A *De Nuevo* Algorithm for Genome Wide Searching of LTR Retrotransposon

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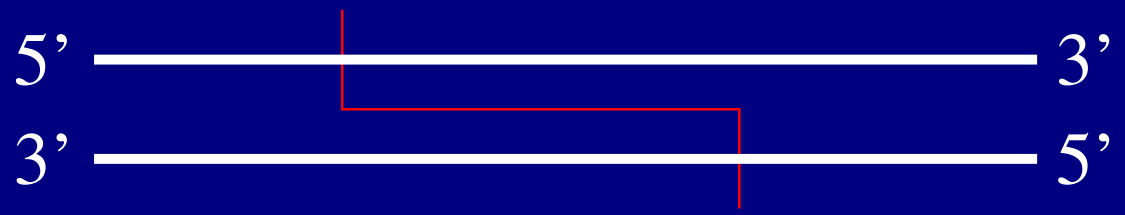
Outline

The Structure of LTR Retrotransposon

- LTR retrotransposon = LTR – inter-portion – LTR
- LTR: length 100 $\sim$ 5,000 bps, $\geq$80% identity
- inter-portion = *gag* – *pol* – *env*, length 1,000 $\sim$ 40,000 bps

The Structure of LTR Retrotransposon



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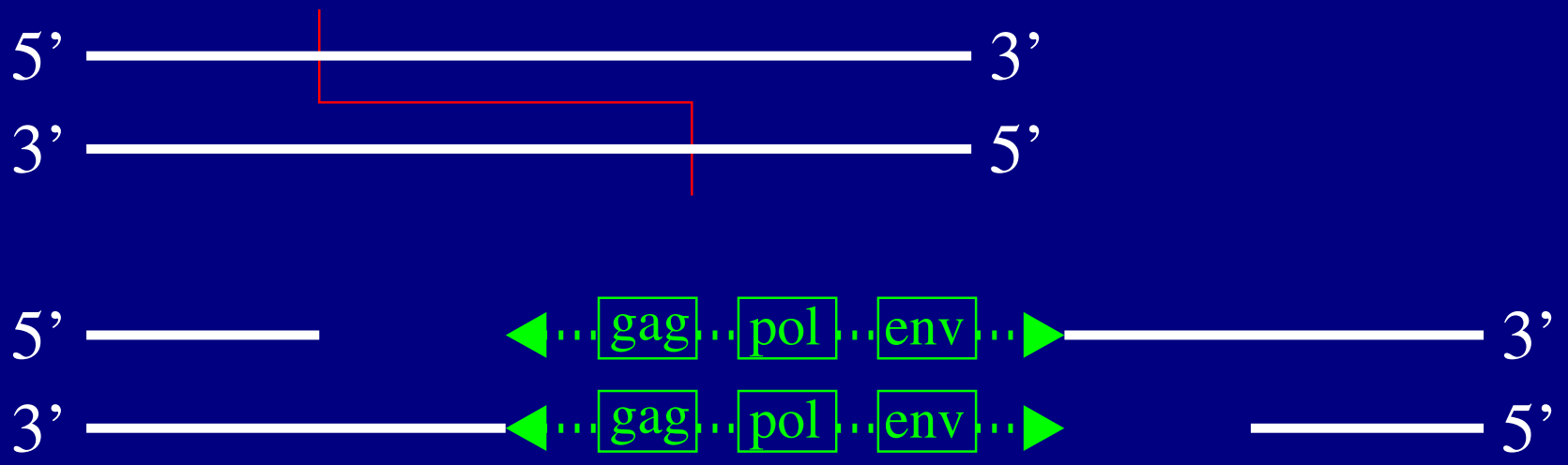

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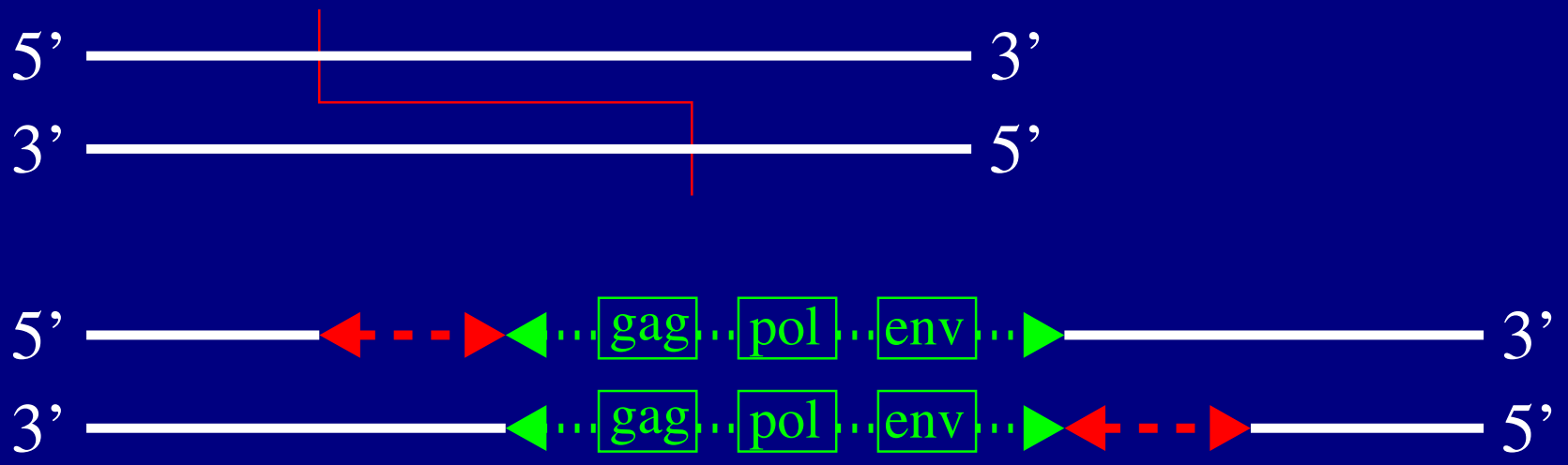

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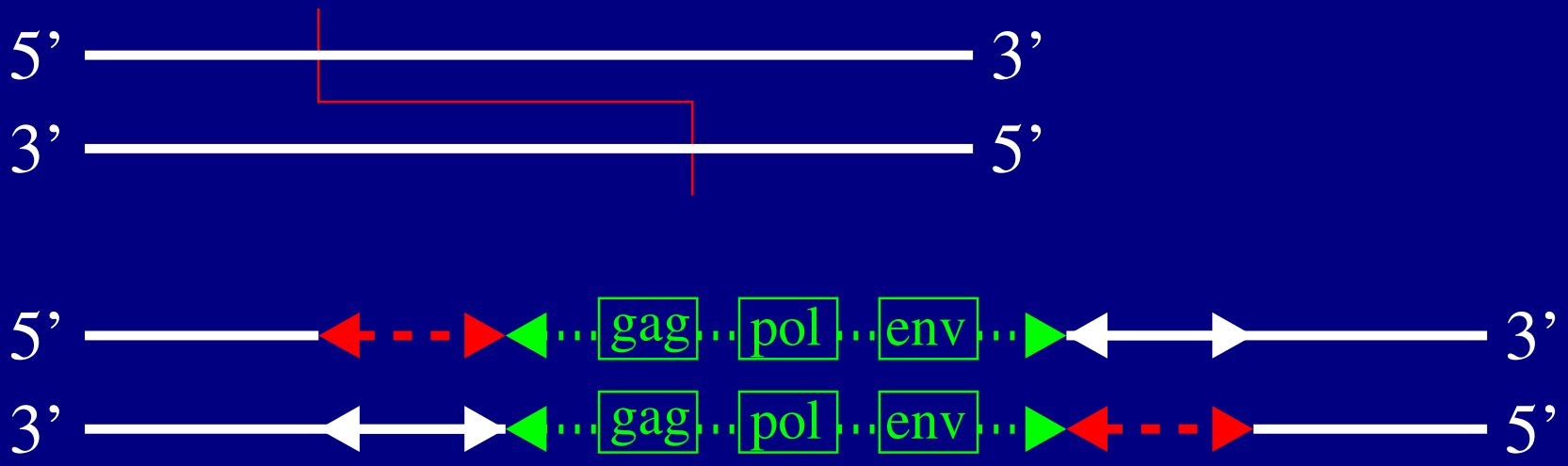

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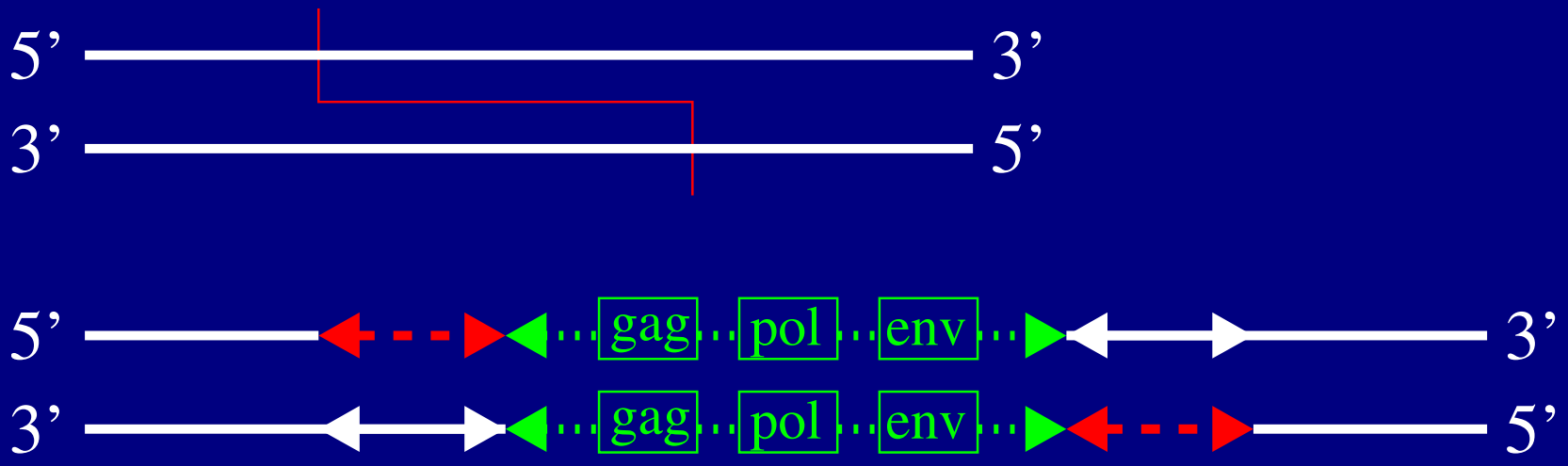

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Strategy for Finding LTR Retrotransposon

1. Finding all pairs of LTRs.
   - searching maximal exact pairs using suffix array and discarding the maximal exact pair such that substrings don't locate within the length of inter-portion
   - combining maximal exact pairs where the left substrings and right substrings of each maximal exact pair are simultaneously within the length of LTR
2. Verifying inter-portion of each pair of LTRs.
   - domain search using `Pfam` + `hmmsearch`.

LTR — *gag* — *pol* — *env* — LTR

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Maximal Exact Pair

Definition

A maximal exact pair (MEP) in a sequence S, denoted by (p_1, p_2, ℓ) is a pair of identical substrings α and β in S such that the character to the immediate left (right) of α is different than the character to the immediate left (right) of β.

Example

TACTATCACTCATGCTA

1234567890123456 7

For the above sequence, MEPs of length 3 or more are

ACT: (2, 8) AT: (5, 12)

CTA: (3, 15) CT: (9, 15)

TA: (1, 4), (1, 16)

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Text Indexing (Pattern Retrieval)

Idea

- Preprocess the text : $O(m)$ time
- Searching : $O(n + occ)$ time

Index data structures

Exact match

- Suffix Trie
- Suffix Tree
- Suffix Array
- String B-tree

Approximate match

- Suffix Tree
- Suffix Array
- Q-grams
- Q-samples

Suffix

Definition

Suffix S_i is a substring of S that starts at position i and ends at position $|S|$.

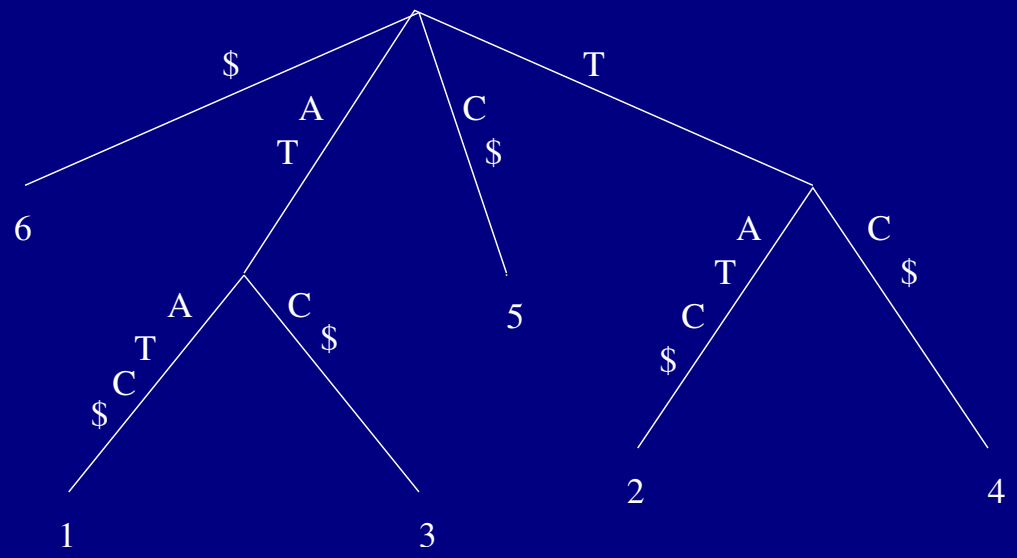
Example

Given $S = \texttt{ATATC}$,

$$
\begin{aligned}
S_1 &= \texttt{ATATC\$} \\
S_2 &= \texttt{TATC\$} \\
S_3 &= \texttt{ATC\$} \\
S_4 &= \texttt{TC\$} \\
S_5 &= \texttt{C\$} \\
S_6 &= \texttt{\$}
\end{aligned}
$$

Suffix Tree

The compacted trie of all suffixes of a string, e.g., `ATATC`



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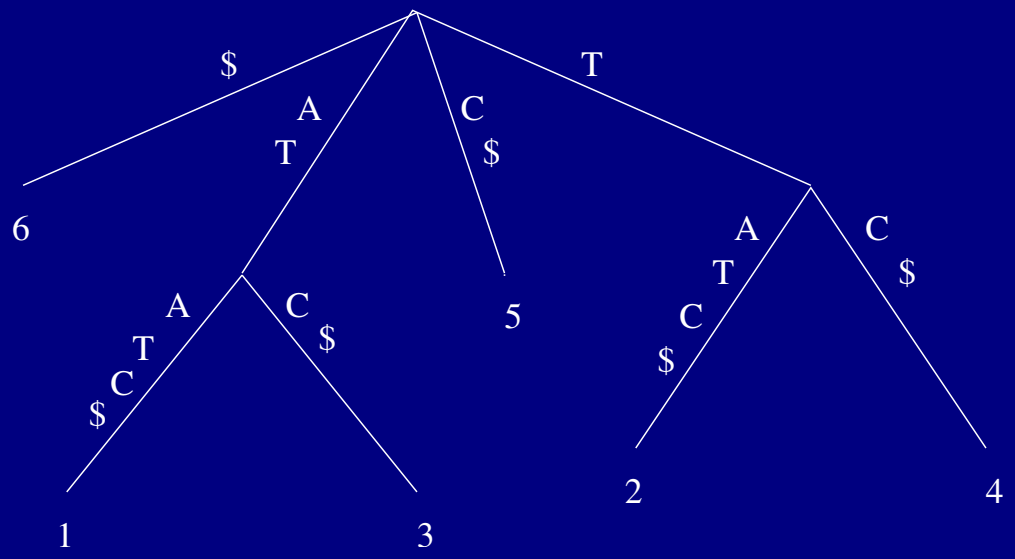

- Each leaf node is numbered to suffix number.

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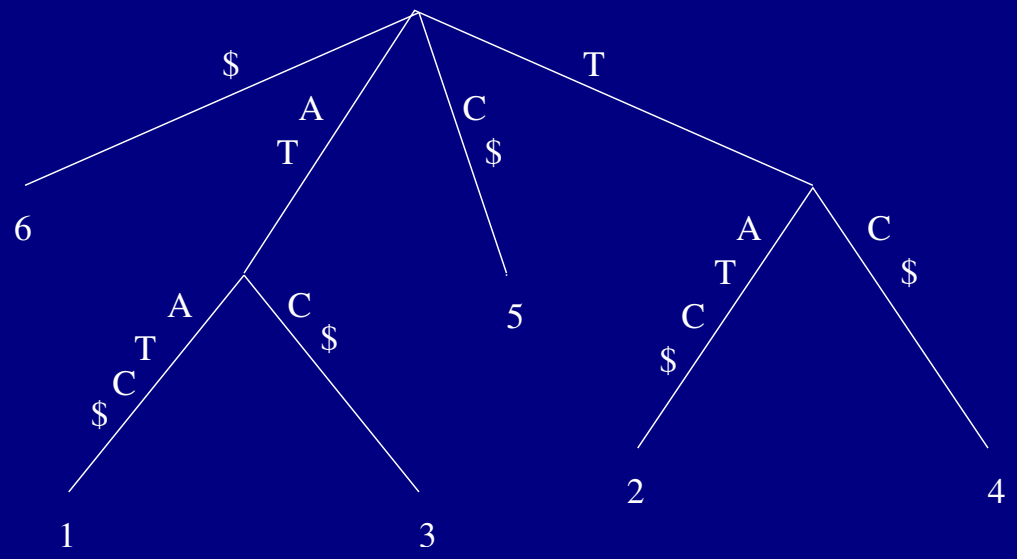

- The concatenation of the edge-labels on the path from the root to leaf i exactly spell out the suffix of S that starts at position i.

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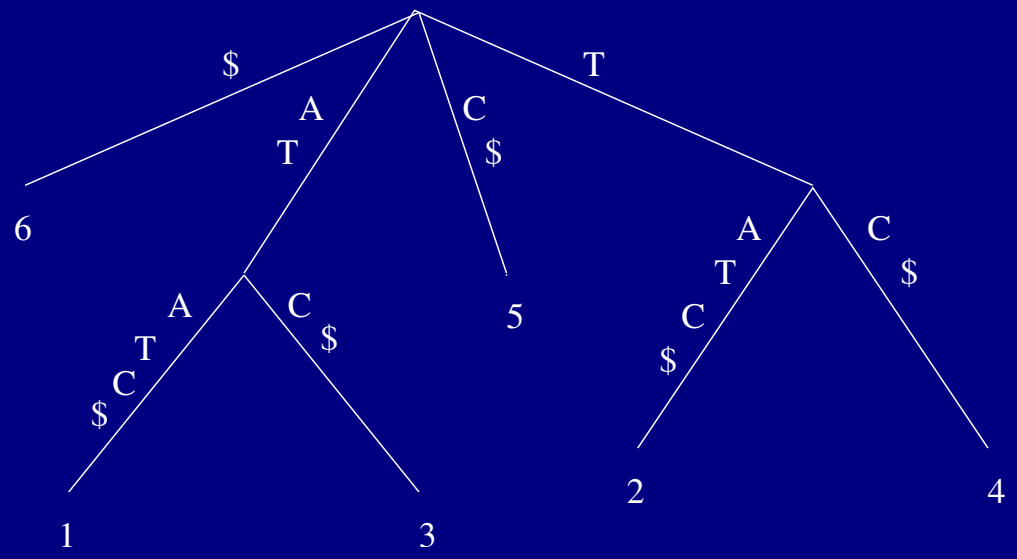


- Each internal node except the root has at least two children and each edge is labeled with a nonempty substring of S.

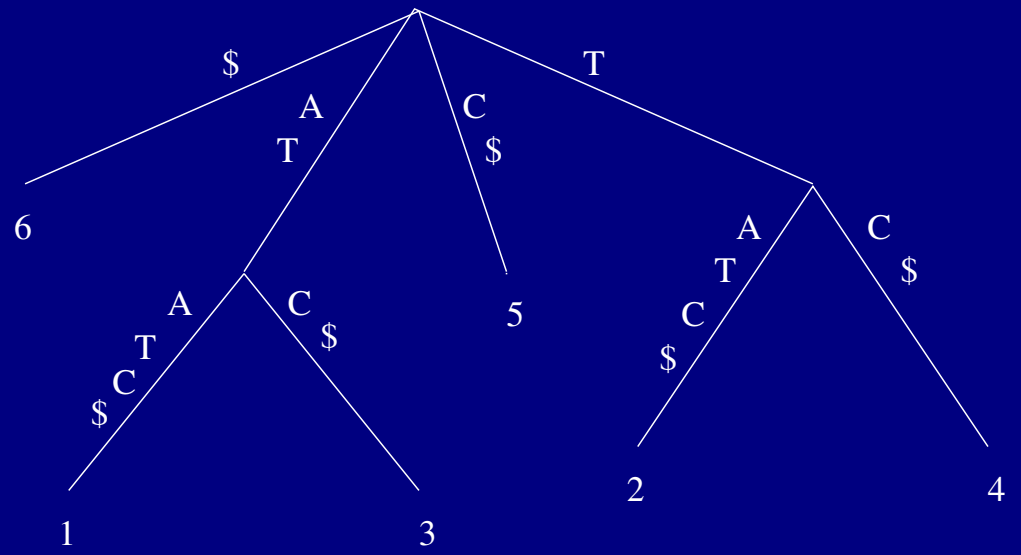
Pattern Retrieval Problem

Definition

Given a pattern P of length n and a text T of length m, find the positions of all occurrences of P in T

Example

$T =$ `ATATC`



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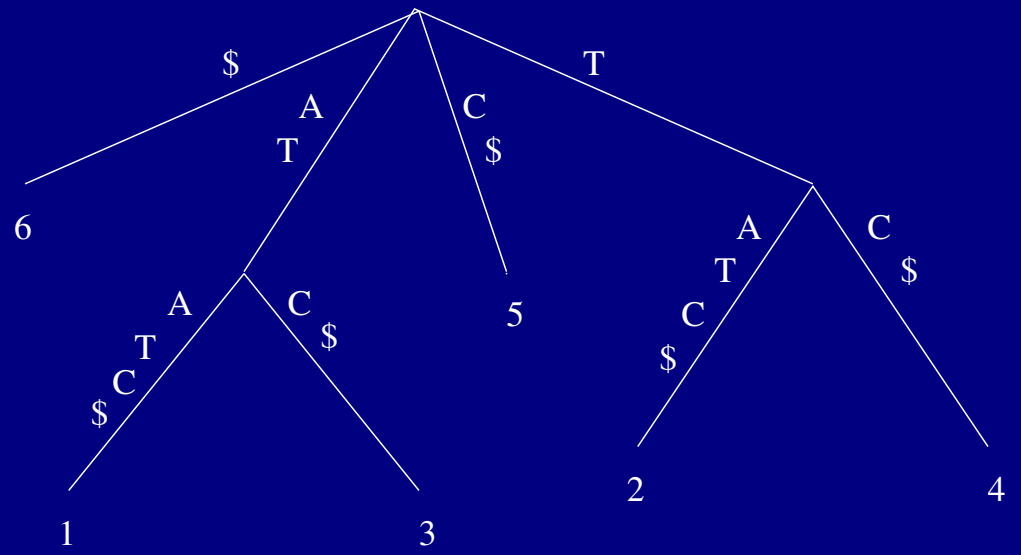
Given a pattern P of length n and a text T of length m, find the positions of all occurrences of P in T

Example

$T =$ `ATATC`
$P =$ `ATA`



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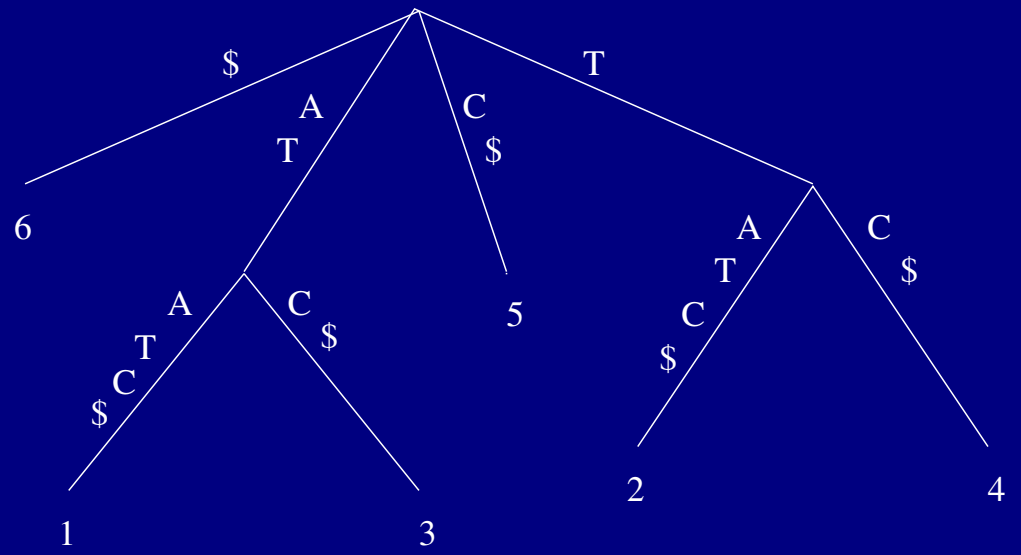

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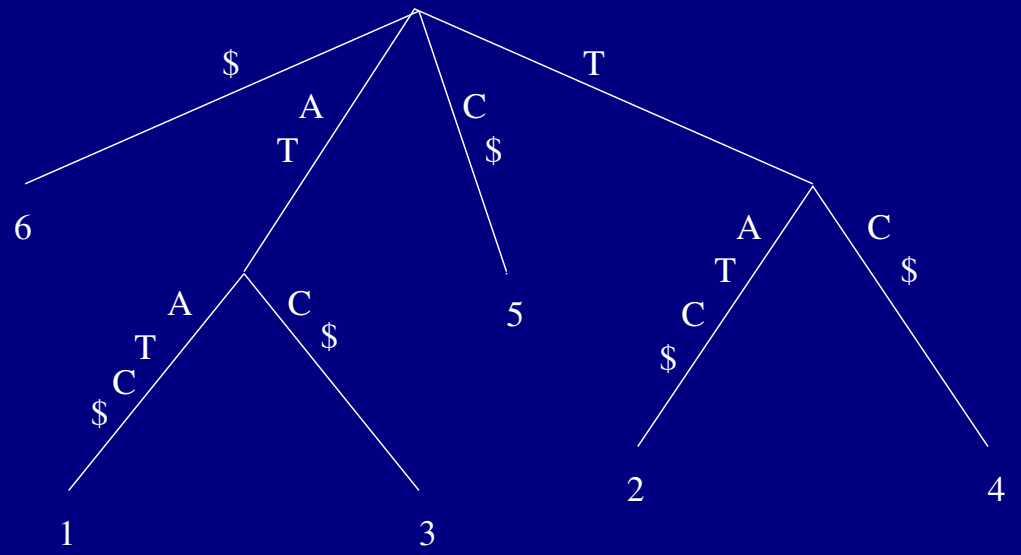
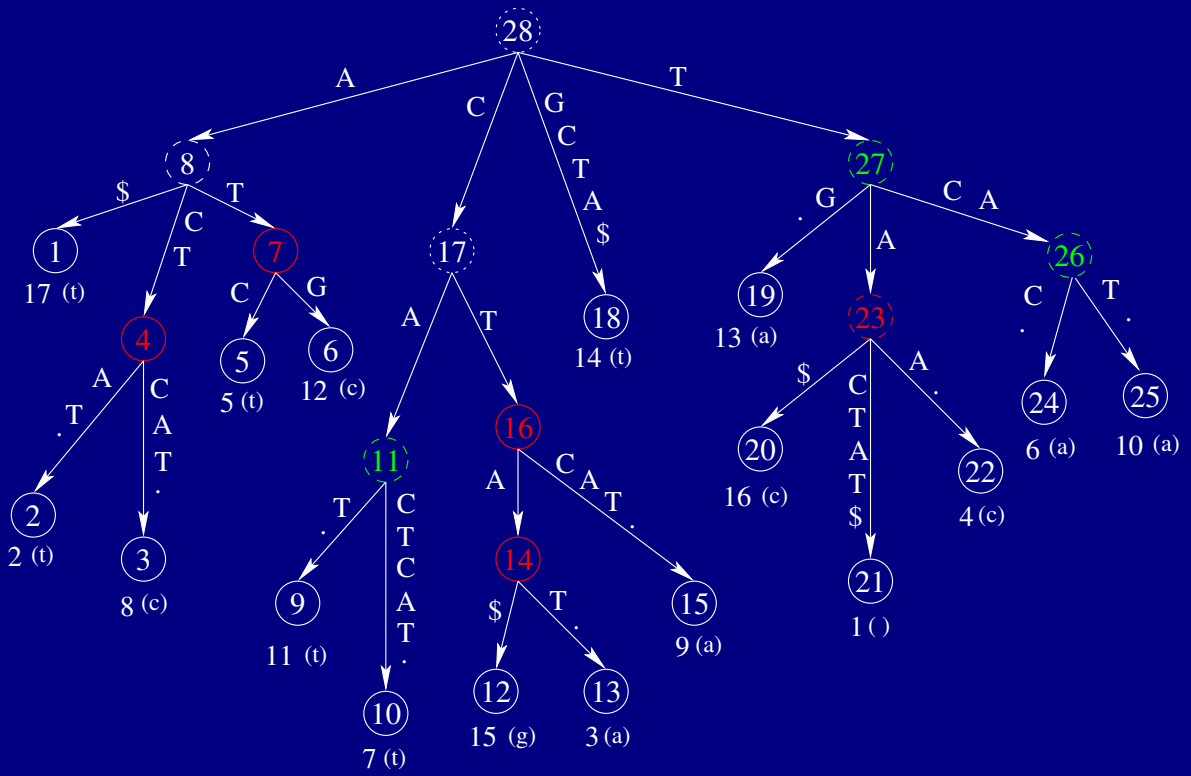


Complexity of Suffix Tree

1. Preprocessing
   - Constant alphabet size : $O(m)\log|\Sigma|$ time and $O(m)$ space
     - Weiner (1973) [10]
     - McCreight (1976) [8]
     - Ukkonen (1995) [9]
   - Integer alphabet : $O(m)$ time
     - Farach (1997) [1]
2. Searching: $O(n)\log|\Sigma| + occ$ time

Finding All MEPs



Left	Pos list
v_{12}	G 15
v_{13}	A 3
v_{14}	A 3 G 15

MEP: (3,15,3)

v_{15}	A 9
v_{16}	A 3,9 G 15

MEP: (9,15,2)

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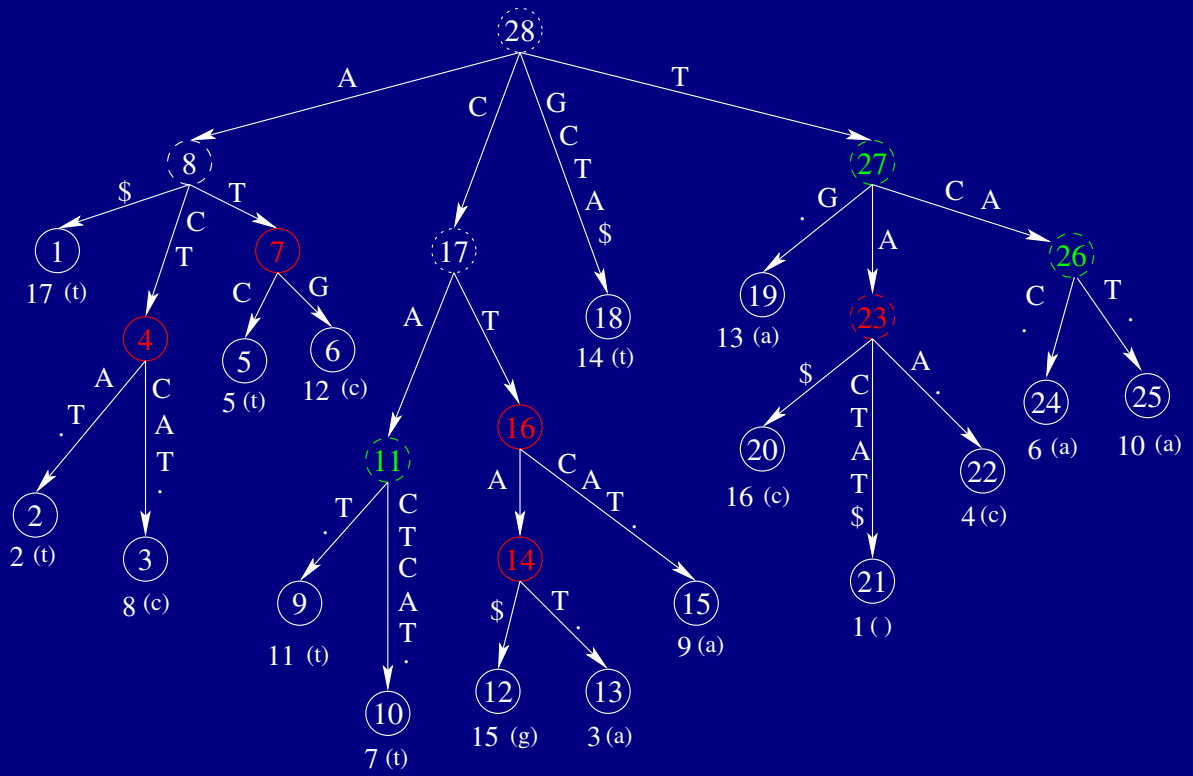

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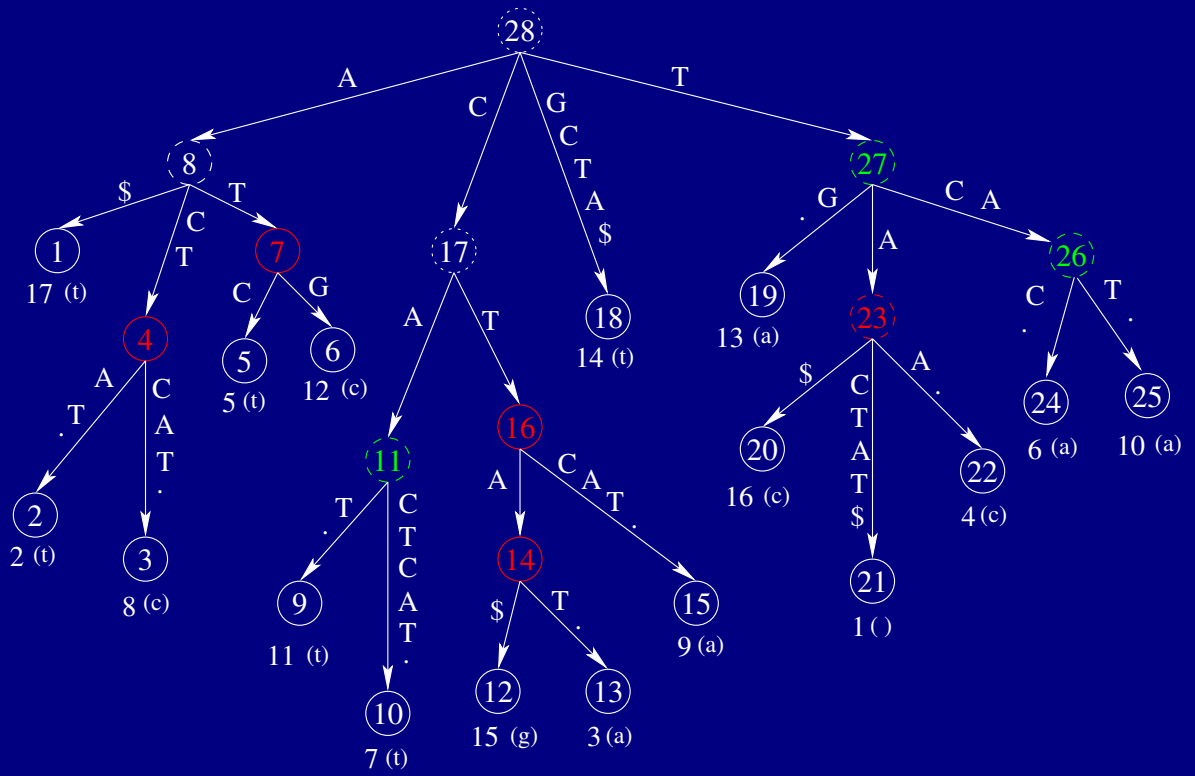

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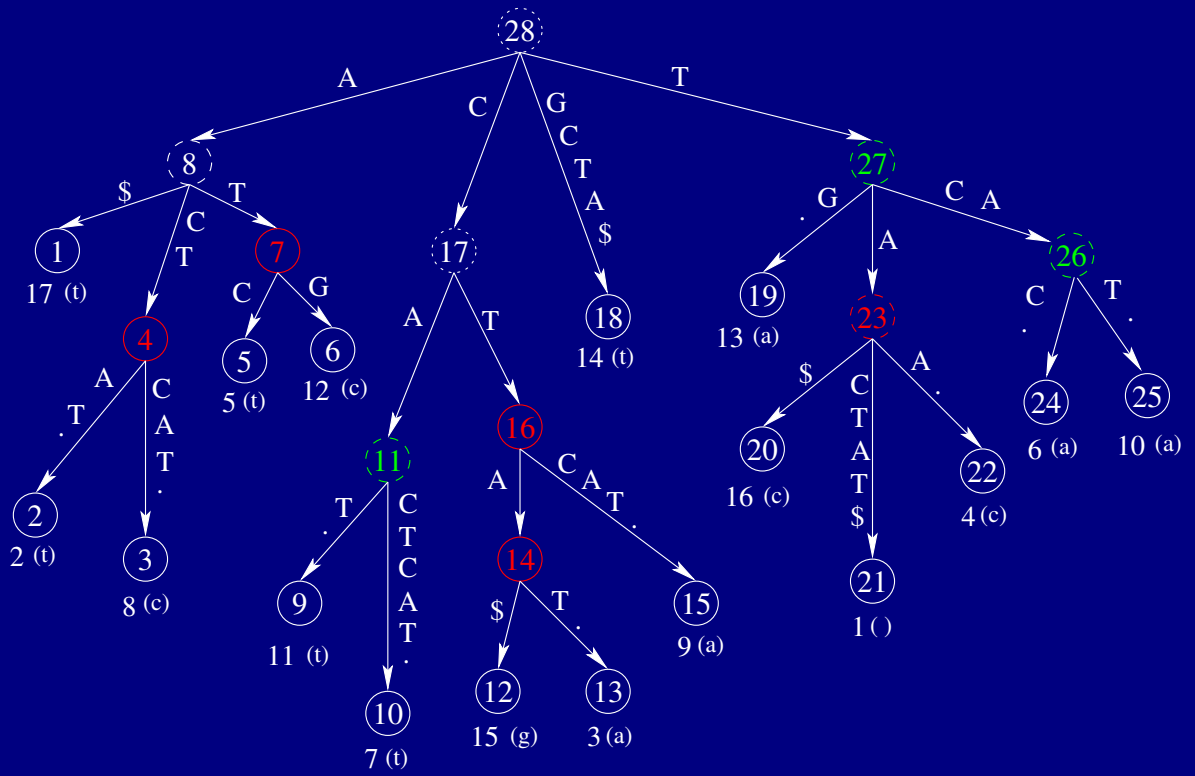

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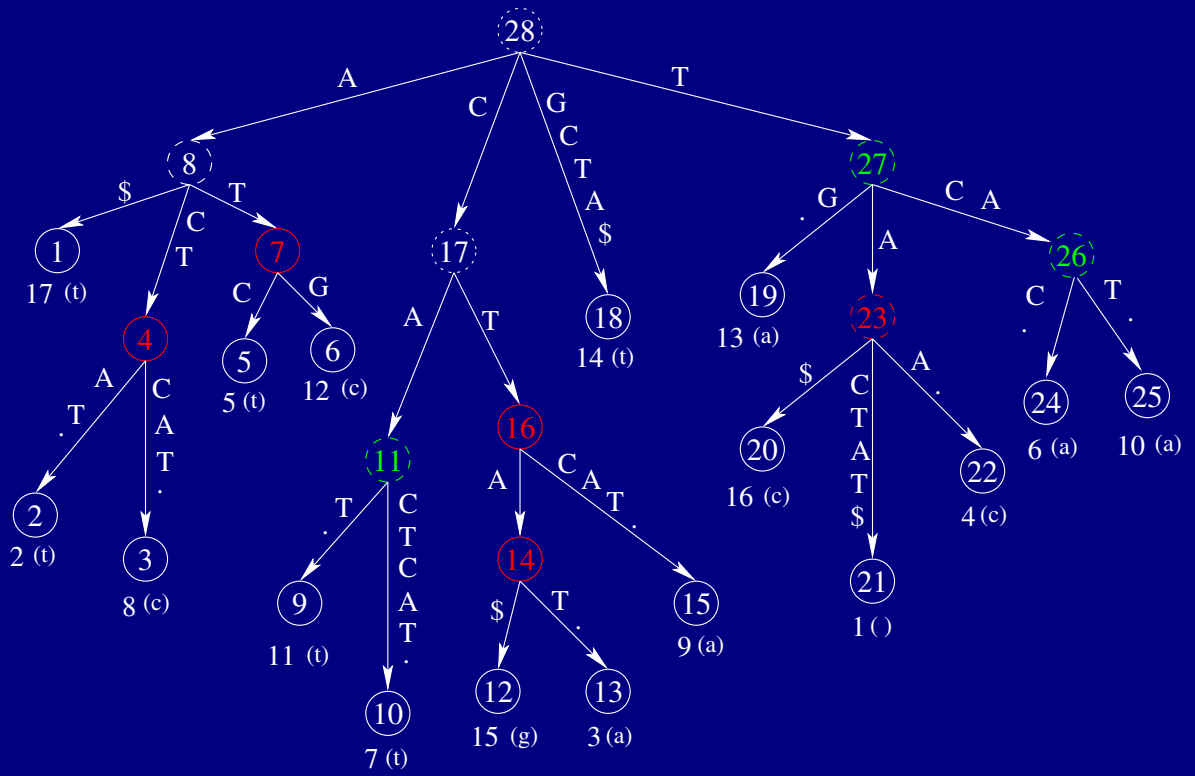

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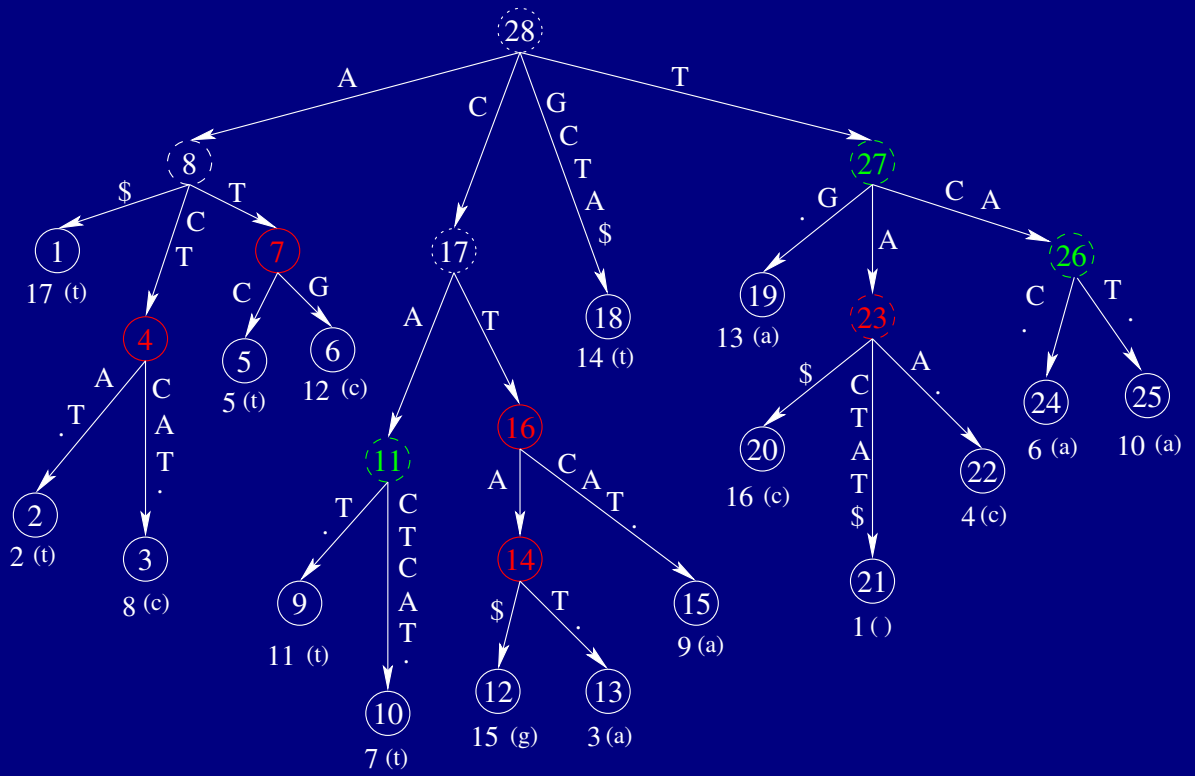

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Finding All MEPs

- Build a suffix tree for S
- $L_x(v)$: the list of leaf numbers in the subtree of node v with a left character x.
  e.g., $L_G(12) = \{15\}, L_A(16) = \{3, 9\}$.
- Do bottom up traversal of tree.
  For a node v, create a linked lists $L_x(v)$ indexed by all left character x.
  - Leaf node: create $L_x(v) = \{i\}$ where x is a left character and i is a suffix number for v.
  - Internal node:
    - $C(v)$: a set of children of v.
    - $D(v)$: a set of left characters of leaves in v's subtree.
    - For each $x \in D(v)$ and each $w \in C(v)$, do Cartesian product of $L_x(w)$ with $L_{x'}(w')$ for $x' \neq x$ and $w' \neq w$.

Finding All MEPs (cont.)

- Any pair in the list gives the starting positions of a maximal pair.
- Finally, for each x, compute $L_x(v)$ by union of $L_x(w)$ for every w.

- Let k' be the number of maximal pairs from Cartesian product, then Cartesian product takes $O(k')$ time.
- union can be done in $O(|\Sigma|)$ time using linked list.

- Totally $O(m + k)$ time and $O(m)$ space where k is the number of maximal pairs.

Implementation

1. Construct a suffix array for a given sequence of length n
   1. Larsson and Sadakane [7]: $O(n \log n)$
   2. Kim *et. al* [5], Ko and Aluru [6], Kärkkäinen and Sanders [3]: $O(n)$
2. Compute longest common prefix of adjacent sorted suffixes
   1. Kasai *et. al* [4]: $O(n)$
3. Traverse suffix array from bottom-up
   1. Gusfield [2]: $O(n)$
   2. leaf node: make a linked list for each pair of genome and left character
   3. branch node: Cartesian product and union children's linked lists if the length of its path label is above a threshold T_m

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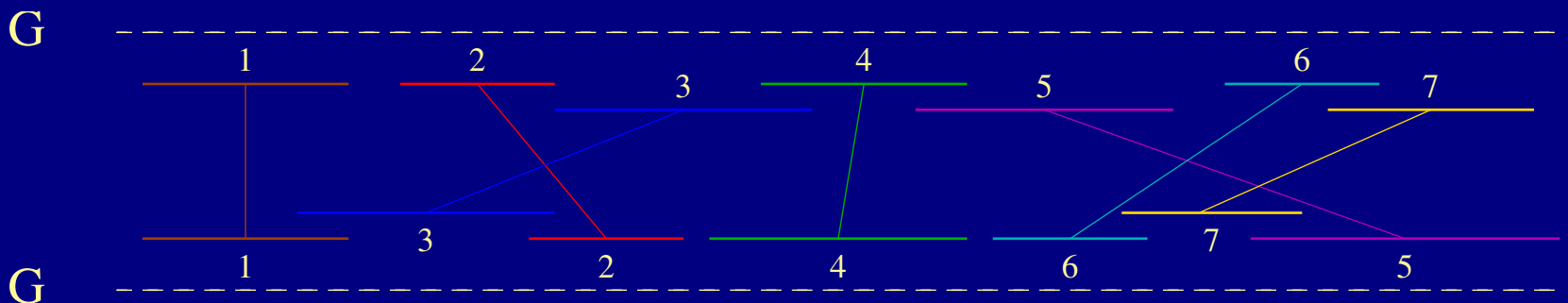
Chaining Problem

Definition

Given n MEPs $M_1, \cdots, M_n$, find the chain C of colinear non-overlapping MEPs such that its total score is maximum over all other chains. The total score of a chain is defined as

$$Score(C) = \sum_i (f(M_i) - g(M_{i+1}, M_i))$$

where $f(M_i)$ is the weight of M_i and $g(M_{i+1}, M_i)$ is the gap cost of connecting M_i to M_{i+1}.



Previous Work

- Graph based algorithm takes $O(n^2)$ time
- Geometric based algorithm is subquadratic (sparse dynamic programming)
  - Zhang et al. (1994) used space division with a kd-tree (no complexity analysis was given).
  - Myers and Miller (1995) used orthogonal range search with a range tree yielding a complexity of $O(nlog^k n)$ time and $O(nlog^{k-1} n)$ space.
  - Abouelhoda et al. (2003) used a range tree supported by fractional cascading and enhanced with priority queues and its complexity is $O(n \log^{k-2} n \log \log n)$ time and $O(n \log^{k-2} n)$ space.

Sparse Dynamic Programming

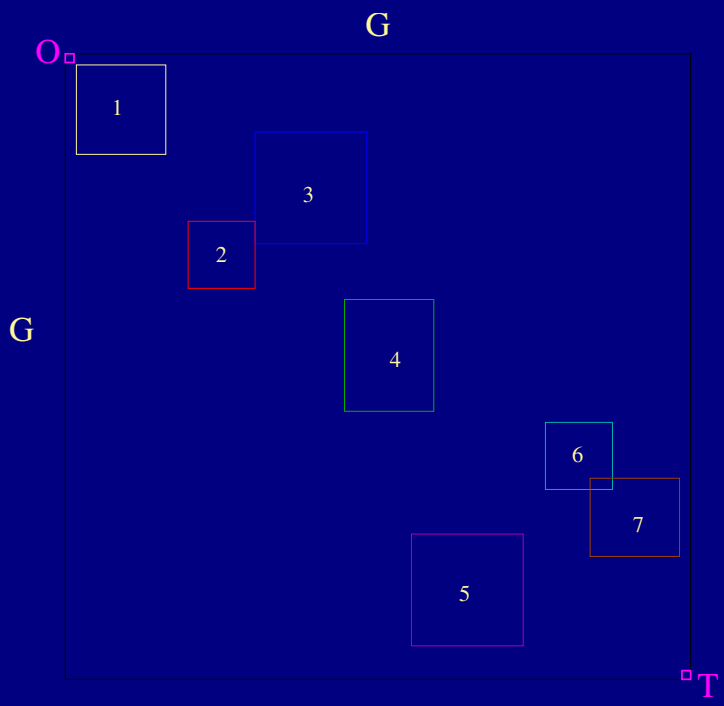
Definition

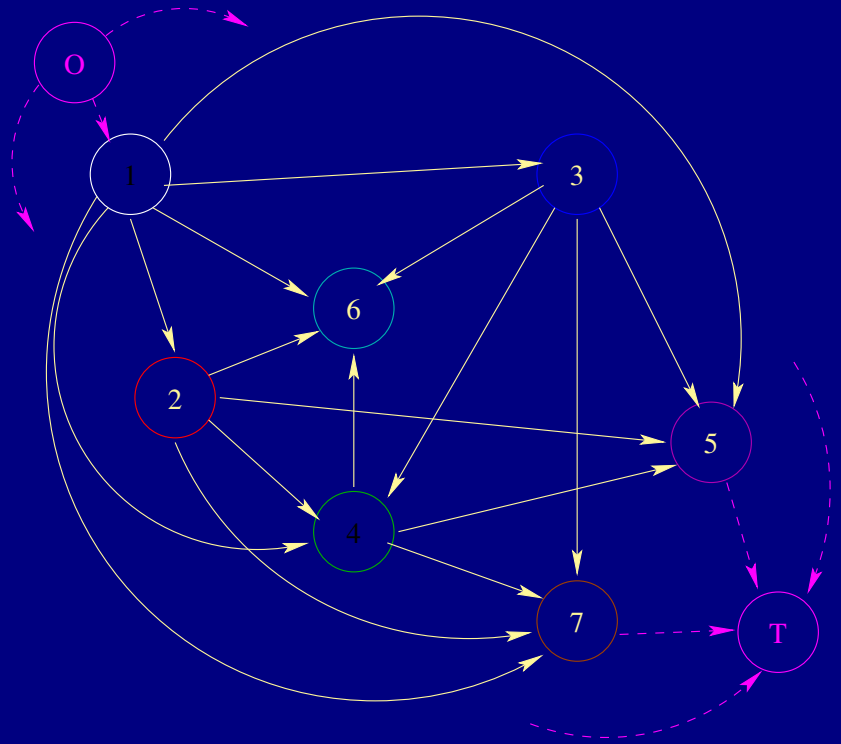
The maximum score can be computed by the recurrence

$$Score(M_j) = f(M_j) + \max_i \{0, Score(M_i) - g(M_i, M_j) : M_i \ll M_j\}$$

where $M_i \ll M_j$ means $end(M_i).p_r < start(M_j).p_r$ for all $r \in \{1, 2\}$ and $g(M_i, M_j)$ is the gap cost of connecting M_i to M_j.

Graph Based Algorithm



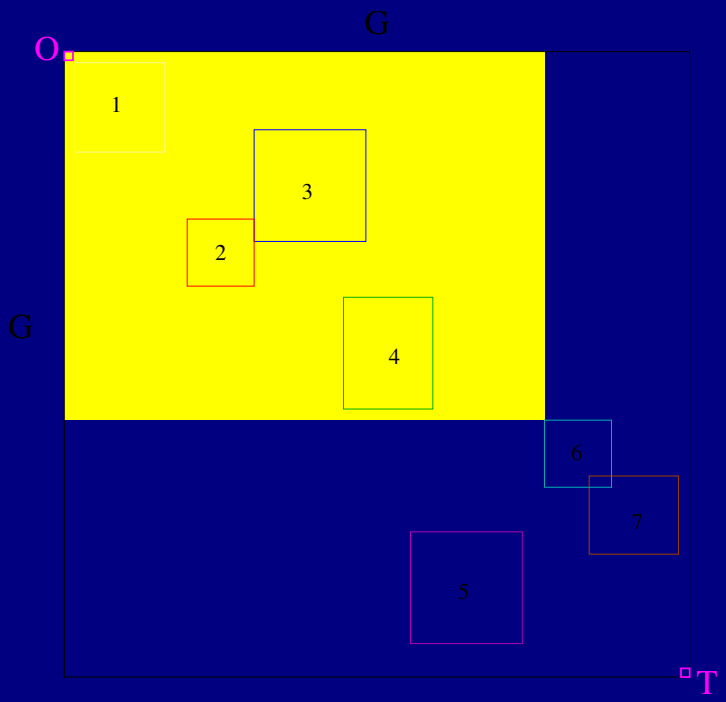


- Vertex : MEP with weight $f(M_i)$
- Edge : gap cost $g(M_i, M_j)$
- Chaining problem is converted to maximal weighted chain problem for a weighted graph and solved by Dynamic Programming.

Geometric Based Algorithm

Definition (RMQ (Range Maximum Query))

Retrieves the MEP M_i whose end point lies in the hyper-rectangle bounded by $start(M_j)$ and O such that $Score(M_i) - g(M_i, M_j)$ is maximum.



Geometric Based Algorithm

Definition (RMQ (Range Maximum Query))

Retrieves the MEP M_i whose end point lies in the hyper-rectangle bounded by $start(M_j)$ and O such that $Score(M_i) - g(M_i, M_j)$ is maximum.

The recurrence

$$Score(M_j) = f(M_j) + \max_i 0, Score(M_i) - g(M_i, M_j) : M_i \ll M_j$$

can be written as

$$Score(M_j) = f(M_j) + RMQ(O, start(M_j)$$

where O is a imaginary MEM with weight zero.

Gap Cost in L

In L_1 metric,

$$g_1(M_i, M_j) = \sum_{i \in \{1,2\}} (start(M_j).p_i - end(M_i).p_i).$$

In L_∞ metric,

$$g_\infty(M_i, M_j) = \max_{i \in \{1,2\}} (start(M_j).p_i - end(M_i).p_i)$$

However, any metric doesn't represent the real gap cost.

Implementation

1. Select two adjacent anchors that are apart no more than T_d.
2. Compute locally optimal chains by dynamic programming:
   1. Align each region between two adjacent anchors by Needleman-Wunsch algorithm.
   2. If its alignment score is below a preset threshold T_{nw}, then two anchors are not chained.

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