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An Exact Algorithm for Sorting by Weighted Preserving Genome Rearrangements

Tom Hartmann, Matthias Bernt, and Martin Middendorf

Abstract—The preserving Genome Sorting Problem (pGSP) asks for a shortest sequence of rearrangement operations that transforms a given gene order into another given gene order by using rearrangement operations that preserve common intervals, i.e., groups of genes that form an interval in both given gene orders. The wpGSP is the weighted version of the problem were each type of rearrangement operation has a weight and a minimum weight sequence of rearrangement operations is sought. An exact algorithm – called `CREx2` – is presented, which solves the wpGSP for arbitrary gene orders and the following types of rearrangement operations: inversions, transpositions, inverse transpositions, and tandem duplication random loss operations. `CREx2` has a (worst case) exponential runtime, but a linear runtime for problem instances where the common intervals are organized in a linear structure. The efficiency of `CREx2` and its usefulness for phylogenetic analysis is shown empirically for gene orders of fungal mitochondrial genomes.

Index Terms—genome rearrangements, transposition, inversion, tandem duplication random loss, mitochondria, fungi, common interval

1 Introduction

During evolution the arrangement of the genes on the genomes of species has been shaped by various types of mutations that modify the order of the genes and/or their orientation. Such mutations are called rearrangement operations, genome rearrangements, or (simply) rearrangements. Inversions (I), transpositions (T), and inverse transpositions (iT) are important types of rearrangements for unichromosomal genomes with an equal gene content. These three types of rearrangements plus the tandem duplication random loss ($TDRL$) rearrangement are assumed to be major evolutionary mechanisms for the evolution of metazoan mitochondrial gene orders [1], [2], [3]. Gene order analysis aims to infer phylogenetic information by explaining differences in the gene orders of contemporary species [4]. Two central problems in this research area are the sorting problem and the distance problem. Whereas the sorting problem asks for a parsimonious sequence of rearrangements, called a scenario, that transforms one given gene order into another given gene order, the distance problem aims to determine only the number of rearrangements in such a scenario. The computational complexity of these problems depends on the types of the considered rearrangements (see [4] for an overview), e.g., for I as well as for $TDRL$ polynomial time algorithms are known [5], [6], whereas for transpositions the problems are NP-hard [7] and approximation algorithms [8] or greedy heuristics [9] are available.

In order to compute realistic reconstructions in a parsimony framework it can be helpful to employ a weighting scheme that reflects the likelihood of the occurrence of different rearrangements during the evolution of different taxa. For inversions efficient algorithms are available that employ weights which depend on the length of the inverted segment [10]. Weighting with respect to the type of rearrangement (I, T, and iT) as well as weighting with respect to the rearrangement length have been explored in [9]. In [11] the authors present a polynomial sized Integer Linear Program, called `GeRe-ILP`, that solves the sorting problem for I, T, and iT with predefined weights. The weighted TDRL rearrangement problem has been studied in [6], where the weight of a TDRL has been defined as α^k, where α is a parameter and $k \in \mathbb{N}$ is the number of genes that are influenced by the $TDRL$. For $\alpha = 1$ and $\alpha \geq 2$ algorithms have been presented in [6]. In addition, it has been shown for $\alpha = 1$ that it is sufficient to consider $TDRLs$ that influence the whole genome, because the weight of every $TDRL$ is the same in this case.

To find realistic reconstructions it might be useful to consider conserved gene clusters, i.e., groups of genes that are in close proximity in all the given gene orders. The rationale is that gene clusters which have been preserved during evolution, e.g., due to functional constraints or evolutionary inertia, are most likely present also in the ancestral genomes. Therefore, algorithms should enforce scenarios that preserve gene clusters in all intermediate gene orders. Such scenarios and the corresponding rearrangements are called preserving. Rearrangement problems that account for conserved gene clusters, which are usually modeled as common intervals [12], have already been studied in the literature. The idea to make use of common intervals for the comparison of gene orders has been presented in [12], [13]. In particular, the distance problem and the sorting problem for preserving inversions was studied intensively, e.g., see [14], [15], [16], [17], [18]. The main idea of the presented algorithms, e.g., [19], [20], is to use a generating subset of the common intervals. For a recent overview on sorting algorithms that use preserving inversions see [21].

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In [16] the distance problem for preserving inversions was shown to be NP-hard. Nevertheless, by using the strong interval tree data structure [19], which encodes all common intervals efficiently, an FPT algorithm with linear runtime for all instances where the common intervals are organized in a linear structure has been proposed in [22], [23]. In [24] it was shown that the algorithm has polynomial average case runtime for general problem instances. For the DCJ rearrangement operation (a generalization of I, T, and iT, see [25]) algorithms for preserving genome rearrangements have been developed that are efficient for problem instances where the common intervals are organized in a nonlinear structure [26]. By detecting patterns in the strong interval tree two algorithms have been described that heuristically compute rearrangement scenarios: one algorithm in [27] and algorithm `CREx` in [28]. The latter algorithm is more general and considers rearrangements of types I, T, iT, and $TDRL$.

In this paper, we study the weighted sorting problem for two given gene orders, which contain the same set of (unduplicated) genes, for the following types of rearrangements: I, T, iT, and $TDRL$. It is assumed that each rearrangement has to preserve the common intervals for the two given gene orders and that each type of rearrangement has an assigned weight. We present an exact algorithm, called `CREx2`, that improves the `CREx` heuristic in the following aspects: i) `CREx2` allows the incorporation of rearrangement weights, and ii) `CREx2` provides an exact solution even when the common intervals are organized in a nonlinear structure. `CREx2` has a linear runtime if the common intervals are organized in a linear structure and a (worst case) exponential runtime otherwise.

The paper is organized as follows. Definitions are given in Section 2. Theoretical results are shown in Section 3 and Section 4. `CREx2` is presented in Section 5. Experimental results for `CREx2` when applied to mitochondrial gene order data of fungi are presented in Section 6. A conclusion is given in Section 7.

2 Preliminaries

A *signed permutation* λ of length n, denoted by $\lambda = (\lambda(1) \dots \lambda(n))$, is a bijection $\lambda\colon [1:n] \to [1:n]$, where each element $\lambda(i)$ has a sign ($+$ or $-$). Signed permutations are used as a formal model for gene orders in which each element represents a gene and the sign represents its orientation [29]. When the context is clear a signed permutation is simply denoted as a permutation and the $+$ sign of elements is omitted. The set of all signed permutations of length n is denoted by $s\mathcal{P}_n$. The signed permutations $(1\ 2 \dots n)$ and $(\text{-}n \dots \text{-}2\ \text{-}1)$ are denoted by ι and -ι, respectively. An *interval* of a permutation λ is a non-empty set of (unsigned) elements that are consecutive in λ. $I(\lambda)$ is the set of all intervals of λ.

Let λ be a permutation. A *rearrangement* ρ for λ is an operation that, when applied to λ, changes the position or sign of some of the elements of λ. The resulting permutation is denoted by $\rho \circ \lambda$. The rearrangements that are considered in this paper can be characterized by the intervals that they influence as described in the following (see also Figure 1). An *inversion* ρ_I for λ is an interval X of λ containing the elements whose order is reversed and the sign of every affected element is switched in $\rho_I \circ \lambda$. A *transposition* ρ_T for λ is a pair (X, Y) of disjoint intervals X, Y of λ that are consecutive, i.e., $X, Y, X \cup Y \in I(\lambda)$, such that the order of both intervals is switched in $\rho_T \circ \lambda$. An *inverse transposition* ρ_{iT} for λ is a pair (X, Y), where X, Y are two disjoint and consecutive intervals, i.e., $X, Y, X \cup Y \in I(\lambda)$, such that in $\rho_{iT} \circ \lambda$ the order of X and Y is switched and in addition the order of the elements in X is reversed and their signs are inverted. In this work two special cases of inverse transpositions are considered: *prefix inverse transpositions* (piT), where $X = \{\lambda(1), \dots, \lambda(n-1)\}$, $Y = \{\lambda(n)\}$ and *suffix inverse transpositions* (siT), where $X = \{\lambda(2), \dots, \lambda(n)\}$ and $Y = \{\lambda(1)\}$. A *tandem duplication random loss* is a duplication of an interval of λ, such that the duplicated interval is placed adjacently, followed by a loss of one copy of each redundant gene. Formally, a $TDRL$ ρ_{TDRL} for λ is a pair (X, Y) containing two disjoint subsets X, Y of $[1:n]$ such that $X \cup Y$ is an interval in λ, X (respectively Y) contains the elements that are kept in the left (respectively right) copy in $\rho_{TDRL} \circ \lambda$, and $\rho_{TDRL} \circ \lambda \neq \lambda$ (see Figure 1 for an example). A $TDRL$ (X, Y) for λ is called *minimal* if for all proper subsets $X' \subset X$, $Y' \subset Y$ it holds that $(X', Y) \circ \lambda \neq (X, Y) \circ \lambda \neq (X, Y') \circ \lambda$. It is not hard to see that for each $TDRL$ (X, Y) there exists a uniquely defined minimal $TDRL$ (X', Y') with $X' \subseteq X$ and $Y' \subseteq Y$, see Example 1.

A *sequence* for a $\lambda \in s\mathcal{P}_n$ is a series of rearrangements $(\rho_1, \dots, \rho_l)$ such that ρ_i is a rearrangement for $\rho_{i-1} \circ \dots \circ \rho_1 \circ \lambda$, $i \in [1:l]$. Let $S = (\rho_1, \dots, \rho_l)$ be a sequence for λ, then $(\rho_i, \dots, \rho_j)$ with $1 \leq i \leq j \leq l$ is called a *subsequence* of S. The application of sequence S to λ is denoted by $S \circ \lambda$. If a sequence S for λ transforms λ into π, i.e., $S \circ \lambda = \pi$, then S is called a *scenario* for λ and π.

Let $\mathcal{R}$ be the set of rearrangements for all $\lambda \in s\mathcal{P}_n$. The *weight* of a rearrangement in $\mathcal{R}$ is given by a weight function $\omega : \mathcal{R} \to \mathbb{R}_{>0}$. In the case that the weight of a rearrangement is determined by its type $X \in \{I, T, iT, TDRL\}$ the corresponding weight is denoted by ω_X. If the type X of a rearrangement ρ is ambiguous, i.e., $X \subset \{I, T, iT, TDRL\}$ and $|X| \geq 2$, then the weight of ρ is defined as $\omega(\rho) := \min(\{\omega_Y : Y \in X\})$. Note that every minimal $TDRL$ is a $TDRL$ and therefore the weight of a minimal $TDRL$ is also denoted by ω_{TDRL}, if it is not a transposition. The *weight* of a sequence (scenario) S for λ (and π) is given by the sum of the weights of its rearrangements. A scenario for λ and π with minimal weight is called *parsimonious*.

A *common interval* of a set of permutations is an interval that occurs in each permutation of the given set [12]. The set of all common intervals of a set $\Pi \subseteq s\mathcal{P}_n$ is denoted by $C(\Pi)$. A permutation $\lambda \in s\mathcal{P}_n$ is *consistent* with Π if $C(\Pi) = C(\Pi \cup \lambda)$. Let λ be consistent to Π, then a rearrangement ρ for λ is *preserving* for Π if $\rho \circ \lambda$ is consistent with Π. A sequence (scenario) $(\rho_1, \dots, \rho_l)$ for λ (and π) is *preserving* for Π if for all $i \in [1:l]$ the permutation $\rho_i \circ \dots \circ \rho_1 \circ \lambda$ is consistent with Π. A scenario for λ and π that is preserving for Π and has a minimum weight is called *parsimonious preserving scenario* for λ and π. A common interval $I \in C(\Pi)$ is *strong* if every other common interval $J \in C(\Pi)$ is either disjoint, included in I, or includes I, i.e., $I \cap J = \emptyset$, $J \subseteq I$, or $I \subseteq J$. See Example 1 and Figure 2 for examples of common and strong intervals.

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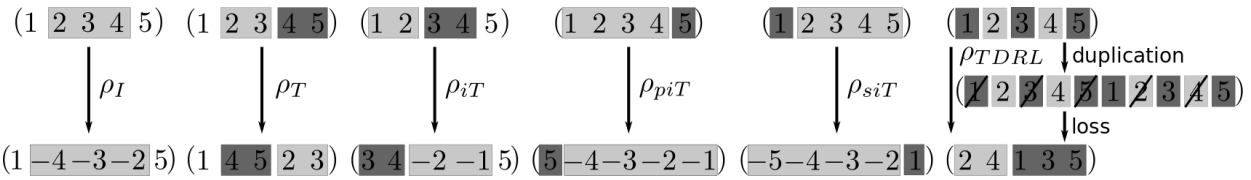

Figure 1. Rearrangements for ι considered in this work (from left to right): $\rho_I = \{2,3,4\}$; $\rho_T = (\{2,3\},\{4,5\})$; $\rho_{iT} = (\{1,2\},\{3,4\})$; $\rho_{piT} = (\{1,2,3,4\},\{5\})$; $\rho_{siT} = (\{2,3,4,5\},\{1\})$; $\rho_{TDRL} = (\{2,4\},\{1,3,5\})$. Bright and dark gray squares illustrate the sets X and Y, respectively.

Example 1. Consider $\Pi = \{(1\ -2\ 4\ 3\ -6\ 5), \iota\}$. The permutation $\lambda = (1\ 2\ 3\ 4\ -6\ 5)$ is consistent with Π, since $C(\Pi) = C(\Pi \cup \lambda)$, where the common intervals of Π are $\{1,2,3,4,5,6\}$, $\{2,3,4,5,6\}$, $\{1,2,3,4\}$, $\{3,4,5,6\}$, $\{2,3,4\}$, $\{1,2\}$, $\{3,4\}$, $\{5,6\}$, $\{1\}$, $\{2\}$, $\{3\}$, $\{4\}$, $\{5\}$, and $\{6\}$. The strong common intervals of Π are $\{1,2,3,4,5,6\}$, $\{1,2\}$, $\{3,4\}$, $\{5,6\}$, $\{1\}$, $\{2\}$, $\{3\}$, $\{4\}$, $\{5\}$, and $\{6\}$. One sequence for $(1\ -2\ 4\ 3\ -6\ 5)$ is $(\rho_I = \{5,6\}, \rho_T = (\{2\},\{3,4\}))$. For equally weighted rearrangements, e.g., $1 = \omega_I = \omega_{iT} = \omega_T = \omega_{TDRL}$, a parsimonious scenario for $(1\ -2\ 4\ 3\ -6\ 5)$ and ι that is consistent for Π is $S = (\rho_T = (\{3\},\{4\}), \rho_I = \{2\}, \rho_{iT} = (\{6\},\{5\}))$ and $\omega(S) = 3$. A $TDRL$ for λ is $(\{1,2,4,5\},\{3,6\})$ and the corresponding minimal $TDRL$ is $(\{4,5\},\{3,6\})$.

Since every two strong intervals are either disjoint or one includes the other, the strong intervals of Π form a hierarchy, which is captured by the strong interval tree. Strong interval trees [19], [22] are an important data structure for genome rearrangement analysis [22], [27], [28], since it can encode all $\mathcal{O}(n^2)$ common intervals of a set of permutations with $\mathcal{O}(n)$ nodes [22]. Formally, for $\Pi \subseteq s\mathcal{P}_n$ and $\lambda \in s\mathcal{P}_n$ that is consistent with Π a *strong interval tree* of Π and λ is an ordered and rooted tree where the node set is the set of strong common intervals of Π, the edge set is defined by their minimal inclusion relation, and the child nodes of a node are ordered as the corresponding intervals in λ, see Figure 2. Observe that the following facts hold for a strong interval tree: i) each node is an interval in λ since λ is consistent with Π, ii) the leaves are the single elements $1,\ldots,n$, and iii) the root is the set $\{1,\ldots,n\}$.

The *degree of* a node N, denoted by $\deg(N)$, of a rooted tree is the number of its child nodes. Let N be an inner node of the strong interval tree of Π and λ, permutation $\pi \in s\mathcal{P}_n$ be consistent with Π, and $N_1,\ldots,N_{\deg(N)}$ be the child nodes of N in this order. The *quotient permutation* of N (with respect to π) is the permutation $\pi_{|N}$ which satisfies that $\pi_{|N}(i)$ precedes $\pi_{|N}(j)$ if and only if the interval N_i is to left of the interval N_j in π for $i \neq j$. A quotient permutation $\pi_{|N}$ is *linear increasing* (*linear decreasing*) if $\pi_{|N} = (1 \ldots \deg(N))$ (respectively $\pi_{|N} = (\deg(N) \ldots 1)$) holds. Permutation $\pi_{|N}$ is *prime* if it is neither linear increasing nor linear decreasing. Node N is *linear* (*prime*) with respect to π if $\pi_{|N}$ is linear increasing or linear decreasing (respectively prime).

Let $\Pi \subseteq s\mathcal{P}_n$ and $\lambda, \pi \in s\mathcal{P}_n$ be consistent with Π. The *signed strong interval tree* (SIT) of Π, λ, and π, denoted by $\mathcal{T}^{\lambda}(\pi,\Pi)$, is the strong interval tree of Π and λ, where nodes that are linear with respect to π and leaves have an additional sign that is determined as follows: i) a linear inner node N gets the sign $+$ (respectively $-$) if $\pi_{|N}$ is linear increasing (respectively decreasing) with respect to π, ii) a leaf node gets the sign $+$ if the corresponding element has the same sign in π and λ and the sign $-$ otherwise. Note that no sign is assigned to a prime node. If all inner nodes of a SIT are linear (with respect to π), then the SIT is called *linear*. Otherwise, the SIT is called *prime*. Both types of SITs are considered in this paper because both occur in biological applications. Whereas pairwise comparisons of metazoan mitochondrial gene orders often correspond to instances with linear SITs [30], this is different for fungal mitochondrial gene orders where our investigation shows that instances with linear SIT occur in less than 5% of the cases (for details see Section 6).

The sign of a linear node or leaf node N is denoted by $\mathcal{S}(N)$ and $-\mathcal{S}(N)$ is the opposite sign of N, i.e., $-\mathcal{S}(N) = +$ (respectively $-\mathcal{S}(N) = -$) if $\mathcal{S}(N) = -$ (respectively $\mathcal{S}(N) = +$). An interval X of λ is called a *prime-sibling* with respect to π and Π if X is a union of child nodes of

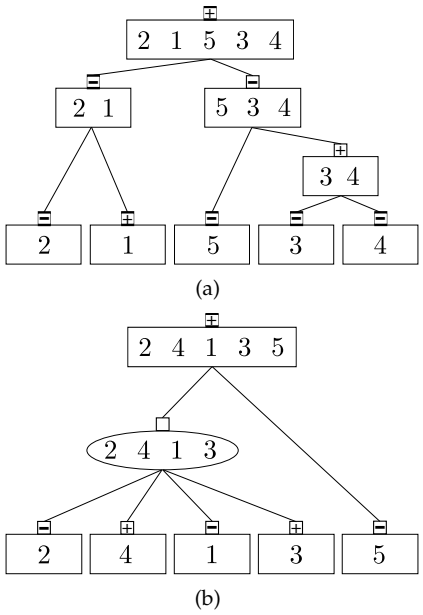

Figure 2. (a): Linear SIT $\mathcal{T}^{\lambda}(\iota,\{\lambda,\iota\})$ with $\lambda = (-2\ 1\ -5\ -3\ -4)$. Linear (prime) vertices are represented by rectangles (respectively ellipses). The sign of a node is shown at the top of the rectangles. The common intervals of $\{\lambda,\iota\}$ are $\{1,2\}$, $\{3,4\}$, $\{3,4,5\}$, $\{1,2,3,4,5\}$, $\{1\}$, $\{2\}$, $\{3\}$, $\{4\}$, and $\{5\}$ and each of these intervals is strong as well. The node $\{5,3,4\}$ is linear decreasing since $\iota_{|\{5,3,4\}} = (2\ 1)$ and the node $\{3,4\}$ is linear increasing since $\iota_{|\{3,4\}} = (1\ 2)$. For equally weighted rearrangements, a parsimonious preserving scenario for λ and ι is $S = (\rho_T = (\{3\},\{4\}), \rho_I = \{3,4,5\}, \rho_{piT} = (\{2\},\{1\}))$. (b): Prime SIT $\mathcal{T}^{\lambda'}(\iota,\{\lambda',\iota\})$ with $\lambda' = (-2\ 4\ -1\ 3\ -5)$. The interval $\{1,3,4\}$ is a prime-sibling. For equally weighted rearrangements, one parsimonious preserving scenario for λ' and ι is $S = (\rho_I = \{1,2,4\}, \rho_{iT} = (\{4\},\{2,3\}), \rho_I = \{5\})$.

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a prime node in $\mathcal{T}^{\lambda}(\pi, \Pi)$. Figure 2 gives examples for the definitions related to SITs.

The *weighted preserving Genome Sorting Problem* (wpGSP) is to find for a set of rearrangements $\mathcal{R}$, a weight function $\omega : \mathcal{R} \to \mathbb{R}_{>0}$, and signed permutations $\lambda, \pi \in s\mathcal{P}_n$ a parsimonious preserving scenario for λ and π. Figure 3 illustrates a parsimonious preserving scenario for a given wpGSP.

3 Generalized Preserving Rearrangements

In this section some theoretical results for preserving scenarios are shown. In the following, let $\Pi \subseteq s\mathcal{P}_n$ and let $\lambda \in s\mathcal{P}_n$ and $\pi \in s\mathcal{P}_n$ be consistent with Π.

The following proposition is adapted from [22] and it is one reason for the success of the SIT data structure for computing preserving rearrangements.

Proposition 1 ([22]). Let I be an interval of a permutation $\pi' \in \Pi$. Then, $I \in C(\Pi)$ if and only if I is a node of $\mathcal{T}^{\lambda}(\pi, \Pi)$ or the union of consecutive child nodes of a linear node of $\mathcal{T}^{\lambda}(\pi, \Pi)$.

Proposition 1 is the foundation for specifying rearrangements that preserve common intervals in terms of the SIT. Such a specification has been presented for inversions in [22] and the following theorem generalizes this specification.

Theorem 1. Let $S = (\rho_1, \ldots, \rho_l)$ be a sequence for λ, $\lambda_i := \rho_i \circ \ldots \circ \rho_1 \circ \lambda$ with $i \in [1 : l]$, and $\lambda_0 := \lambda$. Then, S is preserving for Π if and only if for all $j \in [0 : l-1]$ each linear node in $\mathcal{T}^{\lambda_j}(\pi, \Pi)$ is a linear node in $\mathcal{T}^{\lambda_{j+1}}(\pi, \Pi)$.

Proof: $\Rightarrow$) Assume that S is preserving for Π, i.e., for all $j \in [1 : l]$ the permutation λ_j is consistent with Π. Let $I \in C(\Pi)$ be a node in $\mathcal{T}^{\lambda_j}(\pi, \Pi)$ with $j \in [0 : l-1]$. Then, by the definition of the SIT the strong interval I is also a node in $\mathcal{T}^{\lambda_{j+1}}(\pi, \Pi)$, since the nodes in $\mathcal{T}^{\lambda_j}(\pi, \Pi)$ and $\mathcal{T}^{\lambda_{j+1}}(\pi, \Pi)$ are the strong intervals of Π. Now, let $I \in C(\Pi)$ be a linear node in $\mathcal{T}^{\lambda_j}(\pi, \Pi)$ with child nodes $I_1, \ldots, I_{\deg(I)}$ in that order. Then, the order of the child nodes of I in $\mathcal{T}^{\lambda_{j+1}}(\pi, \Pi)$ is either $I_1, \ldots, I_{\deg(I)}$ or its reverse, i.e., $I_{\deg(I)}, \ldots, I_1$. This can be seen by the following argumentation. For a contradiction assume that the order of the child nodes of I in $\mathcal{T}^{\lambda_{j+1}}(\pi, \Pi)$ is neither $I_1, \ldots, I_{\deg(I)}$ nor $I_{\deg(I)}, \ldots, I_1$. Then, there exist two child nodes I_i and I_{i+1} of I that are not consecutive in $\mathcal{T}^{\lambda_{j+1}}(\pi, \Pi)$, whereas they are consecutive in $\mathcal{T}^{\lambda_j}(\pi, \Pi)$. By Proposition 1 the set $I_i \cup I_{i+1}$ is a common interval of $\Pi \cup \lambda_j$, since it is a union of consecutive child nodes of a linear node, i.e., $I_i \cup I_{i+1} \in C(\Pi \cup \lambda_j)$. On the other hand, by Proposition 1 it holds that $I_i \cup I_{i+1} \notin C(\Pi \cup \lambda_{j+1})$, since I_i and I_{i+1} are neither consecutive child nodes of a linear node in $\mathcal{T}^{\lambda_{j+1}}(\pi, \Pi)$ nor $I_i \cup I_{i+1}$ is a node in $\mathcal{T}^{\lambda_{j+1}}(\pi, \Pi)$. The first fact holds, since I_i and I_{i+1} are not consecutive in $\mathcal{T}^{\lambda_{j+1}}(\pi, \Pi)$. The latter fact holds, since $I_i \cup I_{i+1}$ is not a node in $\mathcal{T}^{\lambda_j}(\pi, \Pi)$ and since both $\mathcal{T}^{\lambda_j}(\pi, \Pi)$ and $\mathcal{T}^{\lambda_{j+1}}(\pi, \Pi)$ have the same nodes, i.e., the same strong common intervals of Π. Therefore, $I_i \cup I_{i+1} \in C(\Pi \cup \lambda_j)$ and $I_i \cup I_{i+1} \notin C(\Pi \cup \lambda_{j+1})$, which contradicts the assumption that S is preserving for Π, since $C(\Pi) = C(\Pi \cup \lambda_j) \neq C(\Pi \cup \lambda_{j+1}) = C(\Pi)$, i.e., λ_{j+1} is not consistent with Π. Consequently, the order of the child nodes of I in $\mathcal{T}^{\lambda_{j+1}}(\pi, \Pi)$ is either unchanged, i.e., $I_1, \ldots, I_{\deg(I)}$, or reversed, i.e., $I_{\deg(I)}, \ldots, I_1$. In both cases, I is linear in $\mathcal{T}^{\lambda_{j+1}}(\pi, \Pi)$, which proves the result.

$\Leftarrow$) Assume that for all $j \in [0 : l-1]$ it holds that each linear node N in $\mathcal{T}^{\lambda_j}(\pi, \Pi)$ is a linear node in $\mathcal{T}^{\lambda_{j+1}}(\pi, \Pi)$. Consider a common interval $I \in C(\Pi \cup \lambda_j)$ with $j \in [0 : l-1]$. By Proposition 1 strong interval I is a node in $\mathcal{T}^{\lambda_j}(\pi, \Pi)$ or I is a union of consecutive child nodes of a linear node of $\mathcal{T}^{\lambda_j}(\pi, \Pi)$. If I is a node in $\mathcal{T}^{\lambda_j}(\pi, \Pi)$, then I is also a node in $\mathcal{T}^{\lambda_{j+1}}(\pi, \Pi)$, since by the definition of a SIT the nodes of a SIT $\mathcal{T}^{\sigma_1}(\sigma_2, \Sigma)$, with $\Sigma \subseteq s\mathcal{P}_n$ and $\sigma_1, \sigma_2 \in s\mathcal{P}_n$ consistent with Σ, are the strong common intervals of Σ, which are not influenced by σ_1 or σ_2. If I is a union of consecutive child nodes of a linear node N in $\mathcal{T}^{\lambda_j}(\pi, \Pi)$, then $I \in C(\Pi \cup \lambda_{j+1})$, since consecutive child nodes of a linear node in $\mathcal{T}^{\lambda_j}(\pi, \Pi)$ are also consecutive in $\mathcal{T}^{\lambda_{j+1}}(\pi, \Pi)$. This can be seen by the following argumentation. Since N is linear in $\mathcal{T}^{\lambda_j}(\pi, \Pi)$ and $\mathcal{T}^{\lambda_{j+1}}(\pi, \Pi)$ the order of the child nodes of N is either unchanged, i.e, N is linear increasing (respectively decreasing) in $\mathcal{T}^{\lambda_j}(\pi, \Pi)$ and $\mathcal{T}^{\lambda_{j+1}}(\pi, \Pi)$, or reversed, i.e., N is linear increasing (decreasing) in $\mathcal{T}^{\lambda_j}(\pi, \Pi)$ and linear decreasing (respectively increasing) in $\mathcal{T}^{\lambda_{j+1}}(\pi, \Pi)$. Note that no other case satisfies that N is linear in $\mathcal{T}^{\lambda_j}(\pi, \Pi)$ and $\mathcal{T}^{\lambda_{j+1}}(\pi, \Pi)$. If the order of child nodes of N is unchanged, then obviously consecutive child nodes of N in $\mathcal{T}^{\lambda_j}(\pi, \Pi)$ are also consecutive in $\mathcal{T}^{\lambda_{j+1}}(\pi, \Pi)$. If the order of child nodes of N is reversed, then each two child nodes N_1, N_2 of N that are consecutive in $\mathcal{T}^{\lambda_j}(\pi, \Pi)$ (in that order) are consecutive in $\mathcal{T}^{\lambda_{j+1}}(\pi, \Pi)$ in the reversed order. In both cases it holds that $I \in C(\Pi \cup \lambda_{j+1})$. Consequently, for all $j \in [0 : l-1]$ λ_j is consistent with Π, i.e., S is preserving for Π. □

For the interested reader, the proofs of the following two corollaries of Theorem 1 are given in the supplementary material. The following corollary of Theorem 1 shows that a preserving sequence for λ retains the consecutiveness of the child nodes of linear nodes of $\mathcal{T}^{\lambda}(\pi, \Pi)$.

Corollary 1. Let $S = (\rho_1, \ldots, \rho_l)$ be a sequence for λ that is preserving for Π, $\lambda_i := \rho_i \circ \ldots \circ \rho_1 \circ \lambda$ with $i \in [1 : l]$, and $\lambda_0 := \lambda$. Then, for each linear node N in $\mathcal{T}^{\lambda_j}(\pi, \Pi)$ it holds that consecutive child nodes of N are consecutive in $\mathcal{T}^{\lambda_{j+1}}(\pi, \Pi)$, where $j \in [0 : l-1]$.

By Corollary 1 a preserving rearrangement can change the SIT only as follows: i) the order of the child nodes of a linear node N is reversed and the sign of N is switched, ii) the sign of a leaf node is switched, and iii) the order of the child nodes of a prime node is permuted. In case iii) the consequences for a prime node N are that either N becomes linear and gets a corresponding sign or N remains prime (and therefore has no sign).

The following corollary of Theorem 1 specifies the preserving rearrangements for several types of rearrangements in terms of the SIT.

Corollary 2. Let ρ be a rearrangement for λ of type I, T, iT, or minimal $TDRL$. Then ρ is preserving for Π if and only if one of the following holds:

i) $\rho = X$ is of type I where X is a prime-sibling with respect to π and Π or $\rho = (X, Y)$ is of type T, iT,

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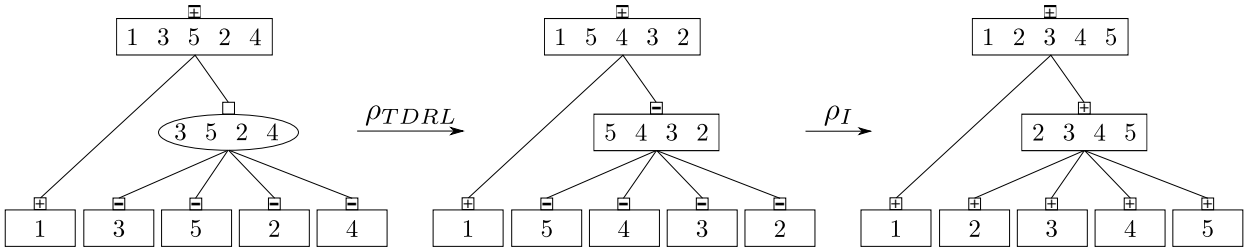

Figure 3. Parsimonious scenario $(\rho_{TDRL} = (\{4,5\},\{2,3\}), \rho_I = \{2,3,4,5\})$ for $\lambda = (1\ {-3}\ {-5}\ {-2}\ {-4})$ and ι that is preserving for $\{\lambda, \iota\}$. This scenario is a solution of the wpGSP defined by all rearrangements of type $X \in \{I, T, iT,$ minimal $TDRL\}$, $\omega(\rho) = 1$ for all rearrangements ρ, and λ and ι. Illustrated are from the left to the right $\mathcal{T}^{\lambda}(\iota,\{\lambda,\iota\})$, $\mathcal{T}^{\rho_{TDRL}\circ\lambda}(\iota,\{\lambda,\iota\})$, and $\mathcal{T}^{\rho_I\circ\rho_{TDRL}\circ\lambda}(\iota,\{\lambda,\iota\})$. Observe that ρ_{TDRL} transforms the prime node $\{2,3,4,5\}$ in $\mathcal{T}^{\lambda}(\iota,\{\lambda,\iota\})$ into a linear node in $\mathcal{T}^{\rho_{TDRL}\circ\lambda}(\iota,\{\lambda,\iota\})$ that has a $-$ sign.

or minimal $TDRL$ where X and Y are prime-siblings with respect to π and Π;

ii) $\rho = X$ is of type I, where X is a linear node in $\mathcal{T}^{\lambda}(\pi,\Pi)$;

iii) $\rho = (X,Y)$ is of type T, where X and Y are the only child nodes of a linear node $X \cup Y$ in $\mathcal{T}^{\lambda}(\pi,\Pi)$;

iv) $\rho = (X,Y)$ is of type iT, where Y is the first or last child of a linear node $X \cup Y$ in $\mathcal{T}^{\lambda}(\pi,\Pi)$.

To describe the consequences of Corollary 2 for finding parsimonious preserving scenarios the following definition is needed. Consider a rearrangement ρ that is preserving for Π and of type I, T, iT, or minimal $TDRL$. Then $\rho = X$ or $\rho = (X,Y)$. Rearrangement ρ *acts* on a node N of $\mathcal{T}^{\lambda}(\pi,\Pi)$ if X (respectively $X \cup Y$) is a node in $\mathcal{T}^{\lambda}(\pi,\Pi)$ or is a union of child nodes of a node N in $\mathcal{T}^{\lambda}(\pi,\Pi)$. Corollary 2 shows that each of the considered rearrangements acts on a node of $\mathcal{T}^{\lambda}(\pi,\Pi)$. A consequence of Corollary 2 is that a preserving rearrangement of type $X \in \{I, T, iT,$ minimal $TDRL\}$ that acts on a linear node N is uniquely determined, i.e., if there exist two rearrangements ρ and ρ' of type X that act on N, then $\rho = \rho'$. Note that uniqueness does not necessarily hold for rearrangements that act on a prime node of the SIT. Figure 4 illustrates the effects of preserving rearrangements of types I, T, piT, siT, and minimal $TDRL$ that act on a node of a SIT. The figure illustrates also the effect on the signs of the nodes.

The following proposition shows that there exist parsimonious preserving scenarios that have a specific structure.

Proposition 2. Consider scenarios for λ and π that consist only of rearrangements of types I, T, iT, and minimal $TDRL$ and that are preserving for Π. There exists such a scenario $S = (\rho_1,\ldots,\rho_k)$ that is parsimonious and where each rearrangement ρ_i, $i \in [1:k]$, acts on a node of $\mathcal{T}^{\lambda}(\pi,\Pi)$ and for each node N of $\mathcal{T}^{\lambda}(\pi,\Pi)$ the rearrangements that act on N are a subsequence of S. Moreover, for each order of the nodes of $\mathcal{T}^{\lambda}(\pi,\Pi)$ there exists such a parsimonious scenario were the subsequences of rearrangements that act on the different nodes have the same relative order as their nodes.

Proof: Observe, there exists always a scenario for λ and π that is preserving for Π and consists only of rearrangements of the type I. Hence, there exists also a parsimonious scenario for λ and π that is preserving for Π. Let $S' = (\rho_1,\ldots,\rho_k)$ be such a parsimonious scenario. It follows from Corollary 2 that each rearrangement acts on a node in $\mathcal{T}^{\lambda}(\pi,\Pi)$. Now, consider two rearrangements ρ_i and

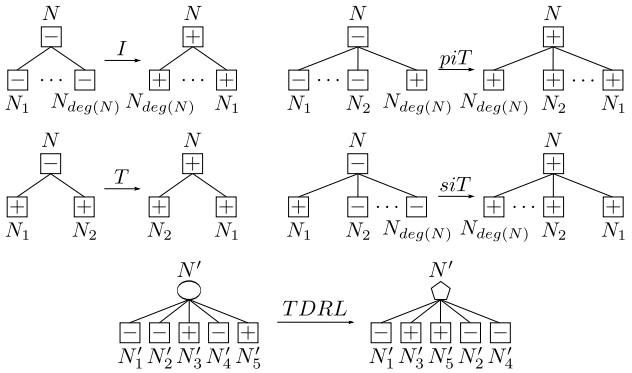

Figure 4. Preserving rearrangements of type I, T, piT, and siT that act on a linear node N and an example of a preserving rearrangement of type $TDRL$ that acts on a prime node N', which is illustrated by an ellipse. Node N, its child nodes $N_1,\ldots,N_{\deg(N)}$, and the child nodes $N'_1,\ldots,N'_5$ of N' are represented by their signs. Illustrated is the case where all child nodes of N and N' are linear. If a child node is prime, then it has no sign. A pentagon illustrates that the node N' can either remain prime or it becomes linear (and gets a corresponding sign) by the application of the $TDRL$. Observe that the rearrangement of type $TDRL$ does not change the signs of the child nodes of N'.

ρ_{i+1}, $i \in [1:k-1]$, of S' that act on different nodes N_i and N_{i+1} of $\mathcal{T}^{\lambda}(\pi,\Pi)$. Then, it holds that a parsimonious preserving scenario $S'' := (\rho_1,\ldots,\rho_{i-1},\rho'_{i+1},\rho'_i,\rho_{i+2},\ldots,\rho_k)$ for π and λ exists such that i) either $\rho'_i = \rho_i$ or ρ'_i and ρ_i are of the same type, $\rho'_i = (Y,X)$, and $\rho_i = (X,Y)$ and ii) either $\rho'_{i+1} = \rho_{i+1}$ or ρ'_{i+1} and ρ_{i+1} are of the same type, $\rho'_{i+1} = (Y,X)$, and $\rho'_i = (X,Y)$. This can be seen by the following argumentation. Since the nodes N_i and N_{i+1} are different it holds that either $N_i \cap N_{i+1} = \emptyset$, $N_i \subset N_{i+1}$, or $N_{i+1} \subset N_i$.

Consider first the case $N_i \cap N_{i+1} = \emptyset$. Due to the hierarchical structure of the nodes of $\mathcal{T}^{\lambda}(\pi,\Pi)$, it is easy to see that ρ_i (respectively ρ_{i+1}) changes only the order of nodes in a subtree rooted at N_i (respectively N_{i+1}). Since $N_i \cap N_{i+1} = \emptyset$ both subtrees are disjoint. Therefore, the order of the child nodes of N_i (respectively N_{i+1}) is unchanged by the application of ρ_{i+1} (respectively ρ_i). Consequently, ρ_{i+1} is a rearrangement for λ_{i-1} and ρ_i is a rearrangement for $\rho_{i+1} \circ \lambda_{i-1}$ and $\rho_{i+1} \circ \rho_i \circ \lambda_{i-1} = \rho_i \circ \rho_{i+1} \circ \lambda_{i-1}$. Since $\rho_{i+1} \circ \rho_i \circ \lambda_{i-1} = \rho_i \circ \rho_{i+1} \circ \lambda_{i-1}$, in this case it holds that S'' is a scenario for λ and π.

Now consider the case $N_i \subset N_{i+1}$. Assume that N_i is a child node of N_{i+1}. Since ρ_{i+1} acts on N_{i+1} it can only change the relative order of its child nodes or it can

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inverse some of its child nodes. If ρ_{i+1} does not inverse N_i then clearly both sequences of rearrangements (ρ_i, ρ_{i+1}) and (ρ_{i+1}, ρ_i) have the same effect. Now consider the case that ρ_{i+1} inverses node N_i. If ρ_i is of type T, I, or iT it is clear that both sequences (ρ_i, ρ_{i+1}) and (ρ_{i+1}, ρ_i) have the same effect. If $\rho_i = (X, Y)$ is a minimal $TDRL$ then the sequences (ρ_i, ρ_{i+1}) and (ρ'_{i+1}, ρ_i) have the same effect were $\rho'_{i+1} = (Y, X)$, i.e., the elements that are kept in the left copy and in right copy have been exchanged. If N_i is a successor of N_{i+1} but not a child node the proof is similar. The remaining case $N_{i+1} \subset N_i$ can be done analogously to the case $N_i \subset N_{i+1}$.

It is not hard to see that the proposition follows by an iterative application of the described interchange of to pairs of neighboured rearrangements that act on different nodes. □

Proposition 2 proves the existence of parsimonious preserving scenarios that consists of consecutive subsequences that act on different nodes. Algorithm `CREx2`, which is presented in Section 5, computes for given λ and π such a parsimonious scenario for λ and π that is preserving for $\{\pi, \lambda\}$ such that the subsequences that act on different nodes of the SIT have the same relative order as the bottom-up order of the nodes of $\mathcal{T}^{\lambda}(\pi, \{\pi, \lambda\})$.

4 Weighted Preserving Rearrangements

The various types of rearrangements occur during the evolution of diverse taxa with different likelihoods. In order to compute realistic scenarios it is useful to employ a weighting scheme for the different types of rearrangements. In this section we investigate the problem to calculate the weights of preserving parsimonious scenarios of rearrangements that are weighted by their type.

Let $\Pi \subseteq s\mathcal{P}_n$, $\pi, \lambda \in s\mathcal{P}_n$ consistent with Π, N be a node of $\mathcal{T}^{\lambda}(\pi, \Pi)$, and $\mathcal{R}_{|N}$ be the set of rearrangements that are of type I, T, iT, or minimal $TDRL$ and act on N. For N and a sign $s \in \{+, -\}$ let $\kappa(N, s)$ denote the minimum weight of a preserving scenario S for λ and $S \circ \lambda$ such that all nodes in the subtree rooted at N in $\mathcal{T}^{S\circ\lambda}(\pi, \Pi)$ have sign s. Observe that when N is the root of the SIT, the value $\kappa(N, +)$ is the minimal weight of a scenario for λ and π. In the following we show that the values $\kappa(N, s)$ can easily be calculated if N is a leaf node or a linear node and otherwise, i.e., N is a prime node, the calculation of $\kappa(N, s)$ is NP-hard.

Consider first the case that N is a leaf node. By Corollary 2 the sign of a leaf node can only be modified by a rearrangement of type I. Therefore, in this case $\kappa(N, s) = \omega_I$ if $s \neq \mathcal{S}(N)$ and, otherwise, $\kappa(N, s) = 0$.

Consider now the case that N is a linear node. In the following it is shown that if N is a linear node, then only a small constant number of different weight values for preserving scenarios have to be considered. This is due to the fact that every type of preserving rearrangement which acts on a linear node N is uniquely determined (Corollary 2) and that (under the set of considered rearrangements) a preserving scenario with more than 3 rearrangements cannot be parsimonious, which is shown in the following Proposition 3.

Let $\kappa_i(N, s)$, for $i \in [0:3]$, be auxiliary weight functions which give the minimum weight of a scenario S with exactly i rearrangements acting on a node N such that all nodes in the subtree rooted at N in $\mathcal{T}^{S\circ\lambda}(\pi, \Pi)$ have sign s. In the following some specific $\kappa_i(N, s)$, $i \in [0:3]$, are described and Proposition 3 shows that the minimum of these weight functions is $\kappa(N, s)$. The corresponding (possibly parsimonious) scenarios are illustrated in the supplementary figures S3-S5.

Recall that $\kappa(N_i, \pm)$, $i \in [1 : \deg(N)]$, denotes the minimum weight of a preserving scenario for the child node N_i of N and that $\mathcal{S}(N)$ is the sign of node N. Further, let $s \in \{-, +\}$ be the desired sign. Note that any rearrangement ρ from $\mathcal{R}_{|N}$ switches the sign of the linear node N, since ρ acts on N. Therefore, for the application of an even (respectively odd) number of rearrangements it cannot hold that the sign of N in $\mathcal{T}^{S\circ\lambda}(\pi, \Pi)$ is s if $\mathcal{S}(N) \neq s$ (respectively $\mathcal{S}(N) = s$). Hence, if $i \in \{1, 3\}$ and $\mathcal{S}(N) = s$, then $\kappa_i(N, s) = \infty$, and if $i \in \{0, 2\}$ and $\mathcal{S}(N) \neq s$, then $\kappa_i(N, -s) = \infty$.

No rearrangement: If $\mathcal{S}(N) = s$, then one option is to apply no rearrangement that acts on N and apply rearrangements only to its $\deg(N)$ child nodes $N_1, \ldots, N_{\deg(N)}$ in order to adjust their signs to s. The weight of such a scenario is given by $\kappa_0(N, s) = \sum_{i=1}^{\deg(N)} \kappa(N_i, s)$. If $\mathcal{S}(N) \neq s$ then $\kappa_0(N, s) = \infty$.

One rearrangement: If $\mathcal{S}(N) \neq s$, then one possibility is to apply one rearrangement that acts on N satisfying that N and all its child nodes have the sign s. By Corollary 2, the weight $\kappa_1(N, s)$ has to consider the weight of every type of preserving rearrangement plus the weight to realize the corresponding signs of the child nodes. Thus, $\kappa_1(N, s) = \min\{\mathcal{K}_{1,1}, \mathcal{K}_{1,2}, \mathcal{K}_{1,3}\}$, where $\mathcal{K}_{1,1} = \omega_I + \sum_{i=1}^{\deg(N)} \kappa(N_i, -s)$ is the weight of applying an I, $\mathcal{K}_{1,2} = \omega_T + \kappa(N_1, s) + \kappa(N_2, s)$ is the weight of applying a T if $\deg(N) = 2$ and otherwise $\mathcal{K}_{1,2} = \infty$, and $\mathcal{K}_{1,3} = \omega_{iT} + \min\{\kappa(N_1, s) + \sum_{i=2}^{\deg(N)} \kappa(N_i, -s), \kappa(N_{\deg(N)}, s) + \sum_{i=1}^{\deg(N)-1} \kappa(N_i, -s)\}$ is the weight of applying an iT. If $\mathcal{S}(N) = s$ then $\kappa_1(N, s) = \infty$.

Two rearrangements: If $\mathcal{S}(N) = s$, then instead of applying rearrangements only to the child nodes of N (no rearrangement case), there is also the possibility to apply two rearrangements that act on N in order to change the signs of its child nodes simultaneously. Therefore, $\kappa_2(N, s) = \min\{\mathcal{K}_{2,1}, \mathcal{K}_{2,2}, \mathcal{K}_{2,3}\}$, where the weight of applying an I and a T is given by $\mathcal{K}_{2,1} = \omega_I + \omega_T + \kappa(N_1, \text{-}s) + \kappa(N_2, \text{-}s)$ if $\deg(N) = 2$ and otherwise $\mathcal{K}_{2,1} = \infty$, the weight of applying two successive iT of the same type is given by $\mathcal{K}_{2,2} = 2\omega_{iT} + \kappa(N_1, -s) + \sum_{i=2}^{\deg(N)-1} \kappa(N_i, s) + \kappa(N_{\deg(N)}, -s)$, and the weight of applying a T and an iT is given by $\mathcal{K}_{2,3} = \omega_T + \omega_{iT} + \min\{\kappa(N_1, -s) + \kappa(N_2, s), \kappa(N_1, s) + \kappa(N_2, -s)\}$ if $\deg(N) = 2$ and otherwise $\mathcal{K}_{2,3} = \infty$. If $\mathcal{S}(N) \neq s$ then $\kappa_2(N, s) = \infty$.

Three rearrangements: If $\mathcal{S}(N) \neq s$, only an application of one T and two iT can be parsimonious. Therefore, $\kappa_3(N, s) = \omega_T + 2\omega_{iT} + \kappa(N_1, -s) + \kappa(N_2, -s)$ if $\deg(N) = 2$, $\deg(N_1) > 2$, $\deg(N_2) > 2$, and $\omega_I > \omega_T + 2\omega_{iT}$ holds. Otherwise $\kappa_3(N, s) = \infty$. If $\mathcal{S}(N) = s$ then $\kappa_3(N, s) = \infty$.

The following proposition shows that it is sufficient to consider only $\kappa_0(N, s)$, …, $\kappa_3(N, s)$ for different weight values for preserving scenarios.

Proposition 3. Let $\Pi \subseteq s\mathcal{P}_n$, $\pi, \lambda \in s\mathcal{P}_n$ consistent with Π, and N be a linear node of $\mathcal{T}^{\lambda}(\pi, \Pi)$. The set of possible

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rearrangements are all rearrangements of type I, T, iT that are preserving for Π with given positive weights ω_I, ω_T, respectively ω_{iT}. Let $s \in \{+,-\}$ be a given sign. Then the total weight for a parsimonious (preserving) scenario S that transforms λ into a permutation $S \circ \lambda$ such that all nodes within the subtree with root N in $\mathcal{T}^{S\circ\lambda}(\pi,\Pi)$ are linear nodes with sign s is $\sum_{\rho\in S}\omega(\rho) = \min(\kappa_0(N,s),\kappa_2(N,s))$ if $s = \mathcal{S}(N)$ and $\sum_{\rho\in S}\omega(\rho) = \min(\kappa_1(N,s),\kappa_3(N,s))$ otherwise.

Proposition 3 can be proven by showing that all other sequences with different weights than $\kappa_i(N,s)$, $i \in [0:3]$, of successive rearrangements cannot lead to a parsimonious scenario. As an example for a scenario that cannot be parsimonious, observe that the successive application of two preserving T that act on the same linear node cannot be a subsequence of a parsimonious scenario, since they neutralize each other (see supplementary Figure S1(b)). A straightforward proof of Proposition 3 is given in the supplementary material.

Now, consider the case that N is a prime node. In this case a preserving rearrangement that acts on N can arbitrarily change the order of the child nodes of N. Therefore, the set of possibly parsimonious scenarios cannot be reduced as it is done in the linear case. To calculate $\kappa(N,s)$ a weight-minimum scenario, which may include weighted rearrangements of the type I, T, iT, and $TDRL$, for the signed quotient permutation of N and ι (respectively -ι) has to be calculated. Thereby, the signed quotient permutation of N is the quotient permutation of N where every element is assigned to either $+$ or $-$ depending of the sign of the corresponding child node of N. If a child node of N is prime (and therefore has no sign), then all possible sign combinations for this node have to be considered. Note that in this case the calculation of $\kappa(N,s)$ is an NP-hard optimization problem [7]. Algorithm `CREx2`, which is presented in the following section, solves this problem by an Integer Linear Programming.

5 Dynamic Programming Algorithm CREx2

In this section algorithm `CREx2` is presented that solves the wpGSP problem for the set $\mathcal{R}$ of rearrangements of type I, T, iT, or minimal $TDRL$ that are weighted with respect to their type and $\lambda, \pi \in s\mathcal{P}_n$.

`CREx2` is a dynamic programming algorithm that computes the weights $\kappa(N,s)$ with three different routines depending on whether a node N is a leaf, linear, or prime. For leaf nodes and linear nodes N the weights $\kappa(N,s)$ are calculated directly and the weights for prime nodes are handled with an adjusted version of algorithm `GeRe-ILP` [11]. Algorithm 1 shows the pseudocode of `CREx2`. In the following we describe how `CREx2` determines $\kappa(N,s)$ and implicitly also a corresponding scenario.

`CREx2` is called for the root node of the SIT $\mathcal{T}^{\lambda}(\pi,\{\pi,\lambda\})$. Recursive function calls (Line 3) for each child node N_i, $i \in [1:\deg(N)]$, of a node N pre-compute the necessary weights $\kappa(N_i,\pm)$. The base case of the recursion are the leaf nodes (lines 4-7). Note that in the considered rearrangement model the sign of a leaf node N can only be modified by a rearrangement of type I (Corollary 2). Hence,

Algorithm 1: Pseudocode of `CREx2` algorithm.

```
   Data: node N of T^λ(π, {π, λ})
   Result: κ(N,+), κ(N,−)
1  κ(N,+) ← ∞; κ(N,−) ← ∞;
2  for N_i ∈ {N_1, ..., N_deg(N)} do    // recursively
   compute child weights
3  |  κ(N_i,+), κ(N_i,−) ← CREx2(N_i);
4  if N is a leaf node then              // base case
5  |  κ(N, S(N)) ← 0;
6  |  κ(N, -S(N)) ← ω_I;
7  |  return (κ(N,+), κ(N,−));
8  if N is linear then                   // case linear node
9  |  κ(N, S(N)) ← min(κ_0(N, S(N)), κ_2(N, S(N)));
10 |  κ(N, -S(N)) ← min(κ_1(N, -S(N)), κ_3(N, -S(N)));
11 else                                  // case prime node
12 |  κ(N, ±) ← GeRe-ILP(π_|N, ±ι);
13 return (κ(N,+), κ(N,−))
```

for a leaf N $\kappa(N,s) = \omega_I$ if $s \neq \mathcal{S}(N)$ and $\kappa(N,s) = 0$ otherwise (see lines 5-7).

For an inner node N (lines 8-12) the value of $\kappa(N,s)$ can be computed from a parsimonious preserving scenario S that transforms N to a linear node with sign s. In addition, the weight of S plus the weight to change the signs of the child nodes of N to s (using preserving scenarios) must be minimum. The cases of a linear node N (lines 8-10) and a prime node N (lines 11-12) are handled differently by `CREx2`. This is described in more detail in the following.

Consider first the case that N is a linear node. By Proposition 3 the minimum weight $\kappa(N,s)$ for a linear node N can be computed as: $\kappa(N,s) = \min(\kappa_0(N,s),\kappa_2(N,s))$ if $s = \mathcal{S}(N)$ and $\kappa(N,s) = \min(\kappa_1(N,s),\kappa_3(N,s))$ otherwise (see lines 9-10).

Now, consider the case that N is a prime node. `CREx2` handles this case with an adjusted version of `GeRe-ILP` [11]. For given $\lambda \in s\mathcal{P}_n$, $\pi \in s\mathcal{P}_n$, and weights ω_I, ω_T, and ω_{iT}, `GeRe-ILP` calculates a parsimonious scenario for λ and π using rearrangements of types T, I, and iT. In order to be used by `CREx2`, the ILP formulation of `GeRe-ILP` has been adjusted as follows:

1) The set of rearrangements considered in `GeRe-ILP` was extended by type minimal $TDRL$. This was done by adding $\mathcal{O}(n^2)$ binary variables and $\mathcal{O}(n^3)$ constraints to the ILP formulation.
2) `GeRe-ILP` calculates $\kappa(N,s)$ and therefore it assigns signs to child nodes of N such that the signed permutation $\pi_{|N}$ can be sorted into ι if $s = +$ or into -ι if $s = -$ with a parsimonious scenario. Therefore, the values $\kappa(N_i,\pm)$ of the child nodes $N_1,\ldots,N_{\deg(N)}$ of N, which have been pre-computed by recursive function calls, are used. The objective of `GeRe-ILP` has been adjusted to find a parsimonious scenario for $\pi_{|N}$ and $\pm\iota$ and the corresponding signs.
3) In order to handle the exponential runtime behaviour of `GeRe-ILP`, a time limit $\mathcal{L}$ can be set by the user of `CREx2`. If the runtime of `GeRe-ILP` reaches $\mathcal{L}$ either the best so-far found solution is returned or, if no solution has been found, heuristic `CREx` [28] is applied to give an approximate fallback solution. In this case,

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the signs of the elements of the quotient permutation are chosen such that the sum of the weights to sort the corresponding child nodes of the prime node are minimum. Note that this choice is locally the optimal decision. However, in some cases this decision might be unfavourable. Clearly, in both cases the solution might not be exact. Note, if $\mathcal{L}$ is used the total runtime of CREx2 can exceed $\mathcal{L}$ since $\mathcal{L}$ is a runtime bound only for handling a single prime node N.

In summary, the adjusted version of GeRe-ILP computes the minimum weight $\kappa(N, s)$ for a prime node N when using rearrangements of types T, I, iT, and minimal $TDRL$ which are weighted by their type (see Line 12) (For detailed information on the adjustments of GeRe-ILP see the supplementary material).

For a runtime analysis of CREx2 let $\lambda, \pi \in s\mathcal{P}_n$ and $\mathcal{T}^{\lambda}(\pi, \{\pi, \lambda\})$ be a SIT of $\{\pi, \lambda\}$, λ, and π. By recursion, Algorithm 1 is called once for each of the at most $\mathcal{O}(n)$ nodes of $\mathcal{T}^{\lambda}(\pi, \{\pi, \lambda\})$. For a leaf node the weights $\kappa(N, \pm)$ can be computed in constant time. For linear nodes at most a small constant number of weight values are evaluated using only the given weights and the weights of the subtrees rooted at the child nodes. Therefore, in the case that the SIT is linear, only a constant amount of time is necessary per node of the SIT. Hence, the CREx2 algorithm has a runtime of $\mathcal{O}(n)$ for solving the wpGSP if the given SIT is linear. If the SIT is prime, the runtime of CREx2 is dominated by the runtime of the introduced variant of GeRe-ILP which is exponential in the worst case.

Algorithm CREx2 is implemented in C++ using Gurobi Optimizer 7.0 and is freely available from http://pacosy.informatik.uni-leipzig.de/crex2.

6 Experiments

Algorithm CREx2 has been applied to analyze the gene orders of the protein coding genes and the ribosomal RNA genes of the mitochondrial genomes of all fungi species that are available in NCBI RefSeq release 77 [31]. The gene orders were obtained with an improved version[1] of MITOS [32], which is the standard tool for gene annotation of mitochondria. All 160 obtained gene orders that contain the metazoan standard set of 13 protein coding genes and two ribosomal RNA genes were used. This data set contains 79 unique gene orders and each gene order contains exactly 15 genes. All computations were performed on a single core of an AMD Opteron 2435 with 2.6 GHz.

All 6162 (directed) pairwise comparisons between the 79 fungi gene orders were calculated by CREx2 with equally weighted rearrangements and a time limit of $\mathcal{L} = 300$ seconds. Out of the 6162 pairwise comparisons only 292 (4.7%) have a linear SIT. Within the time limit 3657 (60.97%) comparisons were solved exactly. The remaining (possibly not exact) 2505 comparisons were recomputed with $\mathcal{L} = 600$. Thereby, the results were improved for 318 comparisons and 305 of them have been solved exactly. In summary, 4280 (69.46%) of all pairwise comparisons were solved exactly using $\mathcal{L} = 600$.

1. unpublished http://mitos2.bioinf.uni-leipzig.de

In the following, we discuss the results separately for three subsets of pairwise comparisons: A) instances for which exact solutions were computed, B) instances with solutions where exactness is not guaranteed, and C) all instances.

The median runtime to compute a solution for an instance in set A, B, and C, is $62.5s$, $1405.8s$, and $505.8s$, respectively. As expected, the median runtime for set A is much smaller than the median runtime for B. Whereas the median runtime is relatively small for sets A and C, the average runtimes are $472.9s$ and $887.4s$, respectively. This indicates that both sets contain outliers with a very large runtime. The average runtime to compute a solution in set B is $1830.1s$. The supplementary Figure S2 shows box plots of the runtimes needed to compute the solutions for each of the sets A, B, and C.

Since the runtime of GeRe-ILP increases significantly with an increasing length of the scenarios, one would assume that the average number of rearrangements in the constructed scenarios is greater in set B than in set A. However, the distributions of the number of preserving rearrangements in the constructed scenarios are not substantially different, see Figure 5(a). The average number of rearrangements for instances in B (4.9) is even slightly smaller than the average number of rearrangements for instances in A (5.0). This could indicate that the fallback solutions of heuristic CREx – which are used if GeRe-ILP finds no solution – or the potentially inexact solutions returned by GeRe-ILP are actually exact or close to it. However, the fraction of $TDRL$s within the constructed scenarios is significantly higher for instances in B than for instances in A, see Figure 5(b). The relatively small average number of rearrangements for instances in B can also be explained by the high number of prime nodes, since a prime node allows the application of $TDRL$s which can mimic a sequence of transpositions.

In a second experiment the results of CREx2 on the complete data set are compared to the results of CREx. For all sets A, B, and C, Figure 6 illustrates the fractions of instances for which one of the algorithms yields a smaller, an equal, or a larger distance. The figure shows that in the 6162 pairwise comparisons (i.e., set C) the resulting distances of CREx and CREx2 are equal for 3124 (50.69%) instances, for 72 (1.16%) instances CREx provides smaller distances than CREx2, and for 2966 (48.13%) instances CREx2 provides smaller values than CREx. For instances in C, this results in an average distance of 5.6 and 4.9 for the results of CREx and CREx2, respectively. It is worth to point out that (despite the simplicity of its heuristical approach) 50.69% of the solutions obtained by CREx are exact for the given data set. Figure 7 also shows that the fraction of instances for which both algorithms generate the same solutions is twice as big in instance set B than in instance set A, which is due to the fallback procedure to use CREx for prime nodes in the case that GeRe-ILP is unable to find a solution within the time limit. Figure 7 shows box plots for the distances obtained by both algorithms for the sets A, B, C, and the set A' of all instances of A for which CREx2 found better solutions than CREx. It can be seen that the median distances for instances in C are 6 and 5 for the results of CREx and CREx2, respectively. The results of both algorithms for instances in

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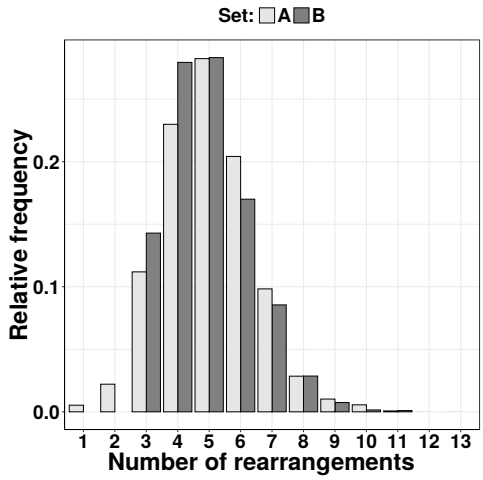
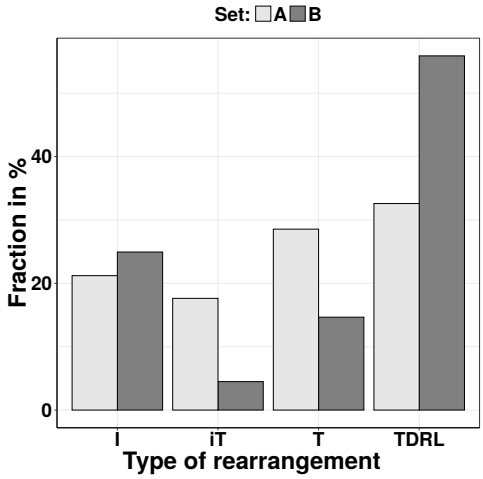


(a)



(b)

Figure 5. (a): Relative frequency of the number of preserving rearrangements used in the constructed scenarios for instances in sets A and B. (b): Fraction of the different types of rearrangements in the constructed scenarios.

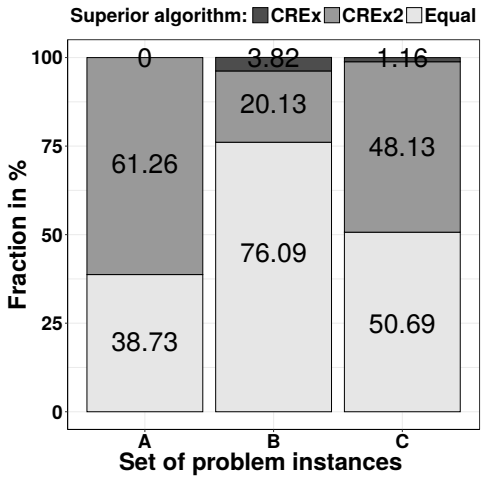


Figure 6. Fractions of problem instances in A, B, and C for which the best distance was produced either by CREx [28], CREx2, or equally by both algorithms.

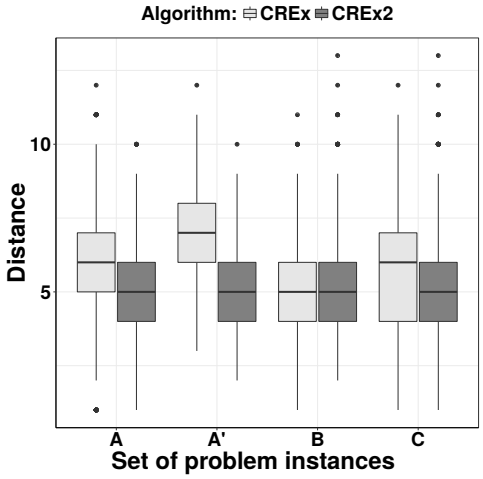


Figure 7. Distances of problem instances in A, A', B, and C that were obtained by CREx [28] and CREx2, where A' is the set of instances from A for which CREx2 produced smaller distances than CREx.

set B are almost equivalent. In particular, the box plots in Figure 7 and the fact that CREx (respectively CREx2) produces smaller distances than CREx2 (respectively CREx) in 3.82% (respectively 20.13%) of all instances in B indicate that if a result of CREx is smaller than the result of CREx2, then their difference is relatively large. However, in the case that CREx2 finds an exact solution, it is likely that the solution is smaller than the solution provided by CREx. For instances with a linear SIT the comparison showed that for 144 (49.3%) instances both algorithms obtained solutions with an equal scenario lengths and for 148 (50.7%) instances CREx2 produced shorter scenarios than CREx. For these 148 instances, the scenarios obtained by CREx2 are in average shorter by 1.44 rearrangements than the scenarios obtained by CREx. Supplementary Figure S7 illustrate the comparison of CREx and CREx2 for instances with linear SIT.

In a third experiment the phylogenetic information that can be obtained from a gene order analysis with CREx2 is investigated. In particular, it was investigated if there exists a linear correlation between the length of a scenario for two gene orders and the similarity of their gene sequences. For each pair of genomes and each protein coding gene a global alignment was computed for the corresponding two nucleotide sequences. This was done with the Biopython [33] implementation of the Needleman-Wunsch algorithm [34] (match 1, gap and mismatch 0). The result is that for set A a negative linear correlation of medium strength ($r < -0.4$) exists between the length of the scenarios and the alignment scores for the genes *atp8*, *nad4*, *nad4l*, *nad6*, *nad3*. For the remaining protein coding genes there exists a weak negative linear correlation ($-0.4 \leq r < -0.14$, p-value < 0.01), see Figure 8 and supplementary Figure S7. This shows that relevant phylogenetic information can be obtained from the lengths of the scenarios that are obtained with CREx2. For set B a weak negative linear correlation was obtained only for the *nad3* gene, see supplementary Figure S8. This could be caused by the approximative nature of the solutions, unsuitable weights, or unconsidered types of rearrangements.

CREx2 provides the possibility to weight preserving re-

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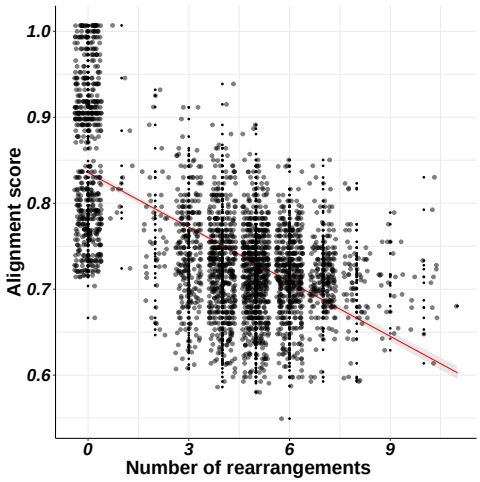
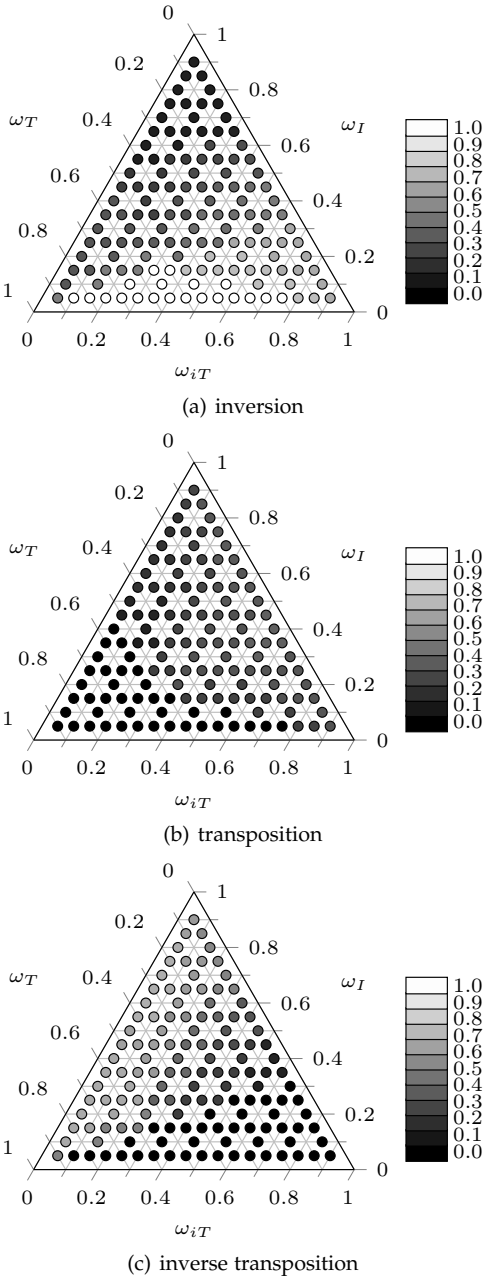


Figure 8. Normalized alignment score of the *atp8* gene for pairs of genomes and their corresponding number of rearrangements in the exact scenarios for set A. Pearson's correlation test gives a correlation coefficient of -0.61 (see regression line) within the 95% confidence interval $[-0.63, -0.58]$. A t-test shows that the linear correlation is significantly not equal to 0 with a p-value smaller than $2.2 * 10^{-16}$.

arrangements by their type. To study how the weighting influences the fraction of the different types of rearrangements in the solutions, the 146 pairwise comparisons with a linear SIT were solved with `CREx2` for different weightings. Figure 9 shows the fraction of different types of rearrangements for the tested weightings. The Figure 9(a) shows how strong a decreasing weight for inversions increases their fraction within the solutions. The fraction varies between 10% (e.g., $\omega_I = 0.9$, $\omega_T = \omega_{iT} = 0.05$) and 100% (e.g., $\omega_I = 0.1$, $\omega_T = \omega_{iT} = 0.45$). The reason why the fraction of inversions does not reach 0% for weightings with a large weight for an inversion is that only inversions can be applied to leaf nodes of the SITs. Figure 9(b) and Figure 9(c) show a smaller variability of the corresponding fractions for T and iT, respectively. In addition, Figure 9(b) shows that variability of the fraction of transpositions is smaller than for inversions and inverse transpositions. This is comprehensible, since transpositions can be applied to a linear node N only if $\deg(N) = 2$.



(a) inversion

(b) transposition

(c) inverse transposition

Figure 9. Average fraction of I (a), T (b), and iT (c) on all scenarios of comparisons with linear SIT for different weightings. Each dot denotes a weighting and its grey value the corresponding fraction of inversions.

7 Conclusion

We have considered the problem to compute parsimonious pairwise rearrangement scenarios that regard conserved gene sets that are formalized as common intervals [12]. An algorithm where weights are determined by the type of a rearrangement has been presented for I, T, iT, and (minimal) $TDRL$. The presented method is based on signed strong interval trees [19], [22] and has a (worst case) exponential runtime, but can compute an exact solution in linear runtime for problem instances where the strong interval tree is linear. Thereby a significant improvement of the heuristic algorithm `CREx` [28] is provided. An empirical evaluation of the algorithm has been conducted on fungal mitochondrial gene orders. Parsimonious rearrangement scenarios can be computed for most pairs of gene orders even if only a small fraction has a linear strong interval tree. A comparison of `CREx` and `CREx2` on fungal mitochondrial gene orders indicates that exact solutions obtained by `CREx2` are likely to improve the solutions of the `CREx` heuristic. It has been shown that exact solutions provide a valuable phylogenetic signal. Finally, it has been shown how different weightings for the types of rearrangements influence the fractions of these types in the constructed solutions.

For future work it is planned to incorporate variants of block interchange genome rearrangement [35] to `CREx2` such that tRNA remolding [36] is considered in the construction of a parsimonious scenario. Further, it is interesting to study the influence of incorporating an inverse $TDRL$ rearrangement, which is a $TDRL$ where the duplicated sequence is inverted.

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