Abstract
Tannier et al. introduced a generalization of breakpoint distance for multichromosomal genomes. They showed that the median problem under the breakpoint distance is solvable in polynomial time in the multichromosomal circular and mixed models. This is intriguing, since in all other rearrangement models (DCJ, reversal, unichromosomal or multilinear breakpoint models), the problem is NP-hard. The complexity of the small or even the large phylogeny problem under the breakpoint distance remained an open problem.

We improve the algorithm for the median problem and show that it is equivalent to the problem of finding maximum cardinality non-bipartite matching (under linear reduction). On the other hand, we prove that the more general small phylogeny problem is NP-hard. Surprisingly, we show that it is already NP-hard (or even APX-hard) for 4 species (a quartet phylogeny). In other words, while finding an ancestor for 3 species is easy, already finding two ancestors for 4 species is hard.

We also show that, in the unichromosomal and the multilinear breakpoint model, the halving problem is NP-hard, thus refuting the conjecture of Tannier et al. Interestingly, this is the first problem which is harder in the breakpoint model than in the DCJ or reversal models.

Keywords: breakpoint distance, median, halving, phylogeny, matching, NP-hard

1. Introduction
While point mutations change the genome sequence of species throughout the evolution, there are also large scale rearrangement mutations, such as inversions or translocations, which affect the order of genes in genome. The gene order data can be used for inferring phylogenetic relationships and for reconstructing phylogenies [1]. A related problem is the reconstruction of ancestral gene orders, which is key to understanding the underlying evolutionary processes.

The simplest model for studying gene orders is the breakpoint model introduced by Sankoff and Blanchette [2]. When two genes (or conserved segments or markers) are adjacent in one genome, but not in the other, we call this position a breakpoint. We can then define the breakpoint distance simply by counting the number of breakpoints.

Sankoff and Blanchette [2] tried to reconstruct the ancestral gene orders, given a phylogenetic tree and gene orders of the extant species, based on the parsimony criterion, i.e., by minimizing the sum of distances along the branches of the tree. This is known as the small phylogeny problem [1] Unfortunately, the problem is NP-hard already when we have 3 species – an important special case known as the median problem. In fact, the median problem turns out to be NP-hard for almost all rearrangement distances (breakpoint [3,5], reversal [6], and DCJ [5]).

One notable exception is the general breakpoint model. Tannier et al. [5] observed that if we drop the condition that genomes are unichromosomal and that all chromosomes are linear, we get a simple model where the median problem is solvable in polynomial time. Even though this model is not very biologically plausible and more realistic models exist, the breakpoint model may still be useful for upper and lower bounds and solutions in this model may serve as good starting points for the more elaborate and complicated models.

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As opposed to the Large-Phylogeny problem, where the phylogenetic tree is not given and is part of the solution

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In this paper, we complete the work started by Tannier et al. [5] on the breakpoint model. We study several rearrangement problems in different variants of the breakpoint model and settle their computational complexity.

1.1. Previous results and our contribution

There are several variants of the breakpoint model depending on what karyotypes do we allow. In the unichromosomal (linear or circular) model, the genome may only consist of one chromosome. In the multilinear model, the genome may consist of multiple linear chromosomes and finally, the mixed model allows for any number of linear and circular chromosomes (even though this is not biologically plausible).

For the unichromosomal model, Pe‘er and Shamir [3] and Bryant [4] showed that the median problem is NP-hard. This result was extended to the multilinear model by Tannier et al. [5] and Zheng et al. [7] showed the NP-hardness for a related problem called guided halving (see Preliminaries).

Curiously, the ordinary halving problem was not studied before in the breakpoint model and also Tannier et al. [5] leave it open. Moreover, they conjecture that the problem is polynomially solvable – this might perhaps be attributed to the fact that the halving problem is polynomially solvable in far more complicated models such as reversal/translocation (RT) [8] or double cut and join (DCJ) [9–12]. Nevertheless, we refute this conjecture (unless P = NP) by proving that the halving problem is NP-complete in the unichromosomal and multilinear models.

Our main contribution is, however, our work in the general (mixed) model. Tannier et al. [5] introduced this model and showed that both median, halving, and guided halving problems are solvable in polynomial time.

Two open questions remained in the work of Tannier et al. [5]. These are also articulated in the monograph by Fertin et al. [13]:

1. The best time complexity for the median and guided halving problems under the breakpoint distance on multichromosomal genomes (with circular chromosomes allowed) is $O(n^3)$, using a reduction to the maximum weight perfect matching problem. It is an open problem to devise an ad-hoc algorithm with better complexity.

2. The small parsimony problem and large parsimony problem under the breakpoint distance is open regarding multichromosomal signed genomes when linear and circular chromosomes are allowed.

We resolve the first question in a positive way by showing a more efficient algorithm running in $O(n \sqrt{n})$ time. This is by reduction to the maximum cardinality matching problem. Moreover, we show that maximum cardinality matching can be reduced back to the breakpoint median (by a linear reduction) and so the two problems have essentially the same complexity. The same technique also improves the algorithms for halving and guided halving.

The second question is resolved in a negative way. Surely, one could expect that the large parsimony problem is NP-hard for this model, since it is NP-hard even for the Hamming distance on binary strings [14]. However, surprisingly, for the breakpoint distance (unlike the Hamming distance), the small phylogeny is NP-hard and it is NP-hard even for 4 species, i.e., a quartet phylogeny. In other words, while the small phylogeny problem is easy for 3 species, it is hard already for 4 species.

The previous work and our new results are summarized in Table 1:

| Breakpoint Model                      | Median | Halving | Guided Halving | Small Phylogeny |
|---------------------------------------|--------|---------|----------------|-----------------|
| unichromosomal (linear or circular)   | NP-C   | NP-C [new] | NP-C [7]       | NP-C [trivially] |
| multilinear                           | NP-C [5] | NP-C [new] | NP-C [7]       | NP-C [trivially] |
| multichromosomal (circular or mixed)  | $O(n^3)$ [5], | $O(n^3)$ [5], | $O(n^3)$ [5], |                  |
|                                       | $O(n \sqrt{n})$ [new] | $O(n)$ [new] | $O(n \sqrt{n})$ [new] | NP-C [new] |

Table 1: Our new results in context of the previously known results. NP-C stands for NP-complete.
1.2. Road map

In the next section, we define the different variants of the breakpoint model and state the rearrangement problems. In Section 3, we refute the conjecture of Tannier et al. [5] and prove that the halving problem is NP-hard. In the following two sections, we study the general breakpoint model. In Section 4, we look at the median problem: we improve upon the algorithm of Tannier et al. [5] and show that it is equivalent to the maximum matching problem. The hardness of the small phylogeny problem is studied in Section 5 and we conclude in Section 6.

2. Preliminaries

2.1. Genome models and the breakpoint distance

We assume that all the genomes have the same gene content and we denote this set of genes by $G$. We also assume that each gene $g \in G$ is an oriented segment of DNA having two ends – a head and a tail. These two ends are called extremities and are denoted $g_h$ and $g_t$, respectively. Let us first describe the circular models which are the most used throughout the paper, since they are easier to work with. We then extend our definitions to account for linear chromosomes.

We represent genome $\pi$ by a set of edges: An edge between extremities $x$ and $y$, called adjacency, indicates that $x$ and $y$ are adjacent in the genome. Note that in circular genomes, every extremity is adjacent to exactly one other extremity, so we can identify genomes with perfect matchings over the set of extremities.

Let us define an auxiliary base matching $B = \{g_h g_t : g \in G\}$ where each edge connects the two ends of some gene. Then all vertices have degree 2 in the union $\pi \cup B$ and $\pi \cup B$ decomposes into a set of cycles, which naturally correspond to the circular chromosomes of our genome (see Fig. 1).

In the general (multichromosomal circular) model, genomes can have multiple circular chromosomes and any perfect matching $\pi$ corresponds to a genome. In the unichromosomal circular model, we require that the genome only consists of a single chromosome, so $\pi \cup B$ is a Hamiltonian cycle as in Fig. 1. Such a matching $\pi$ is sometimes called Hamiltonian matching.

![Figure 1: Example of a circular genome $\pi$ and its representation by a perfect matching.](image)

Let $\pi_1$ and $\pi_2$ be two genomes – two perfect matchings. Then the breakpoint distance between $\pi_1$ and $\pi_2$ is defined as

$$d(\pi_1, \pi_2) = n - \text{sim}(\pi_1, \pi_2),$$

where $n$ is the number of genes and $\text{sim}(\pi_1, \pi_2)$ is the number of common adjacencies. The breakpoint distance satisfies all the properties of a metric and is used in the literature, however, we find it easier to work directly with the similarity measure $\text{sim}(\pi_1, \pi_2)$. 

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To represent linear chromosomes, we add a vertex $T_x$ for each extremity $x$. These vertices are called telomeres and a telomeric adjacency $xT_x$ indicates that $x$ is an end of a linear chromosome (see Fig. 2).

Genomes will again correspond to matchings with a condition that $T_x$ may only be adjacent to $x$. If $\pi$ is such a matching, $\pi \cup B$ consists of cycles and paths ending with telomeres, which correspond to circular and linear chromosomes, respectively. In the mixed model, any such matching $\pi$ represents a genome; in the multilinear model, we require that every chromosome is linear; and in the linear model, we only allow a single linear chromosome.

We can write the breakpoint distance again in the form $d(\pi_1, \pi_2) = n - \text{sim}(\pi_1, \pi_2)$, where this time, $\text{sim}(\pi_1, \pi_2)$ is the number of common adjacencies plus half the number of telomeric adjacencies (as introduced by Tannier et al. [5]).

![Figure 2: Example of a mixed genome $\pi$ and its representation.](image)

### 2.2. Duplicated genomes

We will also work with duplicated genomes that underwent a whole genome duplication and have exactly two copies of each gene. For each gene $g$, let us label the first copy $g^1$ and the second copy $g^2$. Then we can represent a duplicated genome by an ordinary genome $\delta$ over the gene set $\{g^1, g^2 : g \in G\}$. However, note that the labels were introduced arbitrarily and we consider two genomes that differ only in the subscripts of some genes as equivalent. A duplicated genome actually corresponds to the equivalence class $[\delta]$.

We can define the breakpoint distance (similarity) between two duplicated genomes $[\gamma]$ and $[\delta]$ as the minimum distance (maximum similarity) between ordinary genomes $\gamma' \in [\gamma]$ and $\delta' \in [\delta]$. In fact, we can fix one $\gamma' \in [\gamma]$ and take the minimum (maximum) over $\delta' \in [\delta]$.

Let us write $\theta = \pi \oplus [\delta]$ for a perfectly duplicated genome – the result of a whole genome duplication. For each linear chromosome in $\pi$, $\theta$ contains two copies of the chromosome and for each circular chromosome in $\pi$, $\theta$ contains either two copies of the chromosome or one chromosome consisting of the two copies consecutively. The distance between an ordinary genome $\pi$ and a duplicated genome $[\delta]$, also called double distance and denoted $dd(\pi, \delta)$, is then the distance between $\pi \oplus \pi$ and $[\delta]$.

We say that $\pi$ and $[\delta]$ have adjacency $xy$ in common, if $x, y$ are adjacent in $\pi$ and $x^i, y^j$ are adjacent in $\delta$ for some $i$ and $j$. We say that they have the adjacency $xy$ twice in common, if either $x^i, y^j$ and $x^i', y^j'$, or $x^i, y^j$ and $x^i, y^j'$ are adjacent in $\delta$. Tannier et al. [5] showed that the double distance $dd(\pi, \delta)$ can be computed simply as $dd(\pi, \delta) = 2n - \text{sim}(\pi, \delta)$, where $\text{sim}(\pi, \delta)$ is the number of adjacencies in common plus half the number of telomeric adjacencies in common (adjacencies twice in common are counted as 2).

### 2.3. Rearrangement problems

Once we have a genome model and a distance measure, we can define the problems of interest. In general, the focus of our study are problems related to reconstruction of ancestral genomes under the parsimony principle.
Assume that we have two genomes $\pi_1$ and $\pi_2$ and we would like to reconstruct their common ancestor $\alpha$. Using a third, outgroup genome $\pi_3$, we can formulate the task as the Median problem: Given $\pi_1$, $\pi_2$, and $\pi_3$, find genome $\alpha$ (called median) that minimizes the total distance from $\pi_1$, $\pi_2$, and $\pi_3$. In the Breakpoint-Median problem, we are minimizing the breakpoint distance, which is the same as maximizing the median score $S(\alpha) = \sum \text{sim}(\alpha, \pi_1) + \text{sim}(\alpha, \pi_2) + \text{sim}(\alpha, \pi_3)$. Note that the genome model imposes further constraints on the solution – the number and type of chromosomes.

We can generalize the median problem to the median of $k$ genomes problem, where given genomes $\pi_1, \ldots, \pi_k$, we should find genome $\alpha$ that maximizes the score $S(\alpha) = \sum \text{sim}(\alpha, \pi_i)$. However, even more important generalization is the Small-Phylogeny problem, where we are given a phylogenetic tree and gene orders of the extant species (leaves of the tree). The task is to reconstruct all the ancestral genomes, i.e., to find gene orders for each internal vertex, while minimizing the sum of (breakpoint) distances along the edges of the phylogenetic tree. (This is the same as maximizing the sum of similarities along the edges.) The Median problem is a special case of the Small-Phylogeny problem with just 3 species (since there is only one unrooted tree with 3 leaves). On the other hand, median solvers are widely used in practice in the Steinerization approach to reconstruct the ancestors in Small-Phylogeny. Starting with some initial ancestral genomes, we repeatedly replace genomes by medians of the neighboring genomes in the phylogeny, until we converge to some local optimum. Therefore, having a model where the Median problem is efficiently solvable might be of practical significance.

Another classical problem in genome rearrangements is the Halving problem. Imagine a genome $\pi$ that underwent a whole genome duplication. The perfectly duplicated genome $\Theta = \pi \oplus \pi$ was then rearranged through the evolution to its present-day form $\gamma$. In the Halving problem, we would like to reconstruct the pre-duplication ancestor $\pi$ given the present-day genome $\gamma$. More precisely, we would like to find an ordinary genome $\alpha$ that minimizes the double distance from $\gamma$.

In the Halving problem, there are usually many equivalent solutions. For better results, we can use an ordinary outgroup genome $\rho$ (such that the speciation happened before the whole genome duplication) and search for genome $\alpha$ that minimizes $dd(\alpha, \gamma) + d(\alpha, \rho)$. This is called the Guided-Genome-Halving problem.

3. The halving problem

Bryant [4] showed that the median problem is NP-hard in the circular breakpoint model by reduction from the Directed-Hamiltonian-Cycle problem. The halving problem was not studied previously in the breakpoint model but we show that it suffer the same “Hamiltonian” curse as the median problem – in order to find the ancestor, we would in fact have to find a Hamiltonian cycle. Our proof is even simpler than that of Bryant [4].

As the halving problem is polynomially solvable in more realistic models such as the RT model [8] or the DCJ model [9][12], the halving problem under the breakpoint distance will remain a mere curiosity: It is the first problem which is easier in the DCJ or even in the RT model than in the breakpoint model. Furthermore, it is the only known case where halving is NP-hard, while the double distance is computable in polynomial time (in the DCJ model, the opposite is true – halving is easy, while the double distance is NP-hard [5]).

Theorem 1. Halving problem is NP-hard in the circular, linear, and multilinear breakpoint models.

Proof. The proof is by reduction from the Directed-Hamiltonian-Cycle problem. Plesník [15] proved that this problem is still NP-hard for graphs with maximum degree 2 and the construction implies the problem is also NP-hard if all the vertices have in-degree and out-degree 2. Note that such graphs have an Eulerian cycle.

Let $G = (V, E)$ be such a directed graph; the corresponding doubled genome $\delta$ will have two copies of one gene for every vertex in $G$. We create a new graph $G' = (V', E')$, where $V' = \{x_i^1, x_i^2, x_j^2 : x \in V\}$ and the edges in $E'$ are defined as follows: traverse the Eulerian walk and for each edge $xy \in E$, include an edge $x_i^1 y_j^1$ in $E'$, where $i$ and $j$ depend on whether we are visiting the vertices for the first time or for the second time. Note that all edges go from head to tail, $E'$ is a perfect matching, and $G'$ represents the doubled genome $\delta$ consisting of a single circular chromosome.

Let $\alpha$ be a circular genome, a solution to the halving problem. Note that $\delta$ has no double adjacencies, so $\alpha$ can have at most $n$ adjacencies in common (none are twice in common). This maximum can be attained if and only if all the adjacencies in $\alpha$ are of the form $x_i y_j$ (from head to tail) and for each such adjacency, $x_i^1 y_j^1$ is an adjacency in $\delta$ for
contains a directed Hamiltonian path. This problem is still NP-hard and can be reduced to the halving problem.

For the linear and multilinear models, remove one edge \( xy \) from \( G \) and consider the problem of deciding whether \( G \) contains a directed Hamiltonian path. This problem is still NP-hard and can be reduced to the halving problem in the linear models: \( G \) now has an Eulerian path starting in \( y \) and ending in \( x \). We replace the last adjacency \( x^3_y^1 \) in \( \delta \) (corresponding to the removed edge) by two telomeric adjacencies \( x^2_T \delta \) and \( y^1_T \delta \) to get a linear genome. If \( \alpha \) is a linear or multilinear solution to the halving problem, it can reach the maximum similarity if and only if all its adjacencies (including the telomeric adjacencies) are in common with \( \delta \) and this is if and only if contraction of \( \alpha \) is a directed Hamiltonian path in \( G \).

4. Median and halving problems in the general model

From now on, we will study the general breakpoint model, i.e., the multichromosomal circular model where genomes are perfect matchings. We will also note how to extend the results to the mixed model and use the developed techniques for the halving and guided halving problem.

4.1. Breakpoint median

Tannier et al. [5] noticed that finding a breakpoint median can be reduced to finding a maximum weight perfect matching. This can be done in \( O(n^2) \) time by algorithm of Gabow [16] and Lawler [17]. An open problem from Tannier et al. [5] and Fertin et al. [13] asks, whether this can be improved. We answer this question affirmatively by showing an \( O(n \sqrt{n}) \) algorithm.

The solution by Tannier et al. [5] (if we rephrase it using the similarity measure instead of the breakpoint distance) was to create a complete weighted graph \( G \) where vertices are extremities and weight \( w(xy) \) of edge \( xy \) is the number of genomes which contain the adjacency \( xy \). Any perfect matching \( \alpha \) corresponds to some genome and the weight of the matching is equal to its median score \( S(\alpha) \).

Notice that instead of finding a maximum weight perfect matching, we can remove all the zero-weight edges from \( G \) and find an ordinary (not necessarily perfect) matching. We can then complete the genome by joining the free vertices arbitrarily. Since the number of edges in \( G \) is now linear, maximum weight matching can be found in \( O(n^2 \log n) \) time by algorithm of Gabow [18] or even in the state of art \( O(n \sqrt{n}) \) time algorithm by Gabow and Tarjan [19] using the fact that the weights are small integers. More generally and more precisely:

**Theorem 2.** The Breakpoint-Median problem for \( k \) genomes can be solved in \( O(kn \sqrt{n} \cdot \log(kn) \sqrt{\alpha(kn, n) \log n}) \) time in the general model. (Here, \( \alpha(m, n) \) is the inverse Ackermann function.)

We further improve the algorithm for the most important special case, \( k = 3 \): Notice that when \( xy \) is an edge with weight 3, there is no other edge incident to \( x \) or \( y \). Therefore, \( xy \) must belong to the maximum weight matching. Moreover, if \( xy \) has weight 2, there is a maximum weight matching which contains \( xy \). For suppose that \( xu \) and \( yv \) were matched in \( \alpha \) instead. Then \( w(xy) \geq 1 \) and by exchanging these edges for \( xy \) and \( uv \) with weights \( w(xy) = 2 \) and \( w(uv) \geq 0 \) we get a matching with the same or even higher weight.

Thus, we can include all edges of weight 2 and 3 in the matching and remove the matched vertices together with their incident edges. The remaining graph has only unit edge weights, so a maximum cardinality matching algorithm can be used. Algorithm by Micali and Vazirani [20] runs in \( O(m \sqrt{n}) \) time. Thus, we have

**Theorem 3.** The Breakpoint-Median problem for 3 genomes can be solved in \( O(n \sqrt{n}) \) time (in the general model).

Now, one might still wonder whether there is a still better algorithm for the median problem. We show that improving upon our result is very hard, since it would immediately imply a better algorithm for the matching problem, i.e., beating the result of Micali and Vazirani [20] (at least on cubic graphs), which is an open problem for more than 30 years.

Biedl [21] showed that the maximum matching problem is reducible to maximum matching problem in cubic graphs by a linear reduction. This means that we can transform any given graph \( G \) with \( m \) edges to a cubic graph \( G' \) with \( O(m) \) edges such that maximum matching in \( G \) can be recovered from one in \( G' \) in \( O(m) \) time. Thus, any \( O(f(m)) \) algorithm for maximum matching in cubic graphs implies an \( O(f(m) + m) \) algorithm for arbitrary graphs.
We say that a reduction is strongly linear, if it is linear and both the number of vertices and the number of edges increase at most linearly. Such a reduction preserves the running time $O(f(m,n))$ depending on both the number of vertices and the number of edges.

We prove that the **Breakpoint-Median** problem is equivalent to **Matching** under linear reduction and to **Cubic-Matching** under strongly linear reduction. If we write $\leq_{\ell}$ for linear and $\leq_{s\ell}$ for strongly linear reduction, we have

$$\text{Matching} \leq_{\ell} \text{Cubic-Matching} \leq_{s\ell} \text{Breakpoint-Median} \leq_{s\ell} \text{Matching}.$$ 

The first reduction is by Biedl [21] and the last one was shown in Theorem 3 (in fact, a reduction to **Subcubic-Matching**, where the degrees are $\leq 3$, was shown — this is equivalent to **Cubic-Matching** under the strongly linear reduction [21]).

Let $G$ be a cubic graph, an instance of the **Cubic-Matching** problem. The difference between the **Cubic-Matching** and **Breakpoint-Median** problem is that in **Breakpoint-Median**, the input multigraph consists of three perfect matchings, i.e., is 3-colorable. However, not all cubic graphs are 3-colorable (take for example Petersen’s graph).

The solution is to color edges arbitrarily and resolve conflicts as shown in Figure 3(a). We can for example color the ends of edges at each vertex randomly by three different colors. When both ends of an edge are assigned the same color, we color the edge appropriately. When the ends have different color, we subdivide the edge into three parts and use the third color for the middle edge (see Figure 3(a)). Note that the size of a maximum matching in the modified graph is exactly one more than the size in the original graph: If $xy$ is matched in the original, $xu$ and $vy$ can be matched. If $xy$ is not matched, we can still match $uv$.

Now, the modified graph is 3-colorable but not cubic. We remedy this by duplicating the whole graph and connecting the corresponding vertices of low degree as shown in Figure 3(b). As noted above, we may suppose that the auxiliary double edges $a_ua'_u$ and $a_va'_v$ are matched, so $ua_u, u'a'_u, va_v,$ and $v'a'_v$ are not matched and given the solution for the **Breakpoint-Median** problem, we can recover the maximum matching of $G$ in $O(n)$ time. The reduction is obviously linear, so we have

**Theorem 4.** The **Breakpoint-Median** problem (in the general model) has the same complexity as finding maximum cardinality matching in cubic graphs.

4.2. Median in the mixed model

In the mixed model, weight of a telomeric adjacency $xT_x$ is equal to half the number of genomes that contain $xT_x$. If we multiply all weights by 2, we can use the algorithm by Gabow and Tarjan [19] for integer weights, so the result
of Theorem 2 remains valid also in the mixed model.

For the median of 3 genomes, an $O(n \sqrt{n})$ algorithm exists: We observed that we can include all the double and triple adjacencies in the matching. This is also true for the double and triple telomeric adjacencies (edges of weight 1 and 1/2): If $w(xT_x) = 1/2$, $xT_x$ is a triple adjacency and no other edge is incident to neither $x$ nor $T_x$ in $G$. If $w(xT_x) = 1$ but the median $\alpha$ contains adjacency $xy$ instead, then $w(xy) \leq 1$ and since $T_x$ can only be incident to $x$, it must be unmatched (or matched by a zero-weight edge) and so we can replace $xy$ by $xT_x$ in $\alpha$.

The remaining graph consists of edges with unit weight and weight 1/2. Note however that all the 1/2-weight edges are of the form $xT_x$, and there is no other edge incident to $T_x$. We use the doubling trick again: we take two copies of graph $G$, and replace all pairs $xT_x$, $xT_x'$ by a single edge $xx'$ of unit weight. We can then remove all the telomere vertices. The resulting graph will have only unit weight edges and maximum matching exactly twice the size of maximum matching in the original graph.

4.3. Halving problems in the general model

The same tricks can be used for the halving and the guided halving problem. Recall that in the halving problem, given a duplicated genome $\gamma$, we are searching for $\alpha$ that minimizes the double distance $dd(\alpha, \gamma)$ and in the guided halving problem, we are in addition given genome $\rho$ and we are minimizing the sum $dd(\alpha, \gamma) + d(\alpha, \rho)$.

Again, we construct graph $G$, where this time, weight of edge $xy$ is the number of adjacencies among $x^1y^1$, $x^1y^2$, $x^2y^1$, $x^2y^2$ in $\gamma$ and possibly $xy$ in $\rho$ (in case of the guided halving problem). The rest of the solution is identical giving an $O(n \sqrt{n})$ algorithm for the guided halving problem. In the halving problem, the degrees of vertices in $G$ are at most 2 and after including all the double edges in the solution, the remaining graph consists only of cycles and the maximum matching can be found trivially in $O(n)$ time.

5. Breakpoint phylogeny

In the Small-Phylogeny problem, we try to reconstruct the ancestral genomes given a phylogenetic tree and gene orders of the extant species while minimizing the sum of distances along the edges of the tree. This problem is NP-hard for most rearrangement distances and for most models, this follows trivially from the NP-hardness of the Median problem. However, as we have seen in the previous section, this is not the case in the general breakpoint model and the complexity of the Small-Phylogeny problem remained open [5, 13].

In this section, we prove that the Small-Phylogeny problem is NP-hard also in the general breakpoint model. We show that the problem is NP-hard already for 4 species, a special case that we call the Breakpoint-Quartet problem.

Given four genomes $\pi_1, \pi_2, \pi_3, \pi_4$, the Breakpoint-Quartet problem is to find ancestral genomes $\alpha_1, \alpha_2$ that maximize the sum of similarities along the edges of the quartet tree in Figure 4, i.e., the sum

$$S(\alpha_1, \alpha_2) = \text{sim}(\pi_1, \alpha_1) + \text{sim}(\pi_2, \alpha_1) + \text{sim}(\alpha_1, \alpha_2) + \text{sim}(\alpha_2, \pi_3) + \text{sim}(\alpha_2, \pi_4).$$

![Figure 4: Quartet tree.](image)

**Theorem 5.** The Breakpoint-Quartet problem is NP-hard and even APX-hard in the general breakpoint model.

The proof is inspired by the work of Dees [22] who showed that the following problem is NP-hard: Given two graphs $G_1 = (V, E_1)$, $G_2 = (V, E_2)$, find two perfect matchings $M_1 \subseteq E_1$ and $M_2 \subseteq E_2$ with the maximum overlap $M_1 \cap M_2$. The problem is NP-hard even when the components in $G_1$ and $G_2$ are just cycles. In our proof, $\pi_1 \cup \pi_2$ will
correspond to $E_1$, $\pi_1 \cup \pi_2$ will correspond to $E_2$, and the unknown ancestors $\alpha_1, \alpha_2$ will correspond to the unknown perfect matchings $M_1, M_2$.

Our proof is however much more involved and there are two reasons for this: First, the problem formulation does not guarantee that $\alpha_1 \subseteq \pi_1 \cup \pi_2$ and $\alpha_2 \subseteq \pi_3 \cup \pi_4$. We will say that a solution $\alpha_1, \alpha_2$ that satisfies this condition is in a normal form. The hard part of the proof is actually showing that we can transform any solution $\alpha_1, \alpha_2$ into at least as good solution $\alpha'_1, \alpha'_2$ that is in the normal form.

The second major difficulty is that we are maximizing the sum $S(\alpha_1, \alpha_2)$ instead of just the size of the intersection. So a solution with maximum score $S(\alpha_1, \alpha_2)$ does not necessarily maximize the term $\text{sim}(\alpha_1, \alpha_2)$, the size of the intersection. To overcome these difficulties, we had to modify the edge gadget from the original proof and use a more restricted problem for the reduction.

5.1. Overview of the proof

The proof is by reduction from the CUBIC-MAX-CUT problem. Given a graph $G$, the Max-Cut problem is to find a cut of maximum size. We may phrase this as a problem of coloring all vertices in $G$ red or green while maximizing the number of red-green edges. (Partition of $V$ into the red part and the green part defines a cut and its size is the number of edges with endpoints of different color.) In the CUBIC-MAX-CUT problem, the instances are cubic graphs; this variant is still NP-hard and APX-hard [23].

Let $G = (V, E)$ be a given cubic graph, instance of the CUBIC-MAX-CUT problem. We will construct genomes $\pi_1, \pi_2, \pi_3,$ and $\pi_4$ such that the maximum cut in $G$ can be recovered from the solution $\alpha_1, \alpha_2$ of the BREAKPOINT-QUARTET problem in polynomial time.

For each vertex of $G$, there will be a vertex gadget (see Figure 5(a)) made of adjacencies of $\pi_1$ and $\pi_2$. Let $\pi_1$ be the red matching and $\pi_2$ the green matching. As we will prove later, we may suppose that $\alpha_1 \subseteq \pi_1 \cup \pi_2$, so within each vertex gadget, $\alpha_1$ will contain either the red edges of $\pi_1$ or the green edges of $\pi_2$. This naturally corresponds to a red/green vertex coloring in the CUBIC-MAX-CUT problem.

The framed vertices in Figure 5(a) are called “ports” – this is where the three incident edges are attached. For each edge of $G$, an edge gadget is constructed as shown in Figure 5(b). The blue cycles consist of two matchings – the adjacencies of $\pi_3$ and $\pi_4$. Again, as we will prove later, we may suppose that $\alpha_2 \subseteq \pi_3 \cup \pi_4$, i.e., the second ancestor consists only of the blue edges.

For future reference, let us state here again the claims to be proved in the form of a lemma:

**Normal form lemma.** Let $\pi_1, \pi_2, \pi_3, \pi_4$ be an instance of the BREAKPOINT-QUARTET problem constructed from a CUBIC-MAX-CUT instance as described above. Then any solution $\alpha_1, \alpha_2$ can be transformed in polynomial time into a solution $\alpha'_1, \alpha'_2$ such that $S(\alpha'_1, \alpha'_2) \geq S(\alpha_1, \alpha_2)$ and

$$\alpha'_1 \subseteq \pi_1 \cup \pi_2 \quad \text{and} \quad \alpha'_2 \subseteq \pi_3 \cup \pi_4.$$
Once we prove the Normal form lemma, the rest of the proof is easy: If $\alpha_1, \alpha_2$ is any solution in the normal form, term $\text{sim}(\pi_1, \alpha_1) + \text{sim}(\pi_2, \alpha_1)$ is always the same – we get $+6$ for each vertex gadget and $+6$ for each edge gadget. Similarly, term $\text{sim}(\alpha_2, \pi_1) + \text{sim}(\alpha_2, \pi_4)$ is always the same – we get $+9$ for each edge gadget. So the score $S(\alpha_1, \alpha_2)$ is maximized, when $\text{sim}(\alpha_1, \alpha_2) = |\alpha_1 \cap \alpha_2|$ is maximized. Let $uv$ be an edge in our graph $G$ from the Cubic-Max-Cut problem; if we choose matchings of the same color for both vertex gadgets $u$ and $v$, then $\alpha_1$ and $\alpha_2$ can only have one edge in common within the edge gadget $uv$ (see Figure 6(a)). However, if $u$ and $v$ have matchings of different color, then we can set adjacencies of $\alpha_2$ so that $\alpha_1$ and $\alpha_2$ have 2 edges in common (see Figure 6(b)). When we sum up all the contributions, we get $S(\alpha_1, \alpha_2) = 30n + c$, where $n$ is the number of vertices in $G$ and $c$ is the size of the cut corresponding to the matching $\alpha_1$, so a polynomial algorithm for Breakpoint-Quartet would imply a polynomial algorithm for Cubic-Max-Cut.

For the APX-hardness, note that for any graph with $n$ vertices, we can easily find a cut of size $c \geq n/2$. Let $\alpha_1^*, \alpha_2^*$ be an optimal solution for an instance of the Breakpoint-Quartet problem and $\alpha_1, \alpha_2$ a solution such that $S(\alpha_1^*, \alpha_2^*) \leq (1 + \varepsilon)S(\alpha_1, \alpha_2)$. Let both solutions be in the normal form and let $c'$ and $c \geq n/2$ be the sizes of the corresponding cuts. Then $30n + c' \leq (1 + \varepsilon)(30n + c)$ and $c' \leq (1 + \varepsilon)c + 30en \leq (1 + 61\varepsilon)c$. So a $(1 + \varepsilon)$-approximation algorithm for the Breakpoint-Quartet problem gives a $(1 + 61\varepsilon)$-approximation algorithm for the Cubic-Max-Cut problem.

5.2. Notation, terminology, and other conventions

Let $\Pi = \pi_1 \cup \pi_2 \cup \pi_3 \cup \pi_4$ be the set of adjacencies present in at least one extant species. We say that an adjacency $e \in \alpha_1$ is supported, if $e \in \Pi$; otherwise it is unsupported.

Let us name the different types of vertices (extremities) and edges (adjacencies) in the following manner: The framed vertices in Fig. 5(a) are called ports and edges from $\pi_1 \cup \pi_2$ that connect them are called port edges. We use the same names also for other (extant or ancestral) adjacencies which are parallel to these.

Each port consists of two outer extremities called corners and the middle extremity in-between. The set of all ports, corners, and middle vertices is denoted by $P$, $C$, and $M$, respectively ($P = C \cup M$). The set of intermediate extremities between two ports of a vertex gadget is denoted by $I$.

The double edges and the two vertices at the top of Fig. 5(b) are auxiliary – they just complete the matchings into perfect matchings.

As the subgraph of an edge gadget with excluded auxiliary and port edges reminds of a ladder, we use the following “ladder” terminology (see Fig. 5(b)). The red-green double adjacencies are the rails and the blue adjacencies are the rails of the ladder. Again, we use the same name for parallel adjacencies. The set of auxiliary extremities is denoted by $A$ and the set of ladder extremities is denoted by $L$.

We say that $uv$ is an $X$-$Y$-edge if $u \in X$ and $v \in Y$ ($X$ and $Y$ do not have to be disjoint); an $X$-edge is any edge $uv$ such that $u \in X$ or $v \in X$.

In the proof of the Normal form lemma, we will gradually transform a given solution $\alpha_1, \alpha_2$ by exchanging some adjacencies in the solution for other adjacencies. The method is analogous to improving a given matching by an
augmenting path: An $\alpha_i$-alternating cycle is a cycle where edges belonging to $\alpha_i$ and edges not belonging to $\alpha_i$ alternate. We will say that an $C_1, C_2$ is a non-negative pair of cycles for the solution $\alpha_1, \alpha_2$, if $C_i$ is an $\alpha_i$-alternating cycle and exchanging the matched and the unmatched edges of $C_i$ in $\alpha_i$ (for $i = 1, 2$) does not decrease the score:

$$S(\alpha_1 \oplus C_1, \alpha_2 \oplus C_2) \geq S(\alpha_1, \alpha_2).$$

In the figures that follow, we will draw adjacencies of $\alpha_2$ blue and adjacencies of $\alpha_1$ red, green, or yellow: We use red and green for edges in the vertex gadgets that are in common with $\pi_1$ or $\pi_2$, respectively (since this corresponds to choosing the red or green color in the Cubic-Max-Cut problem). We use yellow for the other edges. We use straight lines for the actual adjacencies and wavy lines for the suggested adjacencies in non-negative cycles that should be included instead.

In the proof, we will often say

we may suppose that the solution has property $\mathcal{P}$

as a shorthand for a more precise (and longer) statement

Given any solution $\alpha_1, \alpha_2$, we can transform it to a solution $\alpha_1', \alpha_2'$ with $S(\alpha_1', \alpha_2') \geq S(\alpha_1, \alpha_2)$ having property $\mathcal{P}$ in polynomial time; in particular, if $\alpha_1, \alpha_2$ is an optimal solution, $\alpha_1', \alpha_2'$ is also optimal, with property $\mathcal{P}$. From now on, we will assume that the solution has property $\mathcal{P}$.

5.3. Proof of the Normal form lemma

First, we focus on the adjacencies that the ancestors $\alpha_1$ and $\alpha_2$ have in common. We will show that these may be assumed to be supported. This is an important first step, since we can argue that all the unsupported adjacencies contribute zero to the score.

**Proposition 1.** We may suppose that all red-green double edges are matched in $\alpha_1$ and all blue double edges are matched in $\alpha_2$, i.e., $\pi_1 \cap \pi_2 \subseteq \alpha_1$ and $\pi_3 \cap \pi_4 \subseteq \alpha_2$.

**Proof.** We can replace alternately genome $\alpha_1$ or $\alpha_2$ by the median of its neighbors until we converge to a local optimum. As we have already proved in the previous section, we may assume that a median contains all adjacencies occurring at least twice.

This immediately excludes common unsupported $A$, $I$, and $L$-edges.

**Proposition 2.** We may suppose that $\alpha_1$ and $\alpha_2$ do not contain unsupported $M$-edges. In other words, we may suppose that in both $\alpha_1$ and $\alpha_2$, one of the edges in each port is chosen.

**Proof.** Let $x \in M$. First, consider the case that $xy_1 \in \alpha_1$ and $xy_2 \in \alpha_2$ are both unsupported. Let $p$ be a neighbouring corner vertex; while $x_1y_1$ and $x_2y_2$ contribute only at most +1 to the score (if $y_1 = y_2$), a common adjacency $xp$ would contribute +3; let $pc_1$ and $pc_2$ be the actual adjacencies in $\alpha_1$ and $\alpha_2$; either $z_1 = z_2$ and the common adjacency is unsupported, or $z_1 \neq z_2$: either way, these two edges contribute at most +2 to the score; so $xpz_1y_1x$ and $xpz_2y_2x$ is a non-negative pair of cycles.

Similarly, if one ancestor contains a port edge $xp$ and the other one an unsupported adjacency $xy$ and adjacency $pz$, $xpzxy$ is a non-negative cycle.

**Proposition 3.** We may suppose that all $L$-edges are supported.

**Proof.** In $\alpha_1$, both $L$-edges are the rung edges by Proposition 1. Consequently, contribution of any unsupported $L$-edge in $\alpha_2$ to the score is zero. Let $\ell_1x \in \alpha_2$ be such an edge. Let $\ell_1\ell_2$ be the middle rail edge and let $\ell_2y$ be the adjacency in $\alpha_2$. If $\ell_2y$ is unsupported, $\ell_1\ell_2\ell_3\ell_3\ell_1$ is an augmenting cycle. Otherwise, if $\ell_2y$ is a rail edge, $\ell_1\ell_2\ell_3\ell_3\ell_1$ is a non-negative cycle. The last case is that $\ell_2y$ is a rung edge. Let $\ell_1, \ell_2$ be the other middle rail edge, and let $\ell_1z$ be the adjacency in $\alpha_2$. Again, if $\ell_1z$ is unsupported, $\ell_1\ell_2\ell_3\ell_2z\ell_1\ell_1$ is an augmenting cycle, otherwise it is a rail edge and the cycle is non-negative.
It remains to rule out unsupported $C$–$C$-edges.

**Proposition 4.** We may suppose that there are no common $C$-edges other than port edges.

**Proof.** Let $xb$ be a common $C$–$C$ edge in $\alpha_1$ and $\alpha_2$. In the proof, we will refer to and use the notation of Fig. 7. From what we proved by now, we may assume that $\alpha_1$ contains the rung edges $\ell_a \ell_b$ and $\ell_c \ell_d$, am$_1$ is a common adjacency of $\alpha_1$ and $\alpha_2$, and either $m_2c$ or $m_2d$ is included in $\alpha_2$.

First, assume the latter case that $m_2d \in \alpha_2$ (Fig. 7(a) and 7(b)). Since the $L$-edges are supported, either $\ell_a \ell_c \in \alpha_2$ (Fig. 7(a)) or both $\ell_a \ell_b$ and $\ell_c \ell_d$ belong to $\alpha_2$ (Fig. 7(b)). In either case, we can add ladder edges to form an alternating $b$–$c$ path with score $+1$ that will be a part of our non-negative pair of cycles. Let $cz$ be the unsupported adjacency in $\alpha_2$. Either $cz \not\in \alpha_1$ and $xz \ldots czx$ is a non-negative cycle (see Fig. 7(a)), or $cz$ is common edge and we also have to exchange some edges in $\alpha_1$. In particular, $xbczx$ and $xb \ldots czx$ is a non-negative pair of cycles (see Fig. 7(b)).

Similarly, we can prove the other case when $m_2c \in \alpha_2$; the non-negative cycle pairs are depicted in Fig. 7(c) and 7(d). It can be easily checked, that the proof also works when extremities $x$ and $b$ belong to the same edge gadget (in this case $x$ is $c$ or $d$ and $b$ coincides with $z$). A $C$–$C$-edge connecting two corners of a single port is ruled out by Proposition 2.

Note that if $\alpha_1$ and $\alpha_2$ have a common $z$-edge (Fig. 7(b) and 7(d)), we create a new common unsupported $C$–$C$-edge $xz$. However, the number of common unsupported $C$–$C$-edges is decreased by 1 in all cases.

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**Figure 7:** Different cases that arise when disposing of unsupported common $C$–$C$-edges. The dashed edges represent the underlying edge gadgets; adjacencies of $\alpha_2$ are blue, adjacencies of $\alpha_1$ are yellow, red, and green. Wavy lines are the new suggested adjacencies that should be exchanged for the present ones in the non-negative cycles.

**Corollary 1.** We may suppose that all the common adjacencies of the ancestors $\alpha_1$ and $\alpha_2$ are supported: $\alpha_1 \cap \alpha_2 \subseteq \Pi$. More specifically, we may suppose that the only common edges are port edges and rung edges. Consequently, each unsupported adjacency contributes zero to the score.
We say that $\alpha_1$ is uniform at a vertex gadget, if all the port edges in the gadget have the same color (they all agree with either the $\pi_1$ edges or the $\pi_2$ edges). Next, we prove that $\alpha_1$ may be assumed uniform at all gadgets. Such an ancestor $\alpha_1$ directly corresponds to a cut in $G$.

Here, we use the fact that $G$ is cubic: Imagine that $G$ was a complete bipartite graph $K_{n,n}$ with one more vertex connected to all the other vertices. Then our reduction would not work, since the optimal ancestors would color one bipartition red, the other green and the extra vertex half green half red (i.e., half of the ports would be green and the other half red).

First, let us characterize how the non-uniform gadgets look like.

**Proposition 5.** The following are equivalent:

- $\alpha_1$ is not uniform at a vertex gadget
- there is one unsupported I-edge in $\alpha_1$ incident to the vertex gadget
- there is one unsupported C-edge in $\alpha_1$ incident to the vertex gadget

**Proof.** Let $\alpha_1$ be non-uniform at a vertex gadget. Without loss of generality, let two of the port edges be green and one be red (see Fig. 8(a)). Denote $r$ the red and $g_1$ and $g_2$ the green edges, such that $g_1$ is closer to $r$ (as in Fig. 8(a)). The edge incident to the intermediate extremity between $r$ and $g_1$ is an unsupported I-edge.

Obviously, if two neighbouring extremities in a vertex gadget are incident with unsupported edges, there is an augmenting cycle, so we may suppose that the intermediate edge between $g_1$ and $g_2$ is green and one of the intermediate edges $e$ or $f$ in Fig. 8(a) belongs to $\alpha_1$; the other corner has an unsupported C-edge.

Conversely, if there is an unsupported I-edge or C-edge, the neighbouring ports cannot have edges of the same color (this would imply two neighbouring extremities with unsupported edges in $\alpha_1$).

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We are ready to prove the Normal form lemma.

**Proposition 6.** We may suppose that in each vertex gadget, the port edges of $\alpha_1$ are either all red or all green. In particular, we may suppose that $\alpha_1 \subseteq \pi_1 \cup \pi_2$.

**Proof.** We prove that for each vertex gadget, we may simply look at the three port edges and choose the color by majority vote. In the previous proposition, we have proved that non-uniform gadgets have exactly two unsupported edges so they form cycles as in Fig. 8(b). Fig. 8(c) shows the non-negative cycle that we get by including the majority vote color edges. In each vertex gadget, we may lose 1 point for switching the port edge (if this was a common edge), but we get 1 extra point for increasing the number of supported edges.

**Proposition 7.** We may suppose that $\alpha_2 \subseteq \pi_3 \cup \pi_4$.

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![Figure 8: Non-uniform ancestors at a vertex and a way how to remedy them.](image-url)
Proof. The only remaining edges in $\alpha_2$ that may be outside $\pi_3 \cup \pi_4$ are rung edges and unsupported $C–C$-edges. If $\alpha_2$ contains a rung edge, then in the adjacent port, one corner is covered by a port edge, but the other corner is not and we have an unsupported $C–C$-edge. Conversely, it is easy to see that if $\alpha_2$ contains a $C–C$-edge then in the attached edge gadget, either both rung or both middle rail edges are in $\alpha_2$ and there is a $C–C$-edge incident to a corner of the opposite port. So the edge gadgets with $C–C$-edges form cycles and all the rung edges are in these edge gadgets (see Fig. 9). We will fix both at the same time.

We can join the two corners in an edge gadget by a non-negative alternating path (see Fig. 9); we can lose 1 point for destroying a common adjacency of $\alpha_1$ and $\alpha_2$, but we gain 1 point for increasing the number of supported edges in $\alpha_2$.

This concludes the proof of the Normal form lemma and thus also the proof of NP-hardness and APX-hardness of the **Breakpoint-Quartet** problem.

6. Conclusion

In this paper, we have settled the open problems concerning the computational complexity of different rearrangement problems in the breakpoint models. There are three intriguing questions in this area which remain open. The first two are of theoretical interest and are related to approximability of the **Small-Phylogeny** problem, the third question is more practical:

1. How well can we approximate **Small-Phylogeny**? For example, **Breakpoint-Quartet** problem can be easily formulated as an integer linear program (we can use different variables for the edges only in $\alpha_1$, only in $\alpha_2$, and in the intersection $\alpha_1 \cap \alpha_2$). Its relaxation might lead to an algorithm with some approximation ratio.
2. In the Steinerization approach to ancestral reconstruction, we repeatedly replace the ancestral genomes by medians of genomes in the neighboring nodes of the tree until we converge to a local optimum. Despite the fact that this is the most common approach to ancestral reconstruction (also in the other models) and that preliminary experiments with simulated data suggest that this heuristic performs very well, no guarantees are known for the method (in any model).
3. Finally, the motivation behind the general breakpoint model is that we can solve the median problem in polynomial time. Using the Steinerization method, we can also get very good solutions of the **Small-Phylogeny** problem rapidly. The question is, how useful are these solutions in practice.

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