Comparison of multiple biological sequences

Project in Bioinformatics
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MSA and SP score

$$M = \begin{bmatrix} A & C & C & A & C & C & A & G & - & G & T \\ G & C & - & A & - & C & T & - & A & - & T \\ A & C & C & - & - & A & T & G & A & G & G \end{bmatrix} \begin{array}{l} \rangle \textcircled{1} \\ \rangle \textcircled{2} \end{array} \rangle \textcircled{3}$$

$$A_1 = \begin{bmatrix} A & C & C & A & C & C & A & G & - & G & T \\ G & C & - & A & - & C & T & - & A & - & T \end{bmatrix} \quad \textcircled{1}$$

$$A_2 = \begin{bmatrix} G & C & - & A & \cancel{-} & C & T & - & A & - & T \\ A & C & C & - & \cancel{-} & A & T & G & A & G & G \end{bmatrix} \quad \textcircled{2}$$

$$A_3 = \begin{bmatrix} A & C & C & A & C & C & A & G & - & G & T \\ A & C & C & - & - & A & T & G & A & G & G \end{bmatrix} \quad \textcircled{3}$$

$$\begin{aligned} SP(M) &= \sum_{0 \le c < \ell} \sum_{0 \le i < j < k} d(M_{i,c}, M_{j,c}) \\ &= \sum_{0 \le i < j < k} \sum_{0 \le c < \ell} d(M_{i,c}, M_{j,c}). \end{aligned}$$

MSA and SP score

$$M = \left[\begin{array}{ccccccccccc} A & C & C & A & C & C & A & G & - & G & T \\ G & C & - & A & - & C & T & - & A & - & T \\ A & C & C & - & - & A & T & G & A & G & G \end{array}\right] \begin{array}{l} \big\rangle \text{①} \\ \big\rangle \text{②} \end{array} \Big\rangle \text{③}$$

$$A_1 = \left[\begin{array}{ccccccccccc} A & C & C & A & C & C & A & G & - & G & T \\ G & C & - & A & - & C & T & - & A & - & T \end{array}\right] \quad \text{①}$$

$$A_2 = \left[\begin{array}{ccccccccccc} G & C & - & A & \cancel{-} & C & T & - & A & - & T \\ A & C & C & - & \cancel{-} & A & T & G & A & G & G \end{array}\right] \quad \text{②}$$

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- Dyn. prog.: $O(n^k)$.

MSA and SP score

$$M = \begin{bmatrix} A & C & C & A & C & C & A & G & - & G & T \\ G & C & - & A & - & C & T & - & A & - & T \\ A & C & C & - & - & A & T & G & A & G & G \end{bmatrix} \begin{array}{l} \rangle \textcircled{1} \\ \rangle \textcircled{2} \end{array} \Big\rangle \textcircled{3}$$

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$$SP(M) = \sum_{0 \le c < \ell} \sum_{0 \le i < j < k} d(M_{i,c}, M_{j,c}) = \sum_{0 \le i < j < k} \sum_{0 \le c < \ell} d(M_{i,c}, M_{j,c}).$$

- Dyn. prog.: $O(n^k)$.
- Gusfield and MST algo.: $O(k^2 n^2)$.

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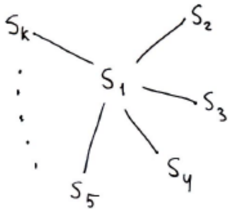
Gusfield's approximation algorithm

$$\arg\min_{S_1} \sum_{s \in S} OPT(S_1, s).$$



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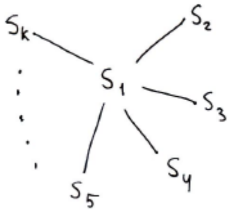

Algorithm GUSFIELD-MSA(S)

```
1: $S_1 \leftarrow center(S)$
2: $M \leftarrow [\,]$
3: for $i = 2$ to $k$ do
4:     $A \leftarrow align(S_1, S_i)$
5:     $M \leftarrow extend(M, A)$
6: end for
7: return $M$
```

Gusfield's approximation algorithm

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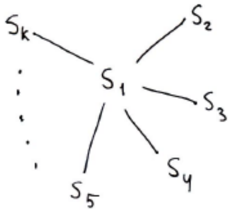

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- Time $O(k^2 n^2)$.

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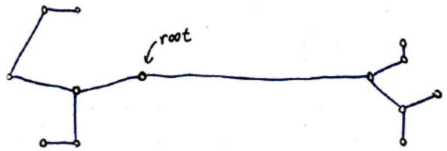
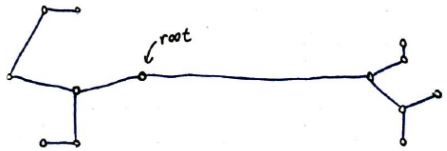
MST algorithm



MST algorithm



Algorithm MST-MSA(MST)

```
1: $M \leftarrow [\,]$
2: for $(S_i, S_j) \in MST$ do
3:     $A \leftarrow align(S_i, S_j)$
4:     $M \leftarrow extend(M, A)$
5: end for
6: return $M$
```

Prim's algorithm

Algorithm MST-PRIM-SIMPLE($G, w, root$)

```
1: for each $u \in V[G]$ do
2:     $key[u] \leftarrow \infty$
3:     $\pi[u] \leftarrow NIL$
4: end for
5: $key[root] \leftarrow 0$
6: for $i = 1$ to $|V[G]|$ do
7:     $u \leftarrow$ FIND-MIN($V[G], key$)
8:     report $(\pi[u], u)$
9:     for each $v \in Adj[u]$ do
10:        if $v \notin MST$ and $w(u, v) < key[v]$ then
11:            $\pi[v] \leftarrow u$
12:            $key[v] \leftarrow w(u, v)$
13:        end if
14:    end for
15: end for
```

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Implementation

```python
def MST_MSA_approx(seq_indices, seqs, sub_matrix, gap_cost):
    M = []
    # Keep track of seq index vs row index in M
    seq_idx_to_row = [None] * len(seq_indices)
    # Iterate MST edges
    MST = MST_prim(seq_indices, seqs, sub_matrix, gap_cost)
    for i in range(len(MST)):
        # Edge (parent, node)
        parent = MST[i][0]
        node = MST[i][1]
        # Fill out dyn. prog. table for pairwise alignment
        table = fill_table(seqs[parent], seqs[node],
                    sub_matrix, gap_cost)
        # Construct opt. pairwise align. from table
        A = construct_alignment(table, seqs[parent], seqs[node],
                sub_matrix, gap_cost)
        if i == 0:
            seq_idx_to_row[parent] = 0
            seq_idx_to_row[node] = 1
            M = A
        else:
            seq_idx_to_row[node] = len(M)
            M = extend_M(M, A, seq_idx_to_row[parent])
    return M
```

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Running time

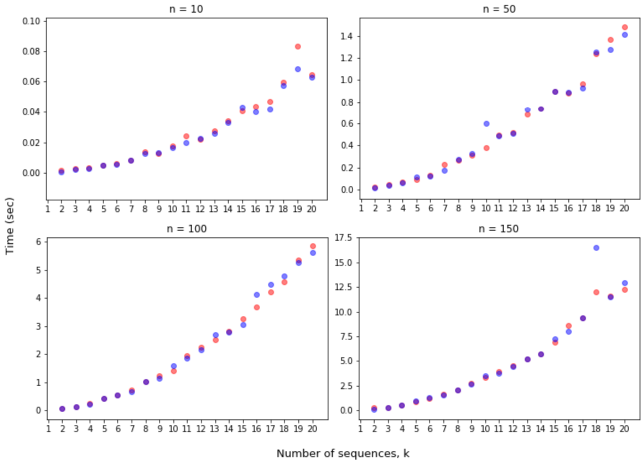


Figure: Running time of the two algorithms on random data as a function of k for four different values of n. Gusfield is red, MST is blue.

Running time

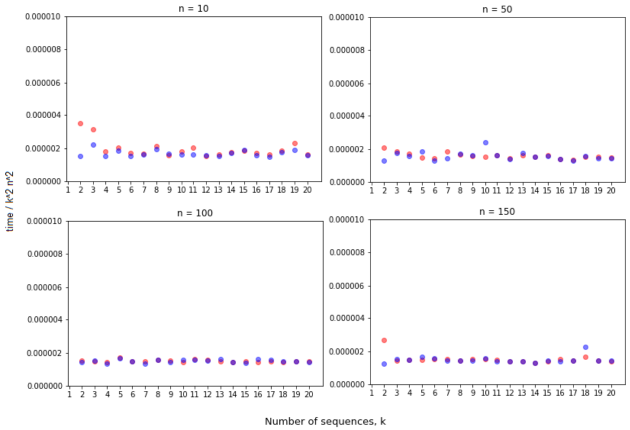


Figure: Running time of the two algorithms divided by expected worst case running time, k^2n^2, on random data. Gusfield is red, MST is blue.

SP score - random data

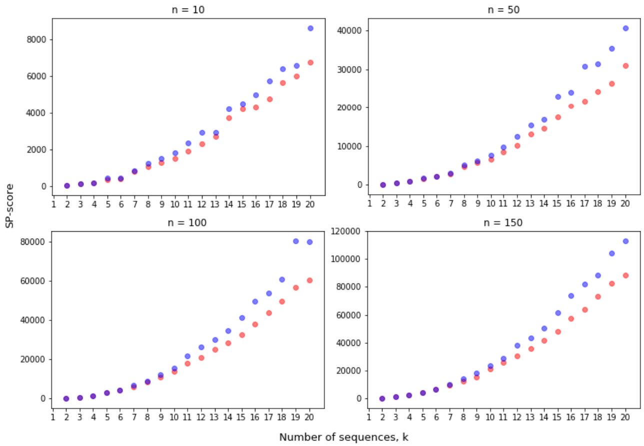


Figure: SP scores for the two algorithms as a function of *k* for four different values of *n* on random data. Gusfield is red, MST is blue.

SP score - low mutation rate data

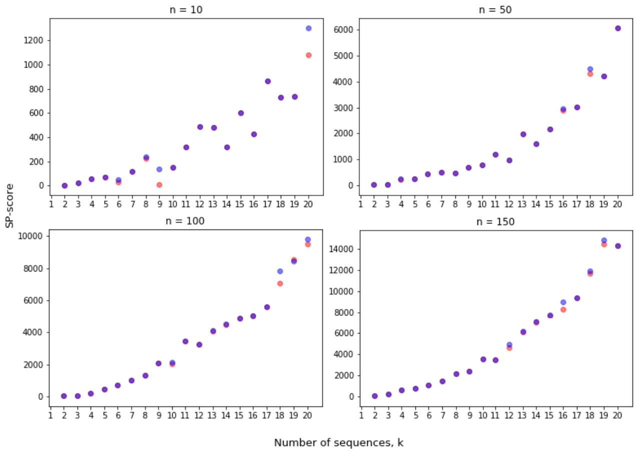
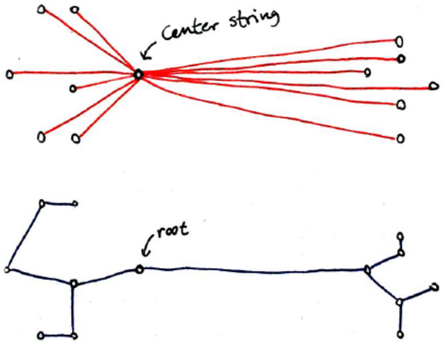


Figure: SP scores for the two algorithms as a function of *k* for four different values of *n* for simulated data with a low substitution rate of 0.05. Gusfield is red, MST is blue.

Clustered data



SP score - two clusters

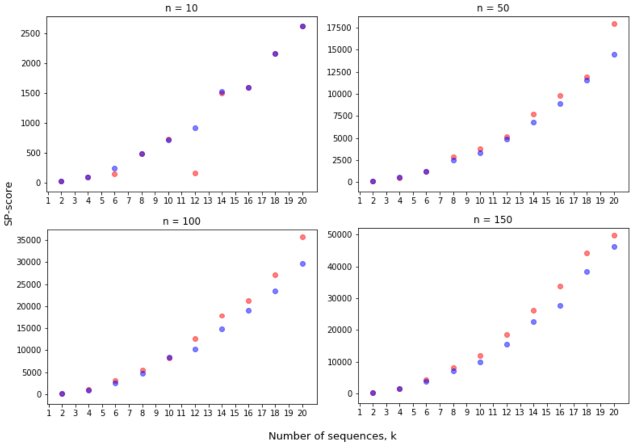
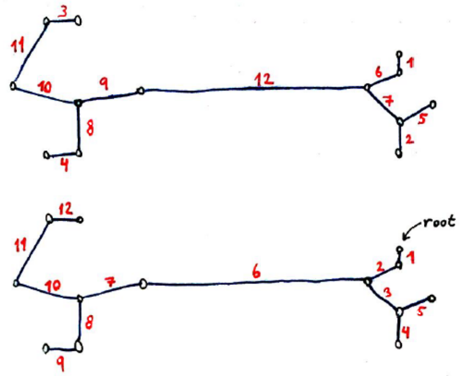


Figure: SP scores for the two algorithms as a function of *k* for four different values of *n* for simulated data consisting of two clusters (each made with a low substitution rate of 0.05). Gusfield is red, MST is blue.

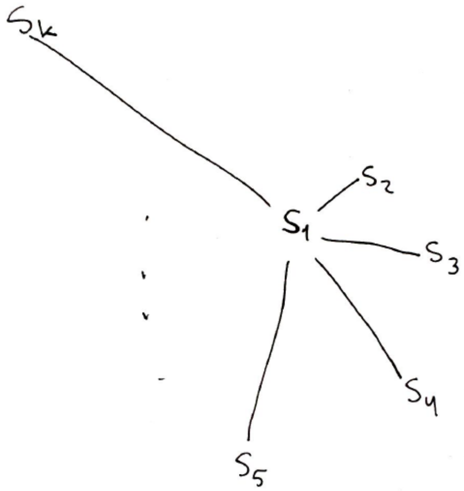
Conclusion

- Random data, high mutation rate: Gusfield is best.
- Low mutation rate: Very similar results.
- Two clusters: MST is best.

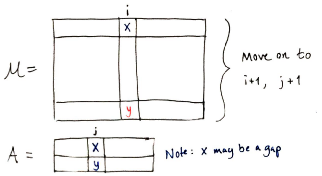
Alternative MST approach: Kruskal



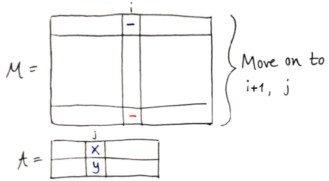
Alternative star tree approach



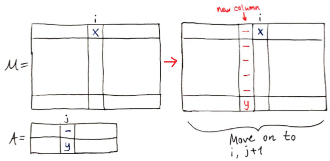
Extending M



M =
A =
i
j
x
y
Move on to i+1, j+1
Note: x may be a gap



M =
A =
i
j
–
x
y
Move on to i+1, j



M =
A =
i
j
x
y
–
new column
Move on to i, j+1

Prim's algorithm using queue

Algorithm MST-PRIM($G, w, root$)

```
for each $u \in V[G]$ do
    $key[u] \leftarrow \infty$
    $\pi[u] \leftarrow NIL$
end for
$key[root] \leftarrow 0$
$Q \leftarrow V[G]$
while $Q \neq \emptyset$ do
    $u \leftarrow \mathrm{EXTRACT\text{-}MIN}(Q)$
    report $(\pi[u], u)$
    for each $v \in Adj[u]$ do
        if $v \in Q$ and $w(u, v) < key[v]$ then
            $\pi[v] \leftarrow u$
            $key[v] \leftarrow w(u, v)$
        end if
    end for
end while
```

FIND-MIN

Algorithm FIND-MIN(V, key)

```
1: $min\_key \leftarrow \infty$
2: $min\_node \leftarrow NIL$
3: **for** $v \in V$ **do**
4:     **if** $v \notin MST$ **and** $key[v] < min\_key$ **then**
5:         $min\_node \leftarrow v$
6:         $min\_key \leftarrow key[v]$
7:     **end if**
8: **end for**
9: **return** $min\_node$
```