Comparison of Minisatellites

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Abstract

In the class of repeated sequences that occur in DNA, minisatellites have been found polymorphic and became useful tools in genetic mapping and forensic studies. They consist of a heterogeneous tandem array of a short repeat unit. The slightly different units along the array are called variants. Minisatellites evolve mainly through tandem duplications and tandem deletions of variants. Jeffreys et al. devised a method to obtain the sequence of variants along the array in a digital code, and called such sequences maps. Minisatellite maps give access to the detail of mutation processes at work on such loci. In this paper, we design an algorithm to compare two maps under an evolutionary model that includes deletion, insertion, mutation, tandem duplication and tandem deletion of a variant. Our method computes an optimal alignment in reasonable time; and the alignment score, i.e., the weighted sum of its elementary operations, is a distance metric between maps. The main difficulty is that the optimal sequence of operations depends on the order in which they are applied to the map. Taking the maps of the minisatellite MSY1 of 609 men, we computed all pairwise distances and reconstruct an evolutionary tree of these individuals. MSY1 (DYF155S1) is a hypervariable locus on the Y chromosome. In our tree, the populations of some haplogroups are monophyletic, showing that one can decipher a micro-evolutionary signal using minisatellite maps comparison.

1 Introduction

Repeated sequences represent a large part of eukaryotic genomes. Among repeats, the class of tandem repeats, whose duplicated units are adjacent along the chromosome, have also been found in other species including bacteria. This class is subdivided further by decreasing order of repeat unit size into satellites, mini-satellites and micro-satellites.

Minisatellites (ms) consist of tandem arrays of short repeat units. Tandem repeats classifications vary and the repeat unit length of ms is considered to be between 7 and 100 bp [VD00] or 10 and 50 bp [JBT98]. Due to a lack of a precise definition of ms, these structures are usually not annotated in sequence data. Nevertheless, amongst the community of biologists there has grown a large interest in ms because of their polymorphism; Variable Number of Tandem Repeats (VTNR) is a synonym for polymorphic ms. This variability is due to tandem duplication, an event that adds a duplicated copy next to the original one, and to the reverse event, tandem deletion. Slippage of DNA polymerase during replication and unequal crossing-over have been hypothesized as mechanisms for these events. As for microsatellites, length variations of ms have been found to be involved in several diseases like diabetes, epilepsy and cancer and there is evidence for other contributions to genome function (see [BJ97, VD00]).

Specific studies reveal that most human ms contain subtly varying repeat units [JBB$^+$97]. In 1991, Jeffreys and colleagues designed a PCR reaction to type Minisatellites Variant Repeat, the MVR-PCR [JMT$^+$91]. Each different unit is a variant. This method provides the sequence of variants along the array in a digital code, where each variant is encoded by a symbol. Such sequences are called **internal** or **minisatellite maps**. This technology has led to major improvements in the knowledge of ms instability processes, among which are: the model of mutation initiation by double strand breaks, the role of flanking sequences, the differences between meiotic and somatic mutations and the phenomenon of polarized variability (see [JBB$^+$97, VD00] for reviews).

Because of their length variability, minisatellites have proven useful in genetic mapping, forensic studies, and the exploration of genetic diversity and population structure. But ms maps give access to the mutation processes of ms at a more detailed level. For instance, they allowed Armour et al. to investigate the Out-of-Africa hypothesis of human origin [AAM$^+$96].

The human minisatellite MSY1, the most variable locus on the Y chromosome, is an ideal tool to investigate the evolution of this haploid chromosome and decipher paternal lineages in human [JBT98]. In [JBT98], the authors typed by MVR-PCR the MSY1 maps of 690 men sampled in various human populations. Their aim was to survey MSY1 diversity in haplogroups and populations. They studied the average maps diversity in some populations, but the lack of a computer-based comparison method impeded a more in-depth study (like reconstructing an evolutionary tree of these individuals.)

To fully exploit the evolutionary information contained in these sequences of variants, it is critical to be able to compare automatically ms maps. In this paper, we provide an alignment algorithm which considers the events of tandem duplication and deletion of a variant and is specific for ms maps. We hypothesize a symmetrical single-step evolutionary model for ms, which we present in Section 2. In Section 3, we detail the algorithm. In Section 4, we apply our method to compare the MSY1 maps from [JBT98] and reconstruct evolutionary trees from the resulting distance matrix.

Notation. As minisatellite maps can be modeled by sequences of symbols, also called strings, we introduce a notation for strings. Let Σ be a finite alphabet of variants. A map s of length n is a string of n symbols of Σ indexed from 1 to n. We denote the i-th *symbol* of s by $s[i]$ for all i with $1 \leq i \leq n$. For any integers i, j, $1 \leq i \leq j < n$, $s_j^i := s[i] \dots s[j]$ is called a *substring* of s. The word *submap* is equivalent to substring. We denote the concatenation of two strings r and s by $r.s$. Throughout the article, let r, s be two maps over Σ of length m and n, respectively.

2 Single-step Evolutionary Model for Minisatellites

In this section we describe our evolutionary model for minisatellites and introduce the notion of arches.

Our model considers five types of evolutionary events on variants: mutation, insertion, deletion, amplification and contraction. Mutation, insertion and deletion are the same events as those considered traditionally in sequence alignments except that they apply to a variant instead of a single residue. Here is an illustration on the sequence abc:

delete b:	$abc \rightarrow ac$
insert d at pos. 3:	$abc \rightarrow abdc$
mutate b in d:	$abc \rightarrow adc$

The two specific events are amplification and contraction (These are shorter names for tandem duplication and tandem deletion.) For example, the sequence abc undergoes an amplification of variant b and then its contraction:

amplification:	$abc \rightarrow abbc$
contraction:	$abbc \rightarrow abc$.

Our model is termed single-step because amplification, resp. contraction, adds, resp. removes, a single variant at a time. A future direction of research is to consider a multiple-steps model where, e.g., a triplication or a quadruplication of a variant may happen in a single event.

To complete our model, we need a quantitative criterion to judge map similarity. For this, each operation is associated with a real positive cost. A sequence of events that transforms s into r is called an alignment. The alignment cost is the sum of its operations costs where aligning two identical variants costs zero. We designate each cost by the uppercase initial of the corresponding event: M, I, D, A and C. Here, we consider a symmetrical model where dual events have the same cost $I = D$ and $A = C$. The observed much higher relative frequencies of amplifications and contractions compared to other events is translated by the fact that they have lower costs: $A, C < M, D, I$. To unify the notation for a mutation and a match we use $M(a, b)$ that is equal to 0 if $a = b$ and to M otherwise. For the sake of simplicity, we consider that all possible mutations cost the same regardless the nucleotidic sequences of the variants. This is a reasonable assumption for the application to minisatellites since variants are long and differ from each other by a few base pairs (see the case of MSY1 in Section 4.) For example, let v_1, v_2 and v_3 be three variants, respectively equal to "cggcgat", "cggcga**c**" and "cgg**a**gat". In our model, to mutate variant v_1 into variant v_2 and to mutate variant v_2 into variant v_3 costs the same, i.e., M, even though it requires one nucleotide substitution in the former, and two nucleotide substitutions in the latter.

Note that a deletion can also be obtained by a mutation plus a contraction and an insertion by an amplification plus a mutation; depending on the operations costs one will be preferred to the other. Indeed, because the model is symmetrical, we have either ($D > M + C$ and $I > A + M$) or ($D \leq M + C$ and $I \leq A + M$). Without loss of generality we assume the first hypothesis (denoted H1). This influences the cost of arch generations/compressions (see Lemma 4) and modifies slightly the algorithm. With H1, at any position except the first one, a variant can be "inserted" by an amplification+mutation, or "deleted" by a mutation+contraction. We denote these operations by A_M and M_C, resp. and they cost $A + M$ and $M + C$, resp. Under these conditions, the alignment cost is a metric; this is important when reconstructing an evolutionary tree from maps data.

Theorem 1 DISTANCE METRIC *The alignment cost is a distance metric.*

Proof (**Distance metric**) We want to show that our alignment cost is a mathematical distance, i.e., that it satisfies i/ the non-negative property, ii/ reflexivity iii/ symmetry and iv/ the triangle inequality. We build our proof on the analysis of metric properties of alignment distances in [SK99, Chapter 9, p. 307-308]. Some properties of the elementary costs are directly transmitted to the distance between maps: i/ the non-negative property, since all elementary costs are non-negative, ii/ reflexivity, since only the match costs zero and iii/ symmetry, since the cost of all dual operations are the same. It remains to prove iv/ the triangle inequality. Let r, s, t be three maps. Let us denote by $d(.,.)$ our alignment distance between any two maps. We need to show that $d(r,t) \leq d(r,s) + d(s,t)$. The triangle inequality might be violated if we cannot combined the alignment from r to s and from s to t into a cheaper alignment from r to t. This can only be the case if any two successive elementary operations that apply to the same position in the alignment cost less than a single operation. So we need to check this for all possible pairs of elementary operations. For this, slightly more complex notations than the ones used in the rest of the paper are useful. First, the alignment alphabet is $\Sigma \cup \{-\}$ where $-$ is the symbol for the absence of variant. If E is an elementary operation, we denote by $E(a,b)$ the operation E that transforms the **source symbol**, a, into the **destination symbol**, b, with $a, b \in \Sigma \cup \{-\}$. So, if a, b, c are three distinct variants of Σ, we denote by $A(-,a)$ the amplification (it transforms $-$ into a from an adjacent a), by $C(a,-)$ the contraction, by $A_M(-,b,a)$ the A_M (it amplifies the adjacent a then mutates it into a b, here the third argument is the adjacent variant on the left), by $M_C(b,-,a)$ the M_C (it mutates a b into an a and contracts the position into the adjacent a, which yields an $-$), by $M(a,b)$ the mutation if $a \neq b$ and the match if $a = b$, by $I(-,a)$ the insertion of an a, and by $D(a,-)$ the deletion of an a. Now, some ordered pairs of two successive operations on the same alignment position are impossible:

- once a position has been inserted, amplified, or amplified + mutated from r to s, it cannot be inserted, amplified, or amplified + mutated again from s to t;
- once a position is present, i.e., after a match or a mutation, the position cannot be inserted, amplified, amplified + mutated again;
- once a position has been removed from r to s, it cannot be removed again from s to t; thus, neither two successive deletions, contractions, or M_C, nor one of the former followed by a mutation or a match are possible;
- $A(-,a)M_C(a,-,b)$ is impossible since to amplify an a requires an a on the left position and to mutate and contract an a into a b we need a b on the left; for the same reason, $A_M(-,b,a)C(b,-)$ is not allowed.

In Table 1, we show that all remaining possible pairs can be replaced by a single operation or no operation at all. In such pairs, the destination symbol of the first operation must be equal to the source symbol of the second operation. This proof is independent of the H1 hypothesis and thus, we include pairs that are not always optimal, nor possible depending on the neighboring variants. It is straightforward to check that single operation costs less than the pair, which proves the triangle inequality and completes the proof. □

The problem we address in this article is to find the optimal global alignment of two maps, that is the alignment with the minimum score, under the single step evolutionary model.

2.1 The Concept of Arch

Let us look step-wise at an artificial example of evolution of the same minisatellite in two individuals (Figure 1). The alphabet of variants is $\{a, b, c, d, e\}$, the ancestor state has map *aaaaa*,

First	Second	Single	First	Second	Single
$A(-,a)$	$C(a,-)$	none	$A(-,a)$	$D(a,-)$	none
$A(-,a)$	$M(a,b)$	$A_M(-,b,a)$	$A_M(-,b,a)$	$D(b,-)$	none
$A_M(-,b,a)$	$M(b,c)$	$A_M(-,c,a)$	$A_M(-,b,a)$	$M(b,a)$	$A(-,a)$
$A_M(-,b,a)$	$M_C(b,-,a)$	none	$I(-,a)$	$D(a,-)$	none
$I(-,a)$	$C(a,-)$	none	$I(-,a)$	$M_C(a,-,b)$	none
$I(-,a)$	$M(a,b)$	$I(-,b)$	$D(a,-)$	$A(-,a)$	$M(a,a)$
$D(a,-)$	$I(-,b)$	$M(a,b)$	$D(a,-)$	$I(-,a)$	$M(a,a)$
$D(a,-)$	$A_M(-,b,a)$	$M(a,b)$	$C(a,-)$	$A(-,a)$	$M(a,a)$
$C(a,-)$	$I(-,a)$	$M(a,a)$	$C(a,-)$	$I(-,b)$	$M(a,b)$
$C(a,-)$	$A_M(-,b,a)$	$M(a,b)$	$M_C(a,-,b)$	$A(-,b)$	$M(a,b)$
$M_C(a,-,b)$	$I(-,a)$	$M(a,a)$	$M_C(a,-,b)$	$I(-,b)$	$M(a,b)$
$M_C(a,-,b)$	$I(-,c)$	$M(a,c)$	$M_C(a,-,b)$	$A_M(-,c,b)$	$M(a,c)$
$M_C(a,-,b)$	$A_M(-,a,b)$	$M(a,a)$	$M(a,b)$	$C(b,-)$	$M_C(a,-,b)$
$M(a,b)$	$D(b,-)$	$D(a,-)$	$M(a,b)$	$M_C(b,-,a)$	$C(a,-)$
$M(a,b)$	$M_C(b,-,c)$	$M_C(a,-,c)$	$M(a,b)$	$M(b,a)$	$M(a,a)$
$M(a,b)$	$M(b,c)$	$M(a,c)$			

Table 1: This table shows all the possible combinations of pairs of elementary operations and for each an equivalent single operation.

the resulting maps in Individuals 1 and 2 are $r := aeaaa$ and $s := aaabbcbddba$, respectively. An alignment is given Figure 2. In Individual 2, the variant b is amplified five times. These amplified variants further mutate and then undergo additional amplifications. This results in a substring whose variants all come from the same ancestor variant, which we call the **seed** of the substring. We can delimit such a substring by the fact that its extremal variants are identical. In our example, the substring of s is *bbcbddb* from position 4 to 10, its seed b is at position 4. During the evolution of this substring, the final variant at each position does not appear in the order of the sequence: at some stage, position 8 has still the ancestor state b and not its final state d, while position 10 is already a b. Thus, such substrings can be obtained by many series of operations, but the optimal way may be order-dependent. If we compute incrementally alignment for longer and longer prefixes, i.e., adding one operation at a time, we cannot find the optimal order of events. For our example substring, if the 9th position first becomes a d, it is not possible to obtain a b at the 10th position by an amplification. So, to recover the optimal series of operations that leads to such a substring, we need to consider it as a whole and not each variant one after the other. This leads to the notion of arches.

Definition 1 *Let s be a map of length n and i, j be two integers such that $1 \leq i < j \leq n$. s_j^i is an **arch** of s if $s[i] = s[j]$.*

In an arch, not all variants need to be the same and an arch may recursively contain other **inner-arches** with different seeds as its, like *dd* in *bbcbddb*. Indeed, once a position with a seed has been mutated into a non-seed variant, it may undergo an amplification which creates an inner-arch.

In the alignment Figure 2, one sees that none of the positions corresponding to *bbcbddb* in s exist in r except the seed position. To mimic evolution, we want to align an arch of s with a single variant of r, the one at the original seed location. In other words, we want to align this seed with a single variant of r and expand additional variants of the arch from its seed. We may see the advent of an arch as a single evolutionary step with a special cost function. Depending on the direction we observe evolution, from s to r or from r to s, we named this

Individual 1

Event	Sequence
	a a a a a
mutation	a **e** a a a

Individual 2

Event	Sequence
	a a a a a
mutation	a a a **b** a
5*amplification	a a a b **b b b b b** a
mutation	a a a b b **c** b b b a
mutation	a a a b b c b **d** b a
amplification	a a a b b c b d **d** b a

Figure 1: Example of evolution of a minisatellite in 2 individuals.

an arch **compression** or **generation**. In our dynamic programming (DP) approach, arch generation/compression are viewed as single operations that express dependencies between two non-neighboring entries of the DP matrix (see Figure 4.)

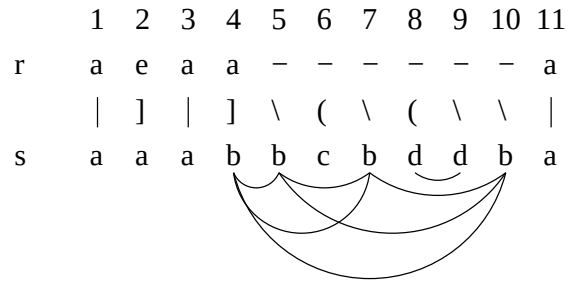

Figure 2: Alignment of the maps of individuals 1 & 2 (see Figure 1). The arch *bbcbddb* and its inner-arches are drawn by curved lines under s. In the middle line, '|', ']', '\', '(' denote resp. a match, a mismatch, an amplification, and an A_M.

Generation and compression of an arch are symmetrical. Generation corresponds to a series of amplifications and mutations (this depends on hypothesis H1, see above) that gives rise to the associated substring from the seed variant, while compression is a series of contractions and mutations that rewinds the substring into its seed. Suppose an arch in s, as no character from r plays a role in such series of events, its optimal cost can be computed independently of r. We denote by $G(t)$ and $K(t)$ respectively the generation and compression costs of an arch t. From now on, we will consider only arch compressions because of the symmetry. In Section 3.2, we explain how to compute the cost of an arch compression and show that it provides an economy of at least M over all other series of operations.

A question arises: as for arches, do we need to consider sequences of operations in which order matters for a submap whose extremal variants are not identical? If we want to recover all possible most parsimonious histories, the answer is yes. The Section 3.5 is devoted to this issue. However, if we only want to compute the distance between the two maps the answer is no. This we prove in Theorem 2.

2.2 Order of Events in an Alignment

The discussion on arches and the example of Figure 1 raise several issues. First, in a single column of an alignment, several events, usually no more than two, may occur. This is the case

of column 6 in Figure 2 which is created by an amplification of the neighboring variant 'b', and a mutation is then needed to transform this b into c. The two operations on the same position are illustrated in the detail of the evolution of Individual 1 in Figure 1. Second, it is clear from this example that the order of events matters. Another example is the following: the amplification that creates the b at position 10 has to be performed before the mutation that turns the b at position 8 into a d. In mathematical terms, the operations are not commutative. Third, alignments do not represent well all these informations that are contained in an history. Actually, **listings**, as defined in [SK99], are better representations for our evolutionary model. The two tables presented in Figure 1 are examples of listings. Given two maps, our algorithm computes the score of an optimal listing. Fourth, the non-commutativity forces us to consider the order of operations to compute the optimal compression or generation of an arch. It explains why we need a specific procedure to compute an arch compression/generation cost, and why this procedure does not consider the arch variant after variant, but uses the submap of the arch as whole. In fact, the non-commutativity increases the computational difficulty.

2.3 Related Works

Traditional global alignment methods do not consider tandem duplication and deletion. The first work that extended the evolutionary model to include such events is the sequence alignment algorithm under the Duplication, Substitution, Indel or DSI-model from Benson [Ben97]. It aims at aligning sequences that may contain tandem repeats. To take into account possible duplication events, the algorithm must identify local repeats in the sequences, which leads to high complexities. Our approach is different since it compares already identified minisatellites. In practice, there exist in-silico and experimental methods for minisatellites detection [Ben99]. Moreover in our model, possible duplicated patterns are the variants, which are known in advance. Another and fundamental difference lies in the treatment of arches. In the DSI model, the cost of a duplication is computed by comparing the new unit to a unit in the other sequence. In a case like individual 2 in our example, the variants b or c, which do not occur in individual 1, would be considered as duplications of the variant a of individual 1. Thus, the DSI model does not reflect the fact that a duplicated unit and its copies are in the same sequence, and cannot cope with the evolution of an arch. On the other hand, Benson provides algorithms for both the single-step and multiple-steps models ([Ben97]). Our approach provides more details on the mutation process. In some way, one could say that it deciphers partly the history of each map to better compare it with the other map. This is related to the problem of reconstructing the duplication history of a tandem repeat sequence. Given the sequence of a tandem repeat, the goal is to find the most parsimonious series of contractions that reduces the sequence to a single motif. This problem has been proposed by Benson & Dong [BD99] and investigated recently for tandemly repeated genes in [EGL02, TWY02].

3 The Alignment Algorithm

In this work, we want to compute the optimal global alignment of two minisatellite maps under the single-step model. In Section 3.1, we present our dynamic programming approach assuming that arch generation and compression are single operations. In Section 3.2, we show how to compute the cost of an arch generation or compression for which we need a maximal set of compatible arches. Then, in Section 3.3, we describe a preprocessing that computes these sets for all arches considered during computation. In Section 3.4, we establish the algorithm complexity. Finally in Section 3.5, we explain how to recover some other optimal listings.

3.1 The Dynamic Programming Computation

We denote by $\mathcal{A}$ the $(n+1) \times (m+1)$ dynamic programming matrix. Its lines and columns are indexed from 0 to n and 0 to m resp. Entry $\mathcal{A}(i,j)$ gives the alignment distance between the prefixes of s and r of length i and j resp., i.e., between s_i^1 and r_j^1, and entry $\mathcal{A}(n,m)$ gives the distance between maps $s := s_n^1$ and $r := r_m^1$. Remember that maps s and r are indexed respectively from 1 to n and from 1 to m. Figure 3 displays the recurrence formula under the hypothesis H1.

Initialization: $\mathcal{A}(0,0) := 0$, $\mathcal{A}(1,0) := D$ and $\mathcal{A}(0,1) := I$. For all other entries the recurrence is:

$$\mathcal{A}(i,j) := \min \begin{cases} \mathcal{A}(i-1,j-1) + M(s[i], r[j]) & \textit{Mutate or Match} \text{ if } i>0 \text{ and } j>0 \\ \mathcal{A}(i-1,j) + C & \textit{Contract} \\ & \text{if } (i>1 \text{ and } (s[i-1]=s[i] \text{ or } s[i]=r[j])) \\ \mathcal{A}(i-1,j) + M + C & \textit{Mutate \& Contract} \text{ if } i>1 \\ \mathcal{A}(i,j-1) + A & \textit{Amplify} \\ & \text{if } (j>1 \text{ and } (r[j-1]=r[j] \text{ or } s[i]=r[j])) \\ \mathcal{A}(i,j-1) + A + M & \textit{Amplify \& Mutate} \text{ if } j>1 \\ \mathcal{A}(l,j) + K(s_i^l) & \textit{Compress arch} \\ & \text{if } i>2, \forall l \in [1,i-2] : s[l]=s[i] \\ \mathcal{A}(i,l') + G(r_j^{l'}) & \textit{Generate arch} \\ & \text{if } j>2, \forall l' \in [1,j-2] : r[l']=r[j] \end{cases}$$

Figure 3: Recurrence.

First, note that deletion and insertion are used only to compute $\mathcal{A}(1,0)$ and $\mathcal{A}(0,1)$. This is because an amplification is not allowed in an empty string and a contraction is not allowed in a one-variant string. For all other entries, when an insertion or a deletion is needed A_M or M_C are used because of H1. The DP recurrence takes the minimum between terms that express the dependencies shown in Figure 4. The first five terms are due to elementary operations and the others to arch generations and compressions. The latter terms depends on the beginning position l', resp. l, of the arch being generated, resp. compressed. The set of positions for l', resp. l, are given by the conditions and thus each line represents multiple terms. An arch of length 2 can be compressed by a single contraction. Symmetrically, generations of arches of length 2 are reducible to an amplification. Such arch compressions and generations are therefore

not considered in the 6^{th} and 7^{th} term of the recurrence. This is why the ending position of an arch is required to be in $[1, i-2]$ with $i > 2$ for compressions and in $[1, j-2]$ with $j > 2$ for generations. A match or a mutation cannot occur in the first row or first column of the matrix; it follows that $i > 0$ and $j > 0$. For any term involving a contraction, resp. an amplification, it is required that there are two adjacent identical variants, which is possible only if $i > 1$, resp. $j > 1$. Consider an alignment between s_i^1 and r_j^1 where s[i] is contracted. s[i] can either be contracted into s[i-1] or r[j]. Indeed, when computing $\mathcal{A}$(i, j), $\mathcal{A}$(i-1, j) is already computed and so we have a series Ω of operations which transforms s_{i-1}^1 in r_j^1. To obtain an alignment between s_i^1 and r_j^1 where s[i] is contracted into s[i-1], we first contract s[i] into s[i-1] and then apply Ω; if we want s[i] to be contracted into r[j], we first apply Ω and then contract s[i] into r[j]. That's why the condition for the contraction is s[i] = s[i-1] or s[i] = r[j]. The condition of the amplification is symmetric: r[j] = r[j-1] or s[i] = r[j].

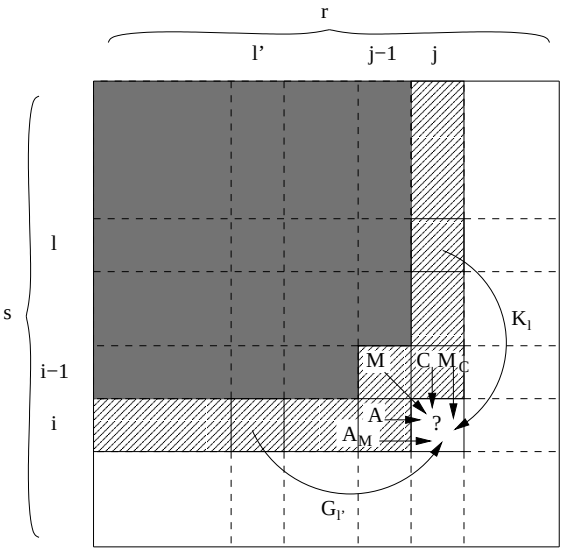

Figure 4: Dependencies in the dynamic programming matrix under H1. To compute cell $\mathcal{A}(i, j)$ we need at most all cells in the striped patch but not the ones in the dark patch. Dependencies are shown by arrows.

Here we demonstrate that our algorithm is correct.

Theorem 2 ALGORITHM CORRECTNESS *The algorithm computes the optimal alignment cost between two maps.*

Proof (**Algorithm correctness**)
Initialization. The optimal alignment between two empty maps costs 0, between an empty map and a one-variant map costs I or symmetrically D.
Induction hypothesis: We assume that $\forall p, q : (p \leq i)$ and $(q \leq j)$ and $(p \neq i$ or $q \neq j)$, $\mathcal{A}[p, q]$ equals the optimal alignment cost between s_p^1 and r_q^1. We prove that the recurrence equation (given p. 8) correctly computes for $\mathcal{A}[i, j]$. Any alignment between s_i^1 and r_j^1 can be decomposed into an alignment of smaller prefixes plus one ending operation. The recurrence takes the minimum between all such possible alignments.

To complete the proof, we need to prove that for substrings s_i^p other than arches, it is useless to consider another ordering of elementary operations than the one induced by the DP computation. This is shown in Lemma 3 and concludes the proof. □

Lemma 3 *When computing $\mathcal{A}$(i, j), the compression of a substring s_i^p, with p ∈ [1, i-1] and s[p] ≠ s[i], leads to a cost greater than or equal to the result of the recurrence equation. To compute alignment cost it is thus useless to consider the compression of a substring which is not an arch.*

Proof (**Lemma 3**) We assume the following induction hypothesis, that is $\forall p, q : (p \leq i)$ and $(q \leq j)$ and $(p \neq i$ or $q \neq j)$, $\mathcal{A}[p, q]$ is optimal. We examine the several ways to compress the submap s_i^p, $s[p] \neq s[i]$, in a single variant either $s[p]$ or $s[i]$, which is aligned with $r[j]$. There are 3 alternatives: **1.** $s[i] = r[j]$ **2.** $s[p] = r[j]$ **3.** $s[i] \neq r[j]$ and $s[p] \neq r[j]$.

1. $s[i] = r[j]$: We align $s[i]$ with $r[j]$, and there are 2 options to compress the substring s_i^p:

   (a) mutate $s[p]$ into $s[i]$, optimally remove the $i - p - 1$ internal variants at cost R, and contract $s[p]$ into $s[i]$. This option leads to a cost equal to $\mathcal{A}(p-1, j-1)+R+M+C$.

   (b) or mutate and contract $s[p]$ in $s[p + 1]$, and optimally remove the $i - p - 1$ internal variants at cost R. It leads to the cost $\mathcal{A}(p - 1, j - 1) + R + M + C$.

   Options (a) and (b) cost the same, say $\mathcal{S} = \mathcal{A}(p - 1, j - 1) + R + M + C$ and we have

   - $\mathcal{A}(p, j) \leq \mathcal{A}(p - 1, j - 1) + M$ (recurrence condition)
   - $\mathcal{A}(i - 1, j) \leq \mathcal{A}(p, j) + R$ (induction hypothesis)

   From these two inequalities we have $\mathcal{A}(i-1, j)+C \leq \mathcal{A}(p-1, j-1)+R+M+C = \mathcal{S}$. As $\mathcal{A}(i - 1, j) + C$ is a term of the recurrence equation, $\mathcal{A}(i, j) \leq \mathcal{S}$ which shows it is useless to consider this option of compression.

2. $s[p] = r[j]$: This case is symmetrical to case 1. where p plays the role of i and vice versa. We can mutate $s[i]$ into $s[p]$, optimally remove the $i - p - 1$ internal variants at cost R, and contract $s[i]$ in $s[p]$. It leads to a cost $\mathcal{S} = \mathcal{A}(p-1, j-1)+R+M+C$. As previously, we have

   - $\mathcal{A}(p, j) \leq \mathcal{A}(p - 1, j - 1)$ (recurrence condition with $s[p] = r[j]$)
   - $\mathcal{A}(i - 1, j) \leq \mathcal{A}(p, j) + R$ (induction hypothesis)

   That gives $\mathcal{A}(i, j) \leq \mathcal{A}(i - 1, j) + M + C \leq \mathcal{A}(p - 1, j - 1) + R + M + C = \mathcal{S}$ and shows it is useless to consider this option of compression.

3. $s[i] \neq r[j]$ and $s[p] \neq r[j]$: We can optimally remove the $i - p - 1$ internal variants at cost R, then we have two symmetrical possibilities as we choose $s[p]$ or $s[i]$ to be mutated into $r[j]$ and the other to be mutated and contracted. In both case, it leads to a cost $\mathcal{S} = \mathcal{A}(p, j) + R + M + C$.

   - $\mathcal{A}(i - 1, j) \leq \mathcal{A}(p, j) + R$ (induction hypothesis)

   So $\mathcal{A}(i - 1, j) + M + C \leq \mathcal{A}(p, j) + R + M + C = \mathcal{S}$. As $\mathcal{A}(i - 1, j) + M + C$ is a term of the recurrence equation, it is useless to consider this option of compression.

As stated, the compression of a submap s_i^p which is not an arch always gives a cost greater than or equal to a cost computed by the recurrence. □

3.2 Costs of Arch Generation and Compression

The arches considered in the main recurrence are sequences of variants whose extremal variants are identical. One extremal variant is assumed to be the ancestor variant of the whole arch. The number of arches on a map of length n is maximal, and in the order of $O(n^2)$, when the map is composed of only one variant.

Definition 2 SIMPLE AND COMPLEX ARCH *An arch of length $k > 1$ is simple if it contains no inner-arches, and complex otherwise. In other words, an arch is simple if each variant occurs only once except the one at its extremity which occurs twice.*

Let us consider first the arch compression of a simple arch of length $k > 1$. There are two ways to rewind this arch. These possibilities are illustrated in Figure 5. Option (i) mutates and contracts the end variant, then removes the $k-2$ internal variants at optimal cost R, while option (ii) first removes the $k-2$ internal variants at optimal cost R and contracts the now adjacent extremal variants in one. In both cases, we are left with a single seed variant. Option (i) costs $R+M+C$ and option (ii) $R+C$; thus, option (ii) is optimal. The economy obtained by choosing the arch compression, i.e., option (ii), is M.

(i)

Event	Sequence				
	$s[i-k+1]$	$s[i-k+2]$	$\ldots$	$s[i-1]$	$s[i]$
mutation	$s[i-k+1]$	$s[i-k+2]$	$\ldots$	$s[i-1]$	$s[i-1]$
contraction	$s[i-k+1]$	$s[i-k+2]$	$\ldots$	$s[i-1]$	
remA	$s[i-k+1]$				

(ii)

Event	Sequence				
	$s[i-k+1]$	$s[i-k+2]$	$\ldots$	$s[i-1]$	$s[i]$
remA	$s[i-k+1]$	$s[i]$			
contraction	$s[i-k+1]$				

Figure 5: Two ways to rewind the arch s_i^{i-k+1}, with $i > k$. Note that $s[i-k+1] = s[i]$ and remA is an abbreviation for "remove all the internal variants (those in the rectangle) at optimal cost R".

Now, consider a complex arch of length k. By definition, it encloses inner-arches. The optimal compression would be to recursively use option (ii) to compress all arches, i.e., the outer-arch and the inner-arches. But not all arches can be compressed. Indeed, when two arches, say u, v, overlap, the seed of u is an internal variant of v and it is not possible to compress v and u, since it would require deleting the seed of u which cannot then be contracted when compressing u. So the optimal compression of a complex arch should maximize the number of arches that are compressed. For this we need to compute the maximal set of arches that can be compressed together; we term them **compatible**.

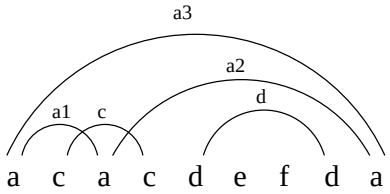

Figure 6: Arches a_1, c and d are simple, while a_2 and a_3 are complex. The following pairs of arches are incompatible: $(a_1, c), (a_1, a_3), (c, a_2), (a_2, a_3)$, while $(a_3, c), (a_3, d), (a_1, a_2), (a_1, d), (a_2, d), (c, d)$ are compatible.

Definition 3 ARCH INCOMPATIBILITY *Two arches are incompatible if they overlap by strictly more than one variant and are not contained in each other, or if they share the same first or the same last position. Compatible is the opposite of incompatible.*

Simple, complex, compatible and incompatible arches are illustrated by Figure 6.

Biologically, the notion of compatibility makes senses. Indeed by definition, the variants in an arch all come from a single ancestor variant. So it is logical that two arches cannot overlap each other, since otherwise it would mean that the variants in the overlap would have two different ancestor variants.

The border condition in Definition 3 means two arches are not compatible if they share the same first or last position. It can be explained by looking at arches a_1, a_2 and a_3 in Figure 6. With this condition, a_3 is not compatible neither with a_1, nor with a_2 while a_1 and a_2 are compatible. Indeed, these three arches can not all be compressed. For instance, if we compress a_2, then only one arch remains to be compressed, a_1 and a_3 become the same.

Lemma 4 ARCH COMPRESSION COST *Let u be an arch of k variants and p the maximum number of compatible arches among all arches including u. Then the optimal compression cost of u is $(k-1) \times C + (k-1-p) \times M$.*

Proof (**Lemma 4**) In the arch, all variants are contracted except the seed; thus, the costs for contractions is $(k-1) \times C$. Of the two extremal variants of a compressed arch, one is contracted in the seed and the other is the remaining seed. Thus, the number of mutations is at most $k-1-p$. Clearly, each mutated variant is either internal to a compressed inner-arch or a remaining seed after compression of all compatible inner-arches or an unpaired variant (i.e., one that is not the extremal variant of any compatible arch). To see that remember that after compression of all compatible inner-arches a complex arch is a simple arch. Therefore, we need at least $k-1-p$ mutations and their total cost is $(k-1-p) \times M$. This gives a total cost of $(k-1) \times C + (k-1-p) \times M$ as claimed. □

Computing the maximal set of compatible arches. As a substring, an arch is associated to an interval of indices. The incompatibility relationship defines an overlap relationship between these intervals (not an overlap+containment relationship). Let $G := (V, E)$ be the graph such that V is the set of intervals associated to arches, and an edge links two intervals if the arches are incompatible. G is an overlap graph. The problem of finding the maximal number of compatible arches is equivalent to finding the max stable set, also known as maximum independent set, of G. By slightly modifying the intervals associated with arches we can enforce that no two intervals have the same endpoints; the number of intervals is then in the order of $\Theta(k^2)$ for an arch of length k. Under this condition, Apostolico et al. [AAH92] reports a $O(|V|^2)$ algorithm for the max stable set of an overlap graph, where $|V|$ denotes the cardinal of V. In fact, they give a better complexity depending on the density of the interval model but in our case, as the density is as large as $|V|$, it is equivalent to $O(|V|^2)$. This algorithm also computes for any interval $\mathcal{I}$, the max stable set for the graph G restricted to all intervals included in $\mathcal{I}$. Assume an interval $\mathcal{J}$ is included in an interval $\mathcal{I}$. One sees that the max stable set of $\mathcal{J}$ depends on the max stable set of $\mathcal{I}$. This is why Apostolico et al. use a DP approach to compute the max stable set of all intervals. We could therefore get the max number of compatible arches for all arches in one run.

3.3 Preprocessing

As we show below, the set of arches whose compressions, resp. generations, are considered in the recurrence in the DP matrix only depends on s, resp. r. Thus using the algorithm of Apostolico et al., we can precompute for s and r the maximum set of compatible arches for each of their arches. This way, we can compute whatever arch generation or compression during the dynamic programming in time $O(1)$. As there are a maximum of $O(n^2)$ arches in s and $O(m^2)$ arches in r, we store the results in a table with n^2 entries for s and a table with m^2 entries for r.

Set of useful arches. Let $1 < i < n$ and $1 < j < m$. We compute the entry $\mathcal{A}(i, j)$. The set of starting positions of arches of s ending at position i is $\mathcal{C}_i := \{0 < l < i \ : \ s[l] = s[i]\}$. This set is independent of j and thus, arches that need to be evaluated are the same for all entries on line i of the matrix. This means that there are at most $i - 1$ possible arches to consider to compute entries of line i of $\mathcal{A}$.
Therefore there are $O(n^2)$ arch compressions and symmetrically $O(m^2)$ arch generations for the whole matrix $\mathcal{A}$.

3.4 Algorithm complexity

Now we investigate the complexity of the whole algorithm.

Theorem 5 ALGORITHM COMPLEXITY *Our algorithm requires* $O(\max(m, n)^4)$ *time and* $O(\max(m, n)^3)$ *space.*

Proof (**Algorithm complexity**)

Matrices of max stable sets : For the map s, we compute a matrix whose entry on the ith line and jth column stores the maximum set of compatible arches of the substring s^i_j, if s^i_j is an arch, and $\emptyset$ otherwise. We need the same matrix for the other map, r. There are $O(n^2)$ arches in s and each becomes a node in the overlap graph, such that $|V| := O(n^2)$. Applying the algorithm of Apostolico requires time $O(|V|^2) = O(n^4)$. A matrix element stores a maximal set of compatible arches which contains $O(n)$ arches because of the compatibility definition. An implementation as randomized or balanced search trees requires $O(n)$ memory and allows searches in $O(\log n)$ time. These matrices for maps s and r requires $O(n^3 + m^3)$ space.

Dynamic programming computation : The matrix $\mathcal{A}$ occupies $O(n \times m)$ memory unit. Any entry depends on three neighboring entries and at most on all previous entries on the same line and the same column. The computation for the different dependencies can be done in $O(1)$ time. When computing $\mathcal{A}(i, j)$, we have to consider at most $i - 1$ arch compressions and $j - 1$ arch generations. So, it takes $\sum_{i:=1}^{n} \left(\sum_{j:=1}^{m} [(i - 1) + (j - 1)] \right) = O(mn^2 + nm^2)$.

Thus, if p denotes $max(m, n)$, the overall complexities are $O(p^4)$ time and $O(p^3)$ space. □

3.5 Other optimal histories and phantom arches

The recurrence we have presented computes the distance between two maps by finding an optimal alignment. In most cases, it exists several optimal alignments and it is interesting to recover more than one. In Figure 7 we show three typical examples where it exists alternative optimal alignments. In example (1), the contraction of a variant a (in the adjacent a) which

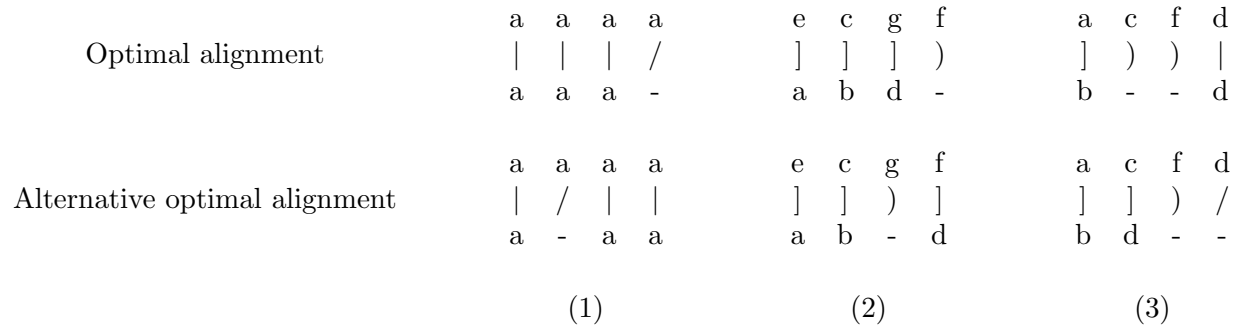

Figure 7: Examples of alternative optimal alignments.

follows a series of three matches, can be performed equivalently at all but the first positions. The contraction and a match commutes. In the second example, the M_C of the f commutes with the mutation at the second position and third position. In those two examples the set of operations remains the same (3 matches and a contraction in the former, 3 mutations and a M_C in the latter), while in the third alignment the set changes. Indeed, one transforms a match in a *distant* contraction and a M_C in a mutation. The two optimal alignments correspond to different evolutionary histories. A *distant* contraction means that the parent variant is not at the adjacent position. The M_C of d must be performed after the removal of f. It is a case of non-commutativity like in an arch. The case of example (3) is a kind of arch in which an extremal variant has disappeared from the sequence but is visible in the other sequence. We term these **phantom arches**.

The histories including phantom arches are of biological relevance and the rest of this section is concerned with their computation. We provide additional lines for the DP recurrence that account for phantom arches and give a procedure to compute their costs. Finally, we show how to adapt the preprocessing and discuss about the complexity of the resulting algorithm.

Phantom arches: Phantom arches are interesting because they point out distant amplifications and contractions, and allow us to discover another history of the sequence evolution. Let us look at an example: s = abcd $\longrightarrow$ abcccd $\longrightarrow$ abcecd $\longrightarrow$ abecd = r. The variant c amplified twice in s has disappeared from r but it remains a trace of this amplification. A possible alignment is:

```
a b c - d
| | [ \ |
a b e c d
```

This alignment shows that the variant c of r comes from an amplification. Another alignment has the same optimal cost but looses the information on the origin of c:

```
a b - c d
| | ( | |
a b e c d
```

Phantom arches allow us to find the traces of ancient amplifications. Note that phantom arches can be viewed only when aligning two sequences, they can not be detected in a sequence alone. To distinguish between the two classes of arches, we qualify a non-phantom arch as **visible**. Compared to visible arches, the compression of a phantom arch requires an additional

mutation.

Recurrence: To take into account phantom arches when computing the alignment we add these four cases to the recurrence :

$\mathcal{A}(l,j) + K(s[i].s_i^{l+1})$	*Compress phantom arch (type 1)* if $i > 2, j > 0$, and $s[i] = r[j], \forall l \in [1, i-2] : s[l] \neq s[i]$
$\mathcal{A}(l,j) + K(s_{i-1}^{l}.s[i]) + M$	*Compress phantom arch (type 2)* if $i > 2, j > 0$, and $s[l] = r[j], \forall l \in [1, i-2] : s[l] \neq s[i]$
$\mathcal{A}(i,l') + G(r[j].r_j^{l'+1})$	*Generate phantom arch (type 1)* if $j > 2, i > 0$, and $s[i] = r[j], \forall l' \in [1, j-2] : r[l'] \neq r[j]$
$\mathcal{A}(i,l') + G(r_{j-1}^{l'}.r[l']) + M$	*Generate phantom arch (type 2)* if $j > 2, i > 0$, and $s[i] = r[l'], \forall l' \in [1, j-2] : r[l'] \neq r[j]$

Compressions, resp. generations, of phantom arches are divided into two subcases depending on which extremal variant match the variant of the other map; this requires that $j > 0$, resp. $i > 0$. A phantom arch of length 2 can be compressed by a M_C or simply a contraction. Symmetrically, generations of arches of length 2 are reducible to a single elementary operation. Such arch compressions and generations are therefore not considered in these additional lines. This is why the ending position of an arch is required to be in $[1, i-2]$ with $i > 2$ for compressions and in $[1, j-2]$ with $j > 2$ for generations.

Computation of the compression cost of a phantom arch going from position l to i, with $0 < l < i \leq n$ in s. The two types of phantom arches are symmetrical; so here and in Lemma 6, we consider only phantom arches of type 1. For type 1, the arch sequence considered for compression is not s_i^l, but $s[i].s_i^{l+1}$. I.e., the first variant is changed to $s[i]$, which is also the end variant. This change creates exactly as many arches as there are other occurrences of $s[i]$ in s_i^{l+1}. We show that knowing the maximal set of compatible arches corresponding to s_i^{l+1} we can deduce the set corresponding to $s[i].s_i^{l+1}$.

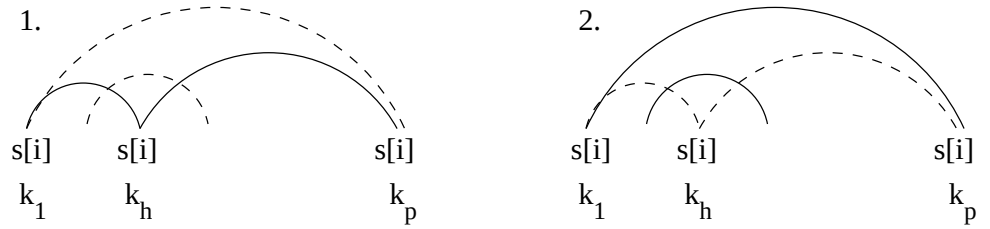

Figure 8: Illustration of the two cases of Lemma 6: plain-line arches belong to the maximum sets while dashed-line arches do not.

Lemma 6 PHANTOM ARCH MAXIMAL SET COMPUTATION (FOR TYPE 1). *Let $\mathcal{Y}, \mathcal{Z}$ be the maximal sets of compatible arches of s_i^{l+1}, $s[i].s_i^{l+1}$ respectively. Let $p > 1$ be an integer and $k_1 := l < \ldots < k_p := i$ be the ordered positions of variant $s[i]$ in $s[i].s_i^{l+1}$. For any h, h' in $[1, p]$ such that $h < h'$, let us denote the arch going from k_h to $k_{h'}$ by $H_{k_h,k_{h'}}$. We have two possible cases illustrated in Figure 8:*

1. *Either it exists $h : 1 < h < p$ such that $H_{k_h,k_p} \in \mathcal{Y}$ and then $\mathcal{Z} := \mathcal{Y} \cup \{H_{k_1,k_h}\}$ and $H_{k_1,k_p} \notin \mathcal{Z}$,*

2. or for all $h : 1 < h < p$ $H_{k_h,k_p} \notin \mathcal{Y}$ *and thus* $\mathcal{Z} := \mathcal{Y} \cup \{H_{k_1,k_p}\}$.

Proof (**Lemma 6**) First, we need the following hint.

Hint 1 *From the arches that are in* $s[i].s_i^{l+1}$ *and not in* s_i^{l+1}*, i.e.,* H_{k_1,k_h} *for all* $h : 1 < h \leq p$*, only one can be added to* $\mathcal{Z}$ *since they are all pairwise incompatible.*

Now, let us note that for any position h such that $1 < h < p$, either both or none of H_{k_1,k_h}, H_{k_h,k_p} belong to $\mathcal{Z}$. Indeed, if one of them does not, it is because an incompatible arch is in $\mathcal{Z}$. This incompatible arch must have one extremal variant on the left of k_h and the other on the right and then be incompatible with both H_{k_1,k_h}, H_{k_h,k_p}. Thus, the latter do not belong to $\mathcal{Z}$. In the opposite case, the same reasoning shows that H_{k_1,k_h} and H_{k_h,k_p} belong to $\mathcal{Z}$. This demonstrate the Hint.
Now we prove the lemma. In the first case of the lemma, $H_{k_h,k_p} \in \mathcal{Y}$, then by the previous argument and by $\mathcal{Z}$ maximality, we can set $\mathcal{Z} := \mathcal{Y} \cup \{H_{k_1,k_h}\}$. Then by Hint 1 $H_{k_1,k_p} \notin \mathcal{Z}$. In the second case of the lemma, we have the opposite situation and we can then set $\mathcal{Z} := \mathcal{Y} \cup \{H_{k_1,k_p}\}$. This is correct since none of H_{k_h,k_p} for $h : 1 < h < p$ is in $\mathcal{Y}$ and these arches are the only incompatible arches with H_{k_1,k_p}. □

Preprocessing: Generalization of the max stable set problem. For the sake of clarity, we assume that visible arches are mapped to subintervals of the integer subset $[1, n]$ and neglect here the constraint of intervals having distinct end-points. We qualify these subintervals of **real**. As mentioned above, the algorithm of [AAH92] builds the associated overlap graph and computes recursively the max stable set for each real subinterval (with the corresponding restricted overlap graph) and then for the whole $[1, n]$. In our problem, to compute the costs of all arch compressions or generations, we need the max stable set for all subintervals of $[1, n]$, i.e., also for subintervals that are not mapped to an arch and that we call **virtual**. In an other work [Riv01], we extend the max stable set problem to the problem of computing the max stable set for each possible subinterval, and report an $\Theta(|V|^2)$ time algorithm to solve it. To save place, we do not present this algorithm here. Applying this algorithm to map s, we can store in an n^2 matrix the max stable set for each subinterval/substring of s. We need the pendant matrix for the arch generations in r. This calculation is made during preprocessing.

Complexity: Applying our extended preprocessing algorithm on map s of length n requires time $\Theta(|V|^2)$. V is the set of arches on s, so $|V| := O(n^2)$. The complexity of this preprocessing is then $O(p^4)$, where p is $\max(m,\ n)$. In the DP matrix, the computation for the different dependencies can be done in $O(1)$ time units except for phantom arches. Applying Lemma 6 for the phantom arch $s[i].s_i^{l+1}$ requires to test $i - l$ times for set membership in a set in the preprocessing matrix for s. This takes $O((i - l)\log(i - l))$ time. Note that a phantom arch and a visible arch finishing at the same position cannot have the same beginning position since the phantom arch has not the same variant at its extremities while the visible arch has. There are at most $i - 1$ arches to consider for the computation of the i-th line of $\mathcal{A}$. Thus, it takes $\sum_{i:=1..n} i^2 \log i = O(n^3 \log n)$ for all lines, and $O(m^3 \log m)$ for all columns. Added up this gives $O(m \times n + n^3 \log n + m^3 \log m) = O(max(m, n)^3 \log(max(m, n))$. The whole complexity remains $O(p^4)$. Taking into account phantom arches does not increase the complexity of our algorithm.

4 Application to the Minisatellite MSY1

MSY1 is a hypervariable ms locus on the human Y chromosome. Its repeat unit is 25 base pairs long and five different variants have been typed by PCR; they differ from each other by at most 3 substitutions. Known minisatellites are usually GC-rich. In MSY1, the nucleotidic sequences of the variants are 75 to 80% AT-rich and have the ability to form an hairpin structure. This structure may hinder the progression of the DNA polymerase and promote tandem amplification and contraction through slippage during replication. The restricted allele length diversity and the observed modular structures advocate in favor of single-step amplifications and contractions [JBT98]. The model we choose seems to be well-suited to MSY1.

M. Jobling provided us with a set of the MSY1 maps of 609 men, for most of which the haplogroup is known, and with an evolutionary tree of the 27 haplogroups. Most individuals are assigned to a population. We computed with our method all pairwise comparisons between these maps and obtained a 609×609 distance matrix. We used a Neighbor-Joining method, BIONJ [Gas97], to reconstruct an evolutionary tree of these individuals. The percent of explained variance of the tree is 95% and confirm that our distances are tree-like. Our tree does not mirror the structure of the haplogroup tree and individuals of different haplogroups are neighbors in it. This reflects the facts that MSY1 evolves extremely rapidly and is constrained in length. The evolutionary signal of the Y chromosomes evolution is only partly decipherable in the MSY1 maps. On a shorter time period, we can look at the evolution inside an haplogroup. For instance the haplogroup 16 contains chromosomes from the Yakut (8 individuals), Siberian Yakut (5), Finnish (10), Mongolian (23) and others (6) populations. The four main populations are by a majority monophyletic: Yakut and Siberian Yakut together (13/13), Finnish (8/10), Mongolian (20/23). Another example is haplogroup 4 which contains only three different populations. As illustrated in Figure 9 the phylogenetic tree built from our distance separates all Japanese individuals from the Tibetan and Mongolian ones. These examples show that comparisons of MSY1 can distinguish between populations inside an haplogroup. This can serve to address micro-evolutionary issues about the Y chromosomes and assign a putative population to an individual of unknown origin. More generally, MSY1 and other ms can play a role in forensic studies and identification. Further results from the MSY1 maps comparisons are under investigation and are not included here.

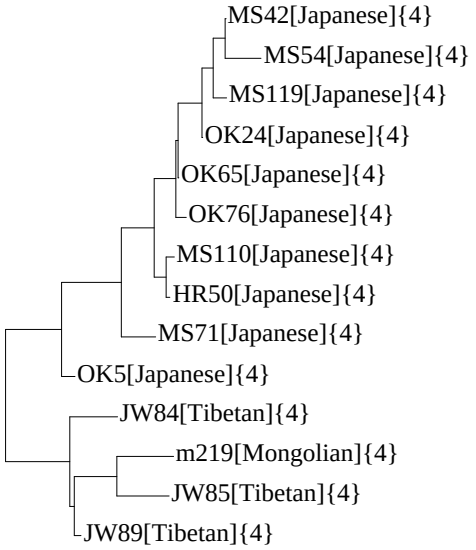

Figure 9: Phylogenetic tree of haplogroup 4 built from a distance matrix produced by our algorithm. Each individual is represented by its code, its population origin and its haplogroup.

5 Conclusion and future work

In this work, we design the first algorithm for the comparison of minisatellite maps. We utilize this method to compare a large set of human maps from the hypervariable locus MSY1 and reconstruct an evolutionary tree of the individuals. Despite the rapid evolution of MSY1, we could distinguish between populations inside haplogroups. This argues in favor of the validity of our approach to address (micro-)evolutionary issues with minisatellite maps comparisons.

There are two main directions for future work:
Generalization of the problem: We envisage to investigate the multiple alignment problem.
Extension of the model: Several extensions of the model are worth considering. For example, we could take into consideration the nucleotidic sequences of variants when computing their mutation costs. We could also relax the single step assumption. It means authorizing tri-, quadru-plication, etc, of a variant instead of only duplications, or allowing duplications of pair, triples, etc, of adjacent variants at a time.

6 Acknowledgments

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