

GENIOMHE

Sequence algorithms

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Contents

Motifs algorithms

1 Motif

1.1 Searching a substring in a string

Algorithm 1 Brute-force search of a motif in a sequence

```
1: function FindMotif( $S$ : Array( $n$ ),  $M$ : Array( $m$ ))
2:   returns a list of position
3:    $pos \leftarrow \{\}$ 
4:    $i \leftarrow 0$ 
5:   while  $i < n - m + 1$  do
6:      $j \leftarrow 0$ 
7:     while  $j < m$  and  $S[i + j] = M[j]$  do
8:        $j++$ 
9:     end while
10:    if  $j = m$  then
11:       $pos \leftarrow pos \cup \{i\}$ 
12:    end if
13:     $i++$ 
14:  end while
15:  return  $pos$ 
16: end function
```

1.2 Using matrices to search motifs

Let S_1 and S_2 be two sequences.

$S_1 = \text{ACGUUCC}$ $S_2 = \text{GUU}$

Let $n = |S_1|$, $m = |S_2|$. The complexity of this algorithm is $\mathcal{O}(n \cdot m)$ to build the matrix, and it requires also to find the diagonals and thus it is a bit less efficient than the ??.

To find repetitions, we can use a comparison matrix with a single sequence against itself. A repetition would appear as a diagonal of ones, not on the main diagonal.

Let $S = \text{ACGUUACGUU}$. Let's write the comparison matrix.

Algorithm 2 Knuth-Morris-Pratt algorithm

```

1: function KMP_Search( $S$ : Array( $n$ ),  $M$ : Array( $m$ ))
2:   returns Integer
3:    $table \leftarrow$  KMP_Table( $M$ )
4:    $c \leftarrow 0$ 
5:    $i \leftarrow 0$ 
6:    $j \leftarrow 0$ 
7:   while  $i < n$  do
8:     if  $S[i] = M[j]$  then
9:        $i \leftarrow i + 1$ 
10:       $j \leftarrow j + 1$ 
11:    end if
12:    if  $j = m$  then
13:       $c \leftarrow c + 1$ 
14:       $j \leftarrow table[j - 1]$ 
15:    else if  $j < n$  and  $M[j] \neq S[i]$  then
16:      if  $j \neq 0$  then
17:         $j \leftarrow table[j - 1]$ 
18:      else
19:         $i \leftarrow i + 1$ 
20:      end if
21:    end if
22:  end while
23:  return  $c$ 
24: end function
25: function KMP_Table( $M$ : Array( $m$ ))
26:  Returns Array( $m$ )
27:   $previous \leftarrow 0$ 
28:   $table \leftarrow$  array of zeros of size  $m$ 
29:  for  $i = 0; i < m; i ++$  do
30:    if  $M[i] = M[previous]$  then
31:       $previous \leftarrow previous + 1$ 
32:       $table[i] \leftarrow previous$ 
33:    else
34:      if  $previous = 0$  then
35:         $previous \leftarrow table[previous - 1]$ 
36:      else
37:         $table[i] \leftarrow 0$ 
38:      end if
39:    end if
40:  end for
41: end function

```

\triangleright Count the number of matches

	A	C	G	U	U	C	C
G	0	0	1	0	0	0	0
U	0	0	0	1	1	0	0
U	0	0	0	1	1	0	0

Table 1.1 Comparison matrix

1 Motif

	A	C	G	U	U	A	C	G	U	U	G	U	U
A	1	0	0	0	0	1	0	0	0	0	0	0	0
C	0	1	0	0	0	0	1	0	0	0	0	0	0
G	0	0	1	0	0	0	0	1	0	0	1	0	0
U	0	0	0	1	1	0	0	0	1	1	0	1	1
U	0	0	0	1	1	0	0	0	1	1	0	1	1
A	1	0	0	0	0	1	0	0	0	0	0	0	0
C	0	1	0	0	0	0	1	0	0	0	0	0	0
G	0	0	1	0	0	0	0	1	0	0	1	0	0
U	0	0	0	1	1	0	0	0	1	1	0	1	1
U	0	0	0	1	1	0	0	0	1	1	0	1	1
G	0	0	1	0	0	0	0	1	0	0	1	0	0
U	0	0	0	1	1	0	0	0	1	1	0	1	1
U	0	0	0	1	1	0	0	0	1	1	0	1	1

Algorithm 3 Construct a comparison matrix

```

1: function ComparisonMatrix( $S$ : Array( $n$ ))
2:    $M \leftarrow$  Array( $n, n$ )
3:   for ( $i = 0; i < n; i ++$ ) do
4:     for ( $j = 0; j < n; j ++$ ) do
5:       if  $S[i] = S[j]$  then
6:          $M[i][j] = 1$ 
7:       else
8:          $M[i][j] = 0$ 
9:       end if
10:    end for
11:  end for
12:  return  $M$ 
13: end function

```

Algorithm 4 Construct the top half of a comparison matrix

```

1: function ComparisonMatrix( $S$ : Array( $n$ ))
2:    $M \leftarrow$  Array( $n, n$ )
3:   for ( $i = 0; i < n; i ++$ ) do
4:     for  $j=i; j < n; j++$  do
5:       if  $S[i] = S[j]$  then
6:          $M[i][j] = 1$ 
7:       else
8:          $M[i][j] = 0$ 
9:       end if
10:    end for
11:  end for
12:  return  $M$ 
13: end function

```

Algorithm 5 Find repetitions (with a set of visited segments)

```

1: function FindRepetitions( $S$ : Array( $n$ ))
2:   returns A list of start and end positions for repeated sequences
3:    $M =$  ComparisonMatrix( $S$ )
4:    $pos = \{\}$ 
5:    $visited = \{\}$ 
6:   for ( $i_{start} = 0; i_{start} < n; i_{start} ++$ ) do
7:     for ( $j_{start} = i_{start} + 1; j_{start} < n; j_{start} ++$ ) do
8:       if  $M[i_{start}][j_{start}] = 1$  and  $(i_{start}, j_{start}) \notin visited$  then
9:          $i = i_{start}$ 
10:         $j = j_{start}$ 
11:        while  $M[i][j] = 1$  do
12:           $i ++$ 
13:           $j ++$ 
14:           $visited = visited \cup \{(i, j)\}$ 
15:        end while
16:         $pos = pos \cup \{(i_{start}, i), (j_{start}, j)\}$ 
17:      end if
18:    end for
19:  end for
20: end function

```

Algorithm 6 Find repetitions with an exploration of diagonals

```

1: function FindRepetitions( $S$ : Array( $n$ ))
2:   returns A list of start and end positions for repeted sequences
3:    $M = \text{ComparisonMatrix}(S)$ 
4:    $pos = \{\}$ 
5:   for ( $diag = 1$ ;  $diag < n$ ;  $diag++$ ) do
6:      $j = diag$ 
7:      $i = 0$ 
8:     while  $i < n$  and  $j < n$  do
9:       if  $M[i][j] = 1$  then
10:         $i_{start} = i$ 
11:         $j_{start} = j$ 
12:        while  $i < n$  and  $j < n$  and  $M[i][j] = 1$  do
13:           $i++$ 
14:           $j++$ 
15:        end while
16:         $pos = pos \cup \{(i_{start}, i - 1), (j_{start}, j - 1)\}$ 
17:      end if
18:       $i++$ 
19:       $j++$ 
20:    end while
21:  end for
22: end function

```

1.3 Automata

An automaton is a tuple $\langle S, s_0, T, \Sigma, f \rangle$

- S the set of states
- s_0 the initial state
- T the set of terminal states
- Σ the alphabet
- f the transition function $f : (s_1, c) \rightarrow s_2$

Example Given the language L on the alphabet $\Sigma = \{A, C, T\}$, $L = \{A^*, CTT, CA^*\}$

π Definition 1: Deterministic automaton

An automaton is deterministic, if for each couple $(p, a) \in S \times \Sigma$ it exists at most a state q such as $f(p, a) = q$

π Definition 2: Complete automaton

An automaton is complete, if for each couple $(p, a) \in S \times \Sigma$ it exists at least a state q such as $f(p, a) = q$.

Algorithm 7 Find repetitions with an exploration of diagonals, without nested while

```

1: function FindRepetitions( $S$ : Array( $n$ ))
2:   returns A list of start positions for repeted sequences and match length
3:    $M = \text{ComparisonMatrix}(S)$ 
4:    $pos = \{\}$ 
5:   for ( $diag = 1$ ;  $diag < n$ ;  $diag ++$ ) do
6:      $j = diag$ 
7:      $i = 0$ 
8:      $l = 0$ 
9:     while  $i < n$  and  $j < n$  do
10:      if  $M[i][j] = 1$  then
11:         $l ++$ 
12:      else
13:        if  $l > 0$  then
14:           $pos = pos \cup \{(i - l, j - l, l)\}$ 
15:           $l = 0$ 
16:        end if
17:      end if
18:       $i ++$ 
19:       $j ++$ 
20:    end while
21:    if  $l > 0$  then
22:       $pos = pos \cup \{(i - l, j - l, l)\}$ 
23:    end if
24:  end for
25:  return  $pos$ 
26: end function

```

Algorithm 8 Find repetitions

```

1: function FindRepetitions( $S$ : Array( $n$ ))
2:   returns A list of start and end positions for repeted sequences
3:    $M = \text{ComparisonMatrix}(S)$ 
4:    $pos = \{\}$ 
5:   for  $i_{start} = 0$ ;  $i_{start} < n$ ;  $i_{start} ++$  do
6:     for  $j_{start} = i_{start} + 1$ ;  $j_{start} < n$ ;  $j_{start} ++$  do
7:       if  $M[i_{start}][j_{start}] = 1$  then
8:          $i = i_{start}$ 
9:          $j = j_{start}$ 
10:        while  $M[i][j] = 1$  do
11:           $M[i][j] = 0$  ▷ Ensure that the segment is not explored again
12:           $i ++$ 
13:           $j ++$ 
14:        end while
15:         $pos = pos \cup \{(i_{start}, i - 1), (j_{start}, j - 1)\}$ 
16:      end if
17:    end for
18:  end for
19: end function

```

Algorithm 9 Check whether a word belongs to a language for which we have an automaton

```

1: function WordInLanguage( $W$ : Array( $n$ ),  $A$ :  $\langle S, s_0, T, \Sigma, f \rangle$ )
2:   returns A Boolean valued to true if the word is recognized by the language automaton
3:    $s \leftarrow s_0$ 
4:    $i \leftarrow 0$ 
5:   while  $i < n$  do
6:      $a \leftarrow W[i]$ 
7:     if  $\exists f(s, a)$  then
8:        $s \leftarrow f(s, a)$ 
9:     else
10:      return false
11:    end if
12:     $i++$ 
13:  end while
14:  if  $s \in T$  then
15:    return true
16:  else
17:    return false
18:  end if
19: end function

```

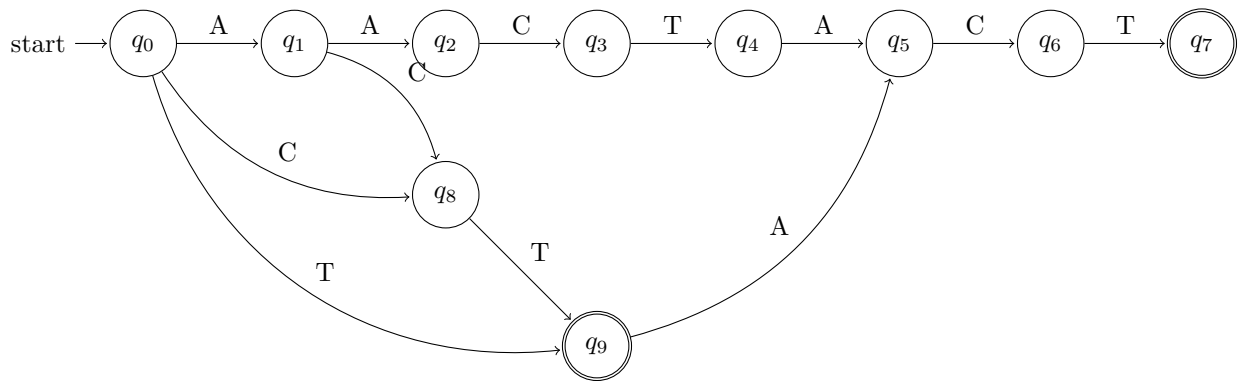


Figure 1.1 Suffix automaton for $S = AACTACT$

1.3.1 Suffix Automaton

Let $S = AACTACT$

A suffix automata recognize all suffix of a given sequence.

The suffix language of S is $\{S, ACTACT, CTACT, TACT, ACT, CT, T\}$.

The complexity of the pattern matching algorithm is $\mathcal{O}(n + m)$, because building the automaton is $\mathcal{O}(m)$

1.3.2 Automata for motif search

Let M be a motif $M = ACAT$.

The alphabet of motif is the same as the alphabet of the sequence. The search automaton is complete. If there exists a letter c in the sequence that is not in the motif alphabet, we can make a virtual transition from each state to the initial state whenever we encounter an unknown letter.

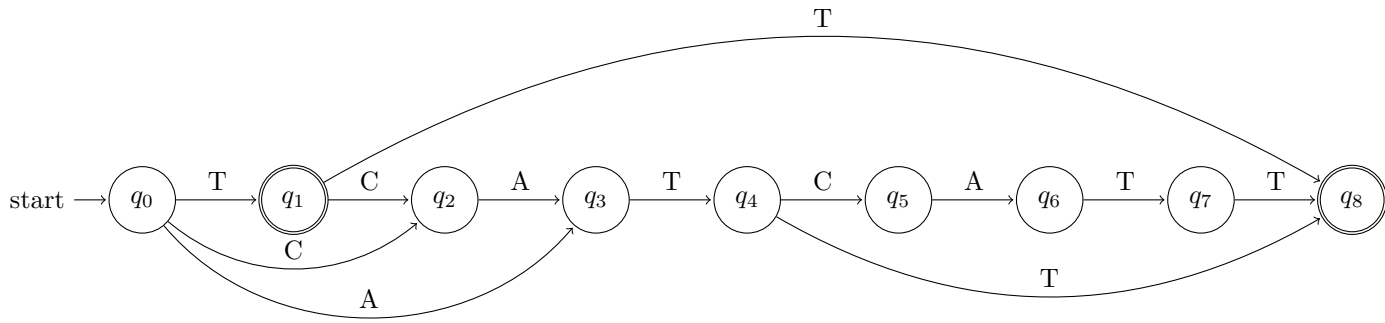


Figure 1.2 Suffix automaton for $S = TCATCATT$

Algorithm 10 Check if a sequences matches a motif, from a suffix automaton $\mathcal{O}(m)$, built from the automaton

```

1: function CheckMotifInSuffixAutomaton( $W$ : Array( $m$ ),  $A$ :  $\langle S, s_0, T, \Sigma, f \rangle$ )
2:   returns Boolean valued to true if the motif is in the sequence
3:    $s \leftarrow s_0$ 
4:    $i \leftarrow 0$ 
5:   while  $i < m$  and  $\exists f(s, W[i])$  do
6:      $s \leftarrow f(s, W[i])$ 
7:      $i ++$ 
8:   end while
9:   if  $i = n$  then
10:    return true
11:  else
12:    return false
13:  end if
14: end function

```

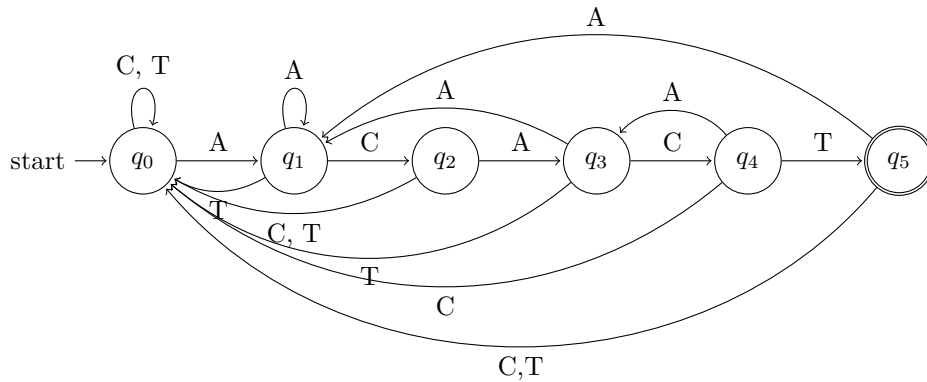


Figure 1.3 Motif search automaton for $M = ACAT$

Algorithm 11 Search a motif in a sequence with an automaton

```

1: function SearchMotif( $S$ : Array( $n$ ),  $A$ :  $\langle S, s_0, T, \Sigma, f \rangle$ ,  $P$ : Array( $m$ ))
2:   returns A set of positions where the motif has been found
3:    $s \leftarrow s_0$ 
4:    $i \leftarrow 0$ 
5:    $pos \leftarrow \{\}$ 
6:   while  $i < n$  do
7:     if  $s \in T$  then
8:        $pos \leftarrow pos \cup \{i - m\}$ 
9:     end if
10:     $s \leftarrow f(s, S[i])$ 
11:     $i++$ 
12:  end while
13:  return  $pos$ 
14: end function

```

Algorithm 12 Check if the a motif automaton recognizes only the prefix of size $m - 1$ of a motif P of size m

```

1: function SearchMotifLastPrefix( $S$ : Array( $n$ ),  $A$ :  $\langle S, s_0, T, \Sigma, f \rangle$ ,  $P$ : Array( $m$ ))
2:   returns A set of positions where the motif has been found
3:    $s \leftarrow s_0$ 
4:    $i \leftarrow 0$ 
5:    $T_{new} \leftarrow \{\}$ 
6:   for  $s \in S$  do
7:     for  $a \in \Sigma$  do
8:       for  $t \in T$  do
9:         if  $\exists f(s, a)$  and  $f(s, a) = t$  then
10:           $T_{new} \leftarrow T_{new} \cup s$ 
11:        end if
12:      end for
13:    end for
14:  end for
15:  while  $i < n$  do
16:    if  $s \in T_{new}$  then
17:      return true
18:    end if
19:     $s \leftarrow f(s, S[i])$ 
20:     $i++$ 
21:  end while
22:  return false
23: end function

```

Algorithm 13 Check if the a motif automaton recognizes only the prefix of size $m - 1$ of a motif P of size m , knowing the sequence of the motif

```

1: function SearchMotifLastPrefix( $S$ : Array( $n$ ),  $A$ :  $\langle S, s_0, T, \Sigma, f \rangle$ ,  $P$ : Array( $m$ ))
2:   returns A set of positions where the motif has been found
3:    $s \leftarrow s_0$ 
4:    $i \leftarrow 0$ 
5:   while  $i < n$  and  $f(s, P[m - 1]) \notin T$  do
6:      $s \leftarrow f(s, S[i])$ 
7:      $i++$ 
8:   end while
9:   if  $f(s, P[m - 1]) \in T$  then
10:    return true
11:  else
12:    return false
13:  end if
14: end function

```

2 Longest common subsequence

Let $S_1 = \text{ATCTGAT}$ and $S_2 = \text{TGCATA}$. In this case the longest common subsequence of S_1 and S_2 is $TCTA$.

Algorithm 14 Construct a longest common subsequence matrix

```
1: function LCSQ_Matrix( $S_1$ : Array( $n$ ),  $S_2$ : Array( $m$ ))
2:    $M \leftarrow$  Array( $m + 1$ ,  $n + 1$ )
3:   for ( $i = 0$ ;  $i < n + 1$ ;  $i++$ ) do
4:     for  $j = 0$ ;  $j < m + 1$ ;  $j++$  do
5:       if  $i = 0$  or  $j = 0$  then
6:          $M[i][j] = 0$ 
7:       else
8:         if  $S_1[i] = S_2[j]$  then
9:            $match = M[i - 1][j - 1] + 1$ 
10:        else
11:           $match = M[i - 1][j - 1]$ 
12:        end if
13:         $gap_1 = M[i - 1][j]$ 
14:         $gap_2 = M[i][j - 1]$ 
15:         $M[i][j] = \max\{match, gap_1, gap_2\}$ 
16:      end if
17:    end for
18:  end for
19:  return  $M$ 
20: end function
```

Algorithm 15 Construct a longest common subsequence matrix keeping the path in memory

```

1: function LCSQ_Matrix_Path( $S_1$ : Array( $n$ ),  $S_2$ : Array( $m$ ))
2:    $M \leftarrow$  Array( $m + 1$ ,  $n + 1$ )
3:    $P \leftarrow$  Array( $m + 1$ ,  $n + 1$ )
4:   for ( $i = 0$ ;  $i < n + 1$ ,  $i++$ ) do
5:      $M[i][0] \leftarrow 0$ 
6:   end for
7:   for ( $j = 0$ ;  $j < m + 1$ ;  $j++$ ) do
8:      $M[0][j] \leftarrow 0$ 
9:   end for
10:  for ( $i = 1$ ;  $i < n + 1$ ;  $i++$ ) do
11:    for ( $j = 1$ ;  $j < m + 1$ ;  $j++$ ) do
12:      if  $i = 1$  or  $j = 0$  then
13:         $M[i][j] = 0$ 
14:      else
15:        if  $S_1[i - 1] = S_2[j - 1]$  then
16:           $M[i][j] \leftarrow M[i - 1][j - 1] + 1$ 
17:           $P[i][j] \leftarrow \swarrow$ 
18:        else if  $M[i][j - 1] \geq M[i - 1][j]$  then
19:           $M[i][j] \leftarrow M[i][j - 1]$ 
20:           $P[i][j] \leftarrow \leftarrow$ 
21:        else
22:           $M[i][j] \leftarrow M[i - 1][j]$ 
23:           $P[i][j] \leftarrow \downarrow$ 
24:        end if
25:      end if
26:    end for
27:  end for
28:  return  $M, P$ 
29: end function

```

Algorithm 16 Backtrack the longest common subsequence

```

1: function LCSQ( $S_1$ : Array( $n$ ),  $S_2$ : Array( $m$ ))
2:    $M, P \leftarrow$  LCSQ_Matrix( $S_1, S_2$ )
3:    $L \leftarrow$  Array( $M[n][m]$ )
4:    $k \leftarrow 0$ 
5:    $i \leftarrow n$ 
6:    $j \leftarrow m$ 
7:   while  $i > 0$  and  $j > 0$  do
8:     if  $P[i][j] = '\diagdown'$  then
9:        $L[k] \leftarrow S_1[i]$ 
10:       $i --$ 
11:       $j --$ 
12:       $k ++$ 
13:     else if  $P[i][j] = '\leftarrow'$  then
14:        $j --$ 
15:     else
16:        $i --$ 
17:     end if
18:   end while
19:   return  $L$ 
20: end function

```

Sequence alignment

3 Definitions

A function d is a distance between two sequences x and y in an alphabet Σ if

- $x, y \in \Sigma^*, d(x, x) = 0$
- $\forall x, y \in \Sigma^* d(x, y) = d(y, x)$
- $\forall x, y, z \in \Sigma^* d(x, z) \leq d(x, y) + d(x, z)$

Here we are interested by the distance that is able to represent the transformation of x to y using three types of basic operations:

- Substitution
- Insertion
- Deletion

Example:

- $sub(a, b) = \begin{cases} 0 & \text{if } a = b \\ 1 & \text{otherwise} \end{cases}$
- $del(a) = 1$
- $ins(a) = 1$

Let $X = x_0x_1 \dots x_{m-1}$, $Y = y_0y_1 \dots y_{n-1}$

An alignment is noted as $z = \begin{pmatrix} \bar{x}_0 \\ \bar{y}_0 \end{pmatrix} \dots \begin{pmatrix} \bar{x}_{p-1} \\ \bar{y}_{p-1} \end{pmatrix}$ of size p . $n \leq p \leq n + m$

$\bar{x}_i = x_j$ or $\bar{x}_i = \varepsilon$ for $0 \leq i \leq p - 1$ and $0 \leq j \leq m - 1$

$\bar{y}_i = y_j$ or $\bar{y}_i = \varepsilon$ for $0 \leq i \leq p - 1$ and $0 \leq j \leq n - 1$

$X' = \bar{x}_0\bar{x}_1 \dots \bar{x}_i \dots \bar{x}_{p-1}$ $Y' = \bar{y}_0\bar{y}_1 \dots \bar{y}_i \dots \bar{y}_{p-1}$ for $0 \leq i \leq p - 1$, $\nexists i$, such that $\bar{x}_i = \bar{y}_i = \varepsilon$

4 Sequence alignment

Algorithm 17 Needleman-Wunsch Algorithm

```
1: procedure FillMatrix( $S_1$ : Array( $m$ ),  $S_2$ : Array( $n$ ))  $\triangleright$   $sub(a, b)$  is the substitution score,  $del(a)$  and
    $ins(a)$  are the deletion and insertion penalty, in regard with the reference  $S_1$  sequence
2:    $M = \text{Array}(m + 1, n + 1)$   $\triangleright$  Initialize the matrix first column and first row
3:    $P = \text{Array}(m, n)$   $\triangleright$  Store the direction of the cell we chose to build the next cell up on.
4:    $M[0][0] = 0$ 
5:   for ( $i = 1; i < m + 1; i ++$ ) do
6:      $M[i][0] = M[i - 1][0] + gap\_penalty$ 
7:   end for
8:   for ( $j = 1; j < n + 1; j ++$ ) do
9:      $M[0][j] = M[0][j - 1] + gap\_penalty$ 
10:  end for  $\triangleright$  Fill the remaining matrix
11:  for ( $i = 1; i < m + 1; i ++$ ) do
12:    for ( $j = 1; j < n + 1; j ++$ ) do
13:       $delete = M[i - 1][j] + gap\_penalty$ 
14:       $insert = M[i][j - 1] + gap\_penalty$ 
15:       $substitute = M[i - 1][j - 1] + sub(S_1[i - 1], S_2[j - 1])$ 
16:       $choice = \min\{delete, insert, substitute\}$ 
17:      if  $substitute = choice$  then
18:         $P[i - 1][j - 1] = '\nwarrow'$ 
19:      else if  $deletion = choice$  then
20:         $P[i - 1][j - 1] = '\leftarrow'$ 
21:      else
22:         $P[i - 1][j - 1] = '\uparrow'$ 
23:      end if
24:       $M[i][j] = choice$ 
25:    end for
26:  end for
27: end procedure
```

Algorithm 18 Needleman-Wunsch Algorithm (Backtrack)

```

1: procedure ShowAlignment( $S_1$ : Array( $m$ ),  $S_2$ : Array( $n$ ))
2:    $extend_1 = ""$ 
3:    $extend_2 = ""$ 
4:    $i = m$ 
5:    $j = n$ 
6:   while  $i > 0$  and  $j > 0$  do
7:     if  $P[i - 1][j - 1] = '\nwedge'$  then
8:        $extend_1 = S_1[i - 1] \circ extend_1$ 
9:        $extend_2 = S_2[j - 1] \circ extend_2$ 
10:       $i --$ 
11:       $j --$ 
12:     else if  $P[i - 1][j - 1] = '\uparrow'$  then
13:        $extend_1 = S_1[i - 1] \circ extend_1$ 
14:        $extend_2 = '-' \circ extend_2$ 
15:        $i --$ 
16:     else
17:        $extend_1 = '-' \circ extend_1$ 
18:        $extend_2 = S_2[j - 1] \circ extend_2$ 
19:        $j --$ 
20:     end if
21:   end while
22:   while  $i > 0$  do
23:      $extend_1 = S_1[i - 1] \circ extend_1$ 
24:      $extend_2 = '-' \circ extend_2$ 
25:      $i --$ 
26:     Insert(0,  $alignment, tuple$ )
27:   end while
28:   while  $j > 0$  do
29:      $extend_1 = '-' \circ extend_1$ 
30:      $extend_2 = S_2[j - 1] \circ extend_2$ 
31:      $j --$ 
32:   end while
33:   print( $extend_1$ )
34:   print( $extend_2$ )
35: end procedure
36: FillMatrix( $S_1, S_2$ )
37: ShowAlignment( $S_1, S_2$ )

```

Algorithm 19 Needleman-Wunsch Algorithm, using proper notation

```

1: procedure FillMatrix( $S_1$ : Array( $m$ ),  $S_2$ : Array( $n$ ))
2:    $M$  = Array( $m + 1$ ,  $n + 1$ )
3:    $P$  = Array( $m$ ,  $n$ )           ▷ Store the direction of the cell we chose to build the next cell up on.
4:    $M[0][0] = 0$ 
5:   for ( $i = 1$ ;  $i < m + 1$ ;  $i++$ ) do
6:      $M[i][0] = M[i - 1][0] + gap\_penalty$ 
7:   end for
8:   for ( $j = 1$ ;  $j < n + 1$ ;  $j++$ ) do
9:      $M[0][j] = M[0][j - 1] + gap\_penalty$ 
10:  end for
11:  for ( $i = 1$ ;  $i < m + 1$ ;  $i++$ ) do
12:    for ( $j = 1$ ;  $j < n + 1$ ;  $j++$ ) do
13:       $delete = M[i - 1][j] + gap\_penalty$ 
14:       $insert = M[i][j - 1] + gap\_penalty$ 
15:       $substitute = M[i - 1][j - 1] + sub(S_1[i - 1], S_2[j - 1])$ 
16:       $M[i][j] = \min\{substitute, insert, delete\}$ 
17:    end for
18:  end for
19: end procedure

```

Algorithm 20 Needleman-Wunsch Algorithm, using proper notation (Backtrack)

```

1: procedure BacktrackAlignment( $S_1$ : Array( $m$ ),  $S_2$ : Array( $n$ ))
2:    $alignment = LinkedList$ 
3:    $i = m$ 
4:    $j = n$ 
5:   while  $i > 0$  and  $j > 0$  do
6:     if  $M[i-1][j-1] = M[i][j] - sub(S_1[i-1], S_2[j-1])$  then
7:        $tuple = \begin{pmatrix} S_1[i-1] \\ S_2[j-1] \end{pmatrix}$ 
8:        $i --$ 
9:        $j --$ 
10:    else if  $M[i-1][j-1] = M[i][j-1] - gap\_penalty$  then
11:       $tuple = \begin{pmatrix} S_1[i-1] \\ \varepsilon \end{pmatrix}$ 
12:       $i --$ 
13:    else
14:       $tuple = \begin{pmatrix} \varepsilon \\ S_2[j-1] \end{pmatrix}$ 
15:       $j --$ 
16:    end if
17:    Insert(0,  $alignment, tuple$ )
18:  end while
19:  while  $i > 0$  do
20:     $tuple = \begin{pmatrix} S_1[i-1] \\ \varepsilon \end{pmatrix}$ 
21:     $i --$ 
22:    Insert(0,  $alignment, tuple$ )
23:  end while
24:  while  $j > 0$  do
25:     $tuple = \begin{pmatrix} \varepsilon \\ S_2[j-1] \end{pmatrix}$ 
26:     $j --$ 
27:    Insert(0,  $alignment, tuple$ )
28:  end while
29: end procedure
30: FillMatrix( $S_1, S_2$ )
31: BacktrackAlignment( $S_1, S_2$ )

```

Algorithm 21 Backtrack a single alignment in a recursive way

```

1:  $S_1$ : Array( $m$ ),  $S_2$ : Array( $n$ ),  $M$ : Array( $m + 1$ ,  $n + 1$ ),
2: function BacktrackRecurse( $i$ ,  $j$ )
3:   if  $i > 0$  and  $j > 0$  then
4:      $substitute = M[i - 1][j - 1]$ 
5:      $delete = M[i - 1][j]$ 
6:      $insert = M[i][j - 1]$ 
7:      $min = \min\{substitute, delete, insert\}$ 
8:     if  $substitute = min$  then
9:        $z = \text{BacktrackRecurse}(S_1, S_2, M, i - 1, j - 1)$ 
10:       $z = \begin{pmatrix} S_1[i - 1] \\ S_2[j - 1] \end{pmatrix} \circ z$ 
11:     else if  $delete = min$  then
12:        $z = \text{BacktrackRecurse}(S_1, S_2, M, i - 1, j)$ 
13:       $z = \begin{pmatrix} S_1[i - 1] \\ \varepsilon \end{pmatrix} \circ z$ 
14:     else
15:        $z = \text{BacktrackRecurse}(S_1, S_2, M, i, j - 1)$ 
16:       $z = \begin{pmatrix} \varepsilon \\ S_2[j - 1] \end{pmatrix} \circ z$ 
17:     end if
18:     else if  $i > 0$  then
19:        $z = \text{BacktrackRecurse}(S_1, S_2, M, i - 1, j)$ 
20:       $z = \begin{pmatrix} S_1[i - 1] \\ \varepsilon \end{pmatrix} \circ z$ 
21:     else if  $j > 0$  then
22:        $z = \text{BacktrackRecurse}(S_1, S_2, M, i, j - 1)$ 
23:       $z = \begin{pmatrix} S_1[i - 1] \\ \varepsilon \end{pmatrix} \circ z$ 
24:     else
25:       return []
26:     end if
27:
28:   return  $z$ 
29:
30: end function
31: function Backtrack( $S_1$ : Array( $m$ ),  $S_2$ : Array( $n$ ),  $M$ : Array( $m + 1$ ,  $n + 1$ ))
32:   return BacktrackRecurse( $S_1, S_2, M, m, n$ )
33: end function

```

Algorithm 22 Backtrack all the optimum alignments in a recursive way

```

1: procedure BacktrackRecurse( $S_1$ : Array( $m$ ),  $S_2$ : Array( $n$ ),  $M$ : Array( $m + 1$ ,  $n + 1$ ),  $i$ ,  $j$ )
2:   if  $i > 0$  and  $j > 0$  then
3:      $substitute = M[i - 1][j - 1]$ 
4:      $delete = M[i - 1][j]$ 
5:      $insert = M[i][j - 1]$ 
6:      $min = \min\{substitute, delete, insert\}$ 
7:     if  $substitute = min$  then
8:        $value = \begin{pmatrix} S_1[i - 1] \\ S_2[j - 1] \end{pmatrix}$ 
9:        $z' = value \circ z$ 
10:      BacktrackRecurse( $S_1$ ,  $S_2$ ,  $M$ ,  $i - 1$ ,  $j - 1$ ,  $z'$ )
11:     end if
12:     if  $delete = min$  then
13:        $value = \begin{pmatrix} S_1[i - 1] \\ \varepsilon \end{pmatrix}$ 
14:        $z' = value \circ z$ 
15:       BacktrackRecurse( $S_1$ ,  $S_2$ ,  $M$ ,  $i - 1$ ,  $j$ ,  $z'$ )
16:     end if
17:     if  $insert = min$  then
18:        $value = \begin{pmatrix} \varepsilon \\ S_2[j - 1] \end{pmatrix}$ 
19:        $z' = value \circ z$ 
20:       BacktrackRecurse( $S_1$ ,  $S_2$ ,  $M$ ,  $i$ ,  $j - 1$ ,  $z'$ )
21:     end if
22:     else if  $i > 0$  then
23:        $value = \begin{pmatrix} S_1[i - 1] \\ \varepsilon \end{pmatrix}$ 
24:        $z' = value \circ z$ 
25:       BacktrackRecurse( $S_1$ ,  $S_2$ ,  $M$ ,  $i - 1$ ,  $j$ ,  $z'$ )
26:     else if  $j > 0$  then
27:        $value = \begin{pmatrix} \varepsilon \\ S_2[j - 1] \end{pmatrix}$ 
28:        $z' = value \circ z$ 
29:       BacktrackRecurse( $S_1$ ,  $S_2$ ,  $M$ ,  $i$ ,  $j - 1$ ,  $z'$ )
30:     else
31:       print( $z$ )
32:     end if
33: end procedure
34: procedure Backtrack( $S_1$ : Array( $m$ ),  $S_2$ : Array( $n$ ),  $M$ : Array( $m + 1$ ,  $n + 1$ ))
35:   return BacktrackRecurse( $S_1$ ,  $S_2$ ,  $M$ ,  $m$ ,  $n$ , [])
36: end procedure

```
