

A Rearrangement Distance for Fully-Labelled Trees

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Abstract

The problem of comparing trees representing the evolutionary histories of cancerous tumors has turned out to be crucial, since there is a variety of different methods which typically infer multiple possible trees. A departure from the widely studied setting of classical phylogenetics, where trees are leaf-labelled, tumoral trees are fully labelled, *i.e.*, every vertex has a label.

In this paper we provide a rearrangement distance measure between two fully-labelled trees. This notion originates from two operations: one which modifies the topology of the tree, the other which permutes the labels of the vertices, hence leaving the topology unaffected. While we show that the distance between two trees in terms of each such operation alone can be decided in polynomial time, the more general notion of distance when both operations are allowed is NP-hard to decide. Despite this result, we show that it is fixed-parameter tractable, and we give a 4-approximation algorithm when one of the trees is binary.

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1 Introduction

Tree rearrangement concerns modifying the topology of a set of elements arranged in a tree and has a large literature [33] on phylogenies, that is, trees whose leaves, and only leaves, are labelled by *taxa*. This setting is convenient, since it is a faithful model of the actual problem that biologists want to solve: to find a plausible evolutionary history that can explain a set of extant species (or individuals) [13] – the internal nodes being the hypothetical ancestral taxa, which are extinct. The problem of inferring phylogenies is centuries old, and there is a rich literature on computational methods, which fall into major groups such as parsimony methods [12, 14], or maximum-likelihood methods [7, 13]. With the wealth of different methods for inferring phylogenetic trees on a given set of taxa, a notion of *rearrangement distance* between output trees can be useful to assess the reliability of methods or even the data itself in inferring such trees. This sparked a body of research on rearrangement distances



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for phylogenetic trees, resulting in rearrangement distance measures such as *nearest neighbor interchange* (NNI) [9], *subtree prune and regraft* (SPR) [5] and *tree bisection and reconnection* (TBR) [2] – interestingly, all such rearrangement distances are NP-hard to decide. See [23] for a comprehensive survey of the above rearrangement distance measures, as well as other more general distance measures for phylogenetic trees, such as the classical Robinson-Foulds distance [30].

This paper focuses on a different, albeit related, biological field: the study of cancer progression. While the theory on cancer progression as an evolutionary process is several decades old [27], only in the past decade are data appearing that allow us to reconstruct in detail the evolutionary history of the progression of various cancers [20, 17] – providing insight into drug resistance and devising therapeutic strategies [26, 37]. In this setting, we have one or more tumor samples where the taxa are cancer *clones* [27, 17], or groups of cancer cells at various stages of mutation – all of which originate from a single *driver mutation*, and the goal is again to construct the most likely evolutionary history of these clones. The key difference in this setting is that – since the tumor is only months old – all of the clones, even the one representing only the driver mutation, are present in the samples, *i.e.*, the internal nodes are extant taxa. In this setting, the inferred evolutionary history is rather a *fully-labelled* tree, where a label represents a single mutation that has been acquired by a clone during evolution. It is quite common to assume that the evolution of mutations follows the *infinite sites assumption* [18, 17, 11] which implies that once a mutation is acquired in a node it is never lost, and thus it will be present in all the clones associated with the descendants of the node. The above assumption motivates the fact that we can label each node with a single mutation. More recently, this assumption has been challenged [24].

There is already a wealth of methods for inferring such fully-labelled cancer evolutionary trees, most of them leveraging bulk sequencing data [20, 17, 38, 11, 4, 8], however methods taking advantage of higher resolution Single Cell Sequencing (SCS) technologies [18, 31] – even some hybrid methods – are beginning to appear [32]. With the amount of data and methods becoming available for inferring cancer evolution, a main challenging problem turns out to be the comparison of the multiple trees that are produced by a single method or by different approaches, see, *e.g.*, [29]. The investigation of operations for defining the rearrangement distance between trees output by these methods is still in its infancy and require the comparison of trees over the same set of mutations, *i.e.*, labels. Indeed, most recent works, *e.g.*, [16] are mainly focused on defining a consensus tree on path, or on ancestor-based distance measures, rather than on transforming a tree into another considering also the topology of the trees and the ancestor-descendant relationship of the labels – since *all* nodes of the trees are now labelled.

While we concentrate in this work on rearrangement distance between fully-labelled trees, this move to fully-labelled trees opens up the discussion to the more general *edit distance* between fully-labelled trees, purportedly introduced in [36], and of which there is a sizeable literature, *e.g.*, [39, 25]. There is even a comprehensive survey on the topic in [3], while a recent implementation is reported in [28, 28]. Even in the context of cancer progression, a recent paper [22] provides a notion of edit distance for multi-labelled trees has been defined with the goal of reconciling two trees over distinct sets of labels into a common one.

In this work, we open the investigation of some notions of the rearrangement distance for two rooted trees which are fully labelled by the same set of labels. Following the existing literature [33, 35] on phylogeny rearrangement, we extend to several operations for rearranging a fully-labelled tree. The distance between a pair of trees is then the shortest sequence of these operations that transforms the first tree into the second tree. The first

operation we introduce is an adaptation of the SPR operation [5] to a fully-labelled tree. We introduce a second operation that consists of a permutation of the labels of the tree – notice that such an operation does not really make sense on leaf-labelled phylogenies. For both operations, we provide an algorithm for computing the shortest sequence of operations needed to transform an input tree into a second input tree. Then we extend this rearrangement measure by allowing both operations: we show that the new computational problem of finding a shortest sequence of operations is NP-hard, but we give a 4-approximation ratio and a fixed parameter algorithm.

2 Preliminaries

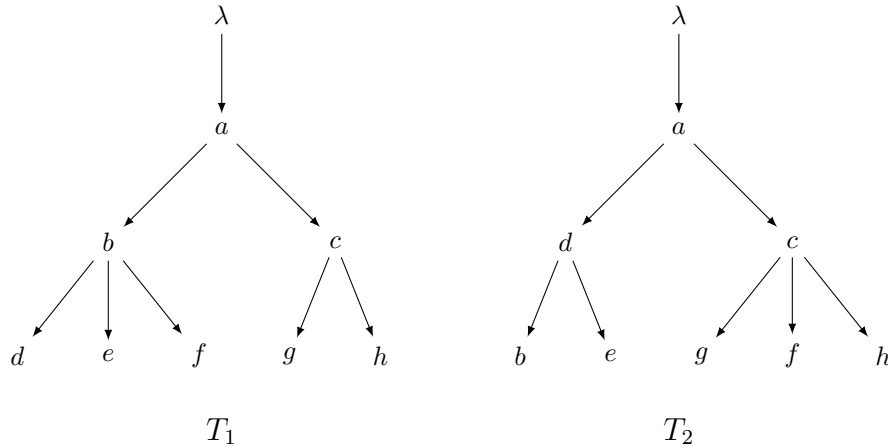
A *tree* is an undirected connected graph $T = (V_T, E_T)$ without cycles: its degree-one vertices are called *leaves*, while the remaining vertices are called *internal* vertices. Trees T_1 and T_2 are *isomorphic*, and we write $T_1 \cong T_2$, if there is a bijective (or one-to-one) mapping $m : V_{T_1} \rightarrow V_{T_2}$ such that $(u, v) \in E_{T_1}$ iff $(m(u), m(v)) \in E_{T_2}$. Such a mapping is referred to as an *isomorphic mapping*, or an *isomorphism*.

A *rooted* tree has an edge between some vertex $w \in V_T$ and an extra *root* vertex $\lambda_T \notin V_T$ which has been added, implicitly directing the edges, *e.g.*, away from the root. We can hence define the *parent* and *child* relationships, $p_T : V_T \rightarrow V_T \cup \{\lambda_T\}$ and $c_T : V_T \cup \{\lambda_T\} \rightarrow 2^{V_T}$ respectively, where $p_T(v) = u$ (resp., $v \in c_T(u)$) if $(u, v) \in E_T \cup \{(\lambda_T, w)\}$ and u is on the path from λ_T to v . Note that since the children $c_T(u)$ of some vertex u is a *set*, hence they are *unordered*, unlike in some notions defined in [3] where an ordering can be specified. Moreover, $|c_T(u)|$ for any u is not of any fixed size, *i.e.*, vertices are of *unbounded degree* – the trees are not necessarily binary, for example. More generally, we say that a node u is an *ancestor* of a node v if u is on the path from λ_T to v , and conversely, v is a *descendant* of u . We extend the above notion of isomorphism to a pair T_1, T_2 of rooted trees by adding the condition that $m(\lambda_{T_1}) = \lambda_{T_2}$.

A tree T is *fully labelled* when its vertices V_T are in a one-to-one correspondence with some set \mathcal{L} of labels, implying that $|V_T| = |\mathcal{L}|$. Since all trees in this paper are rooted and fully labelled, we will henceforth use the term *tree* to denote a rooted, fully labelled tree, and the expression *tree T labelled by \mathcal{L}* to denote a rooted tree T , fully labelled by the set \mathcal{L} of labels. Trees T_1 and T_2 each labelled by \mathcal{L} are *congruent* if T_1 and T_2 are isomorphic, and one of the isomorphisms m also has the property that for every $u \in V_{T_1}$, u and $m(u)$ have the same label. Note that if T_1 and T_2 are congruent, then the unique child of λ_{T_1} has the same label as the unique child of λ_{T_2} . Since all vertices of T_1 and T_2 are uniquely labelled and $\lambda_{T_1}, \lambda_{T_2}$ are special, we refer to a vertex of a tree and its label interchangeably, when this has no effect, while clearly distinguishing them in contexts where it matters.

In this paper, we study some notions of distance between pairs T_1, T_2 of trees based on some *rearrangement operations* that transform T_1 into some T'_1 that is congruent to T_2 . For the sake of simplicity, from now on we will slightly abuse terminology in saying that a sequence of operations transforms T_1 into T_2 . Given a tree T labelled by \mathcal{L} , the operations are:

- **link-and-cut operation:** given labels v , $p_T(v) = u$ and a third label w which is not a descendant of v , remove the edge (u, v) and add the edge (w, v) , effectively switching the parent $p_T(v)$ of v from u to w . We denote this operation $v|u \rightarrow w$.
- **permutation operation:** apply some permutation $\pi : \mathcal{L} \rightarrow \mathcal{L}$ to the labels of V_T . Each label $v \in \mathcal{L}$ of T will have the new label $\pi(v)$ after this operation.



■ **Figure 1** Trees T_1 and T_2 labelled by $\mathcal{L} = \{a, b, c, d, e, f, g, h\}$. The link-and-cut distance $d_\ell(T_1, T_2)$ between T_1 and T_2 is 4 – the sequence $d|b \rightarrow a$; $e|b \rightarrow d$; $f|b \rightarrow c$; $b|a \rightarrow d$ being an example of a smallest sequence of such operations transforming T_1 into T_2 . Notice that the operation $b|a \rightarrow d$ only becomes valid after performing $d|b \rightarrow a$. The permutation distance is $d_\pi(T_1, T_2) = 6$, for example, $\pi = (b\ g\ d\ c)(e\ h)$. Finally, the rearrangement distance is $d(T_1, T_2) = 3$, for example, $(b\ d)$; $f|d \rightarrow c$.

Notice that the link-and-cut operation modifies the topology of the tree, while the permutation operation shuffles the labels without affecting the topology. The link-and-cut operation is so called, following the terminology of [34] – in this article they define the two operations separately, while ours is a certain combination of them. Our link-and-cut operation is quite similar to the *subtree moving (edit distance)* operation of [25], however the operation here has the constraint that the new parent w of child v must be within a certain distance in the tree from the original parent u – the only restriction on our link-and-cut operation is that w cannot be a descendant of v . Both of these operations are invertible: if an operation σ transforms T into T' , then its inverse operation σ^{-1} transforms T' into T . For example, if T' was obtained by applying $v|u \rightarrow w$ to T , then applying $v|w \rightarrow u$ to T' results in T . Similarly, if T' was obtained by applying π to T , then applying π^{-1} to T' results in T . By induction, any sequence of the above operations is invertible.

Additionally, by the definition of permutation, a sequence $\mathcal{S} = \pi_1, \dots, \pi_k$ of permutation operations can be expressed as the single $\pi = \pi_k \cdot \pi_{k-1} \cdots \pi_2 \cdot \pi_1$ – the composition of the permutations of sequence \mathcal{S} . Finally, link-and-cut and permutation operations are interchangeable in a sequence of operations, in the sense that the application of the link-and-cut operation $v|u \rightarrow w$ followed by a permutation π , has the same effect as π followed by the link-and-cut operation $\pi(v)|\pi(u) \rightarrow \pi(w)$ – inspect Figure 1 and Example 2. We have the following important property.

► **Lemma 1.** *Let T_1 and T_2 be each labelled by \mathcal{L} , and $\mathcal{S} = \sigma_1, \dots, \sigma_k$ be a sequence of k operations that transforms T_1 into T_2 . Then there exists a sequence $\mathcal{S}^* = \sigma_1^*, \dots, \sigma_k^*$ of k operations in which all permutation operations precede all link-and-cut operations, and \mathcal{S}^* transforms T_1 into T_2 . We say that \mathcal{S}^* is (sequence \mathcal{S}) in canonical form.*

Proof. We continue to swap consecutive pairs σ_i, σ_{i+1} , $1 \leq i < k$, of operations in sequence \mathcal{S} , where $\sigma_i = u|v \rightarrow w$ is a link-and-cut operation and $\sigma_{i+1} = \pi$ is a permutation operation, with the pair $\sigma_{i+1}, \sigma_i' = \pi(v)|\pi(u) \rightarrow \pi(w)$, until we obtain a sequence \mathcal{S}^* in which all permutation operations precede all link-and-cut operations. By induction on this interchange, the resulting \mathcal{S}^* is of length k and transforms T_1 into T_2 . ◀

► **Example 2.** Consider T_1 and T_2 of Figure 1. The application of the link-and-cut operation $f|b \rightarrow c$ followed by the permutation $\pi = (b\ d)$, has the same effect as π followed by the link-and-cut operation $\pi(f)|\pi(b) \rightarrow \pi(c) = f|d \rightarrow c$.

We now give the following notions of *distance* between trees T_1 and T_2 labelled by \mathcal{L} .

► **Definition 3** (link-and-cut distance). *The link-and-cut distance $d_\ell(T_1, T_2)$ is the length of the shortest sequence of link-and-cut operations which transforms T_1 into T_2 .*

The following Lemma ensures that the definition of link-and-cut distance is well posed. See also Figure 1.

► **Lemma 4.** *Given trees T_1 and T_2 each labelled by \mathcal{L} , there always exists a sequence of link-and-cut operations that transforms T_1 into T_2 .*

Proof. For any node v , $p_{T_1}(v) = u$, such that $p_{T_2}(v) = w$ and w is a descendant of v in T_1 – and thus the operation $v|u \rightarrow w$ is not directly applicable – we prove that there exists a node z on the path from v to w in T_1 (including w) such that $p_{T_2}(z)$ is not a descendant of v in T_2 nor a descendant of z in T_1 . This implies that after applying the valid operation $z|p_{T_1}(z) \rightarrow p_{T_2}(z)$, the operation $v|u \rightarrow w$ becomes valid too. There is always such a node z because, should it not exist, w would be a descendant of v also in T_2 , giving rise to the cycle $(w \rightarrow v \rightarrow \dots \rightarrow w)$ and thus contradicting the fact that T_2 is a tree. ◀

Note that, given a *permutation* π of some set S of elements, we denote its *size* $|\pi|$ as the number of elements perturbed by π , *i.e.*, the size of the set $\{s \in S : \pi(s) \neq s\}$.

► **Definition 5** (permutation distance). *The permutation distance $d_\pi(T_1, T_2)$ is the size $|\pi|$ of the smallest permutation π that transforms T_1 into T_2 .*

Finally, we also define the *size* $|\mathcal{S}|$ of a sequence \mathcal{S} of rearrangement operations as the size of the permutation obtained by composing the permutations of \mathcal{S}^* plus the length of the sequence of link-and-cut operations of \mathcal{S}^* , where \mathcal{S}^* is sequence \mathcal{S} in canonical form.

► **Definition 6** (rearrangement distance). *The rearrangement distance $d(T_1, T_2)$ is the smallest size of any sequence of operations that transforms T_1 into T_2 .*

Clearly, the permutation distance $d_\pi(T_1, T_2)$ is defined only when T_1 and T_2 are isomorphic, and it is evidently well posed. As a direct consequence of this and Lemma 4, the definition of rearrangement distance is also well posed. Moreover, since these operations are invertible, all the above distance measures are symmetric, and they satisfy by definition the triangle inequality: consider, *e.g.*, the rearrangement distance. Given T_1, T_2 and T_3 labelled by the same set of labels, let \mathcal{S}_{12} be a sequence that transforms T_1 into T_2 such that $|\mathcal{S}_{12}| = d(T_1, T_2)$, \mathcal{S}_{23} a sequence that transforms T_2 into T_3 with $|\mathcal{S}_{23}| = d(T_2, T_3)$, \mathcal{S}_{13} a sequence that transforms T_1 into T_3 and $|\mathcal{S}_{13}| = d(T_1, T_3)$. It is evident that the concatenation $\mathcal{S}_{12}\mathcal{S}_{13}$ of \mathcal{S}_{12} and \mathcal{S}_{23} is a sequence that transforms T_1 into T_3 , and by Definition 6 its size is larger or equal to $d(T_1, T_3)$: thus $d(T_1, T_2) + d(T_2, T_3) \geq |\mathcal{S}_{12}\mathcal{S}_{23}| \geq d(T_1, T_3)$. A similar argument shows that the triangular inequality also holds for the link-and-cut distance and the permutation distance.

We now have the important structures.

► **Definition 7** (active set). *Given trees T_1 and T_2 each labelled by \mathcal{L} , we call active the subset $\mathcal{X} \subseteq \mathcal{L}$ of labels which have different parents in T_1 and T_2 , *i.e.*, $v \in \mathcal{X}$ iff $p_{T_1}(v) \neq p_{T_2}(v)$.*

Given trees T_1 and T_2 each labelled by \mathcal{L} , for each vertex v of the active set \mathcal{X} , we can associate with v the pair $(p_{T_1}(v), p_{T_2}(v))$ of the parents of v in the two trees. Let $\mathcal{P}_{(u,w)}$ be the set $\{v : p_{T_1}(v) = u, p_{T_2}(v) = w\}$ – since each vertex has exactly one parent in each tree, each vertex $v \in \mathcal{X}$ belongs to one and only one set $\mathcal{P}_{(u,w)}$. This fact is formalized in the following definition and illustrated in Example 9.

► **Definition 8** (family partition). *Let trees T_1 and T_2 each be labelled by \mathcal{L} : for each vertex $v \in \mathcal{X}$ we denote the set $\mathcal{P}_{(u,w)} = \{v : p_{T_1}(v) = u, p_{T_2}(v) = w\}$. Then \mathcal{P} is the partition of set \mathcal{X} into the nonempty sets $\mathcal{P}_{(u,w)}$, $u, w \in V$. Partition \mathcal{P} is called the family partition of the active set \mathcal{X} , and we denote its size $|\mathcal{P}|$ as the number of different (non-empty) subsets $\mathcal{P}_{(u,w)}$ it is composed of.*

► **Example 9.** Consider T_1 and T_2 of Figure 1. The active set is $\mathcal{X} = \{b, d, e, f\}$. The family partition is composed of the following sets: $\mathcal{P}_{(a,d)} = \{b\}$, $\mathcal{P}_{(b,a)} = \{d\}$, $\mathcal{P}_{(b,d)} = \{e\}$, $\mathcal{P}_{(b,c)} = \{f\}$.

Note that the family partition encodes the elements of any shortest sequence of link-and-cut operations for transforming T_1 into T_2 : $v \in \mathcal{P}_{(u,w)}$ corresponds to operation $v|u \rightarrow w$. It is easy to see, from the proof of Lemma 4, that a shortest sequence of valid link-and-cut operations can be obtained from \mathcal{P} by ordering the set of operations it encodes with respect to a *depth-first traversal* (DFT) of T_1 : $u|p_{T_1}(u) \rightarrow p_{T_2}(u)$ precedes $v|p_{T_1}(v) \rightarrow p_{T_2}(v)$ if u precedes v in a DFT of T_1 . Hence $d_\ell(T_1, T_2) = |\mathcal{X}|$, *i.e.*, the link-and-cut distance is equal to the cardinality of the active set, of which \mathcal{P} is a partition.

3 Computational complexity

In this section we determine the complexity of computing the distance between two trees labelled by the same set of labels, in terms of the three distance measures defined in Section 2. More precisely, despite the fact that the link-and-cut and the permutation distances are polynomial-time computable, computing the rearrangement distance is NP-hard.

3.1 Link-and-cut distance

We first show that we can compute the link-and-cut distance between two trees in linear time by showing that the family partition can be built in linear time.

► **Lemma 10.** *The link-and-cut distance $d_\ell(T_1, T_2)$ between trees T_1 and T_2 each labelled by \mathcal{L} can be computed in time $O(|\mathcal{L}|)$.*

Proof. Since the link-and-cut distance is $|\mathcal{X}|$, it suffices to demonstrate that the family partition \mathcal{P} can be built in time $O(|\mathcal{L}|)$. The procedure is as follows: we first do a DFT of tree T_1 , building an array $p_{T_1}(v)$ of the parents in T_1 , indexed by the child v . We build the same array $p_{T_2}(v)$ for tree T_2 . Then we go through the set \mathcal{L} of labels, in some order: at each label v , should $p_{T_1}(v) = u \neq p_{T_2}(v) = w$, we add v to $\mathcal{P}_{(u,w)}$ of the family partition \mathcal{P} . Then we just sum up the sizes of the non-empty subsets $\mathcal{P}_{(u,w)}$ of \mathcal{P} in order to obtain $|\mathcal{X}| = d_\ell(T_1, T_2)$. Clearly each tree traversal can be done in time $O(|\mathcal{L}|)$, because $|V_{T_1}| = |V_{T_2}| = |\mathcal{L}|$. In going through the labels, for each label v , we either add or do not add the single vertex v to \mathcal{P} , and so this procedure takes time $O(|\mathcal{L}|)$. ◀

3.2 Permutation distance

This subsection is dedicated to proving the following lemma, which shows that we can compute the permutation distance between two trees in cubic time.

► **Lemma 11.** *The permutation distance $d_\pi(T_1, T_2)$ between isomorphic trees T_1 and T_2 each labelled by \mathcal{L} can be computed in time $O(|\mathcal{L}|^3)$.*

We need the following definitions and auxiliary lemmas. The *mismatch number* $\Delta(m)$ of some isomorphic mapping m from tree T_1 to tree T_2 is the number of vertices whose label is not conserved by m . More formally, $\Delta(m) = |\{u \in V_{T_1} : \ell_{T_1}(u) \neq \ell_{T_2}(m(u))\}|$, where $\ell_T : V_T \rightarrow \mathcal{L}$ is the one-to-one correspondence between the vertices V_T of tree T and the set \mathcal{L} of labels. Let $\mathcal{I}(T_1, T_2)$ be the set of isomorphic mappings from T_1 to T_2 . Given isomorphic trees T_1 and T_2 each labelled by \mathcal{L} , let the *mismatch distance* $d_\Delta(T_1, T_2) = \min\{\Delta(m) : m \in \mathcal{I}(T_1, T_2)\}$ be the minimum mismatch number of an isomorphic mapping from T_1 to T_2 . The following equality between permutation distance and mismatch distance holds.

► **Lemma 12.** *Given isomorphic trees T_1 and T_2 each labelled by \mathcal{L} , it follows that $d_\pi(T_1, T_2) = d_\Delta(T_1, T_2)$.*

Proof. Consider an isomorphic mapping m from T_1 to T_2 that has the minimum mismatch number $\Delta(m) = d_\Delta(T_1, T_2)$ and let $\mathcal{L}' \subseteq \mathcal{L}$ be the set of labels of the vertices involved in the set of mismatching vertices between V_{T_1} and V_{T_2} given by m .

Clearly, such labels are in a permutation π which rearranges the labels of tree T_1 to obtain T_2 , while, by construction of m , all the other labels will not be perturbed by π . Then we need to show that such a permutation rearranges the minimum number of distinct labels, that is, its size $|\pi| = d_\pi(T_1, T_2)$ is the permutation distance. Indeed, assume to the contrary that the permutation distance $d_\pi(T_1, T_2) < |\pi|$. This implies the existence of a permutation π' that rearranges fewer labels than π , *i.e.*, $|\pi'| < |\pi|$. Then we show that there exists an isomorphic mapping m' that has mismatch number less than the one of m , contradicting the initial assumption.

Indeed, consider the permutation π' and define the mapping m' from T_1 to T_2 such that $m'(u) = v$ whenever $\pi'(v) = u$. The mapping m' is an isomorphism by the construction of π' , since $m'(\pi'(u)) = u$ for all $u \in V_{T_1}$, and with the application of π' , the two trees are congruent, hence congruency of the labels implies isomorphism of the two trees. This concludes the proof that m' is an isomorphism thus leading to a contraction. ◀

Now the task is to show how we can efficiently find an isomorphic mapping $m \in \mathcal{I}(T_1, T_2)$ from tree T_1 to tree T_2 such that the mismatch number $\Delta(m)$ is minimized – in other words, we need to compute $d_\Delta(T_1, T_2)$. For tree T , let L_T be its set of leaves, and for vertex $u \in V_T$, let $T|u$ be the subtree of T rooted at u – the connected component of T' containing u , where T' is the tree obtained from T by removing the edge $(p_T(u), u)$, and $p_T(u)$ is the parent of u in T . If u and v are both vertices, we slightly abuse notation using $\Delta(u, v)$ to mean the mismatch distance of (the only possible mapping between) u and v , that is $\Delta(u, v) = 0$ if $\ell_{T_1}(u) = \ell_{T_2}(v)$ – that is, the vertex u of T_1 and the vertex v of T_2 have the same label – and $\Delta(u, v) = 1$ otherwise. Recall that the *children* of u in T is the set $c_T(u) = \{v : (u, v) \in E_{T|u}\}$ – let $\mathcal{C}_{u,v}$ be the set of bijective mappings $m : c_{T_1}(u) \rightarrow c_{T_2}(v)$ from the children of $u \in V_{T_1}$, $v \in V_{T_2}$ – clearly any isomorphic mapping in $\mathcal{I}(T_1, T_2)$ is such a mapping when restricted to $c_{T_1}(u)$ and $c_{T_2}(v)$. We define the following (recursive) relationship $D(u, v)$, showing later how we can use it to compute the mismatch distance:

$$D(u, v) = \begin{cases} \Delta(u, v) & \text{if } u \in L_{T_1}, v \in L_{T_2}, \\ \min_{m \in \mathcal{C}_{u,v}} \sum_{z \in c_{T_1}(u)} D(z, m(z)) + \Delta(u, v) & \text{if } T_1|u \cong T_2|v, u \notin L_{T_1}, v \notin L_{T_2}, \\ \infty & \text{otherwise.} \end{cases}$$

We first show how to compute $T_1|u \cong T_2|v$ (true or false) for all $u \in V_{T_1}, v \in V_{T_2}$, since we need it for computing $D(u, v)$. We can build this relationship by extending the time $O(n \log n)$ algorithm of [6], where $n = |V_{T_1}| = |V_{T_2}|$, for determining if two rooted trees are isomorphic.¹ The idea of this algorithm is to first organize each tree in *levels*, where the level of a vertex is its distance from the root – this can be done with a simple DFT of each tree. Suppose each tree has k levels, otherwise they do not have the same number of levels, hence they cannot be isomorphic. Starting from level k in both trees, we move up level by level towards the root in both trees simultaneously. At each level i we perform the following steps: (1) for each vertex u of each tree T on level i , we store a representation of the topology of $T|u$, computing it recursively from the representations stored in the children of u on level $i + 1$; then (2) sort in each tree the vertices at level i by representation²; and finally (3) compare the two resulting sorted orders – only when they are identical, may we proceed to the next level. If we make it all the way to the first level (the root), and we succeed with the 3 steps at this level, then the two trees are isomorphic, otherwise not. We can extend this algorithm with a fourth step: (4) for each pair $u \in V_{T_1}, v \in V_{T_2}$ of vertices on level i , if their representations are identical, then $T_1|u \cong T_2|v$ is true, and false otherwise. Clearly, only for pairs of vertices on the same level, can their subtrees be isomorphic, and so this is an exhaustive search for all such pairs. Since the number of vertices compared in step (4) over all of the levels is no more than n^2 , this computation of $T_1|u \cong T_2|v$ for all pairs $u \in V_{T_1}, v \in V_{T_2}$ of vertices requires time $O(n^2)$. We are now ready to prove that $D(u, v) = d_\Delta(T_1|u, T_2|v)$ for each vertex u of T_1 and v of T_2 .

► **Lemma 13.** *Let trees T_1 and T_2 each be labelled by \mathcal{L} . Then (1) $D(u, v) = d_\Delta(T_1|u, T_2|v)$ for all pairs $u \in V_{T_1}, v \in V_{T_2}$. Moreover, (2) $D(u, v)$ can be computed in time $O(|\mathcal{L}|^3)$.*

Proof. (1) It is essentially a proof by induction. If both u and v are leaves, then $T_1|u \cong T_2|v$ is trivially true and $D(u, v) = \Delta(u, v)$. When $T_1|u \cong T_2|v$ does not hold, then the mismatch distance is undefined.

Otherwise, if u and v are internal vertices, and $T_1|u \cong T_2|v$, then let m be a bijective mapping from the nodes of $T_1|u$ to the nodes of $T_2|v$ minimizing the mismatch distance. By the definition of d_Δ and the construction of m , $d_\Delta(T_1|u, T_2|v) = \sum_{z \in c_{T_1}(u)} d_\Delta(T_1|z, T_2|m(z)) + \Delta(u, v)$. By the inductive hypothesis $\sum_{z \in c_{T_1}(u)} d_\Delta(T_1|z, T_2|m(z)) = \sum_{z \in c_{T_1}(u)} D(z, m(z))$. Combining these two facts implies that $d_\Delta(T_1|u, T_2|v) = \sum_{z \in c_{T_1}(u)} D(z, m(z)) + \Delta(u, v)$. Since m is the bijective mapping minimizing the mismatch distance, no other mapping m' can achieve a smaller value of $\sum_{z \in c_{T_1}(u)} D(z, m(z)) + \Delta(u, v)$, hence $D(u, v) = d_\Delta(T_1|u, T_2|v)$.

(2) Computing $D(u, v)$ when u and v are leaves requires constant time. When u and v are internal nodes – assuming we have already computed $T_1|u \cong T_2|v$ – we compute a *minimum weight* matching in the weighted bipartite graph with $V = c_{T_1}(u) \cup c_{T_2}(v)$ and $E = \{(x, y) : T_1|x \cong T_2|y, x \in c_{T_1}(u), y \in c_{T_2}(v)\}$ with weight function $w : E \rightarrow \mathbb{N}$ such

¹ Note that there is a linear time algorithm in [1], but it assumes that $\log n$ is fixed, where n is the number of vertices – which is the likely the case for all practical instances.

² We assume that there is a total ordering on the representations of the topologies, they are of constant size, and can be compared in constant time – for details see [6, 1]

that $w(x, y) = D(x, y)$. Such a matching can be found in time $O(|V| \log |V| + |V||E|)$ using a Fibonacci heap [15]. If we sum over all of graphs in which we compute these matchings during the recursive computation of $D(u, v)$ for all $u \in V_{T_1}$, $v \in V_{T_2}$, the number of vertices and edges in each graph, these sums will be at most n (vertices) and n^2 (edges) respectively, since both trees have $n = |V_{T_1}| = |V_{T_2}| = |\mathcal{L}|$ vertices. This means that this matching procedure will take overall time $O(|\mathcal{L}|^3)$. Computing $T_1|u \cong T_2|v$ for each pair $u \in V_{T_1}$, $v \in V_{T_2}$ takes time $O(|\mathcal{L}|^2)$ overall, hence computing $D(u, v)$ for all $u \in V_{T_1}$, $v \in V_{T_2}$ has a total running time $O(|\mathcal{L}|^3)$. ◀

Lemma 11 then follows from Lemmas 12 and 13. Notice that, when computing $D(u, v)$ we can also maintain the set $C(u, v)$ of the labels that are *conserved* in the minimum weight matchings, that is, those that are not involved in a mismatch. More precisely, $C(u, v)$ is equal to the union of the $C(x, y)$ over all edges (x, y) of the optimal matching. To that set, we add the label $\ell_{T_1}(u)$ if $\Delta(u, v) = 0$. Once we have all sets $C(u, v)$, the permutation that we want to compute involves exactly the labels not in $C(\lambda_{T_1}, \lambda_{T_2})$. More precisely, the label $\ell_{T_1}(u)$ must be replaced with the label of the vertex $m(u)$, where the isomorphism m can be constructed from the perfect matchings of the optimal solution.

3.3 Rearrangement distance

Finally, we show that deciding the rearrangement distance between two trees is NP-hard. We show this by reduction from 3-dimensional matching, one of Karp's 21 NP-complete problems [21].

In 3-dimensional matching, we are given three disjoint sets A , B and C , along with a set \mathcal{T} of triples (a, b, c) , such that $a \in A$, $b \in B$ and $c \in C$ – essentially a 3-uniform hypergraph H . A *matching* is then a subset $\mathcal{M} \subseteq \mathcal{T}$ such that for every two triples $(a, b, c) \in \mathcal{M}$, $(a', b', c') \in \mathcal{M}$, it follows that $a \neq a'$, $b \neq b'$ and $c \neq c'$, that is, all triples of \mathcal{M} are pairwise disjoint. It is then NP-hard to decide for a given k if there is a matching \mathcal{M} of size k [21]. It has been proved that the problem remains NP-hard even in the case of 3-bounded 1-common 3-dimensional matching, which is a restriction of the problem where the number of occurrences of an element in the triples is at most 3, and each pair of triples has at most one element in common [19]. We also make use of the following structure in this proof.

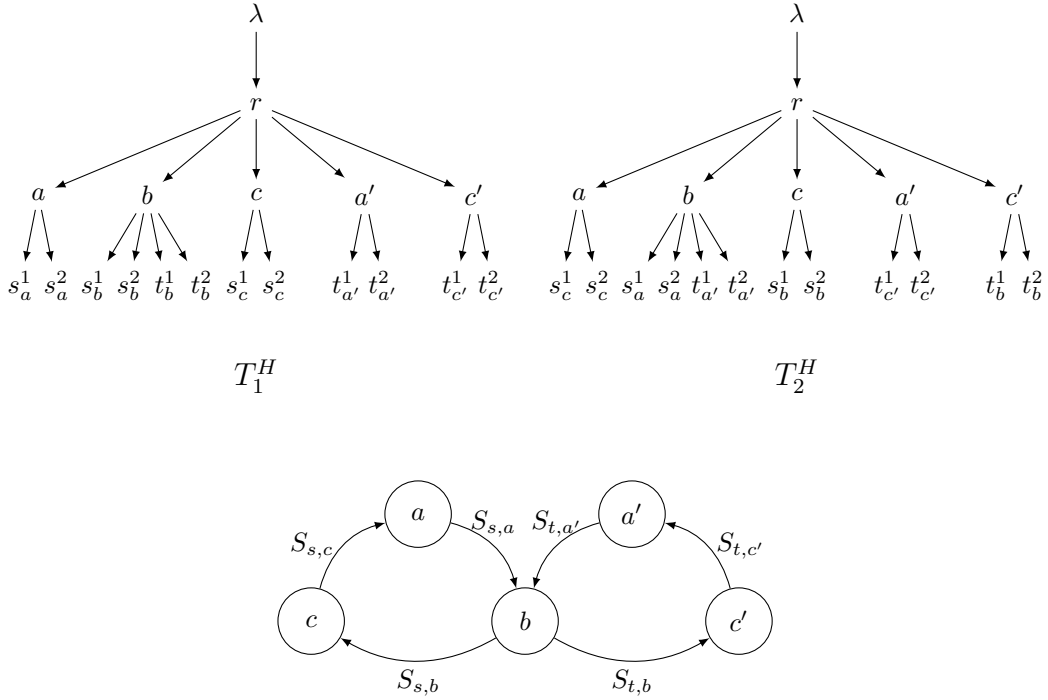
► **Definition 14** (movements graph). *Given trees T_1 and T_2 each labelled by \mathcal{L} , the movements graph G has an edge for every element $\mathcal{P}_{(u,w)}$ of the family partition \mathcal{P} of T_1 and T_2 , that is, $E_G = \{(u, w) : \mathcal{P}_{(u,w)} \in \mathcal{P}\}$, while its vertex set is $V_G = \bigcup_{(u,w) \in E_G} \{u, w\}$.*

We now prove that computing the rearrangement distance is NP-hard.

► **Theorem 15.** *Given trees T_1 and T_2 each labelled by \mathcal{L} , and some integer k , it is NP-hard to decide if $d(T_1, T_2) \leq k$.*

Proof. Reduction from 3-bounded 1-common 3-dimensional matching. We are given an instance H of 3-dimensional matching consisting of a set \mathcal{T} of m triples (a, b, c) over the disjoint sets A , B , C . We construct two trees T_1^H and T_2^H each with $|A| + |B| + |C| + 6m + 2$ vertices, for which the rearrangement distance $d(T_1^H, T_2^H) \leq 3n + 6(m - n)$ if and only if H has a 3-dimensional matching of size n .

Consider such an instance H of 3-dimensional matching as above. In the construction, the trees T_1^H and T_2^H each have a root vertex r , and a vertex for every element of A , B and C – each of which have r as the parent. To each $v \in \{a, b, c\}$ in T_1^H and triple t , we add a



■ **Figure 2** The trees T_1^H and T_2^H given instance H of 3-dimensional matching with $A = \{a, a'\}$, $B = \{b\}$ and $C = \{c, c'\}$ and $\mathcal{T} = \{s = \{a, b, c\}, t = \{a', b, c'\}\}$ (top), and the corresponding movements graph for the trees T_1^H and T_2^H (bottom).

set $S_{t,v} = \{t_v^1, t_v^2\}$ of two (uniquely labelled) children. In T_2^H , we add the sets $S_{t,v}$ of two children to each of these three vertices, but cyclically shifted, with respect to T_1^H , *i.e.*, we add $S_{t,a}$ to b , $S_{t,b}$ to c , $S_{t,c}$ back to a again. Note that this induces in the movements graph G a cycle $\mathcal{C}_t = \{(a, b), (b, c), (c, a)\}$ – see Figure 2. Now, observe that the movements graph G will have cycles of length 3 corresponding to each triple and two cycles may share one common vertex v if the triples share element v . By Lemma 1, a sequence of operations of total size $d(T_1^H, T_2^H)$ will consist of a permutation followed by a sequence of link-and-cut operations. Observe that any permutation involves for each cycle \mathcal{C}_t an edge, two edges or all three edges. Now, the rearrangement distance aims to solve cycles in the movements graph in the sense that after the operations, the movements graph has no edges. Observe that given a cycle \mathcal{C}_t of the movements graph G , then the minimum cost rearrangement to solve \mathcal{C}_t consists of applying a permutation of size 3 involving the three vertices of the cycle, thus of total cost 3. Observe that two cycles sharing a common vertex cannot both be solved by a permutation that is a cyclic shift of the vertices of the cycle, that is they cannot be both solved with cost 3. Moreover, permutations of vertices cannot solve more than one vertex of a cycle \mathcal{C}_t if it is not a cyclic shift of the vertices of \mathcal{C}_t , as cycles do not share edges. In case of a cyclic shift of two vertices of \mathcal{C}_t , (1) a permutation of size 2 and then four link-and-cut operations are required. If instead (2) at most a single vertex of \mathcal{C}_t is involved in a permutation, then six link-and-cut operations are required. We now detail how this implies that $d(T_1^H, T_2^H) \leq 3n + 6(m - n)$ if and only if H has a 3-dimensional matching of size n .

(\Rightarrow) Assume that $d(T_1^H, T_2^H) \leq 3n + 6(m - n)$. By the above observation on how cycles of the movements graph G are solved by the sequence of permutations, cases (1) and (2) for solving cycles have the same cost equal to 6. Thus the only possible way to have a

rearrangement distance less than or equal to $3n + 6(m - n)$ is by taking n disjoint cycles solved by the permutation operation of cost 3. This implies a 3-dimensional matching of size n .

(\Leftarrow) Now, suppose that H has a 3-dimensional matching $\mathcal{M} \subseteq \mathcal{T}$ of size n . This implies that there are n triples that are disjoint and thus the movements graph G has n disjoint cycles. By solving each cycle with a permutation of size 3, $m - n$ cycles are left in the movements graph. The remaining cycles, in the worst case, share common vertices with the cycles solved by the permutations, and thus they can be solved with a cost that is 6 in the worst case. Thus we obtain that $d(T_1^H, T_2^H) \leq 3n + 6(m - n)$, completing the proof. \blacktriangleleft

4 Bounds and approximation

We first give the following important lemma which states that when we apply a permutation to the labels of T_1 obtaining T_1' , the size of the resulting family partition \mathcal{P}' cannot increase or decrease too much with respect to the size of \mathcal{P} .

► **Lemma 16.** *Given trees T_1 and T_2 with corresponding active set \mathcal{X} and family partition \mathcal{P} , if T_1' is the tree (isomorphic to T_1) resulting from the application of permutation π of the labels of T_1 , and \mathcal{X}' and \mathcal{P}' are the active set and the family partition of T_1' and T_2 , respectively, then $|\mathcal{P}| - 2|\pi| \leq |\mathcal{P}'| \leq |\mathcal{P}| + 2|\pi|$.*

Proof. Let a be some label of T_1 which has been perturbed by permutation π , *i.e.*, $\pi(a) = b \neq a$. The new family partition \mathcal{P}' is obtained from \mathcal{P} by means of deletions, insertions and substitutions of subsets. The crucial observation is that such an operation will only affect the *neighborhood* of a , namely the (possibly empty) set of its children $c_{T_1}(a)$ and its parent $p_{T_1}(a)$ in T_1 . Let us consider each child $v \in c_{T_1}(a)$ first. We have the following cases.

- ($v \in \mathcal{P}_{(a,b)} \subseteq \mathcal{X}$): since π makes b the parent of v , which is exactly the parent of v in T_1 , $v \notin \mathcal{X}'$ and $\mathcal{P}_{(a,b)}$ will be missing from \mathcal{P}' ;
- ($v \in \mathcal{P}_{(a,c)} \subseteq \mathcal{X}$, $c \neq b$): after applying π , v will belong to set $\mathcal{P}'_{(b,c)}$, thus $\mathcal{P}_{(a,c)}$ will be replaced by $\mathcal{P}'_{(b,c)}$ in \mathcal{P}' ;
- ($v \notin \mathcal{X}$): then $v \in \mathcal{P}'_{(b,a)}$ in \mathcal{P}' , thus \mathcal{P}' might have an extra element with respect to \mathcal{P} .

Consider now the possible effects of π on $p_{T_1}(a)$. There are two possible scenarios:

- ($b \in \mathcal{P}_{(p_{T_1}(b), p_{T_2}(b))} \subseteq \mathcal{X}$): if $p_{T_2}(b) = p_{T_1}(a)$, then $b \notin \mathcal{X}'$ and if b was the only element of $\mathcal{P}_{(p_{T_1}(b), p_{T_2}(b))}$, the latter will be missing from \mathcal{P}' ; else, $b \in \mathcal{P}'_{(p_{T_1}(a), p_{T_2}(b))}$, thus $\mathcal{P}_{(p_1(b), p_2(b))}$ will be replaced by $\mathcal{P}'_{(p_{T_1}(a), p_{T_2}(b))}$ in \mathcal{P}' ;
- ($b \notin \mathcal{X}$): then $b \in \mathcal{P}'_{(p_{T_1}(a), p_{T_2}(b))}$ in \mathcal{P}' , thus \mathcal{P}' might have an extra element with respect to \mathcal{P} .

In summary, \mathcal{P}' is obtained from \mathcal{P} with up to two deletions and two additions of sets in the family partition for each label involved in the permutation π , thus the result follows. \blacktriangleleft

In the special case where one of the trees, *e.g.*, T_1 , is *binary*, *i.e.*, each node has up to two children, we have the following lemma connecting link-and-cut and rearrangement distance.

► **Lemma 17.** *Given T_1 a binary tree, T_2 any tree, we have that $d_\ell(T_1, T_2) \leq 4 \cdot d(T_1, T_2)$.*

Proof. Suppose that T_2 is optimally obtained from T_1 by applying a permutation π of the labels followed by a number of link-and-cut operations – something we can assume in virtue of Lemma 1. Let T_1' be the tree resulting from the application of permutation π of the labels of T_1 , \mathcal{X}' and \mathcal{P}' the active set and family partition of T_1' and T_2 , respectively. By the construction of the family partition, the optimal number of link-and-cut operations to obtain

T_2 from T_1' is at least $|\mathcal{P}'|$; we thus have that $d(T_1, T_2) = |\pi| + |\mathcal{X}'| \geq |\pi| + |\mathcal{P}'|$. Moreover, Lemma 16 says that $|\pi| \geq \frac{|\mathcal{P}| - |\mathcal{P}'|}{2}$, thus $d(T_1, T_2) \geq \frac{|\mathcal{P}| - |\mathcal{P}'|}{2} + |\mathcal{P}'| = \frac{|\mathcal{P}|}{2} + \frac{|\mathcal{P}'|}{2} \geq \frac{|\mathcal{P}|}{2}$. Now, since T_1 is binary, each set in the family partition \mathcal{P} consists of up to two elements (the elements of $\mathcal{P}_{(x,y)}$ are the ones among the children of x in T_1 that becomes the children of y in T_2 , thus they cannot be more than the number of children of x). It follows that $|\mathcal{X}'| = d_\ell(T_1, T_2) \leq 2 \cdot |\mathcal{P}|$, hence $d(T_1, T_2) \geq \frac{d_\ell(T_1, T_2)}{4}$. ◀

Importantly, we note that Lemma 17 states that the link-and-cut distance algorithm provides a linear 4-approximation for the rearrangement distance when at least one of the trees involved is binary. We have the following corollary from Lemma 17 and Lemma 10.

► **Corollary 18.** *There exists a polynomial time 4-approximation algorithm for the rearrangement distance problem for binary trees.*

5 Fixed parameter tractability

This section is devoted to showing that computing the rearrangement distance between trees T_1 and T_2 is fixed-parameter tractable, essentially via the bounded search tree technique [10]. In this case, the instance also contains a parameter k : in time $O((4k)^{2k^2} n)$ we (1) determine if $d(T_1, T_2) \leq k$ and, if this is the case, (2) find the minimum sequence of operations transforming T_1 into T_2 .

The main idea of our algorithm is that, in virtue of Lemma 1, we can reorder the sequence of operations that transforms T_1 into T_2 so that all permutations precede the link-and-cut operations. Let T^* be the tree obtained from T_1 using only permutations and such that we can optimally obtain T_2 from T^* using only link-and-cut operations. Then $d(T_1, T_2) = d_\pi(T_1, T^*) + d_\ell(T^*, T_2)$. Our algorithm consists of showing that $d_\pi(T_1, T^*)$ is related to the size of the family partition, and that we can compute $d_\ell(T^*, T_2)$ in linear time.

The main consequence of Lemma 1 here is that we can restrict our attention to permutations first (to obtain a tree T^*), and to link-and-cut operations afterwards. Finding such a tree T^* is easier when we want to determine if the rearrangement distance $d(T_1, T_2)$ is at most k .

In fact, a consequence of Lemma 16 is that $d(T_1, T_2) \geq d_\pi(T_1, T^*) \geq |\mathcal{P}|/2$, where \mathcal{P} is the family partition associated with T_1 and T_2 . Notice that any sequence of operations that transforms T_1 into T_2 also transforms \mathcal{X} into the empty set – thus \mathcal{P} into the empty partition.

Since $d(T_1, T_2) \geq |\mathcal{P}|/2$, the first step of our algorithm is to compute the family partition \mathcal{P} of T_1 and T_2 and verify that $k \geq |\mathcal{P}|/2$. If that inequality is not satisfied, then, since as stated above $d_\pi(T_1, T^*) \geq |\mathcal{P}|/2$, it would follow that $d(T_1, T_2) > k$. Hence we can focus on the instances where $k \geq |\mathcal{P}|/2$, that is $|\mathcal{P}| \leq 2k$. Since the family partition is sufficiently small, we can compute all sequences of permutations of at most k labels of \mathcal{X} in time $O((4k)^{2k^2})$. In fact, each of the permutations involves one of the 2^{2k} subsets of vertices of \mathcal{X} , and there can be at most $(2k)!$ permutations of a set of $2k$ elements. Overall there are at most $(2^{2k}(2k)!)^k$ such sequences: it is trivial to organize them in a search tree that can be generated and traversed in linear time, and some crude upper bound results in the desired time bound. Let \mathcal{T} be the set of trees that are obtained by applying to T_1 the sequence of operations corresponding to a node of the search tree.

The second part of our algorithm is to compute $d_\ell(T, T_2)$ for each tree in $T \in \mathcal{T}$, which, by Lemma 10, requires $O(n)$ time for each tree, keeping track of the tree T^* minimizing $d_\pi(T_1, T^*) + d_\ell(T^*, T_2)$. The algorithm has therefore $O((4k)^{2k^2} n)$ time complexity.

6 Open problems

In this paper we provide a NP-hardness proof of the rearrangement distance for trees with vertices of unbounded degree. The computational complexity of the rearrangement distance in the case of bounded degree trees remains an open problem. Mainly it would be of theoretical interest to see if it is still NP-hard for binary trees. On the other hand, we provide a constant approximation algorithm for the rearrangement distance of binary trees. Extending this result to general trees is still open. Such a result could be of interest in developing practical algorithms for comparing tumor phylogenies.

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