Constructing optimal trees from quartets

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We present fast new algorithms for constructing phylogenetic trees from quartets (resolved trees on four leaves). The problem is central to divide and conquer approaches to phylogenetic analysis and has been receiving considerable attention from the computational biology community. Most formulations of the problem are NP-hard. Here we consider a number of constrained versions that have polynomial time solutions.

The main result is an algorithm for determining bounded degree trees with optimal quartet weight, subject to the constraint that the splits in the tree come from a given collection, for example, the splits in the aligned sequence data. The algorithm can search an exponentially large number of phylogenetic trees in polynomial time. We present applications of this algorithm to a number of problems in phylogenetics, including sequence analysis, construction of trees from phylogenetic networks, and consensus methods.

Key Words: quartets, phylogenetic trees, algorithms, consensus, networks

1. INTRODUCTION

The reconstruction of large evolutionary (phylogenetic) trees from smaller subtrees is currently receiving considerable attention in the computational biology community [6, 7, 23, 29, 31, 37, 38].

There is a clear computational advantage to analysing small subsets of taxa (species). It allows for far more intensive analysis and the application of more complex models to reconstruct trees from the sequence data. Tree criteria like, such as maximum likelihood, which are computationally horrendous on larger trees, can be solved quickly on four-leaf trees (quartets)—there are just four possible trees to consider.

There are also biological and statistical advantages of considering only small subsets of sequences at a time. In many cases the actual data limit the number of sequences that can be analysed at one time. The number of sites that can be aligned across four sequences is generally much more than the number of sites that can be aligned across the full set of n sequences, so aligning over the complete set of sequences can result in lost information. Secondly, a recognized source of error in standard tree building methods like neighbor joining is that distantly related sequences can mislead tree reconstruction [29]. If only small sets of sequences are considered at one time then those sets containing distantly related sequences can be down-weighted (or even given a zero weighting, as in [23], [29]).

The main difficulty with quartet based methods is the question of how best to build large trees out of small ones. The general problem—determining a phylogenetic tree that agrees with the largest number of quartets, or maximum weight set of quartets—is NP-hard, by a simple reduction from QUARTET COMPATIBILITY [36]. Exhaustive search is generally infeasible: there are $1 \cdot 3 \cdot 5 \cdot \cdots \cdot (2n-5)$ binary trees on n leaves to choose from. When the number of sequences is limited, and the computational time is not, the exact algorithm of [6] can be used: it runs in time $O(n^4 3^n)$ on n sequences and $O(n^4)$ quartets.

The next alternative to exact solutions is the use of heuristic algorithms for quartet optimization. These have been produced by a number of computer scientists, biologists and mathematicians. The heuristics of Sattath and Tversky [35], Fitch [26], Colonius and Schulze [14], and Bandelt and Dress [1] combine clustering procedures with a pairwise similarity or neighbourliness scores derived from the quartet sets. An alternative agglomerative algorithm for constructing trees from quartets is provided in [8].

A novel variation on the scoring approach is described by Ben-Dor *et al.* [6]. Instead of constructing a similarity score then clustering, they embed the n leafs as points in $\Re^n$ using semi-definite programming, and then apply a nearest neighbour clustering method.

The tree building, or 'puzzling', part of the Quartet Puzzling heuristic of Strimmer and von Haeseler [37] works by ordering the leaf set arbitrarily, constructing a tree on the first four leaves, and then adding new leaves one at a time, attaching each leaf to the edge that gives optimum quartet score. The same approach is used in [38, 15] to optimise according to different, but related, criteria. These procedures can be seen as analogues of the Wagner tree method [24] because they start with a small tree and insert one leaf at a time.

Dekker [17] proposes a method for constructing trees from quartets and other subtrees using quartet inference rules (see also [12]). The Short Quartet Method [23] constructs trees using inference rules and greedy selection of quartets.

One important problem with these heuristic approaches is that there has been little systematic analysis of their strengths and weaknesses. Indeed, the quartet approximation problem seems to be resistant to an approximation theoretic ap-

proach. A version of the problem was shown to have a PTAS by [30], but the complexity of the approximation algorithm is so astronomical that the result is of theoretical interest only.

Polynomial time exact algorithms have been proposed for a number of constrained versions. The Q^* method of Berry and Gascuel [7] can be applied when there is at most one quartet in the input set for each four leaves, and the output tree is constrained to have only quartets from this set. There is always exactly one maximal tree satisfying these conditions. The Q^* method is employed by Kearney [31] to construct trees from quartets selected by an ordinal quartet method.

The Q^* method can be extended by weakening the constraint that all the quartets in the tree come from the input set. The quartet cleaning method [30], C-tree construction [9], and hypercleaning method [10] all allow varying degrees of 'errors' in the input set. All run in polynomial time, and are well suited for the situation when the quartet set is unweighted and almost tree-like.

In this paper we present a polynomial time algorithm for a constrained version of the quartet optimization problem. The algorithms are fast enough to be applied to moderately large data sets. The constraints are not overly restrictive—the algorithm still searches an exponentially large number of trees—and are general enough to be applied to a wide range of phylogenetic problems. Finally, we note that the algorithms can be applied to weighted sets of quartets, with the possibility of more than one quartet for each set of four leaves.

In the remainder of this section we present basic definitions (section 1.1), describe the main result (section 1.2) and outline a number of applications of the algorithm. In section 2 we present the constrained quartet optimization algorithm. In section 3 we show how the algorithm can be applied to the extraction of phylogenies from phylogenetic networks, and describe the efficiency gains that can be made in this application.

1.1. Basic Definitions

Hypotheses about the evolutionary relationships between taxa (species) are usually described in terms of a phylogenetic tree. When no ancestral node is given we have an **unrooted (phylogenetic) tree** which can be formally defined as an acyclic connected graph with no vertices of degree two and all leaves (degree one vertices) labelled uniquely from some leaf set L representing the set of taxa. A phylogenetic tree is **binary** or **resolved** if all internal vertices have degree three.

A phylogenetic tree clearly implies relationships between each subset of its leaf set. This is captured in the notion of induced subtrees. Let T be an unrooted phylogenetic tree, and let A be a subset of its leaf set. Consider the minimal subgraph $T(A)$ of T that connects elements of A. Delete all vertices of degree two in $T(A)$ and identify their adjacent edges, thereby obtaining an unrooted

phylogenetic tree with leaf set A. This tree is called the **subtree of T induced by** A and is denoted $T_{|A}$.

The information contained in a phylogenetic trees can be coded in a number of ways. Here we consider two encodings: sets of splits and sets of quartets.

A **split** $A|B$ is a partition of the leaf set into two non-empty parts, A and B. If we remove an edge e of a phylogenetic tree we divide the tree into two connected components, and induce a split of the leaf set of the tree. This split is called the **split associated with** e, and the set of all such splits in a tree is denoted $splits(T)$. If e is an external edge then we obtain a split $A|B$ with $|A| = 1$ or $|B| = 1$. We call these splits **trivial** splits. Note that T can be reconstructed from the set $splits(T)$.

A **quartet** is a resolved phylogenetic tree on four leaves. There are three possible quartets on a given set of four leaves $\{a, b, c, d\}$. We use $ab|cd$ to denote the quartet where a and b are separated from c and d by the internal edge. A phylogenetic tree T **agrees** with a quartet $ab|cd$ if a, b, c, d are all leaves of T and the path from a to b does not share any vertices with the path from c to d, that is, if $T_{|\{a,b,c,d\}} = ab|cd$. Let $q(T)$ denote the set of quartets that T agrees with. We can reconstruct T from $q(T)$.

To illustrate, we give a simple example (figure 1). We have selected two internal edges and give the associated splits. We have also selected two sets of four leaves, and given the induced quartets.

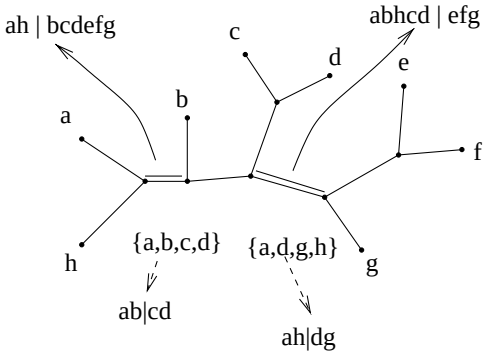

FIG. 1. Splits and quartets of an unrooted phylogenetic tree.

We need three further definitions in order to be able to summarise our results. First, a set of splits $\mathcal{S}$ is **compatible** if $\mathcal{S} \subseteq splits(T)$ for some tree T. Second, a set of splits is **weakly compatible** if for every three splits $A_1|B_1, A_2|B_2, A_3|B_3$, at least one of the intersections $B_1 \cap B_2 \cap B_3$, $B_1 \cap A_2 \cap A_3$, $A_1 \cap B_2 \cap A_3$, $A_1 \cap A_2 \cap B_3$ is empty [3]. Finally, a set of weakly compatible splits $\mathcal{S}$ on X is **maximum** if $|\mathcal{S}| = n(n-1)/2$ (see [3]).

1.2. Main results

Let w be a weighting function defined on the set of all quartets with leaves in L. The weights can be negative and do not have to be integers. We define the weight of the tree to be

$$w(T) = \sum_{ab|cd \in q(T)} w(ab|cd), \tag{1}$$

the sum of all quartet weights in the tree. We will be examining the following problem:

SPLIT CONSTRAINED QUARTET OPTIMIZATION
INSTANCE: Weighting w for the quartets on a leaf set L. Set $\mathcal{S}$ of splits of L. Rational number λ.
PARAMETER: Degree bound d.
QUESTION: Is there a tree T with vertex degree bounded by d and $splits(T) \subseteq \mathcal{S}$ such that $w(T) \geq \lambda$?

Let $n = |L|$ and $k = |\mathcal{S}|$. The computational complexity of this problem can be summarised:

- Polynomial time solvable for bounded d, with time complexity $O(n^4k + n^2dk^{d-1})$ (section 2). Can be improved to $O(n^5)$ time when $\mathcal{S}$ is weakly compatible and d equals 3 or 4 (section 3.1).
- NP-complete without the degree bound d, even when the set of splits $\mathcal{S}$ is *weakly compatible* (see section 3.3).
- Polynomial time solvable *without* degree bound when all quartet weights are non-negative and $\mathcal{S}$ is *maximum weakly compatible* (section 3.2).
- NP-complete when the quartets weights can be negative and d is unbounded, even when $\mathcal{S} = splits(T)$ for some tree T (section 3.3).

The results can be viewed as an extension of the compatibility algorithms of [12]. In [12] the splits, rather than the quartets, are weighted and the criteria of optimization is the sum of the weights of the splits in a tree. The significance of these results is highlighted by the fact that determining an optimal tree with respect to split weights and no degree bound is equivalent to MAX CLIQUE [16] and so inherits the depressing complexity attributes of MAX CLIQUE like W[1]-hardness [19] and non-approximability [5].

1.3. Applications

We outline a number of possible applications of the split constrained quartet optimization algorithms.

1.3.1. Analysis of sequence data

A natural source of splits to serve as a split constraint for the algorithm is the sequence data. We first use an alignment program to determine which positions (or *sites*) in one sequence correspond to which positions in the other sequences. For each position we then obtain a map from the set of sequences to the nucleotide for that sequence at that position. In DNA and RNA there are four nucleotides possible, and so there are eight ways of partitioning the nucleotides into two groups. Each of these partitions can be used to construct a split of the set of sequence set.

We have, then, a three step process for inferring phylogenetic trees from aligned sequence data:

(1) Extract the set $\mathcal{S}$ of splits given by the characters at each site in the data.

(2) For each set of four sequences, score the three possible quartet trees using a standard phylogenetic optimization criterion (e.g. parsimony length, likelihood score). The quartet scores can be scaled to indicate relative confidence.

(3) Apply the constrained quartet optimization algorithm to the set of splits constructed in step (1) with the quartet weighting constructed in step (2).

1.3.2. Extracting trees from phylogenetic networks

An approach to phylogenetic analysis that is growing in popularity is the construction of phylogenetic networks, where the evolutionary relationships are represented by a general graph rather than just a tree.

Phylogenetic networks allow for a more complicated relationship between the different species, and can incorporate recombination, hybridisation, and horizontal gene transfer. In some cases the data itself dictates that a tree representation is not suitable, as in the complex evolutionary relations between viruses, or in intra-specific data with multiple hybridizations.

Phylogenetic networks can also be employed as an intermediary step in phylogenetic tree reconstruction. Often a network program like SplitsTree [22] is used to get a general representation of patterns in the data, and an indication of how 'tree-like' the data actually is. However the problem still remains - given a phylogenetic network how does one best extract a phylogenetic tree?

We apply the constrained quartet optimization algorithms to this problem by first converting the network into a collection of splits. In section 3 we discuss this approach in further detail, and show that time complexity gains can be made by exploiting the structure of the network.

1.3.3. Consensus trees, bootstrapping, and quartet puzzling

A common problem faced by practitioners in evolutionary biology is the representation of a large collection of trees on the same leaf set by a single **consensus** tree. Tree search criteria such as likelihood can have multiple global optima.

Heuristic construction methods (like quartet puzzling [37]) that involve randomness can construct different trees on different runs, and the user will want to make multiple runs in order to achieve a degree of confidence in the final hypothesis. Bootstrapping, and its close cousin jack-knifing, work on the same principle. The data is randomly sampled and these possibly incomplete samples are used as input for the tree reconstruction criteria. The collection of trees obtained is then used to determine confidence levels for a particular evolutionary hypothesis.

By far the most common consensus technique is the majority rule tree, formed from splits that appear in over half of the input trees. Unfortunately this method will often give quite uninformative consensus trees, with few internal edges. A rogue taxa that appears in a large number of different places (perhaps because it is only distantly related to the other taxa) can force the consensus tree to collapse completely. A major drawback of the popular Quartet Puzzling method [37] is that the consensus tree it produces tends to be quite poorly resolved.

The constrained quartet optimization algorithm provides a natural solution to the consensus tree problem. We first construct the set of all splits that appear in at least one of the input trees. If the input trees are binary then this set of splits is guaranteed to contain the set of splits of some binary tree, so we can always use a small degree bound. The quartet weighting can be taken from the input data, as in the previous section, or by counting the number of times each quartet appears in an input tree. In this way the consensus technique can be extended to handle weighted trees. Finally, the constrained quartet optimization algorithm can be used to construct, in polynomial time, a consensus tree for the input set of trees.

1.3.4. Optimal trees with excluded quartets

Suppose that we are given, for each set of four leaves $\{a, b, c, d\}$ a quartet to *exclude*. We wish to find a tree T of optimal quartet weight such that $q(T)$ contains none of the excluded quartets.

We can solve this problem when we also have a degree bound for T. Let Q be the set of excluded quartets. We first construct the set of splits

$$\mathcal{S} = \{A|B : aa'|bb' \notin Q, \text{ all } a, a' \in A,\ b, b' \in B\} \tag{2}$$

This set is weakly compatible [4] and, furthermore, $q(T) \cap Q = \emptyset$ if and only if $splits(T) \subseteq \mathcal{S}$. Hence the problem of finding an optimal tree T containing no excluded quartets reduces to the SPLIT CONSTRAINED QUARTET OPTIMIZATION problem. In section 3 we give efficient algorithms for constrained quartet optimization when $\mathcal{S}$ is weakly compatible.

Note that if we do not force Q to contain an excluded quartet for every set of four leaves then it becomes NP-hard to determine if there exists a binary tree T such that $q(T) \cap Q = \emptyset$ [13].

1.3.5. Optimal trees with a given circular order

A novel approach to phylogenetic tree construction was introduced by Gonet *et al.* in [32]. They first construct a tour $x_1, x_2, \ldots, x_n, x_1$ of the set L of leaves using travelling salesman algorithms. They then look for a phylogenetic tree T on L such that $x_1, x_2, \ldots, x_n, x_1$ is a **circular order** of T, that is, each edge in T lies on exactly two paths connecting adjacent vertices in the tour. There are 2^{n-2} possible circular orderings for a binary tree on n leaves [33].

Construct the set

$$\mathcal{S} = \{\{x_i, x_{i+1}, \ldots, x_j\} | L - \{x_i, x_{i+1}, \ldots, x_j\} : 1 \leq i \leq j \leq n-1\} \quad (3)$$

This set is a maximum weakly compatible. Furthermore, $x_1, \ldots, x_n$ is a circular ordering for a tree T if and only if $splits(T) \subseteq \mathcal{S}$. In section 3.2 we show that the SPLIT CONSTRAINED QUARTET OPTIMIZATION problem can be solved in polynomial time *without a degree bound* when $\mathcal{S}$ is maximum weakly compatible and all quartet weights are non-negative. Hence, given a tour $x_1, \ldots, x_n, x_1$ of L and a positive weight for every quartet on L, we can determine an optimal weight tree T from among the exponentially many trees that have $x_1, \ldots, x_n, x_1$ as a circular order.

2. CONSTRAINED QUARTET OPTIMIZATION ALGORITHMS

The key component of the dynamical programming algorithm of [12] is a data structure called the decomposition table, which we describe in section 2.2. We will also use a decomposition table, though we optimize a different, and more complex, criterion. First, however, we introduce rooted trees and clusters.

2.1. Rooted trees and clusters

A **rooted phylogenetic tree** is defined in the same way as an unrooted phylogenetic tree, except that one vertex, which may have degree two, is distinguished and called the **root**. Given any two vertices u, v in a rooted phylogenetic tree, if the path from u to the root passes through v then we say that u is a **descendent** of v. The descendents of a vertex v that are also adjacent to v are called the **children** of v. A rooted phylogenetic tree is **binary** or **fully resolved** if every internal vertex has exactly two children.

The rooted analogue of a split is a **cluster**. Given a vertex v in a rooted tree the set of leaves that are descendents of v is called the cluster **associated with** v. The set of all clusters associated to vertices in a rooted tree T is denoted $clus(T)$.

We will often be converting rooted trees into unrooted trees. Suppose that T is a rooted tree such that $\mathcal{L}(T) \subset L$ and $\mathcal{L}(T) \neq L$. We let $\text{UNROOT}(T, L)$ be the unrooted tree given by attaching all leaves in $L - \mathcal{L}(T)$ to the root of T and then taking the underlying unrooted topology. For example the trees in figure 2 (i) and 2 (ii) have unrooted equivalents equal to those trees in figure 2 (iii) and 2 (iv).

2.2. The decomposition table

The key data structure in the algorithm is a **decomposition table** $\mathcal{D} = (\mathcal{C}, D)$. Here $\mathcal{C} = C_1, C_2, \ldots, C_K$ is a collection of clusters of some leaf set L, and D is a table with a row $D[i]$ for each cluster C_i. Row $D[i]$ contains a list of unordered tuples $[p_1, p_2, \ldots, p_q]$ satisfying

- $q \geq 2$.
- $C_{p_1}, C_{p_2}, \ldots, C_{p_q}$ are pairwise disjoint.
- $C_i = C_{p_1} \cup C_{p_2} \cup \cdots \cup C_{p_q}$.

Note that one row can contain tuples of varying lengths and that we are not concerned with the ordering of the indices within the tuple. Let $\|\mathcal{D}\|$ denote the sum of the lengths of all the tuples in all the rows of $\mathcal{D}$.

To each row $D[i]$ of the decomposition table we associate a set of rooted trees $\mathcal{T}(\mathcal{D}, i)$, all of which have leaf set C_i. The set $\mathcal{T}(\mathcal{D}, i)$ is defined recursively:

- if $C_i = \{a\}$ for some leaf a then $\mathcal{T}(\mathcal{D}, i)$ contains the single vertex tree with leaf a;
- if $|C_i| \geq 2$ and $D[i] = \emptyset$ then $\mathcal{T}(\mathcal{D}, i) = \emptyset$.
- Otherwise, $\mathcal{T}(\mathcal{D}, i)$ is the set of all possible trees that can be formed by choosing a tuple $[p_1, \ldots, p_r]$ in $D[i]$, choosing subtrees $T_j \in \mathcal{T}(\mathcal{D}, j)$ for each $j = 1, \ldots, r$, and attaching the roots of these subtrees to a new vertex that becomes the root of a rooted tree with leaf set C_i.

Since there may be tuples $[p_1, \ldots, p_r]$ in $D[i]$ with $\mathcal{T}(\mathcal{D}, p_j) = \emptyset$ for some j, we can have $\mathcal{T}(\mathcal{D}, i) = \emptyset$ even though $D[i] \neq \emptyset$.

We use dynamical programming to enumerate or extract the trees in $\mathcal{T}(\mathcal{D}, i)$. Construct a table s by putting $s[i] = 1$ for all i such that $|C_i| = 1$, and putting

$$s[i] = \sum_{\{p_1, p_2, \ldots, p_q\} \in D[i]} s[p_1] \times s[p_2] \times \cdots \times s[p_q] \tag{4}$$

when $|C_i| > 1$. Then $s[i] = |\mathcal{T}(\mathcal{D}, i)|$, and the values $s[i]$ can be calculated in time $O(\|\mathcal{D}\|)$. [12]

Once the trees in $\mathcal{T}(\mathcal{D}, i)$ have been enumerated we can extract trees from the collection as follows:

- If $s[i] = 0$ return $\emptyset$
- else if $|C_i| = 1$ return the single vertex tree labelled by the leaf in C_i.
- else choose a tuple $[p_1, \ldots, p_q]$ such that $s[p_1] \times s[p_2] \times \cdots \times s[p_q] \neq 0$.

Extract trees $T_1, \ldots, T_q$ from $\mathcal{T}(\mathcal{D}, 1), \mathcal{T}(\mathcal{D}, 2), \ldots, \mathcal{T}(\mathcal{D}, q)$ respectively. Attach the roots of $T_1, \ldots, T_q$ to a new vertex that becomes the root of a tree T in $\mathcal{T}(\mathcal{D}, i)$. Return T.

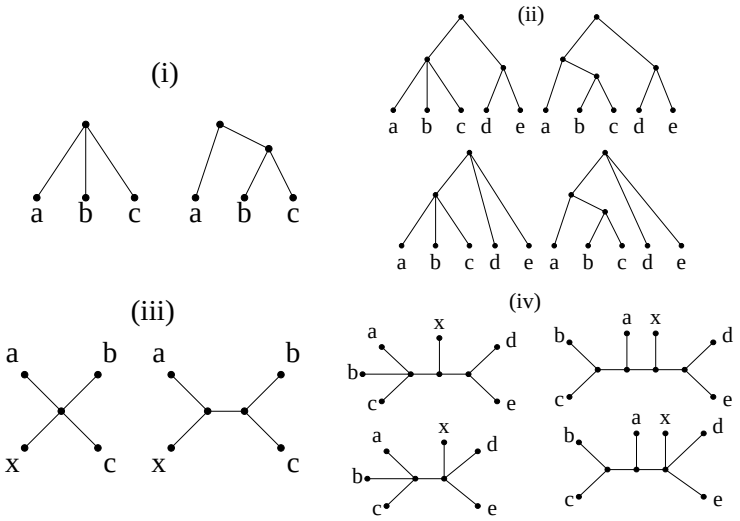

FIG. 2. The trees in (i) $\mathcal{T}(\mathcal{D}, 5)$; (ii) $\mathcal{T}(\mathcal{D}, 9)$; (iii) $\mathcal{T}^*(\mathcal{D}, 5)$; and (iv) $\mathcal{T}^*(\mathcal{D}, 9)$.

To illustrate, we give a simple example. The following table represents a decomposition table for a collection of clusters of the leaf set $L = \{a, b, c, d, e\}$.

i	C_i	$D[i]$	$s[i]$
1	$\{a\}$	–	1
2	$\{b\}$	–	1
3	$\{c\}$	–	1
4	$\{b, c\}$	$[2, 3]$	1
5	$\{a, b, c\}$	$[1, 2, 3], [1, 4]$	2
6	$\{d\}$	–	1
7	$\{e\}$	–	1
8	$\{d, e\}$	$[6, 7]$	1
9	$\{a, b, c, d, e\}$	$[5, 8], [5, 6, 7]$	4

Then $\mathcal{T}(\mathcal{D}, 5)$ contains the two trees in figure 2 (i). Each of the trees in $\mathcal{T}(\mathcal{D}, 5)$ appears as a subtree of two trees in $\mathcal{T}(\mathcal{D}, 9)$, giving a total of 4 trees in $\mathcal{T}(\mathcal{D}, 9)$ (figure 2 (ii)). All other collections $\mathcal{T}(\mathcal{D}, i)$ contain single trees.

Since decomposition tables can be used to store rooted trees, we can also use them to store unrooted trees. First fix a leaf x, acting as an outgroup, and consider a collection $\mathcal{C}$ of clusters on $L - \{x\}$. Let $\mathcal{D}$ be a decomposition table for $\mathcal{C}$. For each $C_i \in \mathcal{C}$ we define the set of unrooted trees

$$\mathcal{T}^*(\mathcal{D}, i) = \{\textsc{unroot}(T, L) : T \in \mathcal{T}(\mathcal{D}, i)\}. \tag{5}$$

The operation UNROOT is described above in section 2.1.

Returning to our example, suppose that $L' = \{a, b, c, d, e, x\}$. Then $\mathcal{T}^*(\mathcal{D}, 5)$ contains the two unrooted trees in figure 2 (iii) while $\mathcal{T}^*(\mathcal{D}, 9)$ contains the four trees in figure 2 (iv).

2.3. Optimal weight trees in decomposition tables

Suppose that $\mathcal{D} = (\mathcal{C}, D)$ is a decomposition table for a set of clusters $\mathcal{C}$ of $L - \{x\}$. The collections $\mathcal{T}^*(\mathcal{D}, i)$ can contain exponentially many trees, even when $\mathcal{D}$ is only polynomial in size. Here we show how to locate, from among these exponentially many trees, a tree with maximum summed quartet weight. The algorithm takes $O(n^4|\mathcal{C}| + n^2\|\mathcal{D}\|)$ time.

We use dynamic programming. At each step we optimize with respect to a modification of the quartet weighting criteria of eqn. 1.

As before, let w be a weighting function for the quartets with leaves in L. For each $C_i \in \mathcal{C}$ put

$$q_i(T) = \{ab|cd \in q(T) : |\{a, b, c, d\} \cap C_i| \geq 3\} \tag{6}$$

and

$$w_i(T) = \sum_{ab|cd \in q_i(T)} w(ab|cd). \tag{7}$$

We optimize $w_i(T)$ over all of the trees in the collection $\mathcal{T}^*(\mathcal{D}, i)$ defined in eqn. 5. Put

$$\mathrm{m}[i] = \max\{w_i(T) : T \in \mathcal{T}^*(\mathcal{D}, i)\} \tag{8}$$

and

$$\mathrm{M}[i] = \{T \in \mathcal{T}^*(\mathcal{D}, i) : w_i(T) = \mathrm{m}[i]\}. \tag{9}$$

Finally, for each tuple $[p_1, p_2, \ldots, p_q] \in D[i]$ we define

$$Q(p_1, \ldots, p_q) = \cup_{j=1}^{q} \{ab|cd : a, b \in C_{p_j}, c \in C_i - C_{p_j}, d \in L - C_{p_j}\} \quad (10)$$

and

$$W(p_1, \ldots, p_q) = \sum_{ab|cd \in Q(p_1,\ldots,p_q)} w(ab|cd). \quad (11)$$

We can now state the basis for the dynamical programming algorithm.

THEOREM 2.1. *If* $|C_i| = 1$ *then* $\mathrm{m}[i] = 0$, *otherwise*

$$\mathrm{m}[i] = \max\{W(p_1, \ldots, p_q) + \sum_{j=1}^{q} \mathrm{m}[j] : [p_1, p_2, \ldots, p_q] \in D[i]\}. \quad (12)$$

Proof. We prove the result by induction on the size of C_i. If $|C_i| = 1$ then $\mathcal{T}^*(\mathcal{D}, i)$ contains only the trivial unrooted tree with no internal edges. This has an empty quartet set and, consequently, zero weight.

Suppose that the result holds for all $C_j \in \mathcal{C}$ such that $|C_j| < |C_i|$. Suppose that $T^* \in \mathrm{M}[i]$. By the definition of $\mathcal{T}^*(\mathcal{D}, i)$ and $\mathrm{M}[i]$ (eqns. 5 and 9) there is $T \in \mathcal{T}(\mathcal{D}, i)$ such that $T^* = \textsc{unroot}(T, L)$. Let $T_1, T_2, \ldots, T_q$ be the maximal subtrees of T rooted at the children of the root of T.

By the definition of $\mathcal{T}(\mathcal{D}, i)$ there is a tuple $[p_1, \ldots, p_q]$ such that for each $j \in \{1, \ldots, q\}$ we have $C_{p_j} = \mathcal{L}(T_j)$ and $T_j \in \mathcal{T}(\mathcal{D}, p_j)$.

Consider an arbitrary quartet $ab|cd \in q_i(T^*)$. Then $|\{a, b, c, d\} \cap C_i| \geq 3$ and exactly one of the following must hold:

- There is $j \in \{1, 2, \ldots, q\}$ such that $|\{a, b, c, d\} \cap C_{p_j}| \geq 3$, or
- There is $j \in \{1, 2, \ldots, q\}$ such that $\{a, b, c, d\} \cap C_{p_j}$ equals $\{a, b\}$ or $\{c, d\}$.

Hence

$$\begin{aligned} w_i(T^*) &= \sum_{j=1}^{q} w_{p_j}(T_j) + W(p_1, \ldots, p_q) && (13) \\ &\leq \mathrm{m}[i] && (14) \end{aligned}$$

by the induction hypothesis applied to $C_{p_1}, \ldots, C_{p_q}$.

Conversely, suppose that $[p_1, \ldots, p_q]$ maximises eqn. 12. There is $T_1, \ldots, T_q$ such that $unroot(T_j, L) \in \mathrm{M}[p_j]$ for all $j = 1, 2, \ldots, q$. Construct a rooted tree T by attaching the roots of $T_1, \ldots, T_q$ to a new root. Then $unroot(T, L) \in \mathcal{T}^*(\mathcal{D}, i)$ and $w_i(T) = \mathrm{m}[i]$. ∎

Theorem 2.1 leads immediately to a compact representation of the optimal trees. We construct a new decomposition table $\mathcal{D}_{opt} = (\mathcal{C}, D_{opt})$ by letting $D_{opt}[i]$ equal the set of tuples $[p_1, \ldots, p_q]$ in $D[i]$ that maximize eqn. 12. It then follows that

COROLLARY 2.1. *For each $C_i \in \mathcal{C}$ we have*

$$\mathrm{M}[i] = \mathcal{T}^*(\mathcal{D}_{opt}, i). \tag{15}$$

To improve the time complexity we precompute the value

$$W[C_i; a, b] = \sum_{x,y \in C_i} w(xy|ab) \tag{16}$$

for all $C_i \in \mathcal{C}$ and all $a, b \in L - C_i$. This takes $O(n^4|\mathcal{C}|)$ time.

It takes a further $O(n^2\|D\|)$ time to calculate $\mathrm{m}[i]$ for all i and construct the optimal tree decomposition table $\mathcal{D}_{opt}$, where we use $\|D\|$ to denote the sum of the tuple lengths over all tuples in all rows of D. The optimal trees can be enumerated using techniques outlined in section 2.2.

The complete algorithm is summarised in ALGORITHM 1.

ALGORITHM 1 (OPTIMALD($\mathcal{D}$,w)).

1. **begin**
2. Sort $\mathcal{C} = \{C_1, \ldots, C_k\}$ so that $C_i \subset C_j$ implies $i < j$.
3. **for** i from 1 to k **do**
4. **for** $a, b \in L - C_i$ **do**
5. $W[i; a, b] \leftarrow \sum_{x,y \in C_i} w(xy|ab)$
6. **end (for)**
7. **end (for)**
8. **for** i from 1 to k **do**
9. **if** $D[i] = \emptyset$ **then**
10. $M[i] \leftarrow 0$
11. **else**
12. $best \leftarrow -\infty$
13. **for all** $[p_1, p_2, \ldots, p_q] \in D[i]$ **do**
14. calculate $W(p_1, p_2, \ldots, p_q])$ using $W[\cdot; \cdot, \cdot]$.
15. $score \leftarrow W(p_1, \ldots, p_q) + \sum_{j=1}^{q} M[p_j]$
16. **if** $score > best$ **then** $D_{opt}[i] \leftarrow \emptyset$
17. **if** $score \geq best$ **then**
18. $D_{opt}[i] \leftarrow D_{opt}[i] \cup \{[p_1, \ldots, p_q]\}$

19. $best \leftarrow score$
20. **end (if)**
21. **end (for all)**
22. **end (if-else)**
23. **end (for)**
24. **end.**

2.4. An algorithm for split constrained quartet optimization

We are now in a position to give the main result. Let w be a weighting on the quartets of a leaf set L, let $\mathcal{S}$ be a set of splits of L, and let d be a degree bound. We will assume that $\mathcal{S}$ contains all of the trivial splits (those that separate a single element from the everything else). Let $n = |L|$ and $k = |\mathcal{S}|$.

Let x be an arbitrary leaf in L. We construct a collection of clusters

$$\mathcal{C} = \{A : A|B \in \mathcal{S}, x \in B\}. \tag{17}$$

and order these $C_1, C_2, \ldots, C_k$ so that $C_i, C_j \in \mathcal{C}$ and $C_i \subset C_j$ implies $i < j$. Hence $C_k = L - \{x\}$, the cluster corresponding to the trivial split $\{x\}|L - \{x\}$.

We construct a decompostion table $\mathcal{D} = (\mathcal{C}, D)$ as follows:

- If $|C_i| = 1$ then $D[i] \leftarrow \emptyset$.
- If $|C_i| > 1$ then

$$D[i] \leftarrow \left\{ [p_1, p_2, \ldots, p_q] : \begin{array}{l} C_{p_1}, \ldots, C_{p_q} \text{ are pairwise disjoint} \\ C_i = C_{p_1} \cup \cdots \cup C_{p_q} \\ q \leq d-1 \end{array} \right\}. \tag{18}$$

This table is called the **complete decomposition table** for $\mathcal{C}$ with degree bound d. It can be constructed in $O(nk^{d-1})$ time, where $k = |\mathcal{C}|$ and $n = |L|$, by considering all tuples of indices of length less than d, computing intersections and union, then determining if they should be included in some row of D.

Furthermore, a simple proof by induction gives

LEMMA 2.1. *[12] If $\mathcal{D}$ is constructed as above, and $C_k = L - \{x\}$, then $T^* \in \mathcal{T}^*(\mathcal{D}, k)$ if and only if T^* has splits in $\mathcal{S}$ and degree bound d.*

The decomposition table $\mathcal{D}_{opt}$ containing the optimal trees in $\mathcal{D}$ can be constructed in $O(n^4k + n^2dk^{d-1})$ time using Algorithm 1. We have now established:

THEOREM 2.2. *The SPLIT CONSTRAINED QUARTET OPTIMIZATION problem can be solved in $O(n^4k + n^2dk^{d-1})$ time.*

3. OPTIMAL QUARTET TREES IN PHYLOGENETIC NETWORKS

The algorithm for SPLIT CONSTRAINED OPTIMIZATION described in the previous sections makes no assumptions about the structure of the set of splits $\mathcal{S}$. In many cases, prior knowledge of the structure of $\mathcal{S}$ allows us to achieve tighter complexity bounds, or even drop the degree constraint altogether.

One structure that arises in applications (see sections 1.3.2, 1.3.4, and 1.3.5) is weakly compatible splits. In section 3.1 we describe gains in efficiency that can be made when the set of input splits $\mathcal{S}$ is weakly compatible. In the case that $\mathcal{S}$ is a maximal collection of weakly compatible splits, and the quartet weights are non-negative, we can solve the SPLIT CONSTRAINED QUARTET OPTIMIZATION problem without having to apply a degree bound (section 3.2).

We conclude with two complexity results. We show that the results in section 3.2 for maximal collections of weakly compatible splits cannot be extended to arbitrary collections of weakly compatible splits (unless $P = NP$). Then we prove the rather suprising result that if we allow negative quartet weights then the SPLIT CONSTRAINED QUARTET OPTIMIZATION problem (with no degree bound) is NP-hard even when the set of splits $\mathcal{S}$ equals $splits(T)$ of some tree T.

3.1. Quartet optimization with weakly compatible splits

Let $\mathcal{S}$ be a collection of weakly compatible splits on L and let d be a degree bound. As in section 2.4 we choose a leaf x and construct

$$\mathcal{C} = \{A : A|B \in \mathcal{S}, x \in B\}. \tag{19}$$

Then $\mathcal{C}$ is a **weak hierarchy** [3], which means that for all $U, V, W \in \mathcal{C}$

$$U \cap V \cap W \in \{U \cap V, U \cap W, V \cap W\}. \tag{20}$$

Define a closure operator $\langle\cdot\rangle_{\mathcal{C}}$ one subsets of $L - \{x\}$ by

$$\langle A\rangle_{\mathcal{C}} = \bigcap_{C \in \mathcal{C}: A \subseteq C} C. \tag{21}$$

Weak hierachies have the property that for every subset A there is $a, a' \in A$ such that $\langle A\rangle_{\mathcal{C}} = \langle\{a, a'\}\rangle_{\mathcal{C}}$ [2]. We write $\langle a, a'\rangle_{\mathcal{C}}$ for $\langle\{a, a'\}\rangle_{\mathcal{C}}$ and construct a table mapping each pair of leaves a, a' to the corresponding subset $\langle a, a'\rangle_{\mathcal{C}}$. The table can be constructed in $O(n^5)$ time using the property that $y \in \langle a, a'\rangle_{\mathcal{C}}$ if and only if there is no cluster $C \in \mathcal{C}$ with $a, a' \in C$ and $y \notin C$.

The first efficiency gain we make is to speed up the calculation of $W[C_i; a, b]$ (eqn. 16). First a special case. Recall that a **chain** is a collection of clusters $\mathcal{A}$ such that $A, B \in \mathcal{A}$ implies $A \subseteq B$ or $B \subseteq A$.

LEMMA 3.1. *If $\mathcal{C}$ is a chain and a and b are any two leaves then we can compute $W[C_i; a, b]$ for all $C_i \in \mathcal{C}$ in $O(n^2)$ time.*

Proof. Suppose that $\mathcal{C} = \{C_1, C_2, \ldots, C_k\}$ where $C_i \subseteq C_j$ or all $i \leq j$. We calculate $W[C_1; a, b]$ directly. Given $W[C_i; a, b]$ we can calculate $W[C_{i+1}; a, b]$ using

$$W[C_{i+1}; a, b] = W[C_i; a, b] + \sum_{\substack{c,d \in C_{i+1} \\ \{c,d\} \not\subseteq C_i}} w(cd|ab) \tag{22}$$

The amortorized complexity is then $O(n^2)$. ∎

When $\mathcal{C}$ is not a chain, which is usually the case, we can apply Lemma 3.1 by first partitioning $\mathcal{C}$ into chains. We use Dilworth's theorem to show that when $\mathcal{C}$ is a weak hierarchy we can partition $\mathcal{C}$ into $O(n)$ chains. Recall that an **anti-chain** is a collection of clusters $\mathcal{A}$ such that $A, B \in \mathcal{A}$ implies $A \not\subseteq B$ and $B \not\subseteq A$.

LEMMA 3.2. *Suppose that $\mathcal{C} = \{A : A|B \in \mathcal{S}, x \in B\}$ for some collection $\mathcal{S}$ of weakly compatible splits on a set X of n elements.*

1.For each element $a \in X - \{x\}$ there are no three elements a_1, a_2, a_3 such that $\langle a, a_1\rangle_{\mathcal{C}}$, $\langle a, a_2\rangle_{\mathcal{C}}$ and $\langle a, a_3\rangle_{\mathcal{C}}$ form an anti-chain in $\mathcal{C}$.

2.$\mathcal{C}$ can be partitioned into $n - 1$ chains.

3.We can partition $\mathcal{C}$ into $O(n)$ chains in $O(n^3)$ time.

Proof. (1) Suppose there was such an anti-chain. Then $a_i \notin \langle a, a_j\rangle_{\mathcal{C}}$ for all $i \neq j$. Put $A_i = \langle a, a_i\rangle_{\mathcal{C}}$ for $i = 1, 2, 3$, and $B_i = X - A_i$. Then each $A_i|B_i$ is a split in $\mathcal{S}$. Furthermore we have

$$x \in B_1 \cap B_2 \cap B_3 \tag{23}$$
$$a_3 \in B_1 \cap B_2 \cap A_3 \tag{24}$$
$$a_2 \in B_1 \cap A_2 \cap B_3 \tag{25}$$
$$a_1 \in A_1 \cap B_2 \cap B_3 \tag{26}$$

which contradicts the weak compatibility of $\mathcal{S}$ (see section 1.1).
(2) Let $\mathcal{A} = A_1, A_2, \ldots, A_k$ be a maximum cardinality antichain in $\mathcal{C}$. Let Y be the set of elements y such that $\langle y, y\rangle_{\mathcal{C}} \in \mathcal{A}$. Let Z be the set of elements z for which there exists z' such that $\langle z, z'\rangle_{\mathcal{C}} \in \mathcal{A}$. Since $\langle y, y\rangle_{\mathcal{C}} \subseteq \langle y, z\rangle_{\mathcal{C}}$ for all z and $\mathcal{A}$ is an anti-chain we must have that Y and Z are disjoint.

The number of clusters $A_i \in \mathcal{A}$ such that $A = \langle y, y\rangle_{\mathcal{C}}$ for some $y \in Y$ is bounded above by $|Y|$. For the remaining clusters in $\mathcal{A}$ there are at least two

elements $a, b \in Z$ such that $A = \langle a, a' \rangle_{\mathcal{C}}$ for some a' and $A = \langle b, b' \rangle_{\mathcal{C}}$ for some b'. By (1) for each element z in Z there are at most two clusters $A_i, A_j \in \mathcal{A}$ such that $A_i = \langle z, z_i \rangle_{\mathcal{C}}$ for some z_i and $A_j = \langle z, z_j \rangle_{\mathcal{C}}$ for some z_j. Hence the number of clusters that do not equal $\langle y, y \rangle_{\mathcal{C}}$ for some $y \in Y$ is bounded above by $|Z|$.

Therefore $|\mathcal{A}| \leq |Y| + |Z| \leq |X - \{x\}| = n - 1$. The maximum size anti-chain contains at most $n - 1$ clusters, so by Dilworth's theorem [18] the collection $\mathcal{C}$ can be covered by $n - 1$ chains.

(3) Since Dilworth's theorem is non-constructive it does not guarantee an efficient algorithm for constructing the covering. Instead we use (1) again. For each $a \in X - \{x\}$ put

$$\mathcal{C}_a = \{A \in \mathcal{C} : A = \langle a, a' \rangle_{\mathcal{C}} \text{ for some } a'\}. \tag{27}$$

Then by (1) we have that $\mathcal{C}_a$ has a maximal antichain of size two, and can hence by decomposed into two chains. It takes $O(n^2)$ time to decompose $\mathcal{C}_a$ into two chains: first construct an incomparability graph for the clusters (noting that $\langle a, a_1 \rangle_{\mathcal{C}} \subseteq \langle a, a_2 \rangle_{\mathcal{C}}$ if and only if $a_1 \in \langle a, a_2 \rangle_{\mathcal{C}}$) and then 2-colouring. Repeating the process for all a gives a partition into at most $2(n-1)$ chains in $O(n^3)$ time. ∎

Note that the bound of $n - 1$ of Lemma 3.2(2) is obtained in the case that $\mathcal{S}$ is maximum weakly compatible.

We now focus our attention on the complete decomposition table for $\mathcal{C}$.

LEMMA 3.3.

1.If $[p_1, p_2]$ is a tuple in a decomposition table for $\mathcal{C}$ then there is a_1, a_2, a_3 such that $C_{p_1} = \langle a_1, a_2 \rangle_{\mathcal{C}}$ and $C_{p_2} = \langle a_1, a_3 \rangle_{\mathcal{C}} - \langle a_1, a_2 \rangle_{\mathcal{C}}$.

2.If $[p_1, p_2, p_3]$ is a tuple in a decomposition table for $\mathcal{C}$ then there is a_1, a_2, a_3, a_4 such that $C_{p_1} = \langle a_1, a_2 \rangle_{\mathcal{C}}$, $C_{p_2} = \langle a_3, a_4 \rangle_{\mathcal{C}}$,

$$C_{p_3} = \langle a_1, a_3 \rangle_{\mathcal{C}} - \langle a_1, a_2 \rangle_{\mathcal{C}} - \langle a_3, a_4 \rangle_{\mathcal{C}}. \tag{28}$$

Proof.

(1) There is y_1, y_1' and y_2, y_2' such that $C_{p_1} = \langle y_1, y_1' \rangle_{\mathcal{C}}$ and $C_{p_2} = \langle y_2, y_2' \rangle_{\mathcal{C}}$. Hence $C_{p_1} \cup C_{p_2} = \langle \{y_1, y_1', y_2, y_2'\rangle_{\mathcal{C}}$. Thus there is $a_1 \in \{y_1, y_1'\}$ and $a_3 \in \{y_2, y_2'\}$ such that $C_{p_1} \cup C_{p_2} = \langle a_1, a_3 \rangle_{\mathcal{C}}$. We can then let a_2 equal the element in $\{y_1, y_1'\} - \{a_1\}$.

(2) This time we choose y_i, y_i' for $i = 1, 2, 3$ such that $C_{p_i} = \langle y_i, y_i' \rangle_{\mathcal{C}}$. Then $C_{p_1} \cup C_{p_2} \cup C_{p_3} = \langle y_1, y_2, y_3, y_1', y_2', y_3' \rangle_{\mathcal{C}}$. There is $a_1, a_3 \in \{y_1, y_2, y_3, y_1', y_2', y_3'\}$ such that $\langle a_1, a_3 \rangle = C_{p_1} \cup C_{p_2} \cup C_{p_3}$. We then choose a_2 and a_4 from $\{y_1, y_2, y_3, y_1', y_2', y_3'\} -$

$\{a_1, a_3\}$ so that $\langle a_1, a_2\rangle_{\mathcal{C}}$ and $\langle a_3, a_4\rangle_{\mathcal{C}}$ equal two of $C_{p_1}, C_{p_2}, C_{p_3}$. The result follows. ▌

We now have the tools we need to derive the efficient algorithm.

THEOREM 3.1. *If $\mathcal{S}$ is a set of weakly compatible splits and d equals 3 or 4 then SPLIT CONSTRAINED QUARTET OPTIMIZATION can be solved in $O(n^{d+2})$ time.*

Proof. Fix x, construct $\mathcal{C} = \{A : A|B \in \mathcal{S},\ x \in B\}$, and the table containing $\langle a, a'\rangle_{\mathcal{C}}$ for each a, a'. This takes $O(n^5)$ time. By Lemma 3.2 we can partition $\mathcal{C}$ into $O(n)$ chains in $O(n^3)$ time. Applying Lemma 3.1 for each chain and each pair of leaves a, b we can calculate the values $W[C_i; a, b]$ for all a, b and all $C_i \in \mathcal{C}$ in $O(n^5)$ time.

By Lemma 3.3 there are at most $O(n^d)$ tuples in the decomposition table, so $\|D\|$ is $O(n^d)$ and the complete decomposition table can be constructed in $O(n^{d+1})$ time. We can now apply algorithm 2.4 to obtain the result. ▌

We conjecture that Theorem 3.1 can be extended for larger values of d, though we suspect that a different proof technique is required. In any case, the complexity of $O(n^6)$ when $d = 4$ is about the limit of a practical algorithm.

3.2. Maximum weakly compatible splits

The maximum cardinality of a collection of weakly compatible splits on a set of n elements is $\binom{n}{2}$. Those collections $\mathcal{S}$ for which $|\mathcal{S}| = \binom{n}{2}$ are called **maximum weakly compatible.**. These collections have a special structure, allowing them to be to be represented in terms of cuts in a circle [3] or as a planar *splitsgraph* [22]. For every tree T there is a maximum weakly compatible set containing $splits(T)$. In many ways, these collections of splits fall between trees and weakly compatible splits in terms of generality and complexity.

Here we show that the structural properties of maximum weakly compatible splits allow us to solve split constrained quartet optimization in polynomial time *without* a degree bound. The key result is

LEMMA 3.4. *Let $\mathcal{S}$ be a maximum weakly compatible set of splits and let T be a tree such that $splits(T) \subseteq \mathcal{S}$. Then there is a binary tree T' such that $splits(T) \subseteq splits(T') \subseteq \mathcal{S}$.*

Proof. By Theorem 5 of [3] we can order the leaf set as $x_0, x_1, \ldots, x_{n-1}$ such that for every split $A|B$ with $x_0 \in B$ we have $A|B \in \mathcal{S}$ if and only if there is i, j for which

$$A = \{x_i, x_{i+1}, \ldots, x_j\}. \tag{29}$$

That is, if and only if A is an **interval** with respect to the ordering $x_1, \ldots, x_{n-1}$.

We preceed by induction. Let d be the maximum degree of any vertex in T. The result holds, trivially, if $d = 3$. Suppose that the result holds for all T with maximum degree less than d, and that T is a tree with maximum degree d.

Let T_0 be the rooted tree with leaf set $L - \{x_0\}$ such that $\text{UNROOT}(T_0, L) = T$. Let v be a vertex of T with degree d. The corresponding vertex v_0 in T_0 has $d-1$ children.

There is $a_1 < a_2 < \cdots < a_d$ such that the cluster sets corresponding to the children of v_0 equal

$$\{\{x_i : a_j \leq i < a_{j+1}\} : j = 1, 2, \ldots, d-1\} \tag{30}$$

If we insert the cluster $\{x_i : a_1 \leq i < a_3\}$ into T_0, and the corresponding split into T, then v will have degree $d-1$ and T will still have splits contained in $\mathcal{S}$. We repeat the process to obtain a tree that contains all the splits of the original tree, has splits contained in $\mathcal{S}$, and maximum degree $d-1$. The result follows from the induction hypothesis. ▌

Suppose now that all quartet weights are non-negative. If $\mathcal{S}$ is a maximum weakly compatible collection of splits and T is a non-binary tree such that $splits(T) \subseteq \mathcal{S}$ then by Lemma 3.4 there is binary T' such that $splits(T) \subseteq splits(T')$. Furthermore, $q(T) \subseteq q(T')$ and since all quartets have non-negative weight we have $w(T) \leq w(T')$. Hence we can find a tree with optimal weight and splits in $\mathcal{S}$ by searching through the just binary trees with splits in $\mathcal{S}$. By theorem 3.1 we now have

THEOREM 3.2. *Let $\mathcal{S}$ be a maximum weakly compatible set of splits of L and let w be a non-negative weighting for quartets of L. We can find a tree T with $splits(T) \subseteq \mathcal{S}$ and maximum quartet weight in $O(n^5)$ time.*

Note that if we drop the non-negativity constraint then the problem becomes NP-hard (Theorem 3.4).

3.3. Complexity results

We conclude with two complexity results, showing that the polynomial time results are, in a sense, tight. First we consider the case when $\mathcal{S}$ is weakly compatible and all quartets have non-negative weight.

THEOREM 3.3. *SPLIT CONSTRAINED QUARTET OPTIMIZATION is NP-complete when d is unbounded, even when all quartet weights are non-negative and $\mathcal{S}$ is weakly compatible.*

Proof. The problem is clearly in NP.

We provide a reduction from the problem of determining a maximum compatible subset of a set of weak compatible splits, which was shown to be NP-complete in [13].

For every split $A_i|B_i \in \mathcal{S}$ there exists a quartet $a_ia_i'|b_ib_i' \in q(A_i|B_i)$ such that $a_ia_i'|b_ib_i' \notin q(A_j|B_j)$ for all other splits $A_j|B_j \in \mathcal{S}$ [3, 4]. Choose one of these quartets for each split and give it weight one. Give all other quartets weight zero. Then for any tree T with leaf set L and $q(T)$ we have

$$\sum_{ab|cd \in q(T)} w(ab|cd) = |splits(T)|. \tag{31}$$

Hence the weight of the optimal weight tree equals the size of the maximum compatible subset of $\mathcal{S}$. ∎

Our second complexity result rules out the possibility of an extension of Theorem 3.2 to include negative quartet weights.

THEOREM 3.4. *SPLIT CONSTRAINED QUARTET OPTIMIZATION is NP-complete when d is unbounded and some quartet weights are negative, even when $\mathcal{S} = splits(T)$ for some tree T.*

Proof. The problem is clearly in NP.

We provide a reduction from VERTEX COVER. Let G be a graph with vertex set V and edge set E. Put $M = 2|V|$. Put $L = \{v', v'' : v \in V\}$ and let T be the tree only containing clusters $\{v', v''\}$ and one central vertex x of degree $|V|$.

Label the internal vertex adjacent to v' and v'' by v. Let Q_E be the set of quartets

$$Q_E = \{u'u''|v'v'' : \{u, v\} \in E\} \tag{32}$$

and let Q_V be the set of quartets

$$Q_V = \{v'v''|w'x' : v, w, x \in V\}. \tag{33}$$

We give each quartet in Q_E weight M and each quartet in Q_V weight $\frac{-2}{(n-2)(n-3)}$, where $n = |V|$.

Suppose that V' is a vertex cover for G with size k. Construct T' with split set $\{\{v', v''\}|(L - \{v', v''\}) : v \in V'\}$. Then $q(T')$ contains all quartets in Q_1 and exactly those quartets in Q_V of the form $v'v''|w'x'$ for some $u \in V$. It follows that T' has summed quartet weight $kM - k$.

Conversely, if T' has summed quartet weight $kM - k$ then T' must contain all quartets in Q_E and only $k\frac{(n-2)(n-3)}{2}$ quartets in Q_V. We can then construct a

vertex cover

$$V' = \{v : \{v', v''\} | (L - \{v', v''\}) \in splits(T')\} \quad (34)$$

for G of size k. ▌

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