Complexity of Modification Problems for Reciprocal Best Match Graphs

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Abstract

Reciprocal best match graphs (RBMGs) are vertex colored graphs whose vertices represent genes and the colors the species where the genes reside. Edges identify pairs of genes that are most closely related with respect to an underlying evolutionary tree. In practical applications this tree is unknown and the edges of the RBMGs are inferred by quantifying sequence similarity. Due to noise in the data, these empirically determined graphs in general violate the condition of being a “biologically feasible” RBMG. Therefore, it is of practical interest in computational biology to correct the initial estimate. Here we consider deletion (remove at most \( k \) edges) and editing (add or delete at most \( k \) edges) problems. We show that the decision version of the deletion and editing problem to obtain RBMGs from vertex colored graphs is NP-hard. Using known results for the so-called bicluster editing, we show that the RBMG editing problem for 2-colored graphs is fixed-parameter tractable.

A restricted class of RBMGs appears in the context of orthology detection. These are cographs with a specific type of vertex coloring known as hierarchical coloring. We show that the decision problem of modifying a vertex-colored graph (either by edge-deletion or editing) into an RBMG with cograph structure or, equivalently, to an hierarchically colored cograph is NP-complete.

Keywords: reciprocal best matches; hierarchically colored cographs; orthology relation; bicluster graph; editing; NP-hardness; parameterized algorithms

1 Introduction

Graph modification problems ask whether there is a set of at most \( k \) edges to delete or to edit (add or delete) to change an input graph into a graph conforming to certain structural prerequisites. In computational biology graph modification problems typically appear as ways to deal with inaccurate data and measurement error, for instance in genome assembly [21] or clustering [4].

Here we consider graph modification problems that arise in the context of orthology assignment. Two genes found in two distinct species are orthologous if they arose through the speciation event that also separated the two species. Biologically, one expects these two genes to have corresponding function. In contrast, paralogous genes, which arose through a duplication event, are expected to have related but distinct functions [17]. The distinction of orthologous and paralogous gene pairs is therefore of key practical importance for the functional annotation of genomes. Most orthology assignment methods that are currently in use for large data sets start from reciprocal best matches [34], i.e., pairs of genes \( x \) in species \( A \) and \( y \) in species \( B \) such that \( y \) is the gene in \( B \) most closely related to \( x \) and \( x \) is the gene in \( A \) most closely related to \( y \), see e.g. [1, 2, 32]. Reciprocal best matches are efficiently computed in practice by quantifying sequence similarity. Conceptually, they are employed because they approximate pairs of reciprocal evolutionarily most closely related
genes. It can be show rigorously, that all pairs of orthologs are also reciprocal best matches in the evolutionary sense [18].

Genes evolve along a gene tree \( T \) from which best matches and reciprocal best matches can be defined (see next section for precise definitions). Reciprocal best match graphs (RBMGs) are vertex-colored graphs where the vertices represent genes and the colors designate the species in which the genes reside [19]. RBMGs have recently been characterized by Geiß et al. [19, 20]. In practical applications, however, estimates of RBMGs are plagued with measurement errors and noise, and thus the empirically inferred graphs usually violate the property of being an RBMG. A natural remedy to reduce the measurement noise is of course to modify the empirical graph to the closest RBMG. In the first part of this contribution we therefore consider the computational complexity of modifying vertex-colored graphs to RBMGs and show that these problems are NP-hard.

Due the importance of orthology, it also of interest to investigate those RBMGs that completely describe orthology relationships rather than containing the orthology relation as a subgraph. It is shown in [20] that the “orthology RBMG” are exactly the hierarchically colored cographs (hc-cographs). These are cographs [10] with a particular vertex coloring. As shown in [36], every cograph admits a hierarchical coloring; more precisely, every greedy coloring [9] of a cograph is hierarchical (but not vice versa).

Simulation studies show that estimates of RBMGs are typically not hc-cographs [18], and thus do not directly describe orthology. In fact, they usually feature both false positive and false negative edges. It is of interest, therefore, to consider the computational problem of modifying a given vertex colored graph to an hc-cograph. In the setting considered here, the assignment of genes to the species in which the occur is perfectly known, hence the coloring of the vertices must not be changed. We therefore stay within the realm of graph modification by insertion/deletion of edges. The vertex coloring only brings additional constraints to the table.

Ignoring these additional constraints arising from the vertex coloring, the analogous problem of editing empirical graphs to the nearest cographs was used to extract phylogenetic information from empirical reciprocal best matches in [24]. The (uncolored) cograph editing problem is known to be NP-complete [28]. Here we show that the colored version remains NP-complete.

## 2 Preliminaries

### Basics

Throughout we consider undirected graphs \( G = (V, E) \) with vertex set \( V \) and edge set \( E \subseteq \binom{V}{2} \). An edge \( \{x, y\} \) between vertices \( x \) and \( y \) will be arbitrarily denoted by \( xy \) or \( yx \). For a graph \( G = (V, E) \) and a subset \( W \subseteq V \) we denote by \( G[W] = (W, F) \) the induced subgraph of \( G \) where \( F \subseteq E \) and \( xy \in F \) for all \( xy \in E \) with \( x, y \in W \).

A vertex coloring of \( G \) is a surjective map \( \sigma : V \rightarrow S \). We will write \( (G, \sigma) \) to indicate the vertex coloring \( \sigma \) of \( G \). A graph \( G \) is properly colored if \( xy \in E \) implies \( \sigma(x) \neq \sigma(y) \). A hub-vertex \( x \in V \) is a vertex that is adjacent to all vertices in \( V \setminus \{x\} \). Thus, a hub-vertex in a properly colored graph \( (G, \sigma) \) always satisfies \( \sigma(x) \neq \sigma(v) \) for any \( v \in V \setminus \{x\} \).

For a graph \( G = (V, E) \) and a vertex \( x \in V \) we define the sets \( V - x := V \setminus \{x\} \) and \( E - x := E \setminus \{xy \mid v \in V\} \). The graph \( G - x := (x, E - x) \) is, therefore, obtained from \( G \) by removing vertex \( x \) and all its incident edges. In addition, we define for a vertex \( x \notin V \) the sets \( V + x := V \cup \{x\} \) and \( E + x := E \cup \{xy \mid v \in V\} \). Thus, the graph \( G + x := (V + x, E + x) \) is obtained from \( G \) by adding vertex \( x \) and all edges of the form \( xy, v \in V \), making \( x \) to a hub-vertex in \( G + x \). Moreover, we write \( G \circ F := (V, E \circ F) \), where \( \circ \in \{\setminus, \triangle\} \) and \( \setminus \), resp., \( \triangle \) denotes the usual set-difference, resp., symmetric difference of two sets. Let \( G = (V, E) \) and \( H = (W, F) \) be two distinct graphs. We write \( G \cup H := (V \cup W, E \cup F \cup \{xy \mid x \in V, y \in W\}) \) for their join.

### Trees

A phylogenetic tree \( T = (V, E) \) (on \( L \)) is a rooted tree with root \( r_T \), leaf set \( L \subseteq V \) and inner vertices \( V^0 = V \setminus L \) such that each inner vertex of \( T \) (except possibly the root) is of degree at least three.

Throughout this contribution, we assume that every tree is phylogenetic.

The restriction \( T' \mid L' \) of a tree \( T \) to a subset \( L' \subseteq L \) of its leaves is the tree with leaf set \( L' \) that is obtained from \( T \) by first taking the minimal subtree of \( T \) with leaf set \( L' \) and then suppressing all vertices of degree two with the exception of the root \( r_{T' \mid L'} \). A star-tree is a tree such that the root is incident to leaves only, i.e, it is either the single vertex graph \( K_1 \) or a tree where the root is a hub-vertex.
The last common ancestor $lca_T(x,y)$ of two distinct leaves $x,y \in L$ is the vertex that is farthest away from the root and that lies on both two paths from $\rho_T$ to $x$ and from $\rho_T$ to $y$. For vertices $u,v \in V$ we write $u \preceq_T v$ if $v$ lies on the unique path from the root to $u$.

Trees can be equipped with vertex labels. The inner vertex label is defined as a map $t : V^0 \to \{0,1\}$. The leaf label is a surjective map $\sigma : L \to S$. In out setting, the map $\sigma$ is used to assign to each gene $u \in L$ the species $\sigma(u) \in S$ in which $u$ resides. Moreover, the labels 0 and 1 on $V^0$ indicate what type of mechanism caused a divergence of lineages: 0 represents gene duplications and 1 designates speciation events.

For a subset $L' \subseteq L$ we write $\sigma(L') = \{\sigma(x) \mid x \in L'\}$. Moreover, we use the notation $\sigma_{L'}$ for the surjective map $\sigma : L' \to \sigma(L')$. We also write $L[s] := \{x \mid x \in L, \sigma(x) = s\}$ for the set of all leaves with color $s$. In addition we will use the notation $(T,t),(T,\sigma)$, resp., $(T,t,\sigma)$ to emphasize that the tree $T$ is equipped with a vertex label $t$, $\sigma$, resp., both.

Hierarchically Colored Cographs A graph $G$ is a cograph if either $G = K_1$ or $G$ is the disjoint union $G = \bigcup G_i$ of two or more cographs $G_i$, or $G$ is the join $G = \bigcirc G_i$ of two or more cographs $G_i$. An important characterization states that $G$ is a cograph if and only if it does not contain a path $P_4$ on 4 vertices as an induced subgraph [10]. Here we are interested in particular in cographs with a particular type of vertex coloring, so-called hierarchically colored cographs [20, 36]. We first define the disjoint union and the join for vertex-colored graphs:

**Definition 1.** Let $(H_1,\sigma_{H_1})$ and $(H_2,\sigma_{H_2})$ be two vertex-disjoint colored graphs. Then $(H_1,\sigma_{H_1}) \bigcirc (H_2,\sigma_{H_2}) := (H_1 \cup H_2,\sigma)$ and $(H_1,\sigma_{H_1}) \cup (H_2,\sigma_{H_2}) := (H_1 \cup H_2,\sigma)$ denotes their join and union, respectively, where $\sigma(x) = \sigma_{H_i}(x)$ for every $x \in V(H_i)$, $i \in \{1,2\}$.

**Definition 2 (hc-cograph).** An undirected colored graph $(G,\sigma)$ is a hierarchically colored cograph (hc-cograph) if

(K1) $(G,\sigma) = (K_1,\sigma)$, i.e., a colored vertex, or

(K2) $(G,\sigma) = (H,\sigma_H) \bigcirc (H',\sigma_{H'})$ and $\sigma(V(H)) \cap \sigma(V(H')) = \emptyset$, or

(K3) $(G,\sigma) = (H,\sigma_H) \cup (H',\sigma_{H'})$ and $\sigma(V(H)) \cap \sigma(V(H')) \in \{\sigma(V(H)),\sigma(V(H'))\}$,

where both $(H,\sigma_H)$ and $(H',\sigma_{H'})$ are hc-cographs.

(K2) ensures that an hc-cograph is always properly colored, cf. [20, Lemma 43]. Definition 2 reduces to the usual recursive definition of cographs when the coloring information is ignored. Thus every hc-cograph is a cograph. The converse, however, is not true. To see this, consider the graph $G = K_1 \cup K_1 = \{(x,y), E = \emptyset\}$ with the coloring $\sigma(x) \neq \sigma(y)$. Although $G$ is clearly a cograph, it violates Property (K2). However, for every cograph $G$ there is a vertex coloring $\sigma$ such that $(G,\sigma)$ is an hc-cograph [36].

To emphasize the number $n$ of distinct colors used for the vertices in an hc-cograph, we often speak explicitly of $n$-hc-cographs.

Orthology and Reciprocal Best Matches Reciprocal best matches are used in practice to estimate orthology. In the following paragraph we clarify the relationship between the two concepts to the extent need here. For a more in-depth discussion we refer to [18].

In the following, let $T = (V,E)$ be a tree on $L$ together with vertex labeling $t : V^0 \to \{0,1\}$ and $\sigma : L \to S$. We distinguish here two relationships (orthology and reciprocal best matches) that may hold between pairs of vertices in $L$. Both relations are defined in terms of the topology of $T$, however, the orthology relations is defined by means of the label $t$ and reciprocal best matches are defined by means of the label $\sigma$.

**Definition 3 ([16]).** Two leaves $x,y \in L$ are orthologs in $(T,t)$ if and only if $t(lca_T(x,y)) = 1$. A graph $G$ is an orthology graph if there is a tree $(T,t)$ such that $xy \in E(G)$ if and only if $t(lca_T(x,y)) = 1$.

Orthology is a symmetric relation. It has been shown that the orthology graphs are exactly the cographs [23, Cor. 4].

**Definition 4.** The leaf $y$ is a best match of the leaf $x$ in the tree $(T,\sigma)$ if and only if $\sigma(x) \neq \sigma(y)$ and $lca_T(x,y) \preceq_T lca_T(x,y')$ for all leaves $y'$ with $\sigma(y') = \sigma(y)$. If $x$ is also a best match of $y$, we call $x$ and $y$ reciprocal best matches. The graph with vertex set $L$ that has precisely all reciprocal best matches of $T$ as its edge is denoted by $G(T,\sigma)$. A properly vertex-colored graph $(G,\sigma)$ is a Reciprocal Best Match Graph (RBMG) if there is a leaf-labeled tree $(T,\sigma)$ such that $G(T,\sigma) = (G,\sigma)$. 

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In other words, $y$ is a best match of $x$ if $y$ is the closest relative of $x$ in comparison with all other leaves from species $\sigma(y)$, see Fig. 1 for an illustrative example. We say that $(G,\sigma)$ is explained by $(T,\sigma)$ if $G(T,\sigma) = (G,\sigma)$ as well as $t(lca_T(x,y)) = 1$ iff $xy \in E(G)$.

Characterizations of 2-RBMGs, 3-RBMGs, and RBMGs that are orthology graphs on $n$ colors have become available [19, 20] very recently. For later reference we summarize these results in

**Theorem 1.** Let $(G,\sigma)$ be a colored graph. Then, the following statements are satisfied:

1. $G$ is an orthology graph if and only if $G$ is a cograph.
2. The following statements are equivalent
   (a) $(G,\sigma)$ is an RBMG and an orthology graph.
   (b) $(G,\sigma)$ is an RBMG and a cograph.
   (c) $(G,\sigma)$ is an $hc$-cograph.
3. $(G,\sigma)$ is a 2-RBMG if and only if $(G,\sigma)$ is a properly 2-colored bicluster graph that contains at least one edge.
4. $(G,\sigma)$ is an $n$-RBMG if and only if $(G,\sigma)$ is properly colored and each of its connected components is an RBMG and at least one connected component $C$ contains all colors, i.e., $|\sigma(V(C))| = n$.

**Proof.** The first statement is equivalent to [23, Cor. 4], the second statement is equivalent to [20, Thm. 9] and the last statement to [20, Thm. 3]. For the third statement, note that [19, Cor. 6] states that $(G,\sigma)$ is a properly 2-colored bicluster graph, whenever $(G,\sigma)$ is a 2-RBMG. Together with Statement (4.) this implies the only-if direction. For the if-direction observe that every properly colored biclique $H = (W,E)$ (which may contain even only one vertex) is an RBMG since it is explained by a star-tree $(T_H,\sigma’)$ on leaf set $W$. Since $(G,\sigma)$ contains an edge, it satisfies the conditions in Statement (4.) and hence, is a 2-RBMG.

We note in passing, that $n$-RBMs can be recognized in polynomial time for $n \leq 3$. However, although a mathematical characterization for $n$-RBMs, $n > 3$ exists, it is still an open problem whether a polynomial-time algorithm for their recognition exists [20].

Vertices in an RBMG $(G,\sigma)$ that have the same color induce, by definition, an independent set in $G$. Moreover, since the definition of $x$ and $y$ being reciprocal best matches does not depend on the presence or absence of vertices $u$ with $\sigma(u) \notin \{\sigma(x),\sigma(y)\}$, we have

**Observation 1.** Let $(G,\sigma)$ be an RBMG explained by $T$ on $L$ and $L’ := \bigcup_{S \subseteq S} L[S]$ be the subset of vertices with a restricted color set $S’ \subseteq S$. Then the induced subgraph $(G[L’],\sigma|_{L’})$ is explained by the restriction $T|_{L’}$ of $T$ to the leaf set $L’$ and thus, an RBMG.
Bicluster Graphs As we shall see, there is a close connection between 2-RBMGs and so-called bicluster graphs. For two sets \( A \) and \( B \), we write \( A \times B := \{\{x, y\} \mid (x, y) \in A \times B\} \). A biclique is a complete bipartite graph \( G = (V, E) \), i.e., \( G \) is either the single vertex graph \( K_1 \) or a bipartite graph with bipartition \( V = V_1 \cup V_2 \) and edge set \( E = V_1 \otimes V_2 \). A bicluster graph is a graph whose connected components are bicliques.

Bicluster graphs have been the subject of several studies, see e.g. \([3, 6, 11, 12, 14, 22, 25, 29, 30]\). Often the problem is to modify a given graph into a biclique or bicluster graph in some or the other way. In this contribution, we will utilize the so-called bicluster deletion and editing problem. Amit [3] showed that these problems are NP-complete.

### Problem 1 (Bicluster Deletion).

**Input:** A bipartite graph \( G = (V, E) \) and an integer \( k \).

**Question:** Is there a subset \( F \subseteq E \) such that \( G \setminus F \) is a bicluster graph and \( |F| \leq k \)?

### Problem 2 (Bicluster Editing).

**Input:** A bipartite graph \( G = (V, E) \) with bipartition \( V = V_1 \cup V_2 \) and an integer \( k \).

**Question:** Is there a subset \( F \subseteq V_1 \otimes V_2 \) such that \( G \triangle F \) is a bicluster graph and \( |F| \leq k \)?

### Theorem 2 ([3]).

**Bicluster Deletion and Bicluster Editing** are NP-complete.

The bicluster completion problem, which consists in finding the minimum number of edges to add so that the resulting graph is a bicluster graph can be solved in polynomial time. To this end it is only necessary to identify connected components and to add edges in each component to form a biclique.

### 3 Complexity Results

In the following we are interested in several problems that are concerned with modifying an colored graph to RBMGs or hc-cographs. In particular, we consider the following decision problems:

### Problem 3 (n-RBMG Deletion / n-hc-cograph Deletion).

**Input:** A properly \( n \)-colored graph \( (G = (V, E), \sigma) \) and an integer \( k \).

**Question:** Is there a subset \( F \subseteq E \) such that \( |F| \leq k \) and \( (G \setminus F, \sigma) \) is an RBMG, resp., hc-cograph?

### Problem 4 (n-RBMG Editing / n-hc-cograph Editing).

**Input:** A properly \( n \)-colored graph \( (G = (V, E), \sigma) \) and an integer \( k \).

**Question:** Is there a subset \( F \subseteq \binom{V}{2} \) such that \( |F| \leq k \) and \( (G \triangle F, \sigma) \) is an RBMG, resp., hc-cograph?

Note that the two problems n-RBMG Deletion and n-hc-cograph Deletion are equivalent to the problem of finding a spanning subgraph \((H, \sigma)\) of \((G, \sigma)\) with a maximum number of edges so that \((H, \sigma)\) is an n-RBMG and an n-hc-cograph, respectively.

### Remark 1.

The input of the latter problems is a properly \( n \)-colored graph \((G = (V, E), \sigma)\). Thus, for all edges \( xy \) in \((G, \sigma)\), we have \( \sigma(x) \neq \sigma(y) \). Clearly, for \( F \subseteq E \) we thus have \( \sigma(x) \neq \sigma(y) \) for all edges \( xy \in F \). Moreover, for the two editing problems n-RBMG Editing and n-hc-cograph Editing, the graph \((G \triangle F, \sigma)\) must in both cases be an RBMG (cf. Thm. 1). This implies that \( \sigma(x) \neq \sigma(y) \) for all edges \( xy \in F \).

In summary, an optimal deletion or edit set \( F \) will never contain pairs \( \{x, y\} \) with \( \sigma(x) = \sigma(y) \).

Note that if \((G, \sigma)\) is an \( n \)-colored but edge-less graph, then Thm. 1(4) implies that \((G, \sigma)\) is not an RBMG. In this case, only the editing problem would be of interest for us. However, this is a trivial endeavor since an optimal edit set \( F \) for \( n \)-colored edge-less graphs always satisfies \( |F| = \binom{n}{2} \). To see this, observe first that we must connect the vertices such that at least one component contains all colors. Moreover, by [20, Cor. 2], there must be an edge for every pair of distinct colors. Thus, \( n \) distinctly colored vertices and connect them all by an edge to obtain the modified graph \((H, \sigma)\). Hence, if \((H, \sigma)\) is disconnected, all its connected components are \( K_1 \)s except the newly created \( n \)-colored complete subgraph. Otherwise, \((H, \sigma)\) is an \( n \)-colored complete graph \( K_n \). It is easy to see that \((H, \sigma)\) is an \( hc \)-cograph and thus, by Thm. 1 an RBMG. Since at least \( \binom{n}{2} \) edges must be added, this editing is optimal and thus, \( |F| = \binom{n}{2} \).
Remark 2. We will exclude the latter trivial case and will, from here on, always assume that 
\((G, \sigma)\) contains at least one edge.

3.1 Graphs on two colors

Since bicluster graphs do not contain induced \(P_3\), they are cographs. This together with Thm. 1 implies

Corollary 1. The following statements are equivalent:
1. \((G, \sigma)\) is a 2-RBMG.
2. \((G, \sigma)\) is a properly 2-colored bicluster graph that contains at least one edge.
3. \((G, \sigma)\) is a 2-RBMG and an orthology graph.
4. \((G, \sigma)\) is a 2-hc-cograph.

In the following we say that \(F\) is an \((RBMG)\) deletion set or an edit set, resp., for a properly \(n\)-colored graph \((G, \sigma)\) if \((G - F, \sigma)\) or \((G \setminus F, \sigma)\), resp., is an \(n\)-RBMG. Moreover, we say that a deletion or edit set \(F\) is optimal if \(F\) has the smallest number of elements among all deletion or edit sets \(F'\) that yield an \(n\)-RBMG \((G \setminus F', \sigma)\).

Lemma 1. Let \((G, \sigma)\) be a bipartite graph whose vertices are colored with 2 colors based on the
bipartition \(V_1, V_2\) of \(V(G)\). Then, the following statements are satisfied:
1. If \(F \subseteq V_1 \otimes V_2\) is a minimum-sized edit set making \(G \Delta F\) to a bicluster graph, then \(G \Delta F\)
   contains at least one edge and \((G \setminus F, \sigma)\) is a 2-RBMG.
2. If \(F \subseteq E\) is a minimum-sized deletion set making \(G \setminus F\) to a bicluster graph, then \(G \setminus F\)
   contains at least one edge and \((G \setminus F, \sigma)\) is a 2-RBMG.

Proof. By Remark 2, we assume that \((G = (V, E), \sigma)\) contains at least one edge. Assume, for
contradiction, that \((G \setminus F, \sigma)\), resp., \(G \Delta F\) does not contain edges and thus, \(F = E\) and \(G \setminus F = G \Delta F\).
Let \(F' = F \setminus \{xy\}\) with \(xy \in E\). In this case, \(G \setminus F' = G \Delta F'\) contains the single edge \(xy\) and hence, is a bicluster graph. However, \(|F'| < |F|\) contradicts the optimality of \(F\). Thus, \(G \setminus F\) and \(G \Delta F\) must contain at least one edge.

We continue with showing that \((G \setminus F, \sigma)\) and \((G \setminus F, \sigma)\) are 2-RBMGs. First observe that
\((G, \sigma)\) is properly 2-colored since the vertices of \(G\) are colored w.r.t. the bipartition \(V_1, V_2\). By the latter arguments, \((G \setminus F, \sigma)\) and \((G \setminus F, \sigma)\) contain at least one edge. Moreover, by construction, \(F\)
contains only (non)edges between distinctly colored vertices. Hence, \(G \setminus F\) and \(G \setminus F\) are properly
2-colored bicluster graphs with at least one edge and thus, by Cor. 1, they are 2-RBMGs.

Taken the latter results, we can easily derive the following

Corollary 2. 2-RBMG Deletion, 2-hc-Cograph Deletion, 2-RBMG Editing, 2-hc-Cograph Editing
are NP-complete.

Proof. By Cor. 1, the two problems 2-RBMG Deletion and 2-hc-Cograph Deletion as well as the
two problems 2-RBMG Editing and 2-hc-Cograph Editing are equivalent. Thus, it suffices to show that 2-RBMG Deletion and 2-RBMG Editing are NP-complete. In order to verify that a
properly 2-colored graph is a 2-RBMG, Cor. 1 implies that it suffices to check that it is a bicluster
graph with at least one edge, a task that can clearly be done in polynomial time. Thus, 2-RBMG
Deletion and 2-RBMG Editing are contained in NP.

We proceed with showing the NP-hardness. To this end let \((G = (V, E), \sigma)\) be an arbitrary instance
of Bicluster Deletion, resp., Bicluster Editing. Thus, \(G = (V, E)\) is a bipartite graph with
division \(V_1 \cup V_2\) of \(G\). Hence, we can establish a 2-coloring \(\sigma\) of \(V\) w.r.t. the two set \(V_1\) and \(V_2\).

If \(F \subseteq E\) is a minimum-sized deletion set making \(G \setminus F\) to a bicluster graph, then Lemma 1
implies that \((G \setminus F, \sigma)\) is a 2-RBMG. Conversely, if \(F \subseteq E\) is a minimum-sized deletion set making
\((G \setminus F, \sigma)\) to a 2-RBMG, then Cor. 1 implies that \(G \setminus F\) is a bicluster graph. This establishes the
NP-hardness of 2-RBMG Deletion and 2-hc-Cograph Deletion.

Assume now that \(F \subseteq V_1 \otimes V_2\) is a minimum-sized edit set making \(GDF\) to a bicluster graph.
Then, by Lemma 1, \((GDF, \sigma)\) is a 2-RBMG. Conversely, suppose that \(F \subseteq \{V_1\}\) is an optimal edit
set for \((G, \sigma)\). By Remark 1, the edit set \(F\) will never contain pairs \(xy\) with \(\sigma(x) = \sigma(y)\). Hence,
\(F \subseteq V_1 \otimes V_2\). This together with Cor. 1 implies that \((G', \sigma)\) is bicluster graph. This establishes the
NP-hardness of 2-RBMG Editing and 2-hc-Cograph Editing. 

3.2 Graphs with more than two colors

Next, we will show that $\text{n-RBMG Deletion}$ and $\text{n-RBMG Editing}$ is NP-hard by employing Cor. 2. To this end, we stepwisely extend an instance $(G, \sigma)$ of $\text{2-RBMG Deletion} / \text{Editing}$ to an instance of $\text{n-RBMG Deletion} / \text{Editing}$ by adding $n - 2$ hub-vertices. This eventually allows us to show that an optimal deletion, resp., edit set for $(G, \sigma)$ is also an optimal deletion, resp., edit set for the constructed $\text{n-RBMG Editing}$ instance.

**Lemma 2.** Let $n > 1$. Then, $(G, \sigma)$ is an $(n - 1)$-RBMG if and only if $(G + x, \sigma')$ with $\sigma'(v) = \sigma(v)$ and $\sigma'(x) \neq \sigma(v)$ for all $v \in V(G)$ is an $n$-RBMG.

**Proof.** Let $(G = (V, E), \sigma)$ be an $(n - 1)$-RBMG. Hence, there is a tree $(T, \sigma)$ that explains $(G, \sigma)$. Add $x$ as a new leaf to $(T, \sigma)$ such that $x$ is incident to the root $r$ of $T$, which results in the tree $(T^x, \sigma')$. To verify that $(G + x, \sigma')$ is an $n$-RBMG, it suffices to show that $(T^x, \sigma')$ explains $(G + x, \sigma')$. Since $(T, \sigma) = (T^x_{\mid V'}, \sigma'_{\mid V'})$ and $\sigma'(x) \notin \sigma(V)$, the RBMG $(G, \sigma)$ is clearly explained by the restriction $(T^x_{\mid V'}, \sigma'_{\mid V'})$. Moreover, we have $lca_{T^x}(x, v) = lca_{T}(x, v') = r$ for all $v, v' \in V$. This and $\sigma'(x) \notin \sigma(V)$ immediately implies $xv \in E(G(T^x))$ for every $v \in V$. Hence, $(G + x, \sigma') = (G(T^x, \sigma'))$, i.e., $(T^x, \sigma')$ explains $(G + x, \sigma')$. This and $|\sigma(V)| + 1 = n = |\sigma'(V + x)|$ implies that $(G + x, \sigma')$ is an $n$-RBMG.

Let $(G + x = (V, E), \sigma')$ be an $n$-RBMG where $\sigma(x) = r$ and let $(T, \sigma')$ be a tree on $L$ that explains $(G + x, \sigma')$. Let $S' = S \setminus \{r\}$ and $L' := \bigcup_{s \in S'} L[s]$. By Obs. 1, $(G + x)[L'] = (G + x, \sigma')$ is an $(n - 1)$-RBMG. By definition, $x$ is the only vertex in $G + x$ with color $r$ and thus $L' = V - x$. This in particular implies that $(G + x)[L'] = G$ and $\sigma(v) = \sigma'_{\mid L'}(v)$ for all $v \in V - x$. Hence, $(G, \sigma)$ is an $(n - 1)$-RBMG.

**Lemma 3.** Let $(G, \sigma)$ be a properly $n$-colored graph with hub-vertex $x$. Moreover, let $F$ be an optimal RBMG deletion, resp., edit set for $(G, \sigma)$. Then, $F$ does not contain any of the edges $xv \in E$.

**Proof.** Let $F$ be an optimal deletion, resp., edit set for $(G, \sigma)$. Assume, for contradiction, that $F$ contains at least one edge $xv \in E$. Partition $F$ into a set $F_x$ that contains all edges of the form $xw \in F$ and $F_{-x} = F \setminus F_x$.

Now, put $H := G \odot F$ with $\ominus = \{\emptyset, \triangle\}$. Thus, $(H, \sigma)$ is an $n$-RBMG that is explained by a tree $(T, \sigma)$ on $L$. Let $S' = S \setminus \{r\}$, where $\sigma(x) = r$, and $L' := \bigcup_{s \in S'} L[s]$. Since $x$ is a hub-vertex in $(G, \sigma)$, $x$ is the only vertex in $(G, \sigma)$ with color $r$ and hence, $L' = V - x$. This and Obs. 1 imply that $(H[L'], \sigma'_{\mid L'})$ is an $(n - 1)$-RBMG and Lemma 4 implies that $(H[L'] + x, \sigma)$ is an $n$-RBMG.

Thus, by construction, $H[L'] + x = G \odot F - x$ and therefore, $(G \odot F - x, \sigma)$ is an $n$-RBMG. However, $|F_{-x}| < |F_{\ominus}| + |F_x| = |F|$; contradicting the optimality of $F$.

**Lemma 4.** Let $(G = (V, E), \sigma)$ be a properly $n$-colored graph and suppose that $(G, \sigma)$ contains a hub-vertex $x$. Let $(H, \sigma') := (G - x, \sigma'_{\mid V - x})$. Then, $F$ is an optimal deletion or edit set with $(G \setminus F, \sigma)$ or $(G \setminus F, \sigma')$ being an $n$-RBMG if and only if $F$ is an optimal set such that $(H \setminus F, \sigma')$, resp., $(H \setminus F, \sigma')$ is an $(n - 1)$-RBMG.

**Proof.** First, assume that $(G, \sigma)$ is a properly $n$-colored graph with hub-vertex $x$. Since $(G, \sigma)$ is properly colored, we have $\sigma(x) = \sigma(v)$ for all $v \in V - x$ by definition of a hub-vertex. Hence, as $(G, \sigma)$ is properly colored, the graph $(H, \sigma')$ must be properly $(n - 1)$-colored. Now let $F$ be an optimal deletion, resp., edit set such that $(G \setminus F, \sigma)$, resp., $(G \setminus F, \sigma')$ is an $n$-RBMG. Assume, for contradiction, that $F$ is not optimal for $(H, \sigma')$. Thus, there exists a set $F' \setminus |F| < |F|$ such that $(H', \sigma')$ is an $(n - 1)$-RBMG, where $H' = H \setminus F'$, resp., $H' = H \setminus F'$. By Lemma 2, the graph $(H' + x, \sigma)$ is an $n$-RBMG and in particular, $H' + x = G \setminus F'$, resp., $H' + x = G \setminus F'$, a contradiction to the optimality of $F$ for $(G, \sigma)$.

Now assume that $F$ is an optimal deletion or edit set for $(H, \sigma')$ and let $\ominus = \emptyset$ or $\ominus = \triangle$, resp. By construction, $H + x = G$ and thus, $(H \odot F) + x = G \odot F$. Since $(H \odot F, \sigma')$ is an $(n - 1)$-RBMG, we can apply Lemma 2 to conclude that $(G \odot F, \sigma)$ is an $n$-RBMG. Thus, $F$ is a deletion, resp., edit set for $(G, \sigma)$. It remains to show that $F$ is an optimal set for $(G, \sigma)$. Assume, for contradiction, that there exists a optimal deletion, resp., edit set $F'$ for $G$ with $|F'| < |F|$ such that $G \odot F'$ is an $n$-RBMG. Lemma 3 implies that $F'$ does not contain edges $xv$. Hence, $x$ remains a hub-vertex in $G \odot F'$. Thus, we can apply Lemma 2 to conclude that the $(n - 1)$-colored induced subgraph $H' = (G \odot F') - x$ that contains all vertices of $G$ with color distinct from $\sigma(x)$, is an $(n - 1)$-RBMG. However, since $F'$ does not contain edges $xv$, we have $H' = (G \odot F') - x = (G - x) \odot F' = H \odot F'$. 

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Hence, \((H \odot F', \sigma')\) is an \((n-1)\)-RBMG and \(|F'| < |F|\); contradicting the optimality of \(F\) for \((H, \sigma')\).

Currently, there are no known polynomial-time algorithm to verify, for arbitrary integers \(n\), whether a given graph \((G, \sigma)\) is an \(n\)-RBMG or not. Hence, we do not know whether \(n\)-RBMG Deletion and \(n\)-RBMG Editing are in NP or not. Nevertheless, NP-hardness can easily be shown.

**Theorem 3.** \(n\)-RBMG Deletion and \(n\)-RBMG Editing is NP-hard.

**Proof.** We prove this statement by induction on the number \(n\) of colors. Cor. 2 implies that the base case \(n = 2\) is NP-complete.

Now assume that \((n-1)\)-RBMG Deletion / Editing is NP-hard, \(n \geq 2\). Let \((H = (V', E'), \sigma')\) be an arbitrary instance of the \((n-1)\)-RBMG Deletion / Editing Problem. Now, we construct an instance \((G, \sigma)\) of the \(n\)-RBMG Editing as follows: Let \(G = (V, E)\) be the graph obtained from \((H, \sigma')\) by adding a new vertex \(x\) that is adjacent to all vertices of \(H\), and thus, a hub-vertex in \((G, \sigma)\), where \(\sigma(v) = \sigma'(v)\) and \(\sigma(x) \neq \sigma'(v)\) for all \(v \in V'\). Thus, \((H, \sigma') = (G - x, \sigma_{V-x})\) and we can apply Lemma 4 to conclude that \(F\) is an optimal set such that \((G \setminus F, \sigma)\), resp., \((G \triangle F, \sigma)\) is an \(n\)-RBMG if and only if \(F\) is an optimal set such that \((H \setminus F, \sigma')\), resp., \((H \bigtriangleup F, \sigma')\) is an \((n-1)\)-RBMG, which completes the proof.

So-far we have shown that \(n\)-RBMG Deletion and \(n\)-RBMG Editing is NP-hard. We continue with showing that the problems \(n\)-hc-Cograph Deletion and \(n\)-hc-Cograph Editing are NP-complete. The proofs are similar to the proofs for the NP-hardness of \(n\)-RBMG Deletion / Editing.

**Lemma 5.** Let \(n > 1\). Then, \((G, \sigma)\) is an \((n-1)\)-hc-cograph if and only if \((G + x, \sigma')\) with \(\sigma'(v) = \sigma(v)\) and \(\sigma'(x) \neq \sigma(v)\) for all \(v \in V(G)\), is an \(n\)-hc-cograph.

**Proof.** By Thm. 1, \((G, \sigma)\) is an hc-cograph if and only it is an RBMG and a cograph. Thus, we can apply Lemma 2 to conclude that \((G, \sigma)\) is an \((n-1)\)-RBMG if and only if \((G + x, \sigma')\) is an \(n\)-RBMG. Hence, it remains to show that \(G\) is a cograph if and only if \(G + x\) is a cograph. Note that \(G_x = (V = \{x\}, E = \emptyset)\) is, by definition, a cograph. Again, by definition, \(G\) is a cograph if and only if \(G \odot G_x = G + x\) is a cograph.

**Lemma 6.** Let \((G, \sigma)\) be a properly \(n\)-colored graph and suppose that \((G, \sigma)\) contains a hub-vertex \(x\). Let \((H, \sigma') = (G - x, \sigma_{V-x})\). Then, \(F\) is an optimal deletion, resp., edit set such that \((G \setminus F, \sigma)\), resp., \((G \triangle F, \sigma)\) is an \(n\)-hc-cograph if and only if \(F\) is an optimal deletion, resp., edit set such that \((H \setminus F, \sigma')\), resp., \((H \bigtriangleup F, \sigma')\) is an \((n-1)\)-hc-cograph.

**Proof.** We show first that an optimal hc-cograph deletion or edit set \(F\) for \((G, \sigma)\) does not contain edges \(xx\). Assume, for contradiction, that \(F\) contains at least one edge \(xx \in E\) and let \(F_{-xx}\) be the set of edges in \(F\) that are not incident to \(x\). Similar arguments as in the proof of Lemma 5 together with Lemma 6 show that \((G \odot F_{-xx}, \sigma)\) is an hc-cograph and thus, \(|F_{-xx}| < |F|\); a contradiction.

Now we can reuse the arguments of the proof of Lemma 4 by utilizing Lemma 5 instead of Lemma 2, which completes the proof of this lemma.

**Theorem 4.** The problems \(n\)-hc-Cograph Deletion and \(n\)-hc-Cograph Editing are NP-complete.

**Proof.** [20, Thm. 11] shows that it can be verified in polynomial time whether a given colored graph \((G, \sigma)\) is an \(n\)-hc-cograph or not. Thus, \(n\)-hc-Cograph Deletion and \(n\)-hc-Cograph Editing are contained in the class NP.

The proofs that \(n\)-hc-Cograph Deletion and \(n\)-hc-Cograph Editing are NP-hard work exactly in the same way as the proof for showing the NP-hardness of \(n\)-RBMG Deletion and \(n\)-RBMG Editing. Simply replace all \(k\)-RBMG by \(k\)-hc-cograph in all of the desired steps and use Lemma 6 instead of Lemma 4.

As a consequence of Theorem 1, we obtain

**Corollary 3.** Let \((G, \sigma)\) be a properly \(n\)-colored graph and \(k\) be an integer. Deciding whether there is a set \(F \subseteq \binom{V}{k}\) of size \(|F| \leq k\) such that \((G \setminus F, \sigma)\), resp., \((G \bigtriangleup F, \sigma)\) is an RBMG and a cograph is NP-complete.
The property of being an RBMG or an hc-cograph is not hereditary. As an example consider the disconnected hc-cograph \((G, \sigma)\) in Fig. 1. Now take vertex \(a_1\) and \(b_2\). We have \(\sigma(a_1) \neq \sigma(b_2)\) and as an induced subgraph \((G[a_1, b_2], \sigma_{a_1b_2})\) a 2-colored but edge-less graph. By Thm. 1(2) and (4), \((G[a_1, b_2], \sigma_{a_1b_2})\) can neither be an hc-cograph nor an RBMG. As a consequence, one cannot use the general results on the complexity of graph modification problems for general hereditary graph classes outlined e.g. in [6].

For the special case of the 2-RBMG Editing problem, however, we can use established results since 2-RBMG Editing and Bicluster Editing are equivalent as long as the input graph contains at least one edge (cf. Remark 2 and Lemma 1). For the Bicluster Editing Problem, Amit [3] gave a factor-11 approximation. Protti et al. [30] showed that Bicluster Editing problem with input \((G = (V, E), \sigma)\) and integer \(k\) is FPT, and can be solved in \(O(4^k + |V| + |E|)\) time by a standard search tree algorithm. Moreover, they showed how to construct a problem kernel with \(O(k^2)\) vertices in \(O(|V| + |E|)\) time. Guo et al. [22] improved the latter results to a problem kernel with \(O(k)\) vertices and an FPT-algorithm with running time \(O(3.24^k + |E|)\). These results together with Cor. 1 imply

**Theorem 5.** 2-RBMG Editing with input \((G, \sigma)\) and integer \(k\), has a problem kernel with \(O(k)\) vertices and an FPT-algorithm with running time \(O(3.24^k + |E|)\).

Moreover, Guo et al. [22] provided a randomized 4-approximation algorithm improving the factor-11 approximation Amit [3]. Due to its importance to integrate and analyze high-dimensional biological data on a large scale many heuristics for the Bicluster Editing problem have been established in the last few years [12, 33, 13, 15, 31, 7, 8, 5, 27, 35], which can directly be applied for the 2-RBMG Editing. For the \(n\)-RBMG Editing and the \(n\)-hc-Cograph Editing problem for an arbitrary number of colors \(n\), there are, to our knowledge, no heuristics nor parameterized algorithms available so-far.

### 4 Summary and Outlook

We have shown that the four problems \(n\)-RBMG Editing, \(n\)-hc-Cograph Editing, \(n\)-RBMG Deletion and \(n\)-hc-Cograph Deletion are NP-hard. In addition, the two \(hc\)-cograph modification problems are NP-complete, and \(hc\)-cograph modification is equivalent to modifying a given graph into an RBMG that represents an orthology relation.

We are left with some open problems. Since the latter four modification problems are NP-hard, it is necessary to design efficient heuristics or parameterized algorithms in order to correct graphs inferred from sequence data to RBMGs or \(hc\)-cographs. Although, we obtained an FPT-algorithm for 2-RBMG Editing as a trivial by-product, so far no further results are available for a general number \(n\) of colors.

Moreover, it is not known whether \(n\)-RBMG Editing for \(n \geq 4\) is in NP or not. While 2- and 3-RBMGs can be recognized in polynomial time [20], it is not known whether there exists polynomial-time algorithms for the recognition of \(n\)-RBMs with \(n \geq 4\). In addition, the complexity of the \(n\)-RBMG Completion Problem (i.e., adding a minimum number of edges to obtain an \(n\)-RBMG) remains unsolved. We emphasize that this problem is not solved by adding to each 2-colored induced subgraphs the minimum number of edges required to turn it into a bicluster graph, see [20, Fig. 8(A)] for a counterexample.

Furthermore, we observed in [18] that for many of the estimated RBMGs the quotient graph w.r.t. the colored thinness relation (which identifies vertices of the same color in \((G, \sigma)\) that have the same color and the same neighborhood) are \(P_4\)-sparse, i.e., each of its induced subgraphs on five vertices contains at most one induced \(P_4\). It is well-known that uncolored \(P_4\)-sparse graphs can be optimally edited to cographs in linear time [28]. This begs the questions whether it is also possible to edit a \(P_4\)-sparse RBMG to an \(hc\)-cograph in polynomial time. More generally, can one efficiently edit a not necessarily \(P_4\)-sparse or a weighted \(P_4\)-sparse RBMG to an \(hc\)-cograph?

In this contribution we have considered graph modification problems for RBMGs. RBMGs are the symmetric part of the Best Match Graphs (BMGs) [19]. In practical applications BMGs are initially estimated from sequence data and then processed to extract (approximate) RBMGs. Thus it seems natural to consider the corresponding digraph modification problems of BMGs. At present, this remains an open problem.
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References

[1] A. M. Altenhoff and C. Desimoz. Phylogenetic and functional assessment of orthologs inference projects and methods. *PLoS Comput Biol.*, 5:e1000262, 2009.

[2] Adrian M Altenhoff, Brigitte Boeckmann, Salvador Capella-Gutierrez, Daniel A Dalquen, Todd DeLuca, Kristoffer Forslund, Jaime Huerta-Cepas, Benjamin Linard, Cécile Pereira, Leszek P Pryszek, Fabian Schreiber, Alan Sousa da Silva, Damian Szklarczyk, Clément-Marie Train, Peer Bork, Odile Lecompte, Christian von Mering, Ioannis Xenarios, Kimmen J Martin, Matthieu Muffato, Peer Bork, Odile Lecompte, Christian von Mering, Ioannis Xenarios, Kimmen J Martin, Matthieu Muffato, Quest for Orthologs consortium, Toni Gabaldón, Suzanna E Lewis, Paul D Thomas, Erik Sonnhammer, and Christophe Desimoz. Standardized benchmarking in the quest for orthologs. *Nature Methods*, 13:425–430, 2016.

[3] N. Amit. The bicluster graph editing problem. Master’s thesis, Tel Aviv University, School of Mathematical Sciences, 2004.

[4] Sebastian Böcker, Sebastian Briesemeister, and Gunnar W. Klaue. Exact algorithms for cluster editing: Evaluation and experiments. *Algorithmica*, 60:316–334, 2008.

[5] Stanislav Busygin, Oleg Prokopyev, and Panos M. Pardalos. Biclustering in data mining. *Computers & Operations Research*, 35(9):2964 – 2987, 2008. Part Special Issue: Bio-inspired Methods in Combinatorial Optimization.

[6] Leizhen Cai. Fixed-parameter tractability of graph modification problems for hereditary properties. *Information Processing Letters*, 58(4):171 – 176, 1996.

[7] Guanhua Chen, Patrick F. Sullivan, and Michael R. Kosorok. Biclustering with heterogeneous variance. *Proceedings of the National Academy of Sciences*, 110(30):12253–12258, 2013.

[8] Y Cheng and GM Church. Biclustering of expression data. In *Proceedings. International Conference on Intelligent Systems for Molecular Biology*, volume 8, pages 93–103, 2000.

[9] C. A. Christen and S. M. Selkow. Some perfect coloring properties of graphs. *J. Comb. Th.*, 27:49–59, 1979.

[10] D. G. Corneil, H. Lerchs, and L. Stewart Burlingham. Complement reducible graphs. *Discr. Appl. Math.*, 3:163–174, 1981.

[11] Milind Dawande, Pinar Keskinocak, Jayashankar M Swaminathan, and Sridhar Tayur. On bipartite and multipartite clique problems. *J. Algorithms*, 41:388–403, 2001.

[12] Gilberto F. de Sousa Filho, Teobaldo L. Bulhões Júnior, Lucídio A. F. Cabral, Luiz Satoru Ochi, and Fábio Protti. New heuristics for the bicluster editing problem. *Annals of Operations Research*, 258:781–814, 2017.

[13] Gilberto F de Sousa Filho, F Cabral Lucídio dos Anjos, Luiz Satoru Ochi, and Fábio Protti. Hybrid metaheuristic for bicluster editing problem. *Electronic Notes in Discrete Mathematics*, 39:35–42, 2012.

[14] P. Drange, F. Reidl, F. S. Villaamil, and S. Sikdar. Fast biclustering by dual parameterization. In Thore Husfeldt and Iyad Kanj, editors, *10th International Symposium on Parameterized and Exact Computation (IPEC 2015)*, volume 43 of *Leibniz International Proceedings in Informatics (LIPIcs)*, pages 402–413, Dagstuhl, Germany, 2015. Schloss Dagstuhl–Leibniz-Zentrum fuer Informatik.

[15] P.G. Drange, Felix Reidl, Fernando Sánchez Villaamil, and Somnath Sikdar. Fast Biclustering by Dual Parameterization. In Thore Husfeldt and Iyad Kanj, editors, *10th International Symposium on Parameterized and Exact Computation (IPEC 2015)*, volume 43 of *Leibniz International Proceedings in Informatics (LIPIcs)*, pages 402–413, Dagstuhl, Germany, 2015. Schloss Dagstuhl–Leibniz-Zentrum fuer Informatik.

[16] Walter M. Fitch. Homology: a personal view on some of the problems. *Trends Genet.*, 16:227–231, 2000.

[17] Toni Gabaldón and Eugene V. Koonin. Functional and evolutionary implications of gene orthology. *Nat Rev Genet.*, 14:360–366, 2013.
[18] M. Geiß, M. González Laffitte, A. López Sánchez, D. I. Valdivia, M. Hellmuth, M. Hernández Rosales, and P. F. Stadler. Best match graphs and reconciliation of gene trees with species trees. *CoRR*, 2019. arXiv:1904.12021.

[19] Manuela Geiß, Edgar Chávez, Marcos González Laffitte, Alitzel López Sánchez, Bärbel M R Stadler, Dulce I. Valdivia, Marc Hellmuth, Maribel Hernández Rosales, and Peter F Stadler. Best match graphs. *J. Math. Biol.*, 78(7):2015–2057, 2019.

[20] Manuela Geiß, Marc Hellmuth, and Peter F. Stadler. Reciprocal best match graphs. *CoRR*, 2019. arXiv q-bio 1903.07920.

[21] Giorgio Gonnella and Stefan Kurtz. RGFA: powerful and convenient handling of assembly graphs. *Peer J.*, 4:e2681, 2016.

[22] Jiong Guo, Falk Hüffner, Christian Komusiewicz, and Yong Zhang. Improved algorithms for bicluster editing. In Manindra Agrawal, Dingzhu Du, Zhenhua Duan, and Angsheng Li, editors, *Theory and Applications of Models of Computation*, pages 445–456, Berlin, Heidelberg, 2008. Springer.

[23] M. Hellmuth, M. Hernandez-Rosales, K. T. Huber, V. Moulton, P. F. Stadler, and N. Wieseke. Orthology relations, symbolic ultrametrics, and cographs. *J. Math. Biology*, 66:399–420, 2013.

[24] Marc Hellmuth, Nicolas Wieseke, Marcus Lechner, Hans-Peter Lenhof, Martin Middendorf, and Peter F. Stadler. Phylogenetics from paralogs. *Proc. Natl. Acad. Sci. USA*, 112:2058–2063, 2015.

[25] Dorit S. Hochbaum. Approximating clique and biclique problems. *J. Algorithms*, 29:174–200, 1998.

[26] B. Jamison and S. Olariu. Recognizing $p_4$-sparse graphs in linear time. *SIAM J. Computing*, 21:381–406, 1992.

[27] Mihee Lee, Haipeng Shen, Jianhua Z. Huang, and J. S. Marron. Biclustering via sparse singular value decomposition. *Biometrics*, 66(4):1087–1095, 2010.

[28] Yunlong Liu, Jianxin Wang, Jiong Guo, and Jianer Chen. Complexity and parameterized algorithms for cograph editing. *Theor. Comp. Sci.*, 461:45–54, 2012.

[29] R. Peeters. The maximum edge biclique problem is NP-complete. *Discrete Applied Mathematics*, 131:651–654, 2003.

[30] Fábio Protti, Maise Dantas da Silva, and Jayme Luiz Szwarcfiter. Applying modular decomposition to parameterized cluster editing problems. *Theory of Computing Systems*, 44:91–104, 2009.

[31] Gregory J Puleo and Olgica Milenkovic. Correlation clustering and biclustering with locally bounded errors. *IEEE Transactions on Information Theory*, 64(6):4105–4119, 2018.

[32] João C. Setubal and Peter F. Stadler. Gene phylogenies and orthologous groups. In João C. Setubal, Peter F. Stadler, and Jens Stoye, editors, *Comparative Genomics*, volume 1704, pages 1–28. Springer, Heidelberg, 2018.

[33] Nora K Speicher, Richard Röttger, Peng Sun, Jan Baumbach, and Jiong Guo. Bi-Force: large-scale bicluster editing and its application to gene expression data biclustering. *Nucleic Acids Research*, 42:e78–e78, 2014.

[34] Roman L. Tatusov, Eugene V. Koonin, and David J. Lipman. A genomic perspective on protein families. *Science*, 278:631–637, 1997.

[35] Heather Turner, Trevor Bailey, and Wojtke Krzanowski. Improved biclustering of microarray data demonstrated through systematic performance tests. *Computational Statistics & Data Analysis*, 48(2):235 – 254, 2005.

[36] D. I. Valdivia, M. Geiß, M. Hellmuth, M. Hernández Rosales, and P. F. Stadler. Hierarchical colorings of cographs. *CoRR*, 2019. arXiv:1906.10031.