Approximate Search for Known Gene Clusters in New Genomes Using PQ-Trees

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Abstract
We define a new problem in comparative genomics, denoted PQ-Tree Search, that takes as input a PQ-tree $T$ representing the known gene orders of a gene cluster of interest, a gene-to-gene substitution scoring function $h$, integer parameters $d_T$ and $d_S$, and a new genome $S$. The objective is to identify in $S$ approximate new instances of the gene cluster that could vary from the known gene orders by genome rearrangements that are constrained by $T$, by gene substitutions that are governed by $h$, and by gene deletions and insertions that are bounded from above by $d_T$ and $d_S$, respectively. We prove that the PQ-Tree Search problem is NP-hard and propose a parameterized algorithm that solves the optimization variant of PQ-Tree Search in $O^*(2^\gamma)$ time, where $\gamma$ is the maximum degree of a node in $T$ and $O^*$ is used to hide factors polynomial in the input size.

The algorithm is implemented as a search tool, denoted PQFinder, and applied to search for instances of chromosomal gene clusters in plasmids, within a dataset of 1,487 prokaryotic genomes. We report on 29 chromosomal gene clusters that are rearranged in plasmids, where the rearrangements are guided by the corresponding PQ-tree. One of these results, coding for a heavy metal efflux pump, is further analysed to exemplify how PQFinder can be harnessed to reveal interesting new structural variants of known gene clusters.

Availability The code for the tool as well as all the data needed to reconstruct the results are publicly available on GitHub (github.com/GaliaZim/PQFinder).

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Supplement Material github.com/GaliaZim/PQFinder

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1 Introduction

Recent advances in pyrosequencing techniques, combined with global efforts to study infectious diseases, yield huge and rapidly-growing databases of microbial genomes [38, 42]. This big new data statistically empowers genomic-context based approaches to functional analysis: the biological principle underlying such analysis is that groups of genes that appear together consistently across many genomes often code for proteins that interact with one another, suggesting a common functional association. Thus, if the functional association and annotation of the clustered genes is already known in one (or more) of the genomes, this information can be used to infer functional characterization of homologous genes that are clustered together in another genome.

Groups of genes that are co-locally conserved across many genomes are denoted gene clusters. The locations of the group of genes comprising a gene cluster in the distinct genomes are denoted instances. Gene clusters in prokaryotic genomes often correspond to (one or several) operons; those are neighbouring genes that constitute a single unit of transcription and translation. However, the order of the genes in the distinct instances of a gene cluster may not be the same.

The discovery (i.e. data-mining) of conserved gene clusters in a given set of genomes is a well studied problem [8, 21, 44]. However, with the rapid sequencing of prokaryotic genomes a new problem is inspired: Namely, given an already known gene cluster that was discovered and studied in one genomic dataset, to identify all the instances of the gene cluster in a given new genomic sequence.

One exemplary application for this problem is the search for chromosomal gene clusters in plasmids. Plasmids are circular genetic elements that are harbored by prokaryotic cells where they replicate independently from the chromosome. They can be transferred horizontally and vertically, and are considered a major driving force in prokaryotic evolution, providing mutation supply and constructing new operons with novel functions [28], for example antibiotic resistance [20]. This motivates biologists to search for chromosomal gene clusters in plasmids, and to study structural variations between the instances of the found gene clusters across the two distinct replicons. However, in addition to the fact that plasmids evolve independently from chromosomes and in a more rapid pace [14], their sequencing, assembly and annotation involves a more noisy process [29].

To accommodate all this, the proposed search approach should be an approximate one, sensitive enough to tolerate some amount of genome rearrangements: transpositions and inversions, missing and intruding genes, and classification of genes with similar function to distinct orthology groups due to sequence divergence or convergent evolution. Yet, for the sake of specificity and search efficiency, we consider confining the allowed variations by two types of biological knowledge: (1) bounding the allowed rearrangement events considered by the search, based on some grammatical model trained specifically from the known gene orders of the gene cluster, and (2) governing the gene-to-gene substitutions considered by the search by combining sequence homology with functional-annotation based semantic similarity.

(1) Bounding the allowed rearrangement events. The PQ-tree [9] is a combinatorial data structure classically used to represent gene clusters [6]. A PQ-tree of a gene cluster describes its hierarchical inner structure and the relations between instances of the cluster succinctly, aids in filtering meaningful from apparently meaningless clusters, and also gives a natural and meaningful way of visualizing complex clusters. A PQ-tree is a rooted tree with three types of nodes: P-nodes, Q-nodes and leaves. The children of a P-node can appear in any order, while the children of a Q-node must appear in either left-to-right or
Figure 1 A gene cluster containing most of the genes of the PhnCDEFGHIJKLMNOP operon [25] and the corresponding PQ-tree. The Phn operon encodes proteins that utilize phosphonate as a nutritional source of phosphorus in prokaryotes. The genes PhnCDE encode a phosphonate transporter, the genes PhnGHIJKLM encode proteins responsible for the conversion of phosphonates to phosphate, and the gene PhnF encodes a regulator. (1)-(3). The three distinct gene orders found among 47 chromosomal instances of the Phn gene cluster. (4). A PQ-tree representing the Phn gene cluster, constructed from its three known gene orders shown in 1-3. (5). An example of a Phn gene cluster instance identified by the PQ-tree shown in (4), and the one-to-one mapping between the leaves of the PQ-tree and the genes comprising the instance. The instance genes are rearranged differently from the gene orders shown in 1-3 and yet can be derived from the PQ-tree. In this mapping, gene F is substituted by gene R, gene N is an intruding gene (i.e., deleted from the instance string), and gene I is a missing gene (i.e., deleted from the PQ-tree).

An example of a PQ-tree is given in Figure 1. It represents a Phn gene cluster that encodes proteins that utilize phosphonate as a nutritional source of phosphorus in prokaryotes [25]. The biological assumptions underlying the representation of gene clusters as PQ-trees is that operons evolve via progressive merging of sub-operons, where the most basic units in this recursive operon assembly are colinearly conserved sub-operons [17]. In the case where an operon is assembled from sub-operons that are colinearly dependent, the conserved gene order could correspond, e.g., to the order in which the transcripts of these genes interact in the metabolic pathway in which they are functionally associated [43]. Thus, transposition events shuffling the order of the genes within this sub-operon could reduce its fitness. On the other hand, inversion events, in which the genes participating in this sub-operon remain colinearly ordered are accepted. This case is represented in the PQ-tree by a Q-node (marked with a rectangle). In the case where an operon is assembled from sub-operons that are not colinearly co-dependent, convergent evolution could yield various orders of the assembled components [17]. This case is represented in the PQ-tree by a P-node (marked with a circle). Learning the internal topology properties of a gene cluster from its corresponding gene orders and constructing a query PQ-tree accordingly, could empower the search to confine the allowed rearrangement operations so that colinear dependencies among genes and between sub-operons are preserved.

(2) Governing the gene-to-gene substitutions. A prerequisite for gene cluster discovery is to determine how genes relate to each other across all the genomes in the dataset. In our experiment, genes are represented by their membership in Clusters of Orthologous
Groups (COGs), where the sequence similarity of two genes belonging to the same COG serves as a proxy for homology. Despite low sequence similarity, genes belonging to two different COGs could have a similar function, which would be reflected in the functional description of the respective COGs. Using methods from natural language processing, we compute for each pair of functional descriptions a score reflecting their semantic similarity. Combining sequence and functional similarity could increase the sensitivity of the search and promote the discovery of systems with related functions.

Our Contribution and Roadmap. In this paper we define a new problem in comparative genomics, denoted \textit{PQ-Tree Search} (in Section 2), that takes as input a PQ-tree \(T\) (the query) representing the known gene orders of a gene cluster of interest, a gene-to-gene substitution scoring function \(h\), integer parameters \(d_T\) and \(d_S\), and a new genome \(S\) (the target). The objective is to identify in \(S\) a new approximate instance of the gene cluster that could vary from the known gene orders by genome rearrangements that are constrained by \(T\), by gene substitutions that are governed by \(h\), and by gene deletions and insertions that are bounded from above by \(d_T\) and \(d_S\), respectively. We prove that \textit{PQ-Tree Search} is \textit{NP}-hard (Theorem 9 in Appendix A).

We define an optimization variant of \textit{PQ-Tree Search} and propose an algorithm (in Section 3) that solves it in \(O(n \gamma d_T^2 d_S^2 (m_p \cdot 2^\gamma + m_q))\) time, where \(n\) is the length of \(S\), \(m_p\) and \(m_q\) denote the number of P-nodes and Q-nodes in \(T\), respectively, and \(\gamma\) denotes the maximum degree of a node in \(T\). In the same time and space complexities, we can also report all approximate instances of \(T\) in \(S\) and not only the optimal one.

The algorithm is implemented as a search tool, denoted PQFinder. The code for the tool as well as all the data needed to reconstruct the results are publicly available on GitHub (\texttt{github.com/GaliaZim/PQFinder}). The tool is applied to search for instances of chromosomal gene clusters in plasmids, within a dataset of 1,487 prokaryotic genomes. In our preliminary results (given in Section 5), we report on 29 chromosomal gene clusters that are rearranged in plasmids, where the rearrangements are guided by the corresponding PQ-tree. One of these results, coding for a heavy metal efflux pump, is further analysed to exemplify how PQFinder can be harnessed to reveal interesting new structural variants of known gene clusters.

Previous Related Works. Permutations on strings representing gene clusters have been studied earlier by \cite{5,15,22,32,39}. PQ-trees were previously applied in physical mapping \cite{2,10}, as well as to other comparative genomics problems \cite{3,7,24}.

In Landau et al. \cite{24} an algorithm was proposed for representation and detection of gene clusters in multiple genomes, using PQ-trees: the proposed algorithm computes a PQ-tree of \(k\) permutations of length \(n\) in \(O(kn)\) time, and it is proven that the computed PQ-tree is the one with a minimum number of possible rearrangements of its nodes while still representing all \(k\) permutations. In the same paper, the authors also present a general scheme to handle gene multiplicity and missing genes in permutations. For every character that appears \(a\) times in each of the \(k\) strings, the time complexity for the construction of the PQ-tree, according to the scheme in that paper, is multiplied by an \(O((a!)^k)\) factor.

Additional applications of PQ-trees to genomics were studied in \cite{1,4,30}, where PQ-trees were considered to represent and reconstruct ancestral genomes.

However, as far as we know, searching for approximate instances of a gene cluster that is represented as a PQ-tree, in a given new string, is a new computational problem.
2 Preliminaries

Let Π be an NP-hard problem. In the framework of Parameterized Complexity, each instance of Π is associated with a parameter k, and the goal is to confine the combinatorial explosion in the running time of an algorithm for Π to depend only on k. Formally, Π is fixed-parameter tractable (FPT) if any instance (I, k) of Π is solvable in time $f(k) \cdot |I|^{O(1)}$, where $f$ is an arbitrary computable function of $k$. Nowadays, Parameterized Complexity supplies a rich toolkit to design or refute the existence of FPT algorithms [11, 12, 13].

**PQ-Tree: Representing the Pattern.** The possible reordering of the children nodes in a PQ-tree may create many equivalent PQ-trees. Booth and Lueker [9] defined two PQ-trees $T, T'$ as equivalent (denoted $T \equiv T'$) if one tree can be obtained by legally reordering the nodes of the other; namely, randomly permuting the children of a P-node, and reversing the children of a Q-node. To allow for deletions in the PQ-trees, a generalization of their definition is given in Definition 1 below. Here, smoothing is a recursive process in which if by deleting leaves from a tree, $T$, some internal node $x$ of $T$ is left without children, then $x$ is also deleted, but its deletion is not counted (i.e. only leaf deletions are counted).

**Definition 1 (Quasi-Equivalence Between PQ-Trees).** For any two PQ-trees, $T$ and $T'$, the PQ-tree $T$ is quasi-equivalent to $T'$ with a limit $d$, denoted $T \preceq_d T'$, if $T'$ can be obtained from $T$ by (a) randomly permuting the children of some of the P-nodes of $T$, (b) reversing the children of some of the Q-nodes of $T$, and (c) deleting up to $d$ leaves from $T$ and applying the corresponding smoothing. (The order of the operations does not matter.)

Figure S5 shows two equivalent PQ-trees (Figure S5a, Figure S5b) that are each quasi-equivalent with $d = 1$ to the third PQ-tree (Figure S5c). The frontier of a PQ-tree $T$, denoted $F(T)$, is the sequence of labels on the leaves of $T$ read from left to right. For example, the frontier of the PQ-tree in Figure 4 is $CDEFMLKJIHG$. It is interesting to consider the set of frontiers of all the equivalent PQ-trees, defined in [9] as consistent frontiers and denoted by $C(T) = \{F(T') : T \equiv T'\}$. Intuitively, $C(T)$ is the set of all leaf label sequences defined by the PQ-tree structure and obtained by legally reordering its nodes. Here, we generalize the consistent frontiers definition to allow a bounded number of deletions from $T$, using quasi-equivalence.

**Definition 2 (d-Bounded Quasi-Consistent Frontiers).** $C_d(T) = \{F(T') : T \preceq_d T'\}$.

Clearly $C_0(T) = C(T)$, and so in a setting where $d = 0$ the latter notation is used. For a node $x$ of a PQ-tree $T$, the subtree of $T$ rooted in $x$ is denoted by $T(x)$, the set of leaves in $T(x)$ is denoted by $\text{leaves}(x)$, and the span of $x$ (denoted $\text{span}(x)$) is defined as $|\text{leaves}(x)|$.

**PQ-Tree Search and Related Terminology.** An instance of the PQ-Tree Search problem is a tuple $(T, S, h, d_T, d_S)$, where $T$ is a PQ-tree with $m$ leaves, $m_p$ P-nodes, $m_q$ Q-nodes and every leaf $x$ in $T$ has a label $\text{label}(x) \in \Sigma_T$; $S = \sigma_1 \ldots \sigma_n \in \Sigma_S^n$ is a string of length $n$ representing the input genome; $d_T \in \mathbb{N}$ specifies the number of allowed deletions from $T$; $d_S \in \mathbb{N}$ specifies the number of allowed deletions from $S$; and $h$ is a boolean substitution function, describing the possible substitutions between the leaf labels of $T$ and the characters of the given string, $S$. Formally, $h$ is a function that receives a pair $(\sigma_t, \sigma_s)$, where $\sigma_t \in \Sigma_T$ is one of the labels on the leaves of $T$, and $\sigma_s \in \Sigma_S$ is one of the characters of the given string, $S$, and returns True if $\sigma_t$ can be replaced with $\sigma_s$, and False, otherwise. Considering the biological problem at hand, $\Sigma_T$ and $\Sigma_S$ are both sets of genes. For $1 \leq i \leq j \leq n$,
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$S' = S[i : j] = \sigma_i...\sigma_j$ is a substring of $S$ beginning at index $i$ and ending at index $j$. The substring $S'$ is a prefix of $S$ if $S' = S[i : j]$ and it is a suffix of $S$ if $S' = S[i : n]$. In addition, we denote $\sigma_i$, the $i^{th}$ character of $S$, by $S[i]$.

The objective of PQ-Tree Search is to find a one-to-one mapping $M$ between the leaves of $T$ and the characters of a substring $S'$ of $S$, that comprises a set of pairs each having one of three forms: the substitution form, $(x, \sigma_s(\ell))$, where $x$ is a leaf in $T$, $\sigma_s \in \Sigma_S$, $h(\text{label}(x), \sigma_s) = \text{True}$ and $\ell \in \{1, \ldots , n\}$ is the index of the occurrence of $\sigma_s$ in $S$ that is mapped to the leaf $x$; the character deletion form, $(\varepsilon, \sigma_s(\ell))$, which marks the deletion of the character $\sigma_s \in \Sigma_S$ from the index $\ell$ of $S$; the leaf deletion form, $(x, \varepsilon)$, which marks the deletion of $x$, a leaf node of $T$.

To account for the number of deletions of characters of $S'$ and leaves of $T$ in $M$, the number of pairs in $M$ of the form $(x, \varepsilon)$ are marked by $\text{del}_x(M)$ and the number of pairs in $M$ of the form $(x, \varepsilon)$ are marked by $\text{del}_y(M)$. Applying the substitutions defined in $M$ to $S'$ resulting in the string $S_M$ is the process in which for every $(x, \sigma_s(\ell)) \in M$, the character $\sigma_s$ at index $\ell$ of $S$ is deleted if $x = \varepsilon$, and otherwise substituted by $x$. This process is demonstrated in Figure S6b. We say that $S'$ is derived from $T$ under $M$ with $d_T$ deletions from the tree and $d_S$ deletions from the string, if $d_T = \text{del}_x(M)$, $d_S = \text{del}_y(M)$ and $S_M \subseteq C_{d_T}(T)$. Thus, by definition, there is a PQ-tree $T'$ such that $F(T') = S_M$ and $T' \supseteq C_{d_T}(T)$. Note that the deletions of the nodes in $T$ to obtain the nodes in $T'$ are determined by $M$. The conversion of $T$ to $T'$ as defined by the derivation is illustrated in Figure S6a.

The set of permutations and node deletions performed to obtain $T'$ from $T$ together with the substitutions and deletions from $S'$ specified by $M$ is named the derivation $\mu$ of $T$ to $S'$. We also say that $M$ yields the derivation $\mu$.

For a derivation $\mu$ of $T$ to $S' = S[s : e]$, we give the following terms and notations (illustrated in Figure S6c). The root of $T$ is the node that $\mu$ derives or the root of the derivation and it is denoted by $\mu.d_T$. For abbreviation, we say that $\mu$ is a derivation of $\mu.v$. The substring $S'$ is the string that $\mu$ derives. We name $s$ and $e$ the start and end points of the derivation and denote them by $\mu.s$ and $\mu.e$, respectively. The one-to-one mapping that yields $\mu$ is denoted by $\mu.o$. The number of deletions from the tree is denoted by $\mu.del_T$. The number of deletions from the string is denoted by $\mu.del_S$. In addition, if $x$ is a leaf node in $T$ and $(x, \sigma_s(\ell)) \in \mu.o$, then $x$ is mapped to $S[\ell]$ under $\mu$. The character $S[\ell]$ is said to be deleted under $\mu$ if $(\varepsilon, \sigma_s(\ell)) \in \mu.o$. If $x \in T(\mu.v)$ is a leaf for which $(x, \varepsilon) \in \mu.o$, then $x$ is deleted under $\mu$. For an internal node of $T$, $x$, if every leaf in $T(x)$ is deleted under $\mu$, then $x$ is deleted under $\mu$, and otherwise $x$ is kept under $\mu$.

We define two versions of the PQ-Tree Search problem: a decision version (Definition 3) and an optimisation version (Definition 4).

**Definition 3 (Decision PQ-Tree Search).** Given a string $S$ of length $n$, a PQ-tree $T$ with $m$ leaves, deletion limits $d_T, d_S \in \mathbb{N}$, and a boolean substitution function $h$ between $\Sigma_S$ and $\Sigma_T$, decide if there is a one-to-one mapping $M$ that yields a derivation of $T$ to a substring $S'$ of $S$ with up to $d_T$ and up to $d_S$ deletions from $T$ and $S'$, respectively.

To define an optimization version of the PQ-Tree Search problem it is necessary to have a score for every possible substitution between the characters in $\Sigma_T$ and the characters in $\Sigma_S$. Hence, for this problem variant assume that $h$ is a substitution scoring function, that is, $h(\sigma_T, \sigma_S)$ for $\sigma_T \in \Sigma_T, \sigma_S \in \Sigma_S$ is the score for substituting $\sigma_S$ by $\sigma_T$ in the derivation, and if $\sigma_T$ cannot be substituted by $\sigma_S$, $h(\sigma_T, \sigma_S) = -\infty$. In addition, we need a cost function, denoted by $\delta$, for the deletion of a character of $S$ and for the deletion of a leaf of $T$ according to the label of the leaf. The score of a derivation $\mu$, denoted by $\mu \text{.score}$, is the sum of scores of all operations (deletions, deletions from the string and substitutions) in $\mu$. 

*Note:* $\mu.o$ denotes the operator of the derivation $\mu$. 

In the optimization version of the PQ-Tree Search problem the goal is to find the optimal derivation $\mu$ for $T$ to $S'$

Given a string $S$ of length $n$, a PQ-tree $T$ with $m$ leaves, deletion limits $d_T, d_S \in \mathbb{N}$, and a boolean substitution function $h$ between $\Sigma_S$ and $\Sigma_T$, decide if there is a one-to-one mapping $M$ that yields a derivation of $T$ to a substring $S'$ of $S$ with up to $d_T$ and up to $d_S$ deletions from $T$ and $S'$, respectively.

To define an optimization version of the PQ-Tree Search problem it is necessary to have a score for every possible substitution between the characters in $\Sigma_T$ and the characters in $\Sigma_S$. Hence, for this problem variant assume that $h$ is a substitution scoring function, that is, $h(\sigma_T, \sigma_S)$ for $\sigma_T \in \Sigma_T, \sigma_S \in \Sigma_S$ is the score for substituting $\sigma_S$ by $\sigma_T$ in the derivation, and if $\sigma_T$ cannot be substituted by $\sigma_S$, $h(\sigma_T, \sigma_S) = -\infty$. In addition, we need a cost function, denoted by $\delta$, for the deletion of a character of $S$ and for the deletion of a leaf of $T$ according to the label of the leaf. The score of a derivation $\mu$, denoted by $\mu \text{.score}$, is the sum of scores of all operations (deletions, deletions from the string and substitutions) in $\mu$. 

In the optimization version of the PQ-Tree Search problem the goal is to find the optimal derivation $\mu$ for $T$ to $S'$.
Now, instead of deciding whether there is a one-to-one mapping that yields a derivation of $T$ to a substring of $S$, we can search for the one-to-one mapping that yields the best derivation (if there exists such a derivation), i.e. a one-to-one mapping for which $\mu.\text{score}$ is the highest.

▶ **Definition 4** (Optimization PQ-Tree Search). Given a string of length $n$, $S$, a PQ-tree with $m$ leaves, $T$, deletion limits $d_T, d_S \in \mathbb{N}$, a substitution scoring function between $\Sigma_S$ and $\Sigma_T$, $h$, and a deletion cost function, $\delta$, return the one-to-one mapping, $M$, that yields the highest scoring derivation of $T$ to a substring $S'$ of $S$ with up to $d_T$ deletions from $T$ and up to $d_S$ deletions from $S'$ (if such a mapping exists).

### 3 A Parameterized Algorithm

In this section we develop a dynamic programming (DP) algorithm to solve the optimization variant of PQ-Tree Search (Definition 4). Our algorithm receives as input an instance of PQ-Tree Search $(T, S, h, d_T, d_S)$, where $h$ is a substitution scoring function as defined in Section 2. Our default assumption is that deletions are not penalized, and therefore $\delta$ is not given as input. The case where deletions are penalized is described in Appendix G. The output of the algorithm is a one-to-one mapping, $M$, that yields the best (highest scoring) derivation of $T$ to a substring of $S$ with up to $d_T$ deletions from $T$ and up to $d_S$ deletions from the substring, and the score of that derivation. With a minor modification, the output can be extended to include a one-to-one mapping for every substring of $S$ and the derivations that they yield.

Brief Overview. On a high level, our algorithm consists of three components: the main algorithm, and two other algorithms that are used as procedures by the main algorithm. Apart from an initialization phase, the crux of the main algorithm is a loop that traverses the given PQ-tree, $T$. For each internal node $x$, it calls one of the two other algorithms: P-mapping (given in Section 3.3) and Q-mapping (given in Appendix F). These algorithms find and return the best derivations from the subtree of $T$ rooted in $x$, $T(x)$, to substrings of $S$, based on the type of $x$ (P-node or Q-node). Then, the scores of the derivations are stored in the DP table.

We now give a brief informal description of the main ideas behind our P-mapping and Q-mapping algorithms. Our P-mapping algorithm is inspired by an algorithm described by Bevern et al. [40] to solve the Job Interval Selection problem. Our problem differs from theirs mainly in its control of deletions. Intuitively, in the P-mapping algorithm we consider the task at hand as a packing problem, where every child of $x$ is a set of intervals, each corresponding to a different substring. The objective is to pack non-overlapping intervals such that for every child of $x$ at most one interval is packed. Then, the algorithm greedily selects a child $x'$ of $x$ and decides either to pack one of its intervals (and which one) or to pack none (in which case $x'$ is deleted). Our Q-mapping algorithm is similar to the P-mapping algorithm, but simpler. It can be considered as an interval packing algorithm as well, however, this algorithm packs the children of $x$ in a specific order.

In the following sections, we describe the main algorithm, the P-mapping algorithm, and afterwards analyse the time complexity. The Q-mapping algorithm, which is also used as a procedure in the main algorithm, is described in Appendix F.
3.1 The Main Algorithm

We now delve into more technical details. The algorithm (whose pseudocode is given in Algorithm 2 in Appendix H) constructs a 4-dimensional DP table $A$ of size $n^3 \times n \times d_T + 1 \times d_S + 1$. The purpose of an entry of the DP table, $A[j, i, k_T, k_S]$, is to hold the highest score of a derivation of the subtree $T(x_j)$ to a substring $S'$ of $S$ starting at index $i$ with $k_T$ deletions from $T(x_j)$ and $k_S$ deletions from $S'$. If no such derivation exists, $A[j, i, k_T, k_S] = -\infty$.

Addressing $A$ with some of its indices given as dots, e.g. $A[j, i, \cdot, \cdot]$, refers to the subtable of $A$ that is comprised of all entries of $A$ whose first two indices are $j$ and $i$. Some entries of the DP table define illegal derivations, namely, derivations for which the number of deletions are inconsistent with the start index, $i$, the derived node and $S$. These entries are called invalid entries and their value is defined as $-\infty$ throughout the algorithm. A more detailed description of the invalid entries is given in Appendix F.

The main algorithm first initializes the entries of $A$ that are meant to hold scores of derivations of the leaves of $T$ to every possible substring of $S$ using the following rule. For every $0 \leq k_S \leq d_S$ and every $x_j \in \text{leaves(root)}$, do:

1. $A[j, i, 1, k_S] = 0$
2. $A[j, i, 0, k_S] = \max_{i' = i, \ldots, i + k_S} h(j, S[i'])$

Afterwards, all other entries of $A$ are filled as follows. Go over the internal nodes of $T$ in postorder. For every internal node, $x$, go in ascending order over every index, $i$, that can be a start index for the substring of $S$ derived from $T(x)$ (the possible values of $i$ are explained in the next paragraph). For every $x$ and $i$, use the algorithm for Q-mapping or P-mapping according to the type of $x$. Both algorithms receive the same input: a substring $S'$ of $S$, the node $x$, its children $x_1, \ldots, x_\gamma$, the collection of possible derivations of the children (denoted by $D$), which have already been computed and stored in $A$ (as will be explained ahead) and the deletion arguments $d_T, d_S$. Intuitively, the substring $S'$ is the longest substring of $S$ starting at index $i$ that can be derived from $T(x)$ given $d_T$ and $d_S$. After being called, both algorithms return a set of derivations of $T(x)$ to a prefix of $S' = S[i : e]$ and their scores. The set holds the highest scoring derivation for every $E(x_j, i, d_T, 0) \leq e \leq E(x_j, i, 0, d_S)$ and for every legal deletion combination $0 \leq k_T \leq d_T, 0 \leq k_S \leq d_S$.

We now explain the possible values of $i$ and the definition of $S'$ more formally. To this end, note that given the node $x$ and some numbers of deletions $k_T$ and $k_S$, the length of the derived substring is $L(x, k_T, k_S) = \text{span}(x) - k_T + k_S$ (see Appendix B). Thus, on the one hand, a substring of maximum length is obtained when there are no deletions from the tree and $d_S$ deletions from the string. Hence, $S' = S[i : E(x, i, 0, d_S)]$ where $E(x, i, k_T, k_S) = i - 1 + L(x, k_T, k_S)$. On the other hand, a shortest substring is obtained when there are $d_T$ deletions from the tree and none from the string. Then, the length of the substring is $L(x, d_T, 0) = \text{span}(x) - d_T$. Hence, the index $i$ runs between 1 and $n - (\text{span}(x) - d_T) + 1$.

We now turn to address the aforementioned input collection $D$ in more detail. Formally, it contains the best scoring derivations of every child $x_j$ of $x$ to every substring of $S'$ with up to $d_T$ and $d_S$ deletions from the tree and string, respectively. It is produced from the entries $A[j, i', k_T, k_S]$ (where each entry gives one derivation) for all $k_T$ and $k_S$, and all $i'$ between $i$ and the end index of $S'$, i.e. $i \leq i' \leq E(x_j, i, 0, d_S)$. For the efficiency of the Q-mapping and P-mapping algorithms, the derivations in $D$ are arranged in descending order with respect to their end point ($\mu\.c$). This does not increase the time complexity of the algorithm, as this ordering is received by previous calls to the Q-mapping and P-mapping algorithms.
In the final stage of the main algorithm, when the DP table is full, the score of a best derivation is the maximum of \( A[m', i, k_T, k_S] : k_T \leq d_T, k_S \leq d_S, 1 \leq i \leq n - (\text{span(root)} - k_T + 1) \) (remember that \( x_m' \) is the root of \( T \)). We remark that by tracing back through \( A \) the one-to-one mapping that yielded this derivation can be found.

3.2 P-Node and Q-Node Mapping: Terminology

Before describing the P-mapping algorithm, we set up some terminology, which is useful both for the P-mapping algorithm and the Q-mapping algorithm (in Appendix F).

We first define the notion of a partial derivation. In the Q-mapping and P-mapping algorithms, the derivation of the input node, \( x \), is built by considering subsets \( U \) of its children. With respect to such a subset \( U \), a derivation \( \mu \) of \( x \) is built as if \( x \) had only the children in \( U \), and is called a partial derivation. Formally, \( \mu \) is a partial derivation of a node \( x \) if \( \mu, v = x \) and there is a subset of children \( U' \subseteq \text{children}(x) \) such that the two following conditions are true. First, for every \( u \in U' \) all the leaves in \( T(u) \) are neither mapped nor deleted under \( \mu \) - that is, there is no mapping pair \((\ell, y) \in \mu, o \) such that \( \ell \in \text{leaves}(u) \). Second, for every \( v \in \text{children}(x) \setminus U' \) the leaves in \( T(v) \) are either mapped or deleted under \( \mu \). For every \( u \in U' \), we say that \( u \) is ignored under \( \mu \). Notice that any derivation is a partial derivation, where the set of ignored nodes \( \langle U' \rangle \) above is empty. Since all derivations that are computed in a single call to the P-mapping or Q-mapping algorithms have the same start point \( i \), it can be omitted (for brevity) from the end point function: thus, we denote \( E_i(x, k_T, k_S) = L(x, k_T, k_S) \). Then, for a set \( U \) of nodes, we define \( L(U, k_T, k_S) = \sum_{x \in U} \text{span}(x) + k_S - k_T \) and accordingly \( E_i(U, k_T, k_S) = L(U, k_T, k_S) \).

We now define certain collections of derivations with common properties (such as having the same numbers of deletions and end point).

Definition 5. The collection of all the derivations of every node \( u \in U \) to suffixes of \( S'[1 : E_i(U, k_T, k_S)] \) with exactly \( k_T \) deletions from the tree and exactly \( k_S \) deletions from the string is denoted by \( D(U, k_T, k_S) \).

Definition 6. The collection of all the best derivations from the nodes in \( U \) to suffixes of \( S'[1 : E_i(U, k_T, k_S)] \) with up to \( k_T \) deletions from the tree and up to \( k_S \) deletions from the string is denoted by \( \mathcal{D}_\leq(U, k_T, k_S) \). Specifically, for every node \( u \in U \), \( k_T' \leq k_T \) and \( k_S' \leq k_S \), the set \( \mathcal{D}_\leq(U, k_T', k_S') \) holds only one highest scoring derivation of \( u \) to a suffix of \( S'[1 : E_i(U, k_T', k_S')] \) with \( k_T' \) and \( k_S' \) deletions from the tree and string, respectively.

It is important to distinguish between these two definitions. First, the derivations in \( D(U, k_T, k_S) \) have exactly \( k_T \) and \( k_S \) deletions, while the derivations in \( \mathcal{D}_\leq(U, k_T, k_S) \) have up to \( k_T \) and \( k_S \) deletions. Second, in \( D(U, k_T, k_S) \) there can be several derivations that differ only in their score and in the one-to-one mapping that yields them, while in \( \mathcal{D}_\leq(U, k_T, k_S) \) there is only one derivation for every node \( u \in U \) and deletion combination pair \((k_T', k_S')\). Note that the end points of all of the derivations are equal.

Definition 6 is used for describing the content of an entry of the DP table, where the focus is on the collection of all the derivations of \( x \) to \( S' \) with exactly \( k_T \) and \( k_S \) deletions, \( D(\{x\}, k_T, k_S) \). For simplicity, the abbreviation \( D(u, k_T, k_S) = D(\{u\}, k_T, k_S) \) is used. In

\[ \mathcal{D}_\leq(U, k_T, k_S) = \bigcup_{u \in U} \bigcup_{k_T' \leq k_T} \bigcup_{k_S' \leq k_S} \max_{\mu, \text{score.}} \sum_{x \in U} \text{span}(x) + k_S' - k_T'. \]
every step of the P-mapping and Q-mapping algorithms, a different set of derivations of the children of \(x\) is examined, thus, Definition 6 is used for \(U \subseteq \text{children}(x)\). In addition, the set of derivations \(\mathcal{D}\) that is received as input to the algorithms can be described using Definition 6 as can be seen in Equation (1) below. In this equation, the union is over all \(U \subseteq \text{children}(x)\) because in this way the derivations of all the children of \(x\) with every possible end point are obtained (in contrast to having only \(U = \text{children}(x)\), which results in the derivations of all the children of \(x\) with the end point \(E_I(\text{children}(x), k_T, k_S)\)).

\[
\mathcal{D} = \bigcup_{U \subseteq \text{children}(x)} \bigcup_{k_T \leq d_T} \bigcup_{k_S \leq d_S} \mathcal{D}_\leq(U, k_T, k_S)
\]

In the P-mapping algorithm for \(C \subseteq \text{children}(x)\), the notation \(x^{(C)}\) is used to indicate that the node \(x\) is considered as if its only children are the nodes in \(C\). Consequently, the span of \(x^{(C)}\) is defined as \(\text{span}(x^{(C)}) = \sum_{c \in C} \text{span}(c)\), and the set \(\mathcal{D}(x^{(C)}, k_T, k_S)\) (in Definition 5 where \(U = \{x^{(C)}\}\)) now refers to a set of partial derivations.

### 3.3 P-Node Mapping: The Algorithm

Recall that the input consists of an internal P-node \(x\), a string \(S'\), limits on the number of deletions from the tree \(T\) and the string \(S'\), \(d_T\) and \(d_S\), respectively, and a set of derivations \(\mathcal{D}\) (see Equation (1)). The output is \(\bigcup_{k_T \leq d_T} \bigcup_{k_S \leq d_S} \arg \max_{\mu \in \mathcal{D}(x^{(C)}, k_T, k_S)} \mu.\text{score}\), which is the collection of the best scoring derivations of \(x\) to every possible prefix of \(S'\) having up to \(d_T\) and \(d_S\) deletions from the tree and string, respectively. Thus, there are \(O(d_T d_S)\) derivations in the output. The pseudocode of our algorithm is given in Algorithm 3 in Appendix H.

The algorithm constructs a 3-dimensional DP table \(\mathcal{P}\), which has an entry for every \(0 \leq k_T \leq d_T, 0 \leq k_S \leq d_S\) and subset \(C \subseteq \text{children}(x)\). The purpose of an entry \(\mathcal{P}[C, k_T, k_S]\) is to hold the best score of a partial derivation in \(\mathcal{D}(x^{(C)}, k_T, k_S)\), i.e. a partial derivation rooted in \(x^{(C)}\) to a prefix of \(S'\) with exactly \(k_T\) deletions from the tree and \(k_S\) deletions from the string. The children of \(x\) that are not in \(C\) are ignored (as defined in Section 3.2) under the partial derivation stored by the DP table entry \(\mathcal{P}[C, k_T, k_S]\), thus they are neither deleted nor counted in the number of deletions from the tree, \(k_T\). (They will be accounted for in the computation of other entries of \(\mathcal{P}\).) Similarly to the main algorithm, some of the entries of \(\mathcal{P}\) are invalid, and their value is defined as \(-\infty\) (for more information see Appendix F). For lack of space, the description of the initialization of \(\mathcal{P}\) is deferred to Appendix C.

After the initialization, the remaining entries of \(\mathcal{P}\) are calculated using the recursion rule in Equation (2) below. The order of computation is ascending with respect to the size of the subsets \(C\) of the children of \(x\), and for a given \(C \subseteq \text{children}(x)\), the order is ascending with respect to the number of deletions from both tree and string.

\[
\mathcal{P}[C, k_T, k_S] = \max \left\{ \mathcal{P}[C, k_T, k_S - 1] \max_{\mu \in \mathcal{D}(x^{(C)}, k_T, k_S)} \mathcal{P}[C \setminus \{\mu.\text{v}\}, k_T - \mu.\text{del}_T, k_S - \mu.\text{del}_S] + \mu.\text{score} \right\}
\]

Intuitively, every entry \(\mathcal{P}[C, k_T, k_S]\) defines some index \(i\) of \(S'\) that is the end point of every partial derivation in \(\mathcal{D}(x^{(C)}, k_T, k_S)\). Thus, \(S'[i]\) must be a part of any partial derivation \(\mu \in \mathcal{D}(x^{(C)}, k_T, k_S)\), so, either \(S'[i]\) is deleted under \(\mu\) or it is mapped under \(\mu\). The former option is captured by the first case of the recursion rule. If \(S''[i]\) is mapped under \(\mu\), then due to the hierarchical structure of \(T(x)\), it must be mapped under some derivation \(\mu'\) of one of the children of \(x\) that are in \(C\). Thus we receive the second case of the recursion rule. We remark that the case of a node deletion is captured by the initialization (further explanation can be found in Appendix D).
Once the entire DP table is filled, a derivation of maximum score for every end point and deletion number combination can be found in $P[child(x), \cdot, \cdot]$ for the output derivations to be ordered with respect to their end point, they need to be extracted by traversing $P[child(x), \cdot, \cdot]$ in the order described in Appendix F and exemplified in Table S1.

The time complexity analysis of the algorithm can be found in Appendix H.5 and the proof of correctness can be found in Appendix H.2.

### 3.4 Complexity Analysis of the Main Algorithm

In this section we compare the time complexity of the main algorithm (in Section 3.1) to the naïve solution for PQ-Tree Search. We note that the proof of correctness of the algorithm can be found in Appendix H.1. The proof of Lemma 7 below is given in Appendix H.4.

> **Lemma 7.** The algorithm in Section 3.1 runs in $O(n^{\gamma}d_T^2d_S^2(m_p2^\gamma + m_q))$ time and $O(d_Td_S(mn + 2^\gamma))$ space, where $\gamma$ is the maximum degree of a node in $T$.

Thus, it is proven that PQ-Tree Search has an FPT solution with the parameter $\gamma$ (Theorem 8).

> **Theorem 8.** PQ-Tree Search with parameter $\gamma$ is FPT. Particularly, it has an FPT algorithm that runs in $O^*(2^\gamma)$ time.

The naïve solution for PQ-Tree Search and its time complexity analysis are given in Appendix E. There we show that it solves PQ-Tree Search in $O(2^{m\gamma}!m^mn_dT + d_S)$ time. We conclude that the time complexity of our algorithm is substantially better, exemplified by considering two complementary cases. One, when there are only P-nodes in $T$ (i.e. $m = m_p$), the naïve algorithm is super-exponential in $\gamma$, and even worse, exponential in $m$, while ours is exponential only in $\gamma$, and hence polynomial for any $\gamma$ that is constant (or even logarithmic in the input size). Second, when there are only Q-nodes in $T$ (i.e. $m = m_q$), the naïve algorithm is exponential while ours is polynomial.

### 4 Methods and Datasets

**Dataset and Gene Cluster Generation.** 1,487 fully sequenced prokaryotic strains with COG ID annotations were downloaded from GenBank (NCBI; ver 10/2012). Among these strains, 471 genomes included a total of 933 plasmids.

The gene clusters were generated using the tool CSBFinder-S [36]. CSBFinder-S was applied to all the genomes in the dataset after removing their plasmids, using parameters $q = 1$ (a colinear gene cluster is required to appear in at least one genome) and $k = 0$ (no insertions are allowed in a colinear gene cluster), resulting in 595,708 colinear gene clusters. Next, ignoring strand and gene order information, colinear gene clusters that contain the exact same COGs were united to form the generalized set of gene clusters. The resulting gene clusters were then filtered to 26,270 gene clusters that appear in more than 30 genomes.

**Generation of PQ-Trees.** The generation of PQ-trees was performed using a program [19] that implements the algorithm described in [24] for the construction of a PQ-tree from a list of strings comprised from the same set of characters. In the case where a character appeared more than once in a training string, the PQ-tree with the minimum consistent

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3 The notation $O^*$ is used to hide factors polynomial in the input size.
frontier size was chosen. The generated PQ-trees varied in size and complexity. The length of their frontier ranged between 4 and 31, and the size of their consistent frontier ranged between 4 and 362,880.

Implementation and Performance. PQFinder is implemented in Java 1.8. The runs were performed on an Intel Xeon X5680 machine with 192 GB RAM. The time it took to run all plasmid genomes against one PQ-tree ranged between 5.85 seconds (for a PQ-tree with a consistent frontier of size 4) and 181.5 seconds (for a PQ-tree with a consistent frontier of size 362,880). In total it took an hour and 47 minutes to run every one of the 779 PQ-trees against every one of the 933 plasmids.

Substitution Scoring Function. The substitution scoring function reflects the distance between each pair of COGs, that is computed based on sentences describing the functional annotation of the COGs (e.g., 'ABC-type sugar transport system, ATPase component'). The "Bag of Words model" was employed, where the functional description of each COG is represented by a sparse vector that is normalized to have a unit Euclidean norm. First, each COG description was tokenized and the occurrences of tokens in each description was counted and normalized using tf–idf term weighting. Then, the cosine similarity between each two vectors was computed, resulting in similarity scores ranging between 0 and 1. The sentences describing COGs are short, therefore each word largely influences the score, even after the tf–idf term weighting. Therefore, words that do not describe protein functions that were found in the top 30 most common words in the description of all COGs were used as stop-words. Two COGs with the same COG IDs were set to have a score of 1.1, and the substitution score between a gene with no COG annotation to any other COG was set to be -0.1. Two COGs with a zero score were penalized to have a score of -0.2 and the deletion of a COG from the query or the target string was set to have a score of zero.

Enrichment Analysis. For each of the four variants in Figure 2.C, a hypergeometric test was performed to measure the enrichment of the corresponding variant in one of the classes in which it appears. A total of 10 p-values were computed and adjusted using the Bonferroni correction; two p-values were found significant (< 0.05), reported in Section 5.

Specificity Score. We define a specificity score for a PQ-tree $T$ of a gene cluster named $S$-score. Let $\hat{T}$ be the least specific PQ-tree that could have been generated for the genes of the gene cluster based on which $T$ was constructed. Namely, a PQ-tree that allows all permutations of said genes, has height 1, is rooted in a P-node whose children (being the leaves of the tree) are the leaves of $T$. Thus, the $S$-score of $T$ is $\frac{|C(\hat{T})|}{|C(T)|}$. For a gene cluster of permutations (i.e. there are no duplications), the computation of $|C(T)|$ is as described in Equation (3), where the set of P-nodes in $T$ is denoted by $T.p$.

$$|C(T)| = 2^{m_q} \cdot \prod_{x \in T.p} |\text{children}(x)|!$$  \hspace{1cm} (3)

For a gene cluster that has duplications, the set $C(T)$ is generated to learn its size. Let $a(\ell, T)$ denote the number of appearances of the label $\ell$ in the leaves of $T$ and let $\text{labels}(T)$ denote the set of all labels of the leaves of $T$. So, the formula for $|C(\hat{T})|$ is as in Equation (4). Clearly, for $T$ with no duplications $|C(\hat{T})| = |F(T)|!$.

$$|C(\hat{T})| = \frac{|F(T)|!}{\prod_{\ell \in \text{labels}(T)} a(\ell, T)!}$$  \hspace{1cm} (4)
5 Results

5.1 Chromosomal Gene Orders Rearranged in Plasmids

The labeling of each internal node of a PQ-tree as P or Q, is learned during the construction of the tree, based on some interrogation of the gene orders from which the PQ-tree is trained [24]. As a result, the set of strings that can be derived from a PQ-tree \( T \), consists of two parts: (1) all the strings representing the known gene orders from which \( T \) was constructed, and (2) additional strings, denoted tree-guided rearrangements, that do not appear in the set of gene orders constructing \( T \), but can be obtained via rearrangement operations that are constrained by \( T \). Thus, the tree-guided rearrangements conserve the internal topology properties of the gene cluster, as learned from the corresponding gene orders during the construction of \( T \), such that colinear dependencies among genes and between sub-operons are preserved in the inferred gene orders.

In this section, we used the PQ-trees constructed from chromosomal gene clusters, to examine whether tree-guided rearrangements can be found in plasmids. The objective was to discover gene orders in plasmids that abide by a PQ-tree representing a chromosomal gene cluster, and differ from all the gene orders participating in the PQ-tree’s construction. PQ-trees that are constructed from gene clusters that have only one gene order or gene clusters with less than four COGs cannot generate gene orders that differ from the ones participating in their construction. Therefore, only 779 out of 26,270 chromosomal gene clusters were used for the construction of query PQ-trees (the generation of the chromosomal gene clusters is detailed in Section 4). Using our tool PQFinder that implements the algorithm proposed for solving the PQ-Tree Search problem, the query PQ-trees were run as queries against all plasmid genomes. This benchmark was run conservatively without allowing substitutions or deletions from the PQ-tree or from the target string. 380 of the query gene clusters were found in at least one plasmid. The instances of these gene clusters in plasmids are provided in the Supplementary Materials as a session file that can be viewed using the tool CSBFinder-S [36].

Tree-guided rearrangements were found among instances of 29 gene clusters. The PQ-trees corresponding to these gene clusters were sorted by a decreasing S-score, where higher scores are given to a more specific tree (details in Section 4). In this setting, the higher the S-score, the smaller the number of possible gene orders that can be derived from the respective PQ-tree. Interestingly, 21 out of these 29 gene clusters code for transporters, namely 20 importers (ABC-type transport systems) and one exporter (efflux pump). The 10 top ranking results are presented in Table 1.

We selected the third top-ranking PQ-tree in Table 1 for further analysis. This PQ-tree was constructed from 7 gene orders of a gene cluster that encodes a heavy metal efflux pump. This gene cluster was found in the chromosomes of 79 genomes (represented by the 7 distinct gene orders mentioned above) and in the plasmids of 7 genomes. The tree-guided rearrangement instance was found in the strain Cupriavidus metallidurans CH34, isolated from an environment polluted with high concentrations of several heavy metals. This strain contains two large plasmids that confer resistance to a large number of heavy metals such as zinc, cadmium, copper, cobalt, lead, mercury, nickel and chromium. We hypothesize that the rearrangement event could have been caused by a heavy metal stress [41]. In the following section we will focus on this PQ-tree to further study its different variants in plasmids.
Approximate Search for Known Gene Clusters in New Genomes Using PQ-Trees

| PQ-tree | S-score | # Genomes | Functional Category               |
|---------|---------|-----------|-----------------------------------|
| 1       | 22.5    | 5 (2)     | Amino acid transport              |
| 2       | 10.0    | 10 (2)    | Carbohydrate transport            |
| 3       | 7.5     | 7 (1)     | Heavy metal efflux                |
| 4       | 7.5     | 1 (1)     | Carbohydrate transport            |
| 5       | 7.5     | 3 (1)     | Amino acid transport              |
| 6       | 7.5     | 9 (1)     | Metabolism                        |
| 7       | 7.5     | 6 (1)     | Carbohydrate transport            |
| 8       | 7.5     | 1 (1)     | Carbohydrate transport            |
| 9       | 7.5     | 1 (1)     | Amino acid transport              |
| 10      | 5.0     | 10 (1)    | Carbohydrate transport            |

Table 1: Ten top ranked PQ-trees for which tree-guided rearrangements were found in plasmids.

5.2 RND Efflux Pumps in Plasmids

The heavy metal efflux pump examined in the previous section (corresponding to the third top-ranking PQ-tree in Table 1), was used as a PQFinder query and re-ran against all the plasmids in our dataset in order to discover approximate instances of this gene cluster, possibly encoding remotely related variations of the efflux pump it encodes. This time, in order to increase sensitivity, a semantic substitution scoring function (described in Section 4) was used, and the parameters were set to $d_T = 1$ (up to one deletion from the tree, representing missing genes) and $d_S = 3$ (up to three deletions from the plasmid, representing intruding genes). An instance of a gene cluster is accepted if it was derived from the corresponding PQ-tree with a score that is higher than 0.75 of the highest possible score attainable by the query. The plasmid instances detected by PQFinder are displayed in Figure S7.

Heavy metal efflux pumps are involved in the resistance of bacteria to a wide range of toxic metal ions [27] and they belong to the resistance-nodulation-cell division (RND) family. In Gram-negative bacteria, RND pumps exist in a tripartite form, comprised from an outer-membrane protein (OMP), an inner membrane protein (IMP), and a periplasmic membrane fusion protein (MFP) that connects the other two proteins. In some cases, the genes of the RND pump are flanked with two regulatory genes that encode the factors of a two-component regulatory system comprising a sensor/histidine kinase (HK) and response regulator (RR) (Figure 2B). This regulatory system responds to the presence of a substrate, and consequently enhances the expression of the efflux pump genes.

The PQ-tree of this gene cluster (Figure 2A) shows that the COGs encoding the IMP and MFP proteins always appear as an adjacent pair, the OMP COG is always adjacent to this IMP-MFP pair, and the HK and RR COGs appear as a pair downstream or upstream to the other COGs. COG3696, which encodes the IMP protein, is annotated as a heavy metal efflux pump protein, while the other COGs are common to all RND efflux pumps. Therefore, it is very likely that the respective gene cluster corresponds to a heavy metal RND pump. The absence of an additional periplasmic protein likely indicates that this gene cluster encodes a Czc-like efflux pump that exports divalent metals such as the cobalt, zinc and cadmium exporter in Cupriavidus metallidurans [27] (Figure 2C(1)).
PQFinder discovered instances of this gene cluster in the plasmids of 12 genomes (Figures 2C(1) and 2D), and it is significantly enriched in the β-proteobacteria class (hypergeometric p-value = 1.09 × 10^{-5}, Bonferroni corrected p-value = 1.09 × 10^{-4}). In addition, three other variants of RND pumps were found as instances of the query gene cluster (Figure 2C(2-4)). The plasmids of three genomes contained instances that were missing the COG corresponding to the OMP gene CzcC (Figure 2C(2)). This could be caused by a low quality sequencing or assembly of these plasmids. An alternative possible explanation is that a Czc-like efflux pump can still be functional without CzcC; a previous study showed that the deletion of CzcC resulted in the loss of cadmium and cobalt resistance, but most of the zinc resistance was retained [27].

Some instances identified by the query, found in the plasmids of six genomes, seem to encode a different heavy metal efflux pump (Figure 2C(3)). This variant includes all COGs from the query, in addition to an intruding COG that encodes a periplasmic protein (CusF). This protein is a predicted copper usher that facilitates access of periplasmic copper towards the heavy metal efflux pump. Indeed, the genomic region of Cus-like efflux pumps that export monovalent metals, such as the silver and copper exporter in Escherichia coli, include this periplasmic protein, in contrast to the Czc-like efflux pump [27]. This variant was found in the plasmids of six bacterial genomes belonging to the class γ-proteobacteria (Figure 2D). This gene cluster is significantly enriched in the γ-proteobacteria class (hypergeometric p-value = 2.13 × 10^{-4}, Bonferroni corrected p-value = 2.13 × 10^{-3}). Surprisingly, all of these strains, except for one, are annotated as human or animal pathogens. Interestingly, previous studies suggest that the host immune system exploits excess copper to poison invading pathogens [18], which can explain why these pathogens evolved copper efflux pumps.

Another variant of the pump, appearing in five genomes (Figures 2C(4) and 2D), resulted from a substitution of the query IMP gene (COG3696) by a different IMP gene (COG0841) belonging to the multidrug efflux pump AcrAB/TolC. The AcrAB-TolC system, mainly studied in Escherichia coli, transports a diverse array of compounds with little chemical similarity [13]. AcrAB/TolC is an example of an intrinsic non-specific efflux pump, which is widespread in the chromosomes of Gram-negative bacteria, and likely evolved as a general response to environmental toxins [45]. In this case, the query gene cluster and the identified variant share all COGs, except for the COGs encoding the IMP genes. The differing COGs are responsible for substrate recognition, which naturally differs between the two pumps, as one pump exports heavy metal while the other exports multiple drugs. When considering the functional annotation of these two COGs, we see that the query metal efflux pump COG encoding the IMP gene is annotated as "Cu/Ag efflux pump CusA", while in the multidrug efflux pump the COG encoding the IMP gene is annotated as "Multidrug efflux pump subunit AcrB". Thus, in spite of the difference in substrate specificity, the semantic similarity measure employed by PQFinder was able to reflect their functional similarity and allowed the substitution between them, while conferring to the structure of the PQ-tree.

6 Conclusions

In this paper, we defined a new problem in comparative genomics, denoted PQ-Tree Search. The objective of PQ-Tree Search is to identify approximate new instances of a gene cluster in a new genome S. In our model, the gene cluster is represented by a PQ-tree T, and the approximate instances can vary from the known gene orders by genome rearrangements that are constrained by T, by gene substitutions that are governed by a gene-to-gene substitution scoring function h, and by gene deletions and insertions that are
A PQ-tree of a heavy metal RND efflux pump, corresponding to the third top scoring result in Table 1. B. An illustration of an RND efflux pump consisting of an outer-membrane protein (OMP), an inner membrane protein (IMP), and a periplasmic membrane fusion protein (MFP) that connects the other two proteins. In addition, a two-component regulatory system consisting of a sensor/histidine kinase (HK) and response regulator (RR) enhances the transcription of the efflux pump genes. C. Representatives of the three different RND efflux pumps found in plasmids. (1) A Czc-like heavy metal efflux pump, (2) A Czc-like heavy metal efflux pump with a missing OMP gene, (3) A Cus-like heavy metal efflux pump, (4) An Acr-like multidrug efflux pump. Additional details can be found in the text. D. The presence-absence map of the three types of efflux pumps found in the plasmids of different genomes. The rows correspond to the genomes in which instances were found, organized according to their taxonomic classes. A black cell indicates that the corresponding efflux pump is present in the plasmids of the genome. The labels below the map indicate the classes α, β, γ, δ-Proteobacteria and Acidobacteria.

bounded from above by integer parameters $d_T$ and $d_S$, respectively.

We proved that the PQ-TREE SEARCH problem is NP-hard and proposed a parameterized algorithm that solves it in $O^*(2^\gamma)$ time, where $\gamma$ is the maximum degree of a node in $T$ and $O^*$ is used to hide factors polynomial in the input size.

The proposed algorithm was implemented as a publicly available tool and harnessed to search for tree-guided rearrangements of chromosomal gene clusters in plasmids. We identified 29 chromosomal gene clusters that are rearranged in plasmids, where the rearrangements are guided by the corresponding PQ-tree. One of those gene clusters, coding for a heavy metal efflux pump, was further analysed to characterize its approximate instances in plasmids. An interesting variant of the analysed gene cluster, found among its approximate instances, corresponds to a copper efflux pump. It was found mainly in pathogenic bacteria, and likely constitutes a bacterial defense mechanism against the host immune response. These results exemplify how our tool can be harnessed to find meaningful variations of known biological systems that are conserved as gene clusters, suggesting that PQ-TREE SEARCH can be further utilized in the domain of comparative functional analysis.

One of the downsides to using PQ-trees to represent gene clusters is that very rare gene orders taken into account in the tree construction could greatly increase the number of allowed rearrangements and thus substantially lower the specificity of the PQ-tree. Thus,
a natural continuation of our research would be to increase the specificity of the model by considering a stochastic variation of PQ-Tree Search. Namely, defining a PQ-tree in which the internal nodes hold the probability of each rearrangement, and adjusting the algorithm for PQ-Tree Search accordingly. In addition, future extensions of this work could also aim to increase the sensitivity of the model by taking into account gene duplications, gene-merge and gene-split events, which are typical events in gene cluster evolution.

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\section{PQ-Tree Search is NP-Hard}

In this section we prove Theorem \ref{thm:np-hard} by describing a reduction from the Job Interval Selection problem (JISP) to PQ-Tree Search.

\begin{theorem}
\textbf{PQ-Tree Search is NP-hard.}
\end{theorem}

JISP was introduced by Nakajima and Hakimi \cite{nakajima1997approximate}. They considered one machine and a collection of non-preemptible jobs, denoted \(1, \ldots, n\), that need to be executed on that machine. Each job \(i\) has an execution time \(t_i\) and \(k_i\) possible starting times, \((s_{i1}, \ldots, s_{ik_i})\). Note that every \(t_i\) and \(s_{ij}\) define an interval on the real line: \([s_{ij}, s_{ij} + t_i]\). The aim is to allocate a starting time for each job such that no two jobs will run simultaneously on the machine. The Job Interval Selection problem (JISP) with \(k\) intervals per job was named JISP\(k\) \cite{keil1998approximate}.

Since its initial definition, the problem has seen many equivalent definitions \cite{nakajima1997approximate, crama2001approximate, crama2001approximate, lee2002approximate}. We use the following formulation for JISP\(k\) based on colors. In this setting, each job \(i\) is encoded as a \(k\)-tuple of intervals on the real line having the color \(i\). Let \(\gamma\) be the number of colors, hence there are \(\gamma\) jobs to be executed. The notation \(I^i_j\) is used to denote the interval with starting time \(s_{ij}\) finishing time \(f_{ij}\) (i.e. duration \([s_{ij}, f_{ij}]\)) and color \(1 \leq i \leq \gamma\) (i.e. it is a part of the \(i\)\)th \(k\)-tuple). The objective is to select exactly one interval of each color (\(k\)-tuple) such that no two intervals intersect.

JISP\(3\) was shown to be NP-complete by Keil \cite{keil1998approximate}. Crama et al. \cite{crama2001approximate} showed that JISP\(3\) is NP-complete even if all intervals are of length 2. We use these results to show that PQ-Tree Search is NP-hard.

\textbf{The Reduction.} Given an instance, \(J\), of JISP\(3\) where all intervals have length 2, an instance of PQ-Tree Search is created. It is easy to see that shifting all intervals by some constant does not change the problem. Hence, assume that the leftmost starting interval starts at 1. Let \(L\) be the rightmost ending point of an interval, so the focus can only be on the segment \([1, L]\) of the real line. Now, an instance of PQ-Tree Search \((T, S, h, d_T, d_S)\) is constructed (an illustrated example is given in Figure \ref{fig:reduction} below):

- **The PQ-tree \(T\):** The root node, root, is a P-node with \(3L - 2 - 3\gamma\) children: \(x_1, \ldots, x_{\gamma}\), \(y_1, \ldots, y_{3L - 2 - 3\gamma}\). The children of root are defined as follows: for every color \(1 \leq i \leq \gamma\), create a Q-node \(x_i\) with four children \(x_{i1}, x_{i2}, x_{i3}, x_{i4}\); for every index \(1 \leq i \leq 3L - 2 - 3\gamma\), create a leaf \(y_i\).

- **The string \(S\):** Define \(S = \sigma_1 \sigma_a \sigma_b \sigma_2 \sigma_a \sigma_b \ldots \sigma_3 \sigma_a \sigma_b \sigma_L\).

- **The substitution function \(h\):** for every interval of the color \(i\), \(I^i_j = [s_{ij}, f_{ij}]\), the function \(h\) returns True for the following pairs: \((x_{ij}, \sigma_a), (x_{ij}, \sigma_b), (y_{ij}, \sigma_a)\) and \((y_{ij}, \sigma_b)\). In addition, every leaf \(y_r\) can be substituted by every letter of \(S\), namely for every index \(1 \leq r \leq 3L - 2 - 3\gamma\), and for every \(s \in \{a, b, 1, \ldots, L\}\) the function \(h\) returns True for the pair \((y_r, \sigma_s)\). For every other pair \(h\) returns False. For the optimization version of the problem, define a scored substitution function \(h'\), such that \(h'(u, v) = 1\) if \(h(u, v) = True\) and \(h'(u, v) = -\infty\) if \(h(u, v) = False\).

- **Number of deletions:** Define \(d_T = 0\) and \(d_S = 0\), i.e. deletions are forbidden from both tree and string.

An example of the reduction is shown in Figure \ref{fig:reduction}. A collection of two \(3\)-tuples (one blue and one red) where each interval is of length 2, i.e. a JISP\(3\) instance, is in Figure \ref{fig:reduction(a)}. Running the reduction algorithm yields the PQ-Tree Search instance in Figure \ref{fig:reduction(b)}. The pairs that can be substituted (i.e. the pairs for which \(h\) returns True) are given by the lines connecting the leaves of the PQ-tree and the letters of the string \(S\). The nodes and
substitutable pairs created due to the blue and red intervals in the JISP3 instance are marked in blue and red, respectively. The substitutable pairs containing a y node are marked in gray. Note that the colors given in Figure S1b are not a part of the PQ-Tree Search instance, and are given for convenience.

Correctness. Let $J$ be an instance of JISP3, and let $(T, S, h, d_T, d_S)$ be the output of the reduction on this instance. We prove that there exists a collection of intervals that is a solution for $J$ if and only if there exists a one-to-one mapping that is a solution to $(T, S, h, d_T, d_S)$.

One Direction. Suppose that there exists a solution to the output instance of PQ-Tree Search of the reduction, $(T, S, h, d_T, d_S)$. This solution is a one-to-one mapping $M$: for every $1 \leq i \leq \gamma$, a set of pairs of the form $(x^i_j, \sigma_k(\ell))$ for $j \in \{s, f, a, b\}$, and for every $1 \leq r \leq 3L - 2 - 3\gamma$, pairs of the form $(y_r, \sigma_k(\ell))$ where $k \in \{1, \ldots, L, a, b\}$ and $1 \leq \ell \leq 3L - 2$.

By the definition of PQ-Tree Search, each $x^i_j$, $y_r$ and $\sigma_k(\ell)$ appear in exactly one pair. Considering the mappings of the children of a node $x_i$, they must be the following: $(x'^i_s, \sigma(\ell))$, $(x'^i_a, \sigma(\ell + 1))$, $(x'^i_b, \sigma(\ell + 2))$ and $(x'^i_f, \sigma_{k+1}(\ell + 3))$. To see this, observe that a node $x'^i_a$ must be mapped to $\sigma_a$, because it is the only letter by which it can be substituted under $h$. In the same way, a node $x'^i_b$ must be mapped to $\sigma_b$. Because $d_T = 0$, $d_S = 0$ and due to the properties of a Q-node, once $x'^i_a$ is mapped to the letter in index $\ell$ (i.e. $(x'^i_a, \sigma(\ell)) \in M$), $x'^i_b$ must be mapped to the letter in index $\ell + 1$ or in index $\ell - 1$ (i.e. the adjacent letter to the one to which $x'^i_a$ is mapped), then $x'^i_a$ must be mapped to the letter in index $\ell + 2$ or $\ell - 2$, respectively, and $x'^i_b$ to $\ell + 3$ or $\ell - 3$, respectively. Since $\sigma_a$ is always the letter preceding $\sigma_b$ in $S$, $x'^i_b$ must be mapped to an index larger by one than the index mapped to $x'^i_a$. Hence, the children of the Q-node $x_i$ are mapped from left to right.

Now, let us derive a solution for the original JISP3 instance from the solution to PQ-
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**Tree Search.** For every 3-tuple of color 1 ≤ i ≤ γ, where (x_i, σ_i(ℓ)) ∈ M, choose the interval I_i = [k, k + 1] from the 3-tuple of color i. For example, if a part of the solution for the PQ-TREE SEARCH instance in Figure S1b is \{(x_1, σ_1(1)), (x_2, σ_2(2)), (x_3, σ_3(3))\} ⊂ M, then I_1 is the interval chosen for the first color (blue) in the derived solution for the JISP3 instance in Figure S1a. Note that I_k is indeed one of the intervals of color i, due to the definition of h, h(x_i, σ_k) = True and h(x_i, σ_{k+1}) = False if only if there is an interval of color i starting at k and ending at k + 1. Thanks to M being a one-to-one mapping, the intervals do not intersect, and for every color there is only one interval chosen.

**Second Direction.** Let us prove that if there is a solution for the original instance of JISP3 J, then there is a solution for (T, S, h, d_T, d_S). Let I = \{I_{j_1}, ..., I_{j_N}\} be a solution of J such that I_{j_1} = [s_{j_1}, f_{j_1}] is the interval chosen for the 3-tuple of color i. First, the solution for the PQ-TREE SEARCH instance (T, S, h, d_T, d_S) is constructed. For every 1 ≤ i ≤ γ, insert the following pairs into M: (x_i, σ_{s_{j_i}}(3s_{j_i} - 2)), (x_i, σ_{s_{j_i}}(3s_{j_i} - 1)), (x_i, σ_{s_{j_i}}(3s_{j_i})), and (x_i, σ_{f_{j_i}}(3f_{j_i} - 2)). For example, if I_2 is the interval chosen from the second (red) 3-tuple in the solution of the JISP3 instance in Figure S1a, then the solution for the PQ-TREE SEARCH instance in Figure S1b includes the pairs \{(x_1, σ_2(4)), (x_2, σ_2(5)), (x_3, σ_3(6)), (x_4, σ_3(7))\}. Observe that only one pair was inserted for every leaf of T, and since no two intervals intersect, every index of S appears in only one pair in M. Hence, a one-to-one mapping between 4γ leaves of T and 4γ indices of S was defined, and 3L - 4γ - 2 additional pairs need to be inserted to M in order to construct a solution for the PQ-TREE SEARCH instance. According to h, every node y_r (1 ≤ r ≤ 3L - 2 - 3γ) can be mapped to every letter σ_k, so arbitrarily insert the pairs (y_r, σ_k(ℓ_r)) to M, such that no index or node appear in more than one pair. (It can be done because there are 3L - 4γ - 2 y nodes and after mapping the 4 children of every one of the γ x_i nodes, 3L - 4γ - 2 characters of S are left without a mapping). Thus, a one-to-one mapping M between all the leaves of T and all the indices of S (i.e. no deletions from S and T) was defined, and it is left to prove that S can be derived from T under M.

The children of a Q-node x_i from left to right are: x_i, x_{i+1}, x_{i+2}, x_{i+3}, and so, because d_T = 0 and d_S = 0 (no deletions from both tree and string), they have to be mapped to consecutive indices of S; this is indeed the case according to our definition of M. The mapping of every y_r is obviously also legal. Finally, root is a P-node, so its children can be arranged in any order, and they are. This completes the proof of correctness of the reduction. ▶

This concludes the proof of Theorem 9

**The Importance of σ_a and σ_b in the Reduction.** In the reduction from JISP3 to PQ-TREE SEARCH the string S was defined such that there is a character σ_i for every 1 ≤ i ≤ L, and between every two such characters there is the sequence σ_aσ_b, i.e. S = σ_1σ_2σ_3...σ_{L-1}σ_L. In addition the PQ-tree T and the substitution function h were defined such that for every color i (1 ≤ i ≤ γ), there are the leaves x_i and x_i in T and h returns True for both (x_i, σ_a) and (x_i, σ_b). For abbreviation these leaves, the multiple appearances of σ_aσ_b in S and the allowed substitutions between them are named ab addition. Here we explain why the ab addition is important.

The necessity arises when considering the first direction of the reduction, i.e. if there exists a solution to the output instance of PQ-TREE SEARCH of the reduction (T, S, h, d_T, d_S), then there is a solution to the JISP3 instance J. Consider the partial instance of JISP3
in Figure S2a. Note that it does not have a solution. Applying a reduction similar to the one defined above but without \textit{ab addition}, results in the \textbf{PQ-Tree Search} instance $(T,S,h,d_S)$ in Figure S2b. The mapping lines in bold in Figure S2b are a solution for that instance.

This contradiction arises because Q-node children can also be ordered from right to left. With \textit{ab addition} a \textbf{PQ-Tree Search} instance is created for which only a left-to-right ordering of the children of a Q-node $x_i$ can be a part of a possible solution. The definition of $h$ dictates that in $\mathcal{M}$ every $x_i^\ell$ will be mapped to a $\sigma_a(j_i)$ and every $x_i^\ell$ will be mapped to a $\sigma_b(\ell_i)$. Because there are no deletions allowed and because of the possible reordering of the children of a Q-node, either $\ell_i = j_i + 1$ (left-to-right) or $\ell_i = j_i - 1$ (right-to-left). In $S$ the character $\sigma_a$ is always to the left of $\sigma_b$, hence there are no indices $j, \ell$ such that $\ell = j - 1$, $S[j] = a$ and $S[\ell] = b$. So, for every $1 \leq i \leq \gamma$, $\ell_i = j_i + 1$. This means that the children of a Q-node $x_i$ are ordered form left to right as needed.

\section*{B The Length of the Derived String}

Given a node $x$ and the numbers of deletions, $k_T$ and $k_S$, the length of $S'$, the string derived from $T(x)$, can be calculated. If there were no deletions, the length of $S'$ is equal to the span of $x$, because every leaf of $T(x)$ is mapped to exactly one character of $S$ (see Figure S3a). Consider the case in which there is one deletion from the tree (Figure S3b). Every one of the leaves in $T(x)$ is mapped to one character of $S$ except for the deleted leaf which is not mapped to any character. So, in this case the derivation is to a substring of length $\text{span}(x) - 1$. In general, if there are $k_T$ deletions from the tree (and none from the string), then the length of the substring derived from $T(x)$ is $\text{span}(x) - k_T$. Now, consider the case in which there is one deletion from the string (Figure S3c). There are $\text{span}(x)$ characters of $S$ that are mapped to the leaves of $T(x)$. One more character is a part of the derived substring, but it is not mapped to any of its leaves. So, in this case $T(x)$ is derived to a substring of length $\text{span}(x) + 1$. In general, if there are $k_S$ deletions from the string (and
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(a) No deletions derives a string of length 3 which is equal to \( \text{span}(x) \).

(b) One deletion from the tree \((x_2)\) derives a string of length 2 which is equal to \( \text{span}(x) - 1 \).

(c) One deletion from the string \((\sigma_3)\) derives a string of length 4 which is equal to \( \text{span}(x) + 1 \).

(d) One deletion from the string \((\sigma_3)\) and one from the tree \((x_2)\) derives a string of length 3 which is equal to \( \text{span}(x) \).

\[ \text{Figure S3} \] An example of the effect the number of deletion from the tree and string have on the length of the derived string. In this example the node, \( x \), has a span of 3 and the one-to-one mapping between the children of \( x \) and the characters of the string are denoted by dotted lines.

none from the tree), the length of the substring derived from \( T(x) \) is \( \text{span}(x) + k_S \). Thus, the definition of the length function \( L(x, k_T, k_S) \).

C. The Initialization of the DP Table in the P-Mapping Algorithm

The P-mapping algorithm initializes \( P \) using the following two rules:

1. If \( L(C, k_T, k_S) = 0 \) and \( k_S = 0 \), then \( P[C, k_T, k_S] = 0 \).
2. If \( C = \emptyset \) and \( k_T = 0 \), then \( P[\emptyset, k_T, k_S] = 0 \).

The first rule refers to a case where \( L(C, k_T, k_S) = 0 \), which means that the derived substring is the empty string and thus no character can be deleted from it; hence, \( k_S \) must equal 0 (and any other value of \( k_S \) is invalid). From the definition of \( L(C, k_T, k_S) \), if \( L(C, k_T, 0) = 0 \), then \( k_T = \sum_{x \in C} \text{span}(x) \), i.e. all nodes \( x \in C \) are deleted. So, the score in \( P[C, k_T, k_S] \) is 0.

The second rule refers to a case where \( C = \emptyset \), i.e. all children of \( x \) are ignored. Similarly to the first rule, a value for \( k_T \) other than 0 is invalid, and will have a \(-\infty\) value. From the definition of \( L \), if \( k_T = 0 \), then \( L(\emptyset, 0, k_S) = k_S \), so all characters from the substring are deleted, and the score is 0.

D. Deleting a Child of a P-Node

In the P-mapping algorithm (Section 3.3) it was claimed that there is no need to add to the recursion rule (Equation 2) a third case for the deletion of a child of the input node, \( x \), because that case is captured in the initialization rules. In the following example it is shown that the first initialization rule (given in Appendix C) is enough to enable the algorithm to find the best derivation even if it includes a node deletion, and that adding the option of deleting a node in the recursion rule is therefore redundant. Consider the P-node \( x \) in Figure S4, which
Then, find the index $i$. Thus, the outline of the naïve algorithm is as follows. For every string with up to $d$ deletions from $S$, it is possible to search for an alignment between every substring of $S$ and every substring of $T$. One way to solve the problem is to go over every string in $C_d(T)$ and try to find an alignment between it and every substring of $S$, when only $d$ deletions are allowed from $S$. Equivalently, it is possible to search for an alignment between every substring of $S$ and every string $S_T \in C_m(T)$ with up to $d$ deletions from $S$ and up to $d_T$ deletions from $S_T$.

Naturally, sequence alignment can be used, but in order to bound the number of deletions, the basic algorithm needs to be modified. The usual 2-dimensional DP-table needs to be extended with two additional dimensions that correspond to the numbers of deletions from $S$ and $S_T$. This way, when filling the table, the best scoring alignment considered so far for every deletion numbers combination can be stored. At the end of the algorithm, the score of the best alignment is the maximum between the entries of the DP-table corresponding to an alignment between $S_T$ and a prefix of $S$ that has a length between $m - d_T$ and $m + d_S$. Thus, the outline of the naïve algorithm is as follows. For every string $S_T \in C_m(T)$ and every possible start index $i$, preform sequence alignment with a bounded number of deletions. Then, find the index $i$ that resulted in the highest scoring alignment.

The size of the DP table is $O(m(m + d_S)d_Td_S)$, but in the first two dimensions only a

### A Comparison with the Naïve Solution

In this section a naïve, alternative, algorithm for the PQ-Tree Search problem is described and its time complexity is analyzed. It is shown that the time complexity of our algorithm is substantially smaller than that of the naïve algorithm.

Solving the PQ-Tree Search problem requires a search for a one-to-one mapping that yields a derivation of a PQ-tree $T$ to a substring of the input string $S$. That is, a substring $S'$ of $S$, such that the deletion of up to $d$ characters from $S'$ and the substitution of some of its characters yields a new string $S'' \in C_{d}(T)$ (see Definition 2). Hence, a naïve way to solve the problem is to go over every string in $C_{d}(T)$ and try to find an alignment between it and every substring of $S$, when only $d$ deletions are allowed from $S$. Equivalently, it is possible to search for an alignment between every substring of $S$ and every string $S_{T} \in C_{m}(T)$ with up to $d$ deletions from $S$ and up to $d_T$ deletions from $S_T$.

Naturally, sequence alignment can be used, but in order to bound the number of deletions, the basic algorithm needs to be modified. The usual 2-dimensional DP-table needs to be extended with two additional dimensions that correspond to the numbers of deletions from $S$ and $S_T$. This way, when filling the table, the best scoring alignment considered so far for every deletion numbers combination can be stored. At the end of the algorithm, the score of the best alignment is the maximum between the entries of the DP-table corresponding to an alignment between $S_T$ and a prefix of $S$ that has a length between $m - d_T$ and $m + d_S$. Thus, the outline of the naïve algorithm is as follows. For every string $S_T \in C_m(T)$ and every possible start index $i$, perform sequence alignment with a bounded number of deletions. Then, find the index $i$ that resulted in the highest scoring alignment.

The size of the DP table is $O(m(m + d_S)d_Td_S)$, but in the first two dimensions only a

![Figure S4](image-url) A P-node $x$ with three leaf children $x_1$, $x_2$, and $x_3$. The only derivations of the children of $x$ that have a score different than $-\infty$ are depicted in dashed lines.
diagonal with a width of $O(d_T + d_S)$ entries needs to be computed. The computation of each entry takes $O(1)$ time and finding the best alignment takes $O(d_T d_S)$. Thus, every run of the sequence alignment with a bounded number of deletions and a specific start index $i$ takes $O(m(d_T + d_S)d_T d_S)$ time. As seen in Section 3.3 there are $O(n)$ possible values for $i$.

Finally, let us bound the number of strings in $C(T)$ which is equal to the number of PQ-trees that are equivalent to $T$. By definition, every legal permutation of the children of an internal node of $T$ results in a new PQ-tree $T'$ that is equivalent to $T$, i.e. $T = T'$ (equivalence and not quasi-equivalence is used here because $C_0(T)$ is considered, i.e. there are no deletions from the tree). The children of a Q-node can be permuted only in one of two ways (left-to-right or right-to-left) and the children of a P-node can be arranged in any order. So, for an internal node $x$ of $T$, for every string resulting from the rearrangement of the children of all the other nodes in $T$, $x$ contributes 2 strings to $C(T)$ if it is a Q-node, and $\gamma!$ strings if it is a P-node. Thus, $|C(T)| = O(2^{m_x} (\gamma!)^{m_x})$. In total, the naïve solution for PQ-Tree Search takes $O(2^{m_x} (\gamma!)^{m_x} nm (d_T + d_S)d_T d_S)$ time.

Both algorithms have a factor of $O(nd_T d_S)$, so it can be ignored and more concise time complexities can be compared: the naïve $O(2^{m_x} (\gamma!)^{m_x} m (d_T + d_S))$ versus our $O(d_T d_S (m_p \gamma 2^\gamma + m_q \gamma))$. In both algorithms the non-polynomial factors in the time complexity are dependent on the number of P-nodes and the number of Q-nodes, so let us consider two complementary cases. First, assume there are only P-nodes in the PQ-tree (i.e. $m = m_p$). In this case, the naïve algorithm has a $(\gamma!)^{m_x} = 2^{O(\gamma \log \gamma)}$ factor, which is super-exponential in $\gamma$, and even worse, exponential in $m$, while our algorithm has a $m_p \gamma 2^\gamma = m \gamma 2^\gamma$ factor which is exponential only in $\gamma$, and in particular polynomial for any $\gamma$ that is constant (or even logarithmic in the input size). Second, assume there are only Q-nodes in the PQ-tree (i.e. $m = m_q$). In this case, the naïve algorithm has a $2^{m_x} = 2^m$ factor, which is exponential and our algorithm has a $m_q \gamma = m \gamma$ factor, which is polynomial.

## F Q-Node Mapping

In this section we describe the Q-mapping algorithm called by the main algorithm described in Section 3.1.

**Objective.** As already mentioned in Section 3 the Q-mapping algorithm receives the following as input.

1. An internal node $x$ that is a Q-node and has $\gamma$ children: $x_1, \ldots, x_\gamma$.
2. A string $S'$ (which is a substring of the original $S$).
3. A collection of derivations $D$ of the children of $x$ to substrings of $S'$. The derivations are grouped by their root nodes $\mu, \nu$, and ordered by their end points, $\mu, \nu.e$.
4. The maximum number of deletions from the tree and string, $d_T$ and $d_S$, respectively.

The output of the algorithm is the set \( \bigcup_{k_T \leq d_T} \bigcup_{k_S \leq d_S} \max_{e \in \mathcal{D}(x, k_T, k_S)} \mu.score \), which is a set of derivations of $x$ to prefixes of $S'$. The set holds the best scoring derivation for every possible deletion number combination $k_T, k_S$ where $0 \leq k_T \leq d_T$ and $0 \leq k_S \leq d_S$. The set is ordered by the end points of the derivations and it is of size $O(d_T d_S)$. Note that the input and output of this algorithm is the same as the input and output of the P-mapping algorithm (Section 3.3), except for the type of the node received as input.

As a start, a solution assuming that the children of the Q-node $x$ can only be arranged in a left-to-right order is demonstrated. The fact that they can also be arranged in a right-to-left order is addressed at the end of this section. The Q-mapping algorithm is a DP algorithm
that uses a 3-dimensional DP table, \( Q \). The pseudocode of our algorithm can be found in Algorithm 4 ahead.

**Notations.** At different stages of the algorithm the node \( x \) is considered as if it has only its first \( i \) children. For an index \( i \) such that \( 1 \leq i \leq \gamma \) (namely, \( i \) is an index of a child of \( x \)), two definitions are given. The first, \( x[i] \), denotes the set of the first \( i \) children of \( x \). Formally, \( x[i] = \{ x_1, \ldots, x_i \} \). The second, \( x^{(i)} \), denotes the node \( x \) considering only its children in \( x[i] \). Consequentially, the span of \( x^{(i)} \) is defined as \( \sum_{j=1}^{i} \text{span}(x_j) \) and the set \( D(x^{(i)}, k_T, k_S) \) (in Definition 5 where \( U = \{ x^{(i)} \} \) now refers to a set of partial derivations. To use \( x^{(i)} \) to describe the base cases of our algorithm, let us define \( x^{(0)} \) (\( x^{(i)} \) for \( i = 0 \)) as a tree with no labeled leaves to map.

**The DP Table.** The purpose of an entry \( Q[i, k_T, k_S] \) is to hold the score of the best partial derivation of \( x^{(i)} \) to a prefix of \( S' \) with exactly \( k_T \) deletions from the tree and exactly \( k_S \) deletions from the string. Namely, only the first \( i \) children of \( x, x_1, \ldots, x_i \), are considered and the rest are ignored. The other children of \( x \), that is \( \text{children}(x) \setminus x[i] \), are accounted for in the computation of other entries of \( Q \). Formally, \( Q[i, k_T, k_S] = \max_{\mu \in D(x^{(i)}, k_T, k_S)} \mu\text{.score} \).

Similarly to the main algorithm (Section 3.1) and the P-mapping algorithm (Section 3.3), some of the entries of the DP table are invalid, and their value is defined as \(-\infty\) throughout the algorithm. Here we give a more detailed description of these entries for all three algorithms and their DP tables. For a given DP table, the invalid entries are the ones that their indices define an illegal derivation. Namely, derivations that have more deletions from the tree than there are leaves in the subtree of \( T \) rooted in the derived node, derivations that have more deletions from the string than there are characters in the derived string, derivations that derive a string that by definition ends in an index larger than the end index of the input string, or derivations that by definition derive a string with a negative length. Thus, an entry \( Q[i, k_T, k_S] \) is invalid if one of the following is true: \( k_T > \sum_{c \in x[i]} \text{span}(c), k_S > L(x[i], k_T, k_S), L(x[i], k_T, k_S) > \text{len}(S'), \) or \( L(x[i], k_T, k_S) < 0 \). Similarly, an entry \( P[C, k_T, k_S] \) is invalid if one of the following is true: \( k_T > \sum_{c \in C} \text{span}(c), k_S > L(C, k_T, k_S), L(C, k_T, k_S) > \text{len}(S'), \) or \( L(C, k_T, k_S) < 0 \). Lastly, an entry \( A[j, i, k_T, k_S] \) is invalid if one of the following is true: \( k_T > \text{span}(x_j), k_S > L(j, i, k_T, k_S), E(j, i, k_S, k_T) > n, \) or \( L(j, i, k_T, k_S) < 0 \).

**Filling the DP Table.** The algorithm initializes \( Q \) as follows. For every \( 0 \leq k_S \leq \text{len}(S') \), \( Q[0, 0, k_S] = 0 \). These entries of the DP table capture the cases in which a prefix of \( S' \) of length \( L(0, 0, k_S) = k_S \) is derived, i.e. there are no leaves to map. Thus, all the characters in \( S'[1 : k_S] \) must be deleted under this partial derivation. This is possible because the allowed number of deletions from the string is exactly the number of characters in the derived substring. Note that \( k_S \leq \text{len}(S') \) because otherwise \( Q[0, 0, k_S] \) is an invalid entry and its value should remain \(-\infty\).

Afterwards, the remaining entries of \( Q \) are calculated using the recursion rule in Equation 5 ahead. The order of computation is ascending with respect to \( i \) (i.e. \( i = 1, \ldots, \gamma \)), for a given \( i \), the order of computation is ascending with respect to the number of deletions from the string (i.e. \( k_S = 0, 1, \ldots, d_S \)), and for a given \( i \) and \( k_S \), the order of computation does not matter. Nonetheless, an ascending order with respect to the number of deletions
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from the tree (i.e. $kT = 0, 1, \ldots, dt$) is set.

$$Q[i, kT, kS] = \max \begin{cases} Q[i, kT, kS - 1] \\ Q[i - 1, kT - \text{span}(x_i), kS] \\ \max_{\mu \in D_{<}(x_i), kS} Q[i - 1, kT - \mu.delT, kS - \mu.delS] + \mu.score \end{cases}$$

The intuition behind Equation (5) is that given a partial derivation, $\mu \in D(x^{(i)}, kT, kS)$, one of the three cases of the rule must be true. The end point of $\mu$ is $E_I(x[i], kT, kS)$, and thus, by definition, $S'[E_I(x[i], kT, kS)]$ is either deleted under $\mu$ (the first case) or it is mapped under $\mu$ (the third case). The partial derivation $\mu$ does not ignore $x_i$, so either it is kept under $\mu$ (the third case), or it is deleted under $\mu$ (the second case).

In the first case, $S'[E_I(x[i], kT, kS)]$ is deleted under $\mu$. Removing the deletion of $S'[E_I(x[i], kT, kS)]$ from $\mu$ (formally defined in Definition 14) results in a partial derivation, $\mu'$, that considers the same set of children of $x$ with the same number of deletions from the tree and one less deletion from the string. That is, $\mu' \in D(x^{(i)}, kT, kS - 1)$, and the score of the best partial derivation with the same properties as $\mu'$ is in $Q[i, kT, kS - 1]$.

In the second case, $x_i$ is deleted under $\mu$. Removing the deletion of $x_i$ from $\mu$ (formally defined in Definition 14) results in a partial derivation of $x^{(i-1)}$ with $kT - \text{span}(x_i)$ deletions from the tree. That is, a derivation in $D(x[i-1], kT - \text{span}(x_i), kS)$, and the score of the best one is in $Q[i - 1, kT - \text{span}(x_i), kS]$. In the third case there is a derivation, $\mu'$, of one of the children of $x^{(i)}$ such that $S'[E_I(x[i], kT, kS)]$ is mapped under it. Because $x_i$ is kept under $\mu$ (in derivation this entry holds) and it is the last child of $x^{(i)}$, then $\mu'$ is a derivation of $x_i$ (i.e. $\mu'.n = x_i$). Otherwise, the ordering of the children of the Q-node $x$ is illegal.

The score of $\mu$ in this case is equal to the score of $\mu'$ plus the score of a partial derivation of $x^{(i-1)}$ with $kT - \mu'.delT$ and $kS - \mu'.delS$ deletions from the tree and string, respectively. The best score of a partial derivation in $D(x^{(i-1)}, kT - \mu'.delT, kS - \mu'.delS)$ is in $Q[i - 1, kT - \mu'.delT, kS - \mu'.delS]$. Thus we try to find the derivation, $\mu'$, of $x_i$ with the end point $E_I(x[i], kT, kS)$ that maximises $\mu'.score + Q[i - 1, kT - \mu'.delT, kS - \mu'.delS]$.

Finding the Solution. Our goal is to find a derivation of $x$ according to all of its children, hence once the entire DP table is filled our solution is in $Q[\gamma, \cdot, \cdot]$. The best derivation for every deletion combination should be ordered with respect to the end point of the derivation. Here we explain how this can be done by simply traversing $Q$ in a predefined order and without any further calculation. First, note that there could be more than one derivation per end point. For example, the second smallest end point (the end point of the second shortest substring derived from $x$) is generated by the deletion combination $(d_T, 1)$, thereby $e = E_I(\gamma, d_T, 1) = \sum_{k=1}^{d_T} \text{span}(x_k) - d_T + 1 = \text{span}(x) - d_T + 1$. The deletion combination $(d_T - 1, 0)$ also yields $e$, $E_I(\gamma, d_T - 1, 0) = \sum_{k=1}^{d_T - 1} \text{span}(x_k) - (d_T - 1) + 0 = \text{span}(x) - d_T + 1 = e$. In fact, only the smallest and largest end points have just one derivation each. The deletion combination $(d_T, 0)$ yields the smallest end point and $(0, d_S)$ yields the largest. Thus, given the $(d_T + 1) \times (d_S + 1)$ sized table $Q[\gamma, \cdot, \cdot]$, the ordered list of derivations can be generated by traversing the table in the order specified in Table 1.

A Second Ordering of the Children. Previously an algorithm to find a one-to-one mapping for a tree rooted in a Q-node assuming its children can only be arranged in a left-to-right order was described. To consider also a right-to-left arrangement, the following minor modification to the algorithm is required. Run the first two parts of the algorithm described above twice,
An example of the ordering between the end points induced by the different deletion combinations. In this example, $d_T = 3$, $d_S = 2$ and the end points are indexed from first to last ($e_i = 1 + e_{i-1}$ for $2 \leq i \leq 6$).

| $k_S$ | 0 | 1 | 2 |
|-------|---|---|---|
| 0     | $e_4$ | $e_5$ | $e_6$ |
| 1     | $e_3$ | $e_4$ | $e_5$ |
| 2     | $e_2$ | $e_3$ | $e_4$ |
| 3     | $e_1$ | $e_2$ | $e_3$ |

**Table S1**

**Algorithm 1 Q-Mapping**

**Input:** $x, S', \mathcal{D}, d_T, d_S$

**Output:** The best derivation of $x$ to every prefix of $S'$

1. $\gamma \leftarrow |\text{children}(x)|$
2. build $Q$ with dimensions $\gamma + 1 \times d_T + 1 \times d_S + 1$;
3. for $k_S = 0$ to $\text{len}(S')$ do
   // initialization
   4. $Q[0, 0, k_S] \leftarrow 0$;
5. end
6. for $i = 1$ to $\gamma$ do
7.   for $k_S = 0$ to $d_S$ do
8.     for $k_T = 0$ to $d_T$ do
9.       compute $Q[i, k_T, k_S]$ according to Equation (5);
10.   end
11. end
12. end
13. return $Q[\gamma, \cdot, \cdot]$;

Each run fills a different DP table. The first run of the algorithm will receive the children of $x$ from left to right (i.e. $x_1$ is the leftmost child of $x$ and $x_\gamma$ is the rightmost child), and will produce a DP table, $Q_L$, holding the best scores of the partial derivations of $x$ that order its children from left to right. The second run will receive the children of $x$ from right-to-left (i.e. $x_1$ is the rightmost child of $x$ and $x_\gamma$ is the leftmost child), and will produce a DP table, $Q_R$, holding the best scores of the partial derivations of $x$ that order its children from right to left.

To find the solution, go over both DP tables as described above (Table S1), but for every deletion combination $k_T, k_S$, return the maximum between $Q_L[\gamma, k_T, k_S]$ and $Q_R[\gamma, k_T, k_S]$.

**Time and Space Complexity.** The DP table is the most space consuming data structure in the described algorithm. Its dimensions are $\gamma + 1 \times d_T + 1 \times d_S + 1$, and the algorithm uses two of them. The computation of an entry of the DP table, $Q[i, k_T, k_S]$, includes two $O(1)$ calculations (the first and second cases of the recursion rule) and going over every derivation of $x_i$ in $\mathcal{D}_x(x[i], k_T, k_S)$. All those derivations have the same root and the same end point, but a different number of deletions. In fact, there are no two derivations of $x_i$ in $\mathcal{D}_x(x[i], k_T, k_S)$ that have the same deletion combination $(k'_T, k'_S)$. Hence, the number of such derivations is equal to the number of deletion combinations, $k_T \cdot k_S$, and so the calculation of an entry of the DP table takes $O(k_Tk_S) = O(d_Td_S)$ time. Thus, the time
To assign deletions a penalization cost (and not only limit them), the algorithm should change the recursion rule also need to change. In the initialization, for every character in the first case where the cost of deleting the recursion rule should be changed to the one in Equation (8). Note that the change is only in character in $\delta : \Sigma_T \cup \Sigma_S \rightarrow \mathbb{R}$. The function defines the penalty of deleting a character from $S$ or a leaf from $T$ according to its label. Then, let us expand $\delta$, and define the deletion penalty of a node $x$ in $T$ as the summation of the deletion penalty of all the leaves in the subtree rooted in $x$. Thus, the set of nodes in $T$ is denoted by $T\text{-nodes}$, and a new function $\Delta : T\text{-nodes} \cup \Sigma_S \rightarrow \mathbb{R}$ is defined in Equation (6) below. Note that the $\Delta$ function can be calculated in advance, by going over $T$ in postorder. This calculation takes $O(m') = O(m)$ time.

$$
\Delta(x) = \begin{cases} 
\delta(x), & \text{if } x \in \Sigma_S \\
\sum_{\ell \in \text{leaves}(x)} \delta(\text{label}(\ell)), & \text{if } x \in T\text{-nodes}
\end{cases} \quad (6)
$$

In addition, the following changes to the main algorithm and to the P-mapping and Q-mapping algorithms are needed. First, the initialization of the main DP table $A$ should change and add to the score of every leaf entry (i.e. $A[j, i, k_T, k_S]$ such that $x_j$ is a leaf) the cost of the deleted nodes and characters. Namely, in Algorithm 2 (given in Appendix H.1) lines 8-9 should be replaced with Equation (7) below. Second, the $\Delta$ function in Equation (6) should be sent from the main algorithm to the Q-mapping and P-mapping algorithms.

$$
A[j, i, 1, k_S] \leftarrow -\Delta(x_j) - \sum_{\ell = i}^{i+k_S-1} \Delta(S[\ell]) \quad (7)
$$

Third, the initialization of the DP table, $P$, and the recursion rule of the P-mapping algorithm need to change. The first initialization rule, where $L(C, k_T, k_S) = 0$ and $k_S = 0$, depicts the case in which every node in $C$ is deleted, hence, the rule should be $P[C, k_T, k_S] = -\sum_{\ell \in C} \Delta(\ell)$. The second rule, where $C = \emptyset$ and $k_T = 0$, concerns the case in which every character in $S'[1 : k_S]$ is deleted, so the rule should be $P[C, k_T, k_S] = -\sum_{\ell = 1}^{i+k_S} \Delta(S'[\ell])$. The recursion rule should be changed to the one in Equation (8). Note that the change is only in the first case where the cost of deleting the $i$th character of $S'$ is subtracted from the score.

$$
P[C, k_T, k_S] = \max \left\{ P[C, k_T, k_S - 1] - \Delta(S[i]) \right\} \quad (8)
$$

Lastly, in the Q-mapping algorithm the initialization of the DP table, $Q$, and the recursion rule also need to change. In the initialization, for every $0 \leq k_S \leq d_S$, $Q[0, 0, k_S] = \infty$.
one-to-one mapping that yields or character in the string is defined the same as it was in derives the string a new partial derivation is true and if the node under µ
\[ \mu.s \] of µ.addDel(x, k_S) - µ.s = µ.score

\[ Q[i, k_T, k_S] = \max \begin{cases} Q[i, k_T, k_S - 1] - \Delta(S[E_I(i, k_T, k_S)]) \\ Q[i - 1, k_T - \text{span}(x_i), k_S] - \Delta(x_i) \\ \max_{\mu \in D_z(x_i, k_T, k_S), \eta.e = x_i} Q[i - 1, k_T - \mu.delT, k_S - \mu.delS] + \mu.score \end{cases} \tag{9} \]

\[ \Delta(S) \]

\[ S \]

\[ T \]

\[ I \]

\[ \eta \]

\[ \mu \]

\[ \eta.o \]

\[ \eta.v \]

\[ \mu.e \]

\[ \mu.s \]

\[ \mu.o \]

\[ \mu.delT \]

\[ \mu.delS \]

\[ \mu.o \setminus \eta.o \]

\[ \mu.v \]

\[ \mu.addDel(x, k_S) \]

\[ \mu.addDel(x, k_S) - \mu.s = \mu.score \]

#### H Correctness and Runtime Analysis of Our Algorithms

In this section we prove the correctness of the PQ-Tree Search algorithm (Appendix H.1), the P-mapping algorithm (Appendix H.2) and the Q-mapping algorithm (Appendix H.3), and prove the time complexity of the PQ-Tree Search algorithm and the P-mapping algorithm. First, some definitions that are used in the proofs are given.

**Addition and Removal of a Derivation.** Given a partial derivation, \( \mu \), which derives an

internal node, \( x \), let us define the removal and addition of another derivation \( \eta \): remove(\( \mu, \eta \)) and add(\( \mu, \eta \)). Both operations are defined only for a derivation \( \eta \) whose root is a node \( x' \in \text{children}(x) \).

**Definition 10.** The operation remove(\( \mu, \eta \)) is defined only if \( \eta \) is the derivation of \( \eta.v \) under \( \mu \) and if at least one among \( \eta.e = \mu.e \) or \( \eta.s = \mu.s \) is true. The operation returns a new partial derivation \( \mu' \) of \( \mu \) that ignores the subtree of \( T \) rooted in the child node \( \eta.v \). If \( \eta.e = \mu.e \), then \( \mu' \) derives the string \( S[\mu.s : \eta.s - 1] \), and if \( \eta.s = \mu.s \), then \( \mu' \) derives the string \( S[\eta.e + 1 : \mu.e] \). In any case the number of deletions from the tree is \( \mu'.delT = \mu.delT - \eta.delT \) and from the string it is \( \mu'.delS = \mu.delS - \eta.delS \). Furthermore, \( \mu.o \setminus \eta.o \) is the one-to-one mapping that yields \( \mu' \).

**Definition 11.** The operation add(\( \mu, \eta \)) is defined only if either \( \eta.s = \mu.e + 1 \) or \( \eta.e = \mu.s - 1 \) is true and if the node \( \eta.v \) is ignored under \( \mu \). The operation returns a new partial derivation \( \mu' \) of \( \mu.v \). The derivation of \( \eta.v \) under \( \mu' \) is \( \eta \), and the mapping or deletion of every other leaf or character in the string is defined the same as it was in \( \mu \). Consequentially, if \( \eta.s = \mu.e + 1 \), then \( \mu' \) derives the string \( S[\mu.s : \eta.e] \), and if \( \eta.e = \mu.s - 1 \), then \( \mu' \) derives the string \( S[\eta.s : \mu.e] \). Furthermore, \( \mu'.delT = \mu.delT + \eta.delT \), \( \mu'.delS = \mu.delS + \eta.delS \) and the one-to-one mapping that yields \( \mu' \) is \( \mu.o \cup \eta.o \).

**Addition and Removal of a Deleted Character.** Given a partial derivation \( \mu \), which derives a string \( S \), and an index \( i \) of \( S \) let us define the removal and addition of a deleted character: removeDel(\( \mu, i \)) and addDel(\( \mu, i \)).

**Definition 12.** The operation removeDel(\( \mu, i \)) is defined only if \( i = \mu.e \) or \( i = \mu.s \), and if \( S[i] \) is deleted under \( \mu \). The operation returns a partial derivation \( \mu' \) with \( \mu.delS - 1 \) deletions from the string. If \( i = \mu.e \), then \( \mu' \) derives the string \( S[\mu.s, \mu.e - 1] \), and if \( i = \mu.s \), then \( \mu' \) derives the string \( S[\mu.s + 1, \mu.e] \). The one-to-one mapping that yields \( \mu' \) is \( \mu.o \setminus \{(e, S[i](i))\} \).
Definition 13. The operation \( \text{addDel}(\mu, i) \) is defined only if \( i = \mu.e + 1 \) or \( i = \mu.s - 1 \). The operation returns a partial derivation \( \mu' \) with \( \mu.del_s + 1 \) deletions from the string. If \( i = \mu.e + 1 \), then \( \mu' \) derives the string \( S[\mu.s, \mu.e + 1] \), and if \( i = \mu.s - 1 \), then \( \mu' \) derives the string \( S[\mu.s - 1, \mu.e] \). The one-to-one mapping that yields \( \mu' \) is \( \mu.o \cup \{(\epsilon, S[i(i))]\} \).

Addition and Removal of a Deleted Node. Given a partial derivation \( \mu \), which derives a string \( S \), let us define the removal and addition of a deleted node: \( \text{removeDel}(\mu, x) \) and \( \text{addDel}(\mu, x) \).

Definition 14. The operation \( \text{removeDel}(\mu, x) \) is defined only if \( x \) is deleted under \( \mu \). The operation returns a partial derivation \( \mu' \) with \( \mu.del_t - \text{span}(x) \) deletions from the tree and \( \mu.del_s \) deletions from the string. The derivation \( \mu' \) ignores \( x \) and derives the same substring derived by \( \mu \). The one-to-one mapping that yields \( \mu' \) is \( \mu.o \setminus \{(\ell, \epsilon) : \ell \in \text{leaves}(x)\} \).

Definition 15. The operation \( \text{addDel}(\mu, x) \) is defined only if \( x \) is ignored under \( \mu \). The operation returns a partial derivation \( \mu' \) with \( \mu.del_t + \text{span}(x) \) deletions from the tree. The substring derived by \( \mu' \) is equal to the substring derived by \( \mu \). The one-to-one mapping that yields \( \mu' \) is \( \mu.o \cup \{(\ell, \epsilon) : \ell \in \text{leaves}(x)\} \).

H.1 The Main Algorithm

In this section we give the pseudocode of the PQ-Tree Search algorithm presented in Section 3.1 (Algorithm 2) and prove its correctness. In this proof, the correctness of the Q-mapping algorithm (Appendix F) and of the P-mapping algorithm (Section 3.3) is assumed. Their correctness will be proven in Appendix H.3 and Appendix H.2 respectively.

For this proof Definition 16 below is used to represent the set of derivations whose score might be in \( \mathcal{A}[j, i, k_T, k_S] \), similarly to the notation in Definition 5.

Definition 16. The set of all derivations to \( S[i, E(x_j, i, k_T, k_S)] \) rooted in \( x_j \) that have exactly \( k_T \) deletions from the tree and exactly \( k_S \) deletions from the string is denoted by \( \mathcal{D}_M(x_j, i, k_T, k_S) \).

Lemma 17. At the end of the algorithm every entry \( \mathcal{A}[j, i, k_T, k_S] \) of the DP-table \( \mathcal{A} \) holds the highest score of a derivation of \( S[i, E(x_j, i, k_T, k_S)] \) rooted in \( x_j \) that has \( k_S \) deletions from the string and \( k_T \) deletions from the tree, i.e. \( \mathcal{A}[j, i, k_T, k_S] = \max_{(j, i, k_T, k_S) \in \mathcal{D}_M(x_j, i, k_T, k_S)} \mu.score \)

Proof. We prove Lemma 17 by induction on the entries of \( \mathcal{A} \) in the order described in the algorithm. Namely, for two entries \( \mathcal{A}[j_1, i_1, k_{T1}, k_{S1}] \) and \( \mathcal{A}[j_2, i_2, k_{T2}, k_{S2}] \), \( \mathcal{A}[j_1, i_1, k_{T1}, k_{S1}] < \mathcal{A}[j_2, i_2, k_{T2}, k_{S2}] \) if and only if \( j_1 < j_2 \) or both \( j_1 = j_2 \) and \( i_1 < i_2 \). If \( j_1 = j_2 \) and \( i_1 = i_2 \), then the order between the entries is chosen arbitrarily.

Base Case. The base case of the algorithm is the initialization of the DP table, where the entries \( \mathcal{A}[j, i, k_T, k_S] \) for \( x_j \in \text{leaves(root)} \) and \( k_T \in \{0, 1\} \) are computed. When \( k_T = 0 \), there are no deletions from the tree. So, \( x_j \) must be mapped to some character \( S[\ell] \) \((i \leq \ell \leq E(x_j, i, 0, k_S))\). In this version of the algorithm the deletion of a character does not change the score of the derivation, so the maximal score of a derivation in \( \mathcal{D}_M(x_j, i, 0, k_S) \) is the maximum score of a mapping of \( x_j \) to some character \( S[\ell] \) \((i \leq \ell \leq E(x_j, i, 0, k_S))\), which is the initialization value of the entry \( \mathcal{A}[j, i, 0, k_S] \). When \( k_T = 1 \), there is one deletion from the tree. The derived subtree \( T(x_j) \) has one leaf, \( x_j \), and so it must be the deleted leaf. All characters in the derived string, \( S[i : E(x_j, i, 1, k_S)] \), must also be deleted. Deletions do not add to the score of the derivation, and so all the derivations in \( \mathcal{D}_M(x_j, i, 1, k_S) \) have a score of 0, which is the initialization value of \( \mathcal{A}[j, i, 1, k_S] \).
**Algorithm 2** PQ-Tree Search

**Input:** $T, S, h, d_T, d_S$

**Output:** The score of the best derivation of $T$ to a substring of $S$ with up to $d_T$ and $d_S$ deletions from $T$ and $S$, respectively

1. build $A$ with dimensions $m' \times n \times d_T + 1 \times d_S + 1$ and initial value $-\infty$;
2. for $j = 1$ to $m'$
   //for each node of $T$ in postorder
   for $i = 1$ to $n$
     if $x_j$ is a Leaf then
       //initialization
       for $k_S = 0$ to $d_S$
         $A[j, i, 1, k_S] \leftarrow 0$;
         $A[j, i, 0, k_S] \leftarrow \max_{i' = 1, \ldots, i + k_S} h(j, S[i'])$;
       end
     end
     $e \leftarrow E(x_j, i, 0, d_S)$;
     if $x_j$ is a Q-node then
       $A[j, i, \cdot, \cdot] \leftarrow \text{Q-Mapping}(x_j, S[i, e], \{A[x_{j_k}, i, \cdot, \cdot] : x_{j_k} \in \text{children}(x_j)\}, d_T, d_S)$;
     end
     if $x_j$ is a P-node then
       $A[j, i, \cdot, \cdot] \leftarrow \text{P-Mapping}(x_j, S[i, e], \{A[x_{j_k}, i, \cdot, \cdot] : x_{j_k} \in \text{children}(x_j)\}, d_T, d_S)$;
     end
   end
19. return $\max_{0 \leq k_T \leq d_T}$ $\max_{0 \leq k_S \leq d_S}$ $\max_{1 \leq i \leq (n - \text{span(root)} - d_T + 1)} A[m', i, k_T, k_S]$;

**Induction Assumption.** Assume that every entry $A[j', i', k_T', k_S']$ such that $A[j', i', k_T', k_S'] < A[j, i, k_T, k_S]$ holds the best score of a derivation from $D_M(x_{j'}, i', k_T', k_S')$. Namely, $A[j', i', k_T', k_S'] = \max_{\mu \in D_M(x_{j'}, i', k_T', k_S')} \mu.\text{score} = OPT(j', i', k_T', k_S')$.

**Induction Step.** For every internal node $x_j$ and possible start index $i$, the algorithm fills the DP table entry $A[j, i, k_T, k_S]$ according to the values returned from the Q-mapping and P-mapping algorithms according to the type of $x_j$. The correctness of these algorithms is proven in Appendix [1.3] and Appendix [1.2] respectively. Hence, it is only necessary to prove that the input the algorithms expect to receive is sent correctly from the main algorithm.

Both the Q-mapping and P-mapping algorithms expect to receive the internal node which should be the root of all the output derivations, a substring $S'$ of $S$, the deletion limits $d_T$ and $d_S$, and a collection of the best scoring derivations of every child of $x$ to every substring of $S'$ with up to $d_T$ and $d_S$ deletions from the tree and string, respectively. By definition an entry in $A[j, i, \cdot, \cdot]$ concerns the derivations of $x_j$ with a start point $i$. The end point of the longest derivation of those derivations is $E(j, i, 0, d_S)$. Hence, the internal node sent to the Q-mapping or P-mapping algorithm is $x_j$ and the substring $S'$ equals $S[i, E(j, i, 0, d_S)]$. The deletion limits $d_T$ and $d_S$ are given as input to the main algorithm. Lastly, the best derivations of the
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Algorithm 3 P-Mapping.

Input: $x, S', D, d_T, d_S$
Output: The best derivation of $x$ to every prefix of $S'$
1. $\gamma \leftarrow |\text{children}(x)|$
2. Build $P$ with dimensions $2^\gamma \times d_T + 1 \times d_S + 1$;
3. for $size = 0$ to $\gamma$ do
4.   foreach $C \subseteq \text{children}(x)$ s.t. $|C| = size$ do
5.     for $k_T = 0$ to $d_T$ do
6.       for $k_S = 0$ to $d_S$ do
7.         if $(L(C, k_T, k_S) = 0$ and $k_S = 0)$ or $(size = 0$ and $k_T = 0)$ then
8.           //initialization
9.           $P[C, k_T, k_S] \leftarrow 0$
10.        else
11.           compute $P[C, k_T, k_S]$ according to Equation (2);
12.        end
13.     end
14.   end
15. end
16. return $P[\text{children}(x), \cdot, \cdot]$;

children of $x_j$ are stored in $A$. Because the nodes of $T$ are indexed in postorder, if $x_c$ is a child of $x_j$, then $c < j$. Hence, for every $i', k'_T, k'_S$, it holds that $A[c, i', k'_T, k'_S] < A[j, i, k_T, k_S]$, and from the induction assumption $A[c, i', k'_T, k'_S] = \text{OPT}(c, i', k'_T, k'_S)$. So, indeed the expected input to the Q-mapping and P-mapping algorithms is correct. This completes the proof. ▶

H.2 P-Node Mapping

In this section we give the pseudocode of the P-mapping algorithm presented in Section 3.3 (Algorithm 3) and prove its correctness.

Lemma 18. At the end of the algorithm every entry of the DP-table, $P[C, k_T, k_S]$, holds the best score for a derivation of $x^{(C)}$ to a prefix of $S'$ with $k_T$ deletions from the tree and $k_S$ deletions from the string, i.e. $P[C, k_T, k_S] = \max_{\mu \in \mathcal{D}(x^{(C)}, k_T, k_S)} \mu.\text{score}$

Proof. We prove Lemma 18 by induction on the entries of $P$ in the order described in the algorithm. Namely, for two entries $P[C_1, k_{T_1}, k_{S_1}]$ and $P[C_2, k_{T_2}, k_{S_2}]$, $P[C_1, k_{T_1}, k_{S_1}] < P[C_2, k_{T_2}, k_{S_2}]$ if and only if

1. $|C_1| < |C_2|$, or
2. $|C_1| = |C_2|$ and $k_{S_1} < k_{S_2}$, or
3. $|C_1| = |C_2|$ and $k_{S_1} = k_{S_2}$ and $k_{T_1} < k_{T_2}$

If $C_1 \neq C_2$, $|C_1| = |C_2|$, $k_{S_1} = k_{S_2}$, and $k_{T_1} = k_{T_2}$ are all satisfied, then the order between the entries is chosen randomly.

Base Cases. There are two types of base cases, as described in the initialization of the DP table.

1. $L(C, k_T, k_S) = 0$ and $k_S = 0$: Let $\mu$ be a derivation of $x^{(C)}$ with $k_T$ and $k_S$ deletions. By definition, $\mu$ derives an empty string, i.e. there are no characters to map to the leaves of
the subtrees rooted in the nodes in \( C \). Hence, every child of \( x \) that is considered (the nodes in \( C \)) must be deleted under \( \mu \). All the nodes in \( C \) can be deleted if the sum of their spans is equal to the allowed number of deletions in \( \mu \) (that is, \( k_T \)). From the definition of \( L(C, k_T, k_S) = 0 \) and the fact that \( k_S = 0 \), we receive that indeed \( k_T = \sum_{c \in C} \text{span}(c) \). Every child node of \( x \) that is kept under \( \mu \) adds to the score of the derivation of \( x \), but there are none in this case. In addition, every deletion from the subtree \( T(x) \) adds nothing to the score (in the penalization-free version of the algorithm). Hence, the score of \( \mu \) must equal 0.

2. \( C = \emptyset \) and \( k_T = 0 \): In this case all of the children of \( x \) are ignored, so there are no leaves to map. Hence, every character of the derived string should be deleted. Note that, the derived string is \( S'[1 : E_I(C, k_T, k_S)] \), and its length is \( L(C, k_T, k_S) = \sum_{c \in C} \text{span}(c) - k_T + k_S = \sum_{c \in S} \text{span}(c) - 0 + k_S = k_S \). So, the number of deletions from the string in this state is exactly the number needed to delete the derived string.

**Induction Assumption.** Assume that every table entry \( D[C', k_T', k_S'] \) such that \( D[C, k_T, k_S] < D[C', k_T', k_S'] \) holds the best score of a derivation in \( D(x^{(C')}, k_T', k_S') \). Namely, \( D[C', k_T', k_S'] = \max_{\mu \in D(x^{(C')}, k_T', k_S')} \mu.\text{score} = \text{OPT}(C', k_T', k_S') \).

**Induction Step.** Towards the proof of the step, we prove the following Equation (10):

\[
\text{OPT}(C, k_T, k_S) = \max_{\mu \in D_s(C, k_T, k_S)} \text{OPT}(C \setminus \{\mu.v\}, k_T - \mu.\text{del}, k_S - \mu.\text{del}s) + \mu.\text{score})
\]  
(10).

\[
\leq: \text{Let } \mu^* \in D(x^{(C)}, k_T, k_S) \text{ be a derivation such that } \mu^*.\text{score} = \text{OPT}(C, k_T, k_S). \text{ By definition, } \mu^* \text{ is a derivation of } x^{(C)} \text{ to the string } S'[1 : E_I(C, k_T, k_S)]. \text{ In a derivation every character of the derived string is either deleted or it is a part of a substring derived from one of the children of } x. \text{ So, either } S'[E_I(C, k_T, k_S)] \text{ is deleted under } \mu^*, \text{ or it is mapped under some derivation of a child of } x, y \in C, \text{ to a substring } S'[i : E_I(C, k_T, k_S)] \text{ (for an index } 0 < i \leq E_I(C, k_T, k_S)).
\]

First, if the former is true, then by removing the deletion of \( S'[E_I(C, k_T, k_S)] \) from \( \mu^*, \text{ removeDel}(\mu^*, E_I(C, k_T, k_S)) \), a derivation \( \mu' \in D(x^{(C)}, k_T, k_S - 1) \) is received. The derivation \( \mu' \) derives the string \( S'[1 : E_I(C, k_T, k_S - 1)] = S'[1 : E_I(C, k_T, k_S)] - 1 \). So, the following Equation (11) is true.

\[
\mu^*.\text{score} = \mu'.\text{score}
\]

\[
\leq \text{OPT}(C, k_T, k_S - 1)
\]

\[
\leq \max_{\mu \in D_s(C, k_T, k_S)} \text{OPT}(C \setminus \{\mu.v\}, k_T - \mu.\text{del}, k_S - \mu.\text{del}s) + \mu.\text{score})
\]  
(11).

Note that even if there is a penalization cost for deletions, the cost for the deletion of \( S'[E_I(C, k_T, k_S)] \) (i.e., \( -\Delta(S'[E_I(C, k_T, k_S)]) \)) is constant in this setting. So, for two derivations \( \eta, \eta' \in D(k_T, k_S - 1, x^{(C)}) \) if \( \eta.\text{score} \leq \eta'.\text{score} \) then \( \eta.\text{score} - \Delta(S'[E_I(C, k_T, k_S)]) \leq \eta'.\text{score} - \Delta(S'[E_I(C, k_T, k_S)]) \). Hence, the conclusion from Equation (11) is still true.

Second, if the latter is true, then there is a node \( y \in C \) for which there is a derivation \( \mu_y \in D \) such that \( \mu_y.c = E_I(C, k_T, k_S) \) and \( \mu.y \) is the derivation of \( y \) under \( \mu^* \). For \( \mu^* \) to be a legal derivation, \( \mu_y \) must be in \( D_s(C, k_T, k_S) \). Hence, \( \mu_y.\text{score} \leq \max_{\mu \in D_s(C, k_T, k_S)} \mu.\text{score} \).
Furthermore, by removing \( \mu_y \) from \( \mu^* \), remove \((\mu^*, \mu.y) \), the received partial derivation, \( \mu' \), is of \( x^{(C)}(y) \) to \( S'[1 : \{ \mu_y, s - 1 \}] \) with \( k_T - \mu_y.del_T \) deletions from the tree and \( k_S - \mu_y.del_S \) from the string. Thus, \( \mu' \in D(k_T - \mu_y.del_T, k_S - \mu_y.del_S, x^{(C)}(y)) \), and so \( \mu'.score \leq OPT(x^{(C)}(y)), k_T - \mu_y.del_T, k_S - \mu_y.del_S \). Note that, indeed \( \mu_y.s = 1 + E_l(C \setminus \{ y \}, k_T - \mu_y.del_T, k_S - \mu_y.del_S) \), as can be seen in the following Equation (12).

\[
\begin{align*}
\mu_y.s &= E_l(C, k_T, k_S) - L(y, \mu_y.del_T, \mu_y.del_S) + 1 \\
&= \sum_{c \in C} \text{span}(c) + k_s - k_T - (\mu_y.del_S - \mu_y.del_T + \text{span}(y)) + 1 \\
&= \sum_{c \in C \setminus \{ y \}} \text{span}(c) + k_S - (k_T - \mu_y.del_T) + 1 \\
&= E_l(C \setminus \{ y \}, k_T - \mu_y.del_T, k_S - \mu_y.del_S) + 1
\end{align*}
\]

By combining our conclusions about \( \mu_y \) and \( \mu' \) together, we receive the following Equation (13).

\[
\mu^*.score = \mu'.score + \mu_y.score \\
\leq OPT(C \setminus \{ y \}, k_T - \mu_y.del_T, k_S - \mu_y.del_S) + \max_{\mu \in D_{\leq}(C, k_T, k_S)} \mu.score \\
\leq \max_{\mu \in D_{\leq}(C, k_T, k_S)} OPT(C \setminus \{ \mu.v \}, k_T - \mu.del_T, k_S - \mu.del_S) + \mu.score \\
\leq \max_{\mu \in D_{\leq}(C, k_T, k_S)} OPT(C \setminus \{ \mu.v \}, k_T - \mu.del_T, k_S - \mu.del_S) + \mu.score + \mu_y.score
\]

So, either \( \mu^*.score = OPT(C, k_T, k_S - 1) \), or \( \mu^*.score = \max_{\mu \in D_{\leq}(C, k_T, k_S)} OPT(C \setminus \{ \mu.v \}, k_T - \mu.del_T, k_S - \mu.del_S) + \mu.score \).

First, if the former is true, let \( \eta \in D(x^{(C)}, k_T, k_S - 1) \) be a derivation with \( \eta.score = OPT(C, k_T, k_S - 1) \). By definition, \( \eta \) derives the substring \( S'[1 : E_l(C, k_T, k_S - 1)] \). Adding to \( \eta \) the deletion of \( S'[E_l(C, k_T, k_S)] \), \( \text{addDel} (\eta, E_l(C, k_T, k_S)) \), results in a derivation \( \eta' \) of \( x^{(C)} \) to the string \( S'[1 : E_l(C, k_T, k_S)] \) with \( k_T \) deletions from the tree and \( k_S \) deletions from the string. The string \( S'[1 : E_l(C, k_T, k_S)] \) is equal to the concatenation of \( S'[1 : E_l(C, k_T, k_S - 1)] \) and \( S'[E_l(C, k_T, k_S)] \). So, \( \eta' \in D(x^{(C)}, k_T, k_S) \), and thus \( \eta'.score \leq OPT(C, k_T, k_S) \). The derivation \( \eta' \) was constructed such that \( \mu^*.score = \eta'.score \), so \( \mu^*.score \leq OPT(C, k_T, k_S) \).

Second, if the latter is true, then let \( \eta^* = \arg \max_{\mu \in D_{\leq}(C, k_T, k_S)} OPT(C \setminus \{ \mu.v \}, k_T - \mu.del_T, k_S - \mu.del_S) + \mu.score \). Adding \( \eta^* \) to a partial derivation \( \eta \in D(x^{(C)} \{ \eta^*.v \}), k_T - \eta^*.del_T, k_S - \eta^*.del_S \), \( \text{add} (\eta, \eta^*) \), results in a partial derivation, \( \eta' \), with \( k_T - \eta^*.del_T + \eta'.del_T = k_T \) deletions from the tree and \( k_S - \eta^*.del_S + \eta'.del_S = k_S \) deletions from the string, that takes into account the children of \( x \) that are in \( C \setminus \{ \eta^*.v \} \cup \{ \eta'.v \} \subset C \). It is a legal partial derivation since \( \eta^* \) derives the node \( \eta^*.v \) that is not in \( C \setminus \{ \eta^*.v \} \) to a string that does not intersect with the string derived by \( \eta \). The string that is derived by \( \eta \) is
We prove the algorithm for the case where the children of $x$ is either deleted or kept and thus $\eta'^* \leq OPT(C, k_T, k_S)$. The partial derivation $\eta'$ was constructed such that $\mu'^*.score = \eta'.score$, so $\mu'^*.score \leq OPT(C, k_T, k_S)$.

From the induction assumption, $\mathcal{P}[C, k_T, k_S - 1] = OPT(C, k_T, k_S - 1)$ and for every $\mu \in \mathcal{D}_\subseteq(C, k_T, k_S)$, $\mathcal{P}[C \setminus \{\mu.v\}, k_T - \mu.del_T, k_S - \mu.del_S] = OPT(C \setminus \{\mu.v\}, k_T - \mu.del_T, k_S - \mu.del_S)$. Thus from Equation (10), it follows that $\mathcal{P}[C, k_T, k_S] = OPT(C, k_T, k_S)$. This completes the proof.

H.3 Q-Node Mapping

In this section we prove the correctness of the Q-mapping algorithm presented in Appendix F. We prove the algorithm for the case where the children of $x$ can only be arranged in a left-to-right order. The proof of the right-to-left order is similar.

Lemma 19. At the end of the algorithm every entry of the DP-table $Q$, $Q[i, k_T, k_S]$, holds the best score of a derivation of $x(i)$ and a prefix of $S'$ with $k_T$ deletions from the tree and $k_S$ deletions from the string, i.e. $Q[i, k_T, k_S] = \max_{\mu \in \mathcal{D}(x(i), k_T, k_S)} \mu.score$.

Proof. We prove Lemma 19 by induction on the entries of $Q$ in the order described in the algorithm. Namely, for two entries $Q[i_1, k_T, k_S]$, $Q[i_2, k_T, k_S]$, $Q[i_1, k_T, k_S] < Q[i_2, k_T, k_S]$ if and only if

- $i_1 < i_2$, or
- $i_1 = i_2$ and $k_S < k_S$, or
- $i_1 = i_2$ and $k_S = k_S$ and $k_T < k_T$.

Base Case. The base case is the initialization of the DP table entries $Q[0, 0, k_S]$ for $0 \leq k_S \leq \text{len}(S')$, with a value of 0. Each of these entries holds the score of some derivation $\mu$ of $x(0)$, i.e. $\mu$ is a partial derivation that ignores all nodes in $T(x)$. In addition $\mu$ derives the substring $S'[1 : L(x(0), 0, k_S)] = S'[1 : k_S]$. Hence, all the characters in $S'[1 : k_S]$ must be deleted under $\mu$. Each deletion does not add to the score of the derivation and there are no mappings under $\mu$ either, so the score of such a derivation is 0.

Induction Assumption. Assume that every table entry $Q[i', k_T', k_S']$ such that $Q[i', k_T', k_S'] < Q[i, k_T, k_S]$ holds the best score of a derivation from $\mathcal{D}(x(i), k_T', k_S')$. Namely, $Q[i', k_T', k_S'] = \max_{\mu \in \mathcal{D}(x(i), k_T', k_S')} \mu.score = OPT(i', k_T', k_S')$.

Induction Step. Towards the proof of the step, we prove the following Equation (15):

$$OPT(i, k_T, k_S) = \max(OPT(i, k_T, k_S - 1),$$

$$OPT(i - 1, k_T - \text{span}(x_i), k_S),$$

$$\max_{\mu \in \mathcal{D}_\subseteq(x(i), k_T, k_S)} \mu.score)$$

(15)

$$\leq \max_{\mu \in \mathcal{D}(x(i), k_T, k_S)} \mu.score = OPT(i, k_T, k_S).$$

By definition, $\mu'$ is a derivation of $x(i)$ to the string $S'[1 : E_i(i, k_T, k_S)]$. Under a derivation every child of the root of the derivation is either deleted or kept and every character of the derived string is either deleted or mapped. Thus, $x_i \in \text{children}(x(i))$ is either deleted
or kept under $\mu^*$, and the character $S'[E_i(i, k_T, k_S)]$ is either deleted or mapped under $\mu^*$. Now, let us consider every case.

First, consider a case in which $x_i$ is deleted under $\mu^*$. By removing the deletion of $x_i$ from $\mu^*$ (removeDel($\mu^*, x_i$)) a partial derivation, $\mu'$, that ignores $x_i$ is received, therefore the root of $\mu'$ is $x^{(i-1)}$. By Definition 14, $\mu'$ has $\mu'.del_T - \text{span}(x_i) = k_T - \text{span}(x_i)$ deletions from the tree and $\mu'.del_S = k_S$ deletions from the string. Hence, $\mu' \in D(x_{i-1}, k_T - \text{span}(x_i), k_S)$ and Equation 16 below is true (remember that a deletion of a node does not change the score of a derivation).

$$\mu^*.score = \mu'.score \leq \text{OPT}(i - 1, k_T - \text{span}(x_i), k_S)$$

$$\leq \max_{\mu' \in D \in (x_{i-1}, k_T, k_S)} \text{OPT}(i - 1, k_T - \mu'.del_T, k_S - \mu'.del_S) + \mu'.score$$

(16)

Second, consider a case in which $S'[E_i(i, k_T, k_S)]$ is deleted under $\mu^*$. By removing the deletion of $S'[E_i(i, k_T, k_S)]$ from $\mu^*$, removeDel($\mu^*, E_i(i, k_T, k_S)$) (see Definition 12), the partial derivation received, $\mu'$, has $k_T$ and $k_S - 1$ deletions from the tree and string, respectively, and its root is $x^{(i)}$. Hence, $\mu' \in D(x^{(i)}, k_T, k_S - 1)$ and Equation 17 below is true (remember that a deletion of a character does not change the score of a derivation).

$$\mu^*.score = \mu'.score \leq \text{OPT}(i, k_T, k_S - 1)$$

$$\leq \max_{\mu' \in D \in (x^{(i)}, k_T, k_S)} \text{OPT}(i - 1, k_T - \mu'.del_T, k_S - \mu'.del_S) + \mu'.score$$

(17)

Lastly, if neither is true, then $S'[E_i(i, k_T, k_S)]$ is mapped under $\mu^*$ and $x_i$ is kept under $\mu^*$. Let $\mu_i$ be the derivation of $x_i$ under $\mu^*$ (there is one because $x_i$ is kept under $\mu^*$). Because $S'[E_i(i, k_T, k_S)]$ is mapped, then it is a part of a substring of $S'[1 : E_i(i, k_T, k_S)]$ that is derived by some derivation, $\mu_j$, such that $\mu_j$ is the derivation of the child node $\mu_j.v \in \text{children}(x^{(i)})$ under $\mu^*$. Since $x_i$ is the rightmost child of $x^{(i)}$ and the children of the Q-node $x$ can only be arranged from left to right (in this proof), $\mu_j.v$ must be $x_i$. Otherwise, the left-to-right ordering is defied. Every child of $x$ can only have one derivation under $\mu^*$, so $\mu_i = \mu_j$. Note that $\mu_i$ must have up to $k_T$ and $k_S$ deletions from the tree and string, respectively, else $\mu^*$ is not a legal derivation. In addition, the end point of $\mu_i$ is $E_i(i, k_T, k_S)$. Let $\mu_i^*$ be the highest scoring derivation of $x_i$ with up to $k_T$ and $k_S$ deletions which has the endpoint $E_i(i, k_T, k_S)$, i.e $\mu_i.score \leq \mu_i^*.score$. By definition, $\mu_i^* \in D \in (x^{(i)}, k_T, k_S)$, hence $\mu_i.score \leq \max_{\mu' \in D \in (x^{(i)}, k_T, k_S)} \mu'.score$. Now, removing $\mu_i$ from $\mu^*$, removeDel($\mu^*, \mu_i$) (see Definition 19), results in a derivation, $\mu'$, with $\mu'.del_T - \mu_i.del_T = k_T - mu_i.del_T$ deletions from the tree and $\mu'.del_S = k_S - mu_i.del_S$ deletions from the string. In addition $\mu'$ ignores $x_i$, and so its root is $x^{(i-1)}$. Hence, similarly to $\mu_i$, $\mu'.score \leq \max_{\mu' \in D \in (i-1, k_T - mu_i.del_T, k_S - mu_i.del_S)} \mu'.score = \text{OPT}(i - 1, k_T - mu_i.del_T, k_S - mu_i.del_S)$. Putting the conclusions on $\mu_i$ and $\mu'$ together
we receive Equation (18) below.

\[
\mu^*.score = \mu_1.score + \mu'.score \\
\leq \max_{\mu \in \mathcal{D}_\leq(x^{(1)}, k_T, k_S)} \mu.score + \text{OPT}(i - 1, k_T - \mu.del_T, k_S - \mu.del_S) \\
\leq \max_{\mu \in \mathcal{D}_\leq(x^{(1)}, k_T, k_S)} \text{OPT}(i - 1, k_T - \mu.del_T, k_S - \mu.del_S) + \mu.score \\
\leq \max_{\mu \in \mathcal{D}_\leq(x^{(1)}, k_T, k_S)} \text{OPT}(i - 1, k_T - \mu.del_T, k_S - \mu.del_S) + \mu.score \\
\leq \max_{\mu \in \mathcal{D}_\leq(x^{(1)}, k_T, k_S)} \text{OPT}(i - 1, k_T - \mu.del_T, k_S - \mu.del_S) + \mu.score
\]

In any case Equation (19) below is true.

\[
\text{OPT}(i, k_T, k_S) = \mu^*.score \\
\leq \max_{\mu \in \mathcal{D}_\leq(x^{(1)}, k_T, k_S)} \text{OPT}(i - 1, k_T - \mu.del_T, k_S - \mu.del_S) + \mu.score
\]
Approximate Search for Known Gene Clusters in New Genomes Using PQ-Trees

The number of leaves in the PQ-tree is insignificant with respect to the P-mapping algorithm) results in a total space complexity \( O(n\gamma d) \) corresponding to every combination of deletion number and start index \((d,i)

\)

holds because there are \( \eta_s.e \) leaves and \( \eta_s.s \) possible start indices for strings of length \( \eta_s.d \). In total, the DP table \( A \) is of size \( O(d_T d_S mn) \).

In the initialization step \( O(d_T d_S mn) \) entries of \( A \) are computed in \( O(1) \) time each. This holds because there are \( m \) leaves and \( n \) possible start indices for strings of length 1. The \( d_T \) and \( d_S \) factors come from the initialization of entries with \(-\infty\). The P-mapping algorithm is called for every P-node in \( T \) and every possible start index \( i \), i.e. the P-mapping algorithm is called \( O(nm_p) \) times. Similarly, the Q-mapping algorithm is called \( O(nm_q) \) times. Thus, it takes \( O(n (m_p \cdot \text{Time(P-mapping)} + m_q \cdot \text{Time(Q-mapping)})) \) time to fill the DP table.

In the final stage of the algorithm (line 21 in Algorithm 2) the maximum over the entries corresponding to every combination of deletion number and start index \((0 \leq k_T \leq d_T, 0 \leq k_S \leq d_S, 1 \leq i \leq n - (\text{span}(x) - d_T + 1)) \) is computed. So, it takes \( O(d_T d_S n) \) time to find the maximum score of a derivation. Tracing back through the DP table to find the actual mapping a does not increase the time complexity.

In Appendix F it is shown that our Q-mapping algorithm takes \( O(\gamma d_T^2 d_S^2) \) time and \( O(d_T d_S \gamma) \) space. From Lemma 20 our P-mapping algorithm takes \( O(\gamma^2 d_T^2 d_S^2) \) time and \( O(d_T d_S 2\gamma) \) space. Thus, in total, our algorithm runs in \( O(n(m_p \cdot \gamma d_T^2 d_S^2 + m_q \cdot \gamma d_T^2 d_S^2)) \) = \( O(n\gamma^2 d_T^2 d_S^2 (m_p \cdot 2\gamma + m_q)) \) time. Adding to the space required for the main DP table the space required for the P-mapping algorithm (the space needed for the Q-mapping algorithm is insignificant with respect to the P-mapping algorithm) results in a total space complexity of \( O(d_T d_S mn) + O(d_T d_S 2\gamma) = O(d_T d_S (mn + 2\gamma)) \). This completes the proof.
H.5 Time and Space Complexity of the P-Mapping Algorithm

Here we prove Lemma 20 below.

Lemma 20. The P-mapping algorithm takes $O(d_T^2d_S^2\gamma^22^\gamma)$ time and $O(d_Td_S2^\gamma)$ space.

Proof. The most space consuming part of the algorithm is the 3-dimensional DP table. The first dimension, $C$, can be any subset of the set $\text{children}(x)$, and therefore it is of size $2^{\text{children}(x)} = 2^\gamma$. The sizes of the second and third dimensions (i.e. $k_T$ and $k_S$) are bounded by $d_T + 1$ and $d_S + 1$, respectively. Hence, the space of the DP algorithm is $O(d_Td_S2^\gamma)$.

The algorithm has three parts: initialization, filling the DP table, and constructing the solution. The most time consuming calculation required in the initialization is the calculation of $L(C, k_T, k_S)$ in the first rule. It requires summing the spans of all nodes in $C$. This calculation will also be required in the second part of the algorithm. To avoid the repetitive calculations, it preformed once for every $(C, k_T, k_S)$ tuple and save the results. This requires $O(d_Td_S2^{\text{children}(x)}) = O(d_Td_S2^\gamma)$ space (for this is the number of such tuples). Each value is calculated in $O(|\text{children}(x)|) = O(\gamma)$ time. Hence, the calculation of all the $L(C, k_T, k_S)$ values (and thus all the $E_I(C, k_T, k_S)$ values) takes $O(d_Td_S\gamma^22^\gamma)$ time and $O(d_Td_S2^\gamma)$ space.

The second step is done by calculating the value of every entry in the $O(d_Td_S2^\gamma)$ entries of $\mathcal{P}$, using the recursion rule in Equation (2). The first line among the rule takes $O(1)$ time, since it involves looking in another entry of $\mathcal{P}$ and basic computations. The second line of the rule involves going over all derivations $\mu \in D_{<}(C, k_T, k_S)$. Namely, going over all derivations with a specific end point, which derives a node in $C$ and has no more than a specific number of deletions from the tree and string (i.e. $\mu.e = E_I(C, k_T, k_S)$, $\mu.v \in C$, $\mu.del \leq k_T$ and $\mu.dels \leq k_S$). The number of deletions from the tree and string are bounded by $d_T$ and $d_S$, respectively, and the number of nodes in $C$ is bounded by the number of children of $x$, $\gamma$. Hence, the time to calculate one entry of $\mathcal{P}$ is $O(d_Td_S\gamma)$. In total, the second part of the algorithm takes $O(d_T^2d_S^2\gamma^22^\gamma)$ time. Finally, to construct the solution the algorithm goes over every deletion combination $k_T, k_S$ once, i.e. it takes $O(d_Td_S)$ time. In total, the algorithm takes $O(d_T^2d_S^2\gamma^22^\gamma) + O(d_Td_S\gamma^22^\gamma) + O(d_Td_S) = O(d_T^2d_S^2\gamma^22^\gamma)$. ◀

I Figures

(a) $T_1$  
(b) $T_2$  
(c) $T_3$  

Figure S5 Three different PQ-trees. $T_2$ can be obtained from $T_1$ by reversing the children of a Q-node (the left child of the root) and by reordering the children of a P-node (the right child of the root), so $T_2 \equiv T_1$. $T_3$ can be obtained from $T_1$ by deleting one leaf and permuting the children of the right child of the root, so $T_1 \preceq T_3$. Now, $T_2 \preceq T_3$ can be inferred, because the $\equiv$ is an equivalence relation. By the definition of frontier, $F(T_1) = ABCDEFG$, $F(T_2) = DCBAEGF$, $F(T_3) = ABDFEG$. 

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The derivation $\mu$ applied on $T$ resulting in $T'$: reorder the children of $x_4$, delete leaves according to $M$ (delete $x_5$ and $x_6$) and perform smoothing (delete $x_7$, the parent node of $x_5$ and $x_6$). The root of $T$, $x_{11}$, is the node that $\mu$ derives, denoted $\mu.v$. Also, $\mu$ is a derivation of $x_{11}$. The nodes $x_5$, $x_6$ and $x_7$ are deleted under $\mu$. The leaves $x_1, x_2, x_3, x_8, x_9$ are mapped under $\mu$. The nodes $x_4, x_{10}, x_{11}$ are kept under $\mu$.

\begin{align*}
S' & : \sigma_1 \sigma_2 \sigma_1 \sigma_2 \sigma_3 \sigma_4 \sigma_5 \sigma_6 \sigma_3 \\
M & : (x_3, \sigma_1(3)) (\varepsilon, \sigma_2(4)) (x_1, \sigma_3(5)) (x_2, \sigma_4(6)) (x_8, \sigma_5(7)) (x_9, \sigma_6(8)) \\
S_M & : x_3 \ x_1 \ x_2 \ x_8 \ x_9
\end{align*}

The derivation $\mu$ on $S'$ resulting in $S_M$: apply substitutions and deletions according to $M$. The substring $S' = S[3 : 8]$ is the string that $\mu$ derives. The character $S[4]$ is deleted under $\mu$. The characters $S[3], S[5], S[6], S[7], S[8]$ are mapped under $\mu$.

\textbf{Figure S6} An illustration of the derivation $\mu$ from the PQ-tree $T$ to the substring $S'$ under the one-to-one mapping $M$ ($\mu.o$) with $\mu.del_T = \text{del}_T(M) = 2$ deletions from the tree and $\mu.del_S = \text{del}_S(M) = 1$ deletions from the string. The start point of the derivation ($\mu.s$) is 3. The end point of the derivation ($\mu.e$) is 8. Notice that that $S_M = F(T')$ and $T \succeq_2 T'$ which means that $S_M \in C_{st}(T)$.
Figure S7 This figure is continued in the next page.
The plasmid instances of the heavy metal efflux pump gene cluster discussed in Section 5.2. The COGs of the query gene cluster are: COG0642, COG0745, COG3639, COG0845, COG1538. The instances were identified using PQFinder and displayed using the graphical interface of the tool CSBFinder-S [36]. X indicates a gene with no COG annotation. The image was edited to display instances of the same genome in separate lines. (b) The functional description of the COGs shown in (a).
Table S2 PQ-trees for which tree-guided rearrangements were found in plasmids. 1 Square brackets represent a Q-node; round brackets represent a P-node. Numbers indicate the respective COG IDs. 2 This column indicates the number of genomes harboring plasmid instances of the respective PQ-tree. The number in brackets indicates the number of genomes harboring a tree-guided gene rearrangement of the corresponding gene cluster.

| PQ-tree | S-score | # Genomes | Functional Category             |
|---------|---------|-----------|---------------------------------|
| 1 [[0683 [0411 0410] [0559 4177]]] 0583]] | 22.5 | 5 (2) | Amino acid transport           |
| 2 (1609 [1653 1175 0395] 3839) | 10.0 | 10 (2) | Carbohydrate transport          |
| 3 [[1538 [3696 0845]] [0642 0745] 0559 4177]] | 7.5 | 7 (1) | Heavy metal efflux              |
| 4 [[2115 1070] [4213 [1129 4214]]] | 7.5 | 1 (1) | Carbohydrate transport          |
| 5 [1960 [2011 1135] [2141 1464]] | 7.5 | 3 (1) | Amino acid transport            |
| 6 [[0596 0599] [3485 3485] 0015]] | 7.5 | 9 (1) | Metabolism                      |
| 7 [[[1129 1172 1172] 1879] 3254] | 7.5 | 6 (1) | Carbohydrate transport          |
| 8 (1609 1869 [[1129 1172] 1879 0524]) | 7.5 | 1 (1) | Carbohydrate transport          |
| 9 [0683 [0559 4177] [0411 0410] 0318]] | 7.5 | 1 (1) | Amino acid transport            |
| 10 (3839 0673 [[0395 1175] 1653]) | 5.0 | 10 (1) | Carbohydrate transport          |
| 11 [0583 (0687 3842 [1176 1177])] | 5.0 | 9 (3) | Amino acid transport            |
| 12 [1012 [0687 3842 [1176 1177]]] | 5.0 | 8 (1) | Amino acid transport            |
| 13 (0284 0461 [0540 1781] 0543 0044 0167) | 3.5 | 1 (1) | Metabolism                      |
| 14 ((2080 1319 1529) 1975 2068) | 3.3 | 6 (1) | Energy production and conversion |
| 15 [0044 [0543 0167] 0284] | 3.0 | 1 (1) | Metabolism                      |
| 16 [1802 [1638 [3090 1593]]] | 3.0 | 7 (1) | Carbohydrate transport          |
| 17 [0410 [[177 0559] 0683]] | 3.0 | 7 (3) | Amino acid transport            |
| 18 [[4770 0511] [1984 2049]] | 3.0 | 4 (2) | Metabolism                      |
| 19 [[2875 [1010 2073] 2243] | 3.0 | 9 (2) | Metabolism                      |
| 20 [[[1175 0395] 1409 3839 1653]] | 2.5 | 5 (2) | Carbohydrate transport          |
| 21 [[2141 0431 0600 0715] 1116] | 2.5 | 2 (2) | Inorganic ion transport         |
| 22 [0601 1173] [0444 0444 0747] | 2.5 | 10 (1) | Amino acid transport            |
| 23 [0583 (3842 1840 1178)] | 2.0 | 1 (1) | Inorganic ion transport         |
| 24 (1464 2141 [1135 2011]) | 2.0 | 7 (3) | Amino acid transport            |
| 25 (0209 2142) [0479 1053] | 2.0 | 2 (1) | Energy production and conversion |
| 26 [[1622 0843] 0109 1845] | 2.0 | 1 (1) | Energy production and conversion |
| 27 (1024 1960 4770 4799) | 1.0 | 4 (1) | Lipid transport                 |
| 28 (1120 0609 0614 1629) | 1.0 | 4 (1) | Inorganic ion transport         |
| 29 (0411 0559 4177 0683 0410 1022) | 1.0 | 3 (1) | Amino acid transport            |