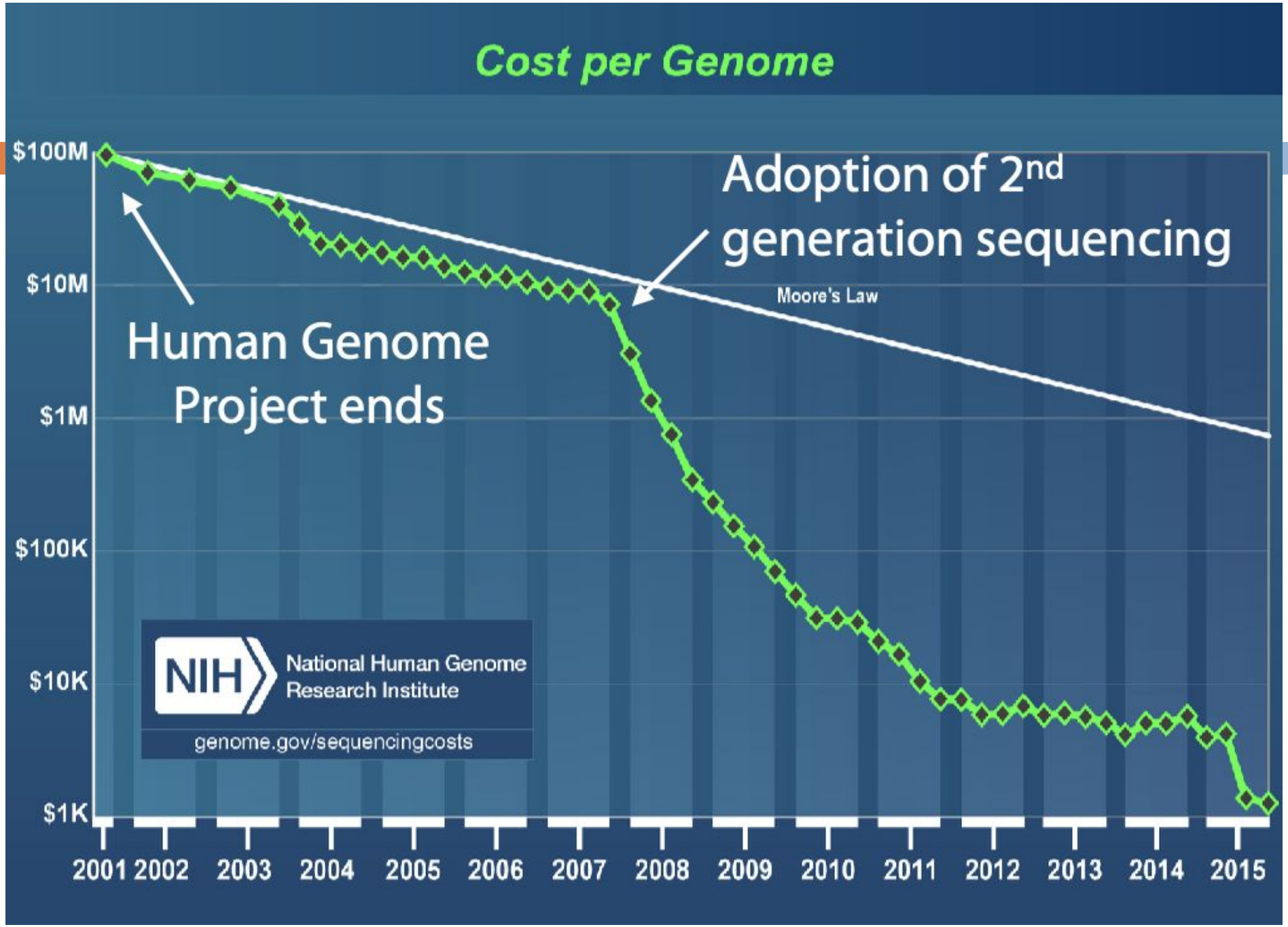
COMBINATORIAL PATTERN MATCHING

CSE 463: INTRODUCTION TO BIOINFORMATICS

Dr M A Nayeem

Outline

- Hash Tables
- Exact Pattern Matching
- Keyword Trees
- Suffix Trees
- Suffix Array
- Burrows-Wheeler Transform (BWT)
- FM Index


Cost per Genome
$100M
$10M
$1M
$100K
$10K
$1K
Human Genome Project ends
Adoption of 2nd generation sequencing
Moore's Law
NIH
National Human Genome Research Institute
genome.gov/sequencingcosts
2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015

Why Personal Genomics

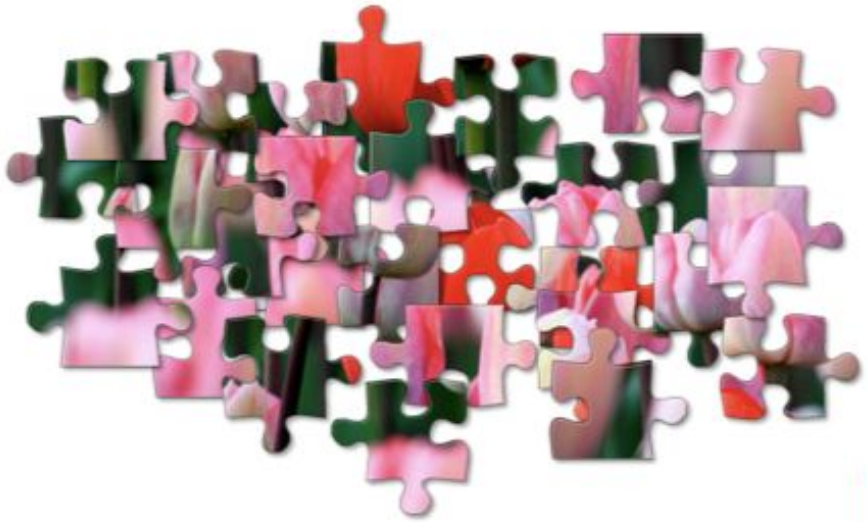
- Nicholas Volker: first person to have life saved by genome sequencing (2010).

- Personal genomics can help us understand the genetic basis of diseases.

Short read mapping

- Short read
  - Second generation or mainly Illumina reads
  - 35-300bp
- Mapping
  - Finding the positions in the genome reads are coming from
- Applications
  - Reference guided genome assembly
  - Looking for SNPs
  - ...

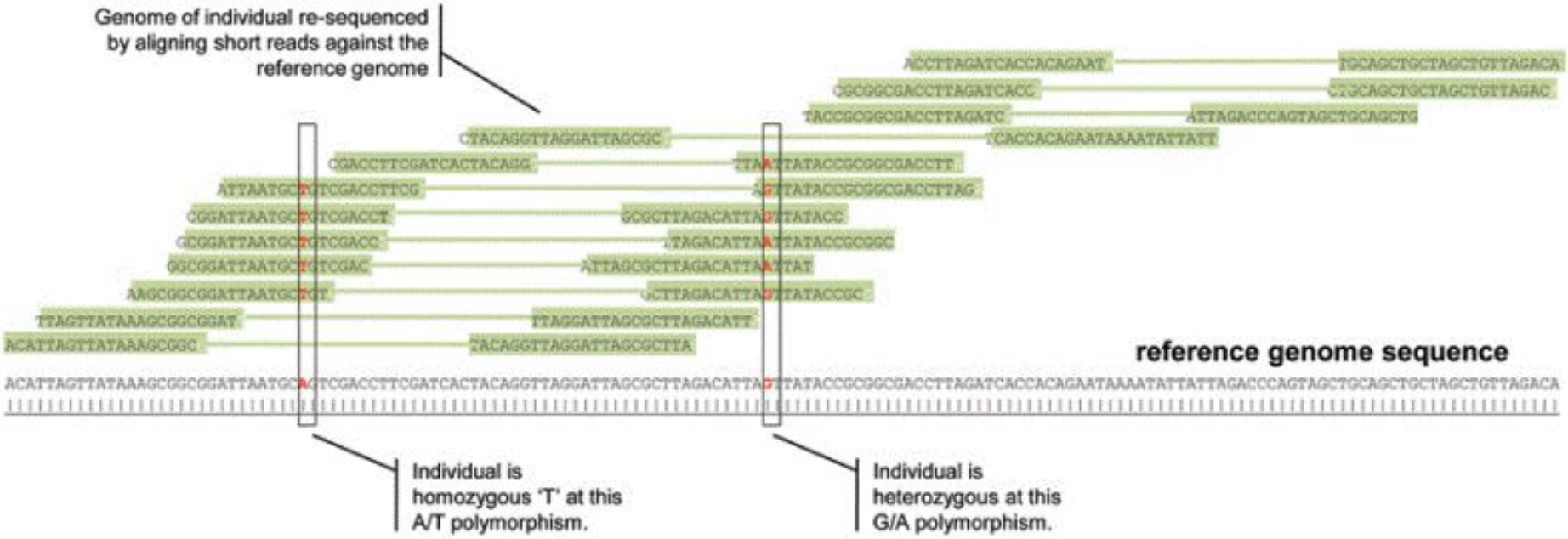
Reference guided assembly



Unrelated humans have genomes that are 99.8-99.9% similar

Reference guided assembly

Reference guided assembly



Exact pattern matching

- Given a pattern (read) and a text (genome), find all positions in the text that matches the pattern?

- This leads us to the **Pattern Matching Problem**.

Pattern Matching Problem

- Goal: Find all occurrences of a pattern in a text.

- Input:
  - Pattern $\boldsymbol{p} = p_1 \ldots p_m$ of length m
  - Text $\boldsymbol{t} = t_1 \ldots t_n$ of length n

- Output: All positions $1 \leq i \leq (n - m + 1)$ such that the m-letter substring of text $\boldsymbol{t}$ starting at i matches the pattern $\boldsymbol{p}$.

Exact Pattern Matching: Brute Force

PatternMatching(**p**,**t**)

1 $m \leftarrow$ length of pattern **p**
2 $n \leftarrow$ length of text **t**
3 for $i \leftarrow 1$ to $(n - m + 1)$
4 if $\boldsymbol{t}_i \ldots \boldsymbol{t}_{i+m-1} = \mathbf{p}$
5 output i

Exact Pattern Matching: An Example

- *PatternMatching* algorithm for:
  - Pattern GCAT
  - Text AGCCGCATCT

Exact Pattern Matching: An Example

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- AGCCGCATCT
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- GCAT

Exact Pattern Matching: Running Time

- *PatternMatching* runtime: O(*nm*)
  - In the worst case, we have to check *m* characters at each of the *n* letters of the text.
  - **Example:** Text = AAAAAAAAAAAAAAAA, Pattern = AAAC

- This is rare; on average, the run time is more like O(*m*).
  - Rarely will there be close to *m* comparisons at each step.

Knuth-Morris-Pratt Algorithm

- Linear time algorithm
- Avoids comparisons with positions in the text that we have already checked

- AGCAGCTAGCTAGT
- AGCTAGT

Knuth-Morris-Pratt Algorithm

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- Avoids comparisons with positions in the text that we have already checked

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Knuth-Morris-Pratt Algorithm

Pattern Matched so far

AGCTAGT AGCTAG __

Proper prefix

Proper suffix

- Compute length of the longest proper prefix of the pattern P that is a proper suffix of P[1:q]
- P[1:q] matched with the text at some point, but p[q+1] failed.

Knuth-Morris-Pratt Algorithm

i	1	2	3	4	5	6	7
$P[i]$	a	b	a	b	a	c	a
$\pi[i]$	0	0	1	2	3	0	1

(a)

Knuth-Morris-Pratt Algorithm

```
KMP-MATCHER(T, P)
 1  n = T.length
 2  m = P.length
 3  π = COMPUTE-PREFIX-FUNCTION(P)
 4  q = 0                                   // number of characters matched
 5  for i = 1 to n                          // scan the text from left to right
 6      while q > 0 and P[q + 1] ≠ T[i]
 7          q = π[q]                        // next character does not match
 8      if P[q + 1] == T[i]
 9          q = q + 1                       // next character matches
10      if q == m                           // is all of P matched?
11          print "Pattern occurs with shift" i − m
12          q = π[q]                        // look for the next match
```

Knuth-Morris-Pratt Algorithm

```
COMPUTE-PREFIX-FUNCTION(P)
 1  m = P.length
 2  let π[1..m] be a new array
 3  π[1] = 0
 4  k = 0
 5  for q = 2 to m
 6      while k > 0 and P[k + 1] ≠ P[q]
 7          k = π[k]
 8      if P[k + 1] == P[q]
 9          k = k + 1
10      π[q] = k
11  return π
```

Short read mapping

- KMP runs in O(n+m)
  - Preprocesses the pattern
  - To map k-reads O(k(n+m)) time is needed
- But typically we need to map many reads to a single genome
- Better to index the genome
  - Hash tables
  - Suffix trees
  - Suffix arrays
  - BWT-FM index

Multiple Pattern Matching (MPM) Problem

- Goal: Given a set of patterns and a text, find all occurrences of any of patterns in text.
- Input: k patterns $\boldsymbol{p}^1,\ldots,\boldsymbol{p}^k$, and text of n characters $\boldsymbol{t} = t_1 \ldots t_n$
- Output: Positions $1 \leq i \leq n$ where the substring of text $\boldsymbol{t}$ starting at i matches one of the patterns $\boldsymbol{p}_j$ for $1 \leq j \leq k$.

Hashing

- Hashing is a very efficient way to store and retrieve data.
- What does hashing do?
  - Say we are given a collection of data.
  - For different entries, generate a unique integer and store the entry in an array at this integer location

Adapted from slides available at www.bioalgorithms.info

Hashing: Definitions

- **Records:** data stored in a *hash table*.
- **Keys:** Integers identifying set of *records*.
- **Hash Table:** The array of keys used in hashing.
- **Hash Function:** Assigns each record to a key.
- **Collision:** Occurs when more than one record is mapped to the same index in the hash table.

Hashing DNA sequences

- Each *k*-mer can be translated into a binary string:
  - **A** can be represented as **00**
  - **T** can be represented as **01**
  - **G** can be represented as **10**
  - **C** can be represented as **11**
  - **Example:** ATGCTA = 000110110100

- After assigning a unique integer to each *k*-mer, it is easy to obtain all start locations of each *k*-mer in a genome.

Adapted from slides available at www.bioalgorithms.info

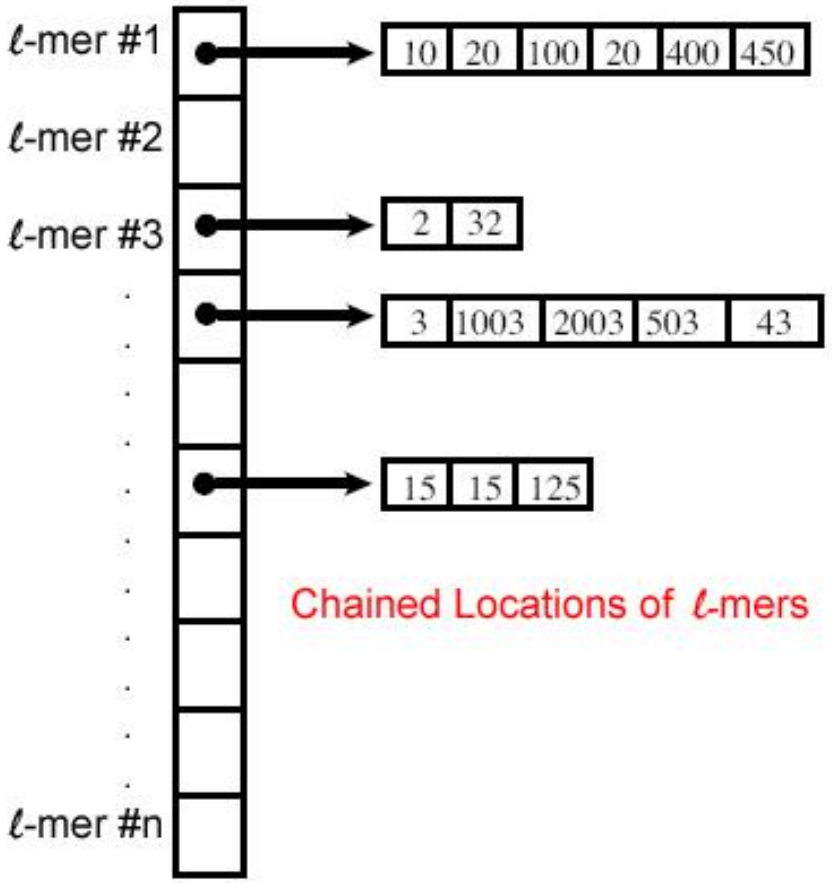
Hashing: Read Mapping

- To map reads exactly:
  1. For all *k*-mers in the genome, note the start position and the sequence where *k* is the read length
  2. Generate a hash table index for each *k*-mer sequence.
  3. At each index of the hash table, store all genome start locations of the *k*-mer that generated the index.
  4. Look up all start positions using the read as the key

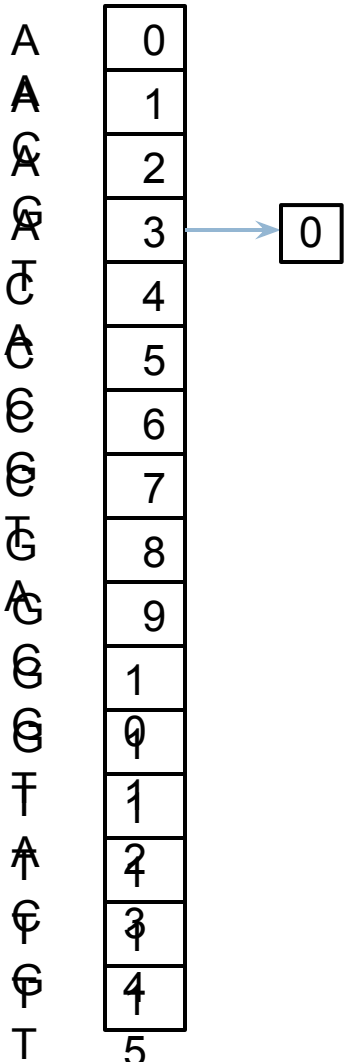
- How do we deal with collisions?

Hashing: Collisions

- In order to deal with collisions:
- "Chain" all start locations of *k*-mers.
- This can be done via a data structure called a **linked list.**

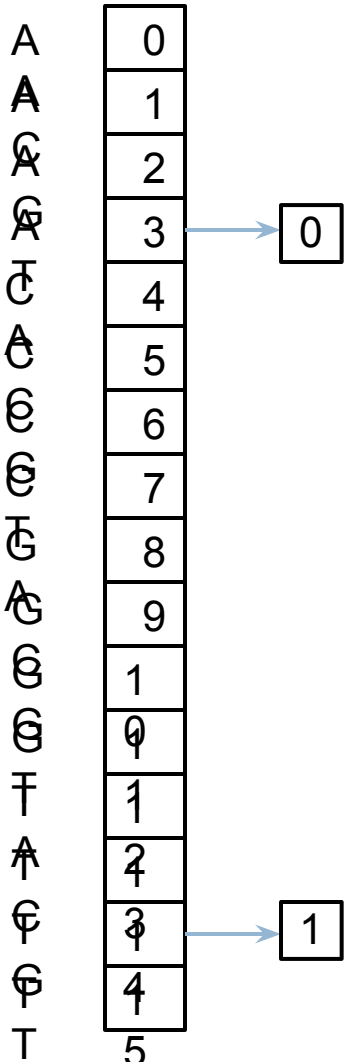


Hashing: Read Mapping



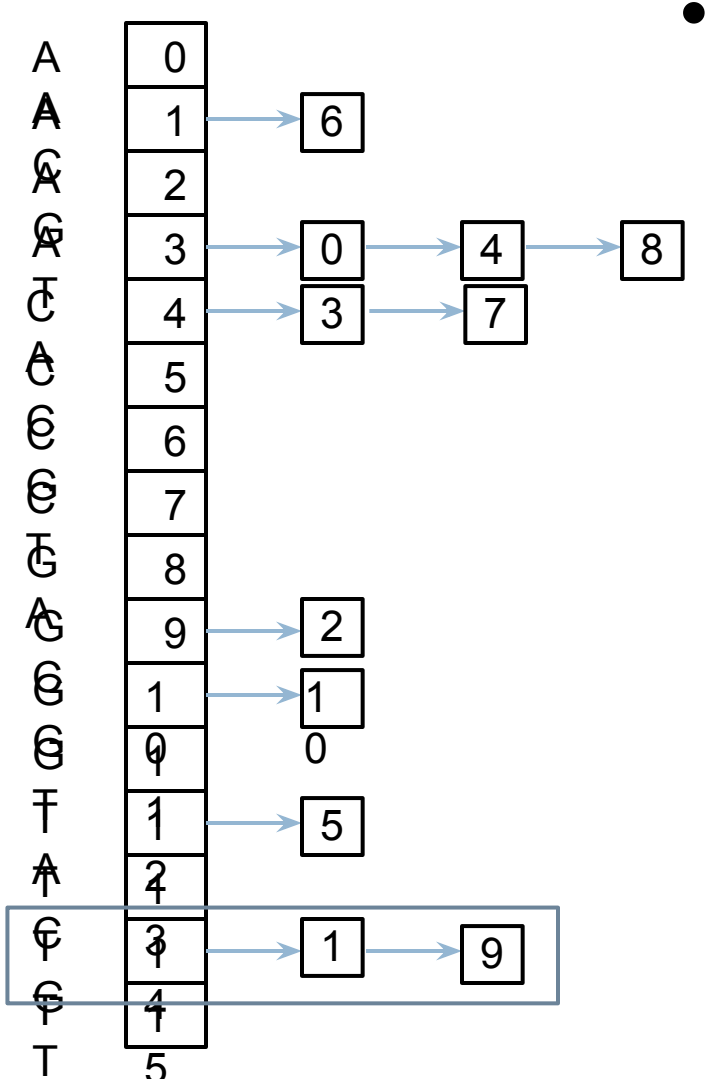
- **Example:** Hash table for ATGCATACATGG

Hashing: Read Mapping



- **Example:** Hash table for ATGCATACATGG

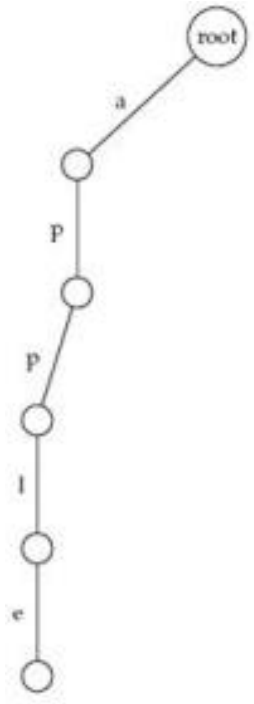
Hashing: Read Mapping



- **Example:** Hash table for ATGCATACATGG
  - **Map** TG
    - Lookup TG
    - At positions 1, 9
  - **Map** GCAT
    - Lookup GC and AT

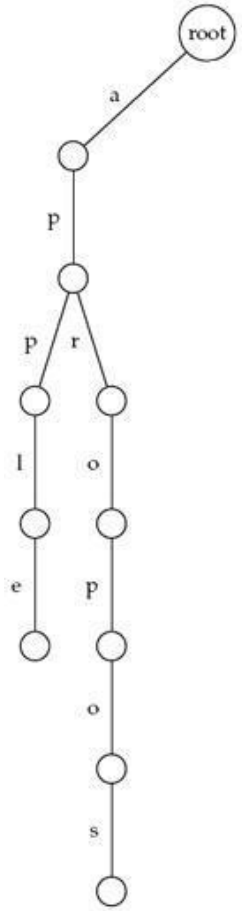
Keyword Trees: Example

- ***Keyword tree:***
  - Apple



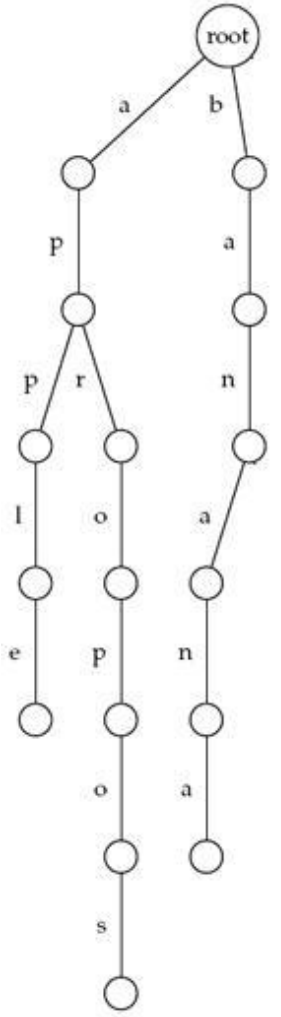
Keyword Trees: Example (cont'd)

- ***Keyword tree*:**
  - Apple
  - Apropos



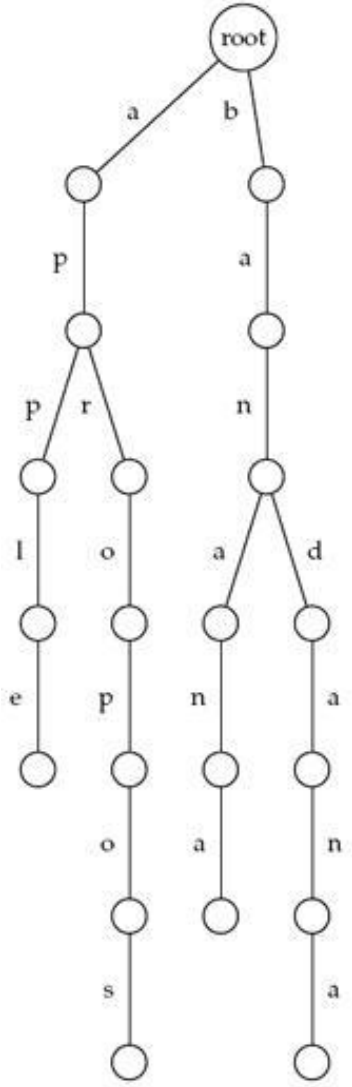
Keyword Trees: Example (cont'd)

- ***Keyword tree*:**
  - Apple
  - Apropos
  - Banana



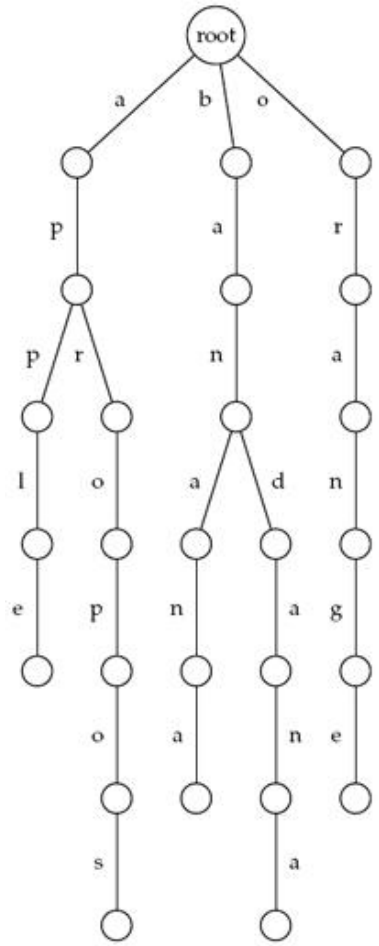
Keyword Trees: Example (cont'd)

- ***Keyword tree*:**
  - Apple
  - Apropos
  - Banana
  - Bandana



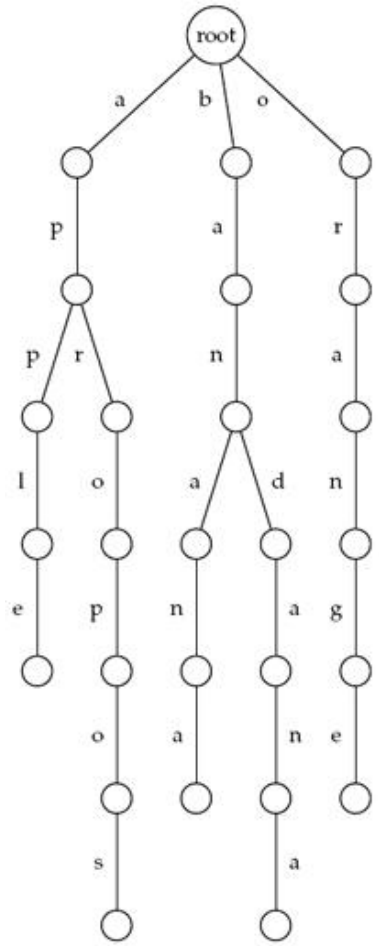
Keyword Trees: Example (cont'd)

- ***Keyword tree*:**
  - Apple
  - Apropos
  - Banana
  - Bandana
  - Orange



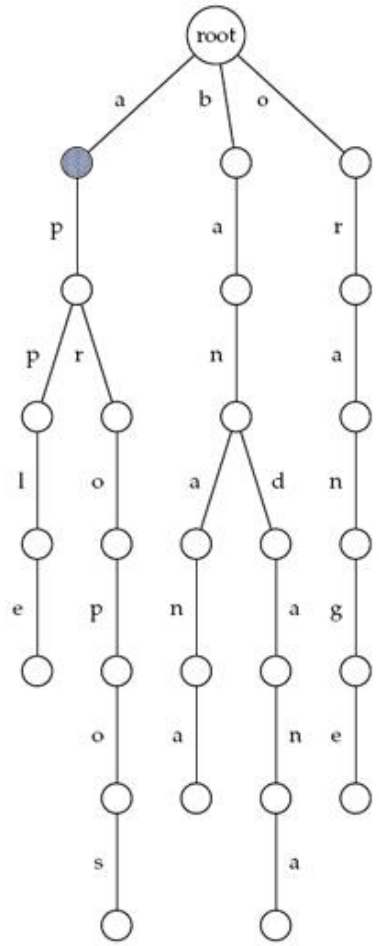
Keyword Trees: Properties

- Stores a set of keywords in a rooted labeled tree
- Each edge labeled with a letter from an alphabet
- Any two edges coming out of the same vertex have distinct labels
- Every keyword stored can be spelled on a path from root to some leaf



Keyword Trees: Threading (cont'd)

- Thread "appeal"
  - appeal



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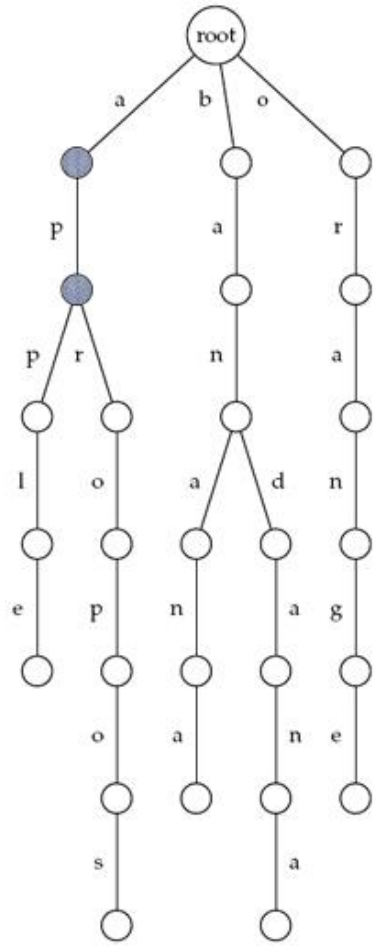

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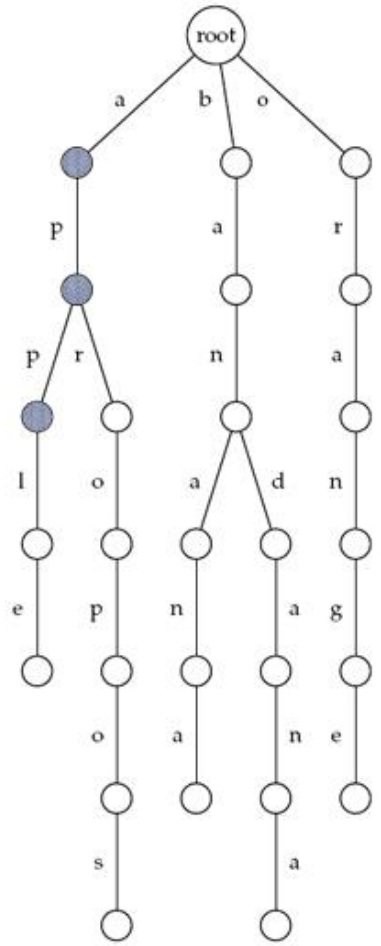

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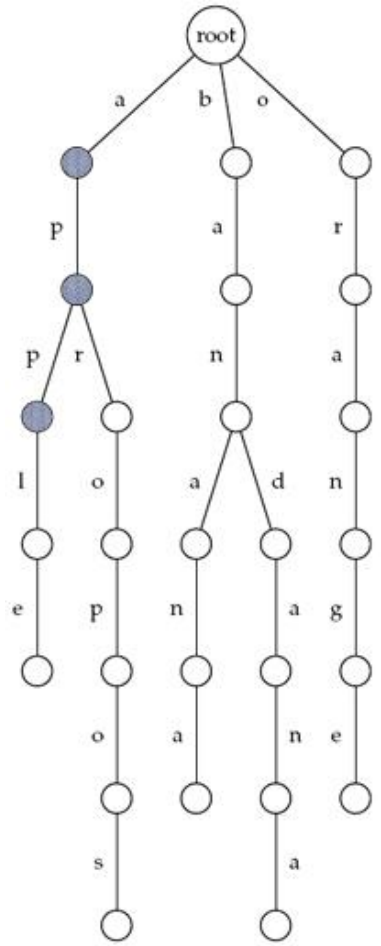

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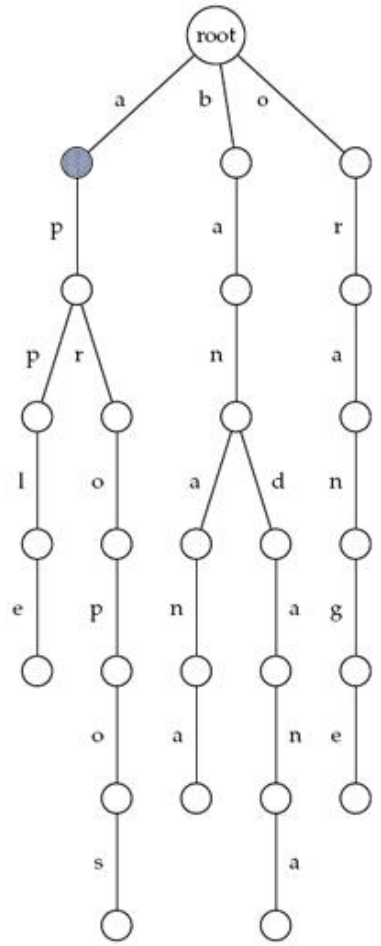
- Thread "apple"
  - apple



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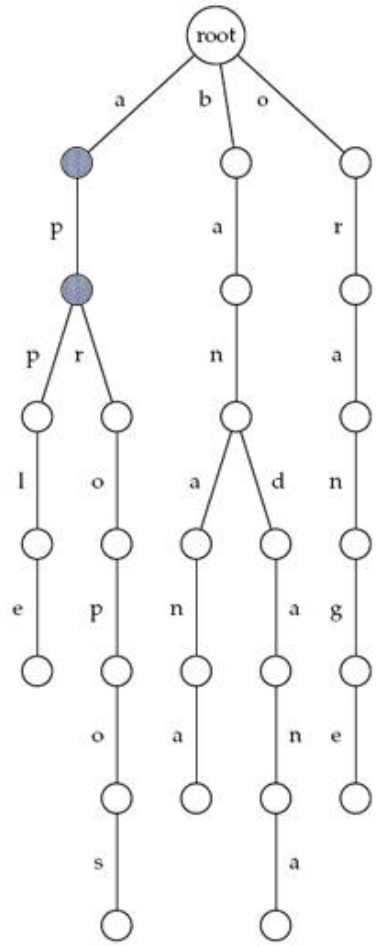

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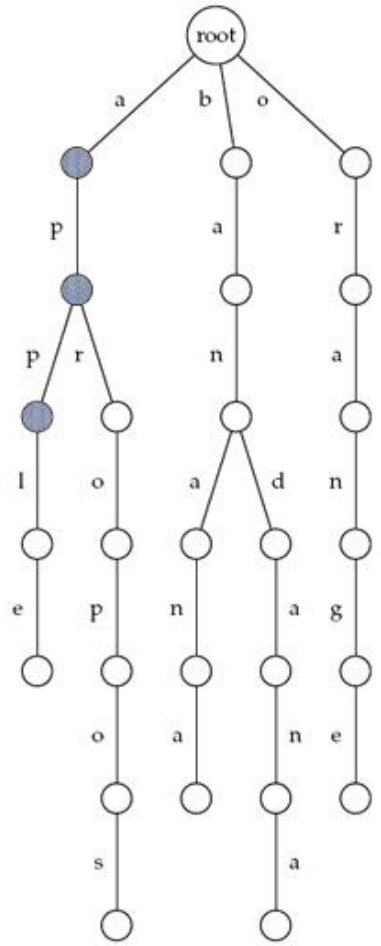

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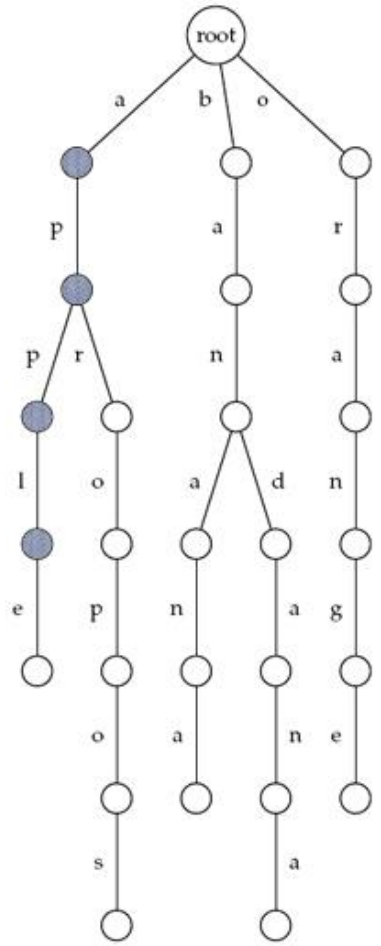

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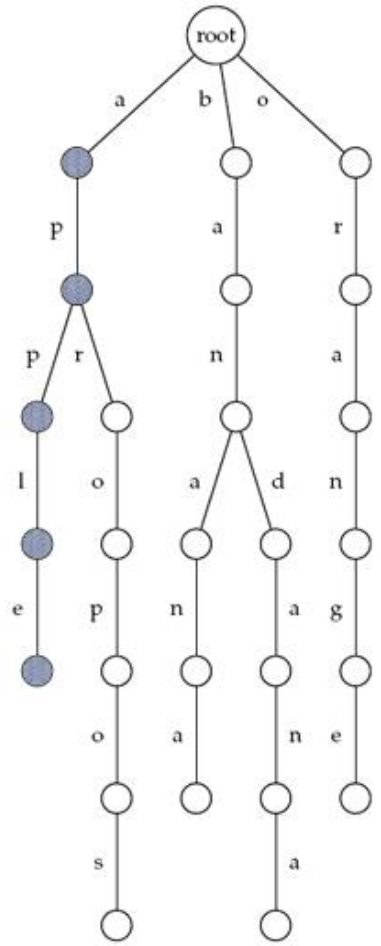
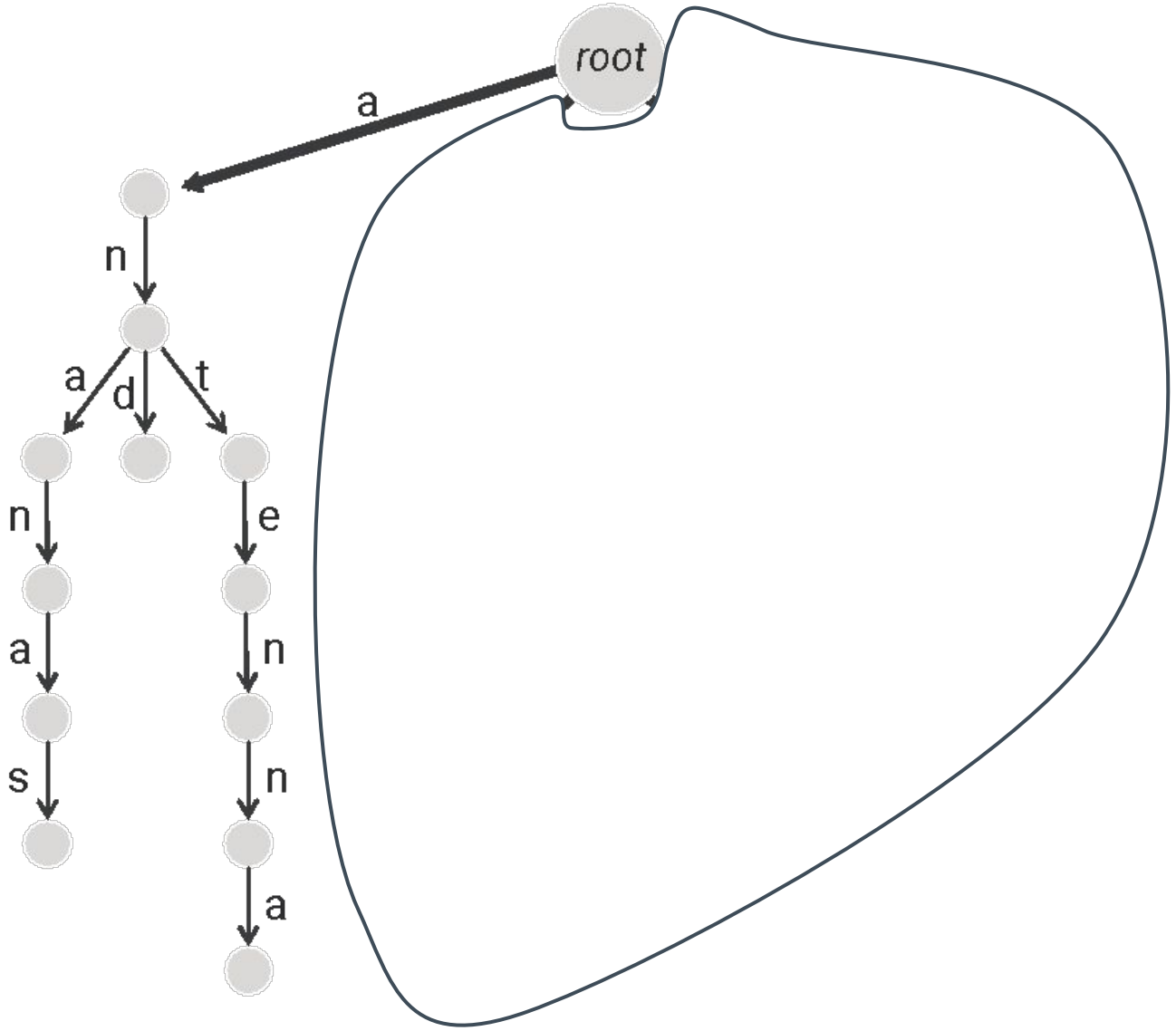


FIGURE 9.1 The trie for the following collection of strings *Patterns*: "ananas", "and", "antenna", "banana", "bandana", "nab", "nana", "pan".



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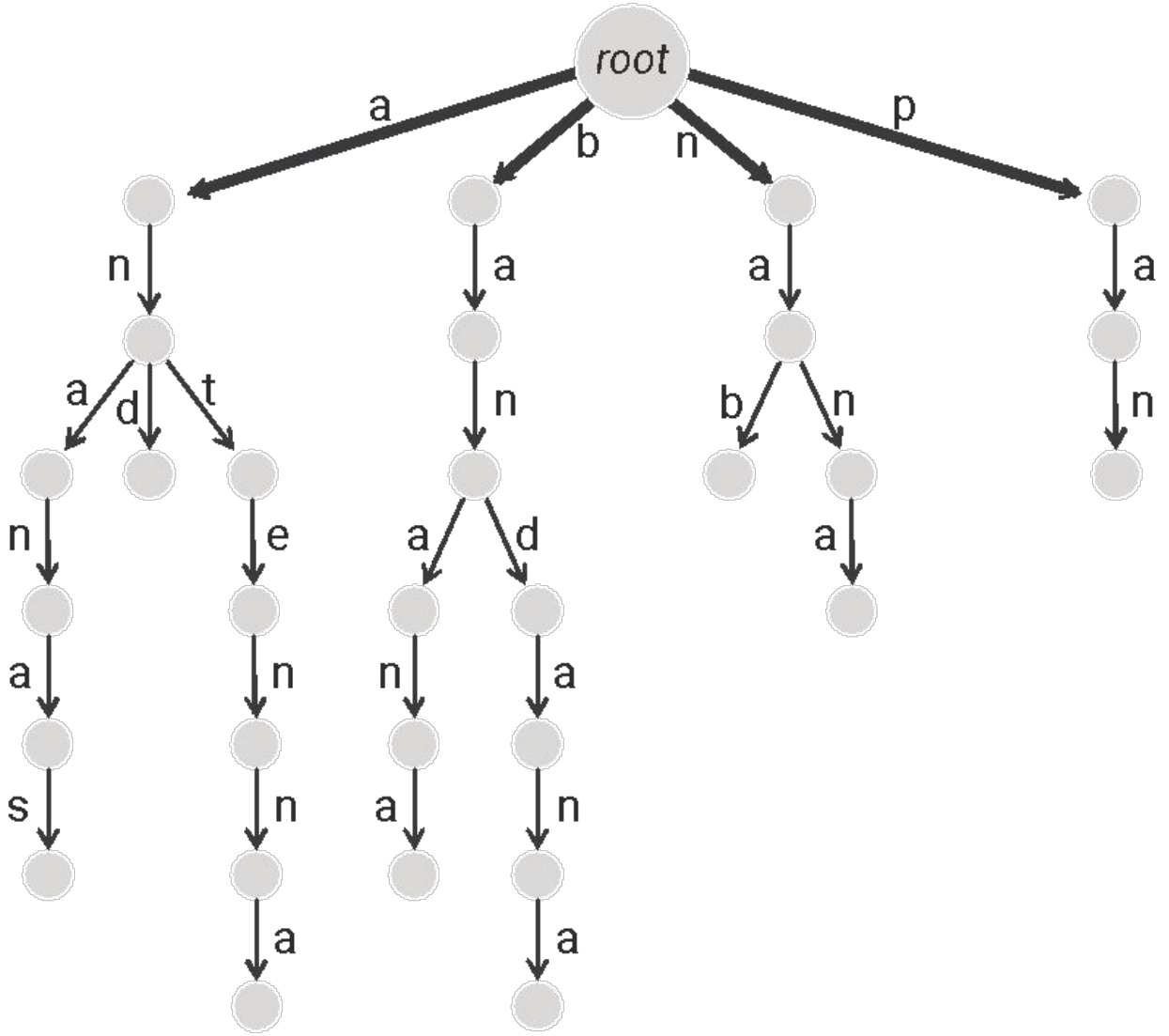

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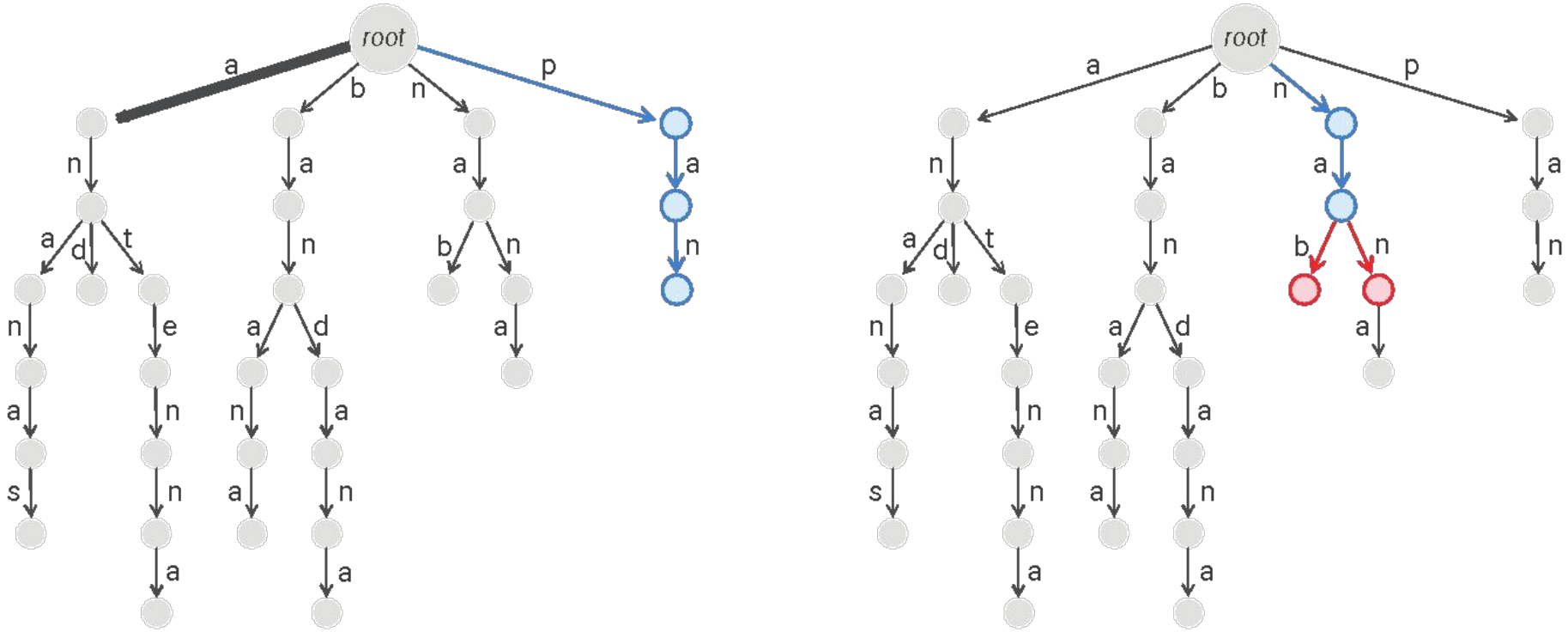


FIGURE 9.2 (Left) The pattern "pan" matches *Text* = "panamabananas" when starting at the beginning of *Text*. (Right) No pattern match is found in TRIE(*Patterns*) for the strings *Patterns* from Figure 9.1 when starting at the third symbol of "panamabananas".

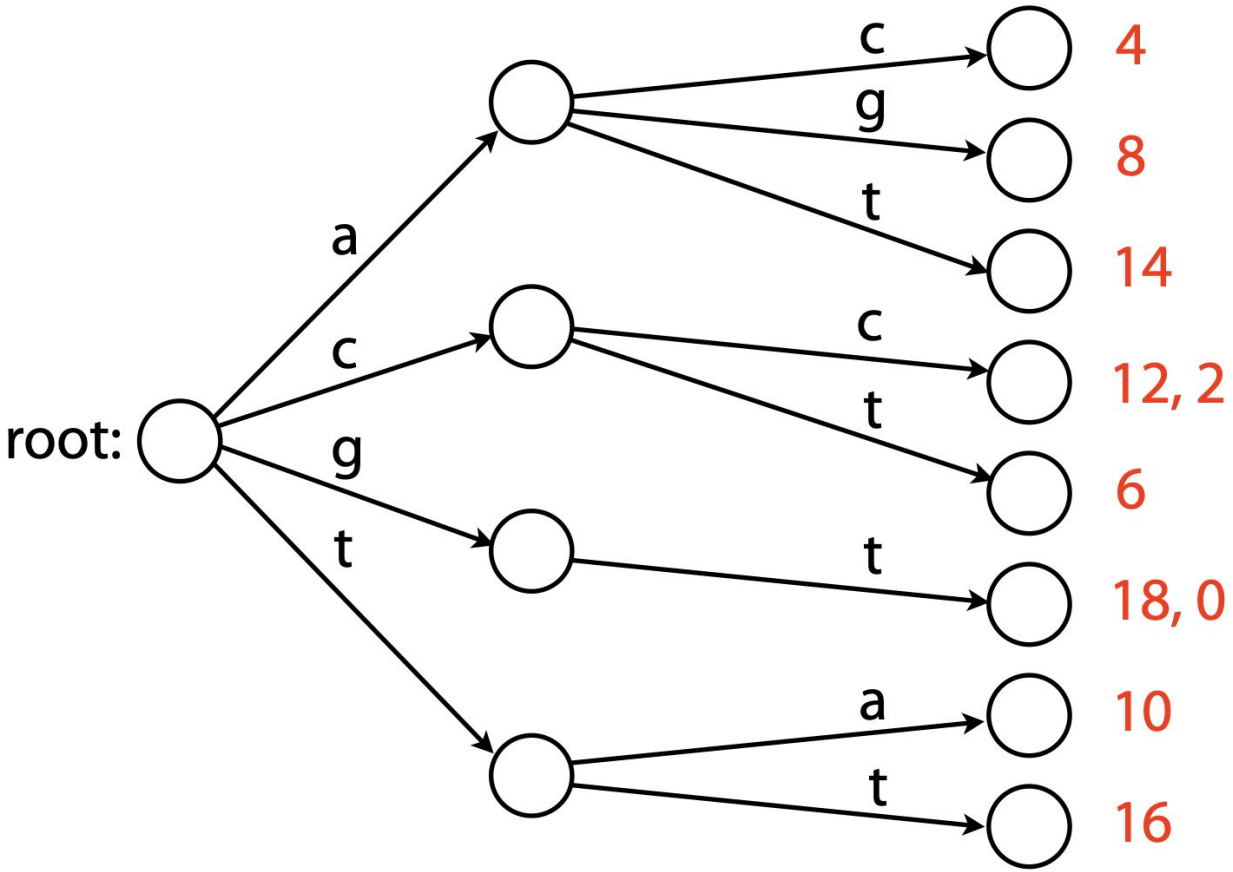
Memory?

- 1 TB

Could use trie to represent *k*-mer index.
Map *k*-mers to offsets where they occur

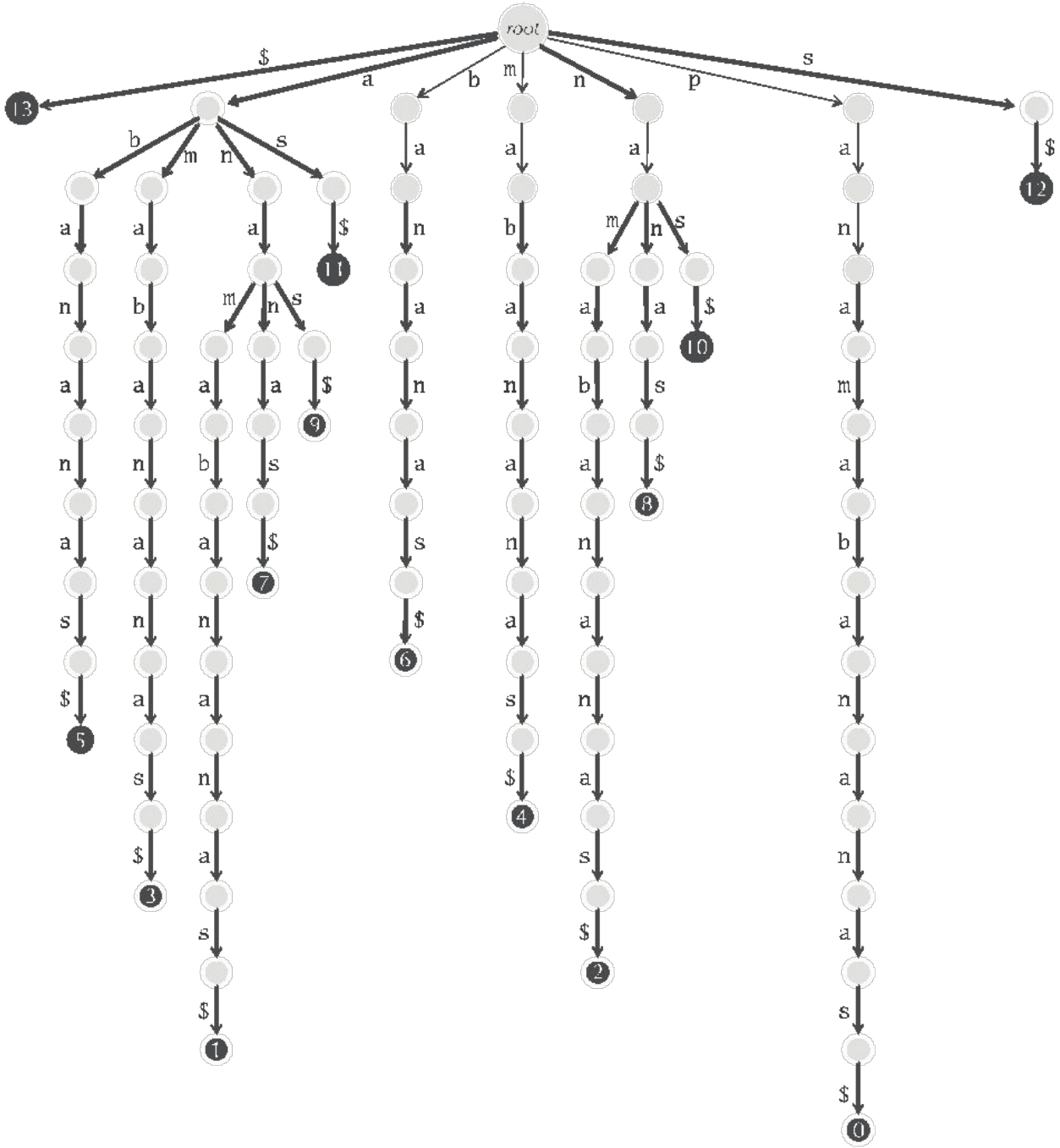
ac	4
ag	8
at	14
cc	12
cc	2
ct	6
gt	18
gt	0
ta	10
tt	16

Index

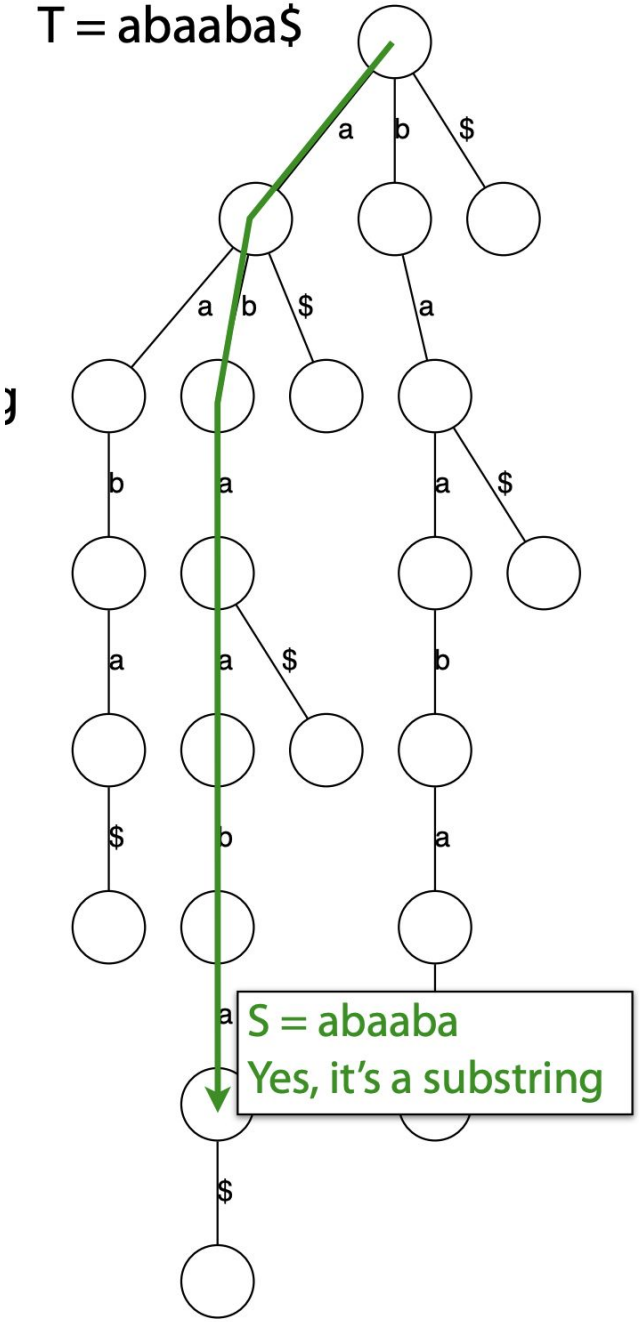


Suffix Trie

Build a **trie** containing all **suffixes** of a text *T*



- ant
- Nana
- ana



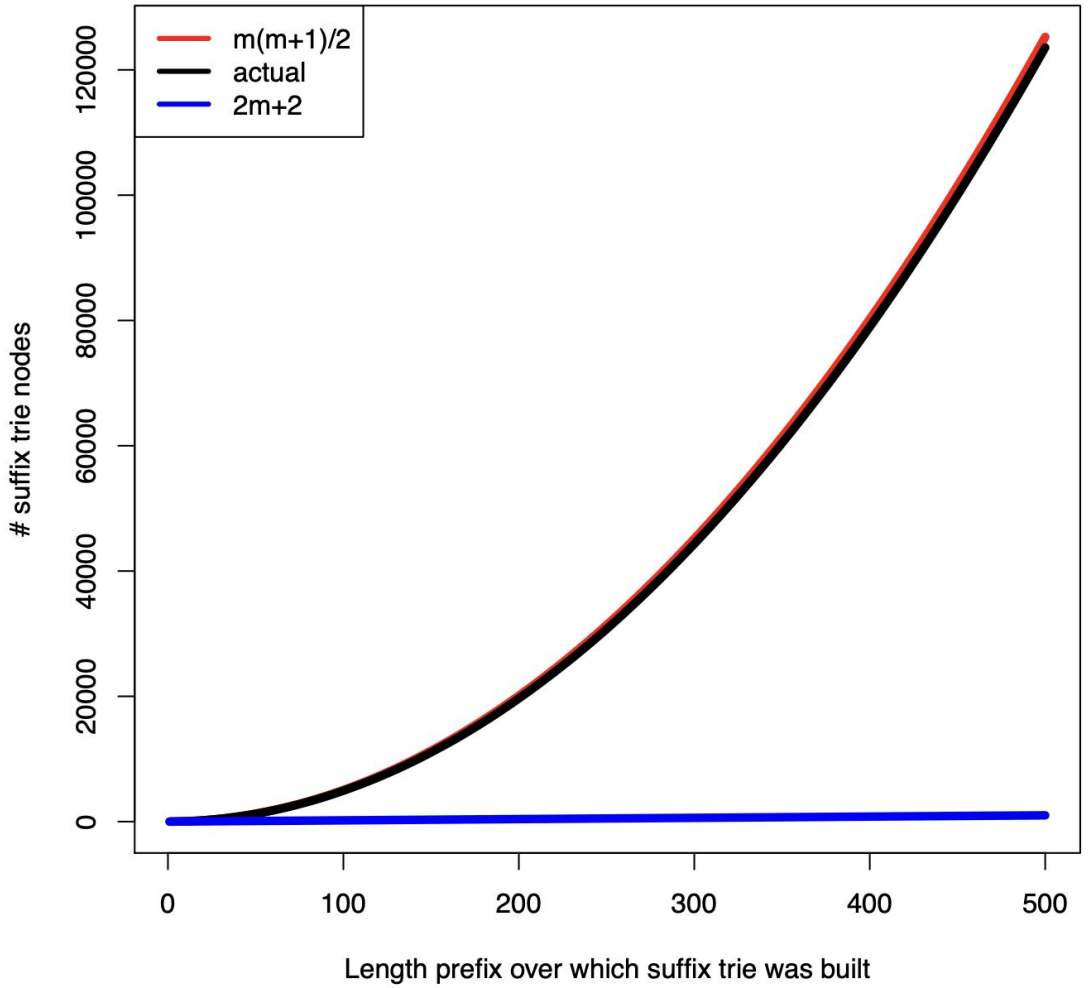
- baa
- aba

Suffix Trie

We saw the suffix trie, but we also saw its size grows *quadratically* with the length of the string

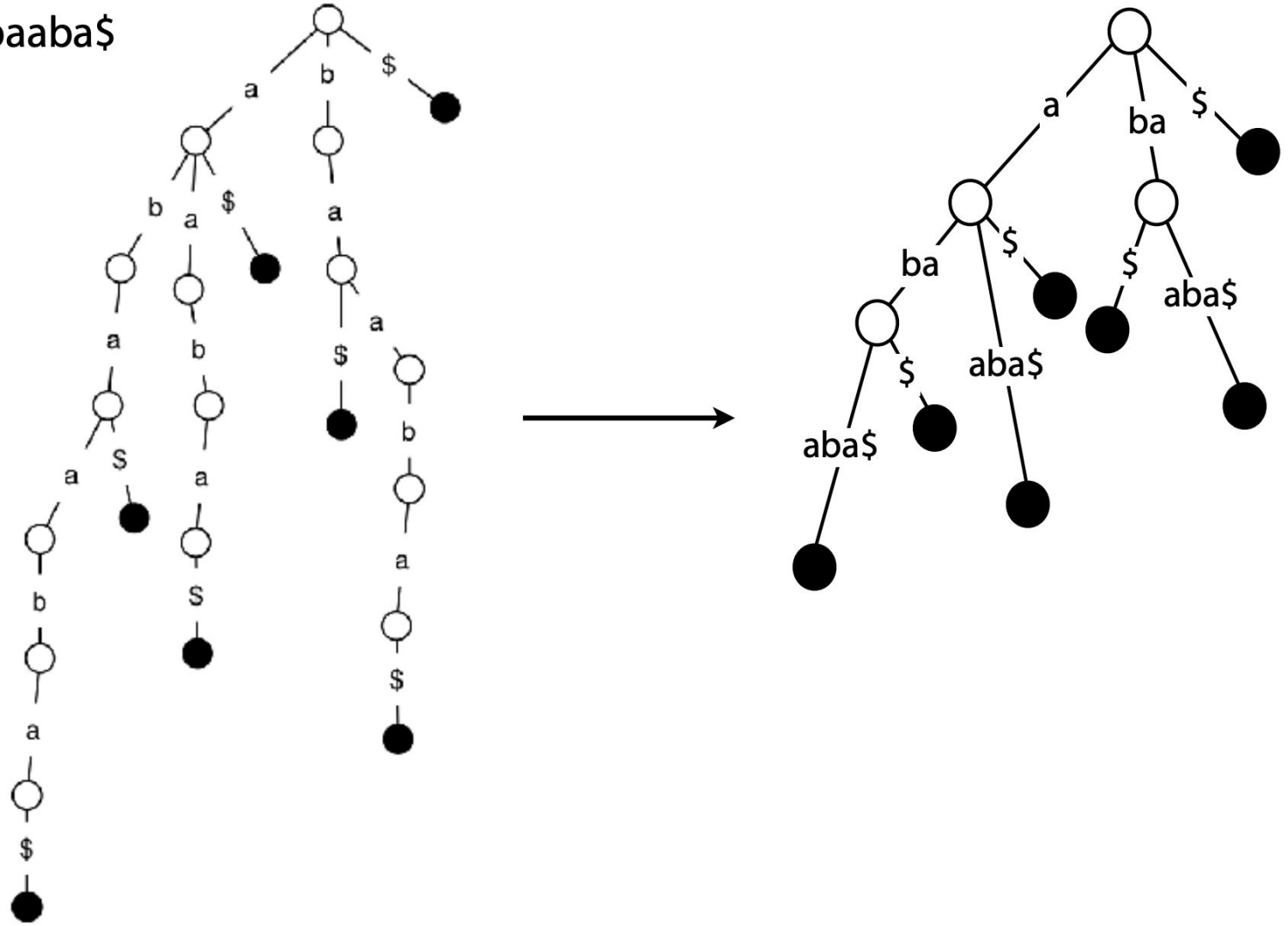
Human genome is $3 \cdot 10^9$ bases long.

If $m = 3 \cdot 10^9$, m^2 is way huge, far beyond what we can store in memory



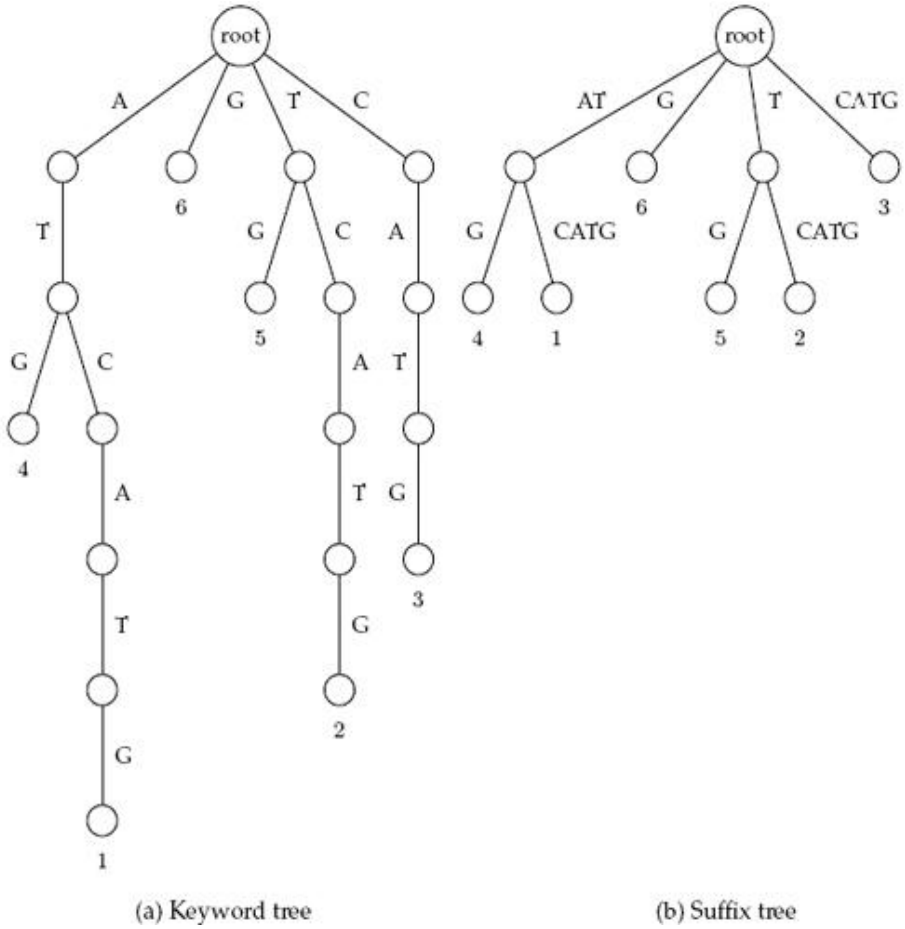
Making it smaller

$T = abaaba\$$

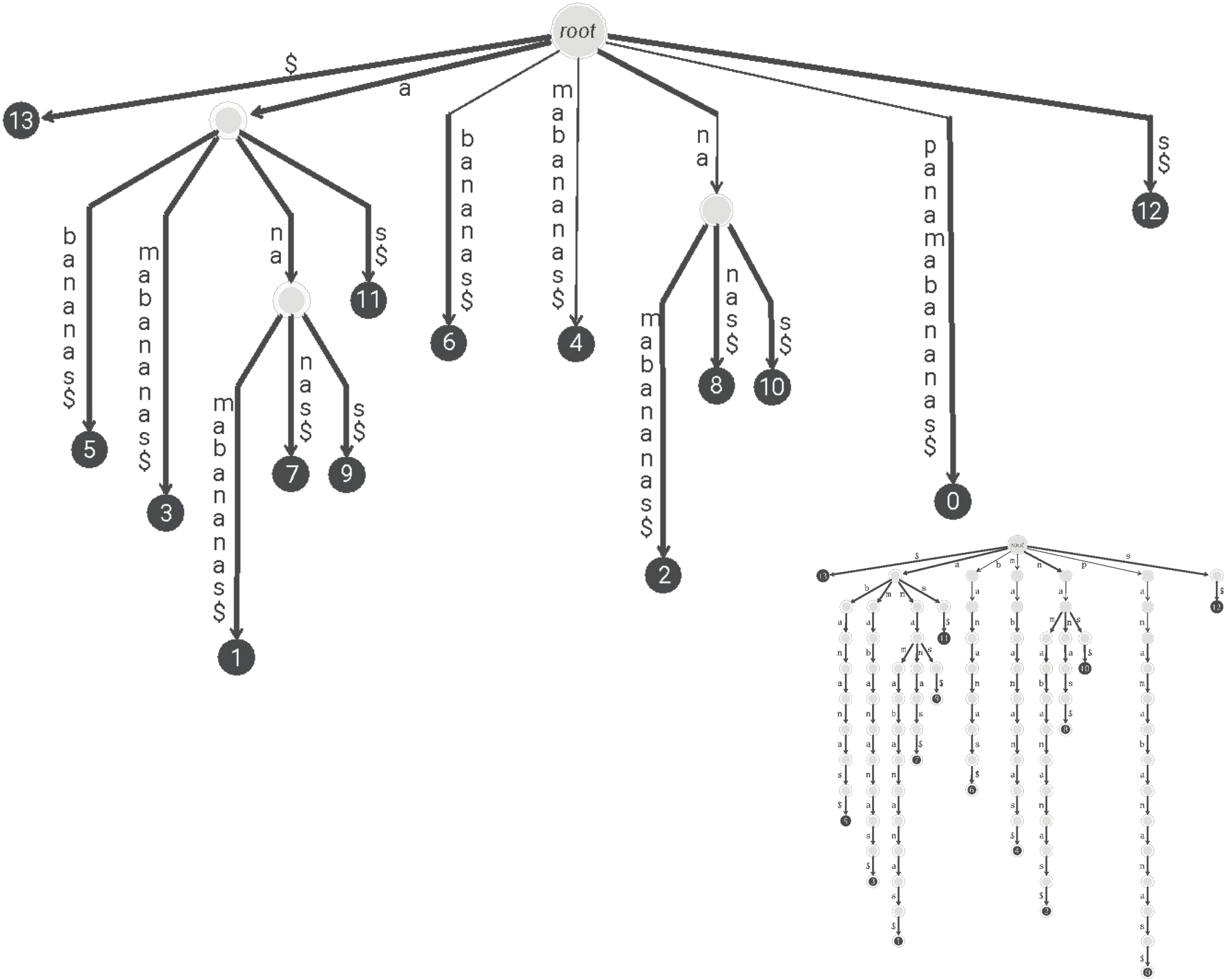


Suffix Tree=Collapsed Suffix Trie

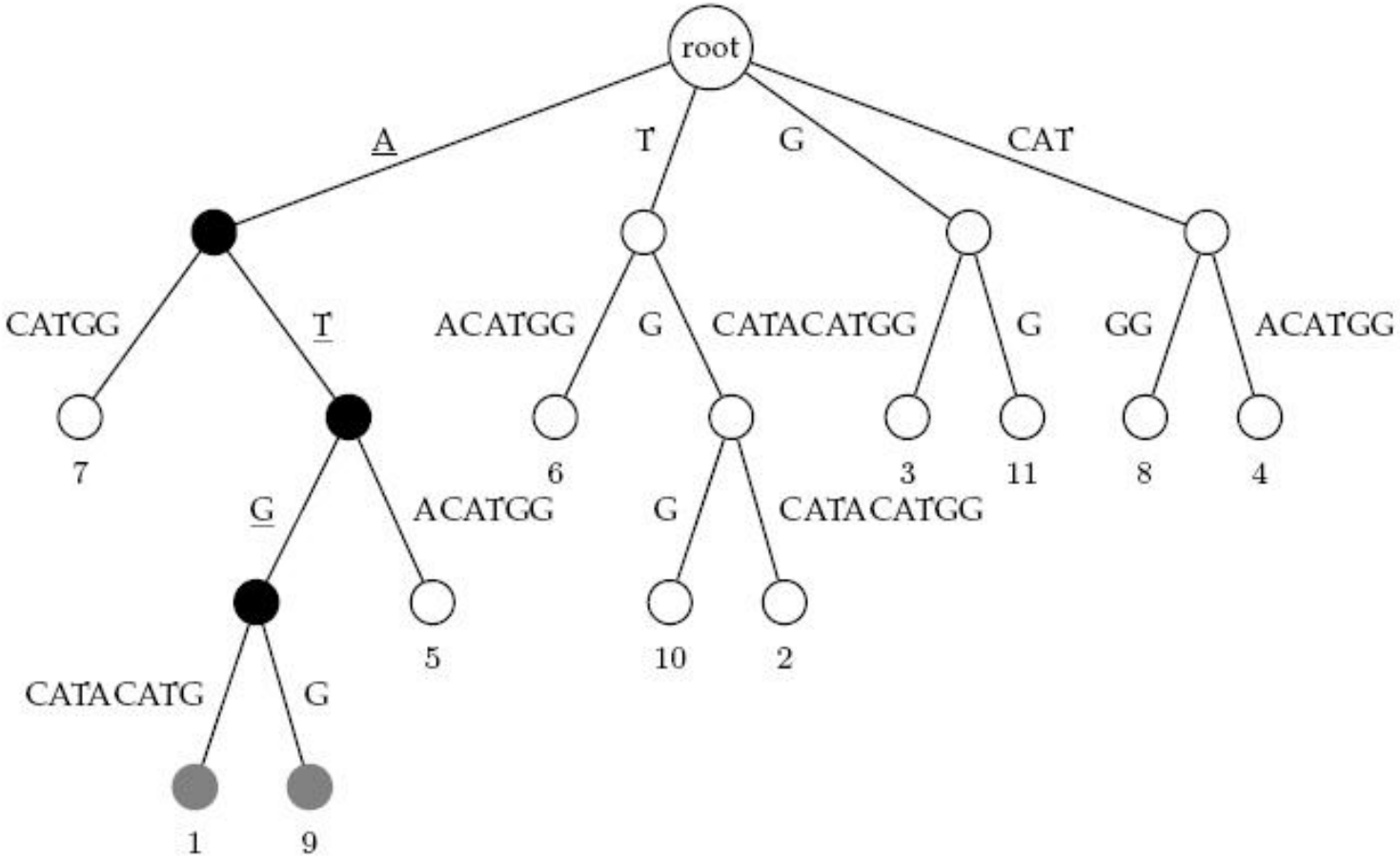
- Similar to keyword trees, except edges that form paths are collapsed
  - Each edge is labeled with a *substring* of a text
  - All internal nodes have at least two outgoing edges
  - Leaves labeled by the index of the pattern.



(a) Keyword tree (b) Suffix tree

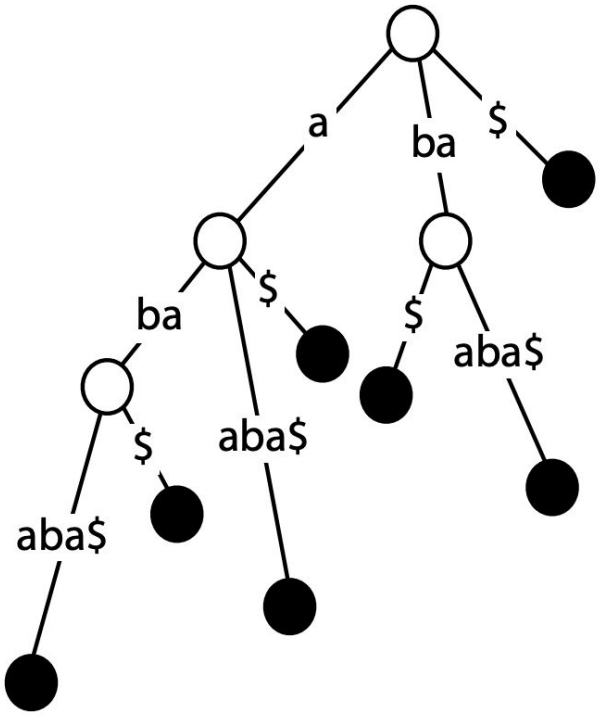

root
$
a
13
banana$
5
mabanana$
3
na
mabanana$
1
na$
7
s$
9
s$
11
banana$
6
mabanana$
4
na
mabanana$
2
na$
8
s$
10
s$
12
pamabanana$
0

Threading ATG through a Suffix Tree



Suffix Tree

$T = \text{abaaba\$} \quad |T| = m$



leaves? ***m***

non-leaf nodes (bound)? ***≤ m - 1***

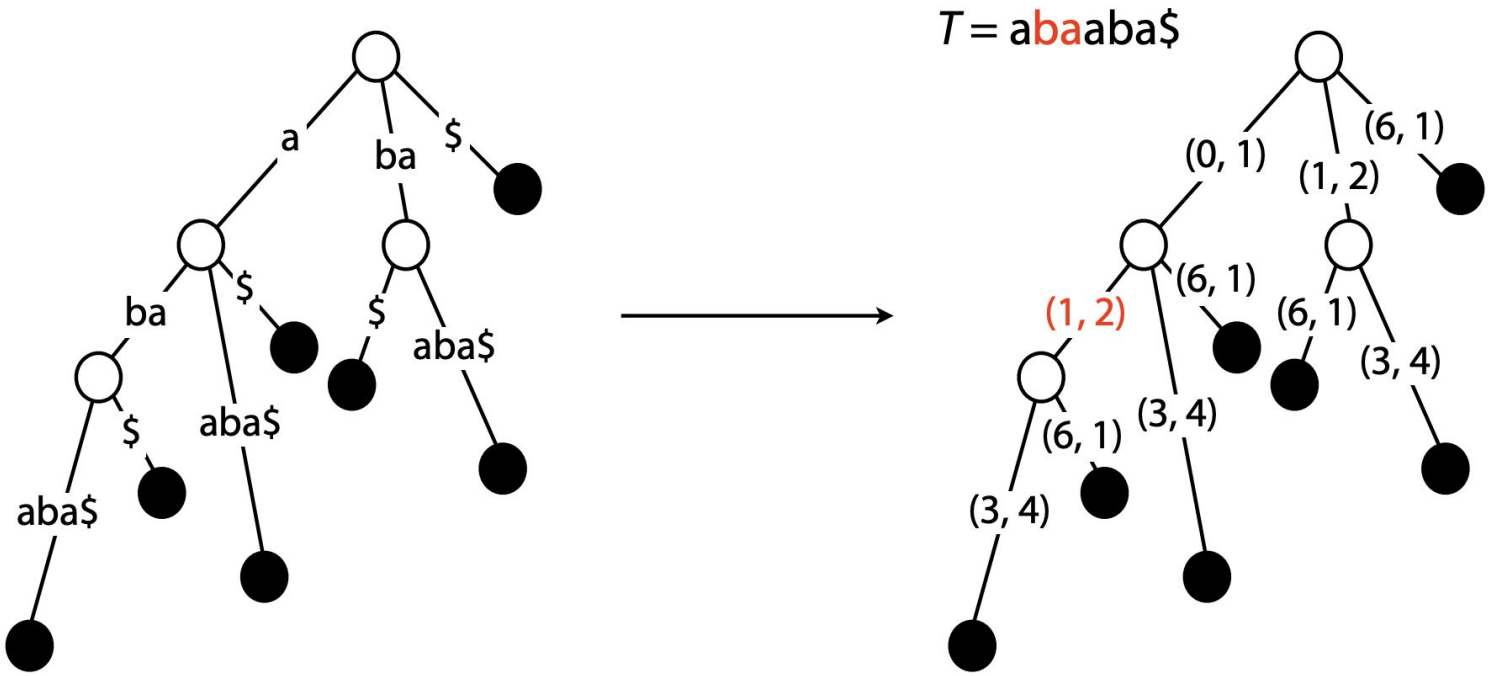
≤ 2*m* -1 nodes total — *O*(*m*)

Is *total size O*(*m*) now?

No: total length of edge labels grows with m^2

Suffix Tree

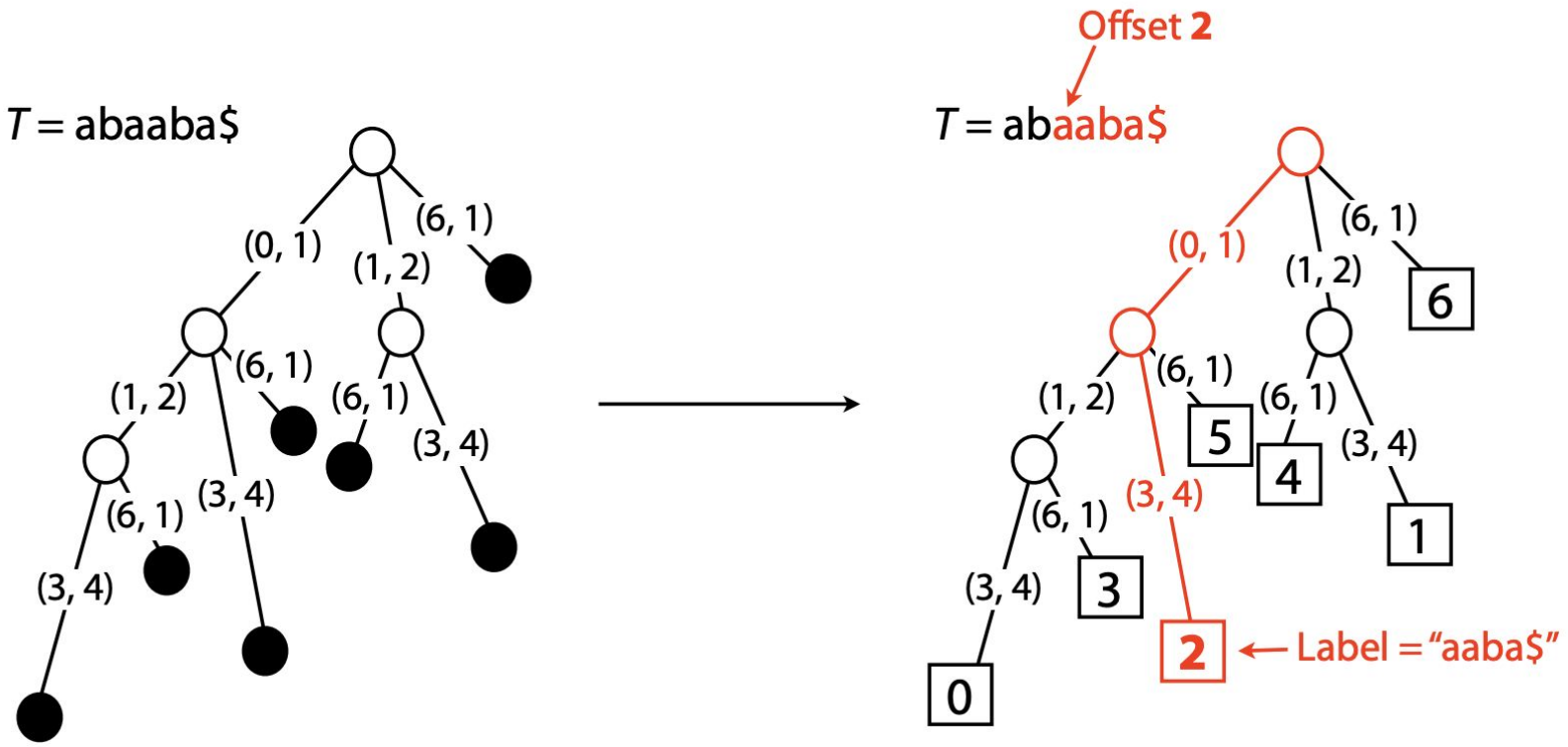
Idea 2: Store *T* itself in addition to the tree. Convert tree's edge labels to (offset, length) pairs with respect to *T*.



Space is now $O(m)$ Suffix trie was $O(m^2)$!

Suffix Tree

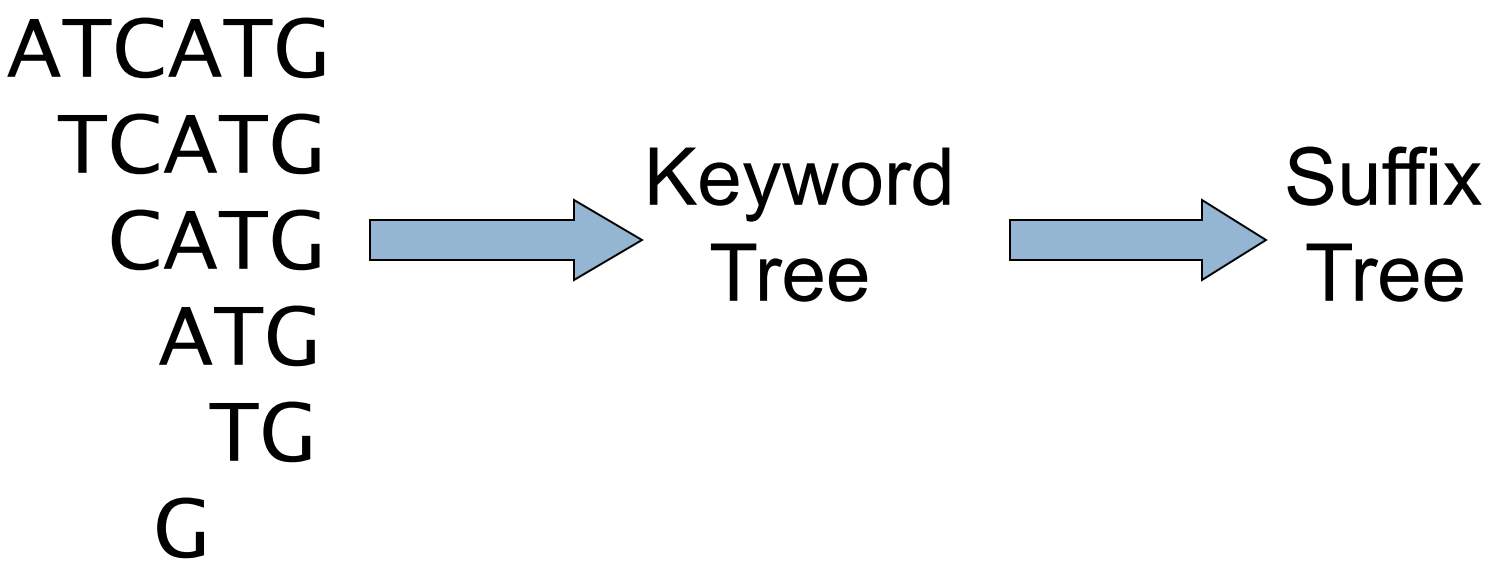
Suffix tree: leaves hold offsets



Space is now $O(m)$ Suffix trie was $O(m^2)$!

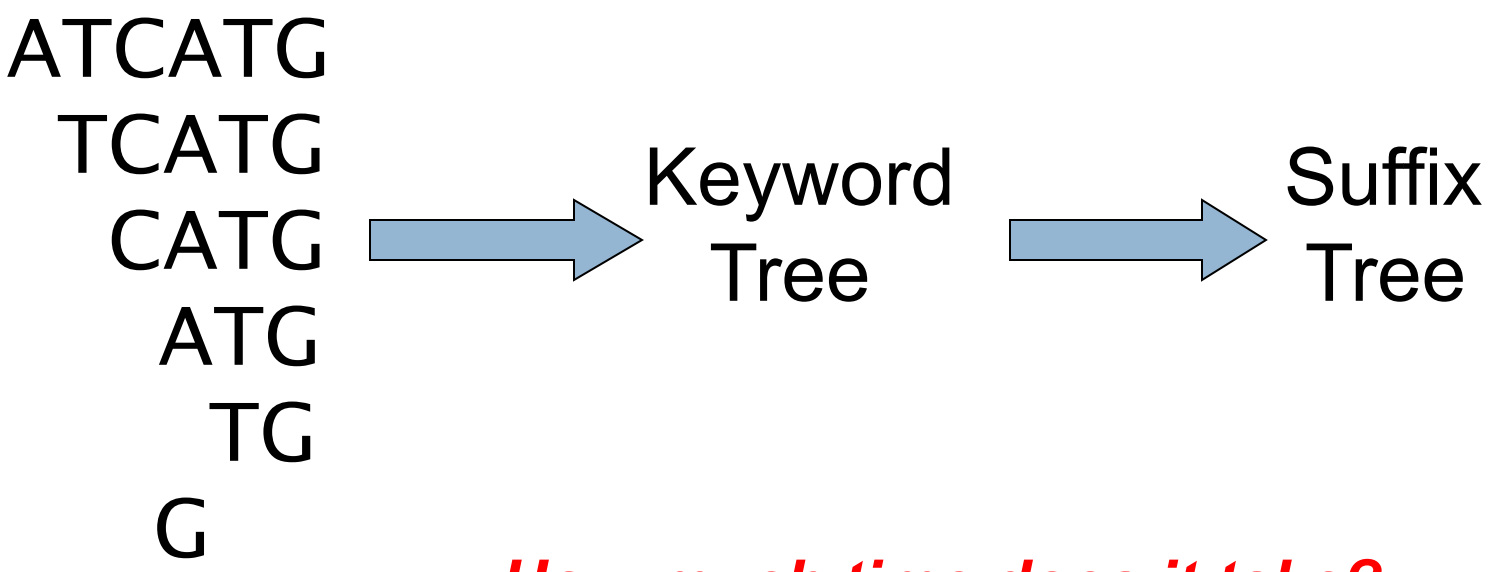
Suffix Tree of a Text

- Suffix trees of a text is constructed for all its suffixes



Suffix Tree of a Text

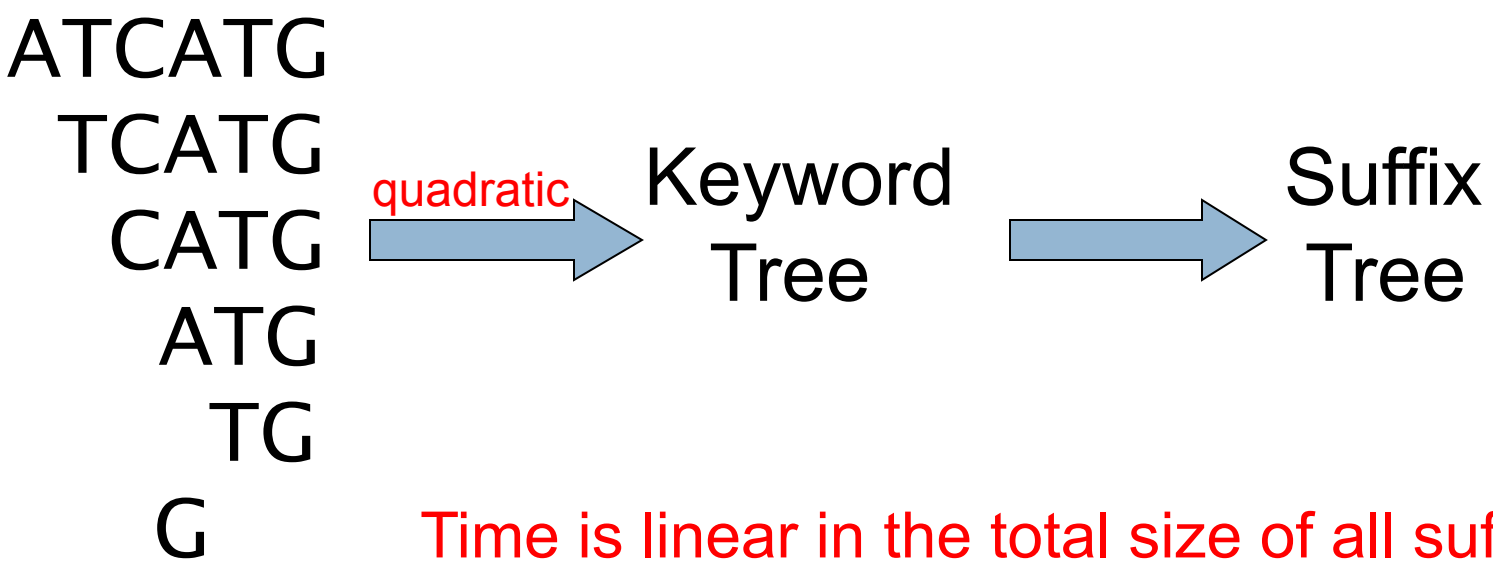
- Suffix trees of a text is constructed for all its suffixes



How much time does it take?

Suffix Tree of a Text

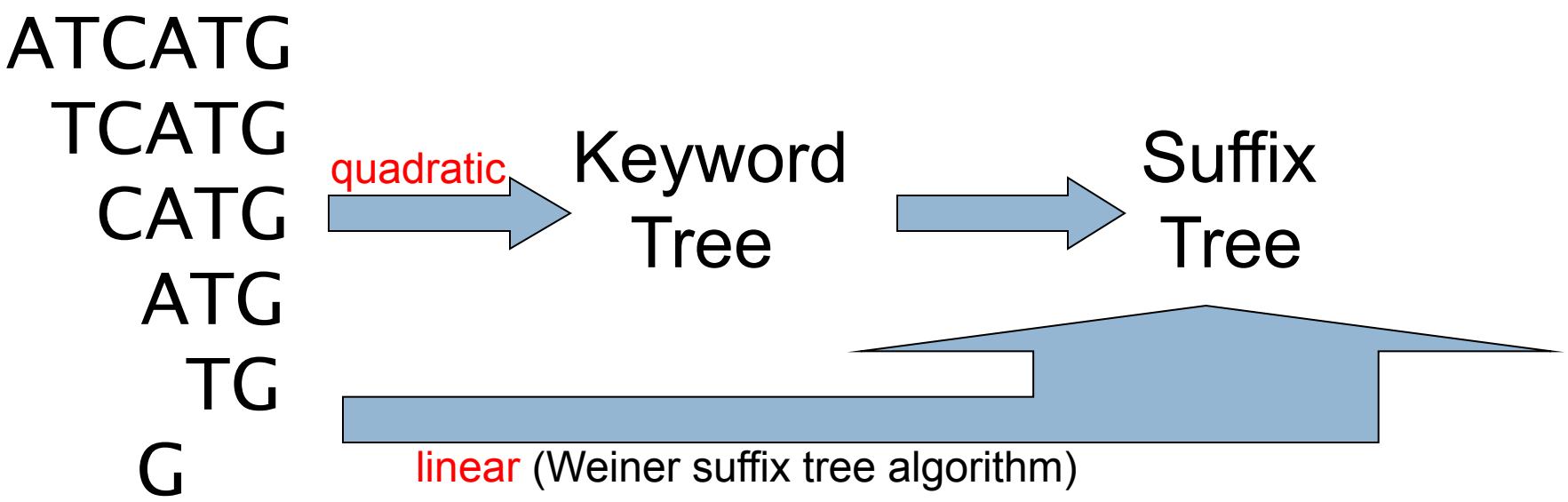
- Suffix trees of a text is constructed for all its suffixes



Time is linear in the total size of all suffixes, i.e., it is quadratic in the length of the text

Suffix Trees: Advantages

- Suffix trees of a text is constructed for all its suffixes
- Suffix trees build faster than keyword trees



Algorithmica (1995) 14: 249–260

Algorithmica

On-Line Construction of Suffix Trees[1]

E. Ukkonen[2]

Abstract. An on-line algorithm is presented for constructing the suffix tree for a given string in time linear in the length of the string. The new algorithm has the desirable property of processing the string symbol by symbol from left to right. It always has the suffix tree for the scanned part of the string ready. The method is developed as a linear-time version of a very simple algorithm for (quadratic size) suffix *tries*. Regardless of its quadratic worst case this latter algorithm can be a good practical method when the string is not too long. Another variation of this method is shown to give, in a natural way, the well-known algorithms for constructing suffix automata (DAWGs).

Key Words. Linear-time algorithm, Suffix tree, Suffix trie, Suffix automaton, DAWG.

Canonical algorithm for $O(m)$ time & space suffix tree construction

Use of Suffix Trees

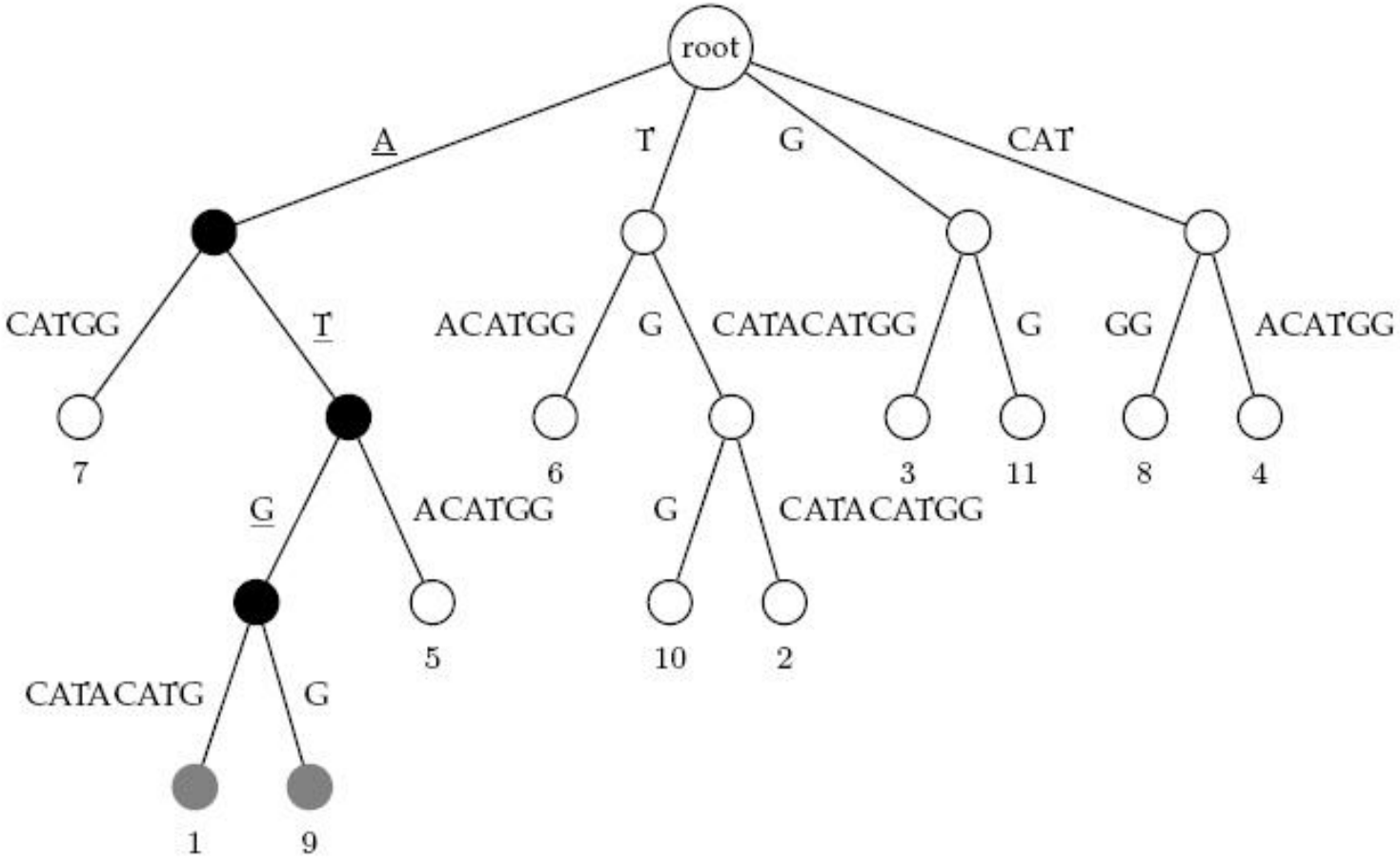
- Suffix trees hold all suffixes of a text
  - i.e., ATCGC: ATCGC, TCGC, CGC, GC, C
  - Builds in O(*m*) time for text of length *m*
- To find any pattern of length ***n*** in a text:
  - Build suffix tree for text
  - Thread the pattern through the suffix tree
  - Can find pattern in text in O(*n*) time!
- O(*n* + *m*) time for "Pattern Matching Problem"
  - Build suffix tree and lookup pattern

Pattern Matching with Suffix Trees

SuffixTreePatternMatching(**p**,**t**)

1 Build **suffix tree** for text **t**
2 Thread pattern **p** through **suffix tree**
3 **if** threading is complete
4 **output** positions of all **p**-matching leaves in the tree
5 **else**
6 **output** "Pattern does not appear in text"

Threading ATG through a Suffix Tree

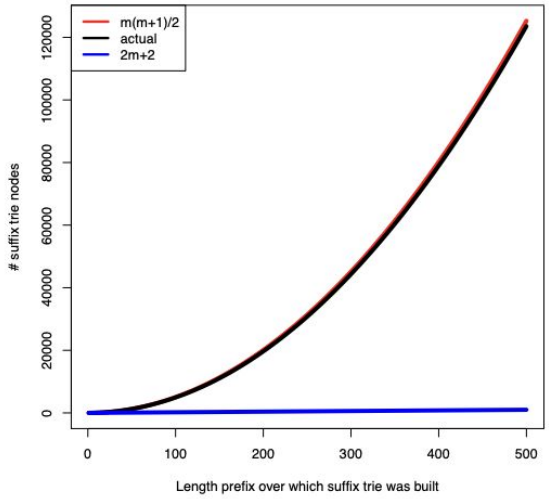


Suffix tree: actual growth

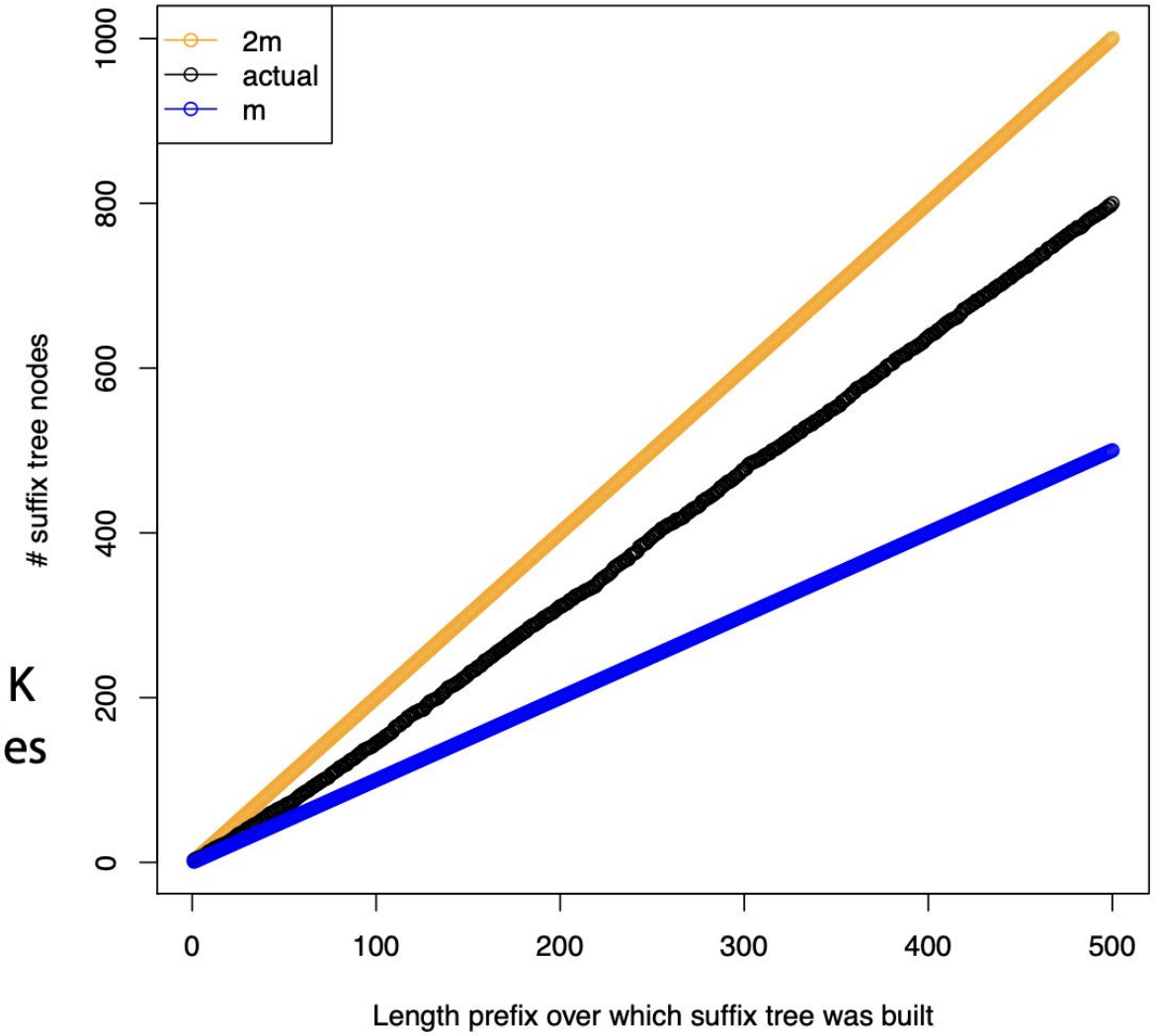
Built suffix trees for the first 500 prefixes of the lambda phage virus genome

Black curve shows # nodes increasing with prefix length

Remember suffix trie plot:



123 K nodes



Suffix Array

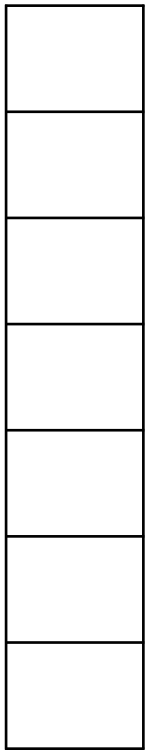
- More space efficient than suffix tree
  - Suffix tree index for human genome >= 47GB
- Lexicographically sort all the suffixes
- Store the starting indices of the suffixes along with the original string

Suffix Array

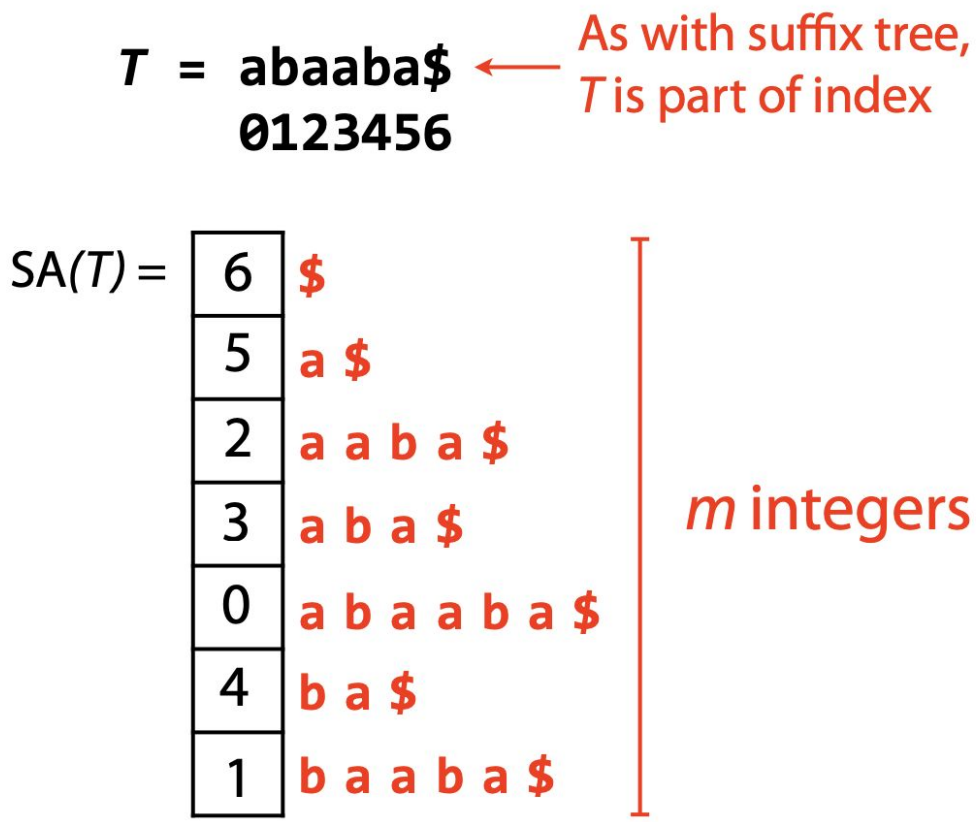
T = abaaba$
0123456

As with suffix tree, *T* is part of index

SA(T) =



Suffix array



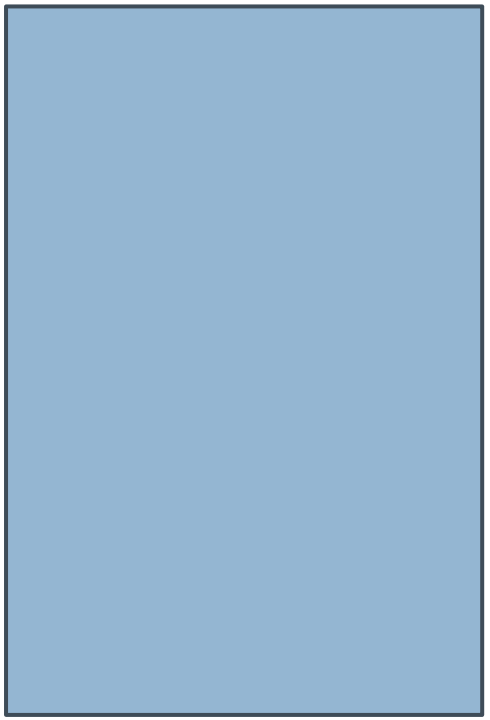
Suffix array of *T* is an array of integers in [0, *m*) specifying lexicographic (alphabetical) order of *T*'s suffixes

Suffix Array

- ATCATG

1	ATCATG$
2	TCATG$
3	CATG$
4	ATG$
5	TG$
6	G$
7	$

Sort the suffixes lexicographically



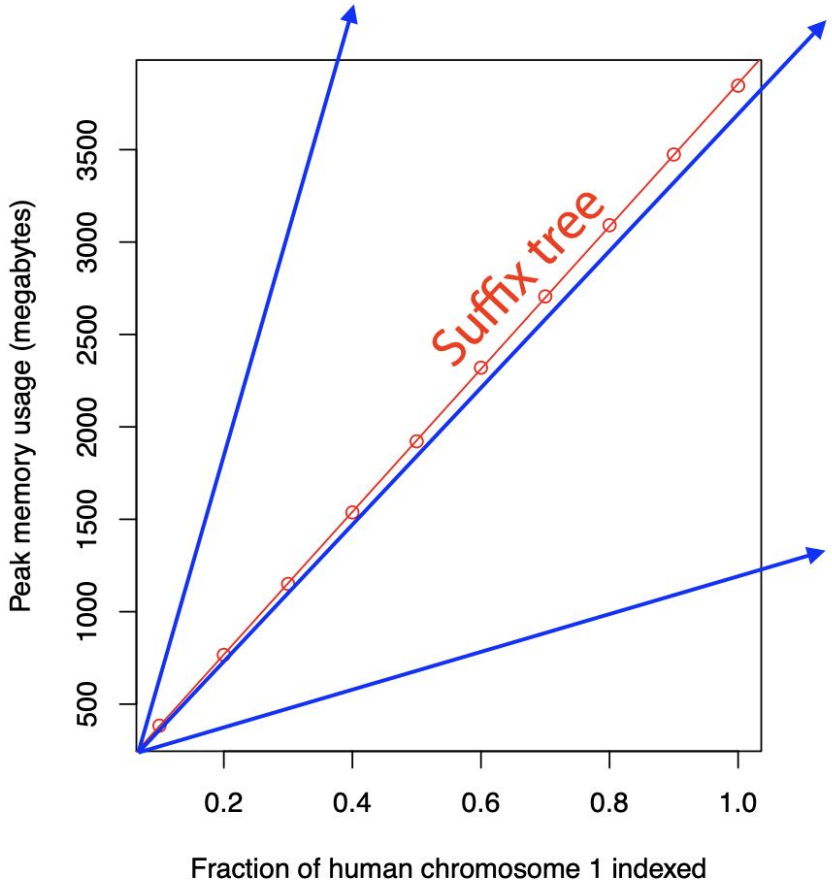
Sorted Suffixes	Starting Positions
$	13
abananas$	5
anabananas$	3
anamabananas$	1
ananas$	7
anas$	9
as$	11
bananas$	6
nabananas$	4
namabananas$	2
nanas$	8
nas$	10
panamabananas$	0
s$	12

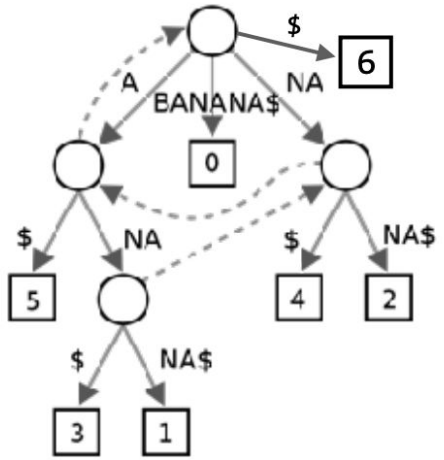
SUFFIXARRAY("panamabananas$") = [13, 5, 3, 1, 7, 9, 11, 6, 4, 2, 8, 10, 0, 12].

Suffix array

O(*m*) space, like suffix tree

Is "constant factor" worse, better, same?

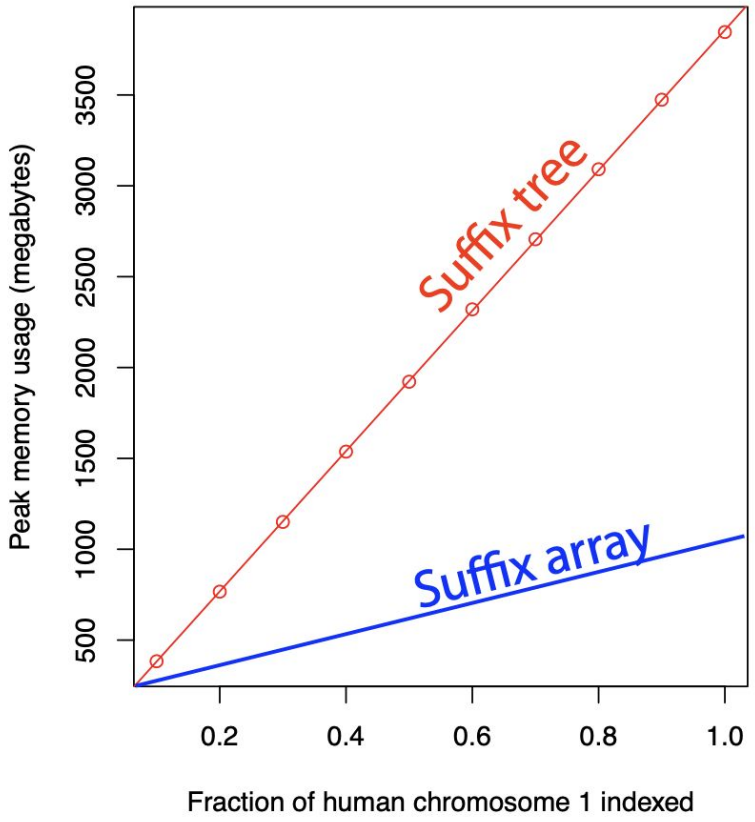


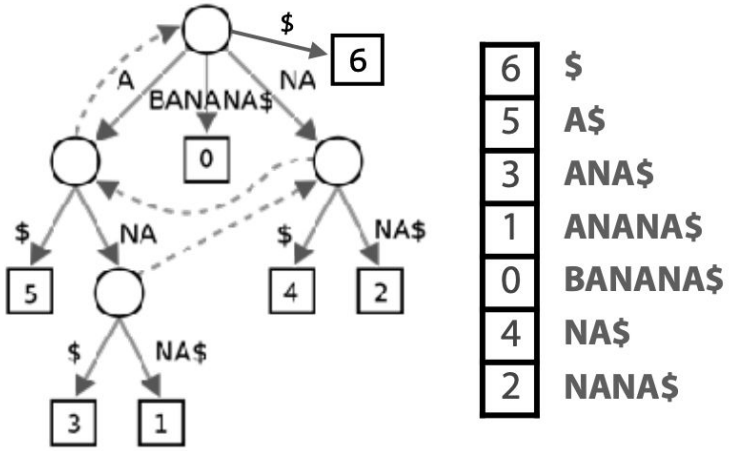


6	$
5	A$
3	ANA$
1	ANANA$
0	BANANA$
4	NA$
2	NANA$

Suffix array

32-bit integers sufficient for human genome, so fits in
~4 bytes/base × 3 billion bases ≈ 12 GB. Suffix tree is >45 GB.





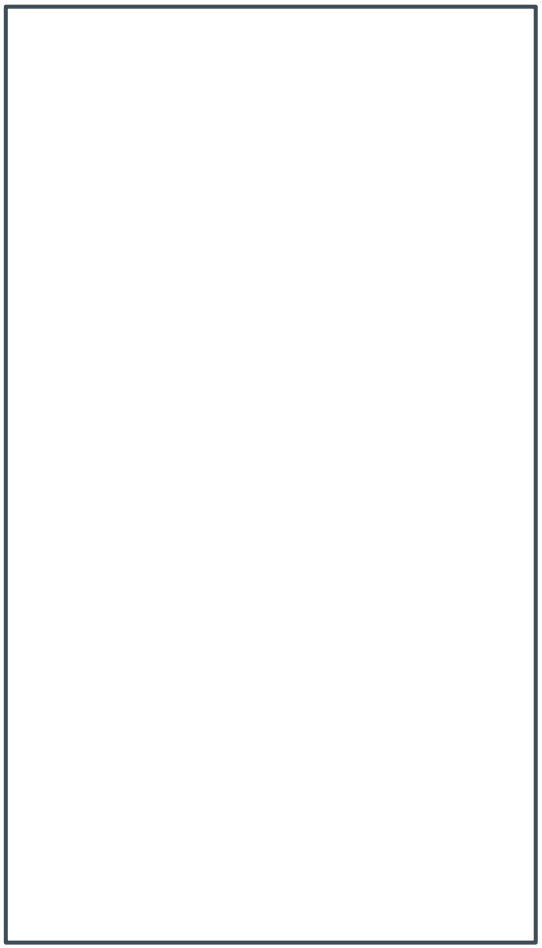
Suffix Array

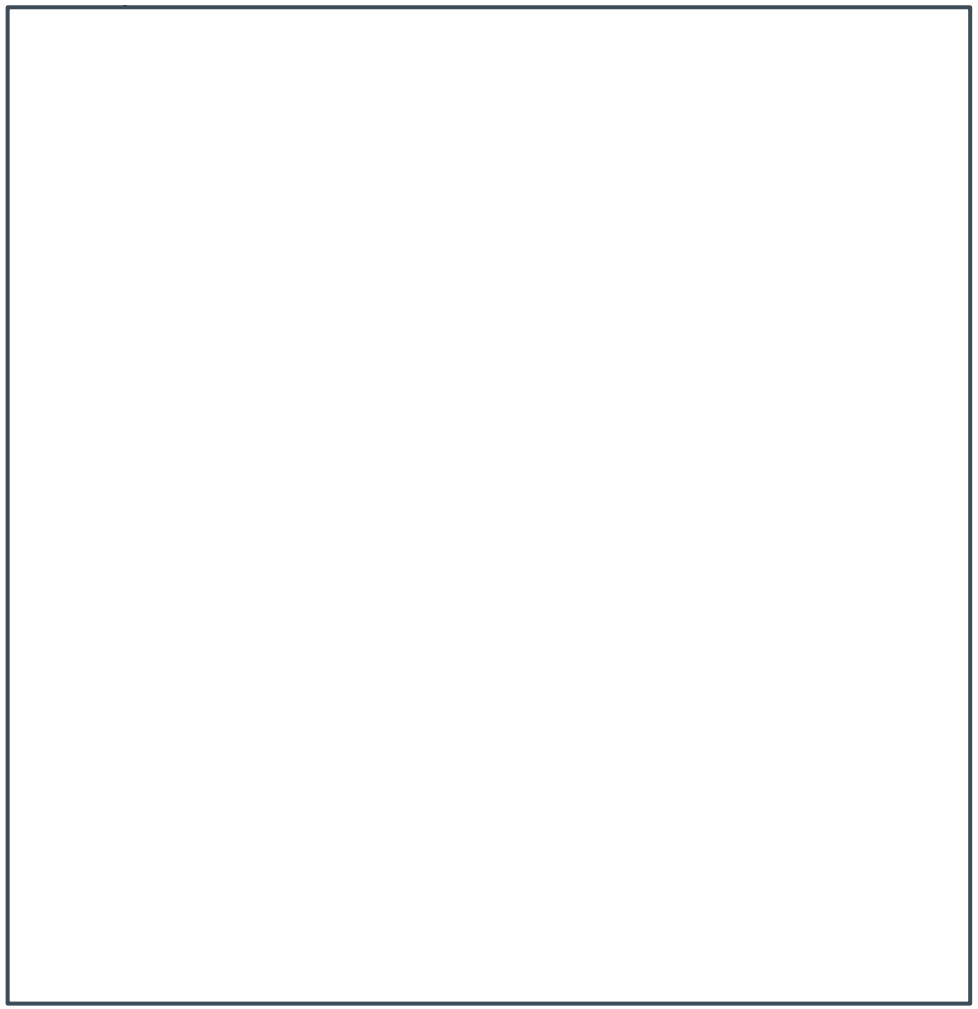
- There exists algorithms to construct suffix array in O(n) time
- Searching is done using binary search
  - Basic binary search would take O(mlogn)
  - Can be done in O(m+logn)

```
PatternMatchingWithSuffixArray(Text, Pattern, SuffixArray)
    minIndex ← 0
    maxIndex ← |Text|
    while minIndex < maxIndex
        midIndex ← (minIndex + maxIndex) / 2
        if Pattern > suffix of Text starting at position SuffixArray(midIndex)
            minIndex ← midIndex + 1
        else
            maxIndex ← midIndex
    first ← minIndex
    maxIndex ← |Text|
    while minIndex < maxIndex
        midIndex ← (minIndex + maxIndex) / 2
        if Pattern < suffix of Text starting at position SuffixArray(midIndex)
            maxIndex ← midIndex
        else
            minIndex ← midIndex + 1
    last ← maxIndex
    if first > last
        return "Pattern does not appear in Text"
    else
        return (first, last)
```

T = panamabananas$

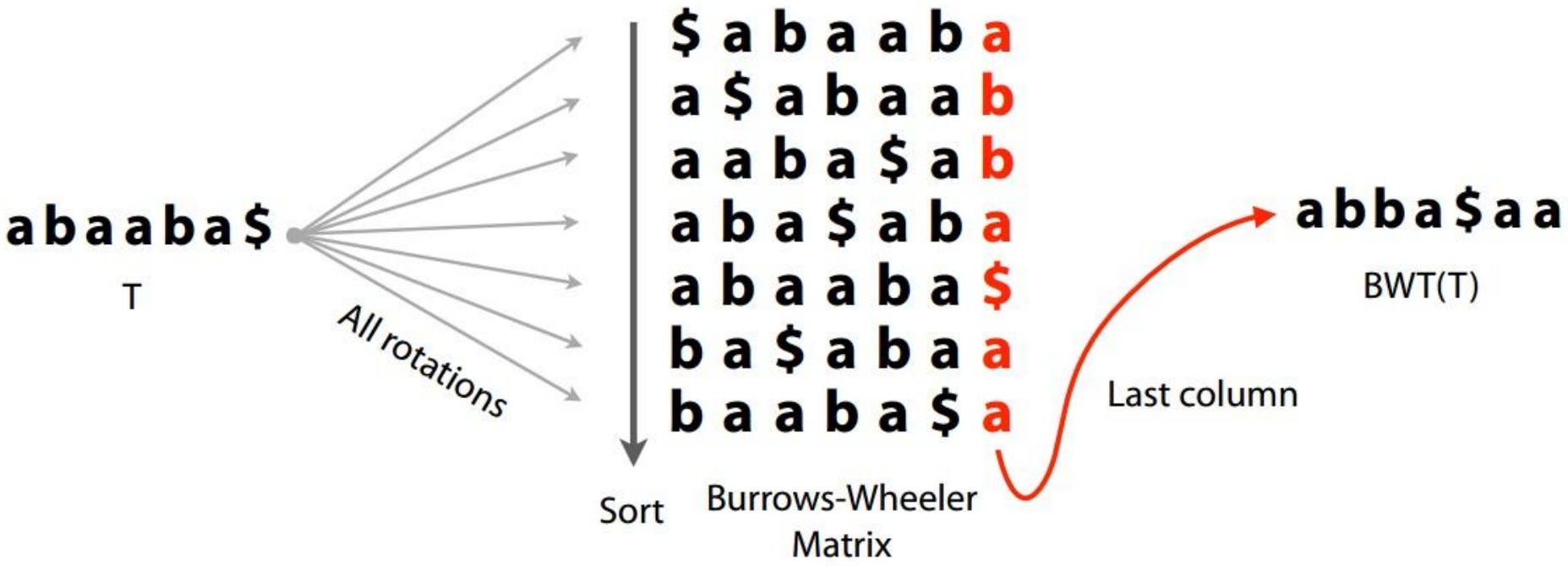
Cyclic Rotations	*M*("panamabananas$")
panamabananas$	





Burrows-Wheeler Transform (BWT)

- Lexicographically sort all the *rotations*



How is it useful for compression? How is it reversible? How is it an index?

Figure from slide by Ben Langmead https://www.langmead-lab.org/teaching.html

Burrows-Wheeler Transform (BWT)

- Sort order is the same for rotations and suffixes
  - Since $ precedes others

T = a b a a b a $

BWM(T)
$ a b a a b a
a $ a b a a b
a a b a $ a b
a b a $ a b a
a b a a b a $
b a $ a b a a
b a a b a $ a

	SA(T)
6	$
5	a $
2	a a b a $
3	a b a $
0	a b a a b a $
4	b a $
1	b a a b a $

Figure from slide by Ben Langmead

Burrows-Wheeler Transform (BWT)

$$BWT[i] = \begin{cases} T[SA[i]-1] & \text{if } SA[i] > 0 \\ \$ & \text{if } SA[i] = 0 \end{cases}$$

T = a b a a b a $

$	a b a a b a
a	$ a b a a b
a	a b a $ a b
a	b a $ a b a
a	b a a b a $
b	a $ a b a a
b	a a b a $ a

BWM(T)

6	$
5	a $
2	a a b a $
3	a b a $
0	a b a a b a $
4	b a $
1	b a a b a $

SA(T)

Burrows-Wheeler Transform (BWT)

- Original motivation was compression
- Rotating and sorting tend to increase run lengths

final char (L)	sorted rotations
a	n to decompress. It achieves compression
o	n to perform only comparisons to a depth
o	n transformation} This section describes
o	n transformation} We use the example and
o	n treats the right-hand side as the most
a	n tree for each 16 kbyte input block, enc
a	n tree in the output stream, then encodes
i	n turn, set $L[i]$ to be the
i	n turn, set $R[i]$ to the
o	n unusual data. Like the algorithm of Man
a	n use a single set of probabilities table
e	n using the positions of the suffixes in
i	n value at a given point in the vector $R
e	n we present modifications that improve t
e	n when the block size is quite large. Ho
i	n which codes that have not been seen in
i	n with ch appear in the {\em same order
i	n with ch. In our exam
o	n with Huffman or arithmetic coding. Bri
o	n with figures given by Bell~\cite{bell}.

Figure 1: Example of sorted rotations. Twenty consecutive rotations from the sorted list of rotations of a version of this paper are shown, together with the final character of each rotation.

Figure from original paper on BWT

Burrows-Wheeler Transform (BWT)

nd Corey (1). They kindly made their manuscript availa ..... a
nd criticism, especially on interatomic distances. We ..... a
nd cytosine. The sequence of bases on a single chain d ..... a
nd experimentally (3, 4) that the ratio of the amounts o ..... u
nd for this reason we shall not comment on it. We wish ..... a
nd guanine (purine) with cytosine (pyrimidine). In oth ..... a
nd ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin ..... a
nd its water content is rather high. At lower water co ..... a
nd pyrimidine bases. The planes of the bases are perpe ..... a
nd stereochemical arguments. It has not escaped our no ..... a
nd that only specific pairs of bases can bond together ..... u
nd the atoms near it is close to Furberg's 'standard co ..... a
nd the bases on the inside, linked together by hydrogen ..... a
nd the bases on the outside. In our opinion, this stru ..... a
nd the other a pyrimidine for bonding to occur. The hy ..... a
nd the phosphates on the outside. The configuration of ..... a
nd the ration of guanine to cytosine, are always very c ..... a
nd the same axis (see diagram). We have made the usual ..... u
nd their co-workers at King's College, London. One of ..... a

LF mapping

- Last to first mapping

$ a b a a b a
a $ a b a a b
a a b a $ a b
a b a $ a b a
a b a a b a $
b a $ a b a a
b a a b a $ a

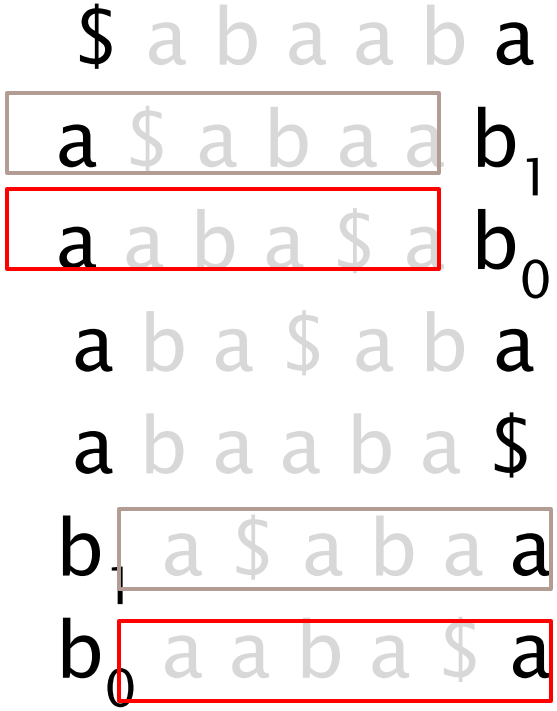
LF mapping

- Assign numbers to distinguish characters
  - a b_0 a a b_1 a $

$ a b a a b a
a $ a b a a b_1
a a b a $ a b_0
a b a $ a b a
a b a a b a $
b_1 a $ a b a a
b_0 a a b a $ a

LF mapping

- They will be in same order in L and F. Why?
  - a b_1 a a b_2 a $



LF Mapping

BWM with T-ranking:

F						*L*
$	a_0	b_0	a_1	a_2	b_1	a_3
a_3	$	a_0	b_0	a_1	a_2	b_1
a_1	a_2	b_1	a_3	$	a_0	b_0
a_2	b_1	a_3	$	a_0	b_0	a_1
a_0	b_0	a_1	a_2	b_1	a_3	$
b_1	a_3	$	a_0	b_0	a_1	a_2
b_0	a_1	a_2	b_1	a_3	$	a_0

LF mapping

- Assign numbers to distinguish characters
  - $a_0\ b_0\ a_1\ a_2\ b_1\ a_3\ \$$

$\$\ a\ b\ a\ a\ b\ a_3$

$a_3\ \$\ a\ b\ a\ a\ b_1$

$a_1\ a\ b\ a\ \$\ a\ b_0$

$a_2\ b\ a\ \$\ a\ b\ a_1$

$a_0\ b\ a\ a\ b\ a\ \$$

$b_1\ a\ \$\ a\ b\ a\ a_2$

$b_0\ a\ a\ b\ a\ \$\ a_0$

LF mapping

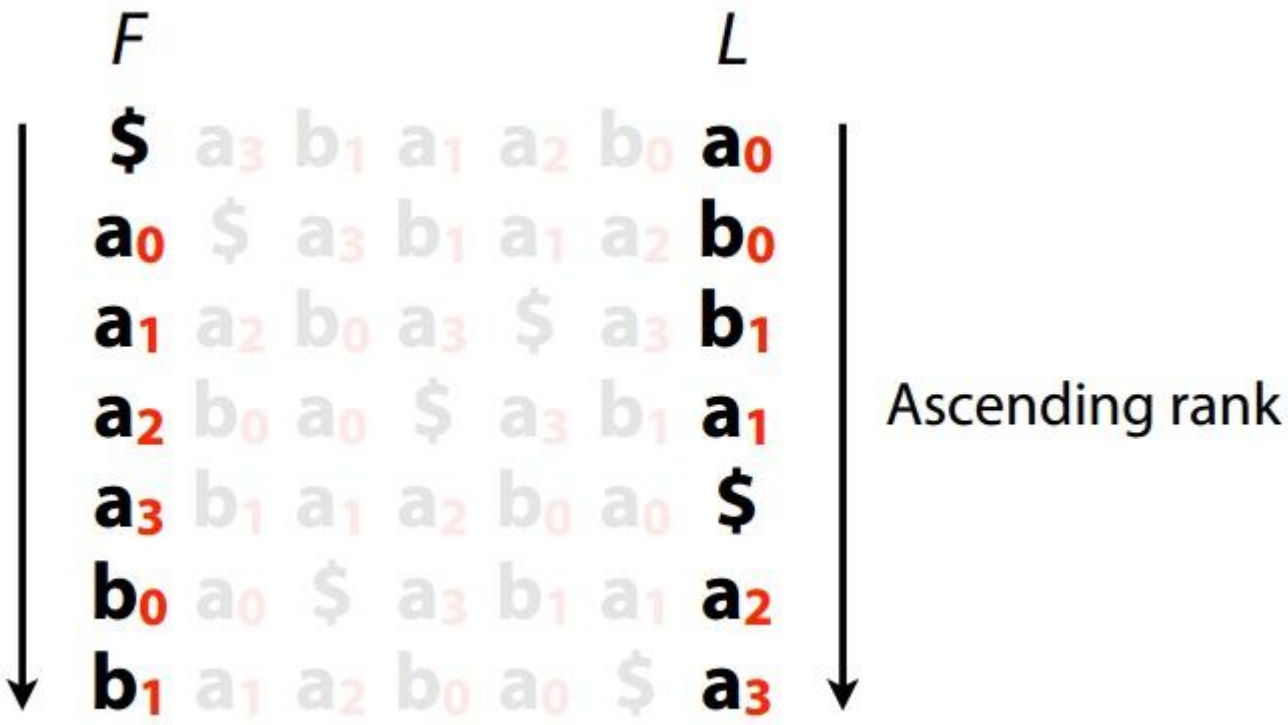


Figure from slide by Ben Langmead

LF mapping

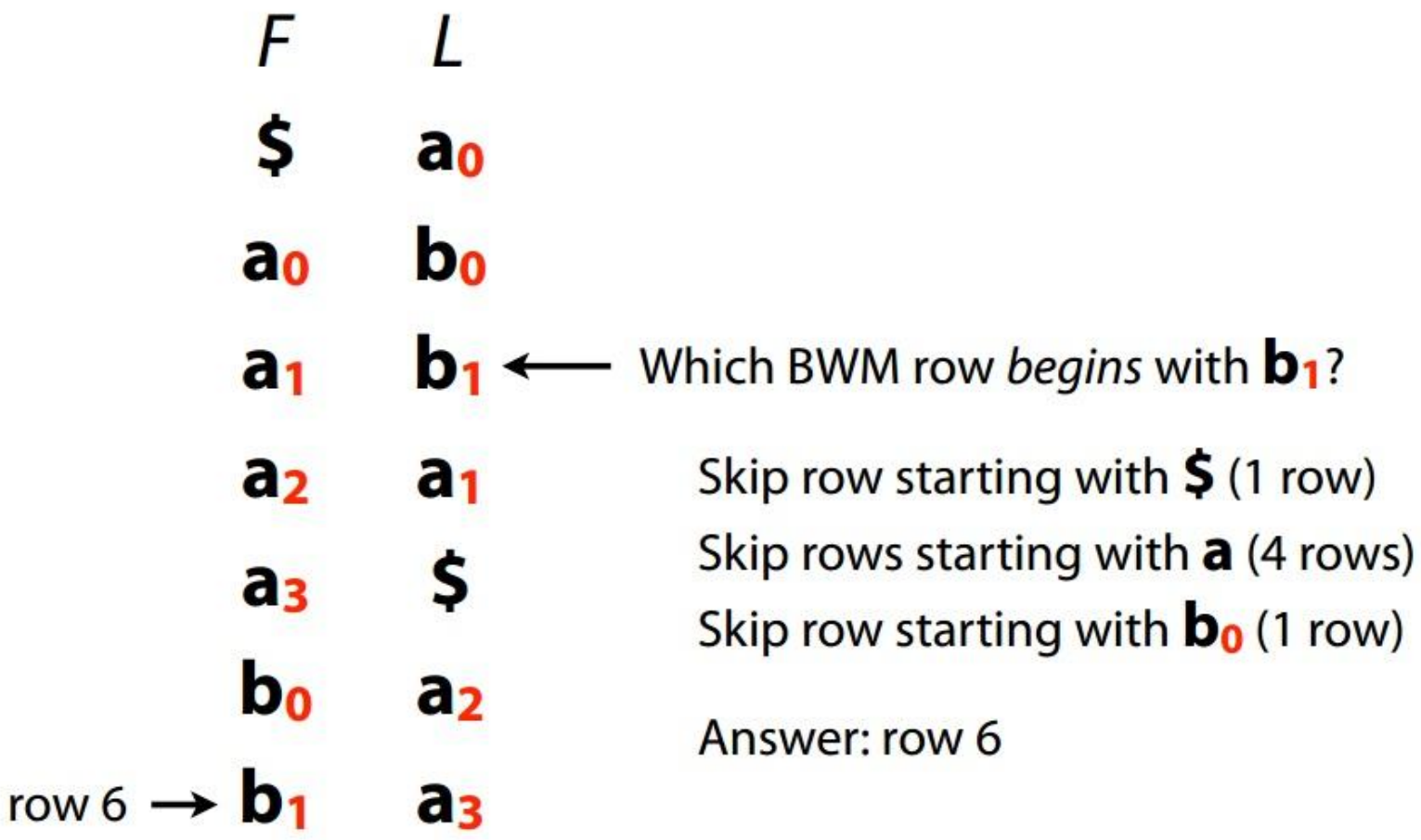
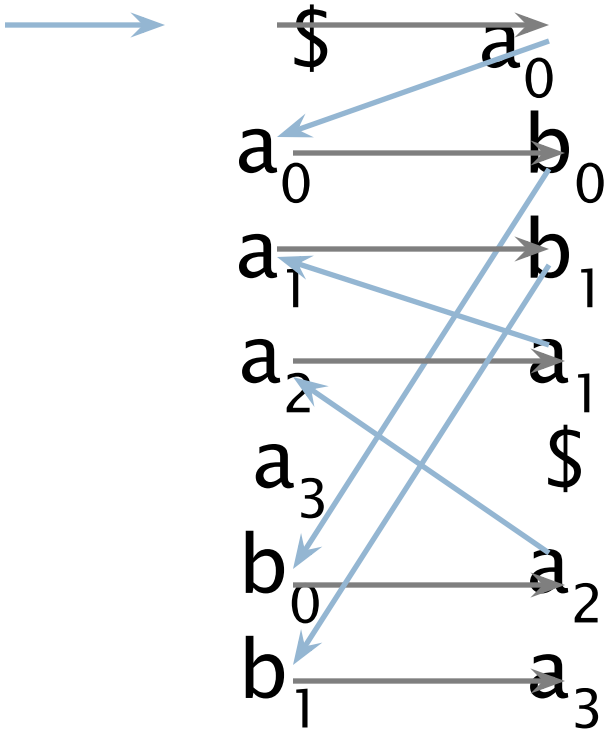


Figure from slide by Ben Langmead

BWT reversing

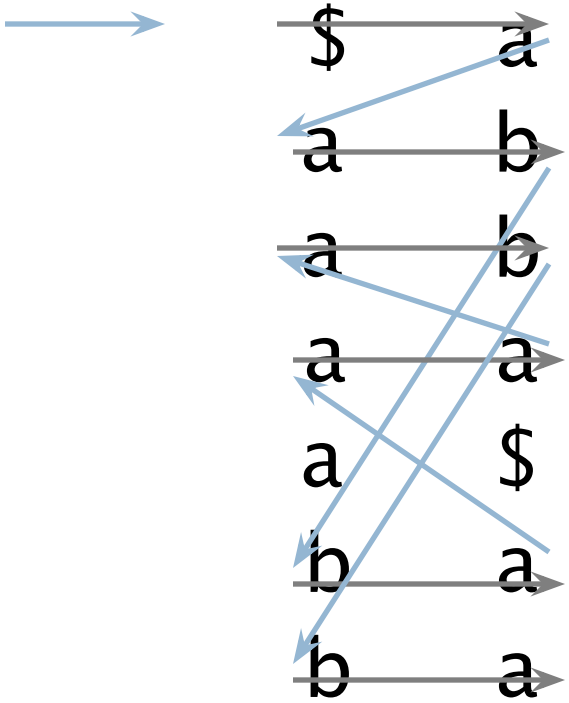
- Reverse BWT from right to left



$a_3b_1a_1a_2b_0a_0\$$

BWT reversing

- Reverse BWT from right to left



abaaba$

Burrows-Wheeler Transform: reversing

Reverse BWT(T) starting at right-hand-side of *T* and moving left

Start in first row. *F* must have **$**.

L contains character just prior to **$**: $\mathbf{a_0}$

Jump to row *beginning* with $\mathbf{a_0}$.

L contains character just prior to $\mathbf{a_0}$: $\mathbf{b_0}$.

Repeat for $\mathbf{b_0}$, get $\mathbf{a_2}$

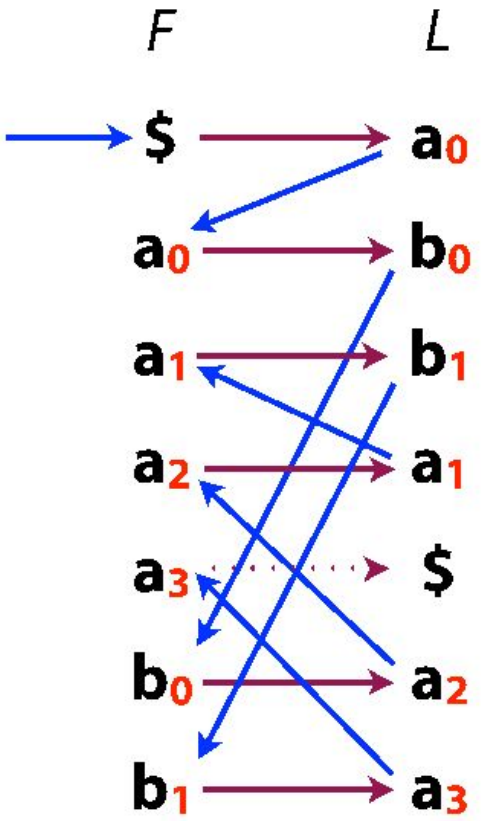
Repeat for $\mathbf{a_2}$, get $\mathbf{a_1}$

Repeat for $\mathbf{a_1}$, get $\mathbf{b_1}$

Repeat for $\mathbf{b_1}$, get $\mathbf{a_3}$

Repeat for $\mathbf{a_3}$, get **$** (done)

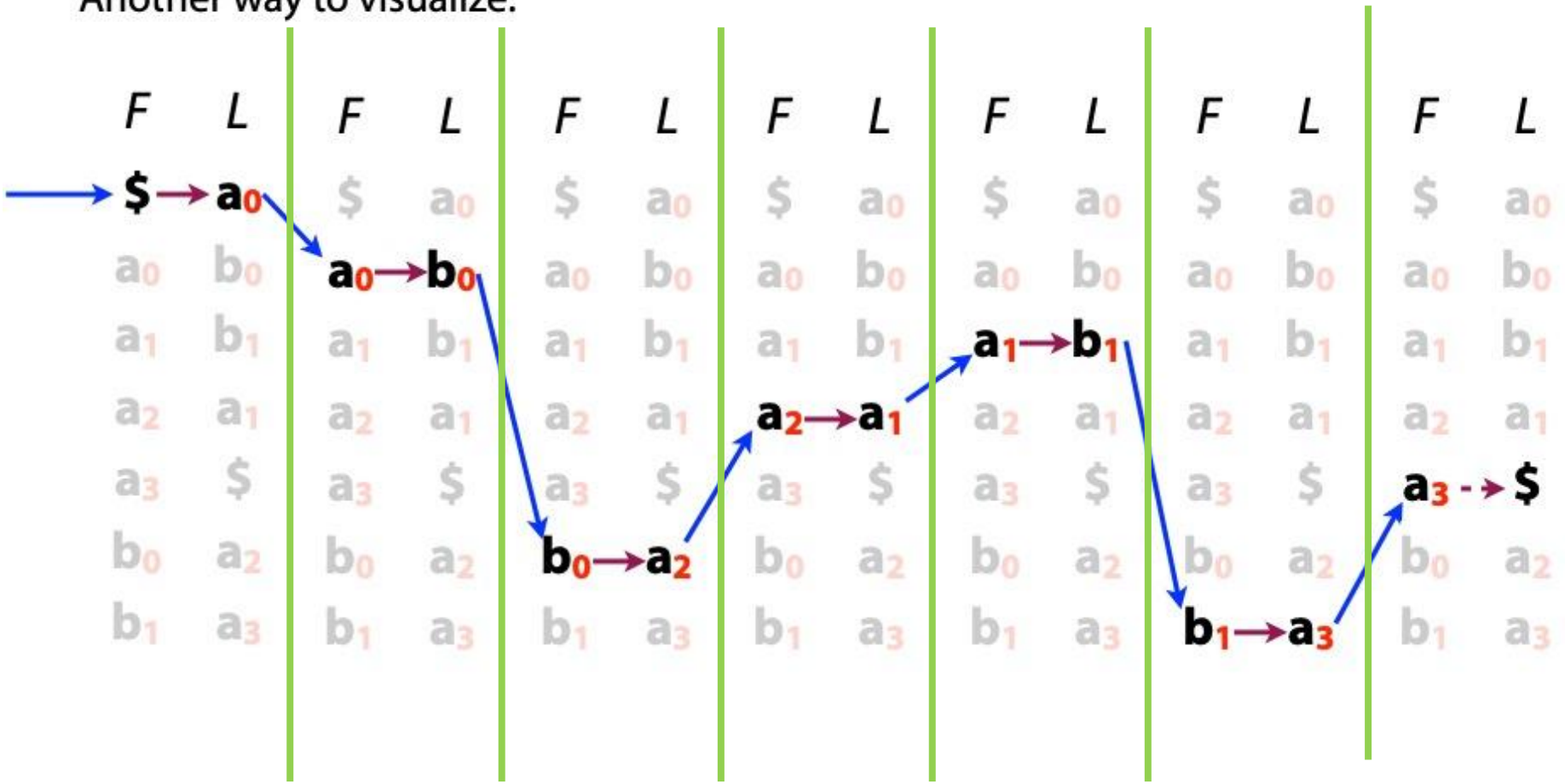
T: $\mathbf{a_3\ b_1\ a_1\ a_2\ b_0\ a_0\ \$}$



In reverse order, we saw = $\mathbf{a_3\ b_1\ a_1\ a_2\ b_0\ a_0\ \$} = T$

Burrows-Wheeler Transform: reversing

Another way to visualize:



T: $a_3\ b_1\ a_1\ a_2\ b_0\ a_0\ \$$

FM index

- FM index
  - Combines the BWT with a few small auxiliary data structures
  - Ferragina and Manzini
- F and L from BWT
  - Both can be compressed

FM index querying

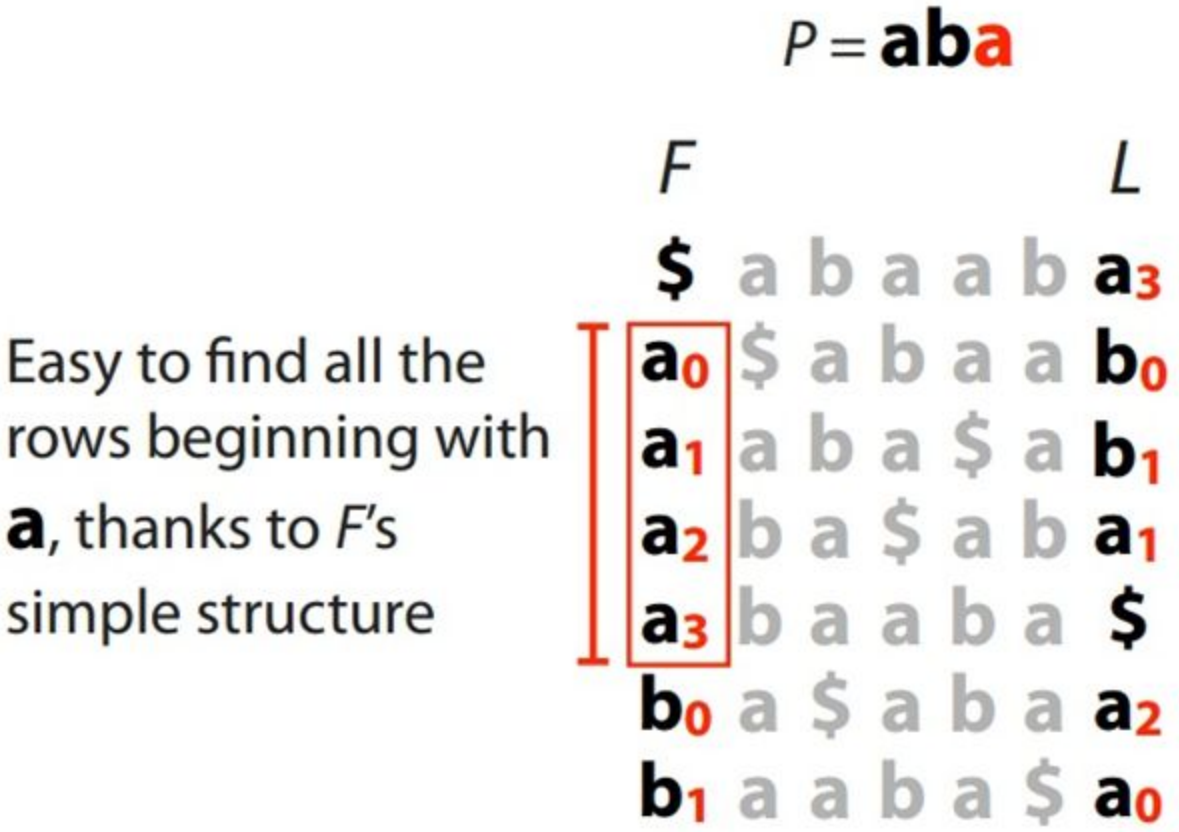


Figure from slide by Ben Langmead

FM index querying

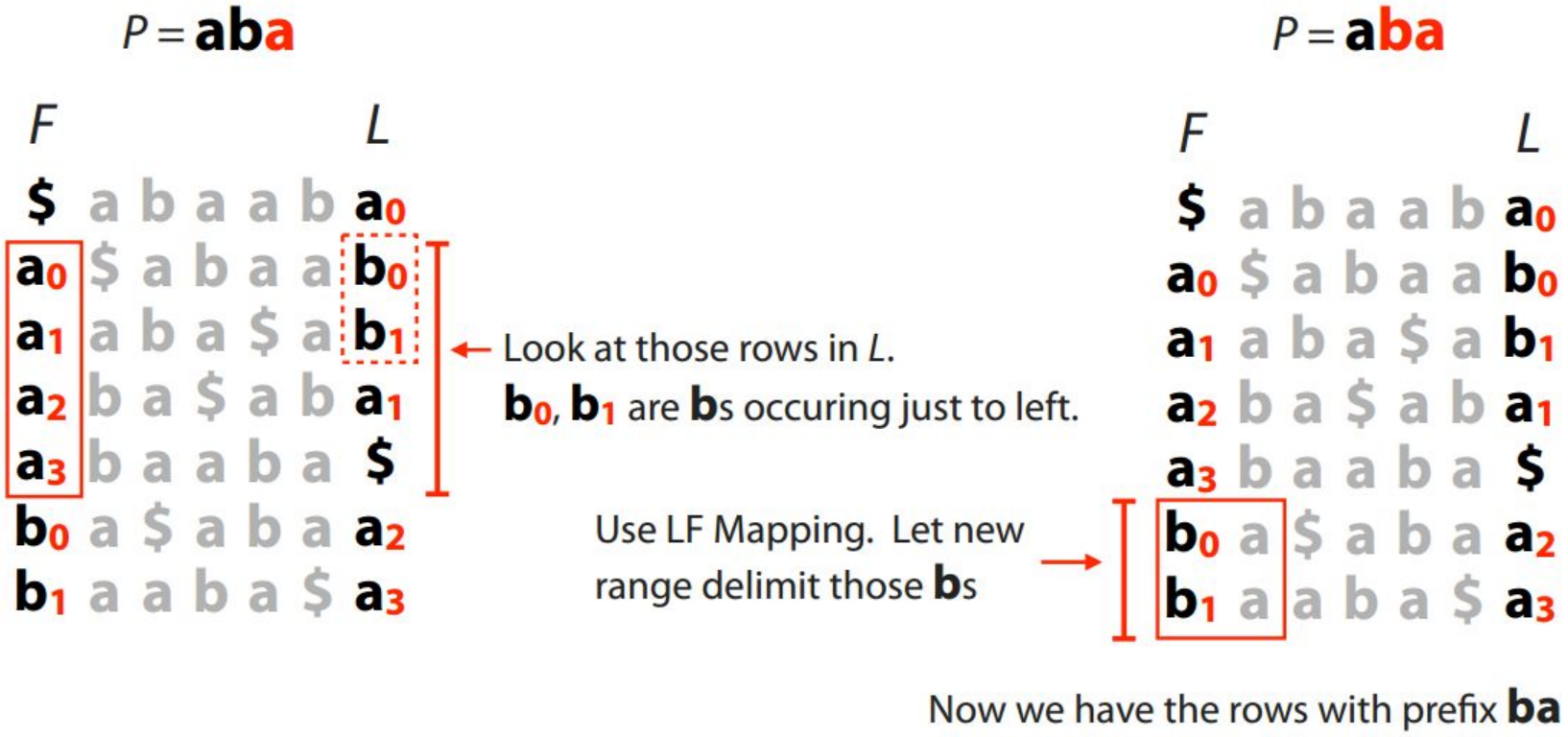


Figure from slide by Ben Langmead

FM index querying

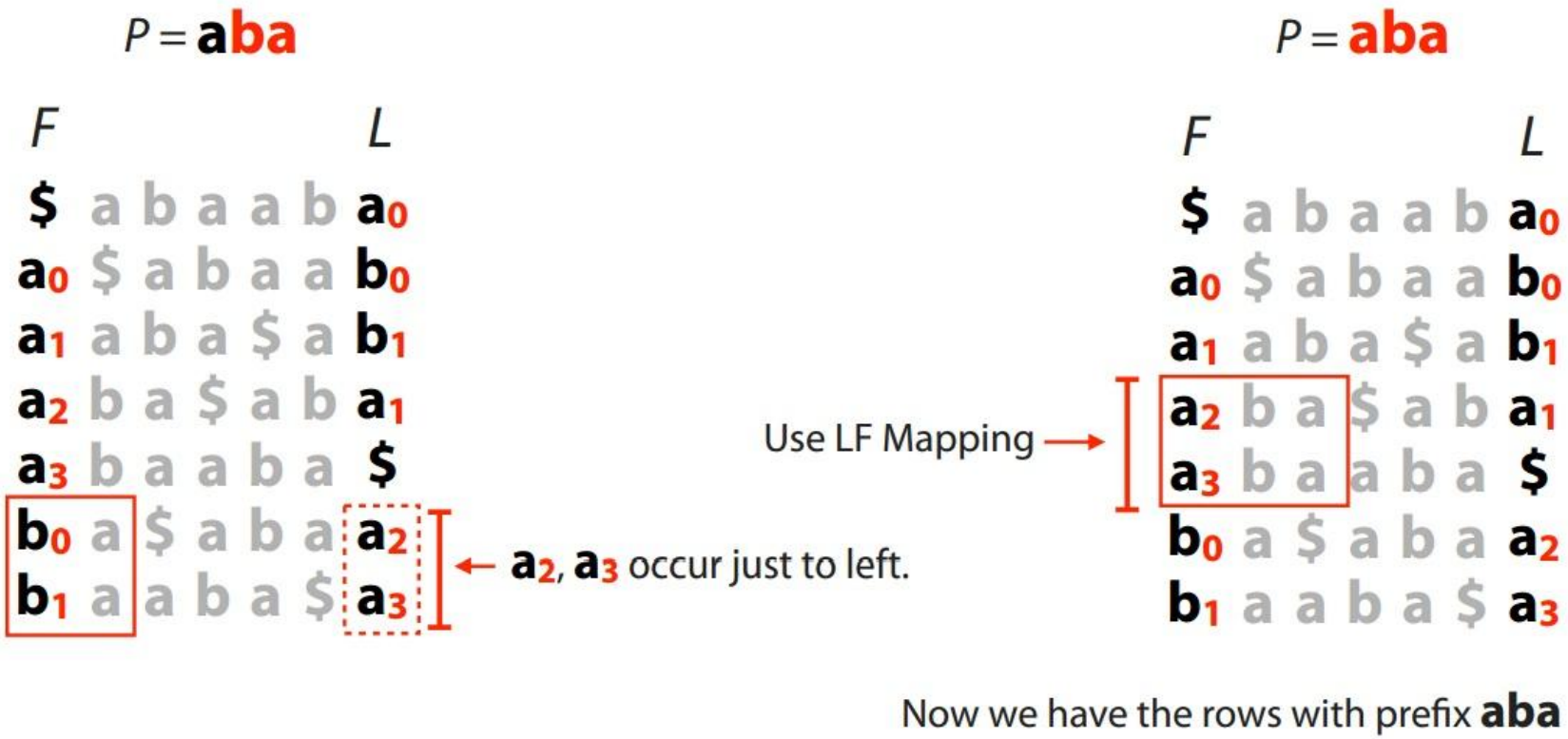
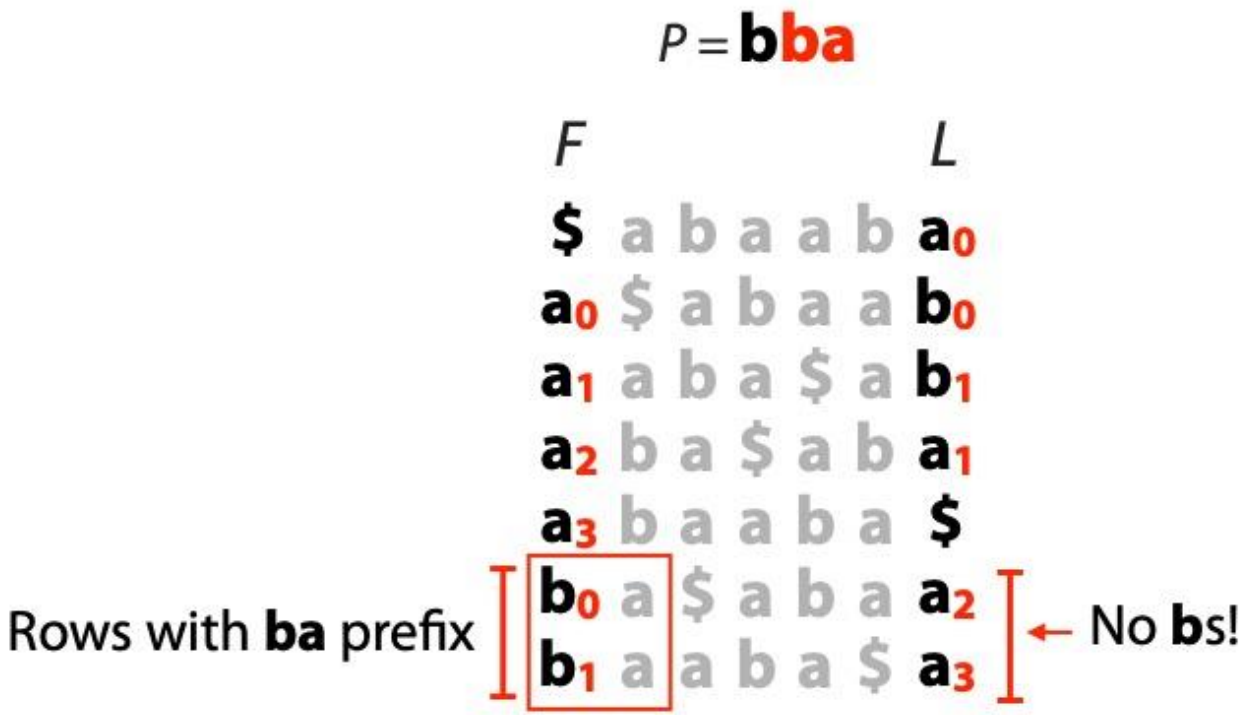


Figure from slide by Ben Langmead


ana
1
6
$1panamabananas1
a1bananas$panam1
a2mabananas$pan1
a3namabananas$p1
a4nanas$panamab1
a5nas$panamaban2
a6s$panamabanan3
b1ananas$panama1
m1abananas$pana2
n1amabananas$pa3
n2anas$panamaba4
n3as$panamabana5
p1anamabananas$1
s1$panamabanana6

FM Index: querying

When *P* does not occur in *T*, we eventually fail to find next character in *L*:



FM index issues

- Where are the matches?
  - Store positions as in suffix array?

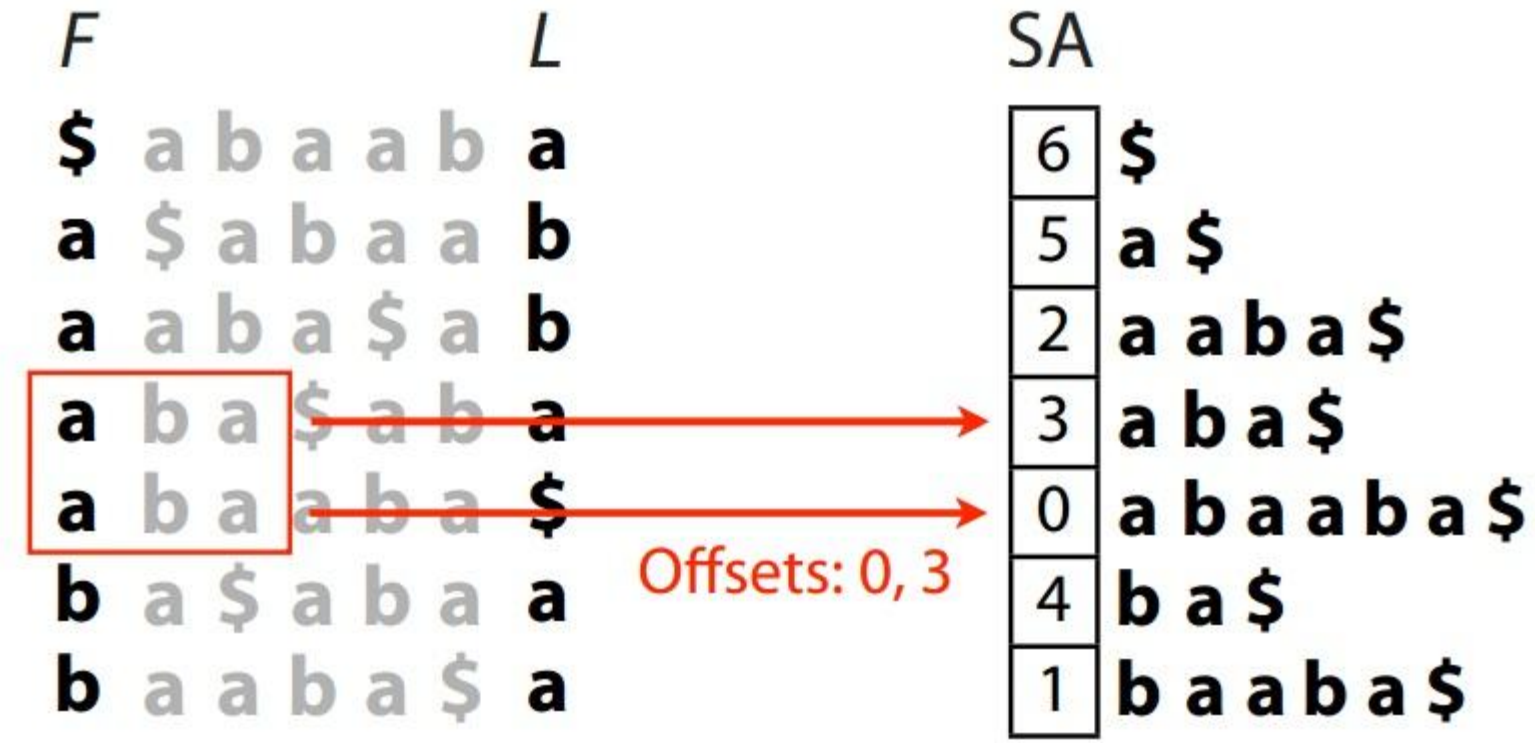
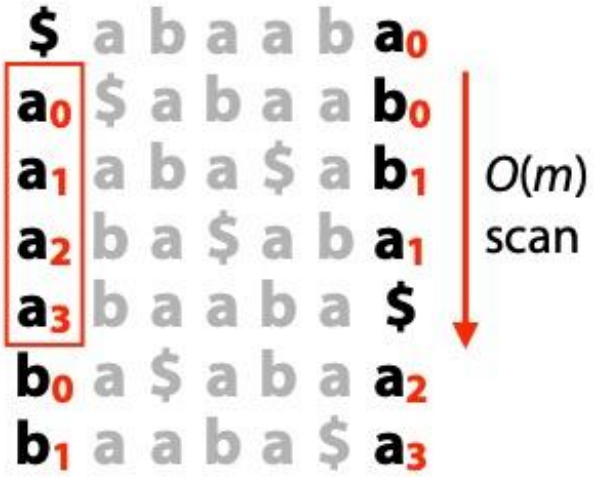


Figure from slide by Ben Langmead

FM index issues

(1) Scanning for preceding character is slow



(2) Storing ranks takes too much space

m integers

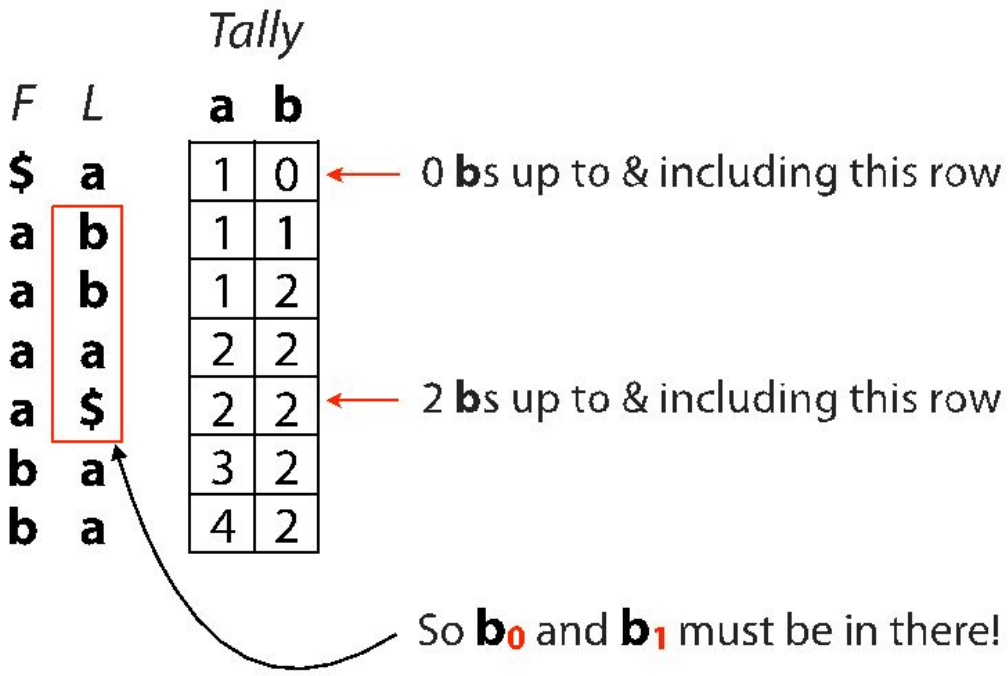
```
def reverseBwt(bw):
    """ Make T from BWT(T) """
    ranks, tots = rankBwt(bw)
    first = firstCol(tots)
    rowi = 0
    t = "$"
    while bw[rowi] != '$':
        c = bw[rowi]
        t = c + t
        rowi = first[c][0] + ranks[rowi]
    return t
```

(3) Need way to find where matches occur in *T:*

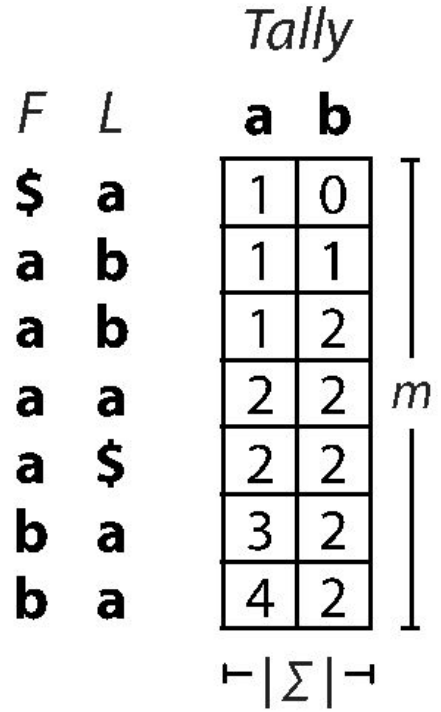
FM Index: fast rank calculations

Is there an fast way to determine which **b**s precede the **a**s in our range?

FM Index: fast rank calculations

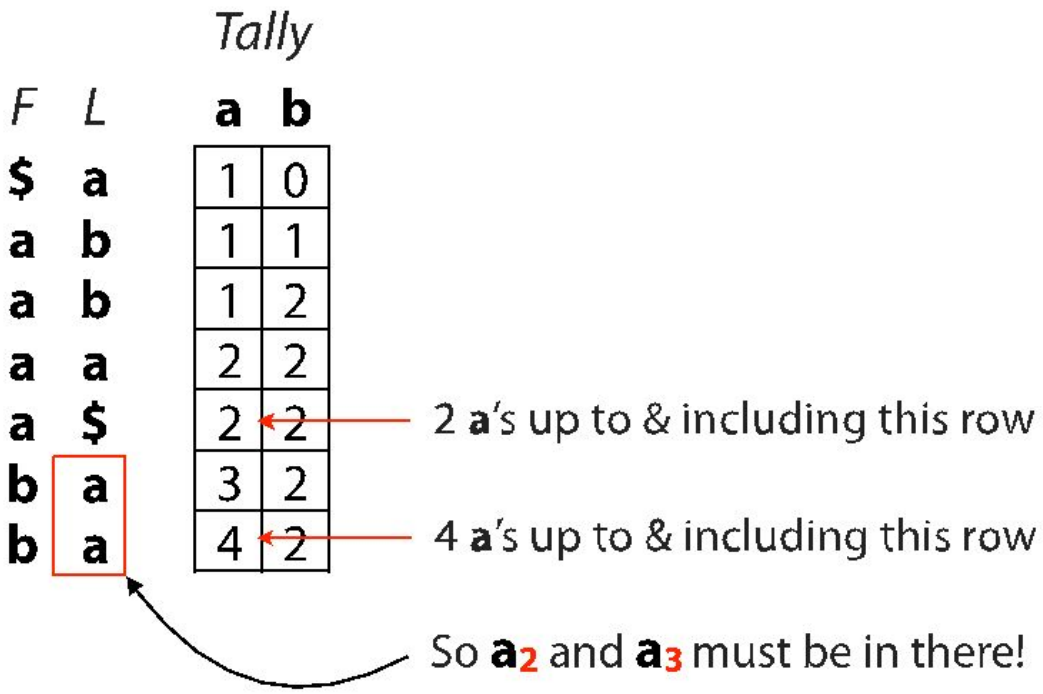


FM Index: fast rank calculations



Tally is $m \times |\Sigma|$ integers
Too big!

FM Index: fast rank calculations



O(1) time; 2 lookups
regardless of range size

FM index issues

- How to get numbers (ranks) for LF mapping?
  - Calculate numbers of each character up to that row

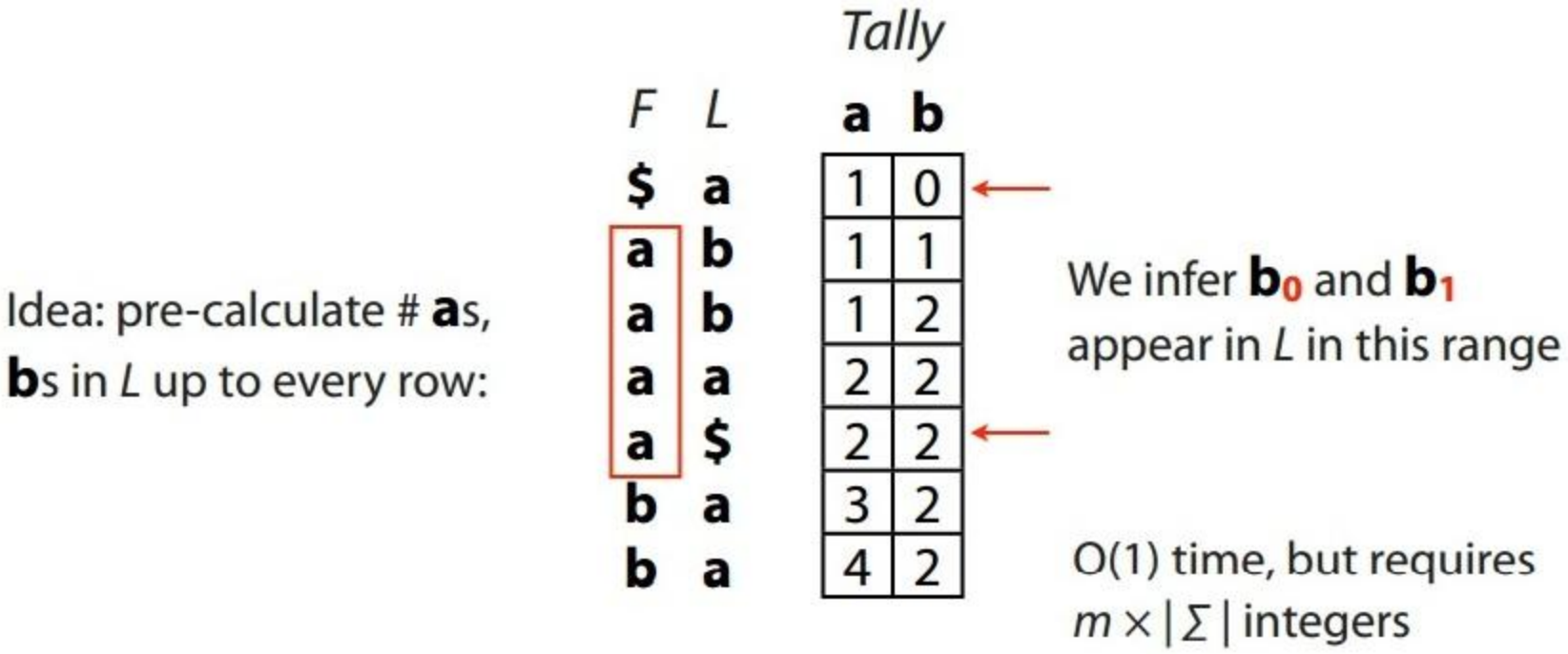
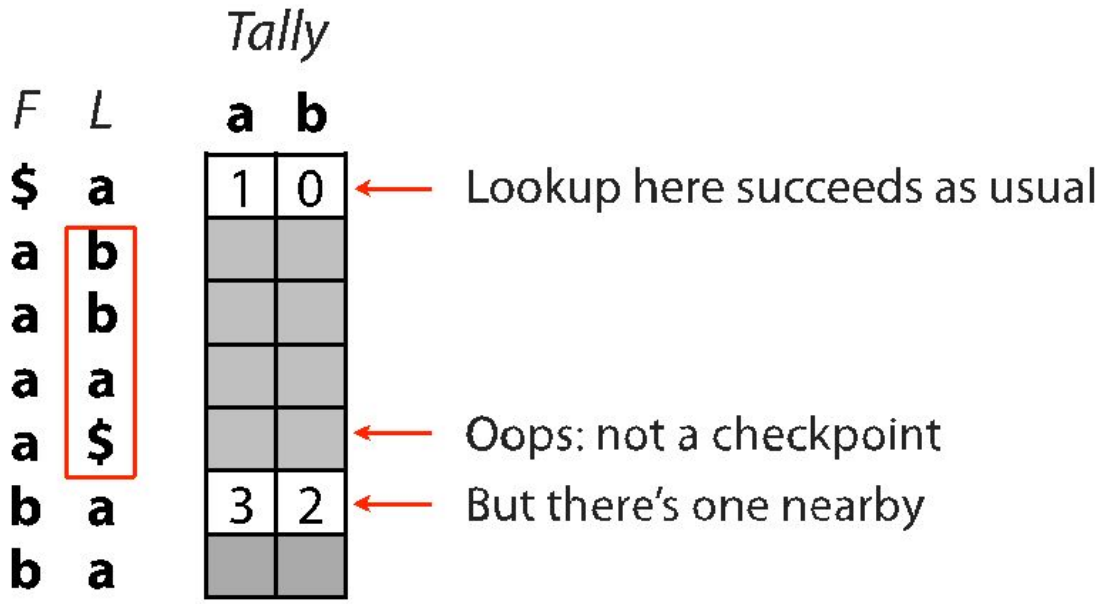


Figure from slide by Ben Langmead

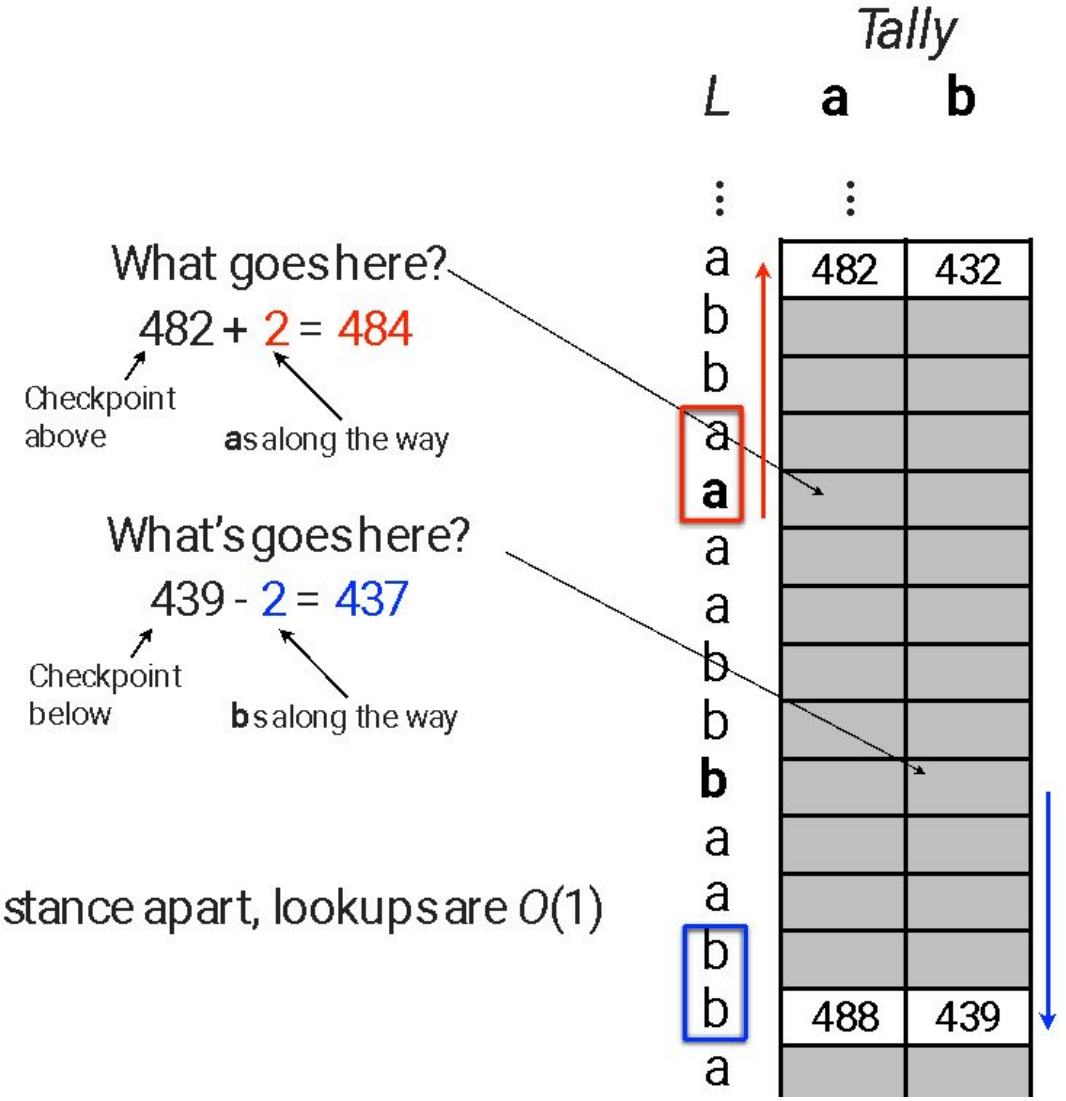
FM Index: fast rank calculations

Next idea: pre-calculate # **a**s, **b**s in *L* up to *some* rows, e.g. every 5th row. Call pre-calculated rows *checkpoints*.



To resolve a lookup for a non-checkpoint row, walk to nearest checkpoint. Use tally at that checkpoint, *adjusted for characters we saw along the way*.

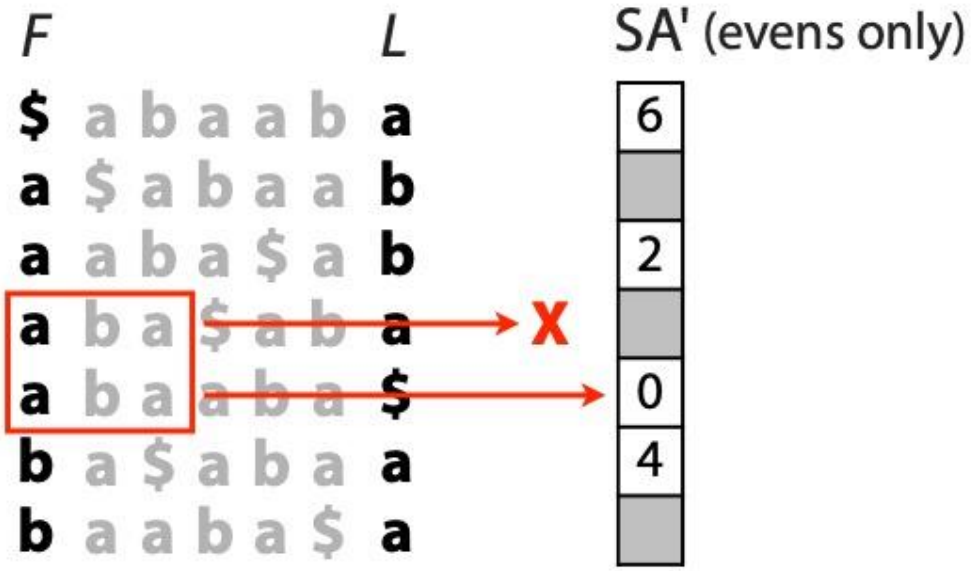
FM Index: fast rank calculations



If checkpoints are $O(1)$ distance apart, lookups are $O(1)$

FM Index: resolving offsets

Idea: store some suffix array elements, but not all



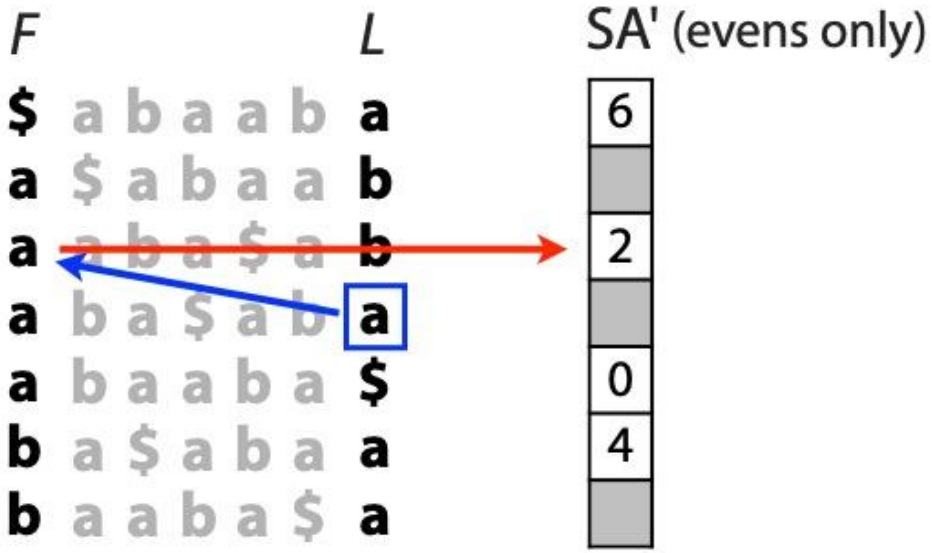
Lookup for row 4 succeeds

Lookup for row 3 fails - SA entry was discarded

FM Index: resolving offsets

LF Mapping tells us that "**a**" at the end of row 3 corresponds to...

... "**a**" at the beginning of row 2



Row 2 of suffix array = 2

Missing value in row 3 = 2 (row 2's SA val) + 1 (# steps to row 2) = **3**

If saved SA values are O(1) positions apart in *T*, resolving offset is O(1) time

FM index

- FM index for human genome can be as small as 1.5 GB
  - With some space-time tradeoff

FM Index

Components of FM Index:

First column (*F*):	$\sim \lvert \Sigma \rvert$ integers
Last column (*L*):	m characters
SA sample:	$m \cdot a$ integers, a is fraction of SA elements kept
Checkpoints:	$m \cdot \lvert \Sigma \rvert \cdot b$ integers, b is fraction of tallies kept

For DNA alphabet (2 bits / nt), T = human genome, $\boldsymbol{a} = 1/32$, $\boldsymbol{b} = 1/128$:

First column (*F*):	16 bytes
Last column (*L*):	2 bits * 3 billion chars = 750 MB
SA sample:	3 billion chars * 4 bytes / 32 = ~ 400 MB
Checkpoints:	3 billion * 4 alphabet chars * 4 bytes / *128* = ~ 400 MB
	Total ≈ 1.5 GB
	~0.5 bytes per input char

(blue indicates what we can adjust by changing *a* & *b*)

https://www.youtube.com/watch?v=kvVGj5V65io&ab_channel=BenLangmead

Short read mapping tools

- Hash based
  - MAQ
  - SOAP
- BWT based
  - Bowtie, Bowtie2
  - SOAP2
  - BWA

References

- Suffix Tree
  - Bioinformatics Algorithms (Part II) - Chapter 9
  - Part I of Algorithms on Strings, Trees and Sequences by Dan Gusfield
- BWT, FM index
  - http://www.cs.jhu.edu/~langmea/resources/bwt_fm.pdf
- Special Thanks to
  - Atif sir, Saifur sir