Lecture 16: Combinatorial Pattern Matching

Study Chapter 9.1 – 9.5

Repeat Finding

- Problem 1: What patterns appear more likely than expected by chance?
  - ATGGTCTAGGTCCTAGTGGTC
- Motivation to find them:
  - Phenotypes arise from copy-number variations
  - Genomic rearrangements are often associated with repeats
  - Functional units depend on genomic patterns
    - *Origin Recognition Complex* (ORC) story

Repeat Finding

- Problem 2: Where are the frequently occurring near matches?
  - ATGGTCTAGGACCTAGTGTTC
- Motivation to find them:
  - Phenotypes arise from copy-number variations
  - Genomic rearrangements are often associated with repeats
  - Functional units depend on genomic patterns
    - *Origin Recognition Complex* (ORC) story

ℓ-mer Repeats

- Long repeats are difficult to find
- Short repeats are easy to find
  - Short repeats are integral to long ones

- Strategy for finding long repeats:

  - Find exact repeats of short subsequences ℓ-mers (ℓ is usually 10 to 13)
  - Extend ℓ-mer repeated seeds into longer, *maximal* repeats
  - Or, consider nearby l-mers frequency and positions to extend to longer patterns

ℓ-mer Repeats (cont'd)

- There are typically many locations where an ℓ-mer is repeated:

GCTTACAGATTCAGTCTTACAGATGGT

- The 4-mer TTAC starts at locations 3 and 17

Extending ℓ-mer Repeats

GCTTACAGATTCAGTCTTACAGATGGT

- Extend these 4-mer matches:

  GCTTACAGATTCAGTCTTACAGATGGT

- Maximal repeat: CTTACAGAT
- Maximal repeats cannot be extended in either direction
- To find maximal repeats in this way, we need ALL start locations of all ℓ-mers in the genome
- **Hashing** lets us find repeats quickly in this manner

Hashing: What is it?

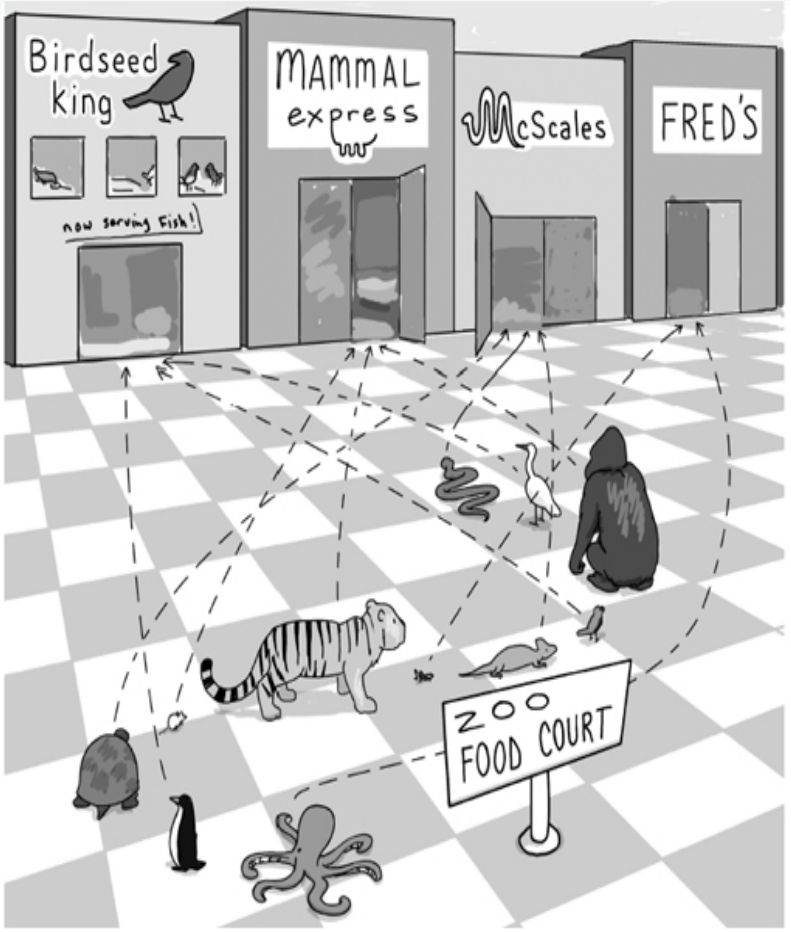
- How hashing works…
  - Generate an integer "key" from an arbitrary record
  - Store record in an data structure indexed by this integer key
- Hashing is a very efficient way to store and retrieve data
  - e.g., Python directories are hashes

Hashing: Definitions

- Hash table: array used in hashing
- Records: data stored in a *hash table*
- Keys: identify sets of *records*
- Hash function: uses a *key* to generate an index to insert at in *hash table*
- Collision: when more than one record is mapped to the same index in the hash table

Hashing: Example

- Where do the animals eat?
- Records: each animal
- Keys: where each animal eats



Records x	Keys $h(x)$
Penguin	1
Octopus	4
Turtle	3
Mouse	2
Snake	3
Heron	1
Tiger	2
Iguana	3
Ape	2
Cricket	4
Sparrow	1

Hashing DNA sequences

- Each ℓ-mer can be translated into a binary string, key = quaternary(seq)
  (**A**, **T**, **C**, **G** can be represented as **0**, **1**, **2**, **3**)
- After assigning a unique integer per ℓ-mer it is easy to store the starting locations of occurance of each ℓ-mer in a genome of length n in $O(l\ n)$ time

Hashing: Maximal Repeats

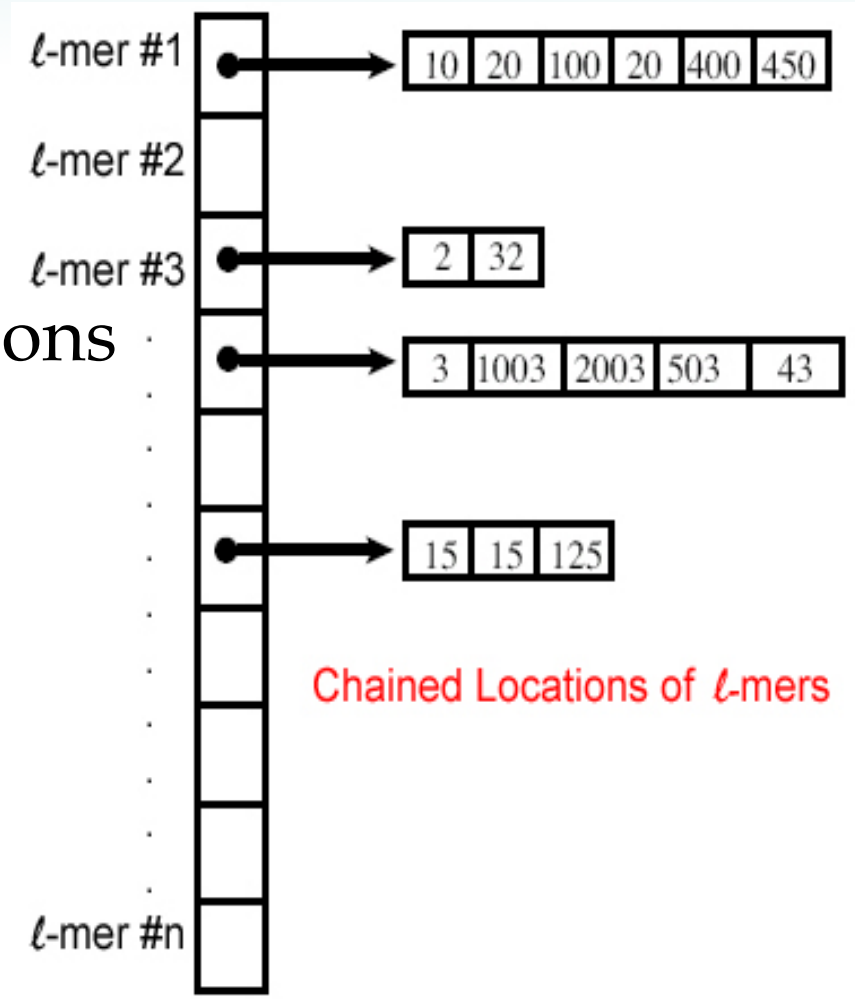
- To find repeats in a genome:
  - For all ℓ-mers in the genome, note its starting position and the sequence
  - Generate a hash table index for each unique ℓ-mer sequence
  - In each index of the hash table, store all genome start locations of the ℓ-mer which generated that index
  - Extend ℓ-mer repeats to maximal repeats
- Problem as l gets big the number of possible patterns becomes larger than the genome's length ($4^l >> n$)

Hashing: Collisions

- Generate hash keys from a reduced space

  Ex. Key = quaternary(seq) % (N/l)

- Leads to possible collisions
- Dealing with collisions:
  - "Chain" tuples of (l-mer, start location) pairs in a linked list



Hashing: Summary

- When finding genomic repeats from ℓ-mers:
  - Generate a hash table index for each ℓ-mer sequence
  - In each index, store all genome start locations of the ℓ-mer which generated that index
  - Extend ℓ-mer repeats to maximal repeats

Pattern Matching

- What if, instead of finding repeats in a genome, we want to find all positions of a particular sequences in given sequence?

- This leads us to a different problem, the ***Pattern Matching Problem***

Pattern Matching Problem

- Goal: *Find all occurrences of a pattern in a text*
- Input: Pattern $\boldsymbol{p} = p_1 \ldots p_n$ and text $\boldsymbol{t} = t_1 \ldots t_m$
- Output: All positions $1 \leq i \leq (m - n + 1)$ such that the n-letter substring of $\boldsymbol{t}$ starting at i matches $\boldsymbol{p}$
- **Motivation**: Searching database for a known pattern

Exact Pattern Matching: A Brute-Force Algorithm

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

1 $n \leftarrow$ length of pattern **p**

2 $m \leftarrow$ length of text **t**

3 for $i \leftarrow 1$ to $(m - n + 1)$

4 if $\boldsymbol{t}_i \ldots \boldsymbol{t}_{i+n-1} = \mathbf{p}$

5 output i

Exact Pattern Matching: An Example

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

GCAT
CGCATC

GCAT
CGCATC

GCAT
CGCATC

GCAT
CGCATC

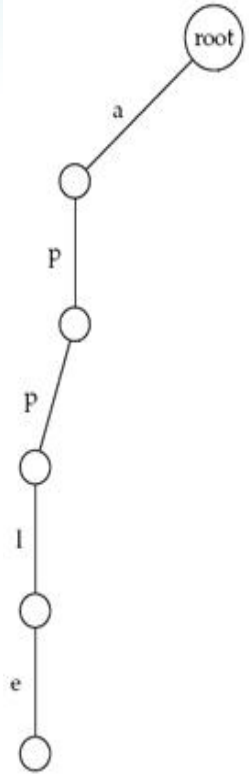
GCAT
CGCATC

Exact Pattern Matching: Running Time

- *PatternMatching* runtime: O(*nm*)
- Probability-wise, it's more like O(*m*)
  - Rarely will there be close to *n* comparisons in line 4
- Worse case:
  Find "AAAAT" in "AAAAAAAAAAAAAAAAT"
- Better solution: suffix trees
  - Can solve problem in O(*m*) time
  - Conceptually related to keyword trees

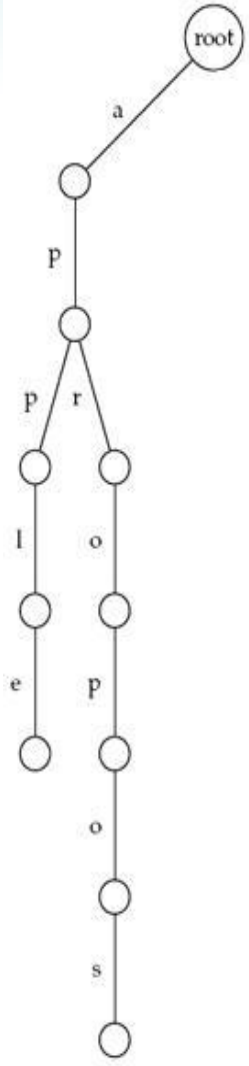
Keyword Trees: Example

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



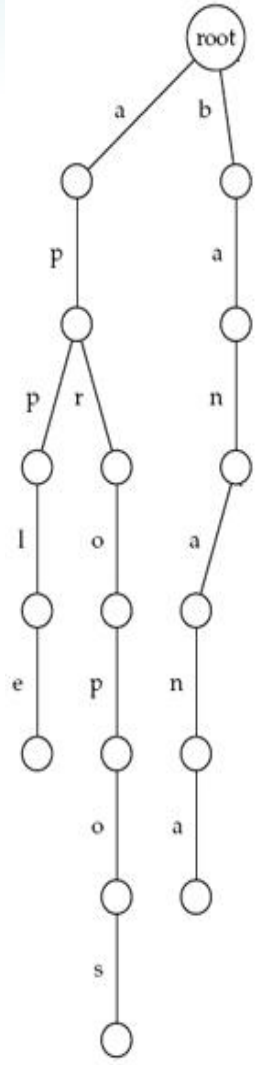
Keyword Trees: Example (cont'd)

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



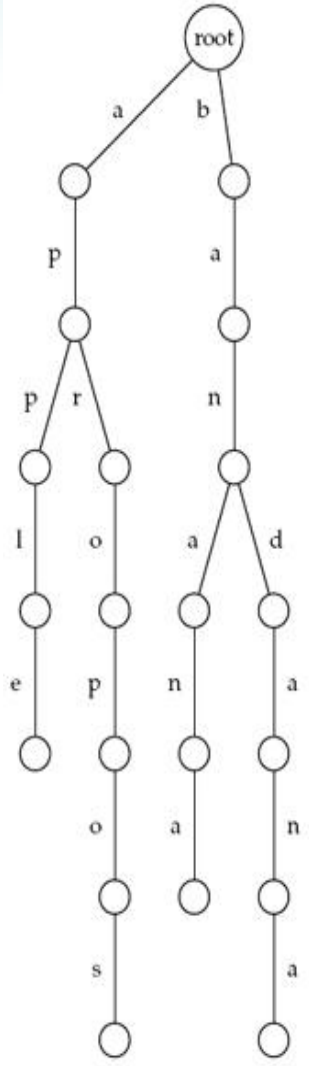
Keyword Trees: Example (cont'd)

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



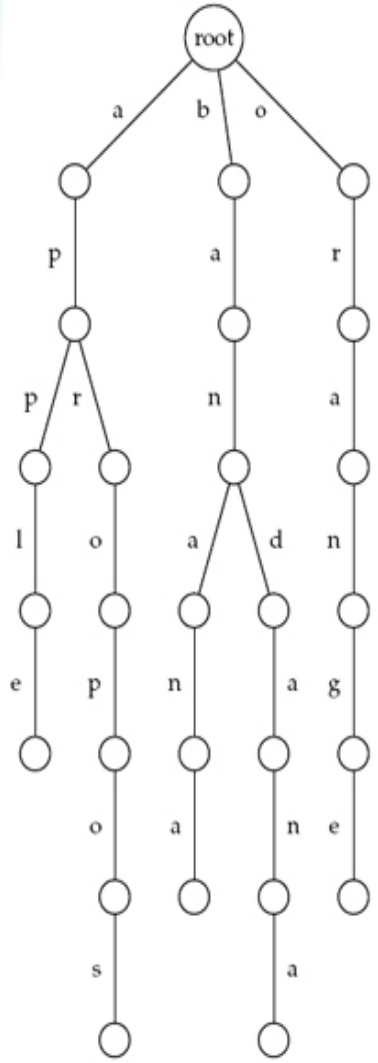
Keyword Trees: Example (cont'd)

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



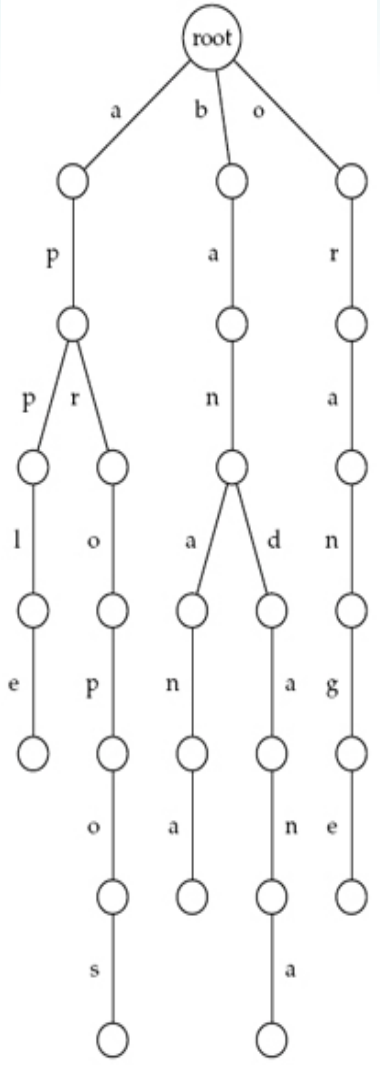
Keyword Trees: Example (cont'd)

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



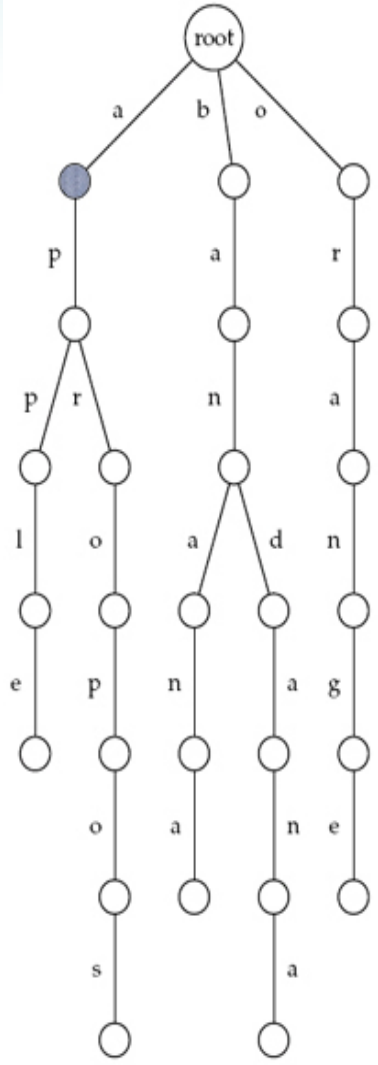
Keyword Trees: Properties

- 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
- Searches are performed by "threading" the target pattern through the tree



Keyword Trees: Threading (cont'd)

- Thread "appeal"
  - appeal



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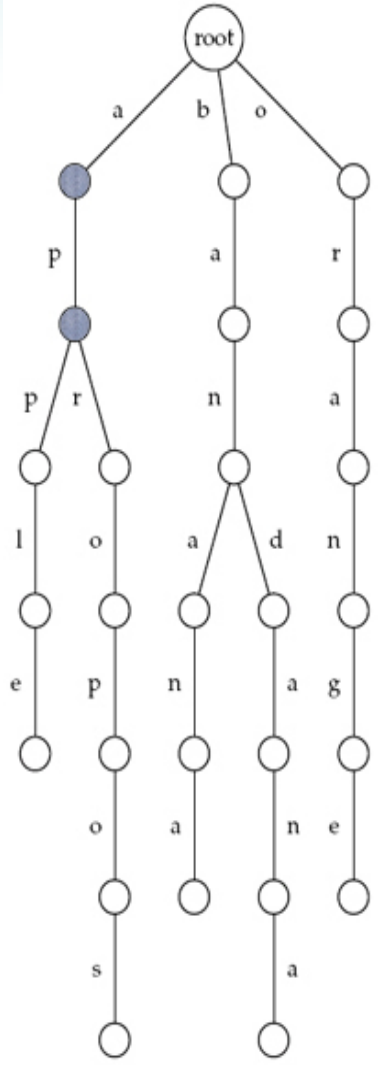

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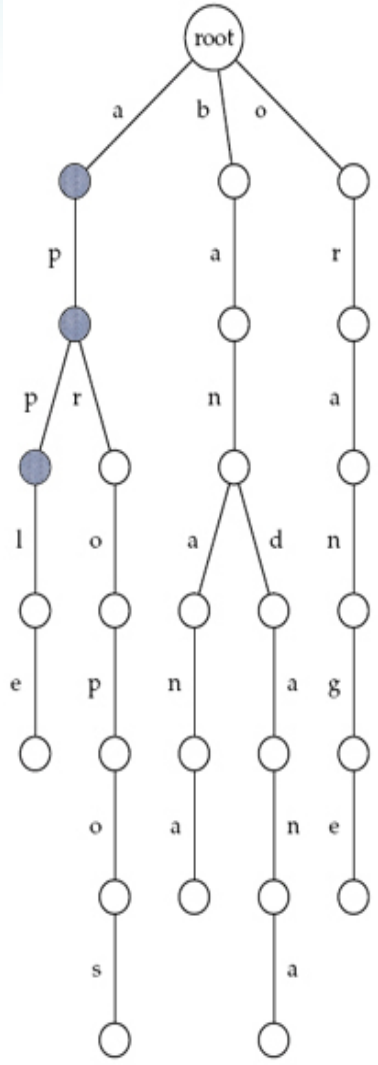

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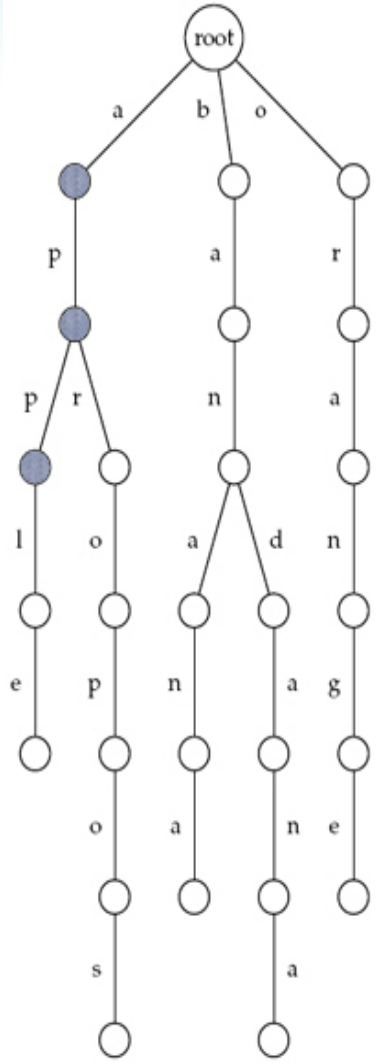
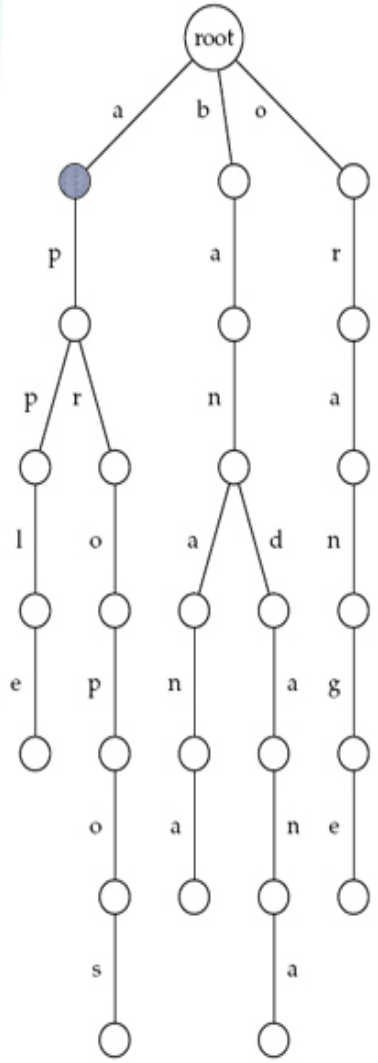


Keyword Trees: Threading (cont'd)

- Thread "apple"
  - apple



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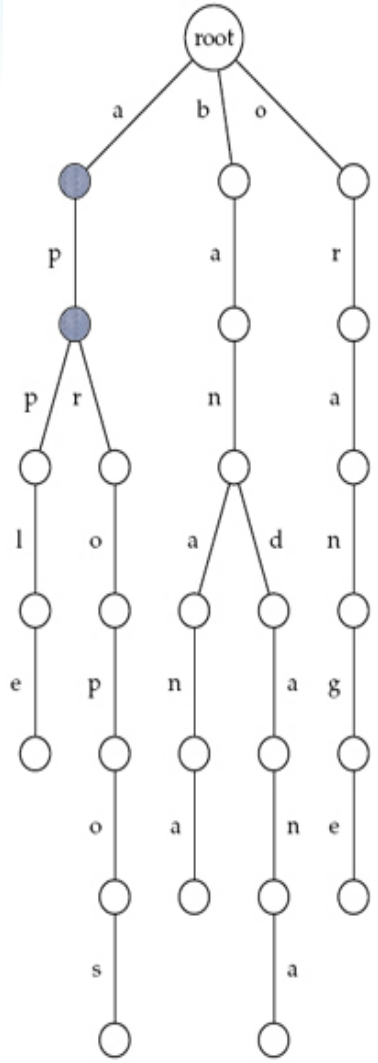

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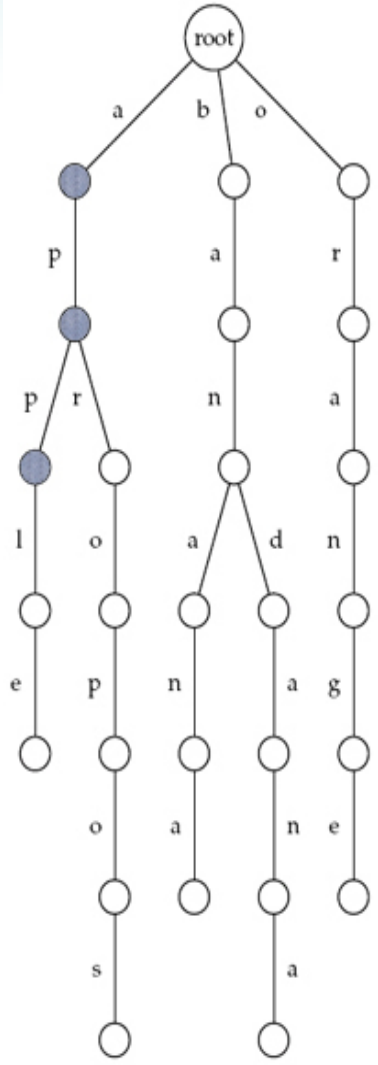

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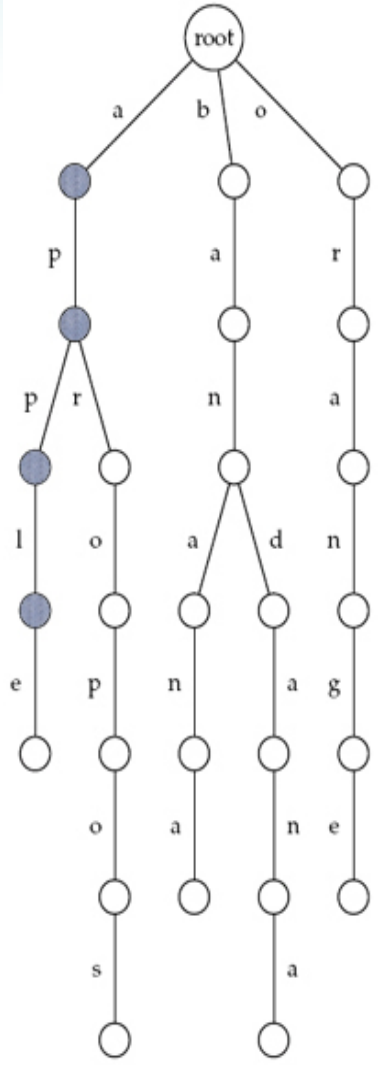
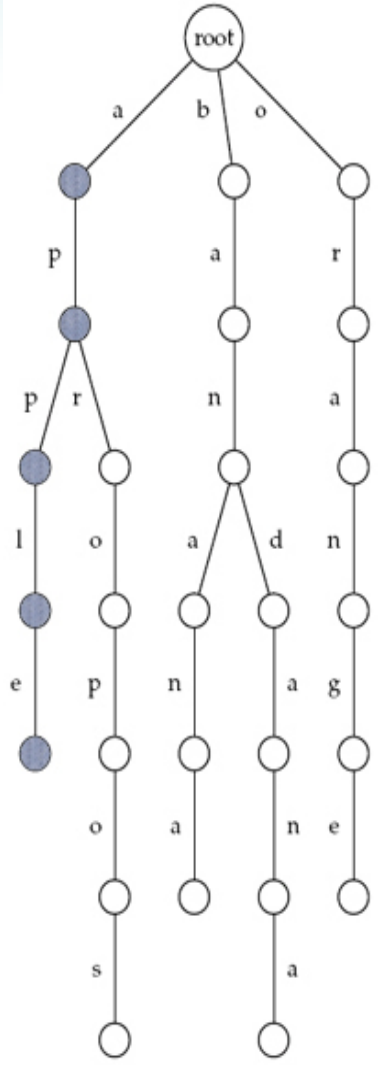


Keyword Trees: Threading (cont'd)

- Thread "apple"
  - apple

Now thread "band", "or", and the nonsense word "apro"

How do you tell "real" words from nonsense? (i.e. include "band", "apples", and "or", but not "appl" and "banan")



Multiple Pattern Matching Problem

- Goal: *Given a set of patterns and a text, find all occurrences of any of patterns in text*

- Input: k patterns $\mathbf{p}^1,\ldots,\mathbf{p}^k$, and text $\mathbf{t} = t_1 \ldots t_m$

- Output: Positions $1 \leq i \leq m$ where substring of **t** starting at i matches $\mathbf{p}_j$ for $1 \leq j \leq k$

- **Motivation**: Searching database for known multiple patterns

Multiple Pattern Matching: Straightforward Approach

- Can solve as *k* "Pattern Matching Problems"
  - Runtime:

    O(kmn)

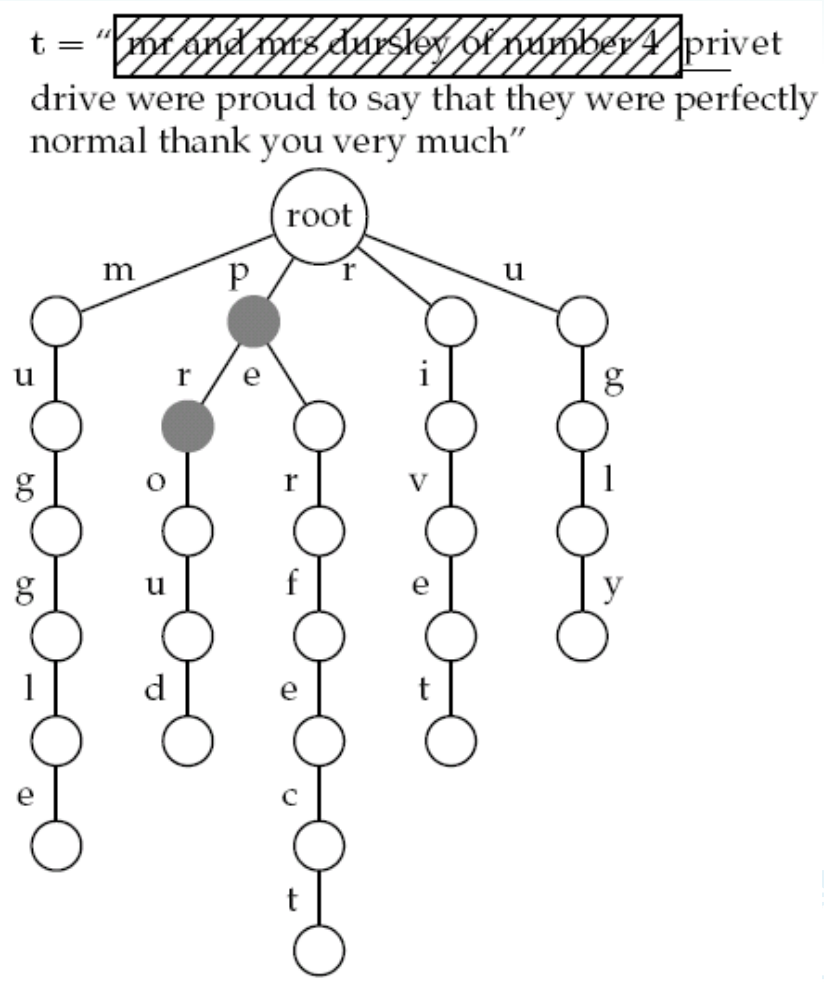
    using the *PatternMatching* algorithm *k* times
  - *m* - length of the text
  - *n* - average length of the pattern

Multiple Pattern Matching: Keyword Tree Approach

- Or, we could use keyword trees:
  - Build keyword tree in O(N) time; N is total length of all patterns
  - With naive threading: O($N + nm$)
  - Aho-Corasick algorithm: O($N + m$)

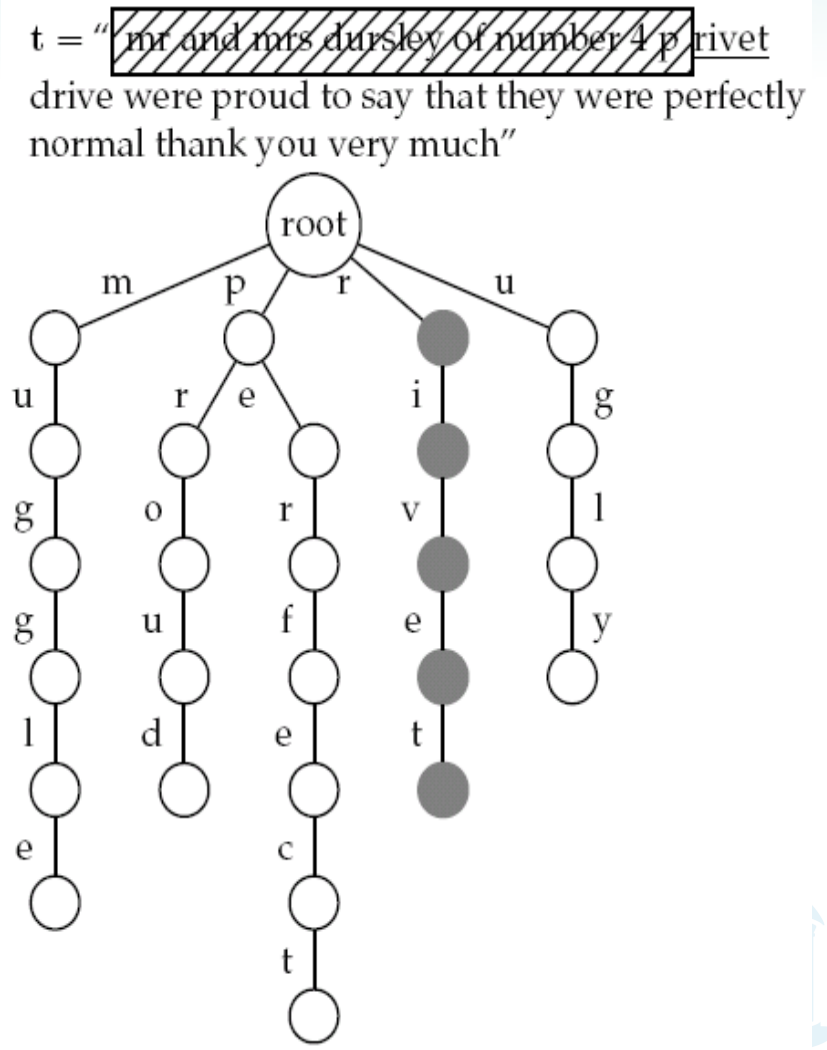
Keyword Trees: Threading

- To match patterns in a text using a keyword tree:
  - Build keyword tree of patterns
  - "Thread" the text through the keyword tree



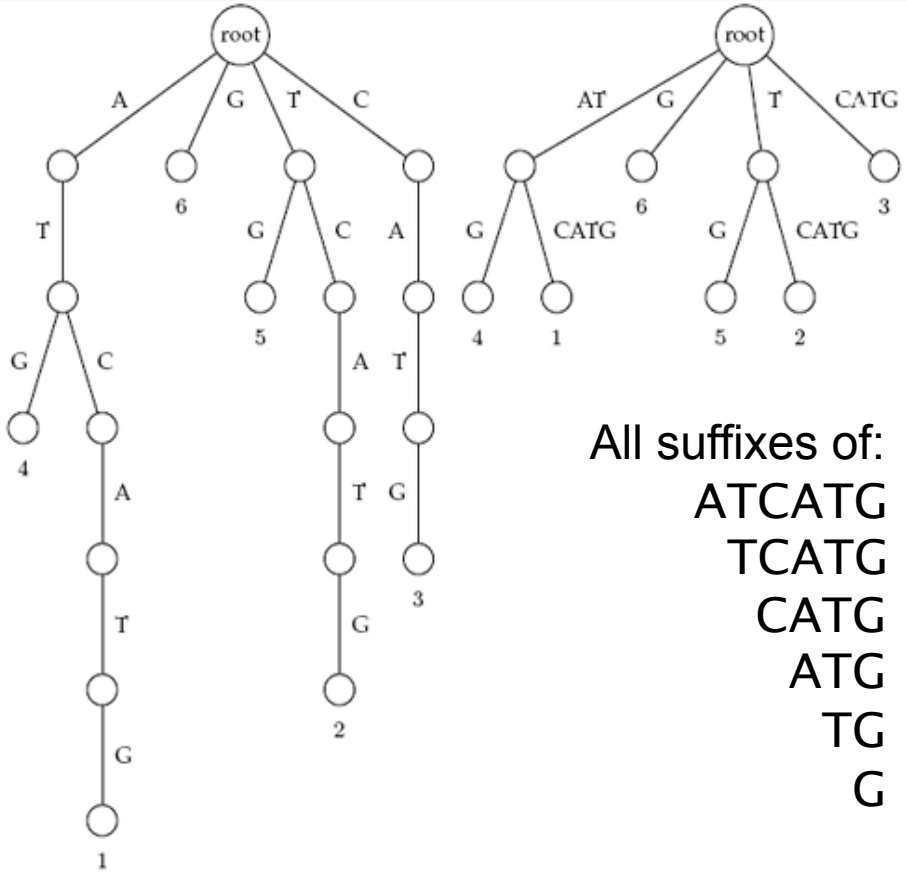
Keyword Trees: Threading

- Threading is "complete" when we reach a leaf in the keyword tree
- When threading is "complete," we've found a pattern in the text



Suffix Trees=Collapsed Keyword Trees

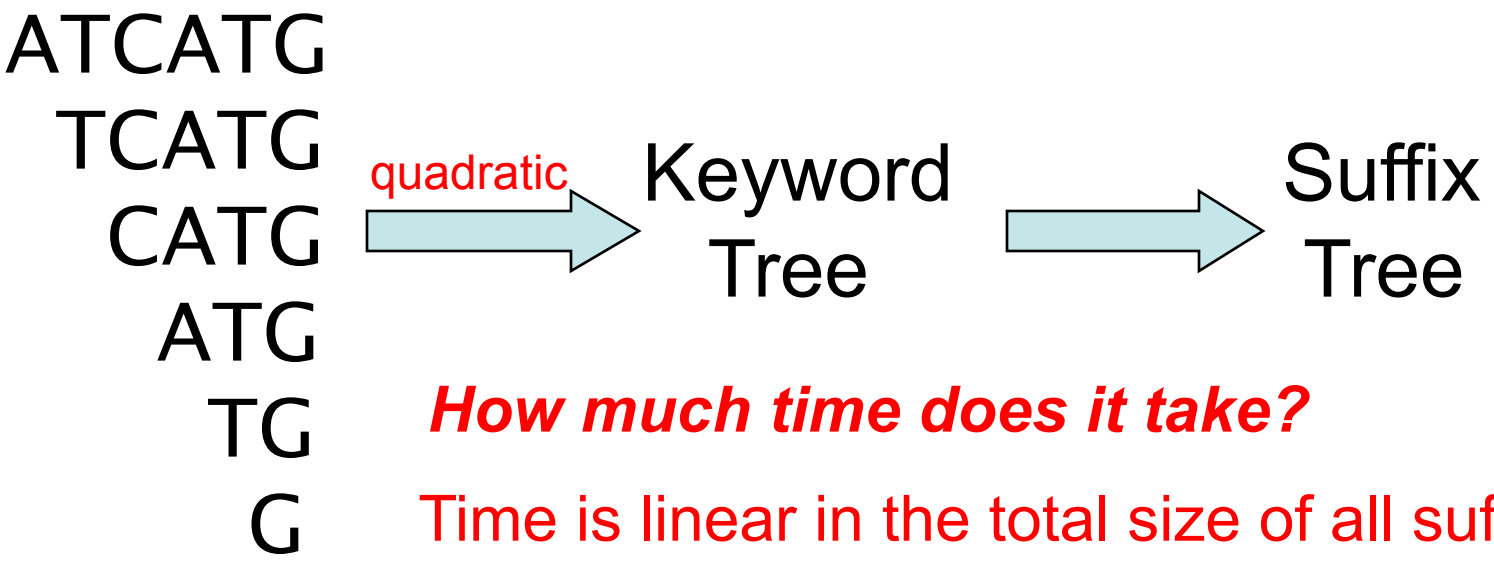
- All suffixes of a given sequence
- Similar to keyword trees, except vertices of out-degree 1 are removed and the "edge" strings on either side are merged
  - Each edge is labeled with a *substring* of a text
  - All internal vertices have at least three edges
  - Terminal vertices, leaves, are labeled by the index of the pattern.



All suffixes of:
ATCATG
TCATG
CATG
ATG
TG
G

Suffix Tree of a Text

- Construct a keyword tree from all suffixes of a text
- Collapse non-branching paths into an edge (path compression)

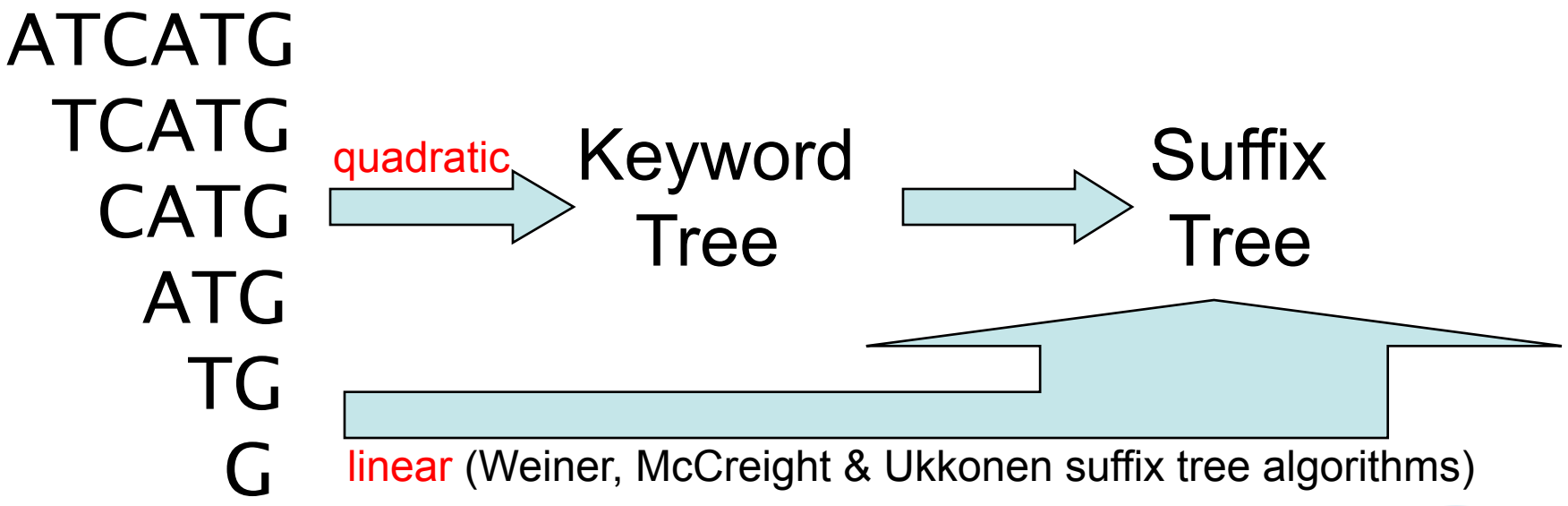


How much time does it take?

Time is linear in the total size of all suffixes, which is quadratic in the length of the text

Suffix Trees: Advantages

- With careful bookkeeping a test's suffix tree can be constructed in a single pass of the text
- Thus, suffix trees can be built faster than keyword trees of suffixes and transforming them

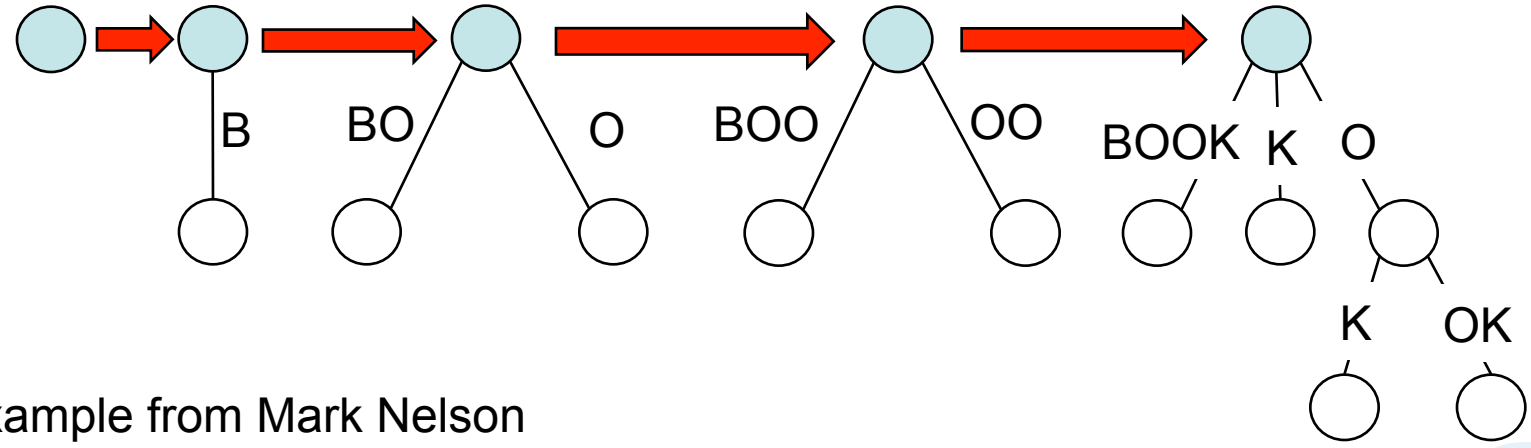


Suffix Tree Construction

- Few books, including ours, delve into the details of suffix tree construction algorithms due to its reputation for being overly complicated.
- Weiner's and McCreight's original linear algorithms for constructing a suffix trees had some disadvantages.
- Principle among them was the requirement that the tree be built in reverse order, meaning that the tree was grown incrementally by adding characters from the end of the input.
- This ruled it out for on-line processing

Ukkonen's Clever Bookkeeping

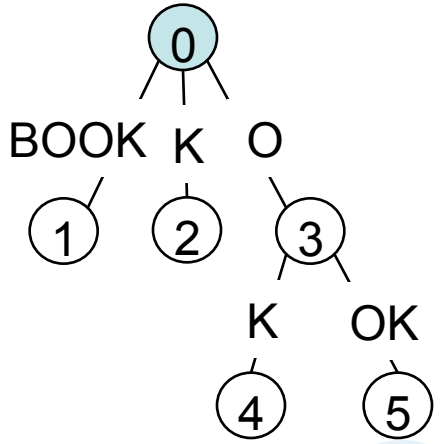
- Esko Ukkonen's construction works from left to right.
- It's incremental. Each step transforms the Suffix Tree of the prefix ending at the i^{th} character to the Suffix Tree ending at the $i+1^{th}$.



Example from Mark Nelson
Dr. Dobb's Journal, August, 1996

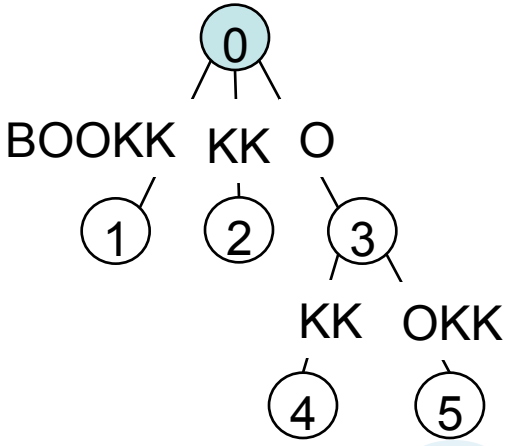
Tree Properties

- Extensions are done by threading each new prefix through the tree and visiting each of the suffixes of the current tree.
- At each step we start at the longest suffix (BOOK), and work our way down to the shortest (empty string)
- Each ends at a node of three types:
  - A leaf node (1,2,4,5)
  - An explicit node (0, 3)
  - An implicit node (Between characters of a substring labeling an edge, such as BO, BOO, and OO).



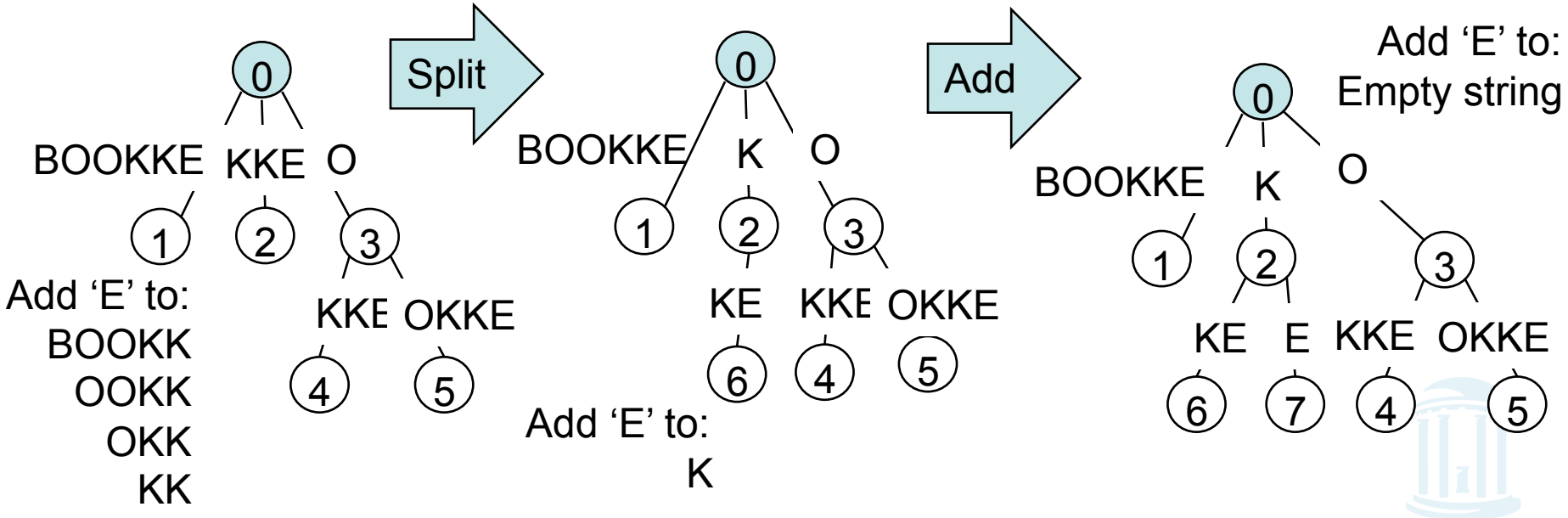
Observations

- There are 5 suffixes in the tree (including the empty string) after adding BOOK
- They are represented by the root and 4 leaves
- Adding the next letter, another 'K', requires visiting each of the suffixes in the existing tree, in order of decreasing length, and adding letter 'K' to its end.
- Adding a character to a leaf node never creates a new explicit node, regardless of the letter
- If the root already has an edge labeled 'K' we just extend it



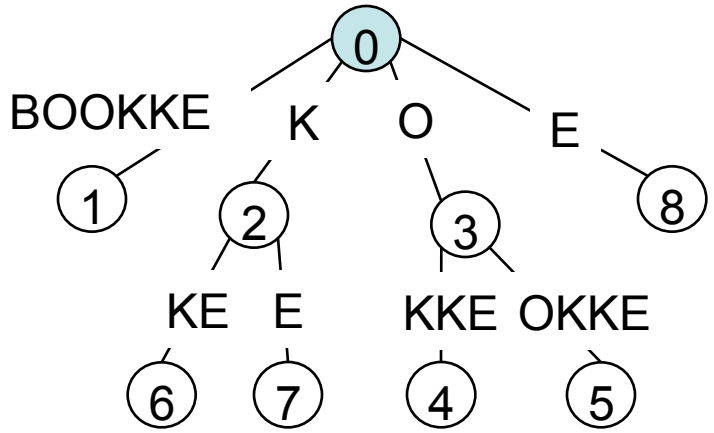
Split and Add Update

- The next step is to add an 'E' to our tree
- As before, add 'E' to each suffix in order of decreasing lengths BOOKK, OOKK, OKK, KK, K
- The first suffix that does not terminate at a leaf is called the "active point" of the suffix tree



Updating an Explicit Node

- After updating suffix K, we still have to update the next shorter suffix, which is the empty string.

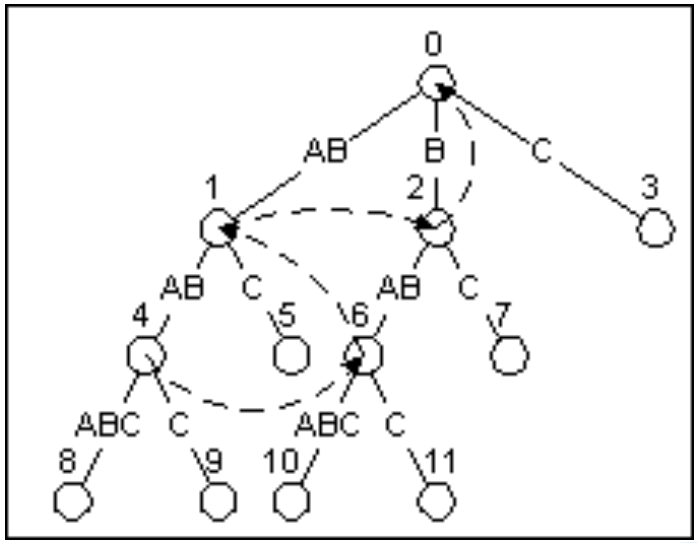


Generalizing

- Once a leaf node, always a leaf node
- Additional characters only extends the edge leading to the leaf (leaves are easy)
- When adding a new leaf, its edge will represent all characters from the i^{th} suffix's starting point to the $i+1^{st}$ text's end. Because of this once a leaf is created, we can just forget about it. If the edge is later split, its start may change but it will extend to the end.
- This means that we only need to keep track of the active point in each tree, and update from there.

One Last Detail

- The algorithm sketch so far glosses over one detail. At each step of an update we need to keep track of the next smaller suffix from the i^{th} update
- To do this a suffix pointer is kept at each internal node
- For Pseudo code
  - Mark Nelson, "Fast String Searching with Suffix Trees" Dr. Dobb's Journal August, 1996
- For proofs of linear space/time performance
  - E. Ukkonen. "On-line construction of suffix trees. Algorithmica, 14(3):249-260, September 1995.



The suffix tree for ABABABC with suffix pointers shown as dashed lines

Use of Suffix Trees

- Suffix trees hold all suffixes of a text, T
  - i.e., ATCGC: ATCGC, TCGC, CGC, GC, C
  - Builds in O(m) time for text of length m
- To find any pattern $\boldsymbol{P}$ in a text:
  - Build suffix tree for text, O(m), $m = |T|$
  - Thread the pattern through the suffix tree
  - Can find pattern in O(n) time! ($n = |P|$)
- O($|\boldsymbol{T}| + |\boldsymbol{P}|$) time for "Pattern Matching Problem" (better than Naïve O($|\boldsymbol{P}|\,|\boldsymbol{T}|$)
  - Build suffix tree and lookup pattern
- Multiple Pattern Matching in O($|\boldsymbol{T}| + k|\boldsymbol{P}|$)

Pattern Matching with Suffix Trees

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

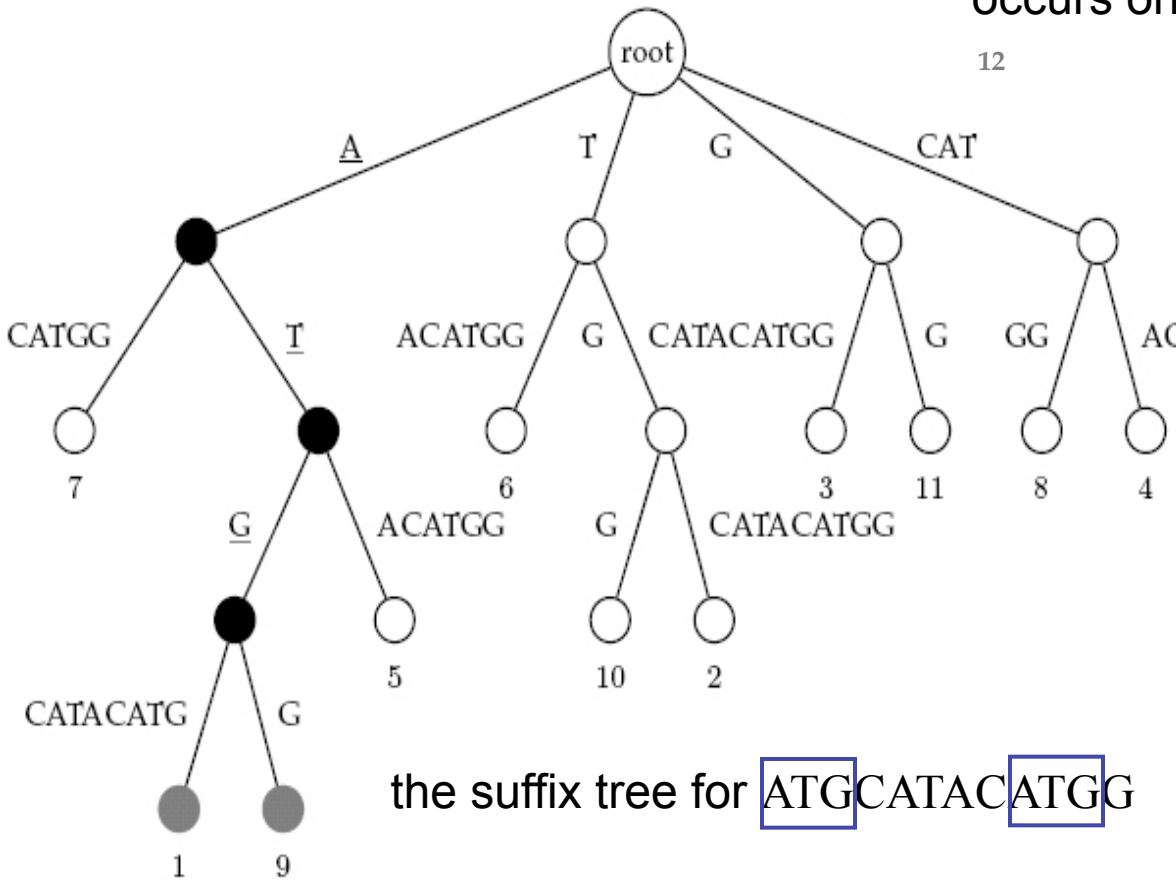
1 Build **suffix tree** for text **t**
2 Thread pattern **p** through **suffix tree**
3 **if** threading is complete
4 traverse all paths from the threading's endpoint to leaves and **output** their positions
5 **else**
6 **output** "Pattern does not appear in text"

Suffix Trees: Example

Threading the pattern ATG

What letter occurs most frequently?
What is the shortest pattern that occurs only once in the string?

12



the suffix tree for ATGCATACATGG

ATGCATACATGG 1
TGCATACATGG 2
GCATACATGG 3
CATACATGG 4
ATACATGG 5
TACATGG 6
ACATGG 7
CATGG 8
ATGG 9
TGG 10
GG 11
G 12

Multiple Pattern Matching: Summary

- Keyword and suffix trees are useful data structures supporting various pattern finding problems
- ***Keyword trees***:
  - Build keyword tree of patterns, and ***thread text*** through it
- ***Suffix trees***:
  - Build suffix tree of text, and ***thread patterns*** through it

Suffix Trees: Theory vs. Practice

- In concept, suffix trees are extremely powerful for making a variety of queries concerning a sequence
  - What is the shortest unique substring?
  - How many times does a given string appear in a text?
- Despite the existence of linear-time construction algorithms, and O(m) search times, suffix trees are still rarely used for genome scale searching
  - Large storage overhead
- Close cousins of the Suffix-Tree (Suffix Arrays and Burrows-Wheeler Transforms) are more common
- Next lecture