 Subset seed automaton

Gregory Kucherov\textsuperscript{1}, Laurent Noé\textsuperscript{1}, and Mikhail Roytberg\textsuperscript{2}

\textsuperscript{1} LIFL/CNRS/INRIA, Bât. M3 Cité Scientifique, 59655, Villeneuve d’Ascq cedex, France, \{Gregory.Kucherov,Laurent.Noé\}@lifl.fr
\textsuperscript{2} Institute of Mathematical Problems in Biology, Pushchino, Moscow Region, 142290, Russia, mroytberg@mail.ru

Abstract. We study the pattern matching automaton introduced in [1] for the purpose of seed-based similarity search. We show that our definition provides a compact automaton, much smaller than the one obtained by applying the Aho-Corasick construction. We study properties of this automaton and present an efficient implementation of the automaton construction. We also present some experimental results and show that this automaton can be successfully applied to more general situations.

1 Introduction

The technique of \textit{spaced seeds} for similarity search in strings (sequences) was introduced about five years ago [2,3] and constituted an important algorithmic development [4,5]. Its main applications have been approximate string matching [2] and local alignment of DNA sequences [3,6,7] but the underlying idea applies also to other algorithmic problems on strings [8,9].

Since the invention of spaced seeds, different generalizations have been proposed, such as seeds with match errors [10,11], \textit{daughter seeds} [12], \textit{indel seeds} [13], or \textit{vector seeds} [14]. In [1], we proposed the notion of \textit{subset seeds} and demonstrated its advantages and its usefulness for DNA sequence alignment. In the formalism of subset seeds, an alignment is viewed as a text over some alphabet $\mathcal{A}$, and a seed as a pattern over a subset alphabet $\mathcal{B} \subseteq 2^\mathcal{A}$. The only requirements made is that $\mathcal{A}$ contains a special letter 1, $\mathcal{B}$ contains a letter $\# = \{1\}$, and every letter of $\mathcal{B}$ contains 1 in its set. The matching relation is naturally defined: a seed letter $b \in \mathcal{B}$ matches a letter $a \in \mathcal{A}$ iff $a$ belongs to the set $b$.

For any seed-based similarity search method, including all above-mentioned types of seeds, an important issue is an accurate estimation of the sensitivity of a seed with respect to a given probabilistic model of alignments. For different probabilistic models, this problem has been studied in [15,16,17]. In [1] we proposed a general framework for this problem that allows one to compute the seed sensitivity for different definitions of seed and different alignment models. This approach is based on a finite automata representation of the set of target alignments and the set of alignments matched by a seed, as well as on a representation of the probabilistic model of alignments as a finite-state transducer.
A key ingredient of the approach of [1] is a finite automaton that recognizes
the set of alignments matched (or hit) by a given subset seed. We call this
automaton a subset seed automaton. The size (number of states) of the subset seed
automaton is crucial for the efficiency of the whole algorithm of [1]. Note that
the algorithm of [16] is also based on an automaton construction, namely on the
Aho-Corasick automaton implied by the well-known string matching algorithm.

Besides its application to the seeding technique for similarity search and
string matching, constructing an efficient subset seed automaton is an interesting
problem in its own, as it provides a solution to a variant of the subset matching
problem studied in literature [18,19,20].

In this paper, we study properties of the subset seed automaton and present
an efficient implementation of its construction. More specifically, we obtain the
following results:

– we present a construction of subset seed automaton that has \( O(w2^s-w) \)
states, compared to \( O(w|A|^{s-w}) \) implied by the Aho-Corasick construction,
where \( s \) and \( w \) are respectively the span and the weight of the seed defined
in the next Section,
– we further motivate our construction by showing that for some seeds, our
construction gives the minimal automaton,
– we prove that our automaton is always smaller than the one obtained by the
Aho-Corasick construction; we provide experimental data that confirm that
for \( |A| = 2 \), our automaton is on average about 1.3 times bigger than the
minimal one, while the Aho-Corasick automaton is about 2.5 times bigger.
For \( |A| = 3 \) the difference is much more substantial: while our automaton
is still about 1.3 times bigger than the minimal one, the Aho-Corasick au-
tomaton turns out to be about 17 times bigger,
– we provide an efficient algorithm that implements the construction of the
automaton such that each transition is computed in constant time,
– we show that our construction can be applied to the case of multiple seeds
and to the general subset matching problem.

The presented automaton construction is implemented in full generality in
HEDERA software package (http://bioinfo.lifl.fr/yass/hedera.php) and has been
applied to the design of efficient seeds for the comparison of genomic sequences.

2 Subset seed matching

The goal of seeds is to specify short string patterns that, if shared by two strings,
have best chances to belong to a larger similarity region common to the two
strings. To formalize this, a similarity region is modeled by an alignment between
two strings. Usually one considers gapless alignments that, in the simplest case,
are viewed as sequences of matches and mismatches and are easily specified by
binary strings \( \{0,1\}^* \), where 1 is interpreted as “match” and 0 as “mismatch”.
A spaced seed is a string over binary alphabet \( \{\#,\_\} \). The length of \( \pi \) is called
its span and the number of \# is called its weight. A spaced seed \( \pi \in \{\#,\_\}^* \)
matches (or hits) an alignment \( A \in \{0, 1\}^* \) at a position \( p \) if for all \( i \in [1..s] \), 
\( \pi[i] = \# \) implies \( A[p + i - 1] = 1 \).

In [1], we proposed a generalization of this basic framework, based on the idea to distinguish between different types of mismatches in the alignments. This leads to representing both alignments and seeds as words over larger alphabets. In the general case, consider an alignment alphabet \( \mathcal{A} \) of arbitrary size. We always assume that \( \mathcal{A} \) contains a symbol 1, interpreted as “match”. A subset seed is defined as a word over a seed alphabet \( \mathcal{B} \), such that

- each letter \( b \in \mathcal{B} \) denotes a subset of \( \mathcal{A} \) that contains 1 \( (b \in 2^\mathcal{A} \setminus 2^\mathcal{A}\{1\}) \),
- \( \mathcal{B} \) contains a letter \( \# \) that denotes subset \( \{1\} \).

As before, \( s \) is called the span of \( \pi \), and the \#-weight of \( \pi \) is the number of \# in \( \pi \). A subset seed \( \pi \in \mathcal{B}^* \) matches an alignment \( A \in \mathcal{A}^* \) at a position \( p \) iff for all \( i \in [1..s] \), \( A[p + i - 1] \in \pi[i] \).

Example 1. For DNA sequences over the alphabet \( \{\text{A, C, G, T}\} \), in [21] we considered the alignment alphabet \( \mathcal{A} = \{1, h, 0\} \) representing respectively a match, a transition mismatch \( (\text{A} \leftrightarrow \text{G}, \text{C} \leftrightarrow \text{T}) \), or a transversion mismatch (other mismatch). In this case, the appropriate seed alphabet is \( \mathcal{B} = \{\#, @, _\} \) corresponding respectively to subsets \( \{1\}, \{1, h\}, \) and \( \{1, h, 0\} \). Thus, seed \( \pi = \# @ _\# \) matches alignment \( A = 10\text{h}1\text{h}11\text{01} \) at positions 4 and 6. The span of \( \pi \) is 4, and the \#-weight of \( \pi \) is 2.

One can view the problem of finding seed occurrences in an alignment as a special string matching problem. In particular, it can be considered as a special case of subset matching [18] where the text is composed of individual characters. It is also an instance of the problem of matching in indeterminate (degenerate) strings [19,20]. Therefore, an efficient automaton construction that we present in the following sections applies directly to these instances of string matching. One can also freely use the string matching terminology by replacing words “seed” and “alignment” by “pattern” and “text” respectively.

3 Subset Seed Automaton

Let us fix an alignment alphabet \( \mathcal{A} \), a seed alphabet \( \mathcal{B} \), and a seed \( \pi = \pi_1 \ldots \pi_s \in \mathcal{B}^* \) of span \( s \) and \#-weight \( w \). Denote \( r = s - w \) and let \( R_\pi, |R_\pi| = r, \) be the set of all non-\# positions in \( \pi \). Throughout the paper, we identify each position \( z \in R_\pi \) with the corresponding prefix \( \pi_{1..z} = \pi_1 \ldots \pi_z \) of \( \pi \), and we interchangeably regard elements of \( R_\pi \) as positions or as prefixes of \( \pi \).

We now define an automaton \( S_\pi = \langle Q, q_0, Q_F, \mathcal{A}, \psi : Q \times \mathcal{A} \to Q, \rangle, q_0 \in Q, Q_F \subseteq Q, \) that recognizes the set of all alignments matched by \( \pi \). The states \( Q \) are defined as pairs \( (X, t) \) such that \( X = \{x_1, \ldots, x_k\} \subseteq R_\pi, t \in [0..s], \) \( \max\{X\} + t \leq s \). The automaton maintains the following invariant condition. Suppose that \( S_\pi \) has read a prefix \( a_1 \ldots a_p \) of an alignment \( A \) and has come to a state \( (X, t) \). Then \( t \) is the length of the longest suffix of \( a_1 \ldots a_p \) of the form \( 1^i, i \leq s, \) and \( X \) contains all positions \( x_i \in R_\pi \) such that prefix \( \pi_{1..x_i} \), matches a suffix of \( a_1 \ldots a_{p-t} \).
Example 2. In the framework of Example 1, consider a seed \( \pi \) and an alignment prefix \( A = a_1 \ldots a_p \) of length \( p = 11 \) given in Figure 1(a) and (b) respectively. The length \( t \) of the last run of 1’s of \( A \) is 2. The last non-1 letter of \( A \) is \( a_9 = h \). The set \( R_\pi \) of non-\# positions of \( \pi \) is \( \{2, 4, 7\} \) and \( \pi \) has 3 prefixes belonging to \( R_\pi \) (Figure 1(c)). Prefixes \( \pi_1 \ldots 2 \) and \( \pi_1 \ldots 7 \) do match suffixes of \( a_1 a_2 \ldots a_9 \), but prefix \( \pi_1 \ldots 4 \) does not. Thus, the state of the automaton after reading \( a_1 a_2 \ldots a_{11} \) is \( \langle \{2, 7\}, 2 \rangle \).

The initial state \( q_0 \) of \( S_\pi \) is the state \( \langle \emptyset, 0 \rangle \). Final states \( Q_F \) of \( S_\pi \) are all states \( q = \langle X, t \rangle \), where \( \max\{X\} + t = s \). All final states are merged into one state \( \langle \emptyset \rangle \).

The transition function \( \psi(q, a) \) is defined as follows. If \( q \) is a final state, then \( \forall a \in A, \psi(q, a) = q \). If \( q = \langle X, t \rangle \) is a non-final state, then

- if \( a = 1 \) then \( \psi(q, a) = \langle X, t + 1 \rangle \),
- otherwise \( \psi(q, a) = \langle X_U \cup X_V, 0 \rangle \) with
  - \( X_U = \{ x \mid x \leq t + 1 \) and \( a \in \pi_x \} \)
  - \( X_V = \{ t + 1 \mid x \in X \) and \( a \in \pi_x \} \)

Example 3. Still in the framework of Example 1, consider seed \( \pi = \#\_@\# \). Then the set \( R_\pi \) is \( \{2, 3\} \). Possible non-final states \( \langle X, t \rangle \) of \( S_\pi \) are states \( \langle \emptyset, 0 \rangle, \langle \emptyset, 1 \rangle, \langle \emptyset, 2 \rangle, \langle \emptyset, 3 \rangle, \langle \{2\}, 1 \rangle, \langle \{3\}, 0 \rangle, \langle \{2, 3\}, 0 \rangle \). All these states are reachable in \( S_\pi \). Figure 2 shows the resulting automaton.
We now study main properties of automaton $S_\pi$.

**Lemma 1.** The automaton $S_\pi$ accepts all alignments $A \in A^*$ matched by $\pi$.

*Proof.* It can be verified by induction that the invariant condition on the states $(X,t) \in Q$ is preserved by the transition function $\psi$. The final state verifies $\max \{X\} + t = s$ which implies that at the first time $S_\pi$ gets into the final state, $\pi$ matches a suffix of $a_1 \ldots a_r$.

**Lemma 2.** The number of states of the automaton $S_\pi$ is no more than $(w+1)2^r$, where $w$ is the $\#$-weight of $\pi$.

*Proof.* Assume that $R_\pi = \{z_1, z_2, \ldots, z_r\}$ and $z_1 < z_2 \cdots < z_r$. Let $Q_i$ be the set of non-final states $(X,t)$ with $\max \{X\} = z_i$. For states $q = (X,t) \in Q_i$, there are $2^{i-1}$ possible values of $X$ and $s - z_i$ possible values of $t$ between 0 and $s - z_i - 1$, as $\max \{X\} + t \leq s - 1$.

Thus,

$$|Q_i| \leq 2^{i-1}(s-z_i) \leq 2^{i-1}(s-i), \quad \text{and}$$

$$\sum_i |Q_i| \leq \sum_i 2^{i-1}(s-i) = (s-r+1)2^r - s - 1. \quad (2)$$

Besides states $Q_i$, $Q$ contains $s$ states $(\emptyset, t)$ ($t \in [0..s-1]$) and one final state. Thus, $|Q| \leq (s-r+1)2^r = (w+1)2^r$.

Note that if $\pi$ starts with $\#$, which is always the case for spaced seeds, then $X_i \geq i+1$, $i \in [1..r]$, and the bound of (1) rewrites to $2^{i-1}(s-i-1)$. This results in the same $w2^r$ bound on number of states as the one for the Aho-Corasick automaton proposed in [16] for spaced seeds (see also Lemma 4 below).

The next Lemma shows that the construction of automaton $S_\pi$ is optimal in the sense that no two states can be merged in general.

**Lemma 3.** Let $A = \{0,1\}$ and $B = \{\#, \_\}$, where $\# = \{1\}$ and $\_ = \{0,1\}$. Consider a seed $\pi = \# \ldots \#$ with $r$ letters $\_$ between two $\#$'s. Then the automaton $S_\pi$ is reduced, that is

(i) each of its states $q$ is reachable, and

(ii) any two non-final states $q', q''$ are not equivalent.

*Proof.* (i) Let $q = (X,t)$ be a non-final state of the automaton $S_\pi$, and let $X = \{x_1, \ldots, x_k\}$ with $x_1 < \cdots < x_k$. Let $A = a_1 \ldots a_k \in \{0,1\}^*$ be an alignment of length $x_k$ defined as follows: $a_p = 1$ if, for some $i \in [1..k]$, $p = x_k - x_i + 1$, and $a_p = 0$ otherwise. Note that $1 \notin X$ and thus $a_{x_k} = 0$. Thus $\psi(\emptyset, A) = (X,0)$ and finally $\psi(\emptyset, A \cdot 1^t) = q$.

(ii) For a set $X = \{x_1, \ldots, x_k\}$ and an integer $t$, denote $X \oplus t = \{x_1 + t, \ldots, x_k + t\}$. Let $q = (X', t')$ and $q'' = (X'', t'')$ be non-final states of $S_\pi$. If $\max \{X'\} + t' > \max \{X''\} + t''$, then let $d = (r+2) - (\max \{X'\} + t')$. Obviously, $\psi(q', 1^d)$ is a final state, and $\psi(q'', 1^d)$ is not.

Now assume that $\max \{X'\} + t' = \max \{X''\} + t''$. Let $g = \max \{v | (v \in X' \oplus t' \text{ and } v \notin X'' \oplus t'') \text{ or } (v \in X'' \oplus t'' \text{ and } v \notin X' \oplus t')\}$. By symmetry,
assume that the maximum is reached on the first condition, i.e. \( g = x'_i + t' \) for some \( x'_i \in X' \). Let \( d = (r + 1) - g \) and consider word \( 0^d1 \). It is easy to see that \( \psi(q', 0^d1) \) is a final state. We claim that \( \psi(q'', 0^d1) \) is not. To see this, observe that none of the seed prefixes corresponding to \( x \in X'' \) with \( x + t'' > x'_i + t' \) can lead to the final state on \( 0^d1 \), due to the last \# symbol of \( \pi \). The details are left to the reader.

Another interesting property of \( S_\pi \) is the existence of a surjective mapping from the states of the Aho-Corasick automaton onto reachable states of \( S_\pi \). This mapping proves that even if \( S_\pi \) is not always minimized, it has always a smaller number of states than the Aho-Corasick automaton. Here, by the Aho-Corasick (AC) automaton, we mean the automaton with the states corresponding to nodes of the trie built according to the classical Aho-Corasick construction [22] from the set of all instances of the seed \( \pi \). More precisely, given a seed \( \pi \) of span \( s \), the set of states of the AC-automaton is \( Q_{AC} = \{ A \in \mathcal{A}^* \mid |A| \leq s \} \) and \( A \) is matched by prefix \( \pi_{1..|A|} \). The transition \( \psi(A, a) \) for \( A \in Q_{AC} \), \( a \in \mathcal{A} \) yields the longest \( A' \in Q_{AC} \) which is a suffix of \( Aa \). We assume that all final states are merged into a single sink state.

**Lemma 4.** Consider an alignment alphabet \( \mathcal{A} \), a seed alphabet \( \mathcal{B} \) and a seed \( \pi \in \mathcal{B}^s \) of span \( s \). There exists a surjective mapping \( f : Q_{AC} \to Q \) from the set of states of the Aho-Corasick automaton to the set of reachable states of the subset seed automaton \( S_\pi \).

**Proof.** We first define the mapping \( f \). Consider a state \( A \in Q_{AC}, |A| = p < s \), where \( A \) is matched by \( \pi_{1..p} \). Decompose \( A = A'1^t \), where the last letter of \( A' \) is not \# . If \( A' \) is empty, define \( f(A) = (\emptyset, t) \). Otherwise, \( \pi_{1..p-t} \) matches \( A' \) and \( \pi[p-t] \neq \# \). Let \( X \) be a set of positions that contains \( p-t \) together with all positions \( i < p-t \) such that \( \pi_{1..i} \) matches a suffix of \( A' \). Define \( f(A) = (X,t) \). It is easy to see that \( (X,t) \in Q \), that \( (X,t) \) exists in \( S_\pi \) and is reachable by string \( A \).

Now show that for every reachable state \( (X,t) \in Q \) of \( S_\pi \) there exists \( A \in Q_{AC} \) such that \( f(A) = (X,t) \). Consider a string \( C \in \mathcal{A}^* \) that gets \( S_\pi \) to the state \( (X,t) \). Then \( C = C'1^t \) and the last letter of \( C' \) is not \#. If \( X \) is empty then define \( A = 1^t \). If \( X \) is not empty, then consider the suffix \( A' \) of \( C' \) of length \( x = \max \{ X \} \) and define \( A = A'1^t \). Since \( \pi_{1..x} \) matches \( A' \), and \( x + t \leq s \), then \( \pi_{1..x+t} \) matches \( A \) and therefore \( A \in Q_{AC} \). It is easy to see that \( f(A) = (X,t) \).

Observe that the mapping of Lemma 4 is actually a morphism from the Aho-Corasick automaton to \( S_\pi \).

Table 1 shows experimentally estimated average sizes of the Aho-Corasick automaton, subset seed automaton, and minimal automaton. The two tables correspond respectively to the binary alphabet (spaced seeds) and ternary alphabet (see Example 1). For Aho-Corasick and subset seed automata, the ratio to the average size of the minimal automaton is shown. Each line corresponds to a seed weight (\#-weight for \( |A| = 3 \)). In each case, 10000 random seeds of different span have been generated to estimate the average.
4 Subset seed automaton implementation

As in section 3, consider a subset seed $\pi$ of $\#$-weight $w$ and span $s$, and let $r = s - w$ be the number of non-$\#$ positions. A straightforward generation of the transition table of the automaton $S_\pi$ can be performed in time $O(r \cdot w \cdot 2^w |A|)$. In this section, we show that $S_\pi$ can be constructed in time proportional to its size, which is bounded by $(w+1)2^w$, according to Lemma 2. In practice, however, the number of states is usually much smaller.

The algorithm generates the states of the automaton incrementally by traversing them in the breadth-first manner. Transitions $\psi(\langle X, t \rangle, a)$ are computed using previously computed transitions $\psi(\langle X', t \rangle, a)$. A tricky part of the algorithm corresponds to the case where state $\psi(\langle X, t \rangle, a)$ has already been created before and should be retrieved.

The whole construction of the automaton is given in Algorithm 1. We now describe it in more details.

Let $R_\pi = \{z_1, \ldots, z_r\}$ and $z_1 < z_2 \cdots < z_r$. Consider $X \subseteq R_\pi$. To retrieve the maximal element of $X$, the algorithm maintains a function $k(X)$ defined by

$$k(X) = \max \{i | z_i \in X\}, \quad k(\emptyset) = 0.$$ 

Let $q = \langle X, t \rangle$ be a non-final and reachable state of $S_\pi$, $X = \{x_1, \ldots, x_i\} \subseteq R_\pi$ and $x_1 < x_2 \cdots < x_i$. We define $X' = X \setminus \{z_{k(X)}\} = \{x_1, \ldots, x_{i-1}\}$ and $q' = \langle X', t \rangle$. The following lemma holds.

**Lemma 5.** If $q = \langle X, t \rangle$ is reachable, then $q' = \langle X', t \rangle$ is reachable and has been processed before in a breadth-first computation of $S_\pi$. 

**Proof.** First prove that $\langle X', t \rangle$ is reachable. If $\langle X, t \rangle$ is reachable, then $\langle X, 0 \rangle$ is reachable due to the definition of transition function for $t > 0$. Thus, there is a word $A$ of length $x_i = z_{k(X)}$ such that $\forall j \in [1..r], z_j \in X$ iff the seed suffix $\pi_{1..z_j}$ matches the word suffix $A_{z_j+1} \cdots A_x$. Define $A'$ to be the suffix of $A$ of length $x_{i-1} = z_{k(X')} = |A'\cdot 1^t|$ and observe that reading $A'$ gets the automaton to the state $\langle X', 0 \rangle$, and then reading $A' \cdot 1^t$ leads to the state $\langle X', t \rangle$. Finally, as $|A'\cdot 1^t| < |A \cdot 1^t|$, then the breadth-first traversal of states of $A_x$ always processes state $\langle X', t \rangle$ before $\langle X, t \rangle$.

To retrieve $X'$ from $X$, the algorithm maintains a function $\text{Fail}(q)$, similar to the failure function of the Aho-Corasick automaton, such that $\text{Fail}(\langle X, t \rangle) = \langle X', t \rangle$ for $X \neq \emptyset$, and $\text{Fail}(\langle \emptyset, t \rangle) = \langle \emptyset, \max\{t-1, 0\} \rangle$. 

| $|A| = 2$ | Aho-Corasick | $S_\pi$ | Minimized | $|A| = 3$ | Aho-Corasick | $S_\pi$ | Minimized |
|---|---|---|---|---|---|---|---|
| $w$ | avg. ratio | avg. | $w$ | avg. ratio | avg. | $w$ | avg. ratio | avg. |
| 9 | 10.98 | 2.26 | 67.04 | 1.266 | 64.18 | 9 | 1103.6 | 16.46 | 96.71 | 1.284 | 87.05 |
| 10 | 140.28 | 2.51 | 70.27 | 1.255 | 55.98 | 10 | 1187.7 | 16.91 | 90.67 | 1.291 | 70.25 |
| 11 | 150.16 | 2.55 | 73.99 | 1.254 | 58.99 | 11 | 1265.3 | 17.18 | 95.05 | 1.291 | 73.65 |
| 12 | 159.26 | 2.57 | 77.39 | 1.248 | 62.00 | 12 | 1346.1 | 17.56 | 98.99 | 1.287 | 76.90 |
| 13 | 168.19 | 2.59 | 80.92 | 1.246 | 64.92 | 13 | 1419.3 | 17.67 | 103.10 | 1.284 | 80.34 |

Table 1. Average number of states of Aho-Corasick, $S_\pi$ and minimal automaton
We now explain how values \(\psi(q,a)\) are computed by Algorithm 1. Note first that if \(a = 1\), state \(\psi(q,a) = \langle X, t + 1 \rangle\) can be computed in constant time (part a. of Algorithm 1). Moreover, since this is the only way to reach state \(\langle X, t + 1 \rangle\), it is created and added once to the set of states.

Assume now that \(a \neq 1\). To compute \(\psi(q,a) = \langle Y, 0 \rangle\), we retrieve state \(q' = \text{Fail}(q) = \langle X', t \rangle\) and then retrieve \(\psi(q',a) = \langle Y', 0 \rangle\). Note that this is well-defined as by Lemma 5, \(q'\) has been processed before \(q\).

Observe now that since \(X'\) and \(X\) differ by only one seed prefix \(\pi_{1..z_k(X)}\), the only possible difference between \(Y\) and \(Y'\) can be the prefix \(\pi_{z_k(X)+t+1}\), depending on whether \(\pi_{z_k(X)+t+1}\) matches \(a\) or not. As \(a \neq 1\), this is equivalent to testing whether \((z_{k(X)}+t+1) \in R_\pi\) and \(\pi_{z_k(X)+t+1}\) matches \(a\). This information can be precomputed for different values \(k(X)\) and \(t\).

For every \(a \neq 1\), we define

\[
V(k,t,a) = \begin{cases} 
\{z_k + t + 1\} & \text{if } z_k + t + 1 \in R_\pi \text{ and } \pi_{z_k+t+1} \text{ matches } a, \\
\emptyset & \text{otherwise.}
\end{cases}
\]

Thus, \(Y = Y' \cup V(k(X),t,a)\) (part c. of Algorithm 1). Function \(V(k,t,a)\) can be precomputed in time and space \(O(|A| \cdot r \cdot s)\).

Note that if \(V(k,t,a)\) is empty, then \(\langle Y, 0 \rangle\) is equal to an already created state \(\langle Y', 0 \rangle\) and no new state needs to be created in this case (part e. of Algorithm 1).

If \(V(k,t,a)\) is not empty, we need to find out if \(\langle Y, 0 \rangle\) has already been created or not and if it has, we need to retrieve it. To do that, we need an additional construction. For each state \(q' = \langle X', t \rangle\), we maintain another function \(\text{RevMaxFail}(q')\), that gives the last created state \(q = \langle X, t \rangle\) such that \(X \backslash z_{k(X)} = X'\) (part d. of Algorithm 1). Since the state generation is breadth-first, new states \(\langle X, t \rangle\) are created in a non-decreasing order of the quantity \((z_{k(X)}+t)\).

Therefore, among all states \(\langle X, t \rangle\) such that \(\text{Fail}(\langle X, t \rangle) = \langle X', t \rangle\), \(\text{RevMaxFail}(\langle X', t \rangle)\) returns the one with the largest \(z_{k(X)}\).

Now, observe that if \(V(k,t,a)\) is not empty, i.e. \(Y = Y' \cup \{z_{k(X)} + t + 1\}\), then \(\text{Fail}(\langle Y, 0 \rangle) = \langle Y', 0 \rangle\). Since state \(\langle Y, 0 \rangle\) has the maximal possible current value \(z_{k(Y)} + 0 = z_{k(X)} + t + 1\), by the above remark, we conclude that if \(\langle Y, 0 \rangle\) has already been created, then \(\text{RevMaxFail}(\langle Y', 0 \rangle) = \langle Y, 0 \rangle\). This allows us to check if this is indeed the case and to retrieve the state \(\langle Y, 0 \rangle\) if it exists (part d. of Algorithm 1).

The generation of states \(\langle X, t \rangle\) with \(X = \emptyset\) represents a special case (part b. of Algorithm 1). Here another precomputed function is used:

\[
U(t,a) = \cup \{x | x \leq t + 1 \text{ and } a \text{ matches } \pi_x\}
\]

\(U(t,a)\) gives the set of seed prefixes that match the word \(1^t \cdot a\). In this case, checking if resulting states have been already added is done in a similar way to \(V(k,t,a)\). Details are left out.
Algorithm 1: computation of $S_\pi$

Data: a seed $\pi = \pi_1 \pi_2 \ldots \pi_s$
Result: an automaton $S_\pi = \langle Q, q_0, Q, \psi \rangle$

$q_F \leftarrow \text{createstate}(\langle \rangle); q_0 \leftarrow \text{createstate}(\langle \emptyset, 0 \rangle);$

/* process the first level of states to set Fail and RevMaxFail */

for $a \in A$ do

if $a \in \pi_1$ then

if $a = 1$ then

\[ (Y, t_y) \leftarrow (\emptyset, 1); \]

else

\[ (Y, t_y) \leftarrow (\{1\}, 0); \]

if $z_k(Y) + t_y \geq s$ then

\[ q_y \leftarrow q_F; \]

else

\[ q_y \leftarrow \text{createstate}(\langle Y, t_y \rangle); \]

\[ \text{Fail}(q_y) \leftarrow q_0; \]

\[ \text{RevMaxFail}(q_0) \leftarrow q_y; \]

push(Queue, $q_y$);

else

\[ q_y \leftarrow q_0; \]

\[ \psi(q_0, a) \leftarrow q_y; \]

/* breadth-first processing */

while Queue $\neq \emptyset$ do

\[ q : \langle X, t_X \rangle \leftarrow \text{pop}(\text{Queue}); q' \leftarrow \text{Fail}(q); \]

for $a \in A$ do

/* compute $\psi(\langle X, t_X \rangle, a) = \langle Y, t_y \rangle$ */

\[ q'_Y : \langle Y', t'_y \rangle \leftarrow \psi(q', a); \]

if $a = 1$ then

\[ Y \leftarrow X; \]

\[ t_y \leftarrow t_X + 1; \]

else

if $X = \emptyset$ then

\[ Y \leftarrow U(t_X, a); \]

else

\[ Y \leftarrow Y' \cup V(k(X), t_X, a); \]

\[ t_y \leftarrow 0; \]

/* create a new state unless it already exists or it is final */

\[ q_{rev} : \langle Y_{rev}, t_{rev} \rangle \leftarrow \text{RevMaxFail}(q'_y); \]

if defined($q_{rev}$) and $t_y = t_{rev}$ and $Y = Y_{rev}$ then

\[ q_y \leftarrow q_{rev}; \]

else if $t_y = t'_y$ and $Y = Y'$ then

\[ q_y \leftarrow q'_y; \]

else

if $z_k(Y) + t_y \geq s$ then

\[ q_y \leftarrow q_F; \]

else

\[ q_y \leftarrow \text{createstate}(\langle Y, t_y \rangle); \]

\[ \text{Fail}(q_y) \leftarrow q'_y; \]

\[ \text{RevMaxFail}(q'_y) \leftarrow q_y; \]

push(Queue, $q_y$);

\[ \psi(q, a) \leftarrow q_y; \]
We summarize the results of this section with the following Lemma.

**Lemma 6.** After a preprocessing of seed \( \pi \) within time \( O(|A| \cdot s^2) \), the automaton \( S_\pi \) can be constructed by incrementally generating all reachable states so that every transition \( \psi(q,a) \) is computed in constant time.

## 5 Possible extensions

An important remark is that the automaton defined in this paper can be easily generalized to the case of multiple seeds. For seeds \( \pi^1, \ldots, \pi^k \), a state of the automaton recognizing the alignments matched by one of the seeds would be a tuple \( <X_1, \ldots, X_k, t> \), where \( X_1, \ldots, X_k \) contain the set of respective prefixes, similarly to the construction of the paper. Interestingly, Lemma 4 still holds for the case of multiple seeds. This means that although the size of the union of individual seed automata could potentially grow as the product of sizes, it actually does not, as it is bounded by the size of the Aho-Corasick automaton which grows additively with respect to subsets of underlying words. In practice, our automaton is still substantially smaller than the Aho-Corasick automaton, as illustrated by Table 2. Similar to Table 1, 10000 random seed pairs have been generated here in each case to estimate the average size.

| \(|A| = 2\) | Aho-Corasick | \( S_\pi \) | Minimized |
|---|---|---|---|
| \( w \) | \( \text{avg. ratio} \) | \( \text{avg. ratio} \) | \( \text{avg.} \) | \( \text{avg. ratio} \) | \( \text{avg. ratio} \) | \( \text{avg.} \) |
| 9 | 224.49 | 2.09 | 122.82 | 1.10 | 111.43 |
| 10 | 243.32 | 2.07 | 129.68 | 1.10 | 117.71 |
| 11 | 264.04 | 2.11 | 137.78 | 1.10 | 125.02 |
| 12 | 282.51 | 2.15 | 144.97 | 1.10 | 131.68 |

| \(|A| = 3\) | Aho-Corasick | \( S_\pi \) | Minimized |
|---|---|---|---|
| \( w \) | \( \text{avg. ratio} \) | \( \text{avg. ratio} \) | \( \text{avg.} \) | \( \text{avg. ratio} \) | \( \text{avg. ratio} \) | \( \text{avg.} \) |
| 9 | 218.08 | 12.09 | 201.69 | 1.15 | 176.27 |
| 10 | 2297.8 | 12.53 | 209.75 | 1.14 | 183.40 |
| 11 | 2456.5 | 12.86 | 218.27 | 1.14 | 191.04 |
| 12 | 2600.6 | 13.14 | 226.14 | 1.14 | 198.00 |

Note that the text can also be composed of subset letters, with two possible matching interpretations [20]: a seed letter \( b \) matches a text letter \( a \) either if \( a \subseteq b \) or if \( a \cap b \neq \emptyset \).

Interestingly, the automaton construction of this paper still applies to these cases with minor modifications due to the absence of text letter 1 matched by any seed letter. With this modification, the automaton construction algorithm of Section 4 still applies. As a test case, we applied it to subset motif \([GACGT][AGT][AG]\) mentioned in [20] as a motif describing the translation initiation site in the \( E.coli \) genome. For a regular 4-letters genomic text, the automaton obtained with our approach has only 138 states, while the minimal automaton has 126 states. For a text composed of 15 subsets of 4 letters and the inclusion matching relation, our automaton contains
139 states, compared to 127 states of the minimal automaton. However, in the case of intersection matching relation, the automaton size increases drastically: it contains 87617 states compared to the 10482 states of the minimal automaton.

References

1. Kucherov, G., Noé, L., Roytberg, M.: A unifying framework for seed sensitivity and its application to subset seeds. JBCB 4(2) (2006) 553–569
2. Burkhardt, S., Kärkkäinen, J.: Better filtering with gapped q-grams. Fundamenta Informaticae 56(1-2) (2003) 51–70
3. Ma, B., Tromp, J., Li, M.: PatternHunter: Faster and more sensitive homology search. Bioinformatics 18(3) (2002) 440–445
4. Brown, D., Li, M., Ma, B.: A tutorial of recent developments in the seeding of local alignment. JBCB 2(4) (2004) 819–842
5. Brown, D.: A survey of seeding for sequence alignments. In: Bioinformatics Algorithms: Techniques and Applications. (2007) to appear.
6. Li, M., Ma, B., Kisman, D., Tromp, J.: PatternHunter II: Highly sensitive and fast homology search. Journal of Bioinformatics and Computational Biology 2(3) (2004) 417–439
7. Noé, L., Kucherov, G.: YASS: enhancing the sensitivity of DNA similarity search. Nucleic Acids Research 33 (web-server issue) (2005) W540–W543
8. Califano, A., Rigoutsos, I.: Flash: A fast look-up algorithm for string homology. In: Proceedings of the 1st International Conference on Intelligent Systems for Molecular Biology (ISMB). (1993) 56–64
9. Tsur, D.: Optimal probing patterns for sequencing by hybridization. In: Proc. 6th Workshop on Algorithms in Bioinformatics (WABI). Volume 4175 of LNCS. (2006) 366–375
10. Schwartz, S., Kent, J., Smit, A., Zhang, Z., Baertsch, R., Hardison, R., Haussler, D., Miller, W.: Human–mouse alignments with BLASTZ. Genome Research 13 (2003) 103–107
11. Sun, Y., Buhler, J.: Choosing the best heuristic for seeded alignment of DNA sequences. BMC Bioinformatics 7(133) (2006)
12. Csíkos, M., Ma, B.: Rapid homology search with two-stage extension and daughter seeds. In: Proceedings of the 11th International Computing and Combinatorics Conference (COCOON). Volume 3595 of LNCS. (2005) 104–114
13. Mak, D., Gelfand, Y., Benson, G.: Indel seeds for homology search. Bioinformatics 22(14) (2006) e341–e349
14. Brejová, B., Brown, D., Vinar, T.: Vector seeds: An extension to spaced seeds. Journal of Computer and System Sciences 70(3) (2005) 364–380
15. Keich, U., Li, M., Ma, B., Tromp, J.: On spaced seeds for similarity search. Discrete Applied Mathematics 138(3) (2004) 253–263 preliminary version in 2002.
16. Buhler, J., Keich, U., Sun, Y.: Designing seeds for similarity search in genomic DNA. In: Proceedings of the 7th Annual International Conference on Computational Molecular Biology (RECOMB). (2003) 67–75
17. Brejová, B., Brown, D., Vinar, T.: Optimal spaced seeds for homologous coding regions. Journal of Bioinformatics and Computational Biology 1(4) (2004) 595–610
18. Cole, R., Hariharan, R., Indyk, P.: Tree pattern matching and subset matching in deterministic $O(n \log^3 n)$-time. In: Proceedings of 10th Symposium on Discrete Algorithms (SODA). (1999) 245–254
19. Holub, J., Smyth, W.F., Wang, S.: Fast pattern-matching on indeterminate strings. Journal of Discrete Algorithms (2006)
20. Rahman, S., Iliopoulos, C., Mouchard, L.: Pattern matching in degenerate DNA/RNA sequences. In: Proceedings of the Workshop on Algorithms and Computation (WALCOM). (2007) 109–120
21. Noé, L., Kucherov, G.: Improved hit criteria for DNA local alignment. BMC Bioinformatics 5(149) (2004)
22. Aho, A.V., Corasick, M.J.: Efficient string matching: An aid to bibliographic search. Communications of the ACM 18(6) (1975) 333–340
23. Amir, A., Porat, E., Lewenstein, M.: Approximate subset matching with don’t cares. In: Proceedings of 12th Symposium on Discrete Algorithms (SODA). (2001) 305–306