Faster Computation of Genome Mappability with One Mismatch

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Overview

Mappability - Definition

k-**Mappability problem:**

- **Input:** A sequence $S[1, n]$ of length n and two integers k and $m \leq n$
- **Output:** An integer array F_k s.t:

$$F_k[i] = |\ \{j \neq i \mid d_H(S[i, i+m-1], S[j, j+m-1]) \leq k\}\ |$$

- $d_H(\cdot, \cdot)$: Hamming Distance
- $S[i, i+m-1]$: The substrings of length m starting at position i

Mappability - Example

- **Input**: $S[1,8] = CCACAACA$ with $m = 3$, $k = 0$ or 1
- **Output:** Integer arrays F_0 and F_1:

Index	1	2	3	4	5	6	7	8
$S[1,8]$	C	C	A	C	A	A	C	A

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- **Output:** Integer arrays F_0 and F_1:

Index	1	2	3	4	5	6	7	8
$S[1,8]$	C	C	A	C	A	A	C	A

Position i	1	2	3	4	5	6
substring	CCA	CAC	ACA	CAA	AAC	ACA
$F_0[i]$	0	0	1	0	0	1
$F_1[i]$	3	2	2	2	1	2

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- **Output:** Integer arrays F_0 and F_1:

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$S[1,8]$	C	C	A	C	A	A	C	A

Position i	1	2	**3**	4	5	6
substring	CCA	CAC	ACA	CAA	AAC	ACA
$F_0[i]$	0	0	1	0	0	1
$F_1[i]$	3	2	2	2	1	2

$F_0[3]$: ACA at index 6
$F_1[3]$: ACA at index 6, CCA at index 1

Mappability - Applications

- Derrien et al. : It is a measure of the approximate repeat structure of the genome with respect to substrings of specific length and a tolerance for mismatches.
- W. Li et al. : It can be used in Designing or interpreting high-throughput short read sequencing experiments
- A.Huda et al. : It can be used to quantify transcription counts in gene expression studies.

Mappability - Previous results

- 0-mappability problem: can be easily solved in linear time using the suffix tree data structure
- $k \geq 1$: Derrien *et al.* proposed a heuristic algorithm to approximate the solution.
- 1-mappability problem: Alzamel *et al.* proposed three linear space algorithms with run times as follows:
  1. An $O(n \log n \log \log n)$ algorithm.
  2. An $O(nm)$ time algorithm.
  3. An $O(n)$ average-case time algorithm for $m = \Omega(\log n)$.
- More recently Alzamel et al. provided a solution for k-mappability using $O(n \min(\log^{k+1} n, m^k))$ time and linear space
- Our result for 1-mappability problem:

  $O(n \log n)$ time and $O(n)$ space.

Our Algorithm Framework

- The algorithm consists of two phases:

1. In the first phase we construct data structures based on the suffix tree of the input string.
    - Side-tree (s-tree)
    - HeavyPath-tree (hp-tree)
2. In the second phase we traverse these data structures and gather the desired values for computing F_1 array.

Heavy Path Decomposition

- Start at the root, w, of the tree. We will consider w as a *light* node.
- Take w's child, v, which has the **largest subtree size** and add it to the heavy path. We will refer to the node v as w's *heavy* child.
- Continue adding nodes to the heavy path in this fashion until we reach a leaf.
- Recurse on each light node adjacent to the heavy path.

Heavy Path Decomposition - Example

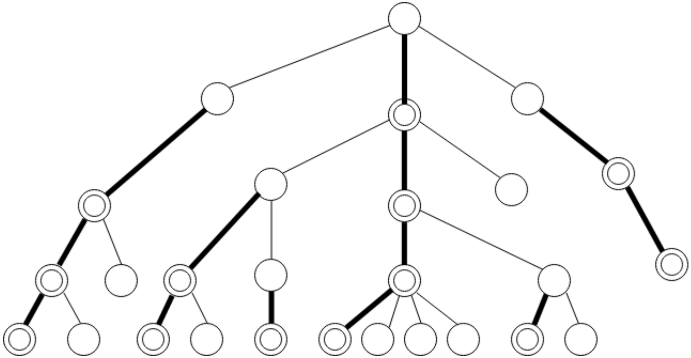


Figure: Nodes without double circles at the root of every heavy path are called light nodes. Double circles are called heavy nodes.

Heavy Path Decomposition - Key Observations

Observation

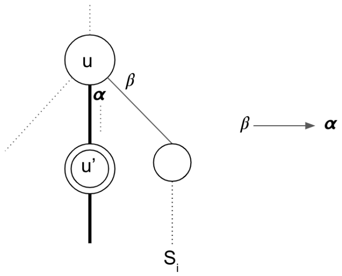
- *For a tree having n nodes, the path from the root to any leaf traverses at most $\lceil \log n \rceil$ light nodes.*
- *The sum of subtree sizes of all light nodes in a tree is $O(n \log n)$.*

Our Algorithm - Phase 1 Preliminaries

u: An internal node
u': u's heavy child
α: The leading character on the edge towards u'.
S_i: The suffix of S starting at position i

Definition

Modified Suffix S_i': is obtained from S_i under subtree of u after replacing its (strDepth(u) + 1)th character by α



Our Algorithm - Phase 1 Preliminaries

Suff(u): The set of suffixes corresponding to the leaves of subtree(u).
u: An internal node
u': u's heavy child

Definition

Side-Tree (s-Tree):
is a compact trie over all modified strings in

$$\text{Suff}'(u) = \{S'_i \mid S_i \in \text{Suff}(u) \setminus \text{Suff}(u')\}$$

s-Tree - Example

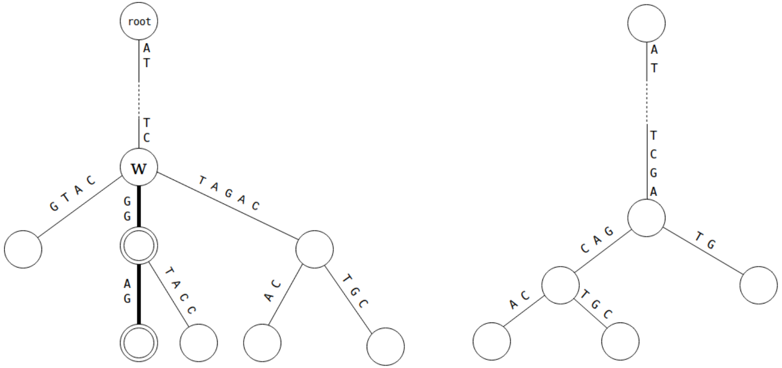
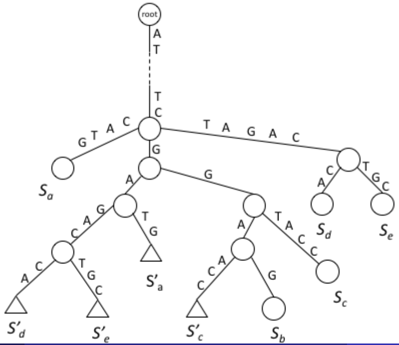


Figure: As an illustration, we show a portion of a suffix tree (on left) and the corresponding s-Tree(·) w.r.t. a light node w (on right).

hp-Tree

Definition

HeavyPath-tree (hp-Tree):
For each light node w , *hp-Tree(w)* is as a compact trie of *s-Trees* of all nodes on the heavy path rooted at w (modified suffixes) **and** Original suffixes corresponding to the leaves of subtree(w).



Our Algorithm - Phase 1

- **Input:** A sequence $S[1, n]$ of length n and two integers $k = 1$ and $m \leq n$

1. Perform a heavy path decomposition of the Suffix Tree of S.
2. Construct a s-Tree for every node u where $\text{strDepth}(u) < m$.
3. Construct a hp-Tree for every light node w where $\text{strDepth}(w) < m$.

Our Algorithm - Phase 2

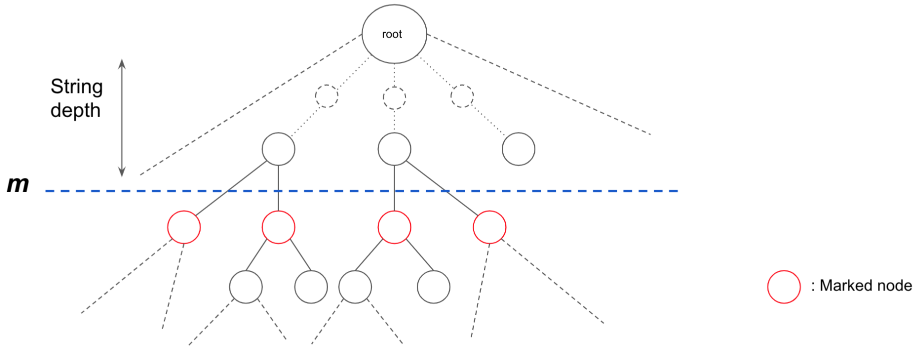
- There are 3 possibilities that can have an effect on the output array F_1 :
  - Two suffixes have already $|LCP| \geq m$
  - Two modified suffixes have $|LCP| \geq m$
  - One original suffix and one modified suffix have $|LCP| \geq m$

$|LCP|=$ Length of the longest common prefix

Phase 2: Step 1 - Processing s-Trees

Definition

A node v is marked iff $\text{strDepth}(\mathit{parent}(v)) < m \leq \text{strDepth}(v)$.



Phase 2: Step 1 - Processing s-Trees

- When $|LCP|$ of two modified suffixes $\geq m$: Scanning s-trees

```
Compute the array $F_0$
Initialize array $F_1$ to zero
for each node $u$ in ST with strDepth($u$) $< m$ do
    for every marked node $v$, in s-Tree($u$) do
        scan leaves of $v$'s subtree
        if leaf corresponds to a modified suffix $S'_i$ then
            $F_1[i]$ is incremented by (size($v$) - $F_0[i] - 1$).
        end if
    end for
end for
```

Phase 2: Step 2 - Processing hp-Trees

- When $|LCP|$ of one modified suffix and one original suffix $\geq m$: Scanning hp-trees

```
for each light node $w$ in ST with strDepth($w$) $< m$ do
    for every marked node $v$ in hp-Tree($w$) do
        Compute the number of modified suffixes $c'$ and the number of
        unmodified suffixes $c$.
        On a second scan of the same leaves:
        if a leaf corresponds to an unmodified suffix $S_i$ then
            increment $F_1[i]$ by $c'$
        else if a leaf corresponds to a modified suffix $S_i'$ then
            increment $F_1[i]$ by $c$.
        end if
    end for
end for
```

Phase 2: Step 3 - Remove double counted matches

- z_i : Marked node on the path towards the leaf corresponding to S_i.

```
for i from 1 to n-m+1 do
    if $z_i$ is a light node then
        increment $F_1[i]$ by $F_0[i]$,
    else
        decrement $F_1[i]$ by $F_0[i]$.
    end if
end for
```

Time and Space complexity

- Time complexity:
  - Phase 1, Constructing s-Trees and hp-Trees: Can be implemented in $O(n \log n)$ time.
  - Phase 2, Processing Trees: Runs in time proportional to the number of leaves in all of the hp-Trees and s-Trees combined. So, this phase also takes $O(n \log n)$.
- Space complexity:
  - Each phase can be maintained at $O(n)$.

Future Work: Solving K-mappability problem

We solved 1-mappability problem in $O(n \log n)$ time and $O(n)$ space.

Can we use the ideas presented here to get a $O(nlog^k n)$ solution for general $k \geq 1$?

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Thank you!