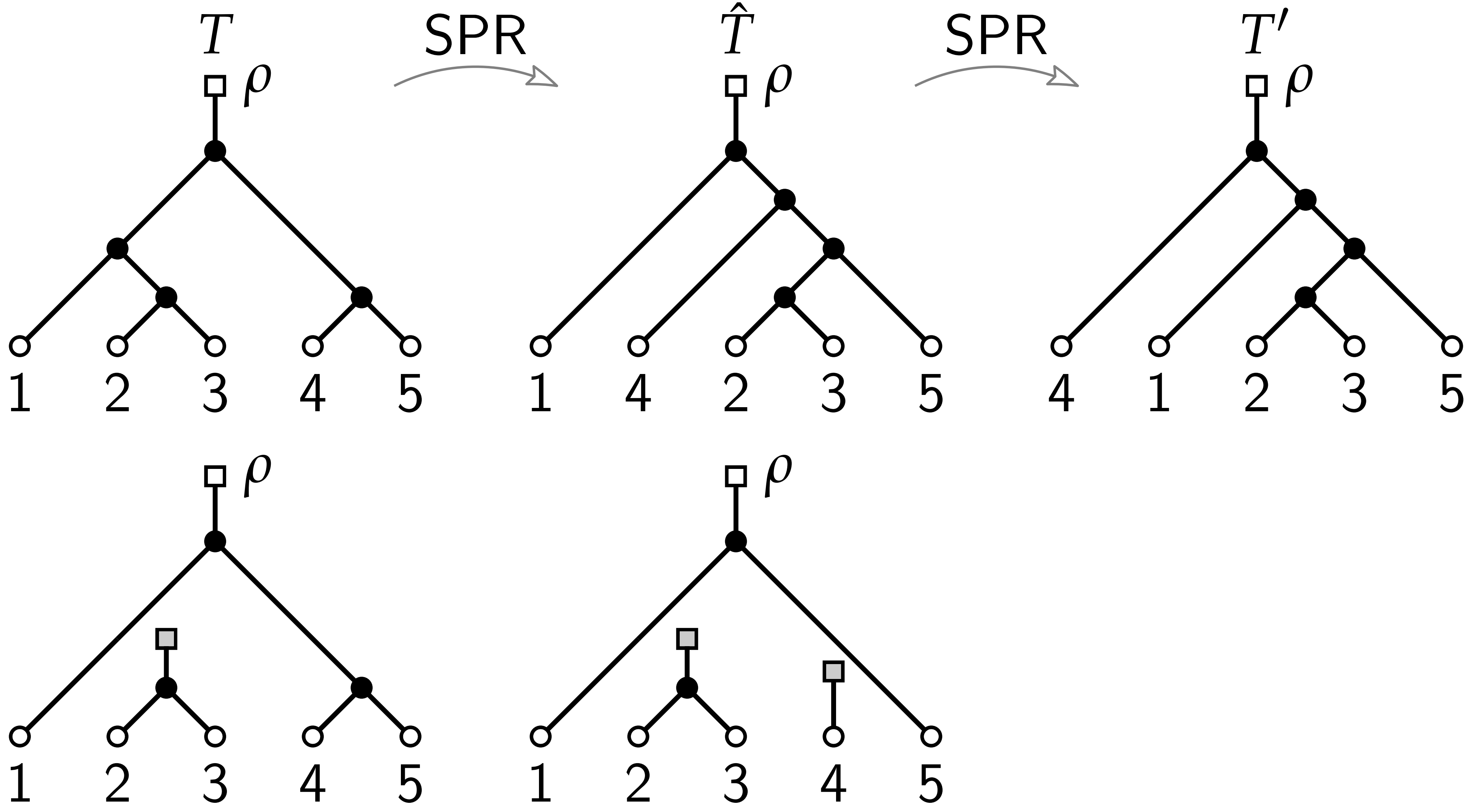
Proof. G is connected and undirected.
All properties of a metric follow. □

. . . but G is huge!

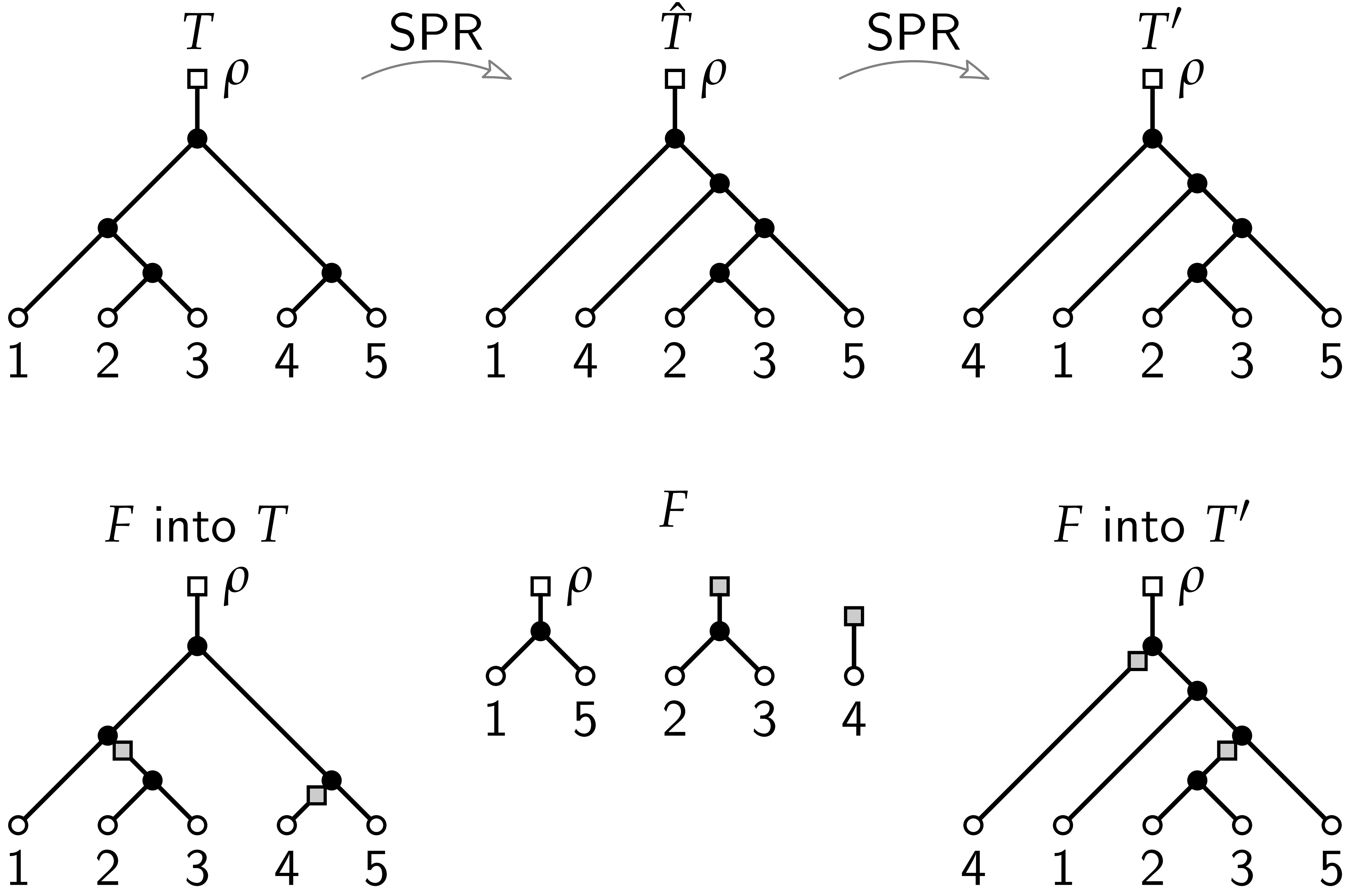
$$|V(G)| = (2n-3)!! = (2n-3) \cdot (2n-5) \cdot \ldots \cdot 5 \cdot 3$$

- Can we rephrase the problem?

Maximum Agreement Forests



Maximum Agreement Forests



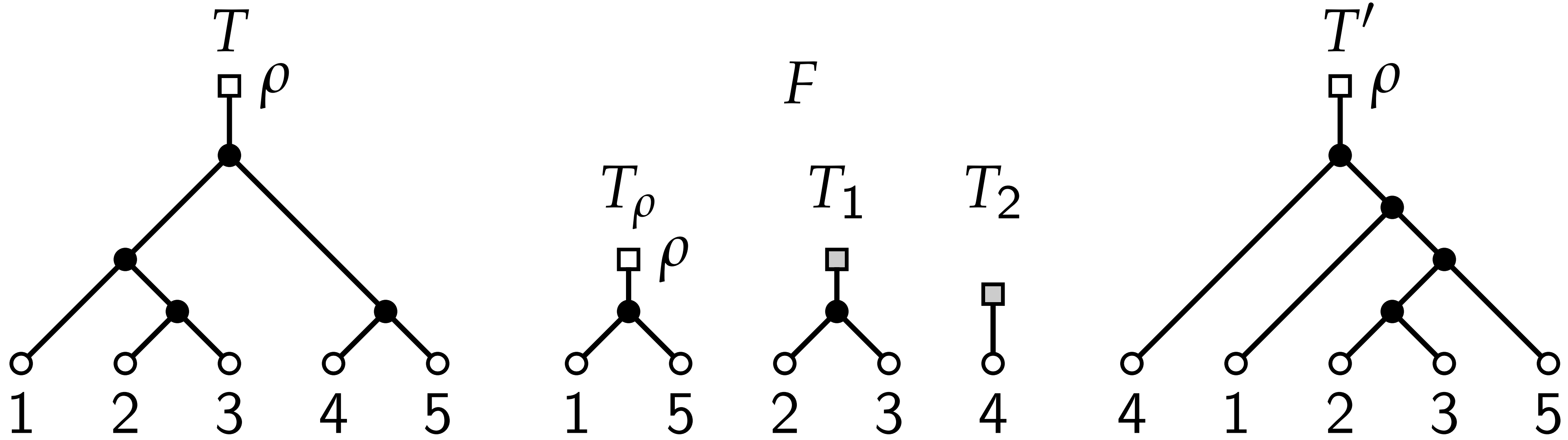
T $\xrightarrow{\text{SPR}}$ $\hat{T}$ $\xrightarrow{\text{SPR}}$ T'

F into T

F

F into T'

Maximum Agreement Forests



An **agreement forest (AF)** F of T and T' is a forest $\{T_\rho, T_1, T_2, \ldots, T_k\}$ such that

- the label sets of the T_i partition $X \cup \{\rho\}$,
- ρ is in the label set of T_ρ, and
- there is an edge-disjoint embedding of the T_is into T and T' where all edges of T and T' are covered. In other words, we can place all T_is onto T and T' such that the T_is do not overlap and every edge of T and T' lies under some T_i.

If k is minimum, F is a **maximum agreement forest (MAF)**.

Characterization

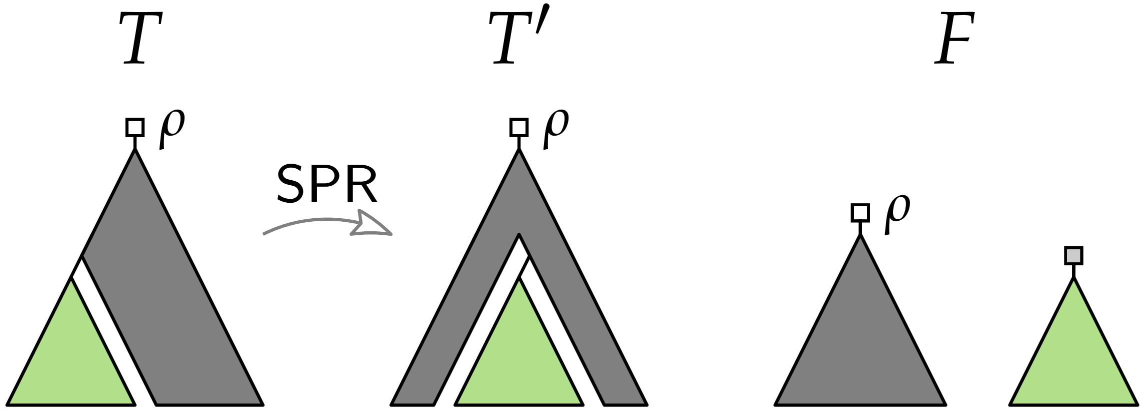
Let T and T' be two phylogenetic trees on X and let $F = \{T_\rho, T_1, T_2, \ldots, T_k\}$ be a MAF of T and T'.
Define

$$\mathrm{m}(T, T') = k = |F| - 1.$$

Theorem 3. $\mathrm{m}(T, T') = \mathrm{d_{SPR}}(T, T')$

Proof of "$\leq$" by induction on $d = \mathrm{d_{SPR}}(T, T')$.

- Case $d = 0$ is trivial and Case $d = 1$ is easy. ✓
- Assume $\mathrm{m}(T, T') \leq \mathrm{d_{SPR}}(T, T')$ holds for all $d \leq \ell$.



Characterization

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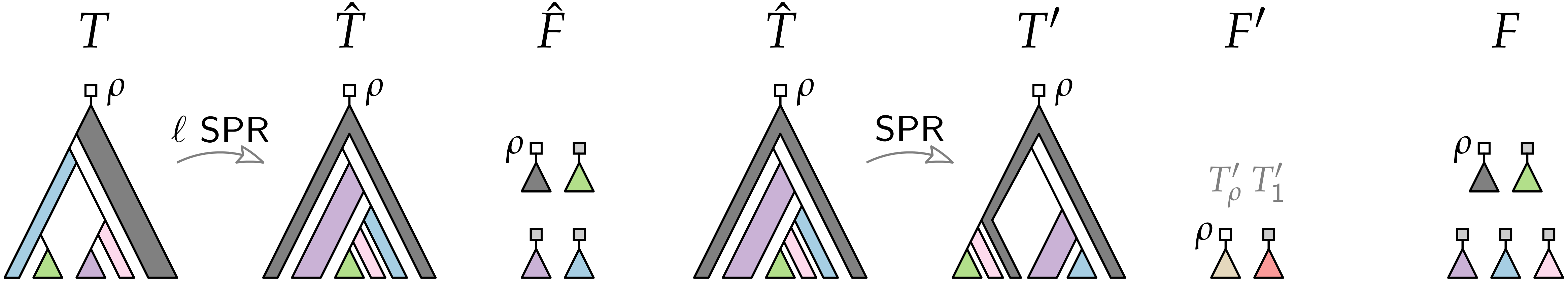
Proof of "$\leq$" by induction on $d = \mathrm{d_{SPR}}(T, T')$.

- If $d = \ell + 1$, then there exists $\hat{T}$ with $\mathrm{d_{SPR}}(T, \hat{T}) = \ell$ and $\mathrm{d_{SPR}}(\hat{T}, T') = 1$.
- $\exists$ MAF $\hat{F}$ for T & $\hat{T}$ of size $\ell + 1$ and MAF F' for $\hat{T}$ & T' of size 2.
- Compose $\hat{T}$ by subtrees of $\hat{F}$. The subtree T'_1 of F' is rooted at one edge of $\hat{T}$ within one subtree of $\hat{F}$.
- Subdivide the corresponding tree to obtain F from $\hat{F}$, which is an AF for T and T'.



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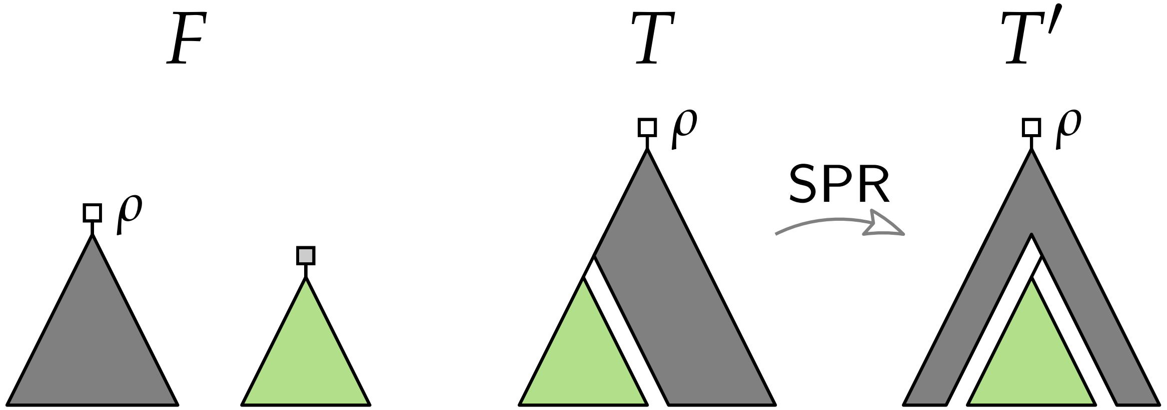
Proof of "$\geq$" by induction on $m = \mathrm{m}(T, T')$.

- Case $m = 0$ is trivial and Case $m = 1$ is easy. ✓
- Assume $\mathrm{m}(T, T') \geq \mathrm{d}_{\mathrm{SPR}}(T, T')$ holds for all $m \leq \ell$.



Characterization

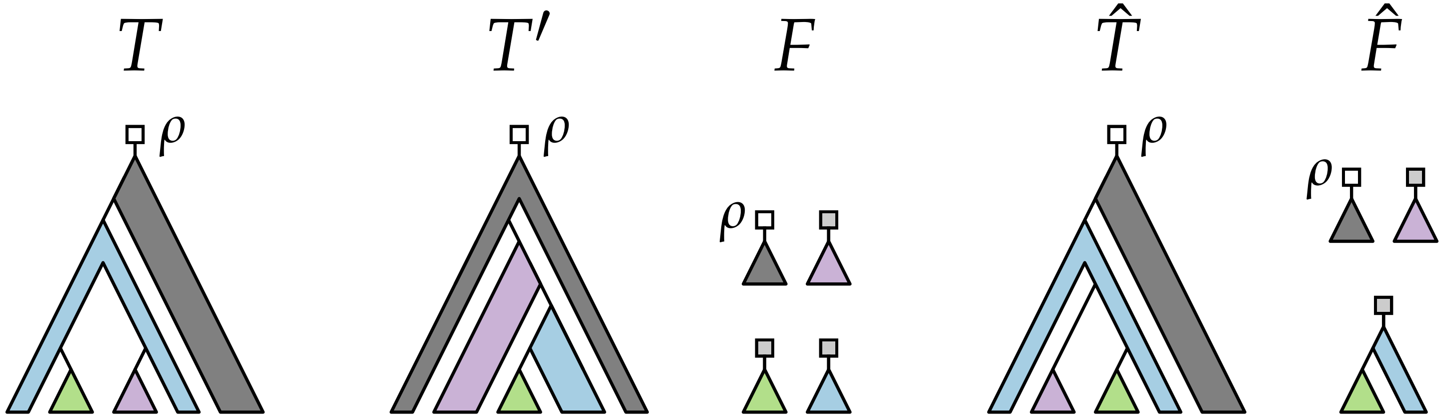
Let T and T' be two phylogenetic trees on X and let $F = \{T_\rho, T_1, T_2, \dots, T_k\}$ be a MAF of T and T'.
Define

$$\mathrm{m}(T, T') = k = |F| - 1.$$

Theorem 3. $\mathrm{m}(T, T') = \mathrm{d_{SPR}}(T, T')$

Proof of "$\geq$" by induction on $m = \mathrm{m}(T, T')$.

- Let F be a MAF of T and T' of size $\ell + 2$.
- There exists a T_i that can be pruned in T due to the nesting structure of subtrees.



- Regraft T_i according to the embedding of F into T' $\Rightarrow$ $\hat{T}$ & $\hat{F}$
- $\hat{F}$ is AF for $\hat{T}$ & T' and $|\hat{F}| = \ell + 1$
- $\Rightarrow \mathrm{d_{SPR}}(\hat{T}, T') \leq \ell$
- $\mathrm{d_{SPR}}(T, \hat{T}) = 1$
- $\mathrm{d_{SPR}}(T, T') \leq \ell + 1 = \mathrm{m}(T, T')$

□

Problem & Plan

Theorem 4. [HJWZ '96, BS '05]
Computing $\mathrm{d}_{\mathsf{SPR}}(T, T')$ is NP-hard.

Proof by reduction from Exact Cover by 3-Sets.

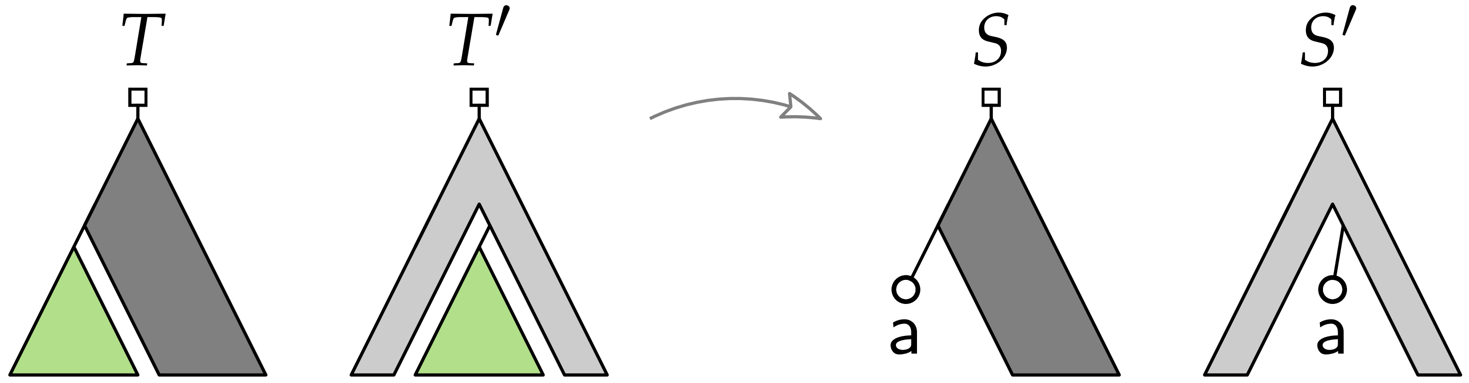
Plan.

- Construct **kernel** of the problem.
  - Replace T and T' with smaller S and S'.
  - Derive $\mathrm{d}_{\mathsf{SPR}}(T, T')$ from $\mathrm{d}_{\mathsf{SPR}}(S, S')$.
- Show that the size of the kernel depends on $\mathrm{d}_{\mathsf{SPR}}(T, T')$.
- Devise an FPT algorithm with respect to $\mathrm{d}_{\mathsf{SPR}}$.
- Sketch an approximation algorithm.

Kernelization – Subtrees

Common subtree reduction.

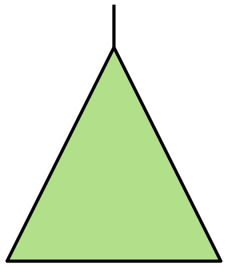
- Replace any subtree (with ≥ 2 leaves) that occurs identically in both trees by a single leaf with a new label.



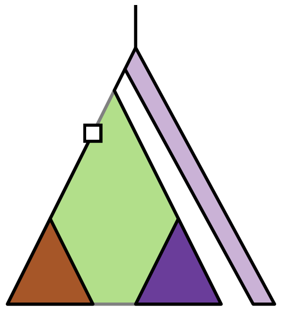
Lemma 5. Applying the common subtree reduction is safe, i.e., $\mathsf{d}_{\mathsf{SPR}}(T, T') = \mathsf{d}_{\mathsf{SPR}}(S, S')$.

Proof.

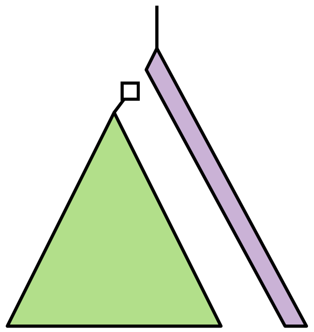
Suppose



is covered by two trees of MAF



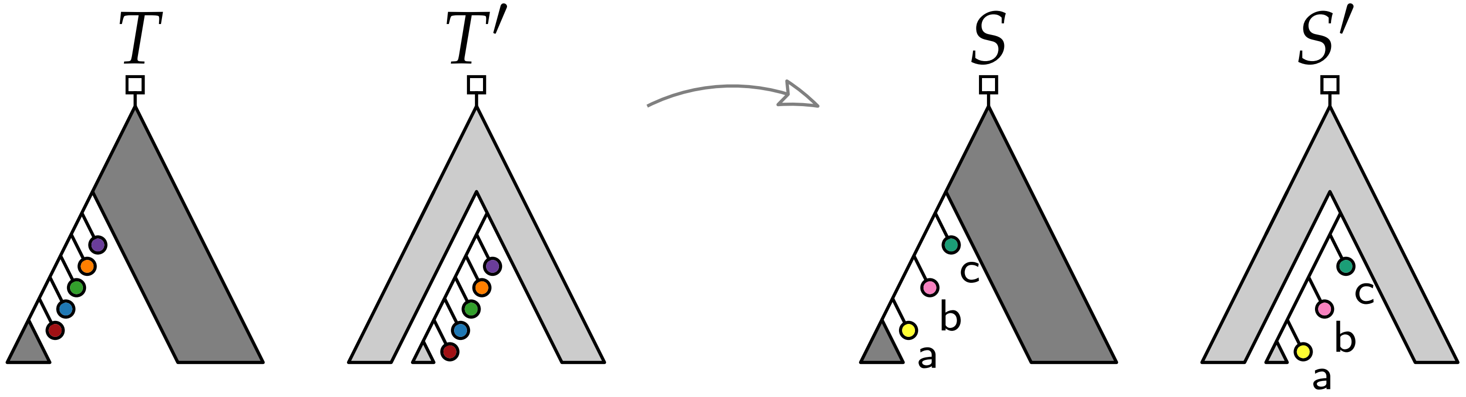
then there is an alternative MAF of the same size



Kernelization – Chains

Chain reduction.

- Replace any chain of leaves that occurs identically (from bottom to top) in both trees by three new leaves.



Lemma 6. Applying chain reduction is safe, i.e., $\mathsf{d_{SPR}}(T, T') = \mathsf{d_{SPR}}(S, S')$.

Proof.

- Show there is a tree with abc-chain in a MAF of S and S'.
- Swap abc-chain with original chain for MAF of T and T'.

Kernelization – Chains

Chain reduction.

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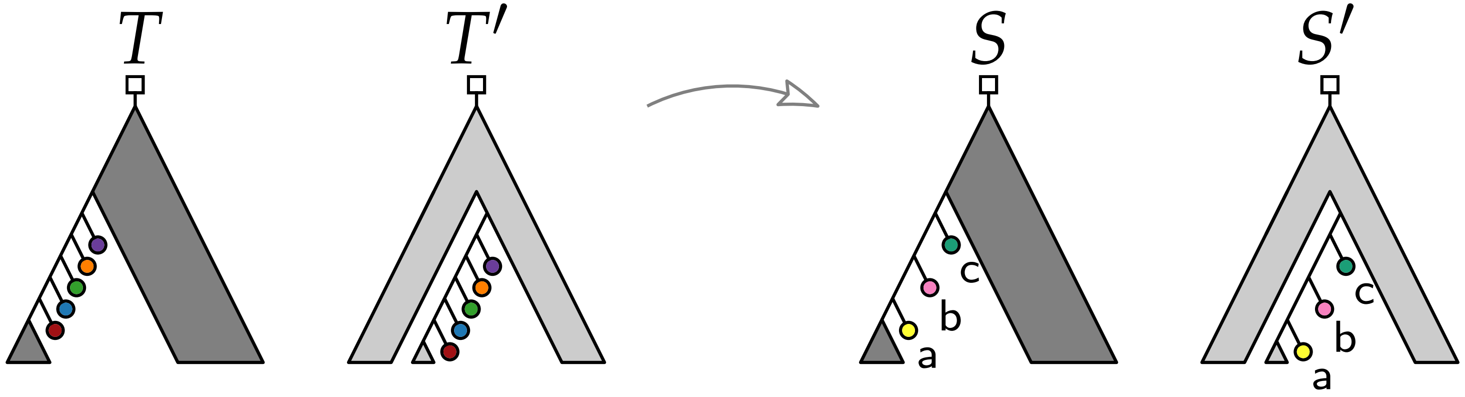
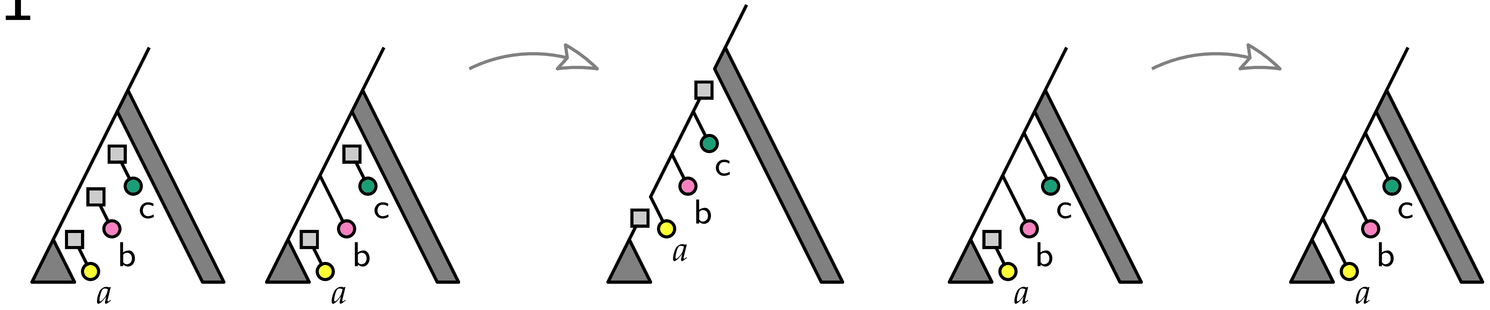


Lemma 6. Applying chain reduction is safe, i.e., $\mathrm{d}_{\mathsf{SPR}}(T,T') = \mathrm{d}_{\mathsf{SPR}}(S,S')$.

Proof.

- Consider embedding of a MAF F into S.

Case 1



Kernelization – Chains

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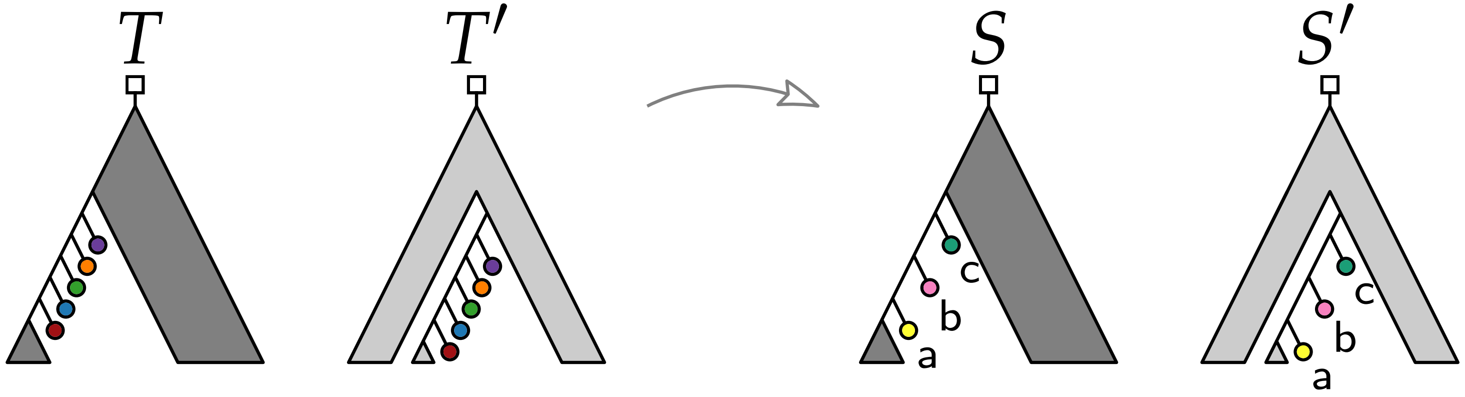

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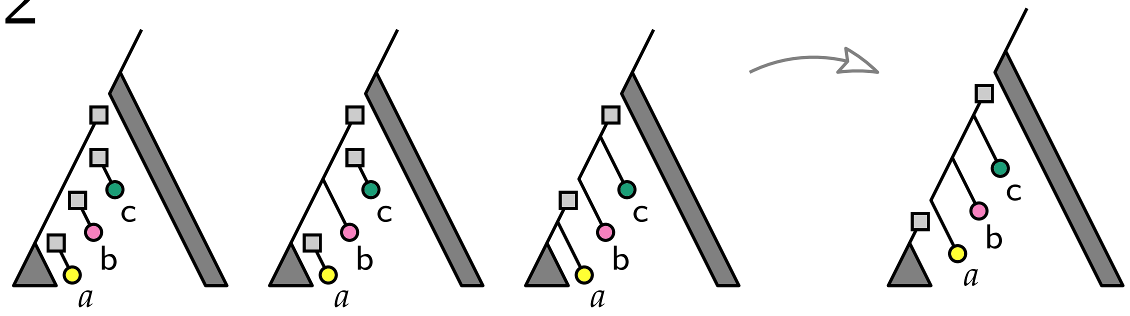
Proof.

- Consider embedding of a MAF F into S.

Case 2



Kernelization – Chains

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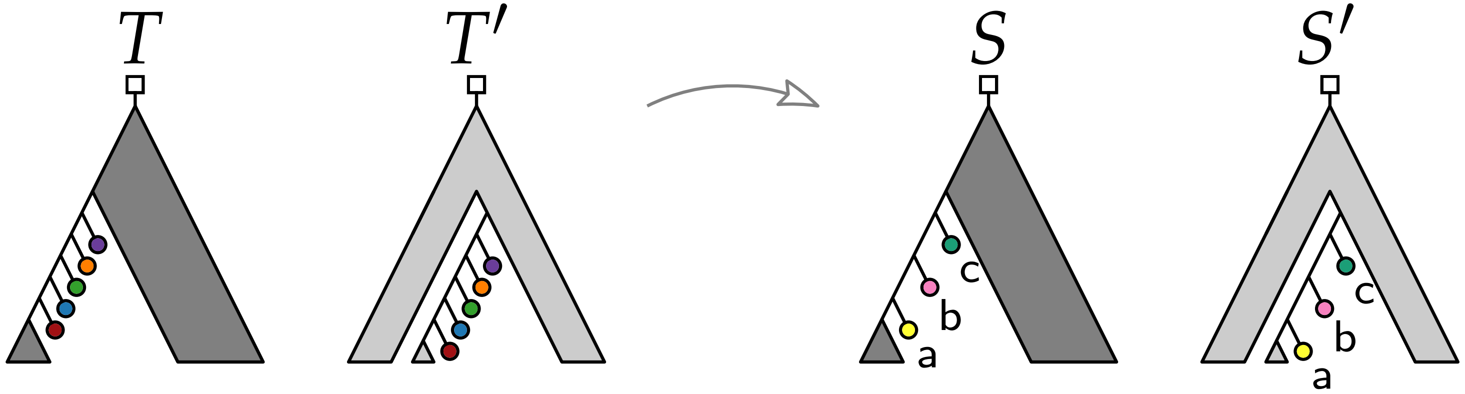
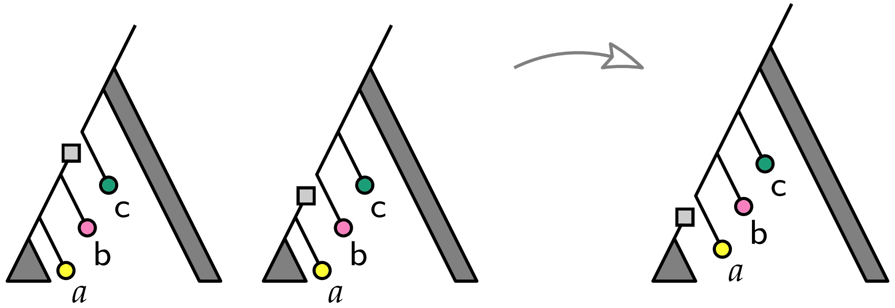


> **Lemma 6.** Applying chain reduction is safe, i.e., $\mathrm{d}_{\mathrm{SPR}}(T,T') = \mathrm{d}_{\mathrm{SPR}}(S,S')$.

Proof.

Case 3

- Consider embedding of a MAF F into S.



Kernelization – Chains

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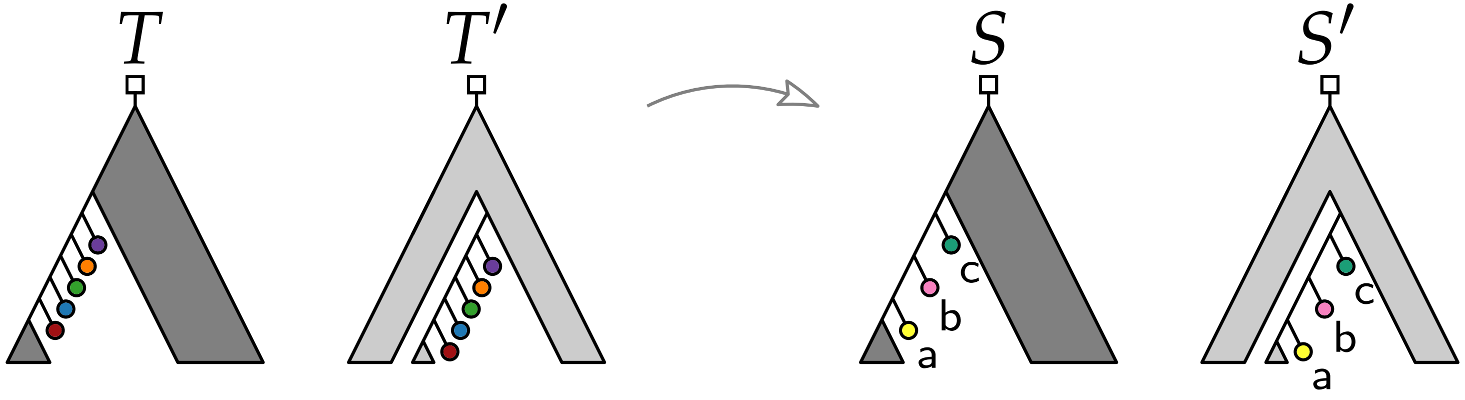
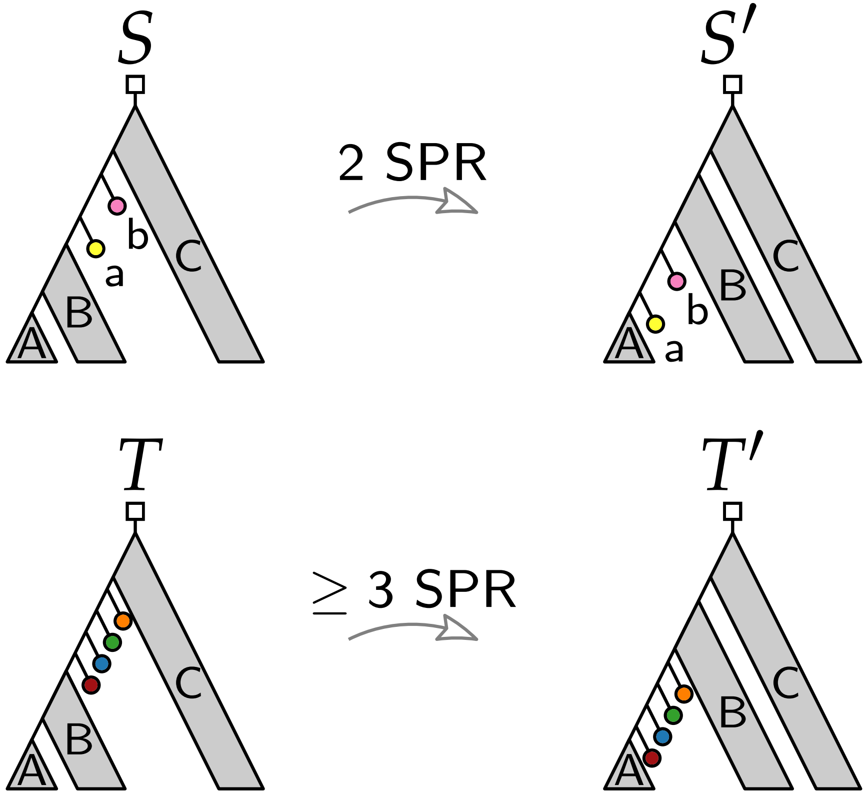


Lemma 6. Applying chain reduction is safe, i.e., $\mathsf{d_{SPR}}(T, T') = \mathsf{d_{SPR}}(S, S')$.

Why not using a chain of length ≤ 2?



Kernel Size

Lemma 7.
Reduce T and T' to S and S' by exhaustively applying the reduction rules. Let S and S' be on X'. Then
$$|X'| \leq 28\,\mathsf{d}_{\mathsf{SPR}}(T,T').$$

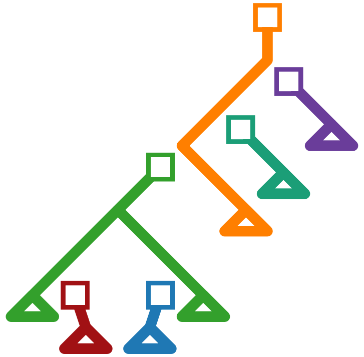
We know
$k = \mathsf{d}_{\mathsf{SPR}}(S,S') = \mathsf{d}_{\mathsf{SPR}}(T,T')$.

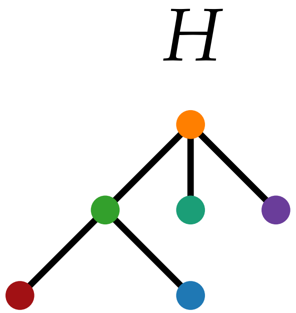
Proof. Let $F = \{T_\rho, T_1, \dots, T_k\}$ be MAF for S and S'.

Let $\mathsf{n}(T_i) := |\{T_j \mid T_j \in F \wedge T_i$ and T_j touch in $S\}|$.

Similarly, let $\mathsf{n}'(T_i) := |\{T_j \mid T_j \in F \wedge T_i$ and T_j touch in $S'\}|$.

Claim 1. $\sum_{i=\rho}^{k} (\mathsf{n}(T_i) + \mathsf{n}'(T_i)) \leq 4k$.





$$|V(H)| = k+1$$
$$= |E(H)| + 1$$

$$\sum_{i=\rho}^{k} \mathsf{n}(T_i) = 2|E(H)| \leq 2k$$

Kernel Size

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$$|X'| \leq 28\,\mathsf{d}_{\mathsf{SPR}}(T, T').$$

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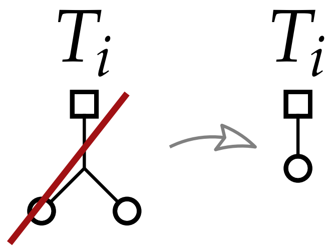
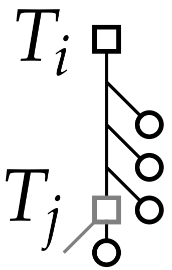
Similarly, let $\mathsf{n}'(T_i) := |\{T_j \mid T_j \in F \wedge T_i \text{ and } T_j \text{ touch in } S'\}|$.

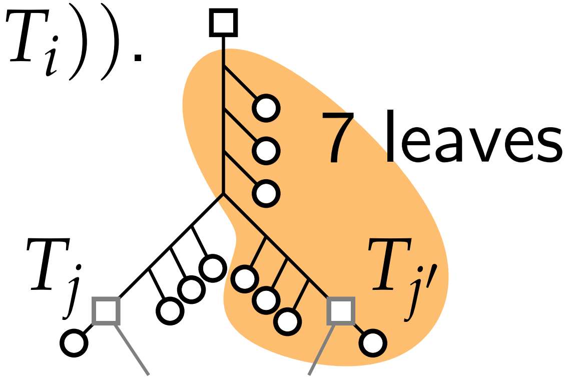
Claim 1. $\sum_{i=\rho}^{k}(\mathsf{n}(T_i) + \mathsf{n}'(T_i)) \leq 4k$.

Claim 2. $\#$ leaves of $T_i \leq 7(\mathsf{n}(T_i) + \mathsf{n}'(T_i))$.

$$|X'| = \textstyle\sum_{i=\rho}^{k} \#\text{ leaves of } T_i$$
$$\leq \textstyle\sum_{i=\rho}^{k} 7(\mathsf{n}(T_i) + \mathsf{n}'(T_i))$$
$$\leq 28k$$







FPT Algorithm

Theorem 8.
Computing $\mathsf{d}_{\mathsf{SPR}}(T, T')$ is fixed-parameter tractable when parameterized by $\mathsf{d}_{\mathsf{SPR}}(T, T')$.

Proof.

- Reduce T and T' to S and S' by exhaustively applying the reduction rules.
- Let S and S' be on X' and let $k = \mathsf{d}_{\mathsf{SPR}}(S, S')$.
- S has at most $4|X'|^2$ neighbors in the SPR-graph G.
  - S has less than $2|X'|$ edges to cut and to attach to.
- Length-k BFS from S visits at most $O\left(\left(4|X'|^2\right)^k\right) = O\left((56k)^{2k}\right)$ trees.

by Lemma 7

- Since $k = \mathsf{d}_{\mathsf{SPR}}(S, S') = \mathsf{d}_{\mathsf{SPR}}(T, T')$, this yields an FPT algorithm.

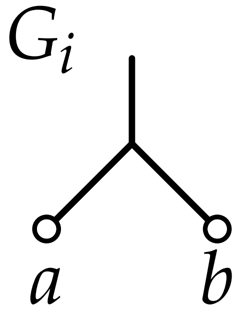
Approximation Algorithm

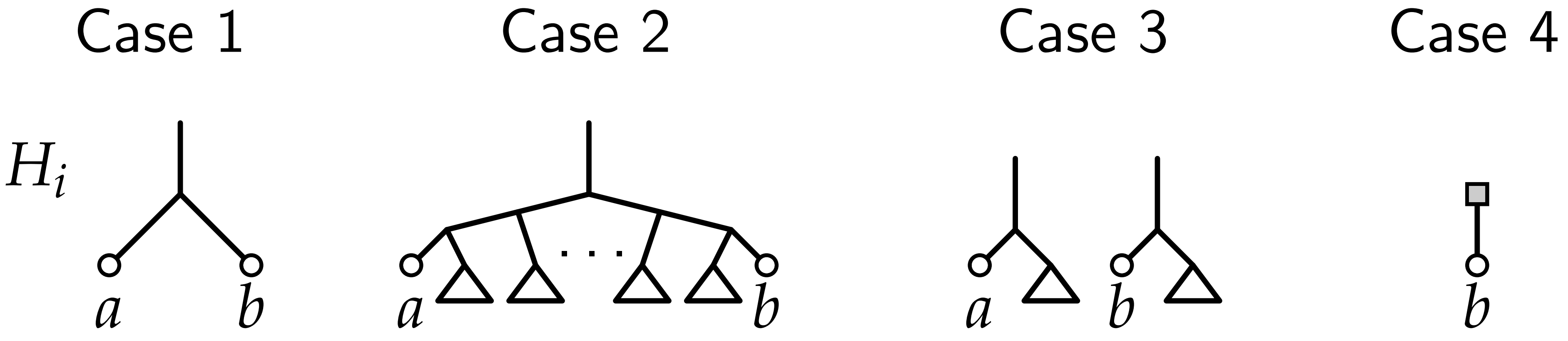
Idea.

- Given trees T and T', which are reduced by the previous rules, we compute an agreement forest F by
- successively making “cuts” and “eliminations”.
- These steps let T and T' shrink further and further.
- Show that $|F|$ is at most $3|F^*|$, where F^* is a MAF of T and T'.

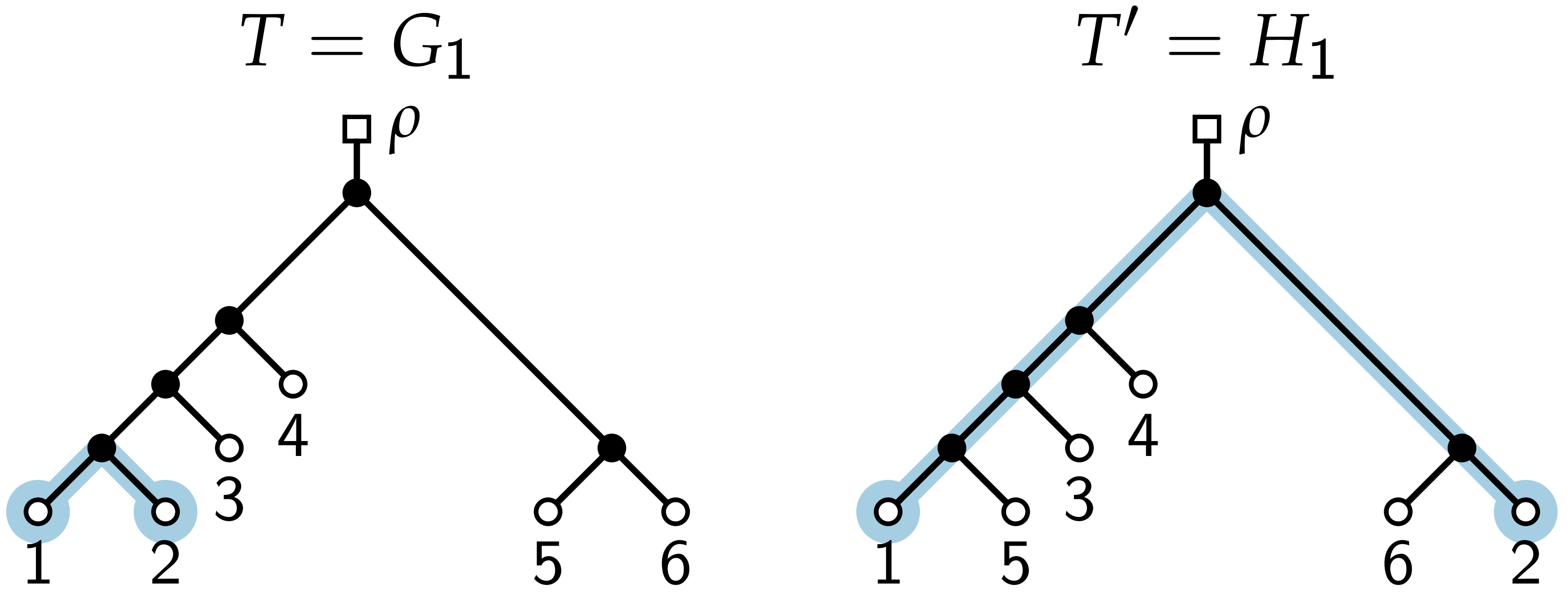
Approximation Algorithm

```
APPROXDSPR($T, T'$)
  $i \leftarrow 1$
  $G_i \leftarrow T$
  $H_i \leftarrow T'$
  while $\exists$ pair of sibling leaves $a$ and $b$ in $G_i$ do
      find the case that applies to $a$ and $b$ in $H_i$
      apply the corresponding modification
      to obtain $G_{i+1}$ from $G_i$ and $H_{i+1}$ from $H_i$
      $i++$
  return $|H_i| - 1$
```





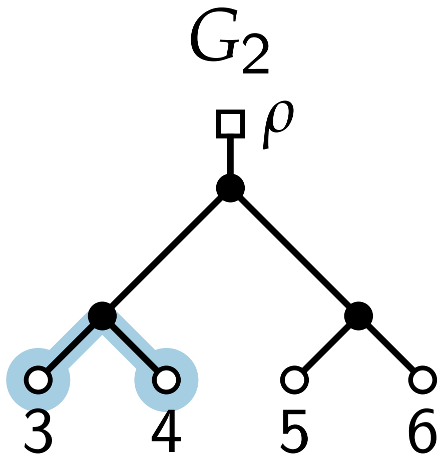
Approximation Algorithm – Example

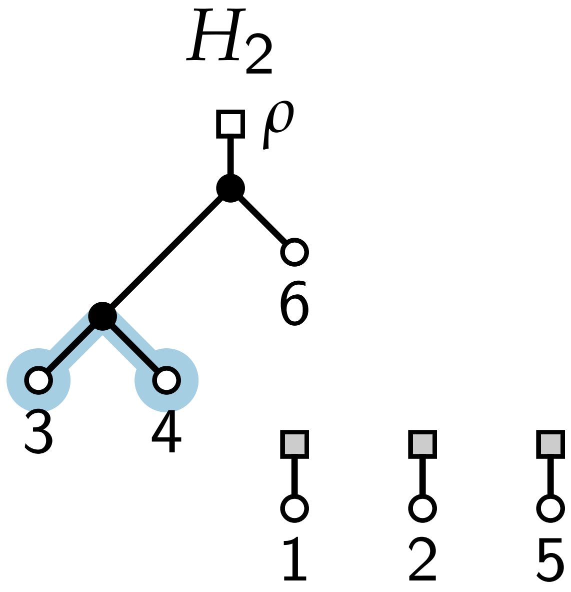


Case 2

- Should we cut off leaf 1 or leaf 2 or everything between them in H_1?
- Do parts of each!

Approximation Algorithm – Example

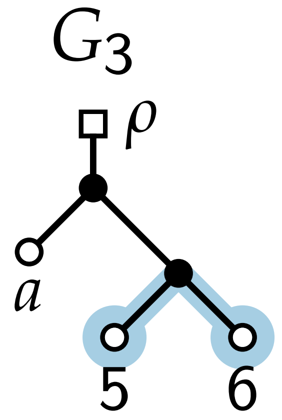


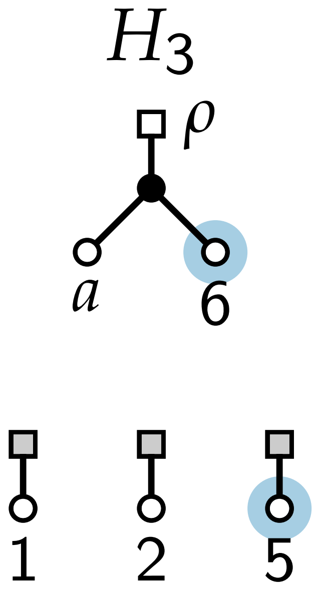


Case 1

- If the same "cherry" (i.e., pair of leaves) occurs in G_i and H_i, we simply reduce it.

Approximation Algorithm – Example

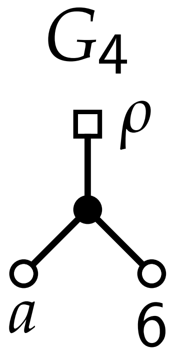


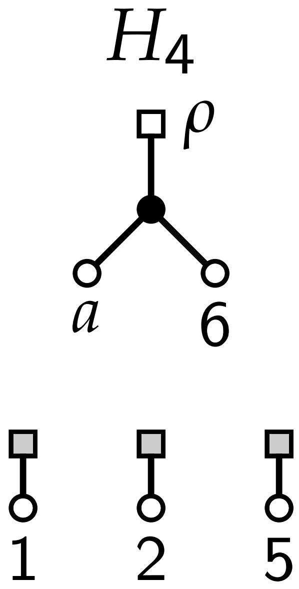


Case 4

- Leaf b is the only leaf of a tree in H_i.
- Cut off b in G_i.

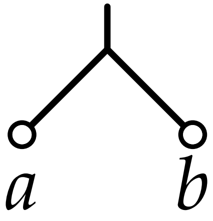
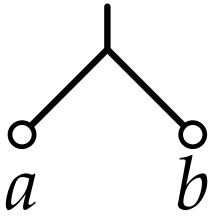
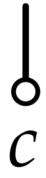
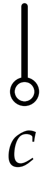
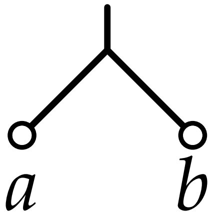
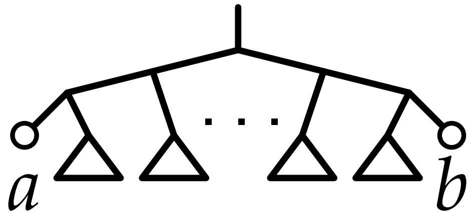
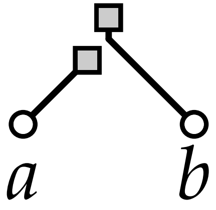
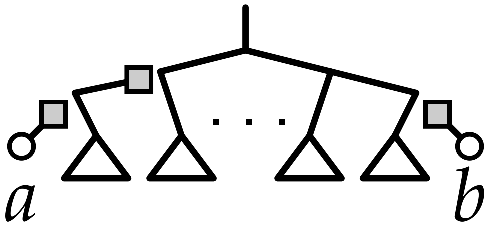
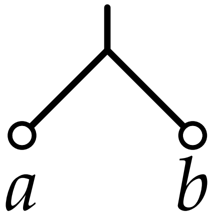
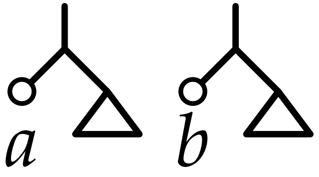
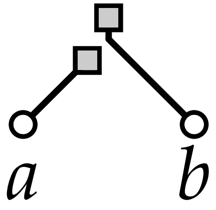
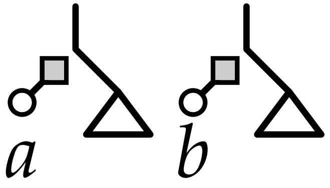
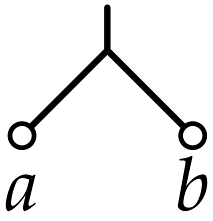
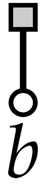
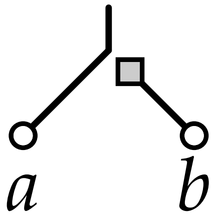
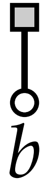
Approximation Algorithm – Example



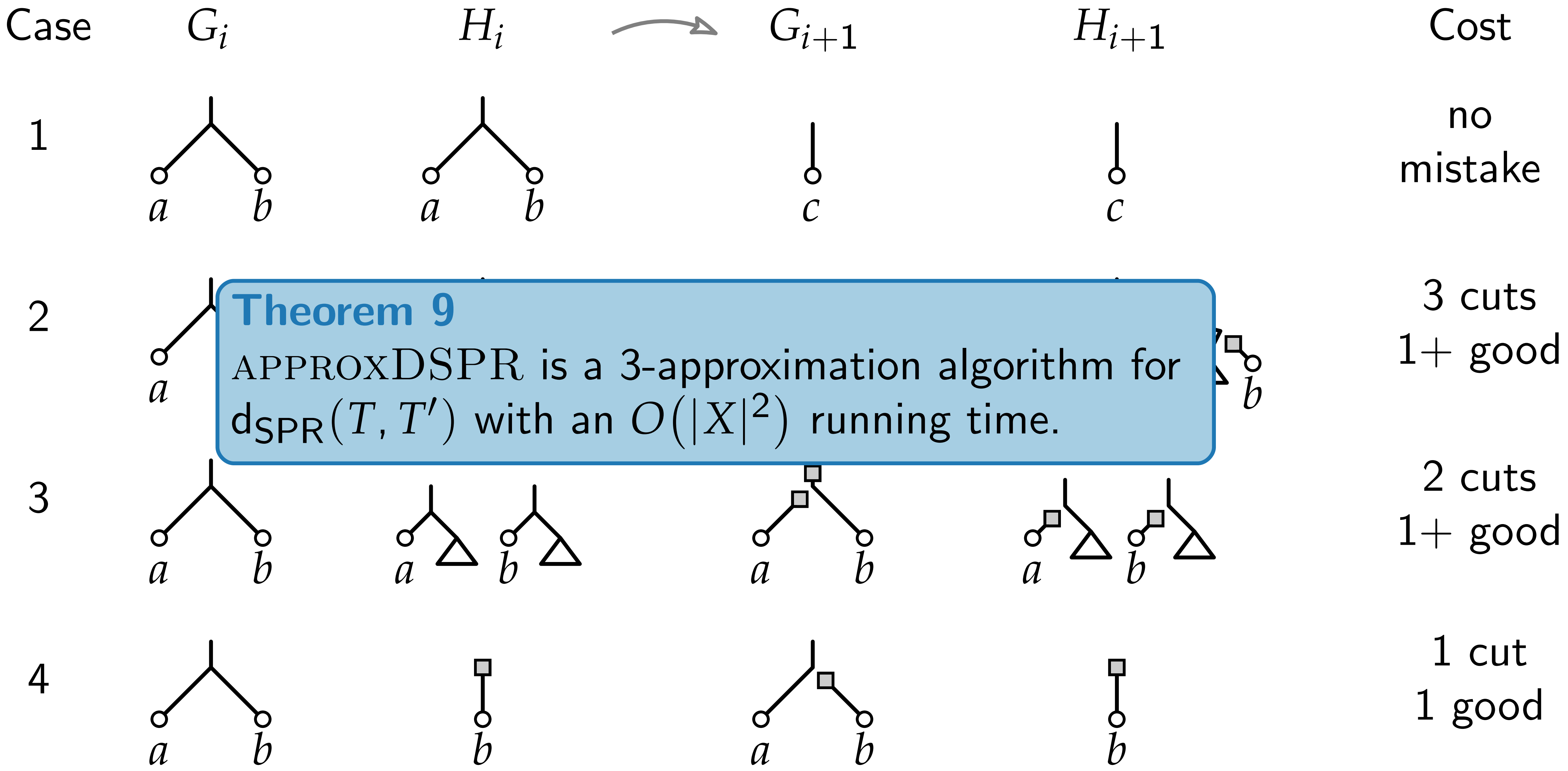


- Return 3.

Approximation Algorithm – Analysis

Case	G_i	H_i	G_{i+1}	H_{i+1}	Cost
1					no mistake
2					3 cuts 1+ good
3					2 cuts 1+ good
4					1 cut 1 good

Approximation Algorithm – Analysis



Case	Cost
1	no mistake
2	3 cuts 1+ good
3	2 cuts 1+ good
4	1 cut 1 good

Theorem 9
$\textsc{approx}\mathrm{DSPR}$ is a 3-approximation algorithm for $\mathsf{d}_{\mathsf{SPR}}(T, T')$ with an $O(|X|^2)$ running time.

Discussion

Kernelization.

- Kernelization is an important technique to construct FPT algorithms.
- Result important since SPR-distance small in practice.
- Reduction rules actually give a kernel of size at most $15k - 9$ (we have shown $28k$).
- With further reduction rules, we can get a size below $11k - 9$. [KL '18]
- Divide & conquer techniques can (in practice) further reduce the problem sizes. [LS '11]

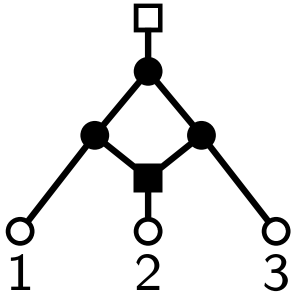
Approximation algorithm.

- There exists a 2-approximation algorithms for the SPR-distance with a running time in $\mathcal{O}(n^3)$. [CHW '17]

Discussion

Phylogenetic trees.

- There are other classes of phylogenetic trees: unrooted, non-binary, ranked, . . .
- Trees can be generalized to **phylogenetic networks**, which can also have indegree 2 outdegree 1 vertices.



Maximum Agreement Forests.

- Reframing (characterizing) a problem in a different way, can sometimes make your life a lot easier.
- MAF can be generalized to Maximum Agreement Graphs, but these do not characterize the SPR-distance of networks anymore. [K '20]

Literature

Original papers:

- [BS '05] Semple C., Bordewich M.: *On the computational complexity of the rooted subtree prune and regraft distance* (for SPR, MAF, characterisation, fpt, divide & conquer)
- [HJWZ '96] Hein J., Jiang T., Wang L., Zhang K.: *On the complexity of comparing evolutionary trees* (for NP-hardness proof)
- [RSW '06] Rodrigues E. M., Sagot M.-F., Wakabayashi Y.: *The maximum agreement forest problem: Approximation algorithms and computational experiments* (for approx. algorithm)

Referenced papers:

- [CHW '17] Chen Z., Harada Y., Wang L.: *A new 2-approximation algorithm for rSPR distance*
- [K '20] Klawitter J.: *The agreement distance of unrooted phylogenetic networks*
- [KL '19] Kelk S., Linz. S.: *New reduction rules for the tree bisection and reconnection distance*
- [LS '11] Linz S., Semple C.: *A cluster reduction for computing the subtree distance between phylogenies*