Computational Genomics
Prof Irit Gat-Viks, Prof. Ron Shamir, Prof. Roded Sharan
School of Computer Science, Tel Aviv University

גנומיקה חישובית
פרופ' עירית גת-ויקס, פרופ' רון שמיר,
פרופ' רודד שרן
ביה"ס למדעי המחשב,אוניברסיטת תל אביב

Suffix trees

December 2018

Suffix Trees

Description follows **Dan Gusfield's** book "**Algorithms on Strings, Trees and Sequences**"

Slides sources: Pavel Shvaiko, (University of Trento), **Haim Kaplan** (Tel Aviv University), Ben Langmead (JHU)

Outline

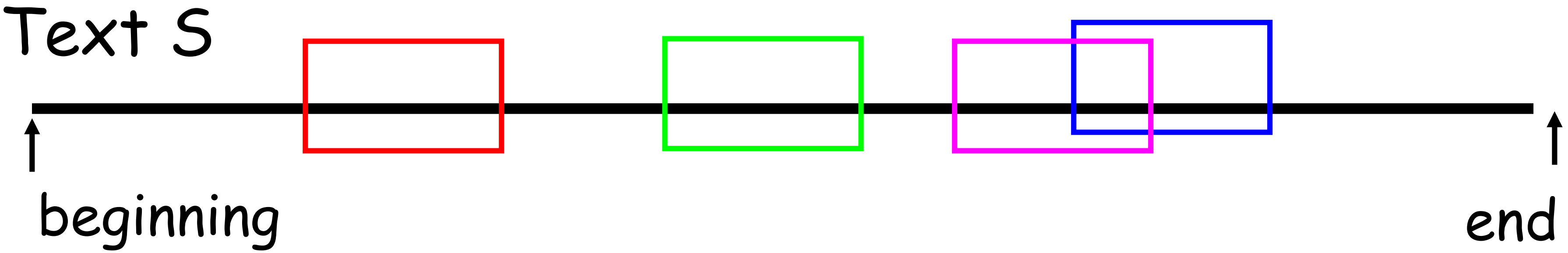
- Introduction
- Suffix Trees (ST)
- Building STs in linear time: Ukkonen's algorithm
- Applications of ST

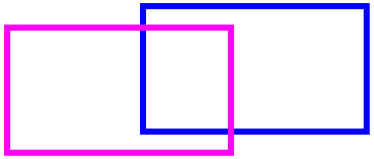
Introduction

Exact String/Pattern Matching

|S| = m,

n different patterns $p_1 \ldots p_n$





Pattern occurrences can overlap

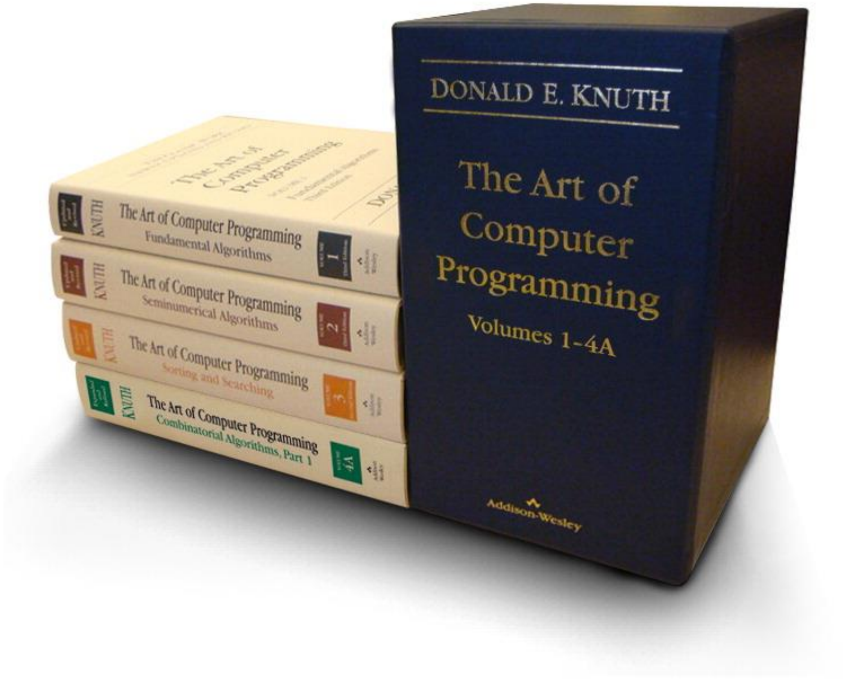
String/Pattern Matching - I

- Given a text S, answer queries of the form: is the pattern p_i a substring of S?
- Knuth-Morris-Pratt 1977 (KMP) string matching alg:
  - $O(|S| + | p_i |)$ time per query.
  - $O(n|S| + \Sigma_i | p_i |)$ time for n queries.
- Suffix tree solution:
  - $O(|S| + \Sigma_i | p_i |)$ time for n queries.

String/Pattern Matching - II

- KMP preprocesses the patterns p_i;
- The suffix tree algorithm:
  - preprocess S in $O(|S|)$: builds a data structure called suffix tree for S
  - when a pattern p is input, the algorithm searches it in $O(|p|)$ time using the suffix tree

Donald Knuth



Prefixes & Suffixes

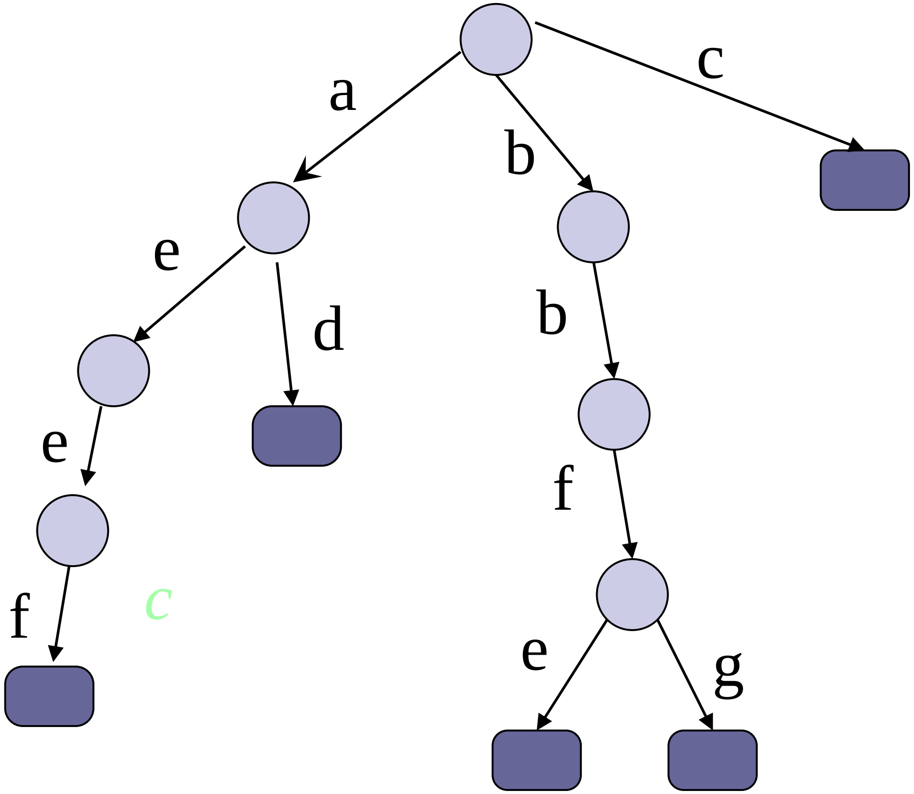
- Notation: S[i,j] =S(i), S(i+1),…, S(j)
- Prefix of S: substring of S beginning at the first position of S ←→ S[1,i]
- Suffix of S: substring that ends at last position ←→ S[i,n]
- S=AACTAG
  - ☐ Prefixes: AACTAG,AACTA,AACT,AAC,AA,A
  - ☐ Suffixes: AACTAG,ACTAG,CTAG,TAG,AG,G
- Note: P is a substring of S iff P is a prefix of some suffix of S.

Suffix Trees

Trie

- A tree representing a set of strings.

{
aeef
ad
bbfe
bbfg
c
}

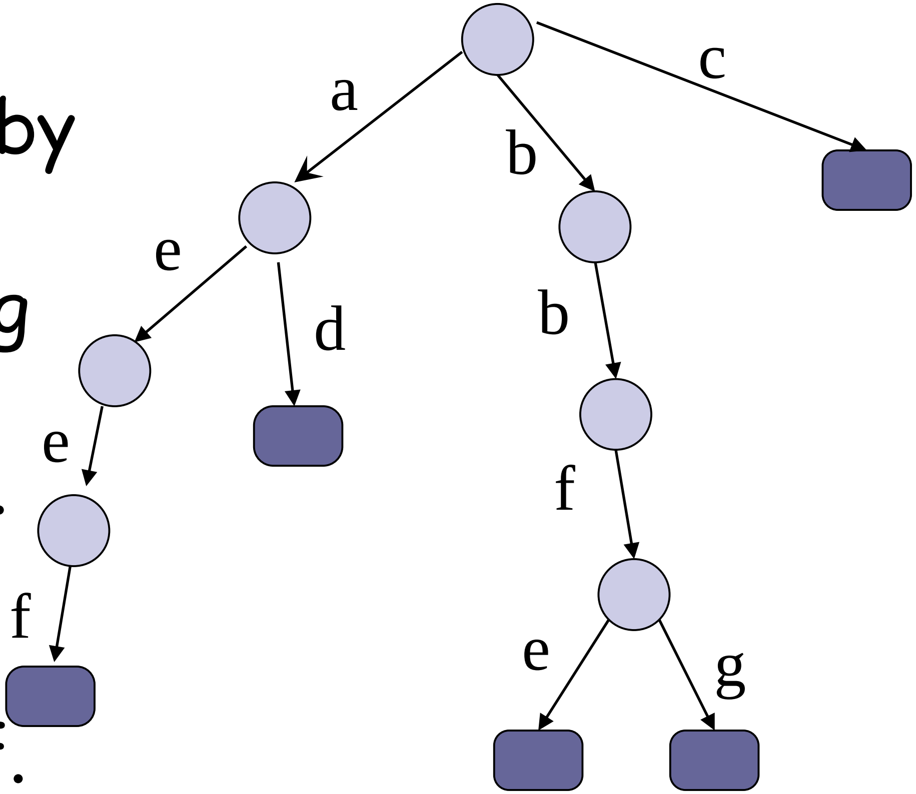


Trie (Cont)

- Assume no string is a prefix of another

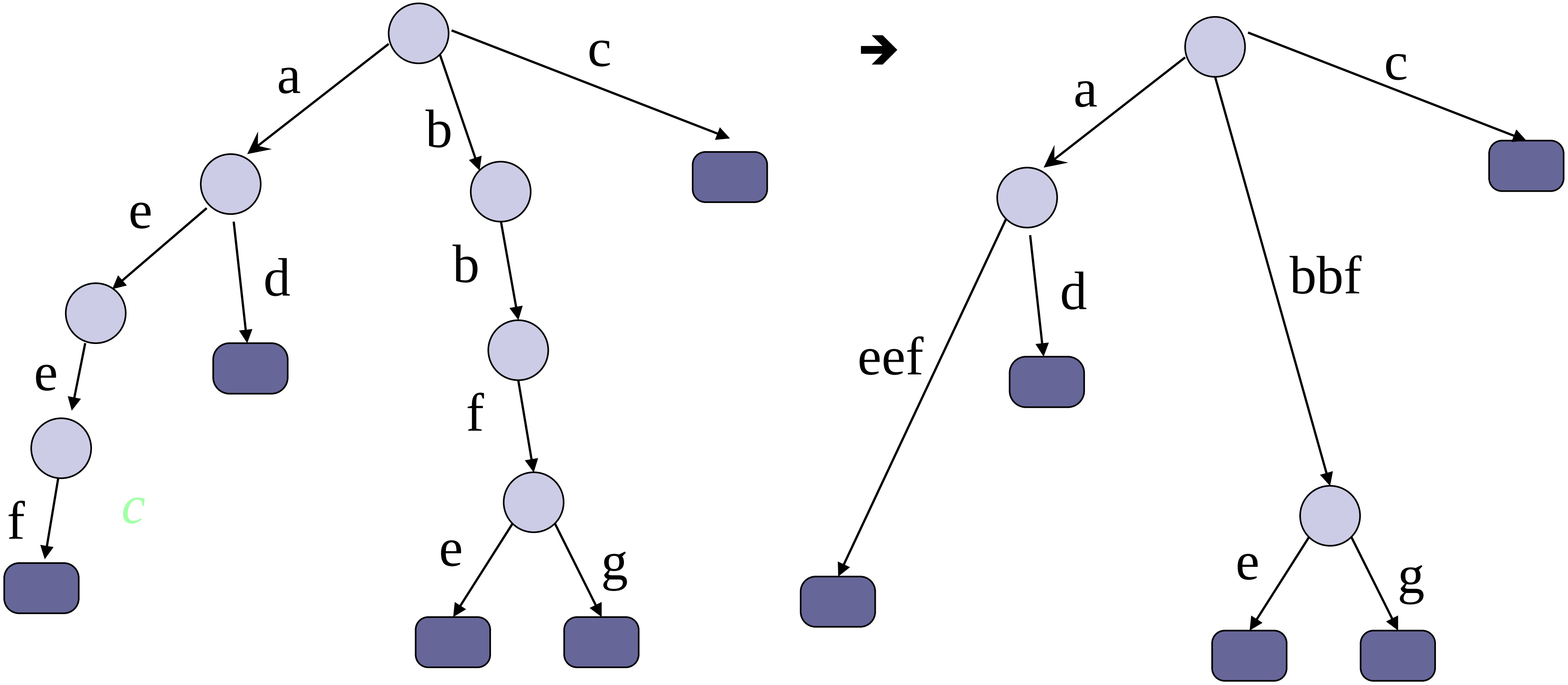
Each edge is labeled by a letter,
no two edges outgoing from the same node are labeled the same.

Each string corresponds to a leaf.



Compressed Trie

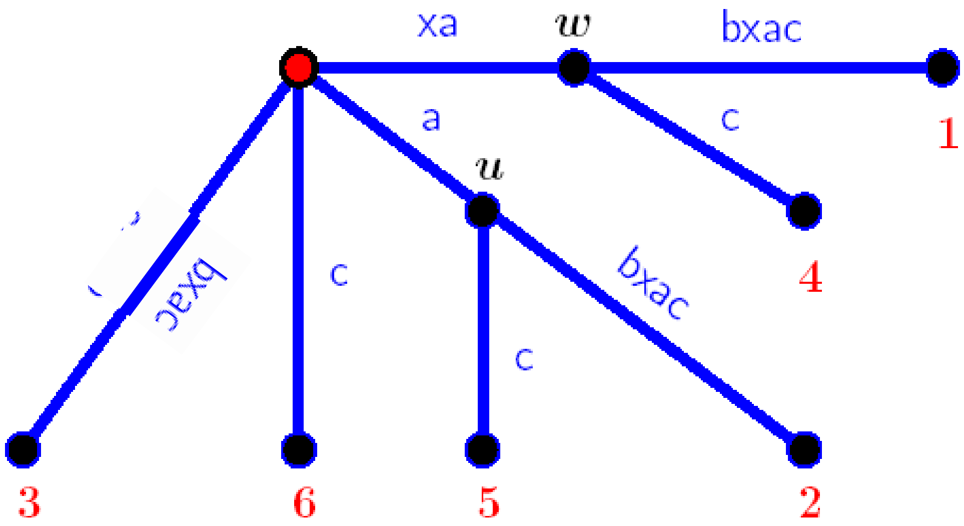
- Compress unary nodes, label edges by strings



Def: Suffix Tree for S $|S| = m$

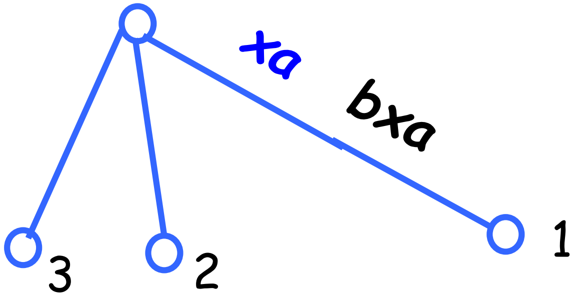
1. A rooted tree T with m leaves numbered 1,…,m.
2. Each internal node of T, except perhaps the root, has ≥ 2 children.
3. Each edge of T is labeled with a nonempty substring of S.
4. All edges out of a node must have labels starting with different characters.
5. For any leaf i, the concatenation of the edge-labels on the path from the root to leaf i exactly spells out S[i,m].

S=xabxac



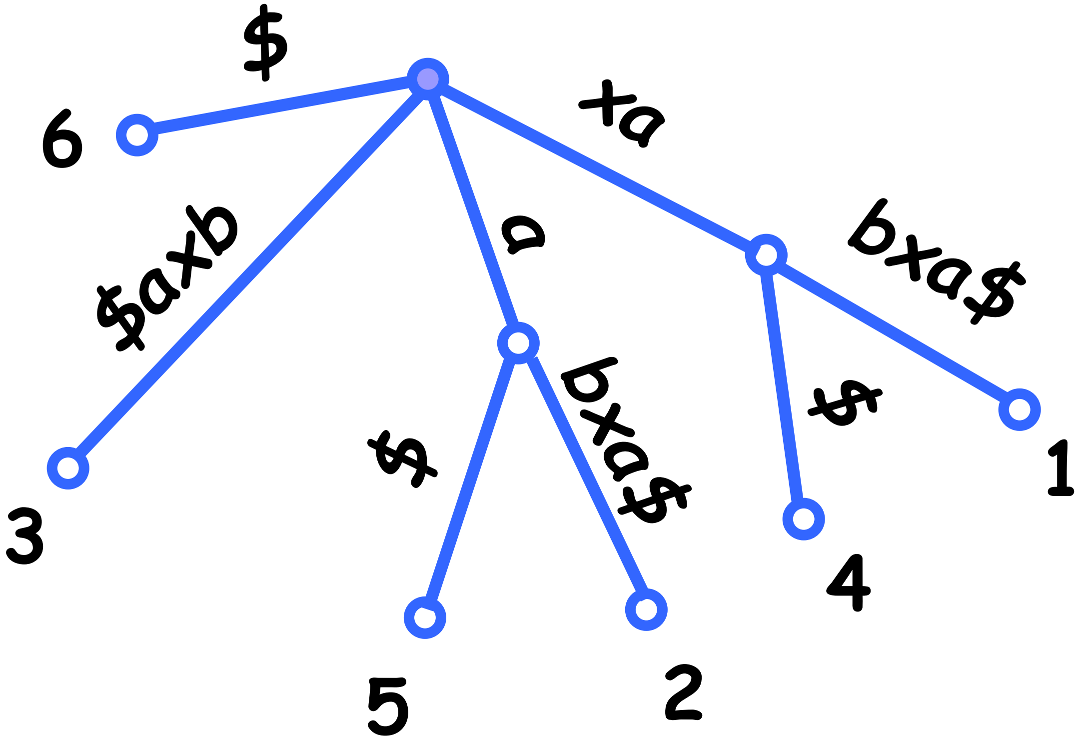
Existence of a suffix tree S

- If one suffix S_j of S matches a prefix of another suffix S_i of S, then the path for S_j would not end at a leaf.
- *S* = *xabxa*
- S_1 = *xabxa* and S_4 = *xa*



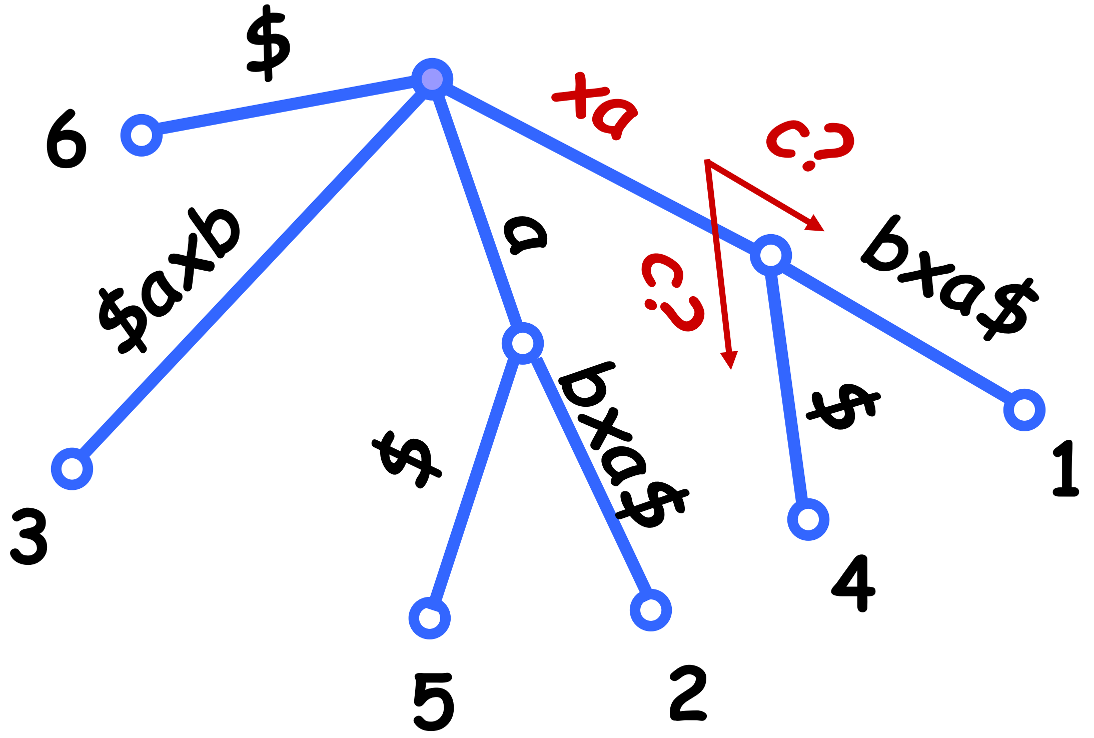
- How to avoid this problem?
  - ☐ Make sure that the last character of *S* appears nowhere else in *S*.
  - ☐ Add a new character $ not in the alphabet to the end of *S*.

Example: Suffix Tree for S=xabxa$



Example: Suffix Tree for S=xabxa$ Query: P = xac

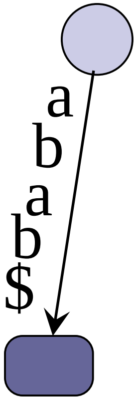
- P is a substring of S iff P is a prefix of some suffix of S.



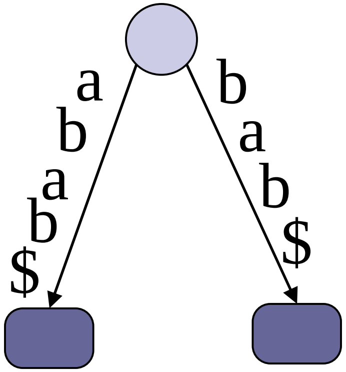
Trivial algorithm to build a Suffix tree

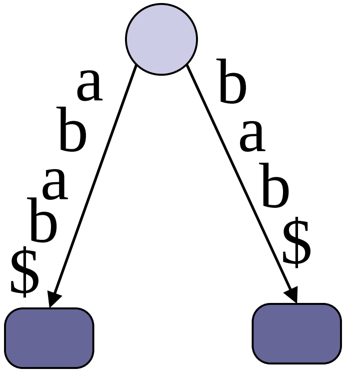
S= abab

Put the largest suffix in

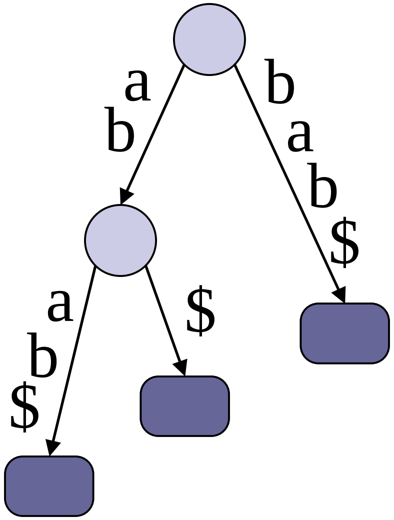


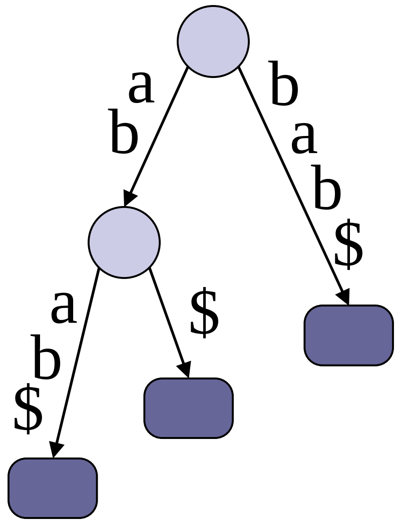
Put the suffix bab$ in



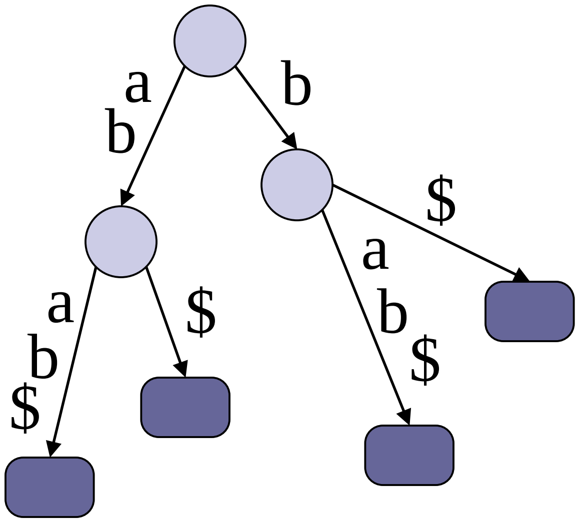


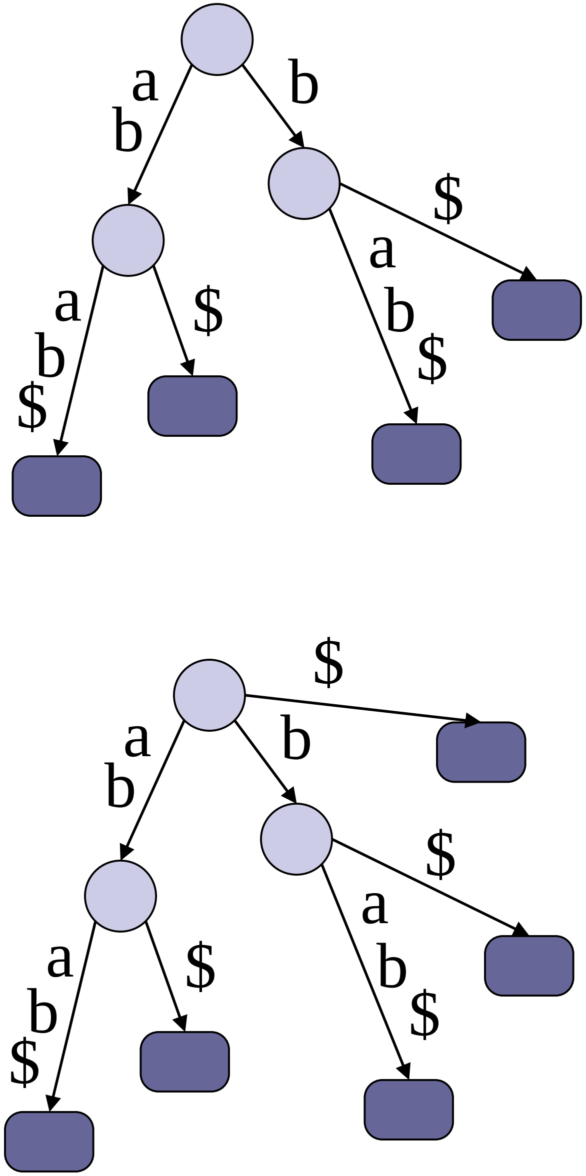
Put the suffix ab$ in



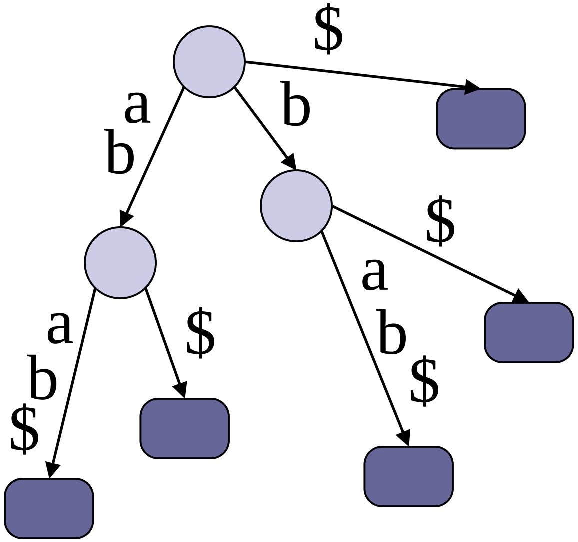


Put the suffix b$ in

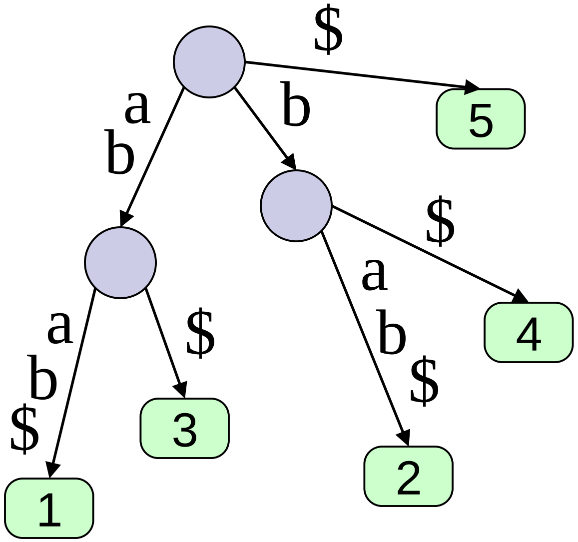




Put the suffix $ in



We will also label each leaf with the starting point of the corresponding suffix.



Analysis

Takes $O(m^2)$ time to build.

Can be done in $O(m)$ time - we will sketch the proof.

See the CG class notes or Gusfield's book for the full details of the proof.

Building STs in linear time: Ukkonen's algorithm

History

- Weiner's algorithm [FOCS, 1973]
    - Called by Knuth "The algorithm of 1973"
    - First linear time algorithm, but much space
- McCreight's algorithm [JACM, 1976]
    - Linear time and quadratic space
    - More readable
- Ukkonen's algorithm [Algorithmica, 1995]
    - Linear time and less space
    - This is what we will focus on
- ….

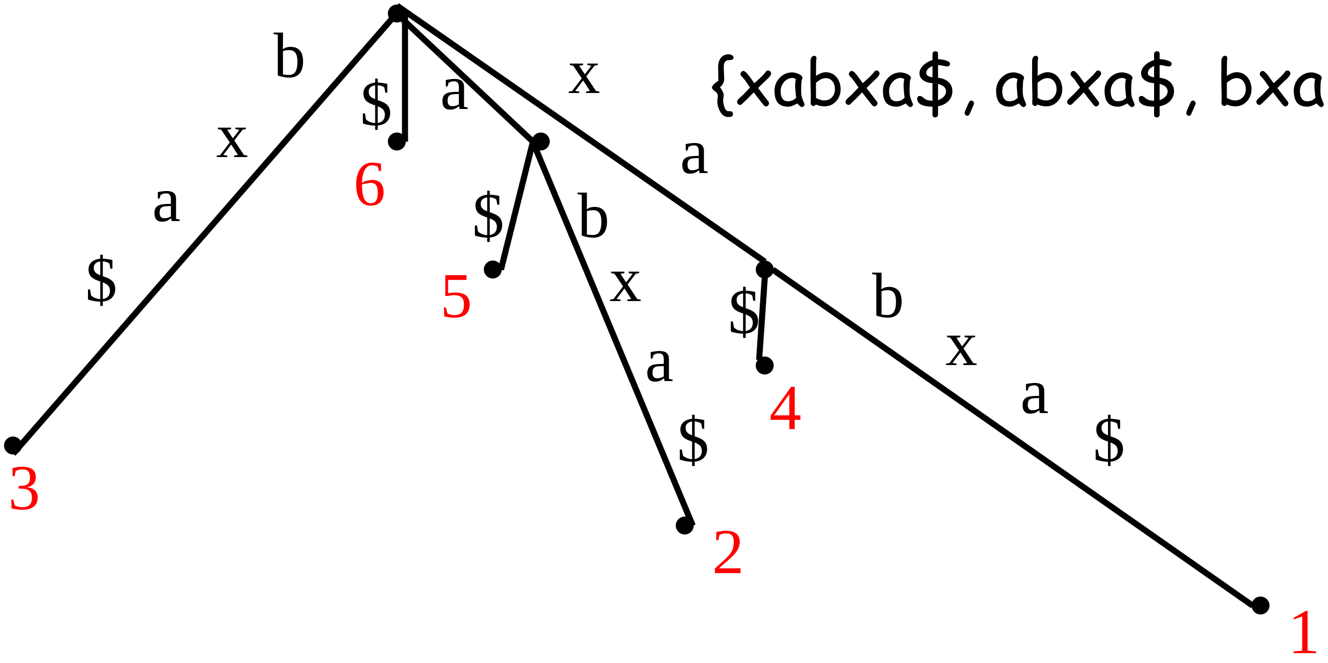
Esko Ukkonen

Implicit Suffix Trees

- Ukkonen's alg constructs a sequence of implicit STs, the last of which is converted to a true ST of the given string.
- An implicit suffix tree for string S is a tree obtained from the suffix tree for S$ by
  - removing $ from all edge labels
  - removing any edge that now has no label
  - removing any node with only one child

Example: Construction of the Implicit ST

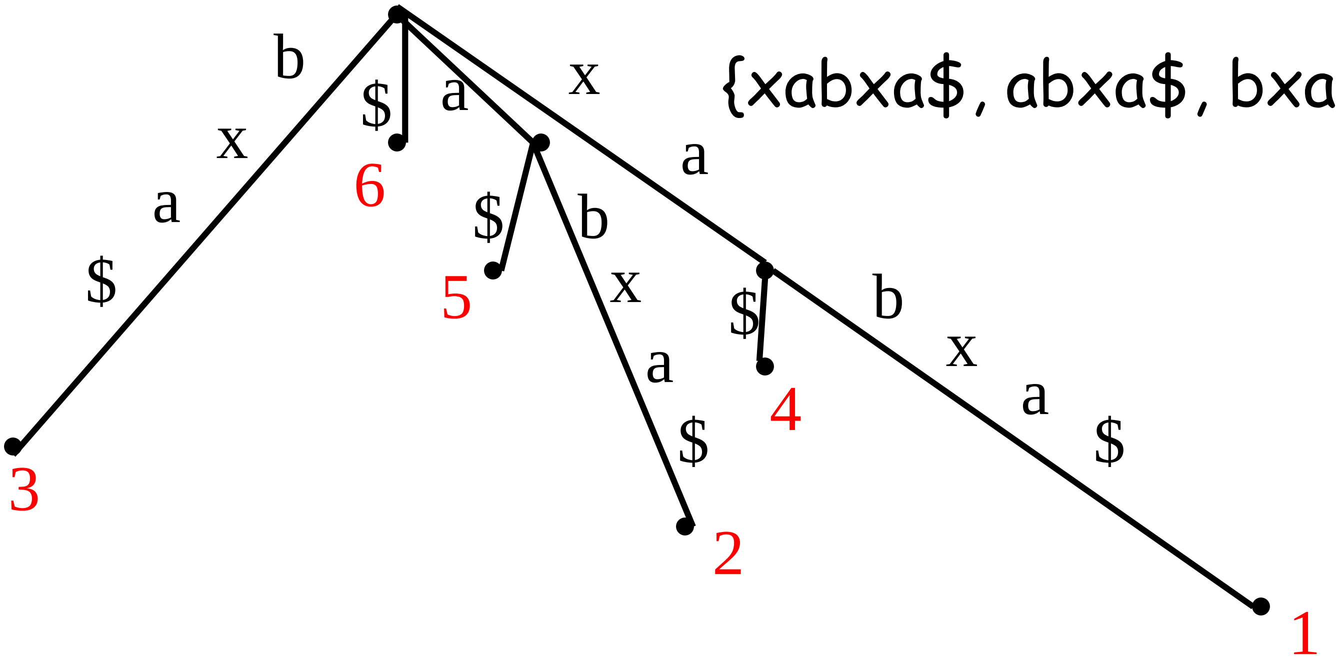
- The tree for xabxa$



{xabxa$, abxa$, bxa$, xa$, a$, $}

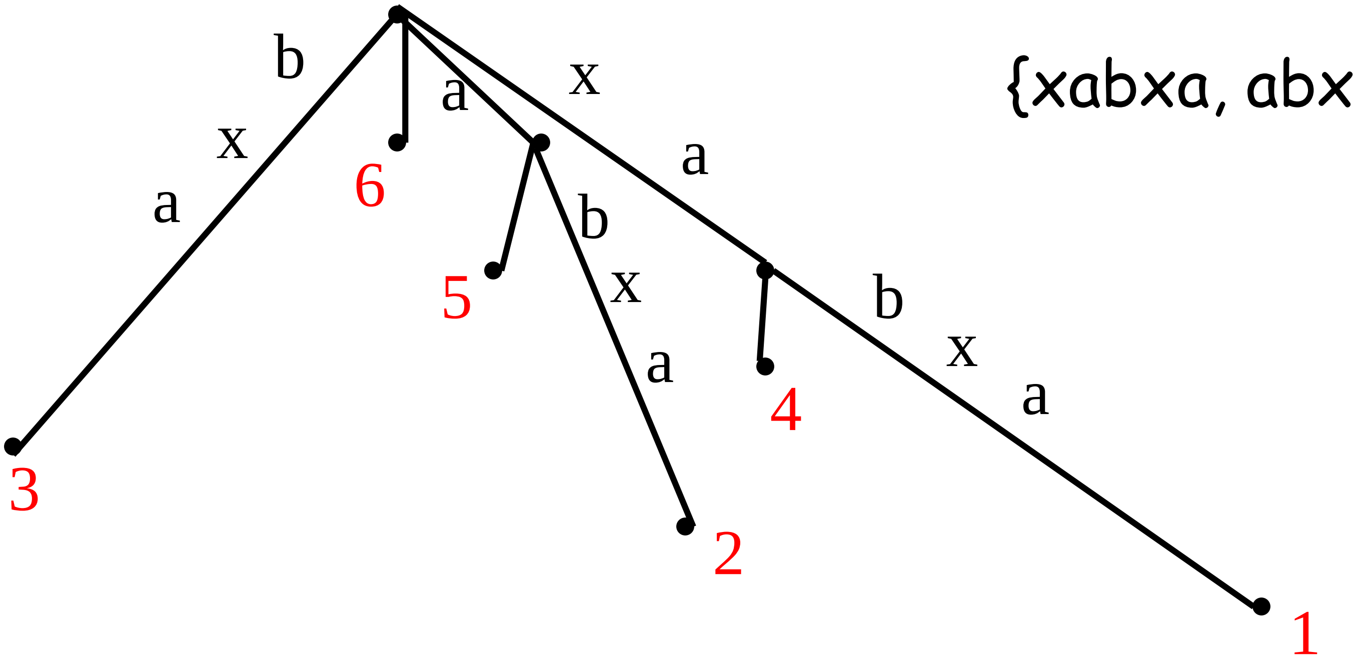
Construction of the Implicit ST: Remove $

- Remove $



{xabxa$, abxa$, bxa$, xa$, a$, $}

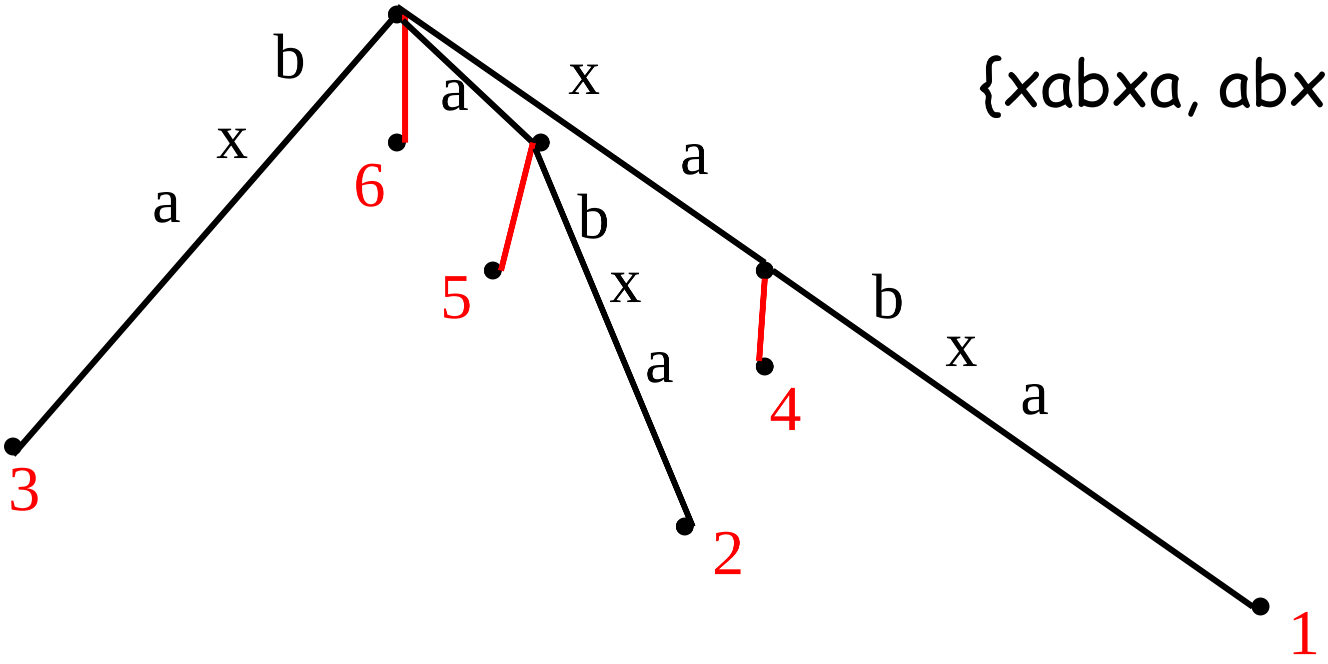
Construction of the Implicit ST: After the Removal of $



{xabxa, abxa, bxa, xa, a}

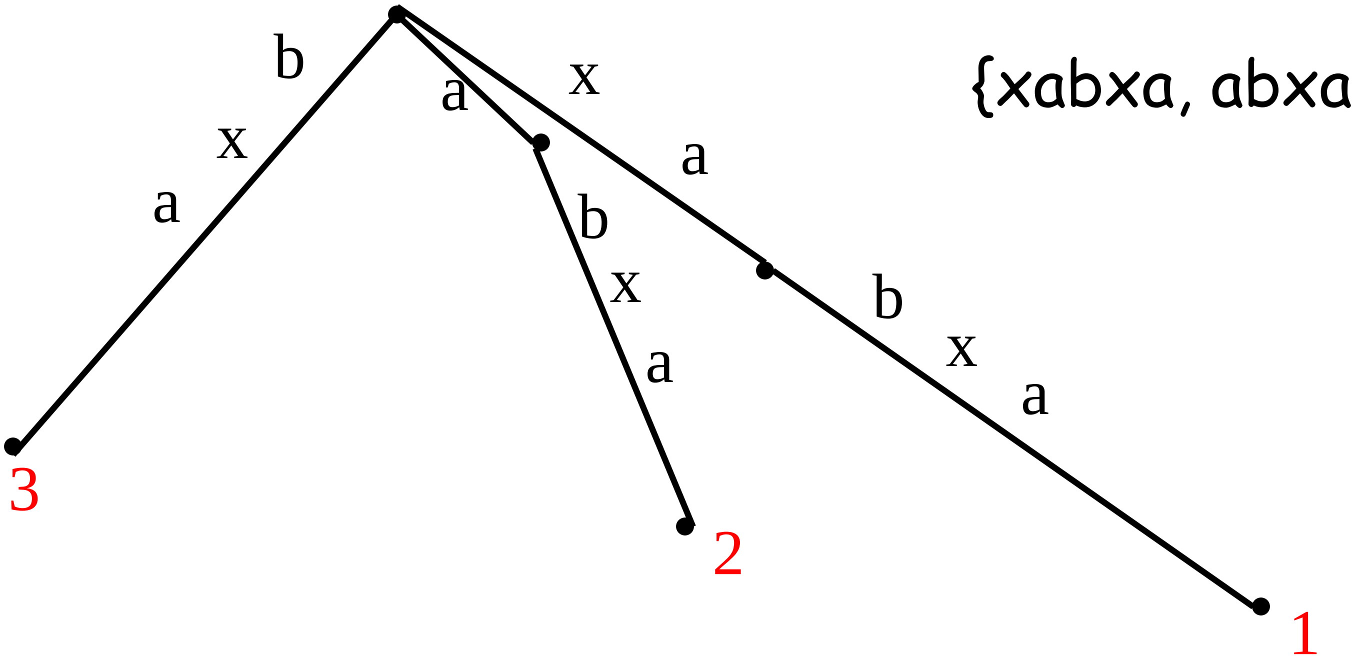
Construction of the Implicit ST: Remove unlabeled edges

- Remove unlabeled edges



{xabxa, abxa, bxa, xa, a}

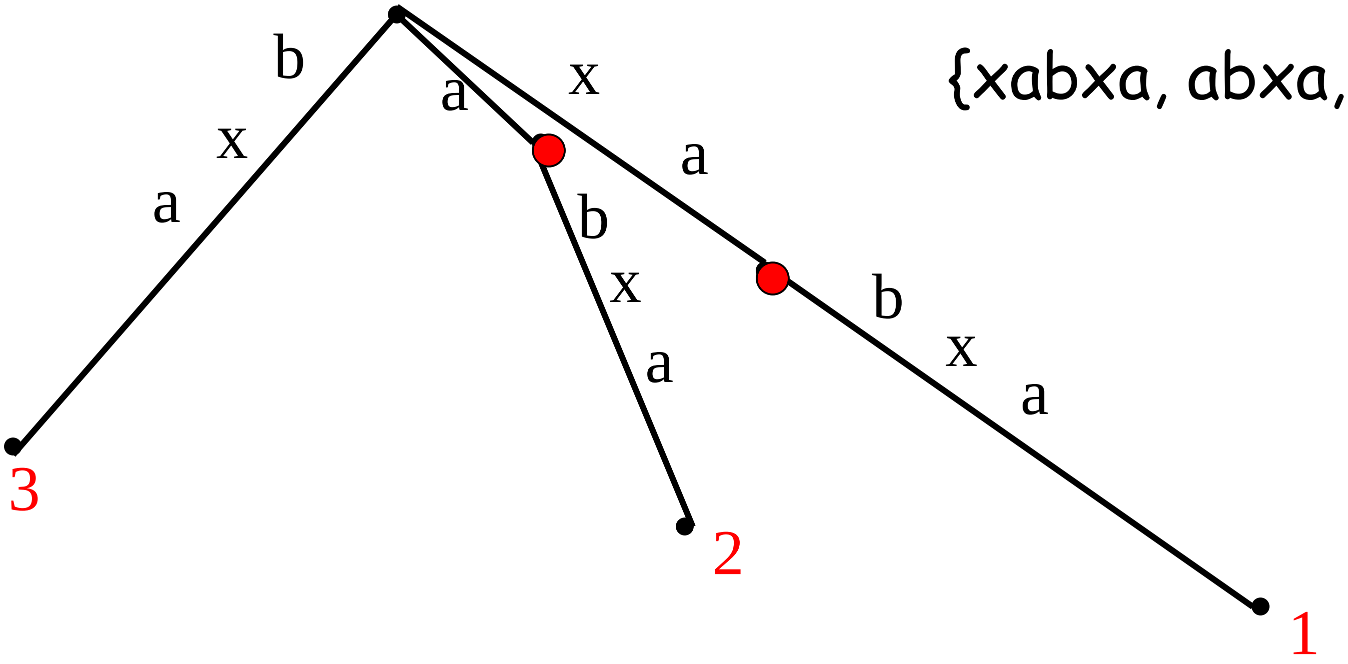
Construction of the Implicit ST: *After the Removal of Unlabeled Edges*



{xabxa, abxa, bxa, xa, a}

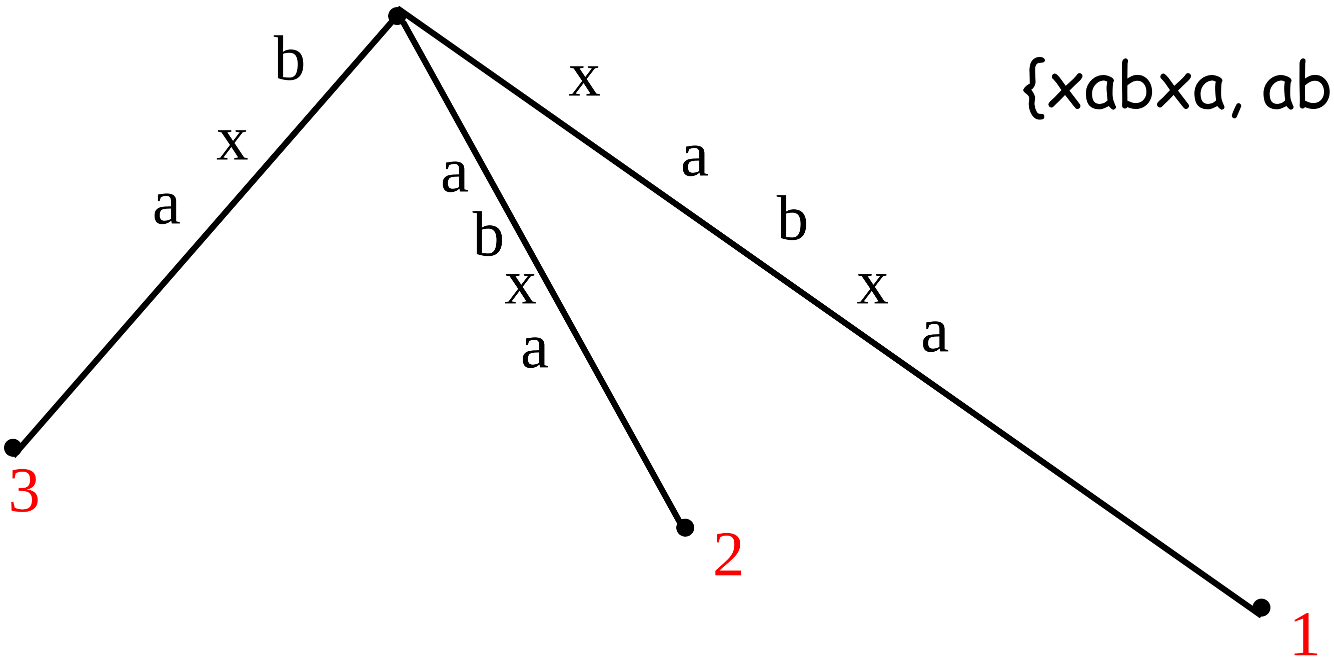
Construction of the Implicit ST: Remove degree 1 nodes

- Remove internal nodes with only one child



{xabxa, abxa, bxa, xa, a}

Construction of the Implicit ST: Final implicit tree



{xabxa, abxa, bxa, xa, a}

- Each suffix is in the tree, but may not end at a leaf.

Implicit Suffix Trees (2)

- An implicit suffix tree for prefix $S[1,i]$ of S is similarly defined based on the suffix tree for $S[1,i]\$$.

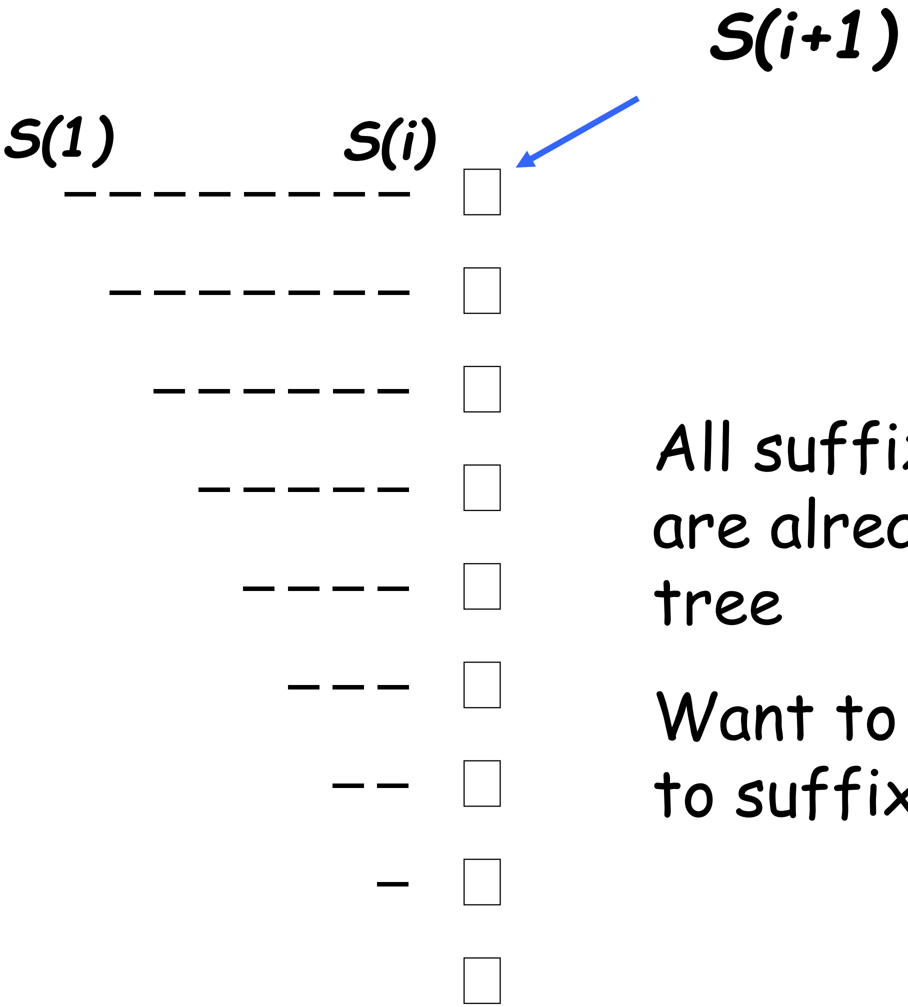
- I_i = the implicit suffix tree for $S[1,i]$.

Ukkonen's Algorithm (UA)

- I_i is the implicit suffix tree of the string $S[1, i]$
- Construct I_1
- /* Construct I_{i+1} from I_i */
- **for** i = 1 to m-1 **do** /* generation ***i+1*** */
  - **for** j = 1 to i+1 **do** /* extension ***j*** */
    - Find the end of the path p from the root whose label is $S[j, i]$ in I_i and extend p with $S(i+1)$ by suffix extension rules;
- Convert I_m into a suffix tree S

Example

- S = xabxa$
- ***(initialization step)***
    - x
- ***(i = 1), i+1 = 2, S(i+1)= a***
    - extend x to xa (j = 1, S[1,1] = x)
    - a (j = 2, S[2,1] = “”)
- ***(i = 2), i+1 = 3, S(i+1)= b***
    - extend xa to xab (j = 1, S[1,2] = xa)
    - extend a to ab (j = 2, S[2,2] = a)
    - b (j = 3, S[3,2] = “”)
- …



All suffixes of S[1,i] are already in the tree

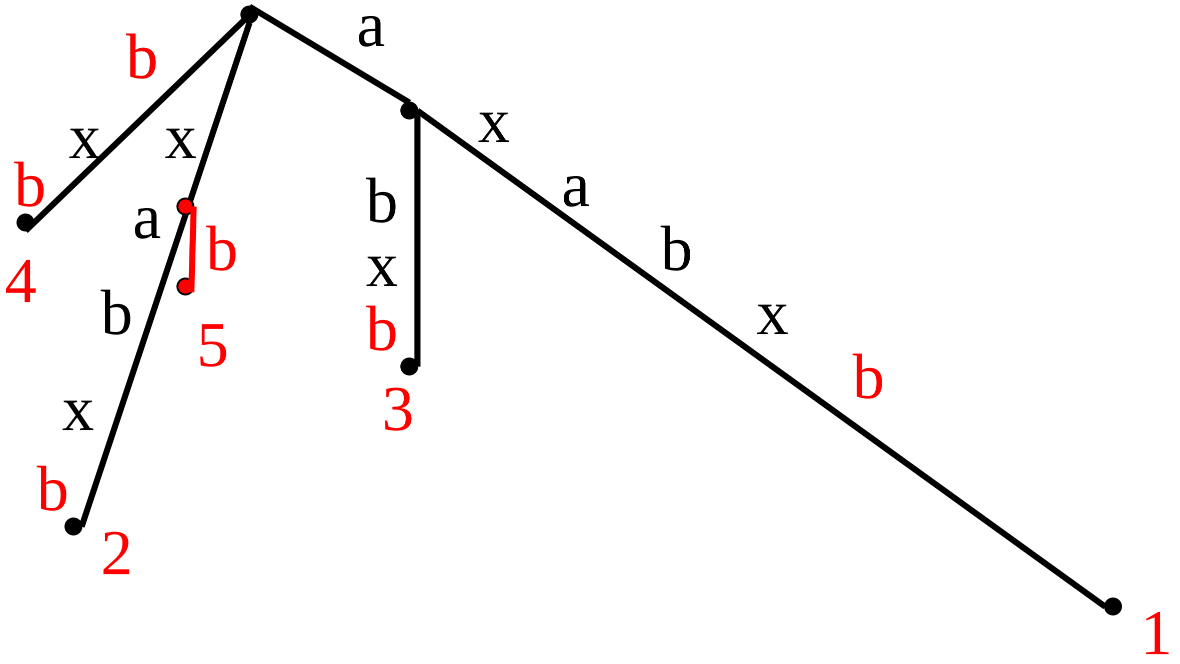
Want to extend them to suffixes of S[1,i+1]

Extension Rules

- **Goal:** extend each $S[j,i]$ into $S[j,i+1]$
- **Rule 1:** $S[j,i]$ ends at a leaf
  - Add character $S(i+1)$ to the end of the label on that leaf edge
- **Rule 2:** $S[j,i]$ doesn't end at a leaf, and the following character is not $S(i+1)$
  - Split a new leaf edge for character $S(i+1)$
  - May need to create an internal node if $S[j,i]$ ends in the middle of an edge
- **Rule 3:** $S[j,i+1]$ is already in the tree
  - No update

Example: Extension Rules

- Constructing the implicit tree for axabxb from tree for axabx

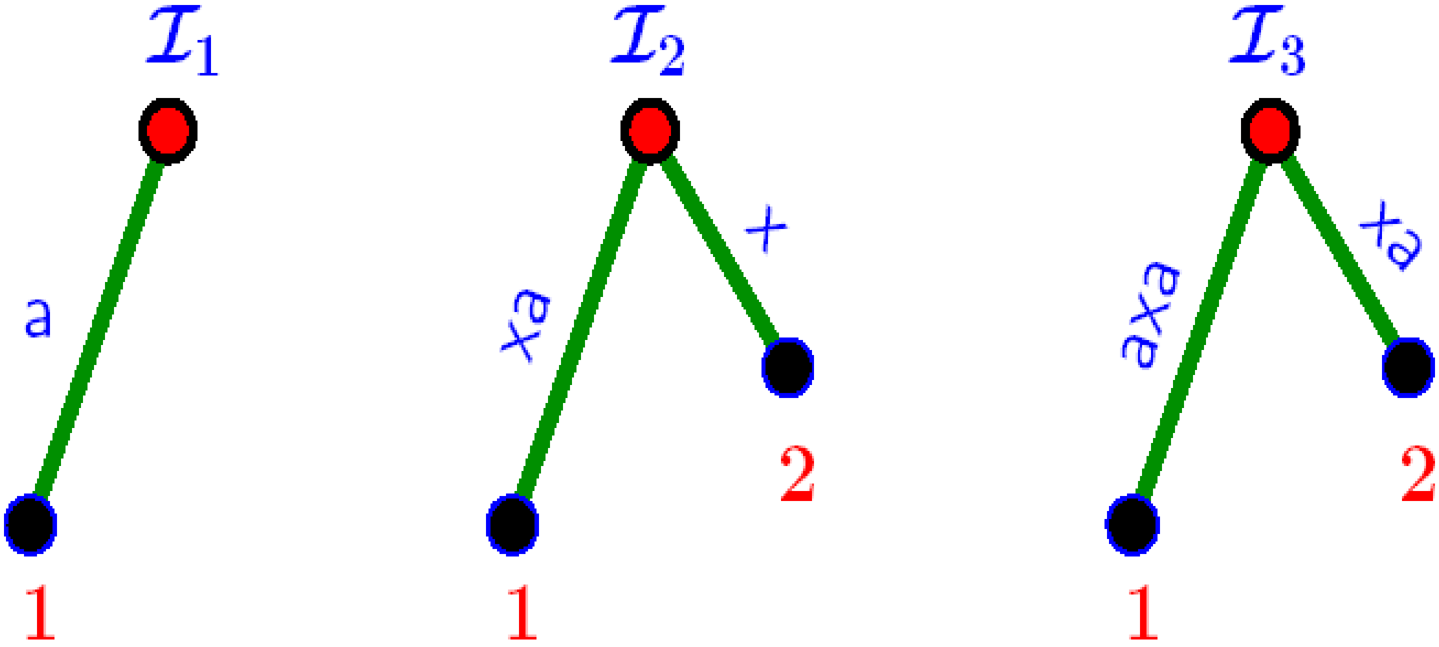


Rule 1: at a leaf

Rule 2: add a leaf edge (and an interior node)

Rule 3: already in tree

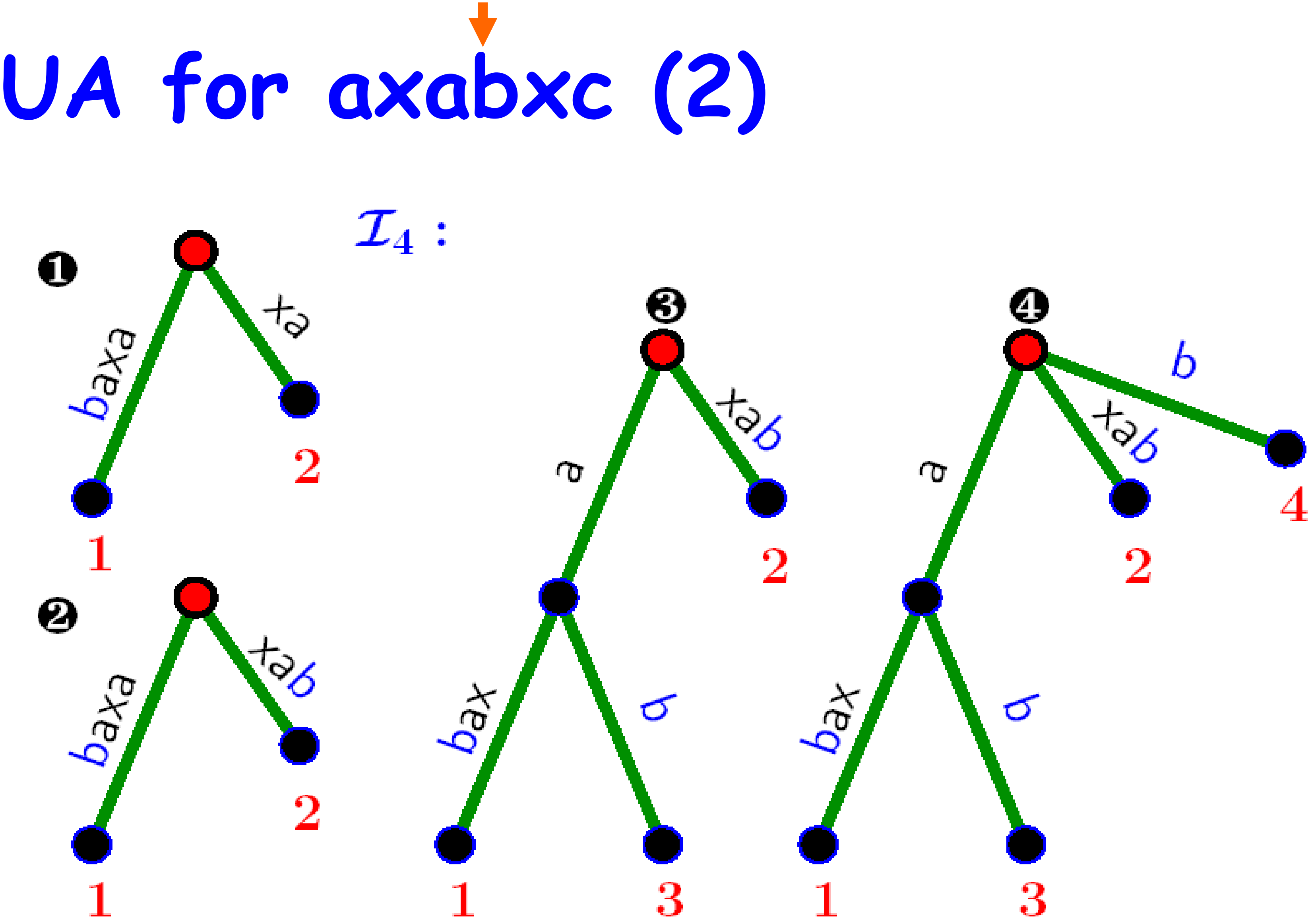
UA for axabxc (1)



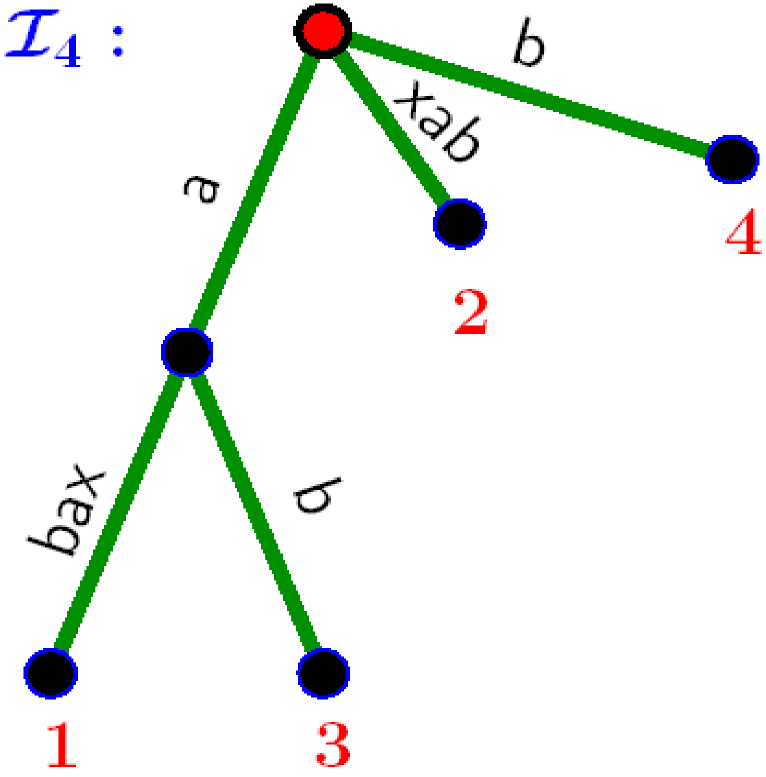
S[1,3]=axa		
E	**S(j,i)**	**S(i+1)**
1	ax	a
2	x	a
3		a

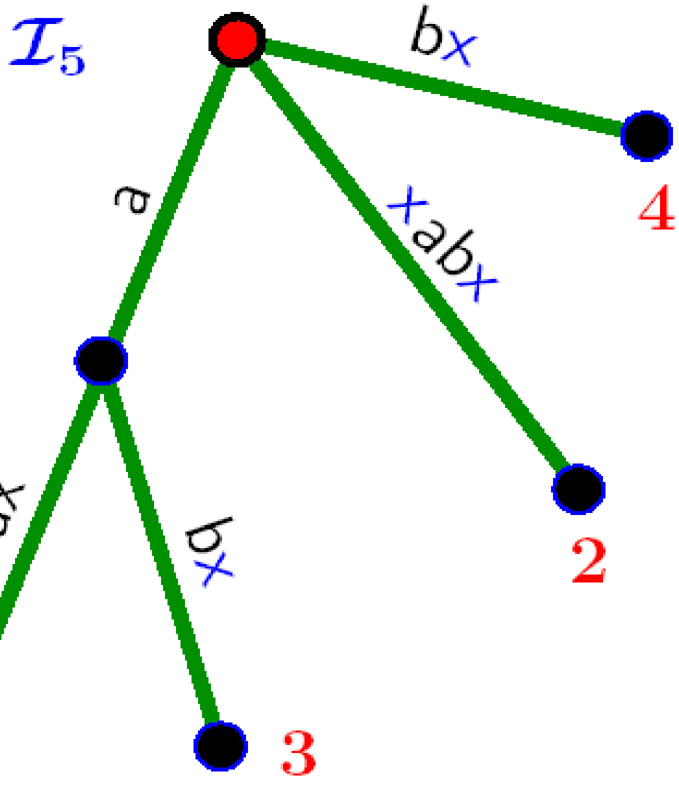
UA for axabxc (2)

$\mathcal{I}_4$:

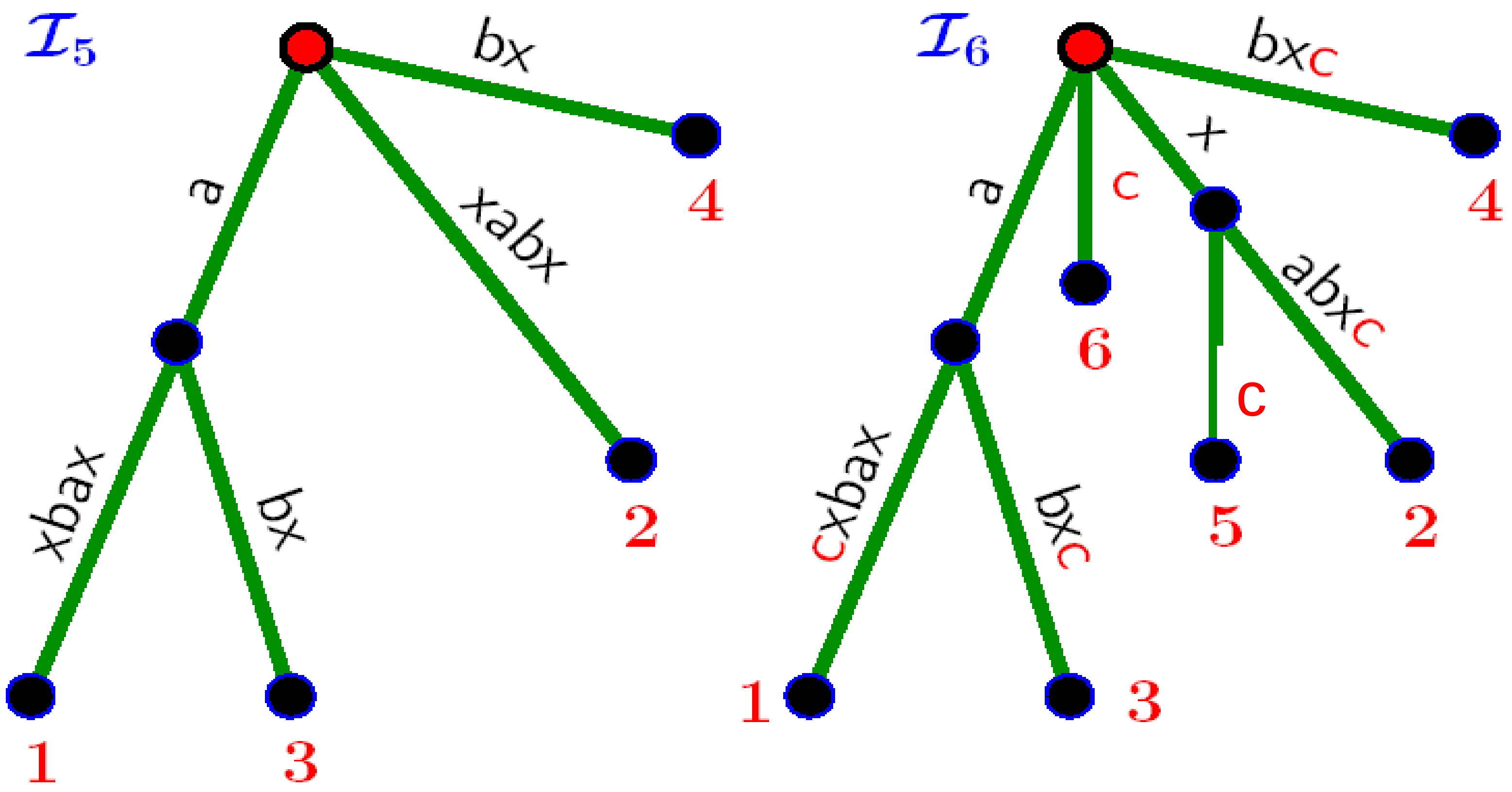


UA for axabxc (3)





UA for axabxc (4)



Observations

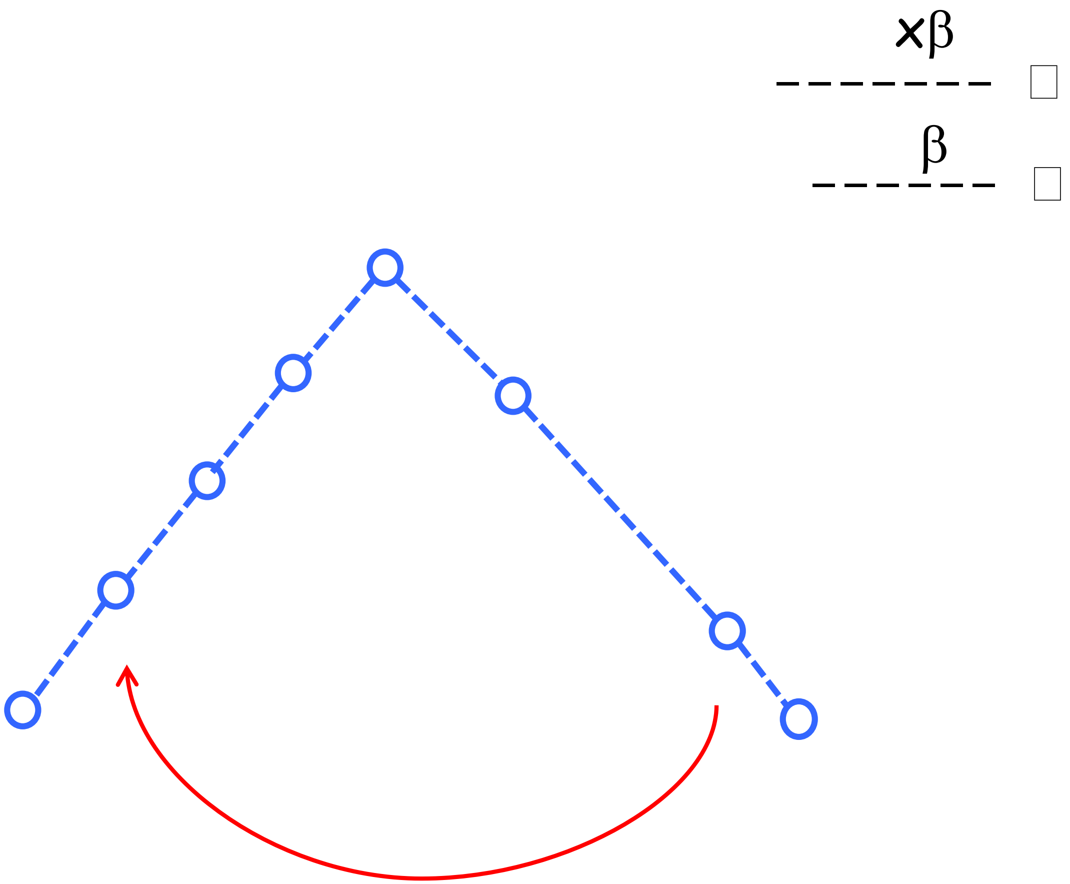
- Once $S[j,i]$ is located in the tree, applying the extension rule takes only constant time
- Naive implementation: find the end of suffix $S[j,i]$ in $O(i-j)$ time by walking from the root of the current tree => I_m is created in $O(m^3)$ time.
- Making Ukkonen's algorithm run in $O(m)$ time is achieved by a set of shortcuts:
  - ☐ Suffix links
  - ☐ Skip and count trick
  - ☐ Edge-label compression
  - ☐ A stopper
  - ☐ Once a leaf, always a leaf

Ukkonen's Algorithm (UA)

- I_i is the implicit suffix tree of the string S$[1, i]$
- Construct I_1
- /* Construct I_{i+1} from I_i */
- **for** i = 1 to m-1 **do** /* generation $\boldsymbol{i+1}$ */
    - ☐ **for** j = 1 to i+1 **do** /* extension $\boldsymbol{j}$ */
        - Find the end of the path **p** from the root whose label is S$[j, i]$ in I_i and extend **p** with S$(i+1)$ by suffix extension rules;
- Convert I_m into a suffix tree S

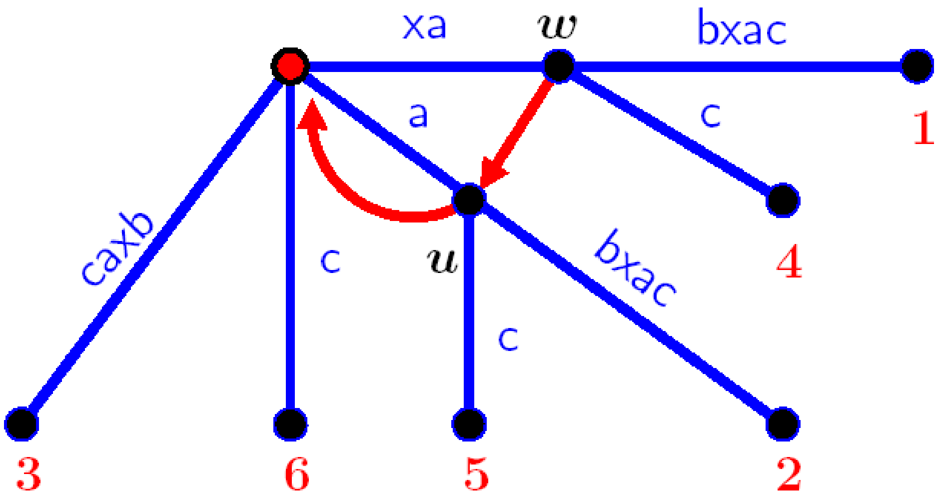
Looking for a shortcut

After we extend a string xβ, we need to extend β.
Can we jump right to its position in the current tree, rather than going down all the way from the root?



Suffix Links

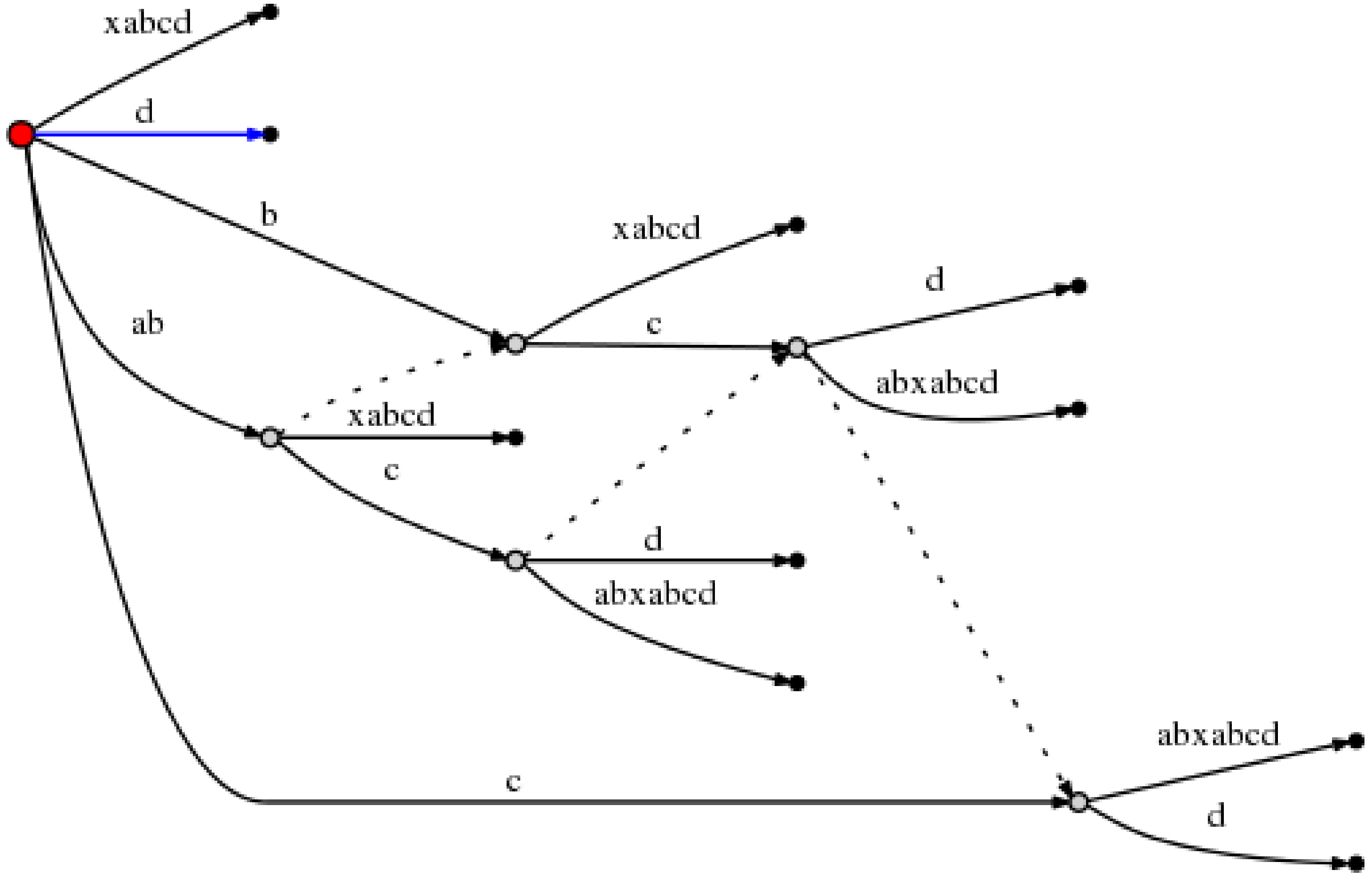
- Consider the two strings β and $x\ \beta$ *(e.g. a, xa in the example below).*
- Suppose some internal node v of the tree is labeled with $x\beta$ (x=char, β= *string, possibly* $\varnothing$) and another node s(v) in the tree is labeled with β
- The edge (v,s(v)) is called the ***suffix link*** **of v**
- Do all internal nodes have suffix links?
- (the root is not considered an internal node)



path label of v: concatenation of the strings labeling edges from root to v

Example: Suffix links

abcabxabcd



https://stackoverflow.com/questions/9452701/ukkonens-suffix-tree-algorithm-in-plain-english

Suffix Link Lemma

If a new internal node v with path-label $x\beta$ is added to the current tree in extension j of some generation $i+1$, then either

- the path labeled β already ends at an internal node of the tree, or
- the internal node labeled β will be created in extension $j+1$ in the same generation $i+1$, or
- string β is empty and s(v) is the root

Suffix Link Lemma

If a new internal node v with path-label $x\beta$ is added to the current tree in extension j of some generation $i+1$, then either

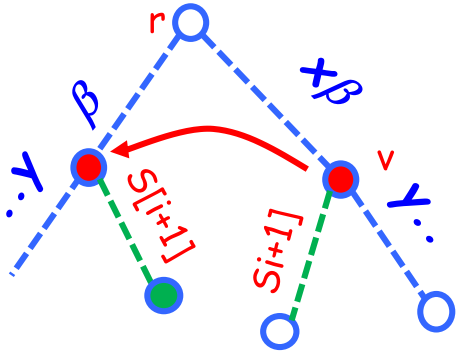
- ☐ the path labeled β already ends at an internal node of the tree, or
- ☐ the internal node labeled β will be created in extension $j+1$ in the same generation

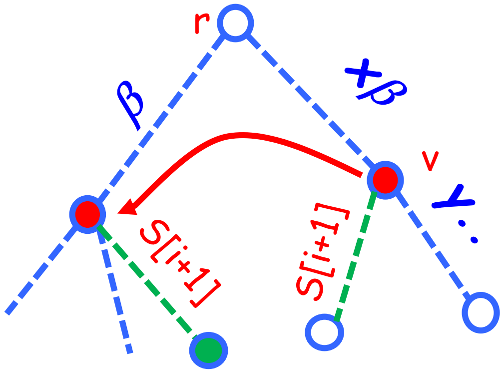
Pf: A new internal node is created only by extension rule 2

- In extension j the path labeled $x\beta$.. continued with some $y \neq S(i+1)$

=> In extension $j+1$, ∃ a path p labeled β..

- ☐ p continues with y only ➔ ext. rule 2 will create a node $s(v)$ at the end of the path β.
- ☐ p continues with two different chars ➔ $s(v)$ already exists.





Corollaries

- Every internal node of an implicit suffix tree has a suffix link from it by the end of the next extension
  - Proof by the lemma, using induction.

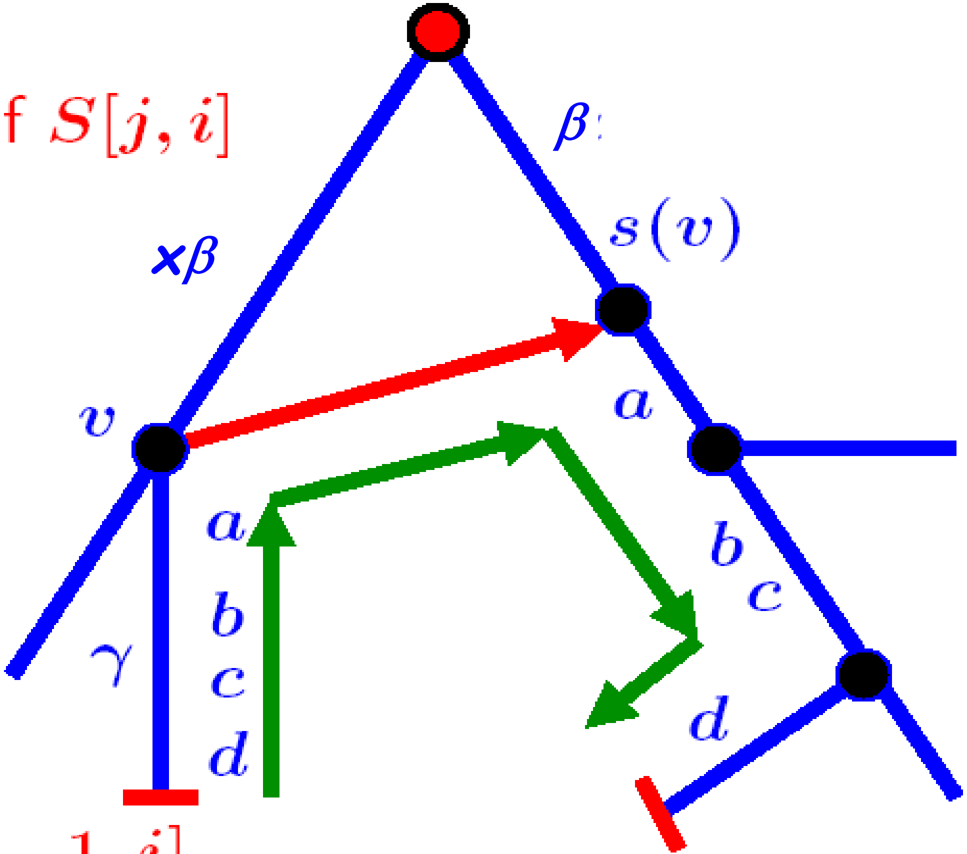
- In any implicit suffix tree I_i, if internal node v has path label $x\beta$, then there is a node $s(v)$ of I_i with path label β
  - Proof by the lemma, applied at the end of a generation

Building I_{i+1} with suffix links - 1

- Goal: in extension *j* of generation *i+1*, find *S[j,i]* in the tree and extend to *S[j,i+1];* add suffix link if needed

Extension j:

find the end of $S[j,i]$



End of $S[j-1,i]$

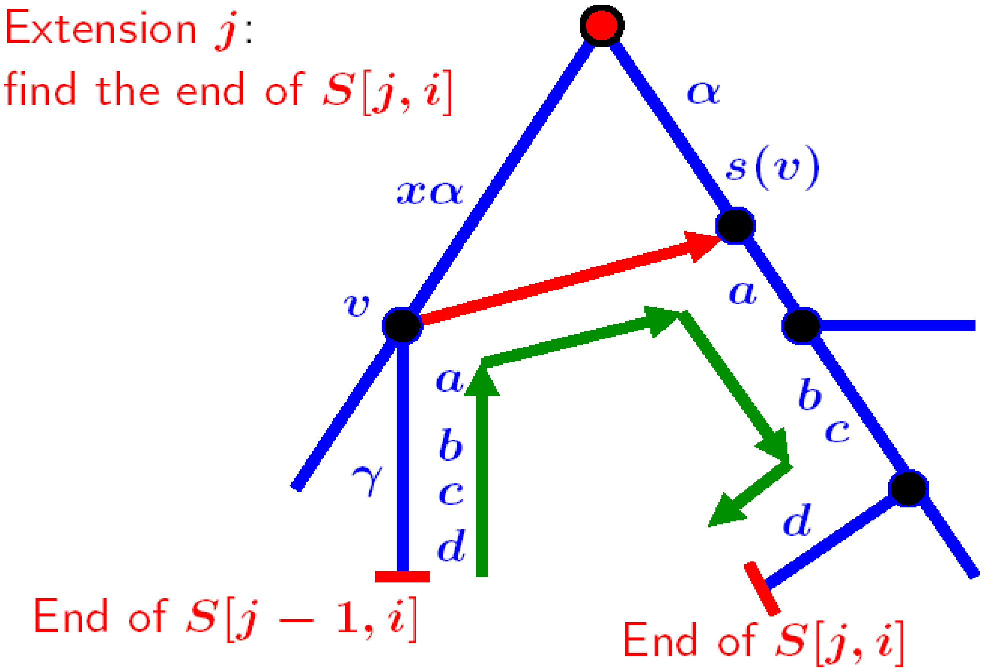
End of $S[j,i]$

Building I_{i+1} with suffix links - 2

- Goal: in extension j of generation $i+1$, find $S[j,i]$ in the tree and extend to $S[j,i+1]$; add suffix link if needed
- $S[1,i]$ must end at a leaf since it is the longest string in the implicit tree I_i
  - Keep pointer to leaf of full string; extend to $S[1,i+1]$ (rule 1)
- $S[2,i] = \beta$, $S[1,i] = x\beta$; let $(v,1)$ be the edge entering leaf 1:
  - If v is the root, descend from the root to find β
  - Otherwise, v is internal. Go to s(v) and descend to find rest of β

Building I_{i+1} with suffix links - 3

- In general: find first node v at or above *S[j-1,i]* that has s.l. or is root; Let γ = string between v and end of *S[j-1,i]*
  - ☐ If v is internal, go to s(v) and descend following the path of γ
  - ☐ If v is the root, descend from the root to find *S[j,i]*
  - ☐ Extend to *S[j,i]S(i+1)* (if not already in the tree)
  - ☐ If new internal node w was created in extension j-1, by the lemma *S[j,i+1]* ends in s(w) => create the suffix link from w to s(w).


Extension j:

find the end of $S[j,i]$

End of $S[j-1,i]$

End of $S[j,i]$

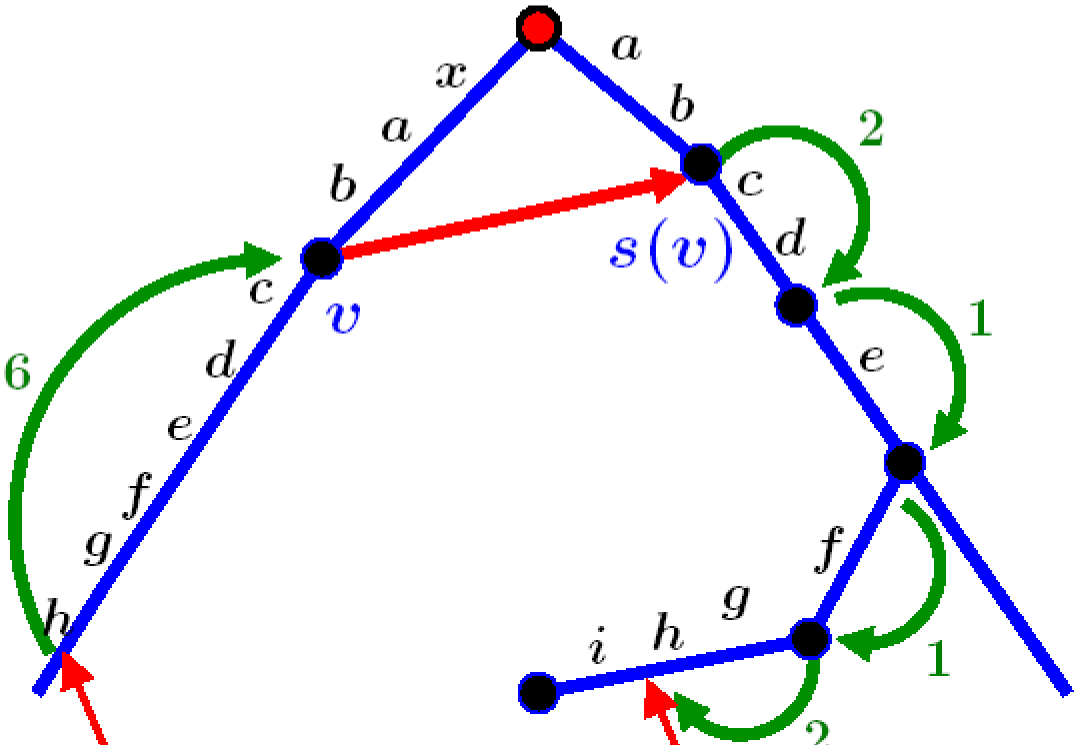
Skip and Count Trick – (1)

- Problem: Moving down from s(v), directly implemented, takes time proportional to $|\gamma|$
- Solution: make running time proportional to the number of nodes in the path searched
- Key: γ surely exists in the current tree; need to search only the first char. in each outgoing node

Skip and Count Trick – (2)

- counter=0; On each step from s(v), find right edge below, add no. of chars on it to counter and if still < $|\gamma|$ skip to child
- After 4 skips, the end of $S[j, i]$ is found.

Can show: with skip & count trick, any generation of Ukkonen's algorithm takes *O*(*m*) time



End of suffix $S[j-1, i]$

End of suffix $S[j, i]$

Interim conclusion

- Ukkonen's Algorithm can be implemented in **O(m^2)** time

A few more smart tricks and we reach O(m) [see scribe or the end of this presentation]

Implementation Issues – (1)

- When the size of the alphabet grows:
  - For large trees suffix, links allow to move quickly from one part of the tree to another. This is slow if the tree isn't entirely in memory.
  - ➔Efficiently implementing ST to reduce space in practice can be tricky.
- The main design issues are how to represent and search the branches out of the nodes of the tree.
- A practical design must balance between constraints of space and need for speed

Representing the branches out of v

- An array of size $\Theta(|\Sigma|)$ at each non-leaf node v
- A linked list of characters that appear at the beginning of the edge-labels out of v.
  - If kept in *sorted order* it reduces the average time to search for a given character
  - In the worst case, it adds time $|\Sigma|$ to every node operation. If the number of children k of v is large, little space is saved over the array, more time
- A balanced tree implements the list at node v
  - Additions and searches take O(logk) time and O(k) space. Option makes sense only when k is fairly large.
- A hashing scheme. The challenge is to find a scheme balancing space with speed. For large trees and alphabets hashing is very attractive at least for some of the nodes

Implementation Issues - (3)

- When m and Σ are large enough, a good design is often a mixture. Guidelines:
  - Nodes near the root tend to have most children → use arrays.
  - If ∃ k very dense levels - form a lookup table of all k-tuples with pointers to the roots of the corresponding subtrees.
  - Nodes in the middle of the tree: hashing or balanced trees.

Applications of Suffix Trees

What can we do with it ?

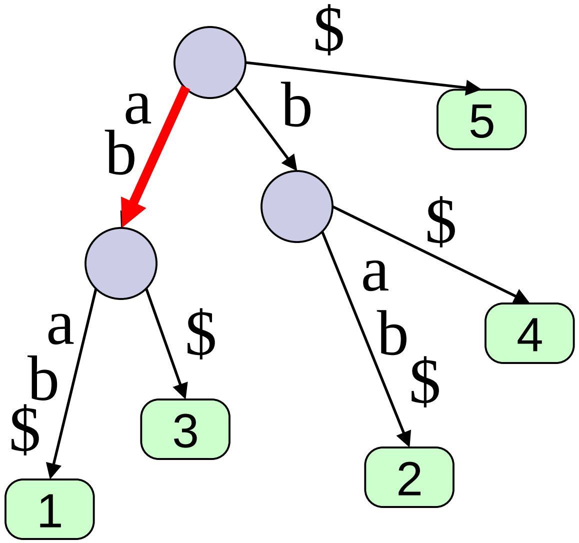
Exact string matching:

Given a Text T, |T| = n, preprocess it such that when a pattern P, |P|=m, arrives we can quickly decide if it occurs in T.

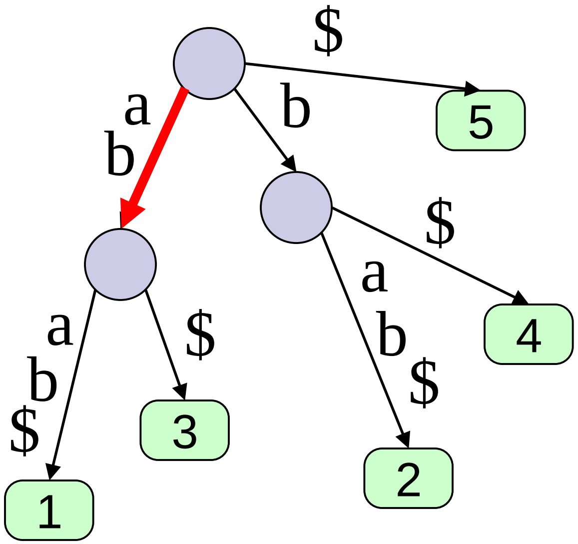
We may also want to find all occurrences of P in T

Exact string matching

In preprocessing we just build a suffix tree in O(m) time



Given a pattern P = ab we traverse the tree according to the pattern.



If we did not get stuck traversing the pattern then the pattern occurs in the text.

Each leaf in the subtree below the node we reach corresponds to an occurrence.

By traversing this subtree we get all k occurrences in O(n+k) time

Generalized suffix tree

Given a set of strings S, a generalized suffix tree of S is a compressed trie of all suffixes of $s \in S$

To associate each suffix with a unique string in S add a different special 'end' char $\$_i$ to each s_i

Example

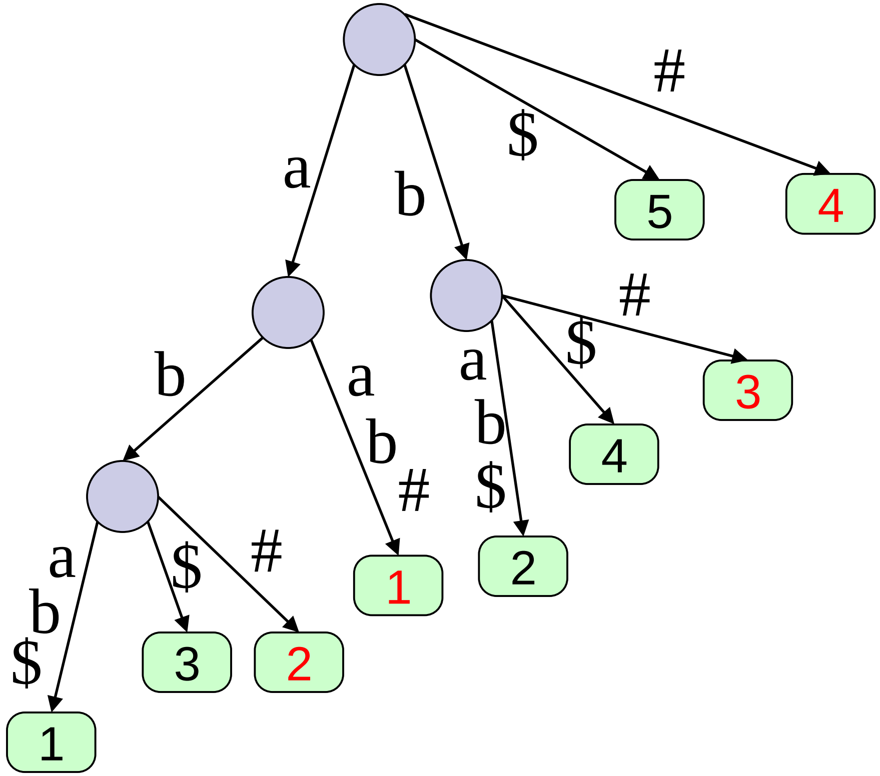
Let s_1=abab and s_2=aab

A generalized suffix tree for s_1 and s_2 :

{

\$	#
b\$	b#
ab\$	ab#
bab\$	aab#
abab\$	

}



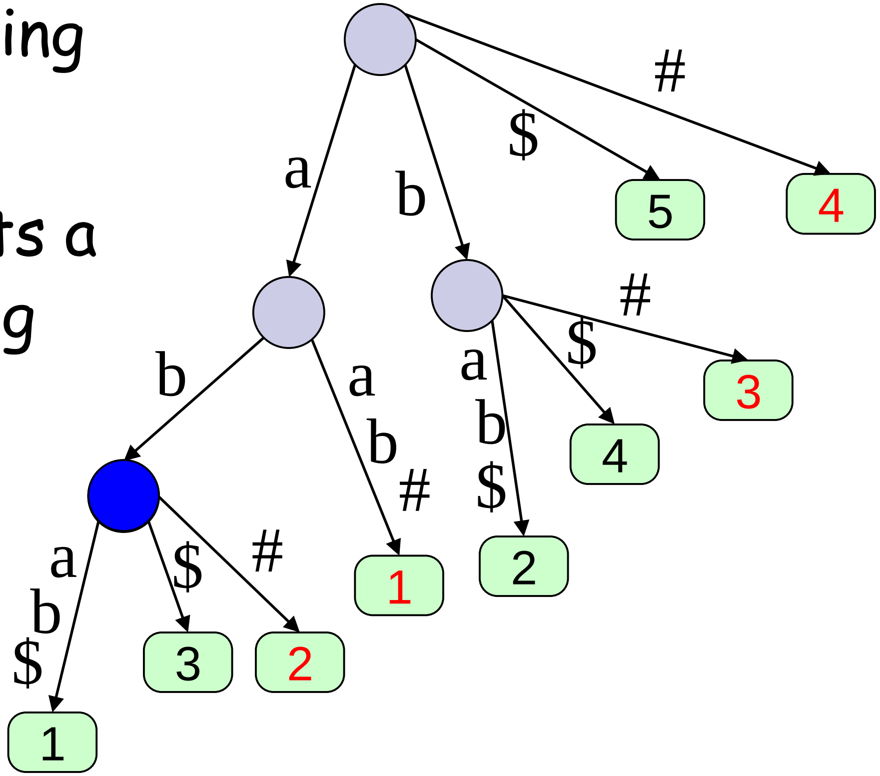
So what can we do with it ?

Matching a pattern against a database of strings

Longest common substring (of two strings)

Every node that has both a leaf descendant from string S_1 and a leaf descendant from string S_2 represents a maximal common substring and vice versa.

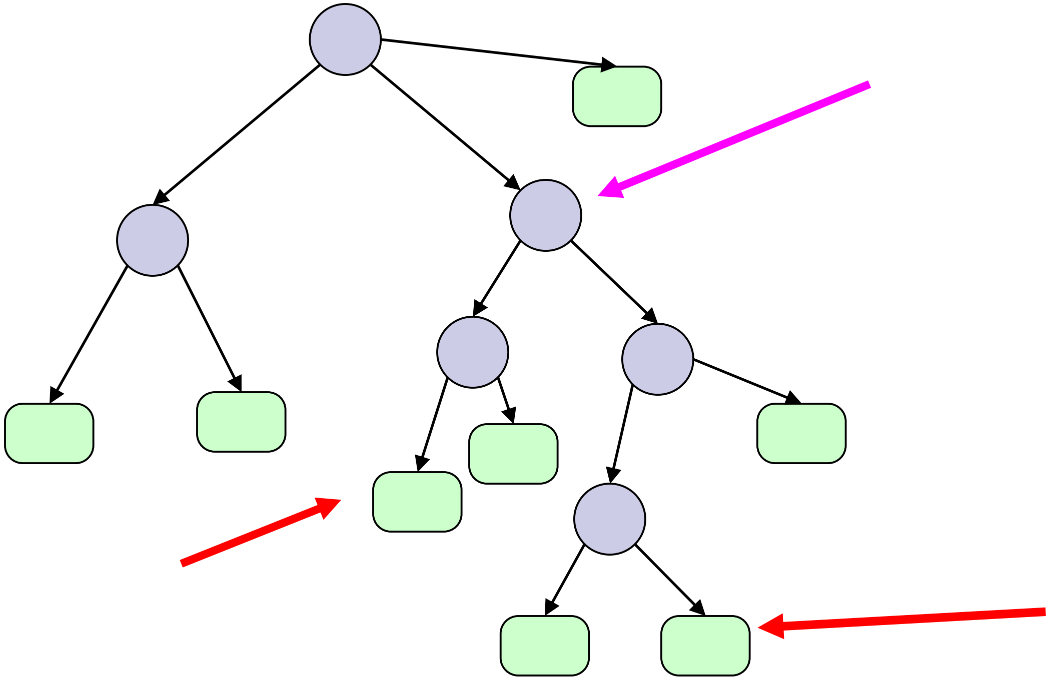
Find such node with largest "label depth"



$O(|S_1|+|S_2|)$ to construct the tree and search it.

Lowest common ancestors

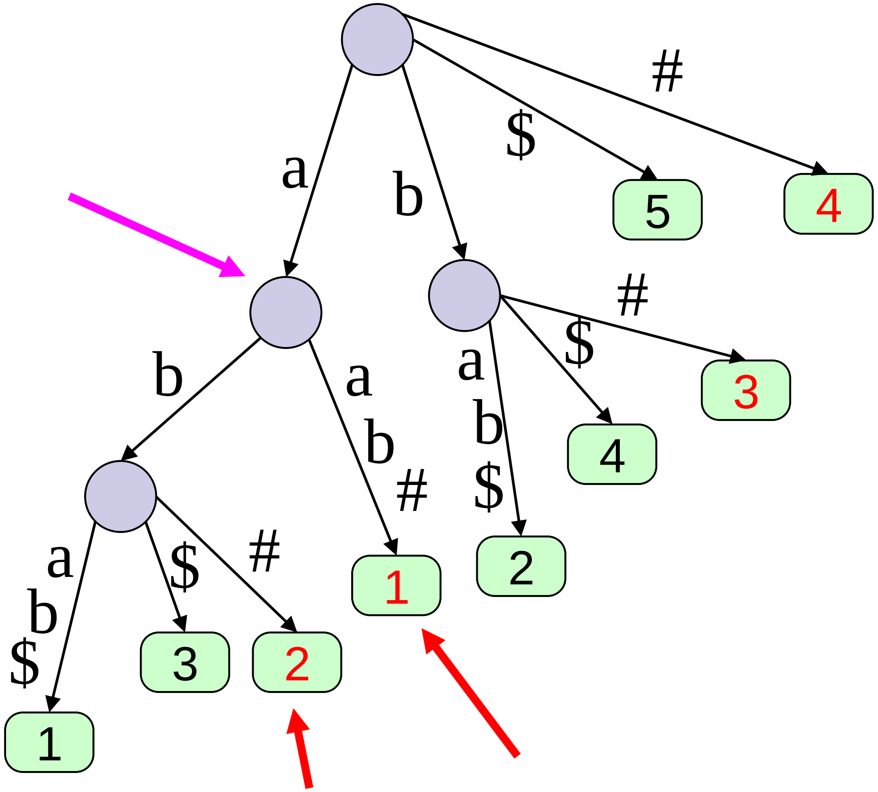
A lot more can be gained from the suffix tree if we preprocess it so that we can answer LCA queries on it



Why?

The LCA of two leaves represents the longest common prefix (LCP) of these two suffixes

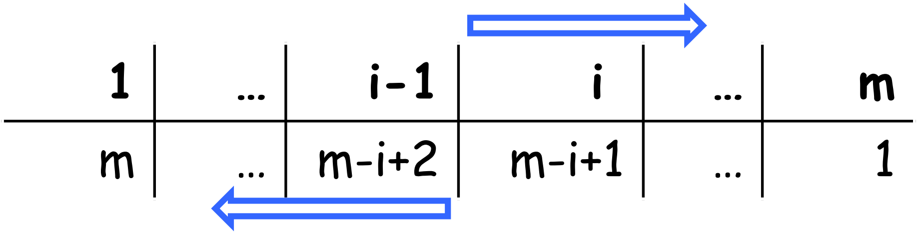
Harel-Tarjan (84), Schieber-Vishkin (88): LCA query in constant time, with linear pre-processing of the tree.



Finding maximal palindromes

- A palindrome: caabaac, cbaabc
- Want to find all maximal palindromes in a string s

s = acbaaba



1	…	i-1	i	…	m
m	…	m-i+2	m-i+1	…	1

The maximal palindrome with center between i-1 and i is the LCP of the suffix at position i of s and the suffix at position m-i+2 of s^r

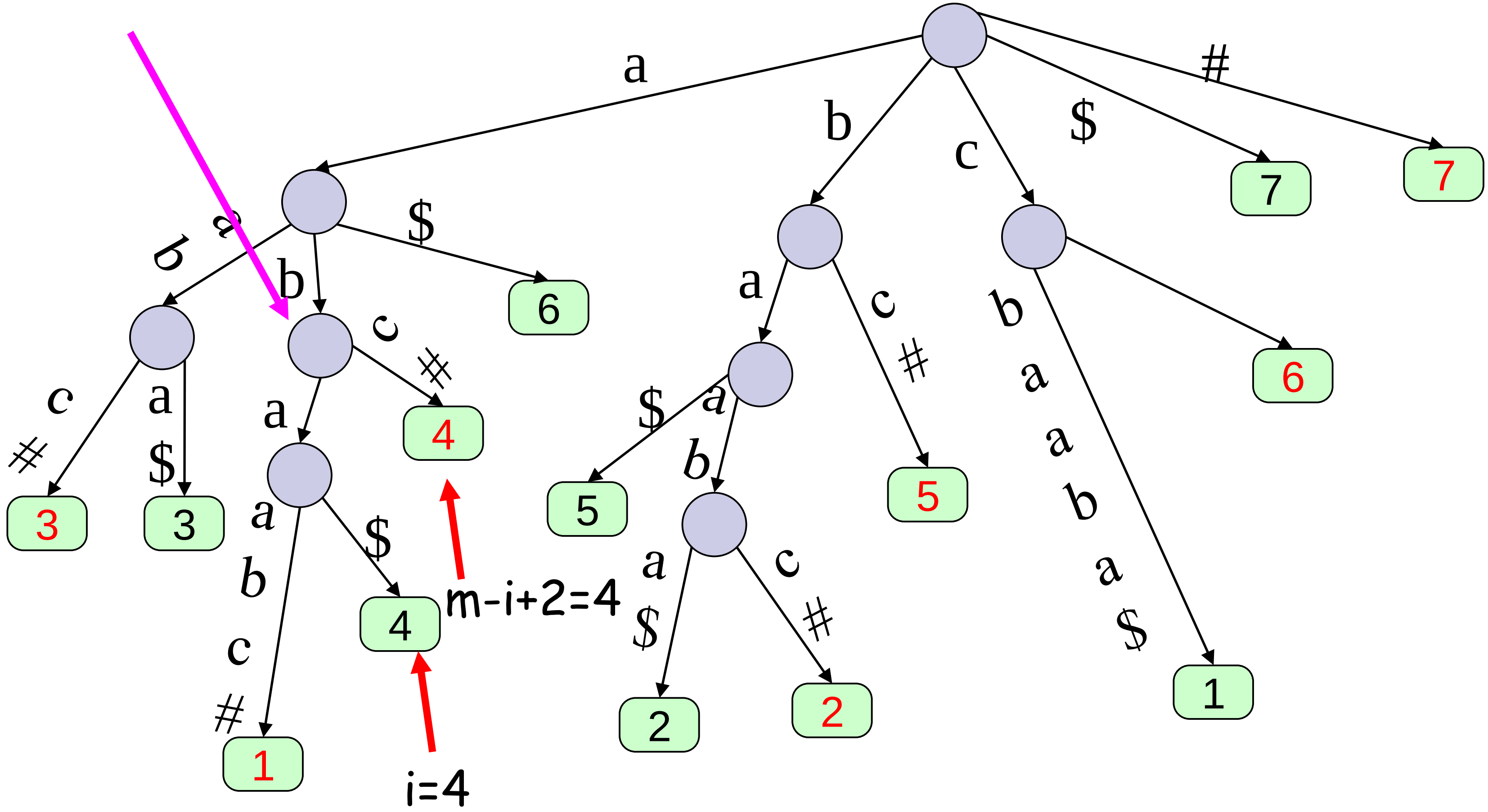
Maximal palindromes algorithm

Prepare a generalized suffix tree for s = cbaaba\$ and s^r = abaabc#

For every i find the LCA of suffix i of s and suffix m-i+2 of s^r

O(m) time to identify all palindromes

Let s = cbaaba$ then s^r = ababc#



SUFFIX ARRAYS

ST Drawbacks

- Space is O(m) but the constant is quite big
- For human genome, space >45GB.

Suffix arrays (U. Mander, G. Myers '91)

- We lose some of the functionality but save space.

Sort the suffixes of S lexicographically

The suffix array: list of starting positions of the sorted suffixes

Suffix Array for panamabananas$

Starting Positions	Sorted Suffixes
13	$
5	abananas$
3	amabananas$
1	anamabananas$
7	ananas$
9	anas$
11	as$
6	bananas$
4	mabananas$
2	namabananas$
8	nanas$
10	nas$
0	panamabananas$
12	s$

Size: For human genome, ~4 bytes per base x 3 billion bases

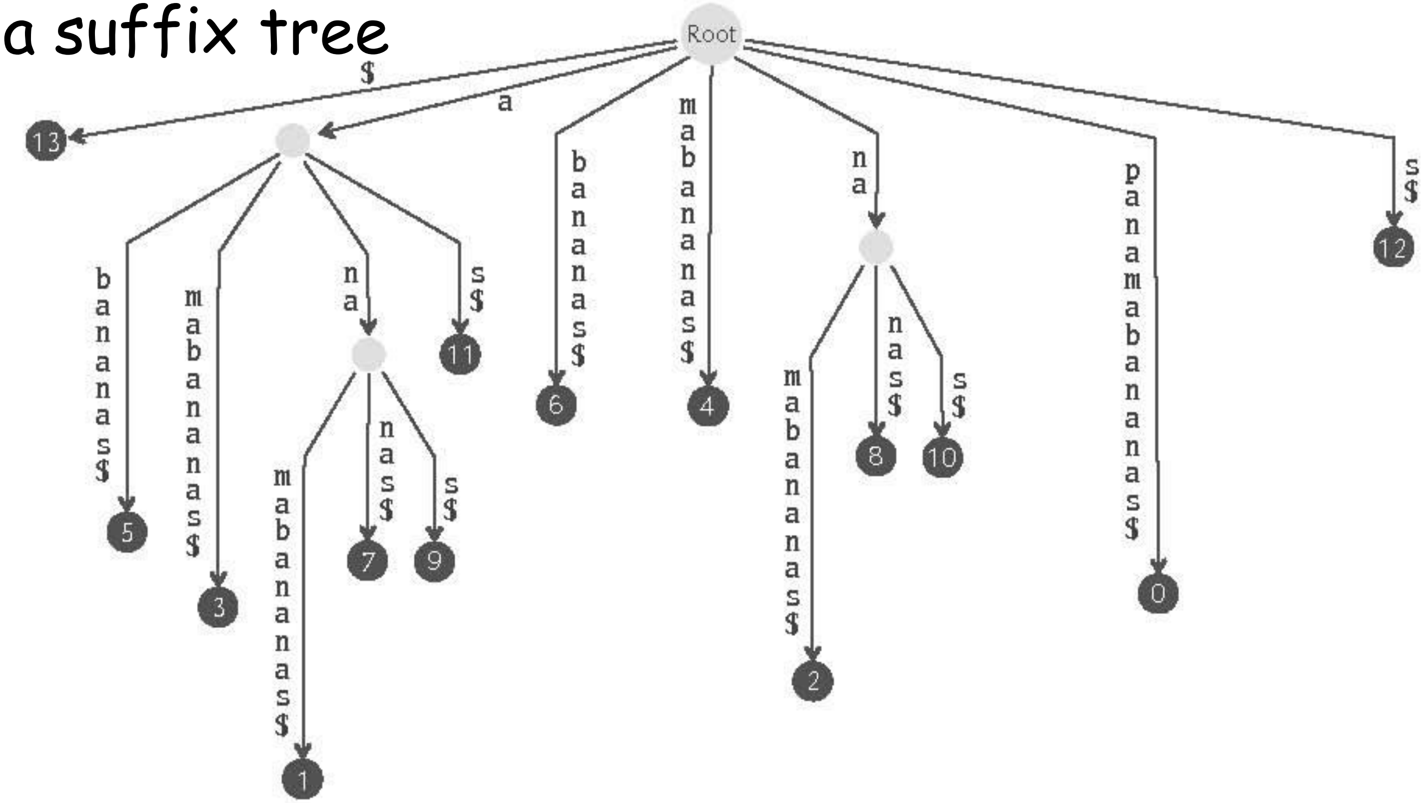
≈ 12 GB

SuffixArray (“panamabananas’)=(13,5,3,1,7,9,11,6,4,2,8,10,0,12)

Pevzner, Compeau Bioinfo Algs 14

How do we build it ?

- Build a suffix tree



- Traverse the tree in DFS, lexicographically picking edges outgoing from each node. SA = leaf label order.
- O(m) time; direct linear time algs known

Pevzner, Compeau Bioinfo Algs 14

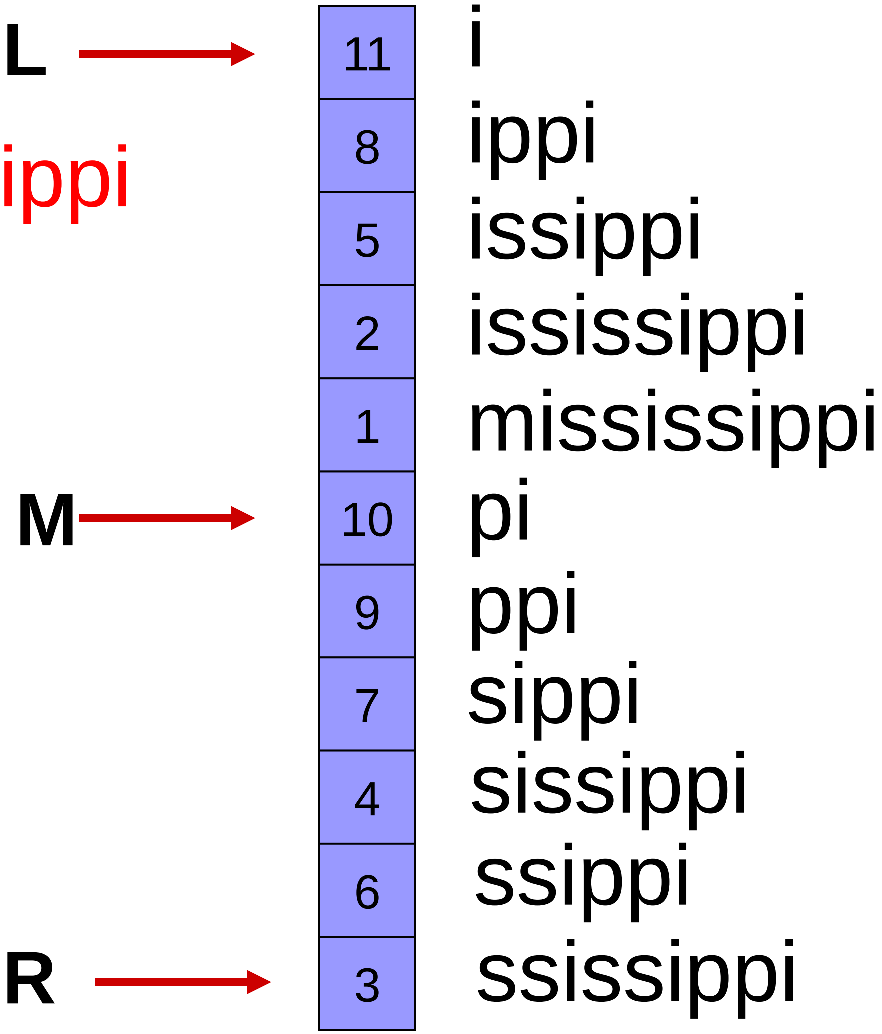
How do we search for a pattern ?

- If P occurs in S then all its occurrences are consecutive in the suffix array.
- Do a binary search on the suffix array

Example

Let S = mississippi

Let P = issa



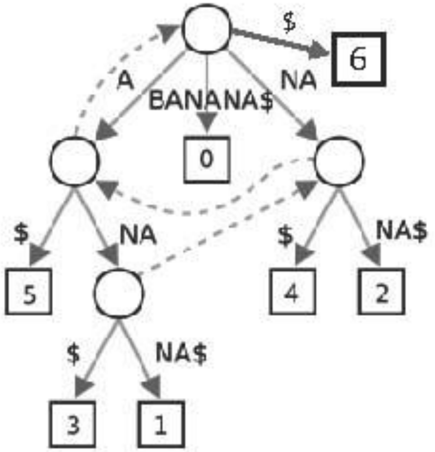
L	11	i
	8	ippi
	5	issippi
	2	ississippi
	1	mississippi
M	10	pi
	9	ppi
	7	sippi
	4	sissippi
	6	ssippi
R	3	ssissippi

For m=|S|, n=|P|:
O(log m) bisections,
O(n) comparisons
per bisection
→ O(nlogm)

Can actually show: O(n+logm) time

Suffix Arrays vs. Suffix Trees - Summary

Just *m* integers, with O(*n* log *m*) query time



Suffix Tree

Suffix Array

Constant factor greatly reduced compared to suffix tree: human genome index fits in ~12 GB instead of > 45 GB

http://www.cs.jhu.edu/~langmea/resources/lecture_notes/

Udi Manber Gene Myers

The end?

The missing pieces in the proof of Ukkonen's Algorithm

§ Edge Label Representation

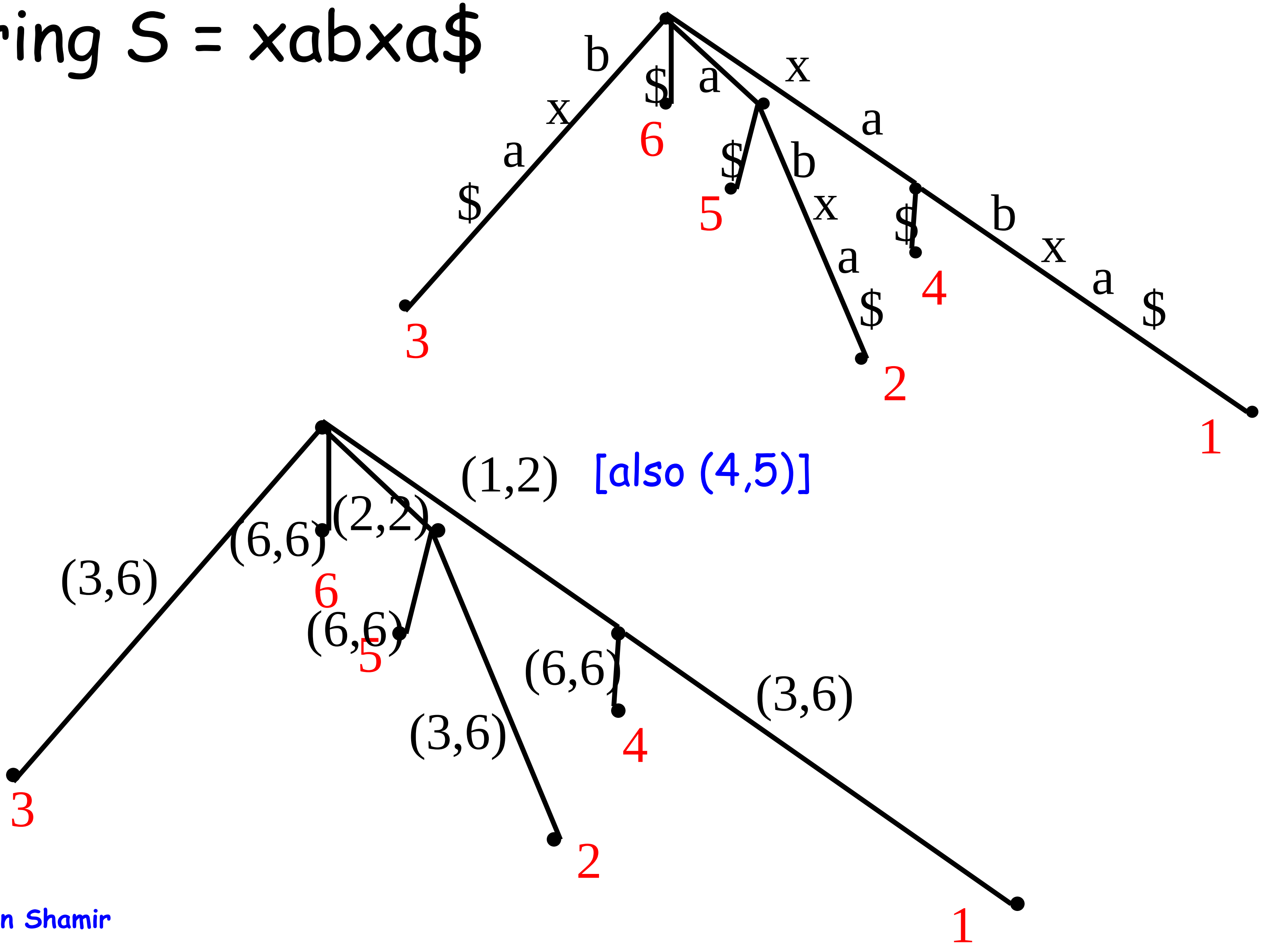
- Problem
  - Edge labels may require $\Omega(m^2)$ space ➔ $\Omega(m^2)$ time
  - Example: S = abcdefghijklmnopqrstuvwxyz
    - Total length is $\Sigma_{j<m+1}\, j = m(m+1)/2$
- Solution
  - Label each edge with a pair of indices indicating the beginning and the end positions of that edge's substring in S
  - Example: instead of label S = abcdefghijklmnopqrstuvwxyz have label (11,36)
  - ≤2m-1 edges, 2 numbers per edge ➔ O(m) space

Modified Extension Rules - with the compact edge labels

- **Rule 1: leaf edge extension**
  - label was (p,i) before extension
  - (p, i) → (p, i + 1)
- **Rule 2: new leaf edge** (phase $i+1$)
  - create edge ($i+1$, $i+1$)
  - split edge (p, q) → (p, w) and (w + 1, q)
- **Rule 3: $S[j,i+1]$ is already in the tree**
  - Do nothing

Edge-label Compression

String S = xabxa$



§Early stopping of a phase

- Obs: In any phase, if rule 3 applies in extension j, it will also apply in all extensions $k>j$ in that phase.
- → end phase $i+1$ on the first time rule 3 applies.
- The extensions after the first execution of rule 3 are said to be done *implicitly*.
- Ex: in phase i+1=7, explicitly extend (1,7), (2,7), (3,7) ← by rule 3; do nothing for (4,7),…,(7,7)

§ Once a leaf, always a leaf (1)

- Obs: If at some point a leaf is created, rule 1 will always apply to it later
  - ☐ → it will remain a leaf in all subsequent phases.
  - ☐ → its label j is maintained in all subsequent phases.
- In any phase, ∃ an initial sequence of consecutive extensions (starting with extension 1) in which only rule 1 or 2 applies.
- Denote j_i : the last extension in this sequence in phase i.
- ➔ in the next phase the first j_i extensions are of leaves and rule 1 applies.
- Note : $j_i \leq j_{i+1}$.

Once a leaf, always a leaf – (2)

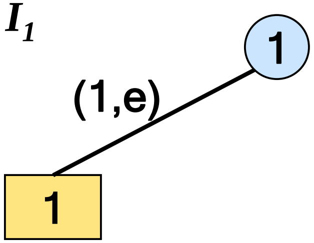
- Let e = global symbol denoting the current end. e is set to $i+1$ at the beginning of phase $i+1$
- When a leaf is created, instead of writing $[p,i+1]$ as the edge label, write $[p, e]$. In all later phases, we implicitly extend the leaf by incrementing e once.
- Perform explicitly extensions j_i+1 and on, until the first rule 3 extension is found, or phase $i+1$ is done.

Single phase algorithm

- Phase $i+1$
  - Increment e to $i+1$ (implicitly extending all existing leaves)
  - Explicitly compute successive extensions starting at j_i+1 and continuing until reaching the first extension j^* where rule 3 applies or no more extensions are needed
  - Set j_{i+1} to j^*-1, to prepare for the next phase
- Obs: Phase i and $i+1$ share at most 1 explicit extension

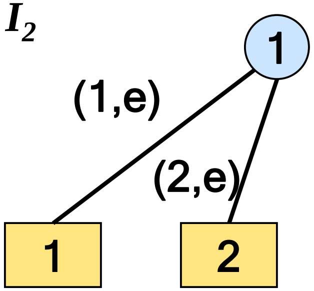
Example: S=axaxbb$ - (1)

I_1



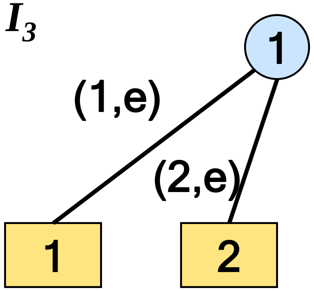
- e = 1, a
- j_1 = 1

I_2



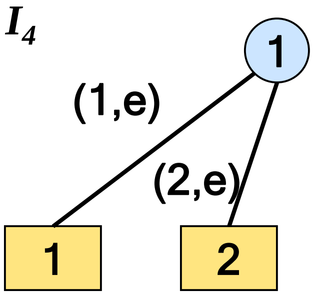
- e = 2, ax
- S[1,2] : skip
- S[2,2] : rule 2, create(2, e)
- j_2 = 2

I_3

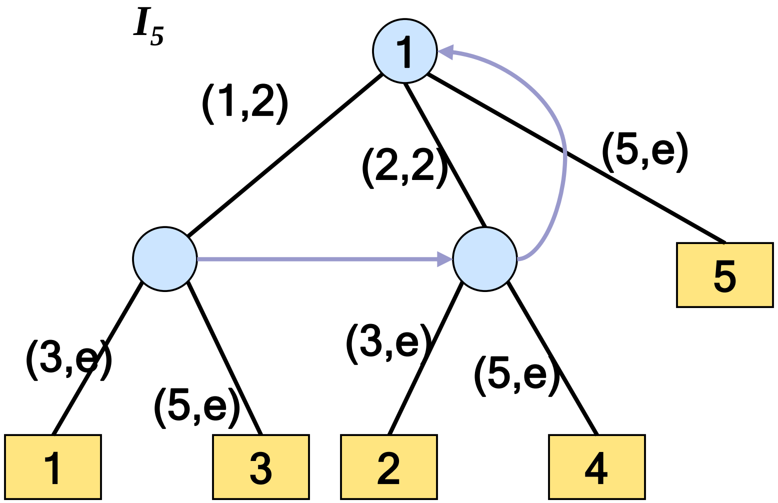


- e = 3, axa
- S[1,3] .. S[2,3] : skip
- S[3,3] : rule 3
- j_3 = 2

Example: S=axaxbb$ - (2)

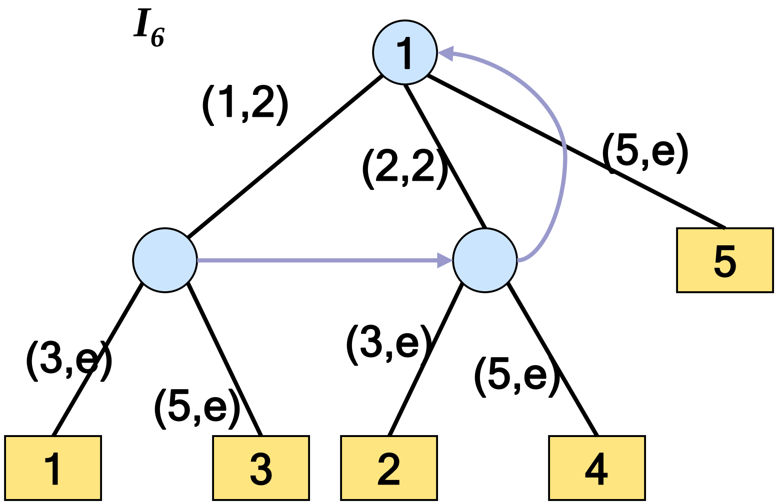


- e = 4, axax
- S[1,4] .. S[2,4] : skip
- S[3,4] : rule 3
- S[4,4] : auto skip
- j_4 = 2

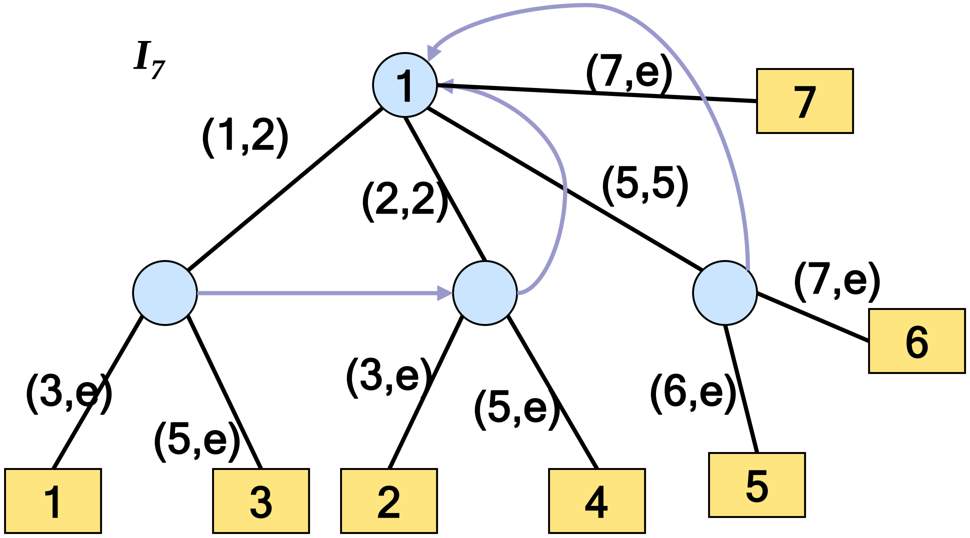


- e = 5, axaxb
- S[1,5] .. S[2,5] : skip
- S[3,5] : rule 2, split (1,e) → (1, 2) and (3,e), create (5,e)
- S[4,5] : rule 2, split (2,e) → (2,2) and (3,e), create (5,e)
- S[5,5] : rule 2, create (5,e)
- j_5 = 5

Example: S=axaxbb$ - (3)



- e = 6, axaxbb
- S[1,6] .. S[5,6] : skip
- S[6,6] : rule 3
- $j_6 = 5$



- e = 7, axaxbb$
- S[1,7] .. S[5,7] : skip
- S[6,7] : rule 2, split (5,e) → (5,5) and (6,e), create (6,e)
- S[7,7] : rule 2, create (7,e)
- $j_7 = 7$

Complexity of UA

- In any phase, all the implicit extensions take constant time => their total cost is **$O(m)$**.
- Totally, only **$2m$** explicit extensions are executed.
- The max number of down-walking skips is **$O(m)$**.
- Time-complexity of Ukkonen's algorithm: **$O(m)$**

	…	11	12	13	14	15	16	17	18	…
Phase i		♣	♣	♣						
Phase i+1				♣	♣	♣	♣	♣		
Phase i+2								♣	♣	

♣: explicit extension

Finishing up

- Convert final implicit suffix tree to a true suffix tree:
  - Add \$ using one more phase
    - Now all suffixes will be leaves
  - Replace e on every leaf edge by m
    - A traversal of tree in $O(m)$ time

The end!