Index-Assisted Approximate Matching

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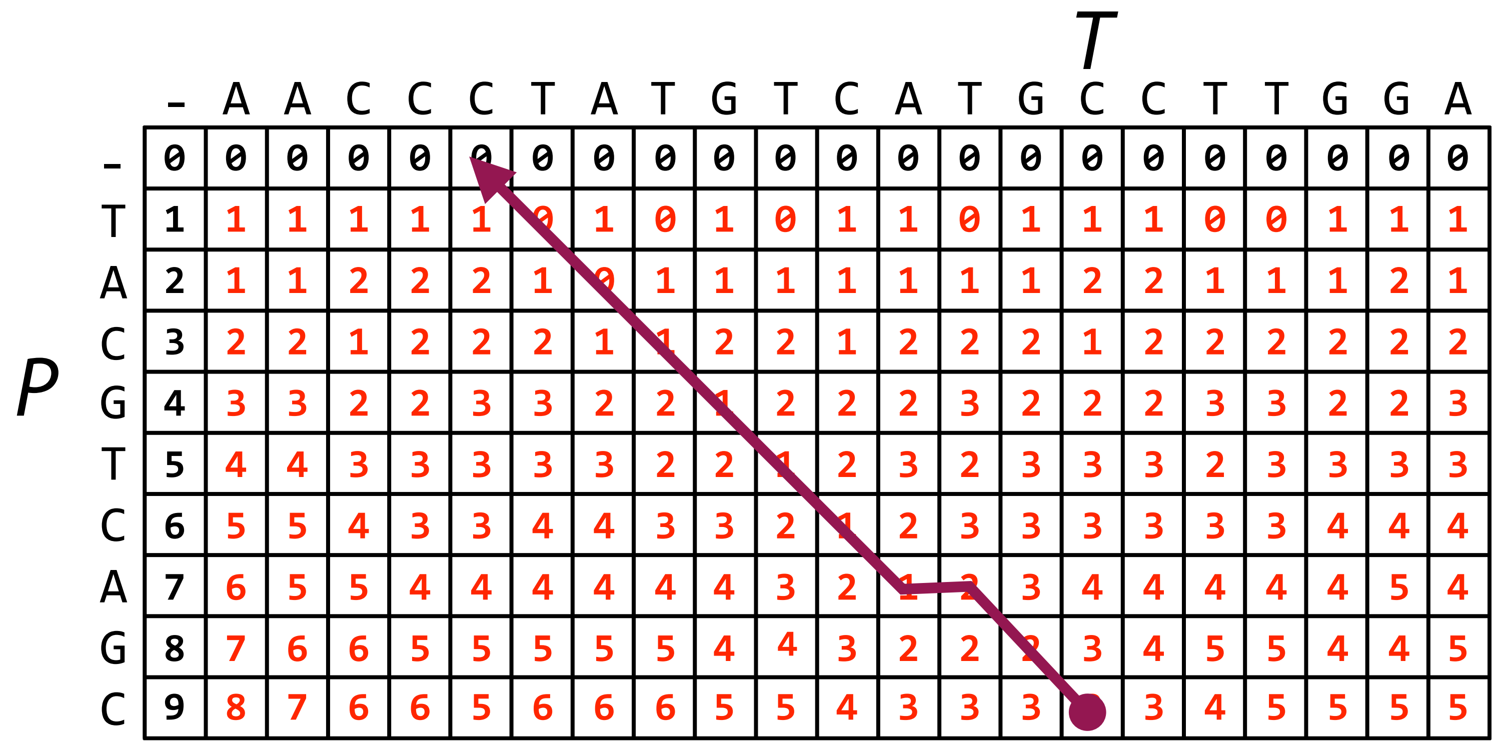
Dynamic programming summary

A powerful set of tools:

- DP deals naturally with both mismatches and gaps
- DP scoring can take into account variation, sequencing error, etc

Along the way we saw an algorithm we might use for read alignment:



	-	A	A	C	C	C	T	A	T	G	T	C	A	T	G	C	C	T	T	G	G	A
-	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
T	1	1	1	1	1	1	0	1	0	1	0	1	1	0	1	1	1	0	0	1	1	1
A	2	1	1	2	2	2	1	0	1	1	1	1	1	1	1	2	2	1	1	1	2	1
C	3	2	2	1	2	2	2	1	1	2	2	1	2	2	2	1	2	2	2	2	2	2
G	4	3	3	2	2	3	3	2	2	1	2	2	2	3	2	2	2	3	3	2	2	3
T	5	4	4	3	3	3	3	3	2	2	1	2	3	2	3	3	3	2	3	3	3	3
C	6	5	5	4	3	3	4	4	3	3	2	1	2	3	3	3	3	3	3	4	4	4
A	7	6	5	5	4	4	4	4	4	4	3	2	1	2	3	4	4	4	4	4	5	4
G	8	7	6	6	5	5	5	5	5	4	4	3	2	2	2	3	4	5	5	4	4	5
C	9	8	7	6	6	5	6	6	6	5	5	4	3	3	3	2	3	4	5	5	5	5

Finding approximate occurrences of *P* in *T*

...but no faster than $O(mn)$ and m is big!!!

A de-motivating example

$$\left.\begin{array}{l} \mathbf{d} = 6 \times 10^9 \text{ reads} \\ \mathbf{n} = 100 \text{ nt} \end{array}\right\} \approx 1 \text{ week-long run of}$$

$\mathbf{m} = 3 \times 10^9$ nt $\approx$ human

Illumina HiSeq 2000

Say we have 1,000 processors, each clocked at 3 GHz, each capable of completing 8 dynamic programming cell updates per clock cycle

(We're being optimistic)

Total of $\mathbf{d} \times \mathbf{m} \times \mathbf{n} = 2 \times 10^{21}$ cell updates

Takes > 2 years

A de-motivating example

$$\left.\begin{array}{l}\mathbf{d} = 6 \times 10^9 \text{ reads} \\ \mathbf{n} = 100 \text{ nt}\end{array}\right\} \approx 1 \text{ week-long run of}$$

$\mathbf{m} = 3 \times 10^9$ nt $\approx$ human

Illumina HiSeq 2000

Problem: our dynamic programming approach is $O(dmn)$

We'll now consider two ideas for how to maintain the power of dynamic programming while diminishing effect of *m*

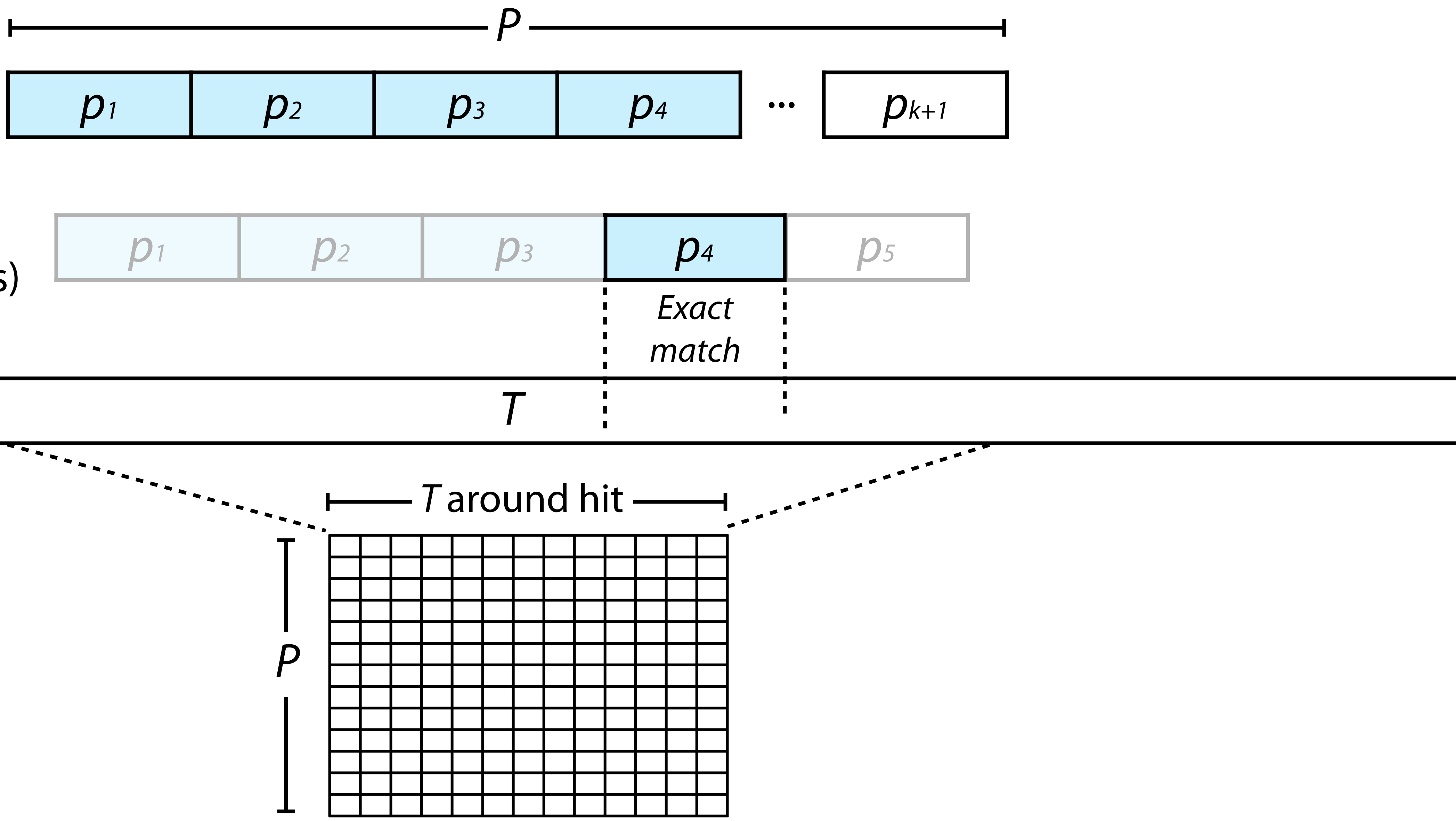
Index-assisted approximate matching

Idea 1: Use index for exact-matching subproblems, follow up with DP

Partition P, like for pigeonhole

Index finds exact partition matches (hits)

Use DP in vicinity of exact matches



Index-assisted approximate matching

Index-assisted function for finding occurrences of *P* in *T* with up to *k* edits:

```python
def queryIndexEdit(p, t, k, index):
    ''' Look for occurrences of p in t with up to k edits using an
        index combined with dynamic-programming alignment. '''
    l = index.ln
    occurrences = []
    seen = set()     # for avoiding reporting same hit twice
    for part, poff in partition(p, k+1):
        for hit in index.occurrences(part): # query index w/ partition
            # left edge of T to include in DP matrix
            lf = max(0, hit - poff - k)
            # right edge of T to include in DP matrix
            rt = min(len(t), hit - poff + len(p) + k)
            mn, off, xcript = kEditDp(p, t[lf:rt])
            off += lf
            if mn <= k and (mn, off) not in seen:
                occurrences.append((mn, off, xcript))
                seen.add((mn, off))
    return occurrences
```

Partition P

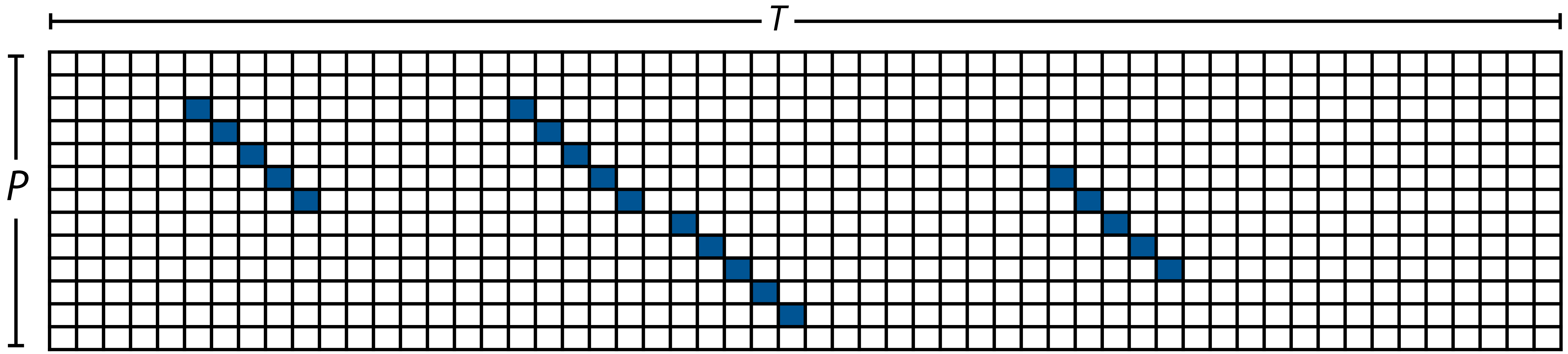
Query index

Dynamic programming

Python example: http://bit.ly/CG_kEdit_idx

Index-assisted approximate matching

Think in terms of the full *P*-to-*T* dynamic programming matrix



Index is identifying diagonal stretches of matches

These are likely to be part of a high-scoring alignment

Many stretches within a few diagonals of each other are even more likely to be part of a high-scoring alignment

Neighborhood search

Idea 2: Use index to find exact occurrences of strings in *P*'s *neighborhood*

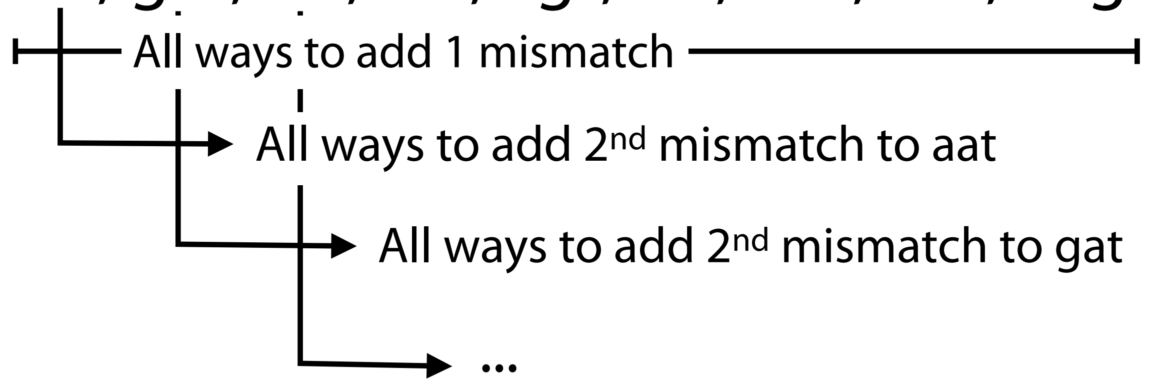
Neighborhood = set of strings within some Hamming / edit distance

The 1-edit neighborhood of cat, using DNA alphabet:

$$\text{cat}, \underbrace{\text{aat, gat, tat, cct, cgt, ctt, caa, cac, cag}}_{\text{All ways to add 1 mismatch}}, \underbrace{\text{ca, ct, at}}_{\text{All ways to delete 1 char}}, \underbrace{\text{acat, ccat, gcat, tcat, ...}}_{\text{All ways to insert 1 char}} \ldots$$

The 2-mismatch neighborhood of cat:

cat, aat, gat, tat, cct, cgt, ctt, caa, cac, cag


All ways to add 1 mismatch
All ways to add 2nd mismatch to aat
All ways to add 2nd mismatch to gat
...

Neighborhood search

Idea 2: Use index to find occurrences of strings in *P*'s "neighborhood"

Is the neighborhood huge? Can we bound it?

If | *P* | = *n*, and | *∑* | = *a*, how many strings are within Hamming distance 1?

$$\underset{P\text{ itself}}{1} + \underbrace{n(a - 1)}_{a\text{ - 1 ways to replace each of }P\text{'s }n\text{ chars}}$$

How many strings are within edit distance 1?

$$1 + n(a - 1) + \underset{\text{Delete each char in }P\text{ *}}{n} + \underbrace{(n + 1)a}_{\substack{n\text{ + 1 positions where we can} \\ \text{insert any of the }a\text{ characters *}}}$$

In both cases, *O*(*an*) strings in the neighborhood

* Some insertions are equivalent. E.g. there are two equivalent insertions of 'a' into 'cat'. Likewise deletions ('caat').

Neighborhood search

How about within Hamming or edit distance 2?

$O(an)$ strings within Hamming or edit distance 1, each with $O(an)$ neighbors within distance 1, so $O(a^2n^2)$

Within distance k?

$O(a^kn^k)$

How much work to query suffix tree with all strings within distance k?

O(n + # occurrences) for each of the $O(a^kn^k)$ strings, so roughly $O(a^kn^{k+1})$

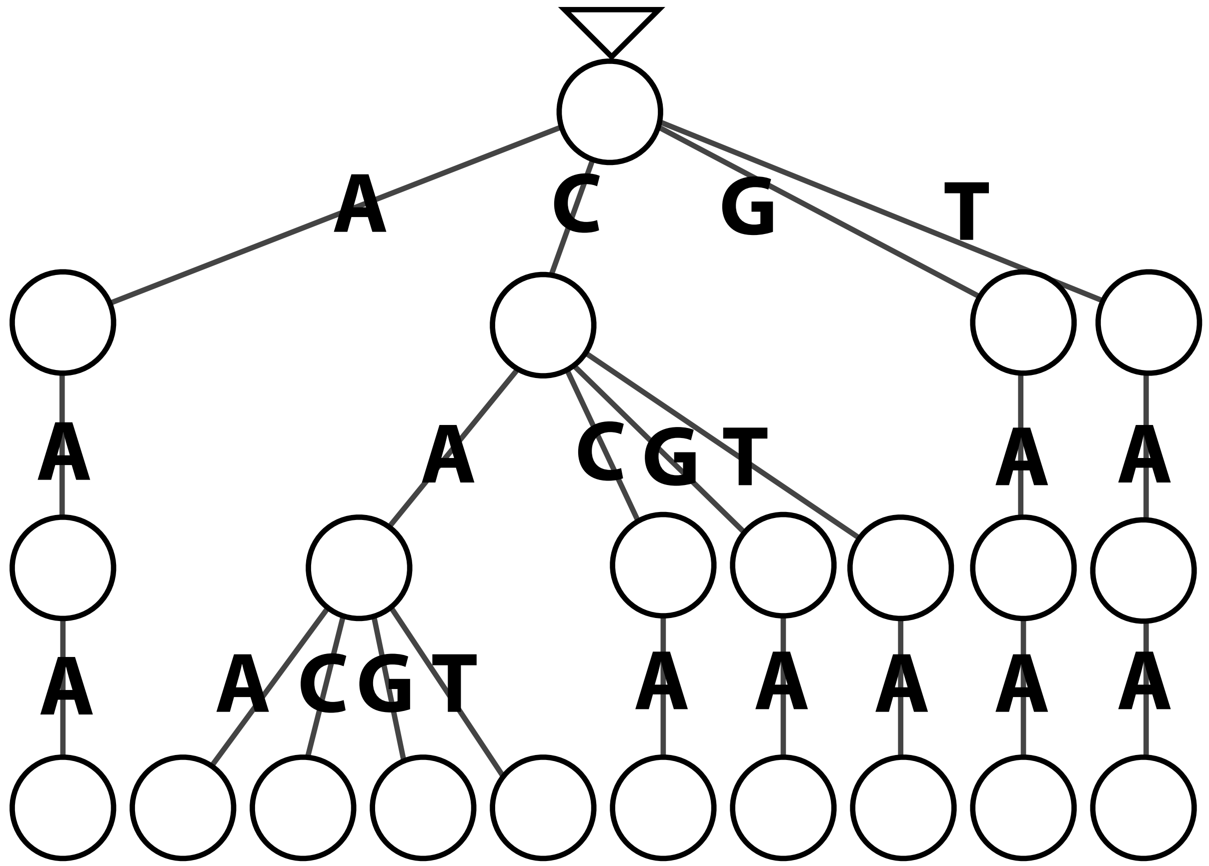
Compare to $O(a^kn^{k+1})$ to $O(mn)$ for full dynamic programming

Good: no m Bad: exponential in k

Neighborhood search

Organize neighborhood of *P* into a trie

Neighbors of P = CAA, within hamming distance 1:

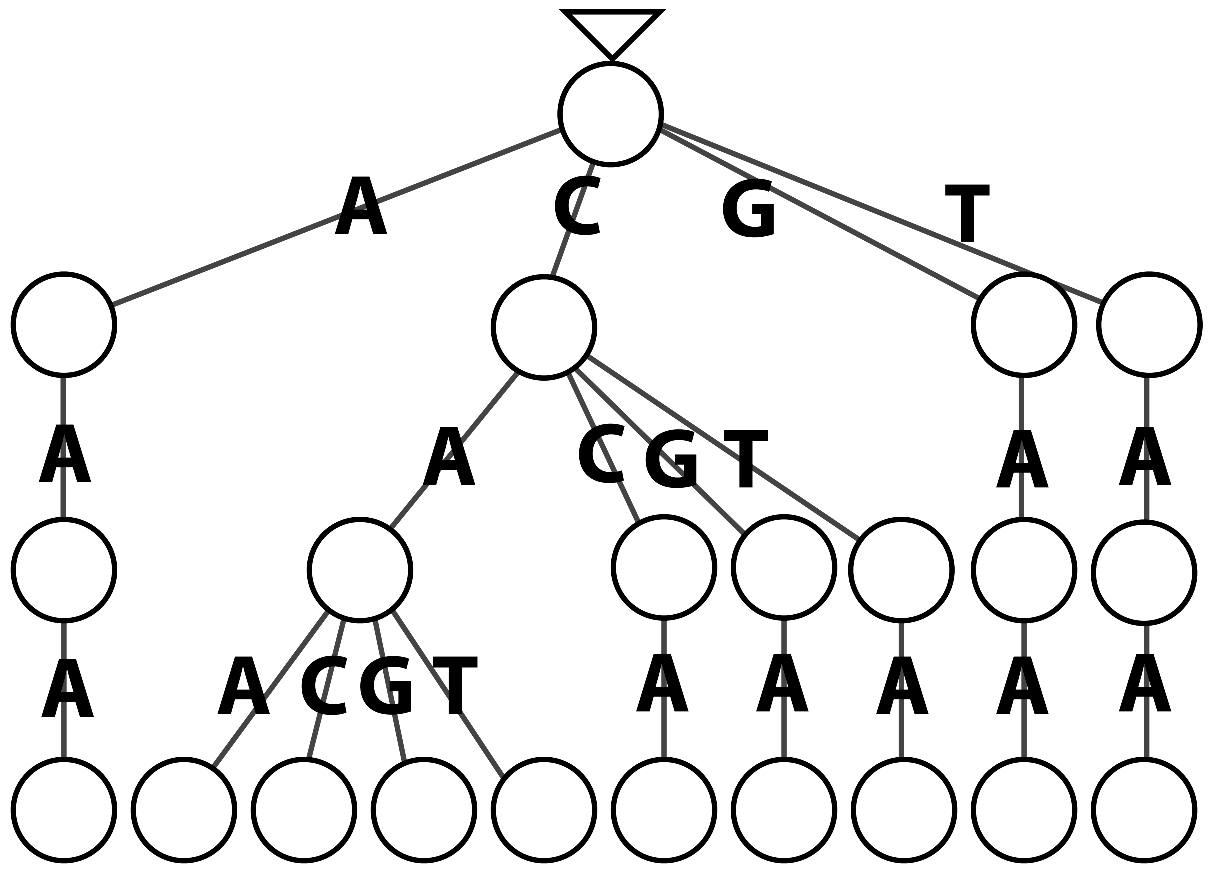


# leaves = # neighbors =
$1 + n(a - 1) = 1 + 3(4 - 1) = 10$

Neighborhood search

Navigating and/or building neighborhood trie is simple with recursion

Assume Hamming distance for now: Move left-to-right across *P* and start with “budget” of *k* mismatches



At each step, for each alphabet character *c*:

- If *c* matches current character in *P*, recursively build subtree starting at next position of *P* with same budget
- If c *mis*matches current character in P *and* budget > 0, recursively build subtree starting at next position of *P* with 1 subtracted from budget. Otherwise if budget = 0, move on.

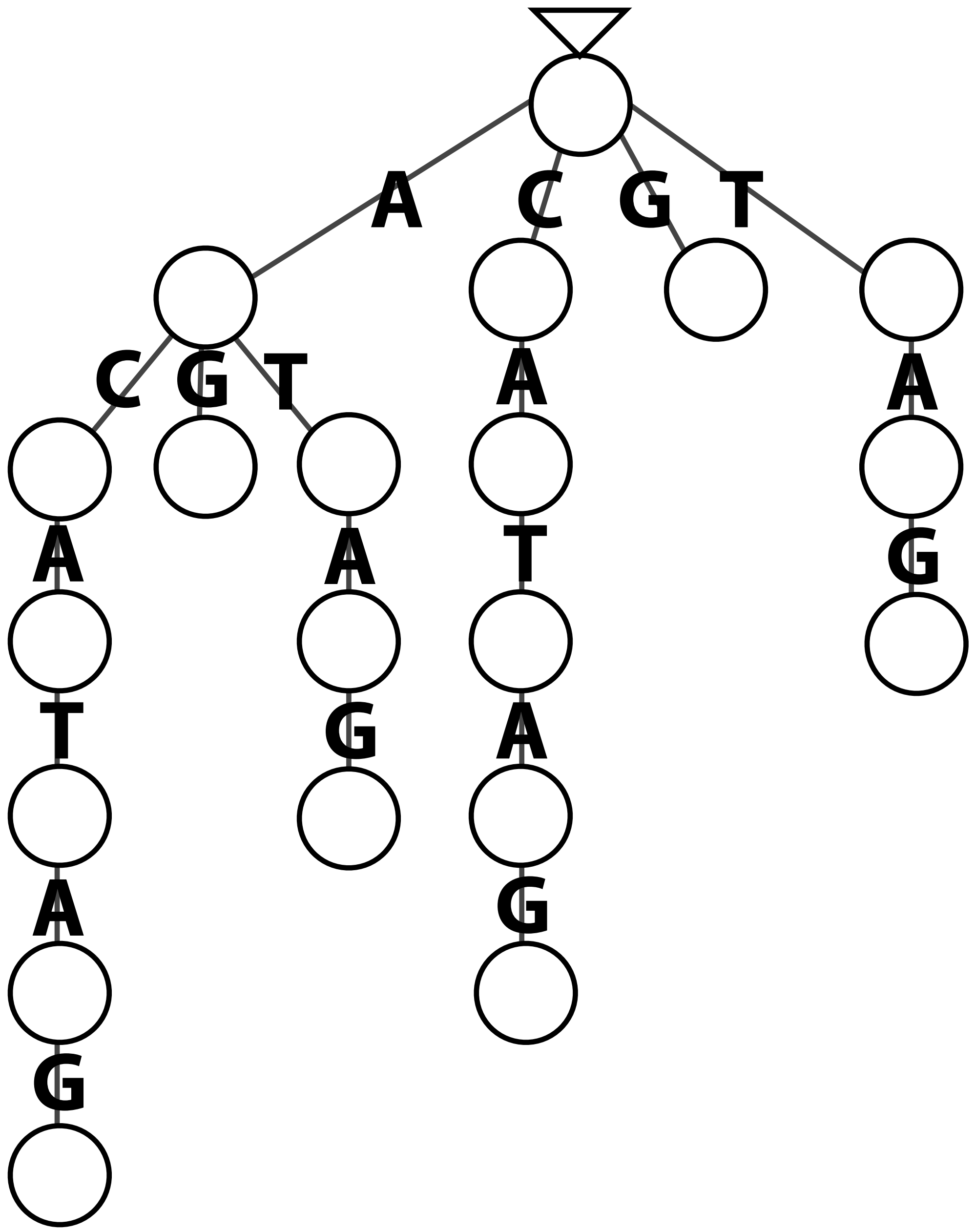
Neighborhood search

```
>>> stringNeighbors("cat", "acgt", edits=1, gaps=False)
['aat', 'gat', 'tat', 'cct', 'cgt', 'ctt', 'caa', 'cac', 'cag', 'cat']
>>> stringNeighbors("cat", "acgt", edits=1, gaps=True)
['acat', 'ccat', 'gcat', 'tcat', 'at', 'aat', 'gat', 'tat', 'caat',
'ccat', 'cgat', 'ctat', 'ct', 'cct', 'cgt', 'ctt', 'caat', 'cact',
'cagt', 'catt', 'ca', 'caa', 'cac', 'cag', 'cata', 'catc', 'catg',
'catt', 'cat']
```

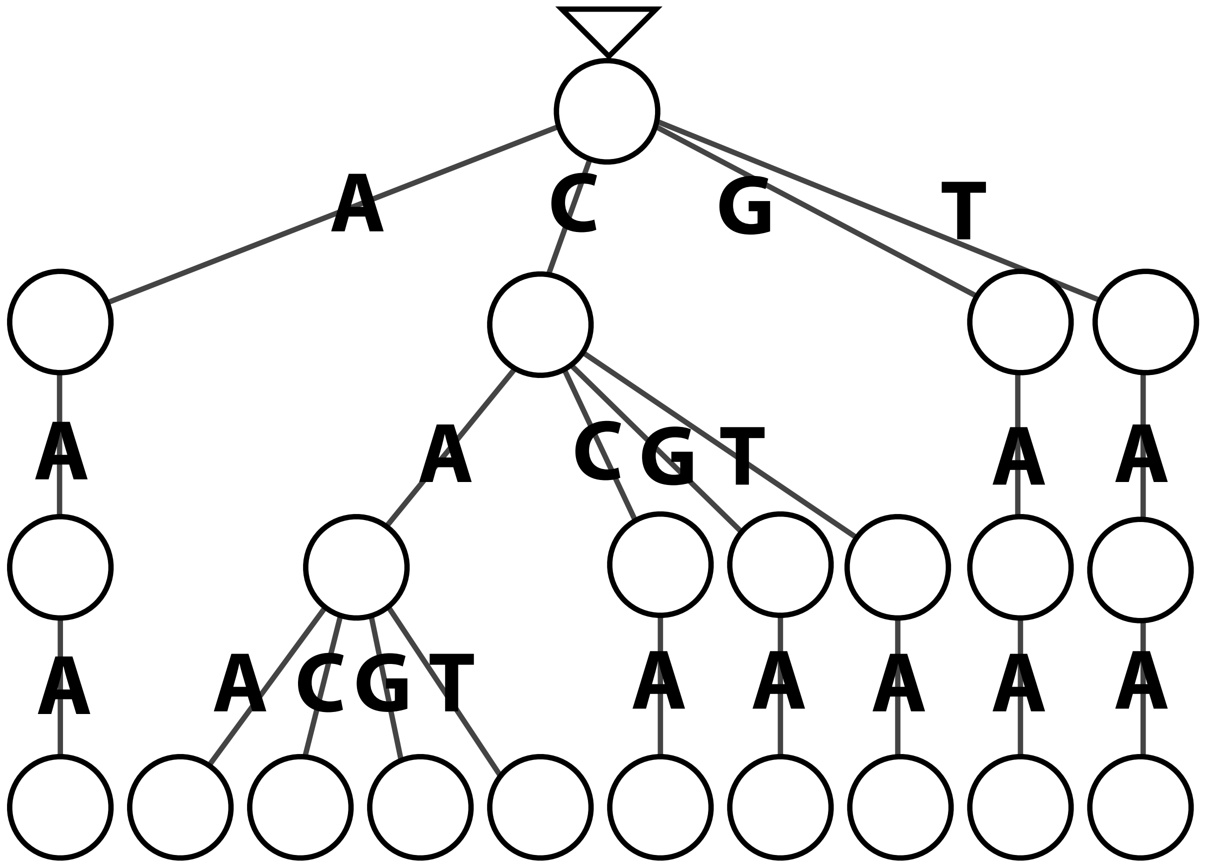
Co-traversal

Say index is a suffix trie. Imagine querying it with each neighbor.

Suffix trie of *T* = ACATAG



Trie for neighborhood within 1 mismatch of *P* = CAA



Co-traversal

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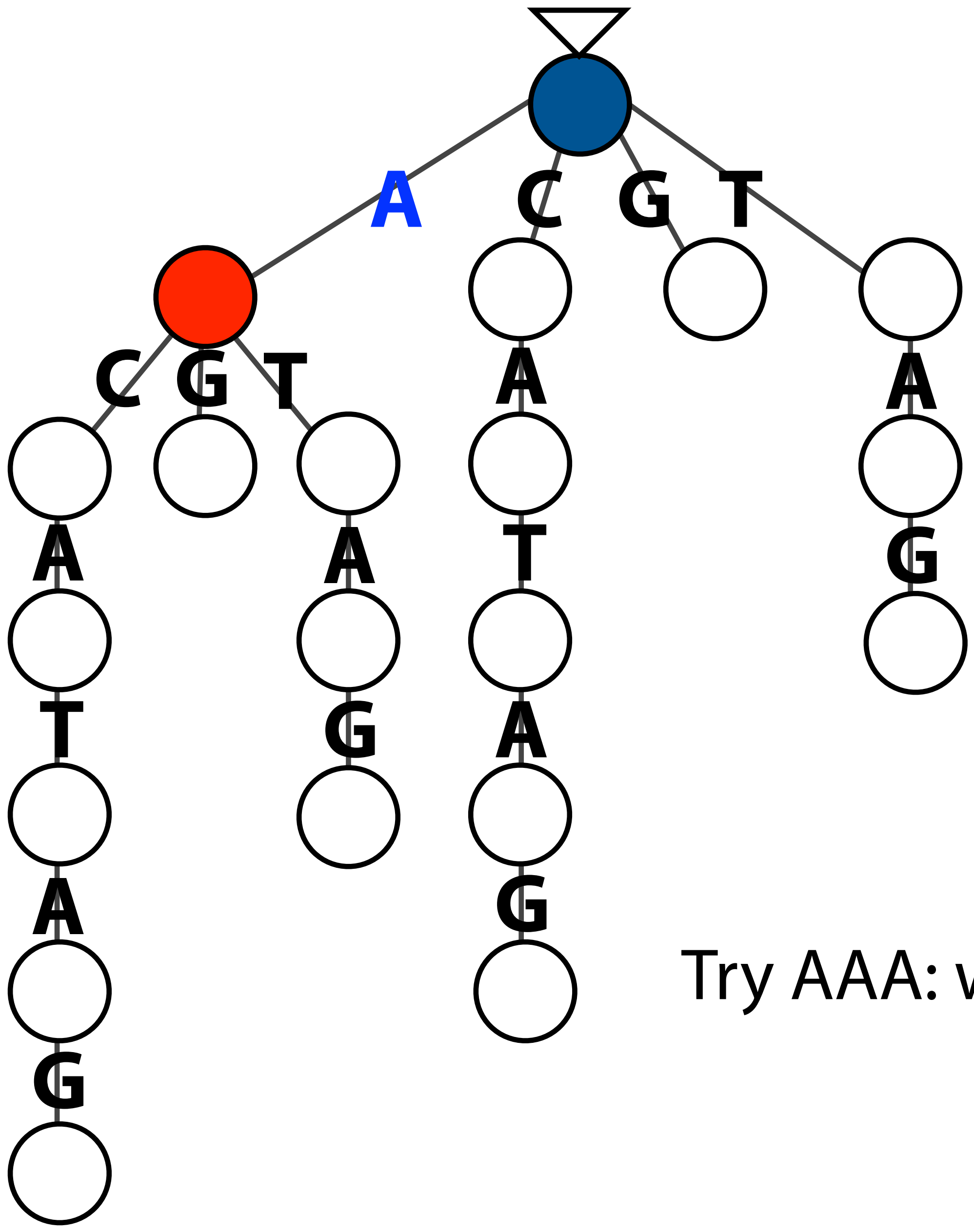

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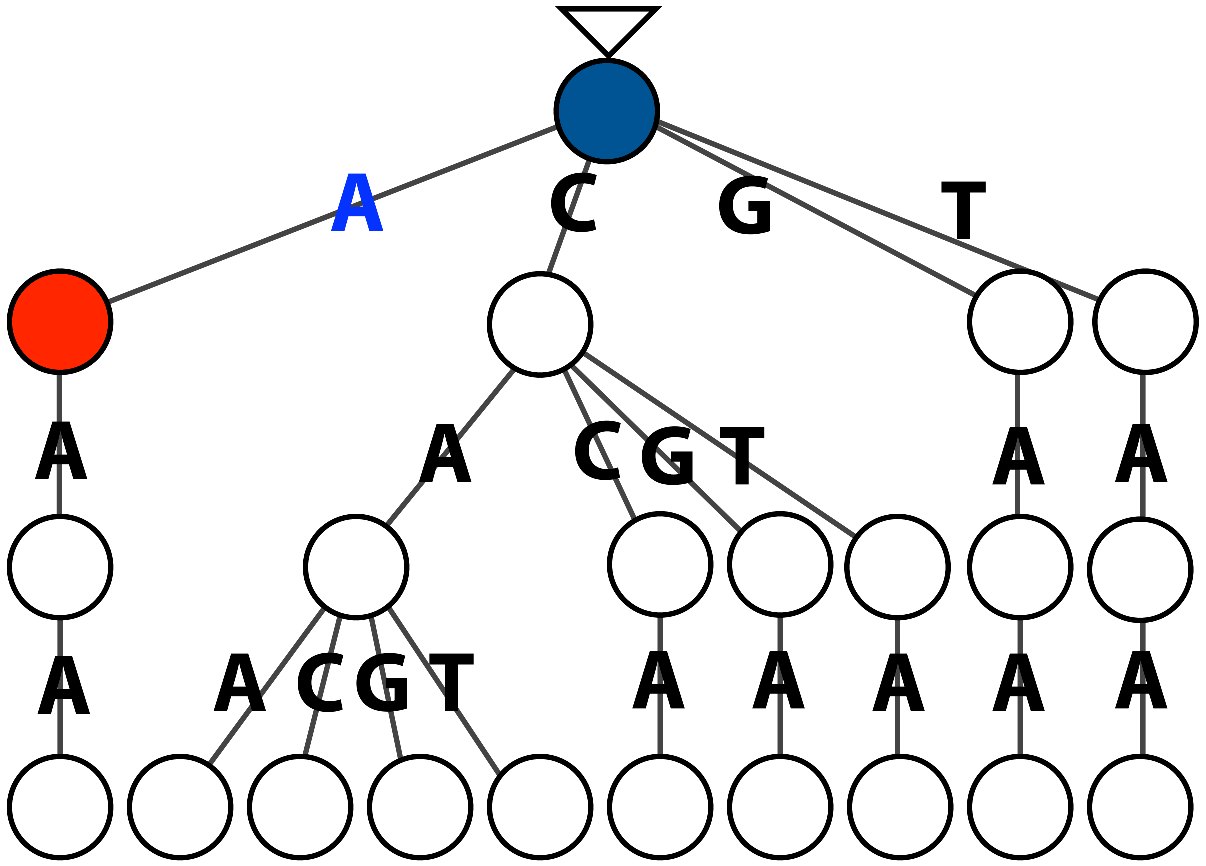
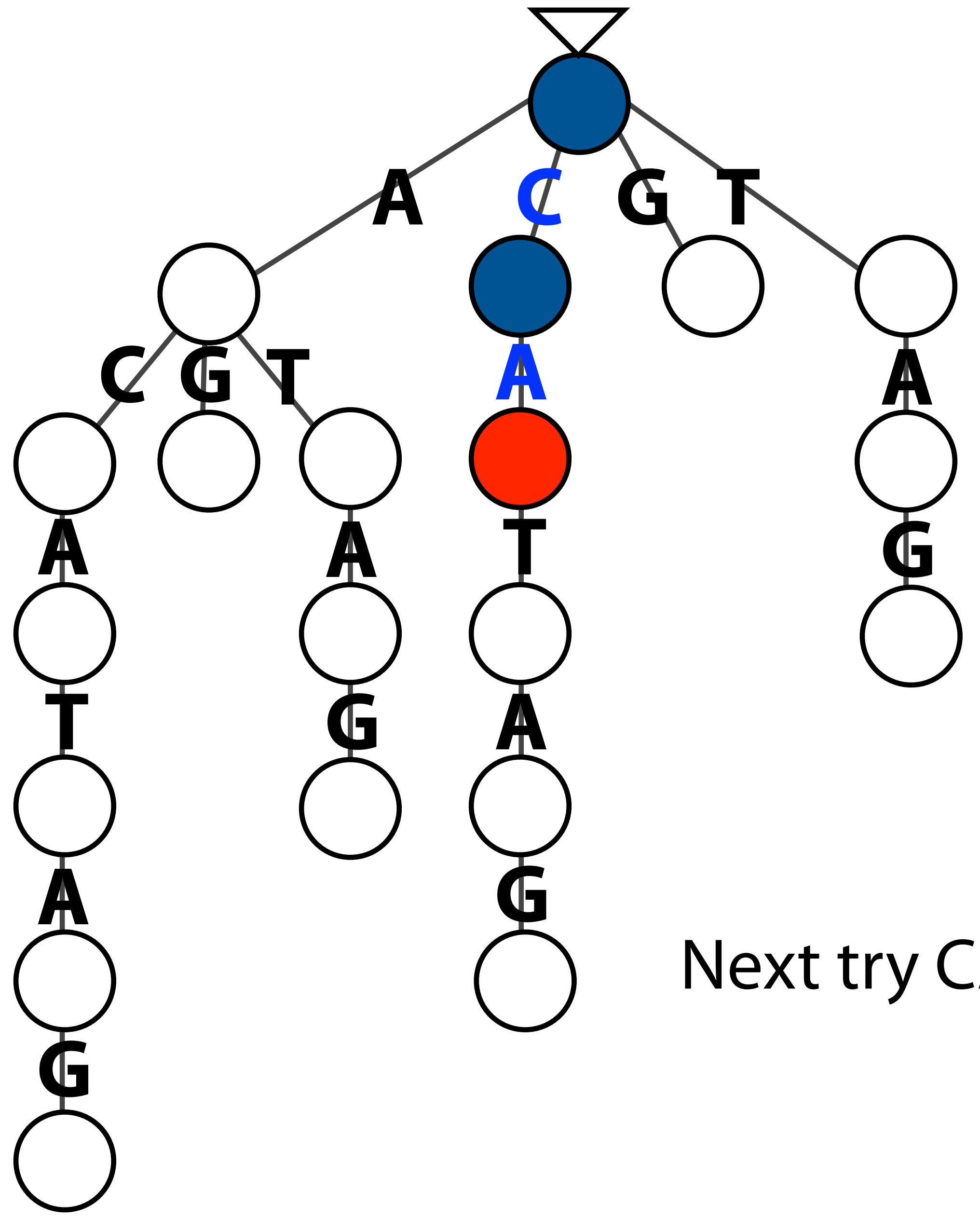


Try AAA: we fall off suffix trie after A, before AA

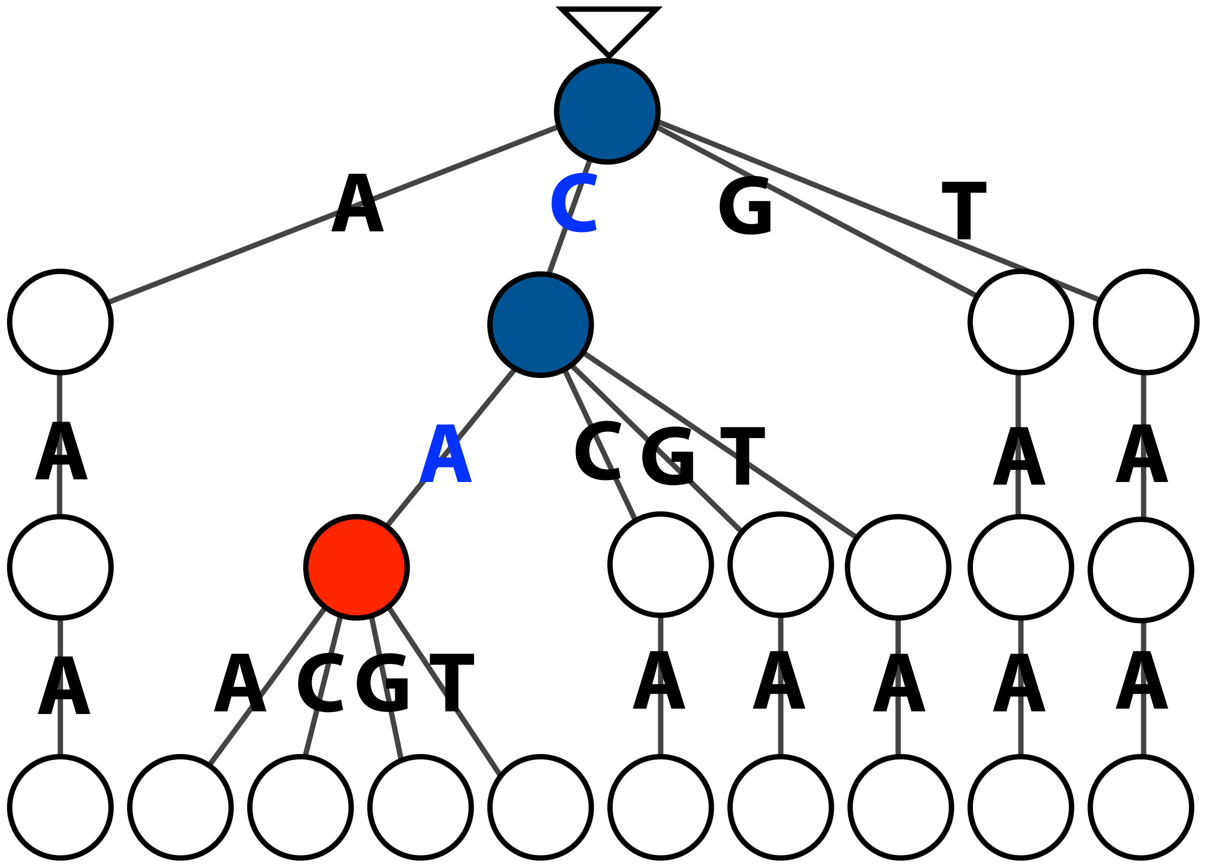
Co-traversal

Say index is a suffix trie. Imagine querying it with each neighbor.

Suffix trie of *T* = ACATAG



Trie for neighborhood within 1 mismatch of *P* = CAA

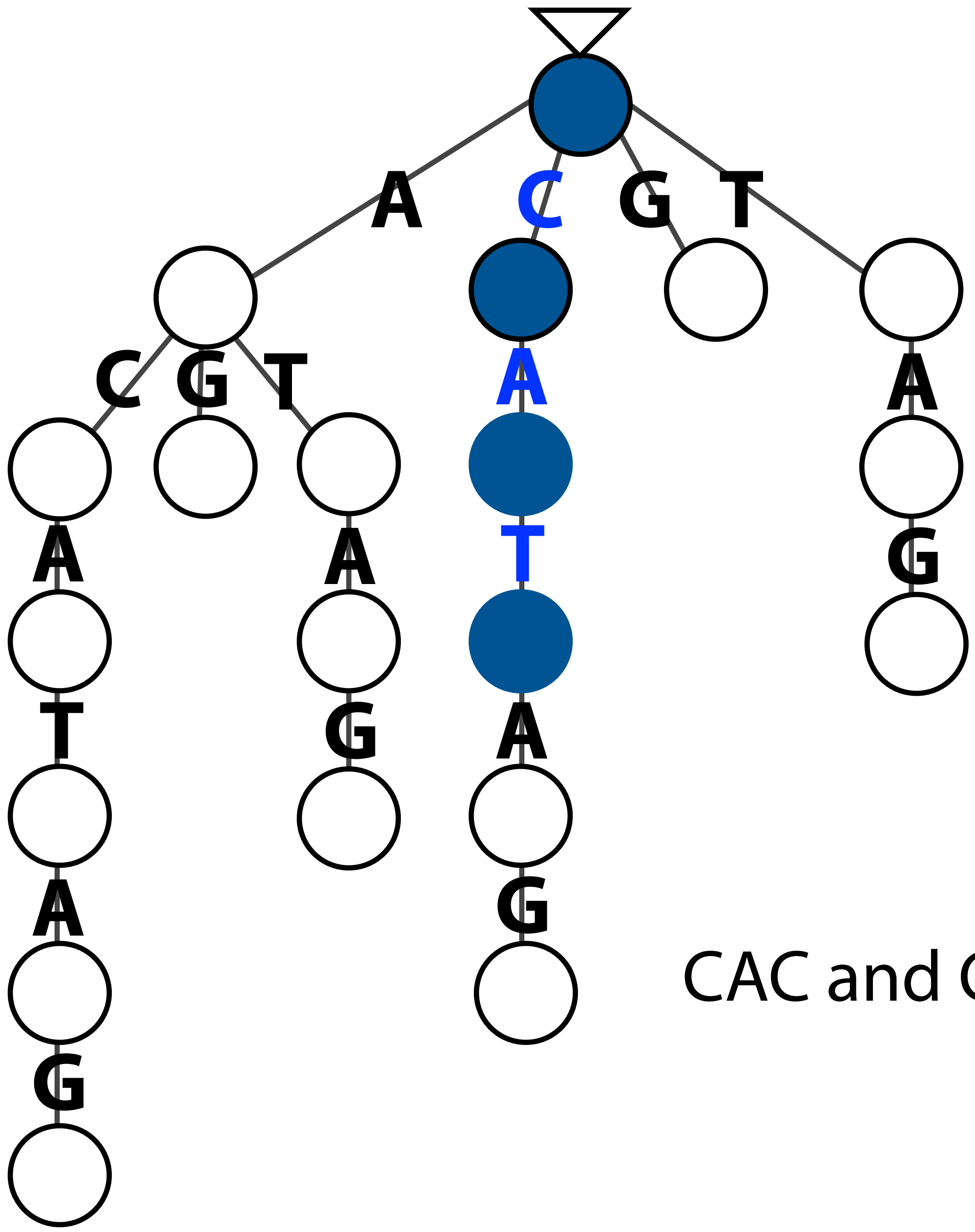


Next try CAA: we fall off suffix trie after CA, before CAA

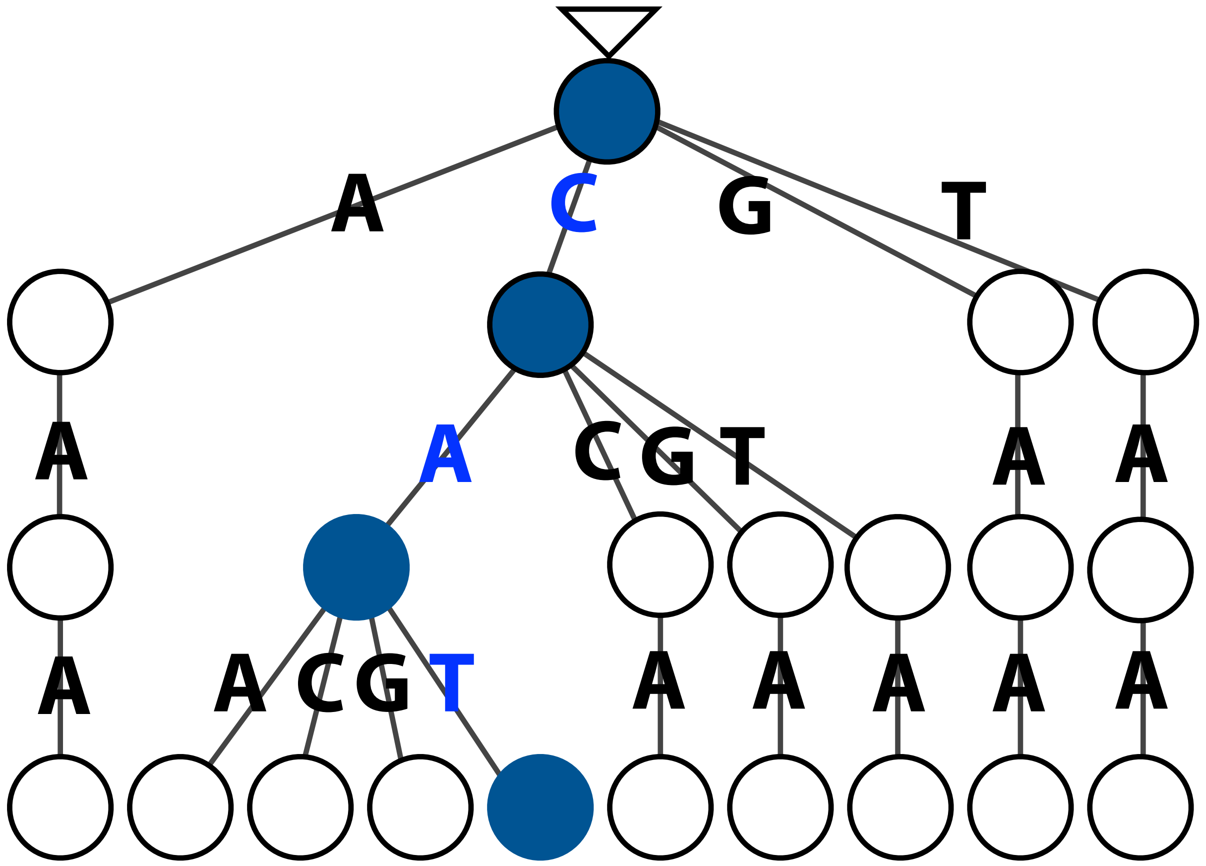
Co-traversal

Say index is a suffix trie. Imagine querying it with each neighbor.

Suffix trie of *T* = ACATAG



Trie for neighborhood within 1 mismatch of *P* = CAA

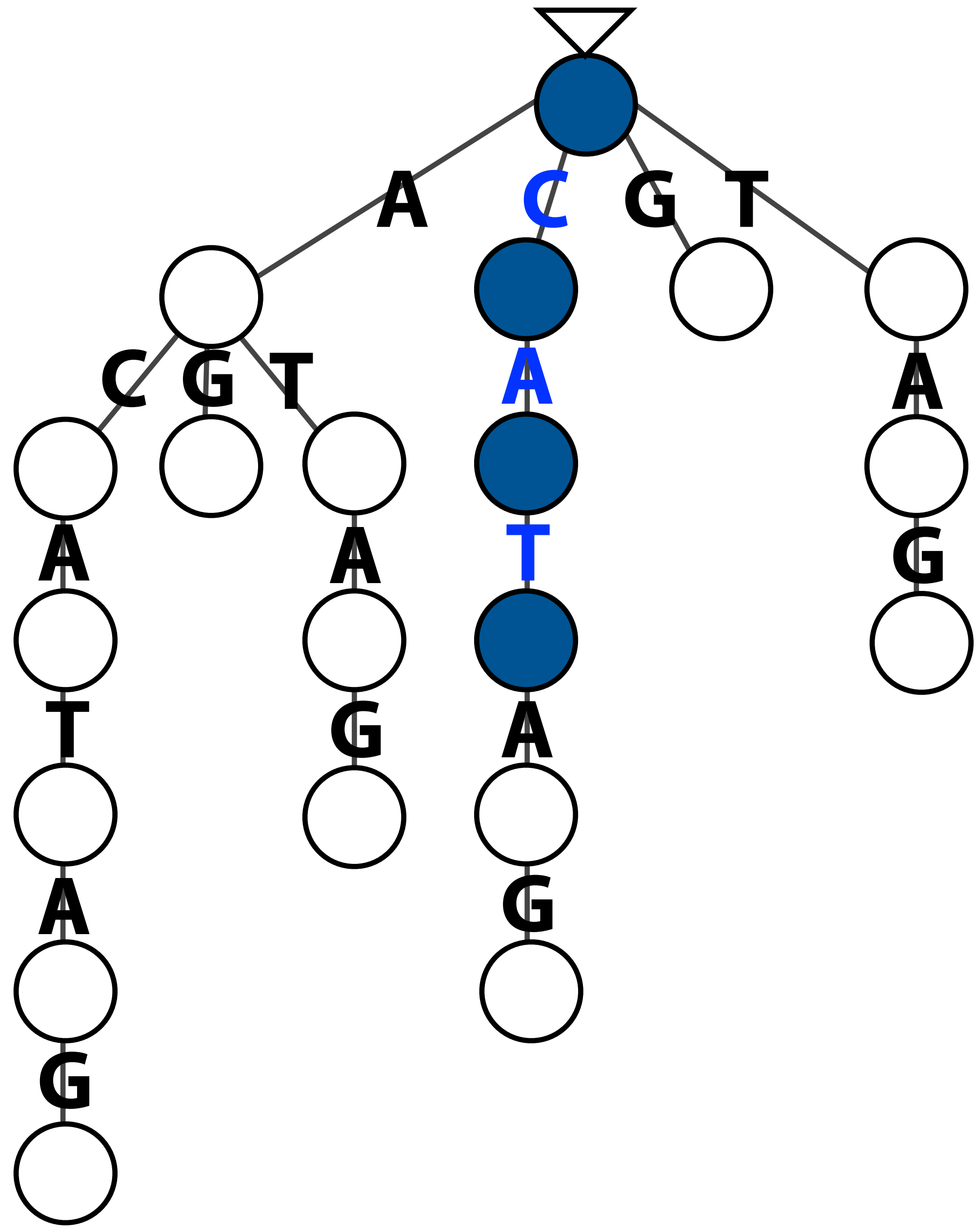


CAC and CAG also fail. Next try CAT: success.

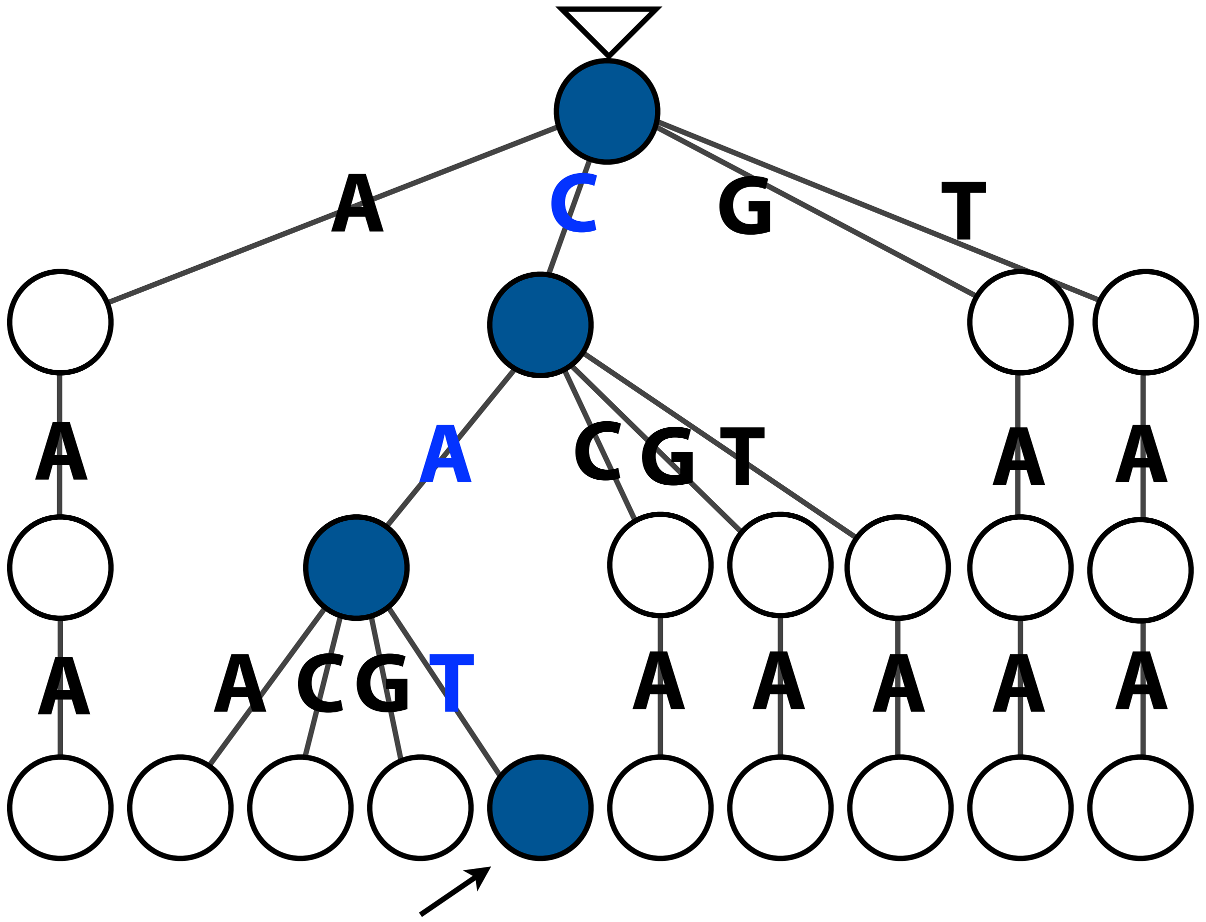
Co-traversal

Say index is a suffix trie. Imagine querying it with each neighbor.

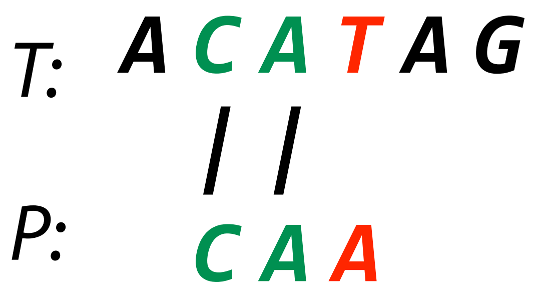
Suffix trie of *T* = ACATAG



Trie for neighborhood within 1 mismatch of *P* = CAA



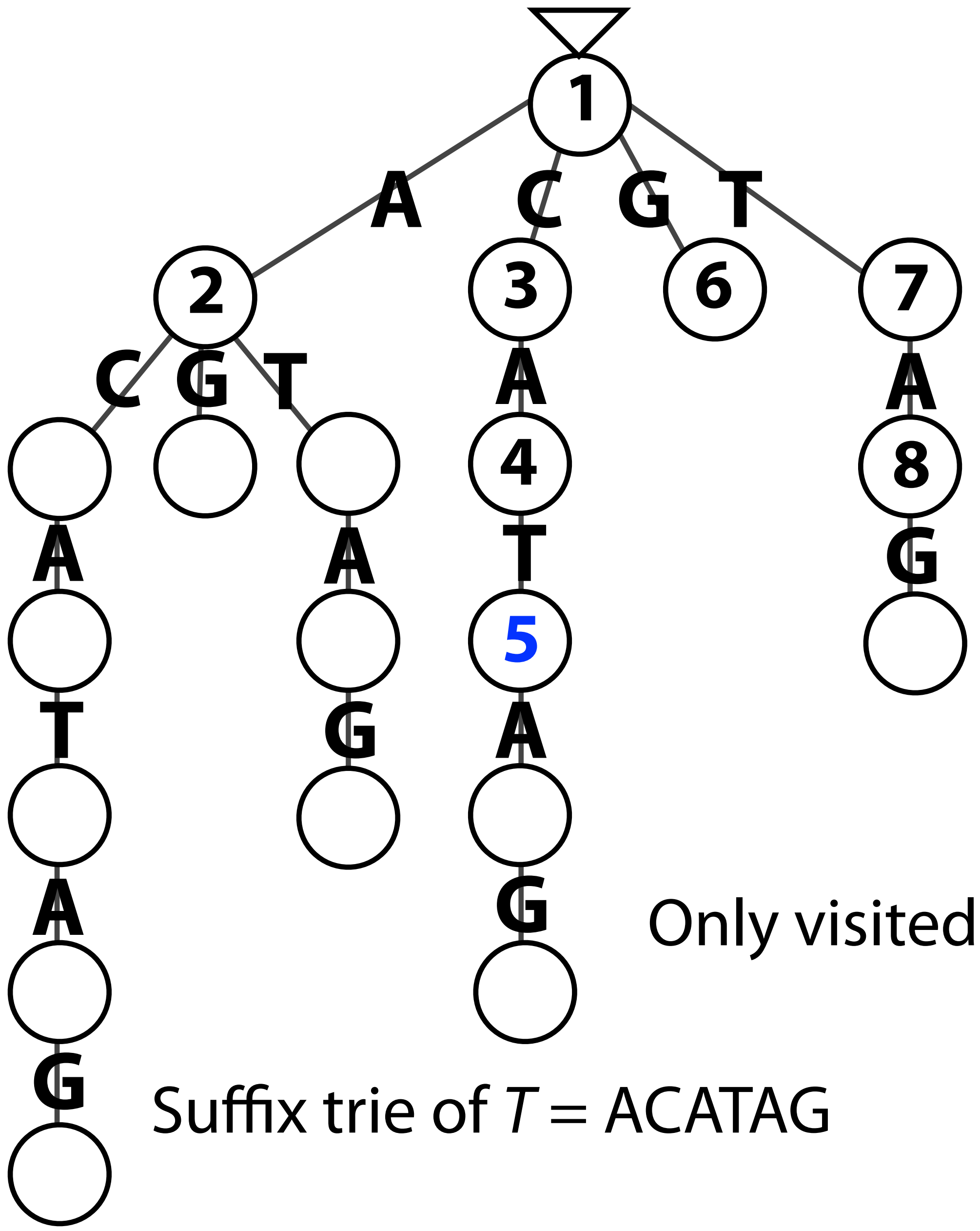
Common path ending in a neighbor leaf corresponds to an alignment of a neighbor of *P* to a substring of *T*



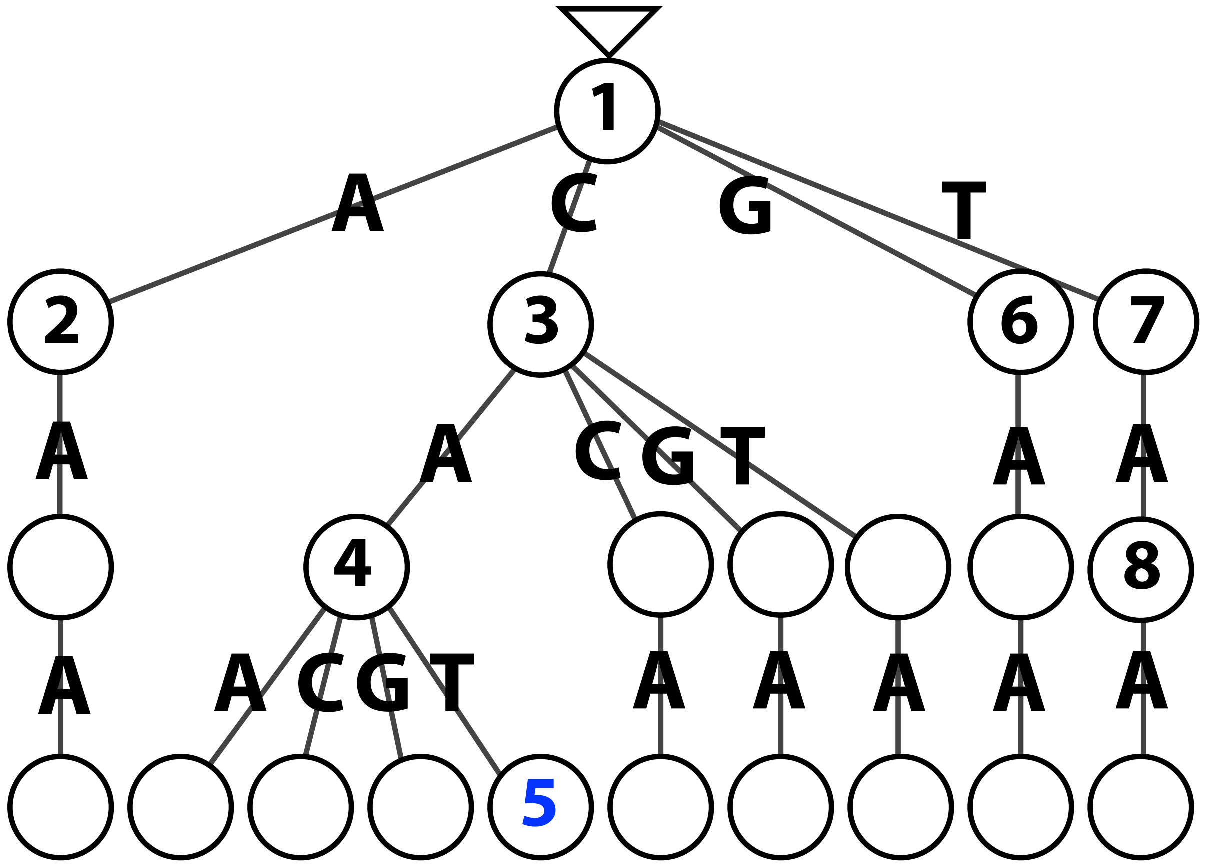
Co-traversal

We can find all such alignments with *co-traversal*: explore all paths that are present in both trees and end in a neighbor leaf

Lexicographical depth-first co-traversal visits node pairs in this order:



Suffix trie of T = ACATAG

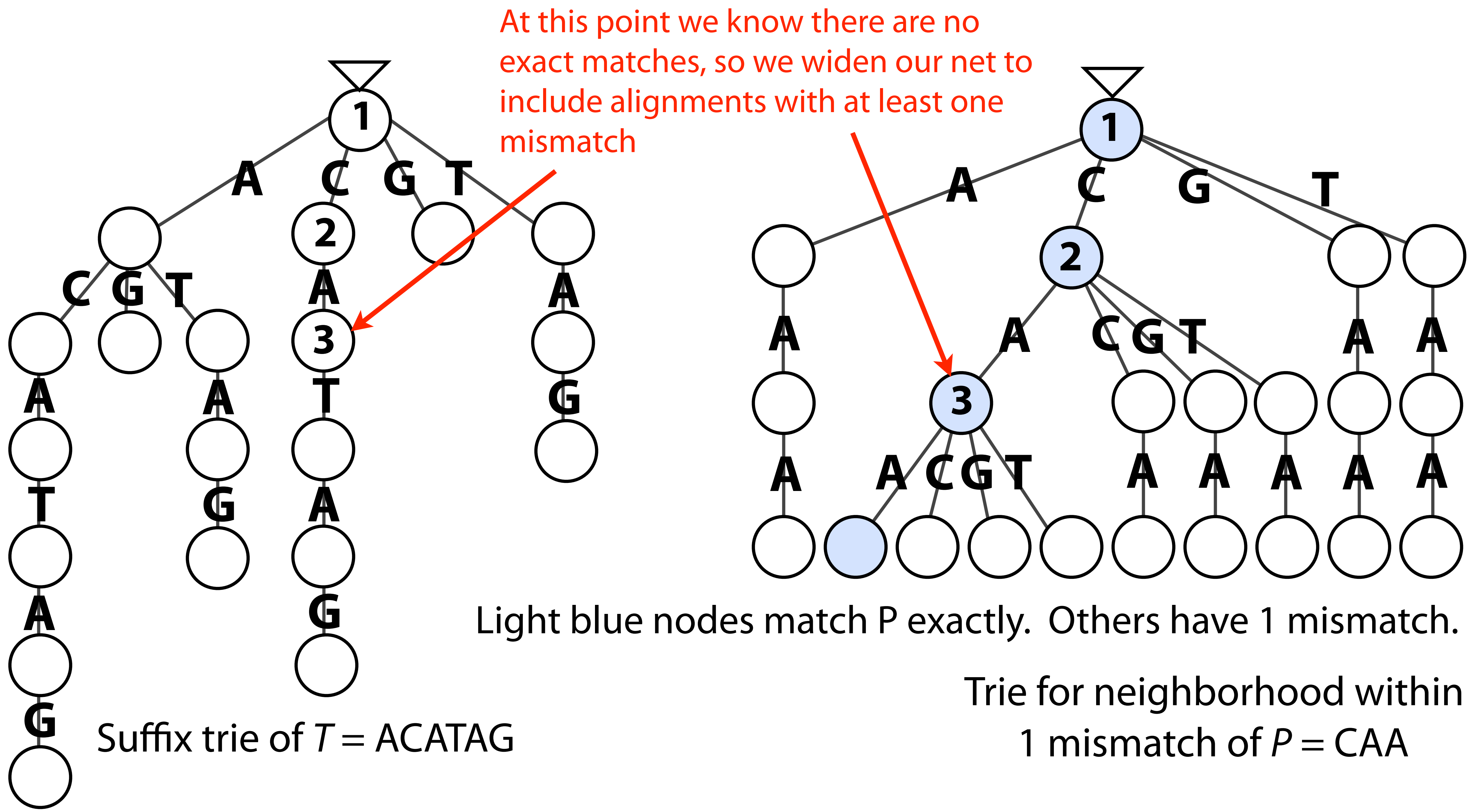


Only visited 8 nodes in these 20- and 22-node tries

Trie for neighborhood within 1 mismatch of P = CAA

Co-traversal

We can also conduct *best-first* search, visiting paths with fewer edits before paths with more edits:



At this point we know there are no exact matches, so we widen our net to include alignments with at least one mismatch
1
2
3
A
C
G
T

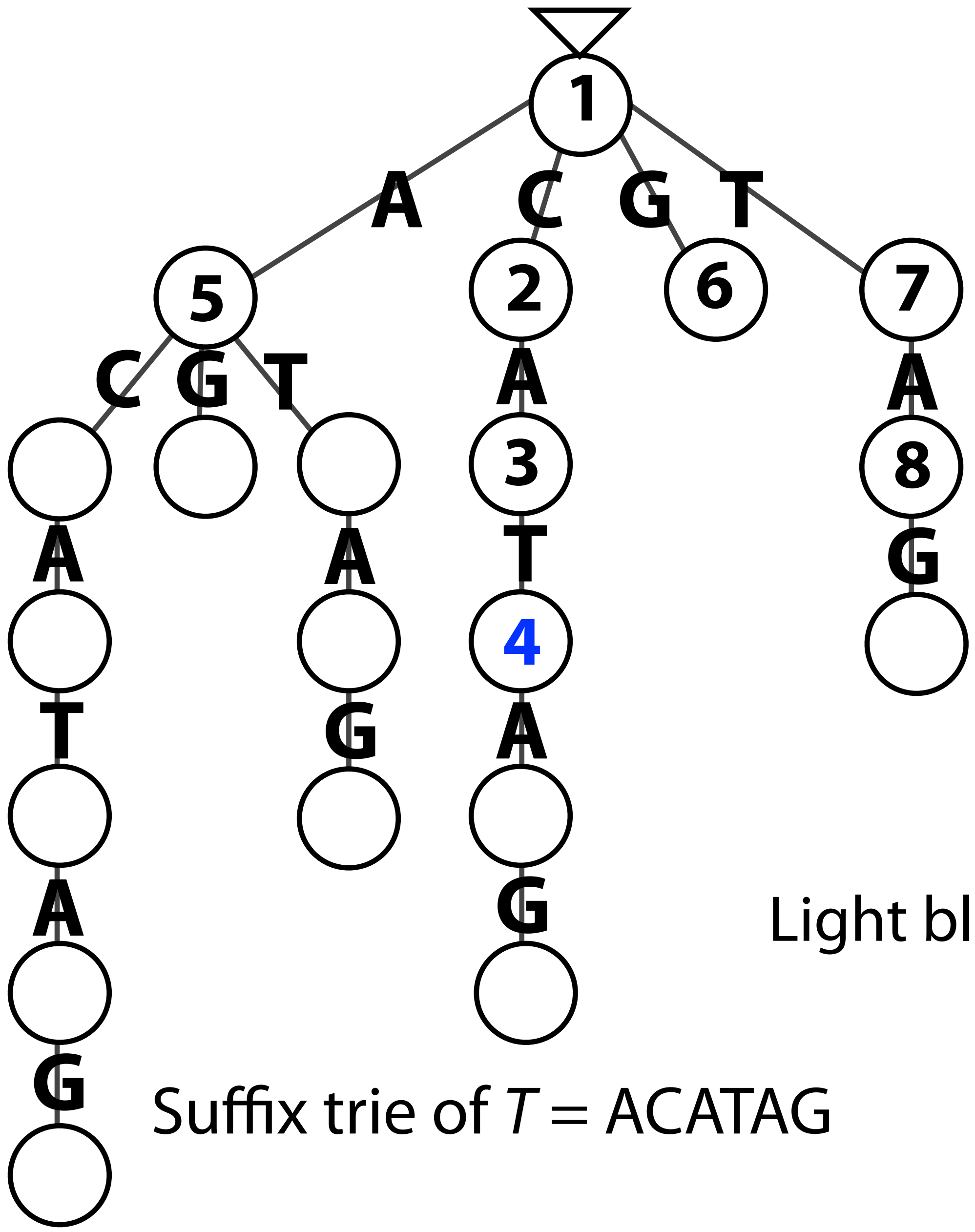
Light blue nodes match P exactly. Others have 1 mismatch.

Suffix trie of T = ACATAG

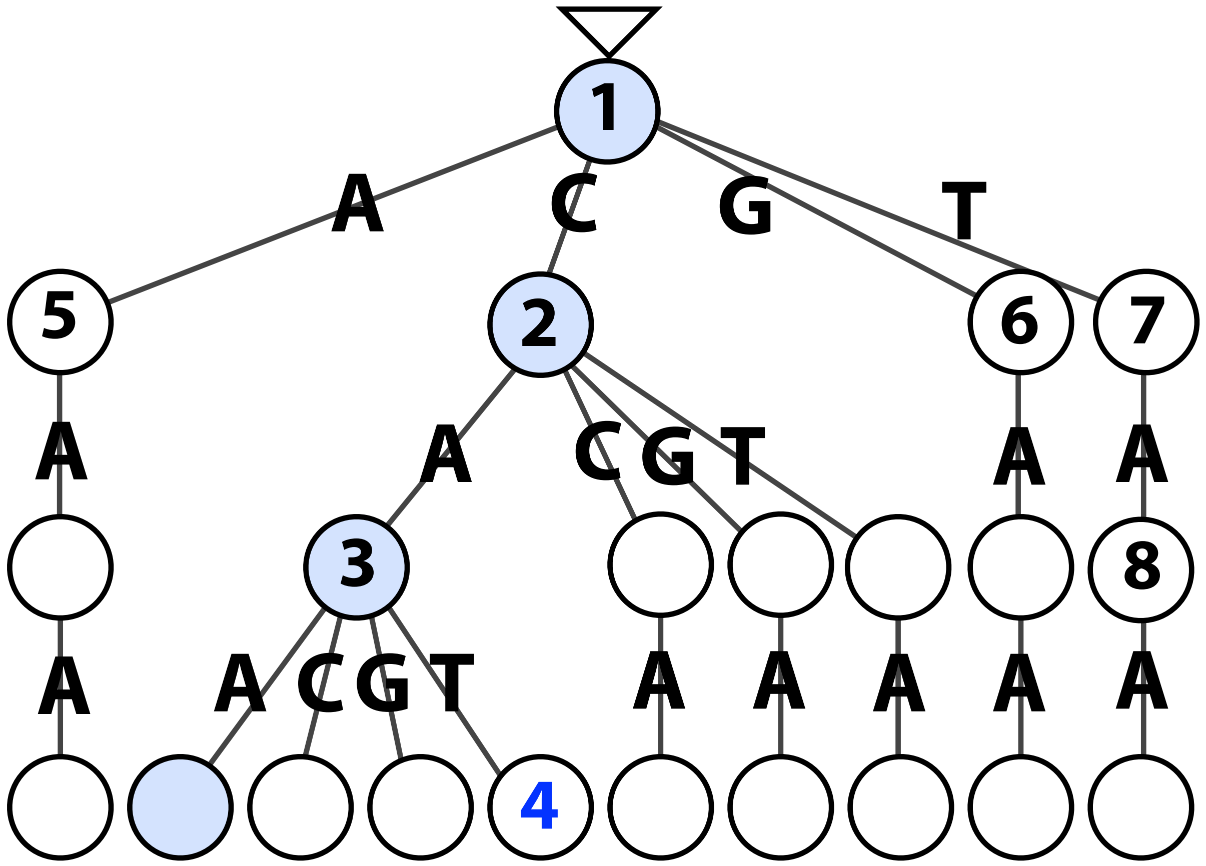
Trie for neighborhood within 1 mismatch of P = CAA

Co-traversal

We can also conduct *best-first* search, visiting paths with fewer edits before paths with more edits:



Suffix trie of *T* = ACATAG

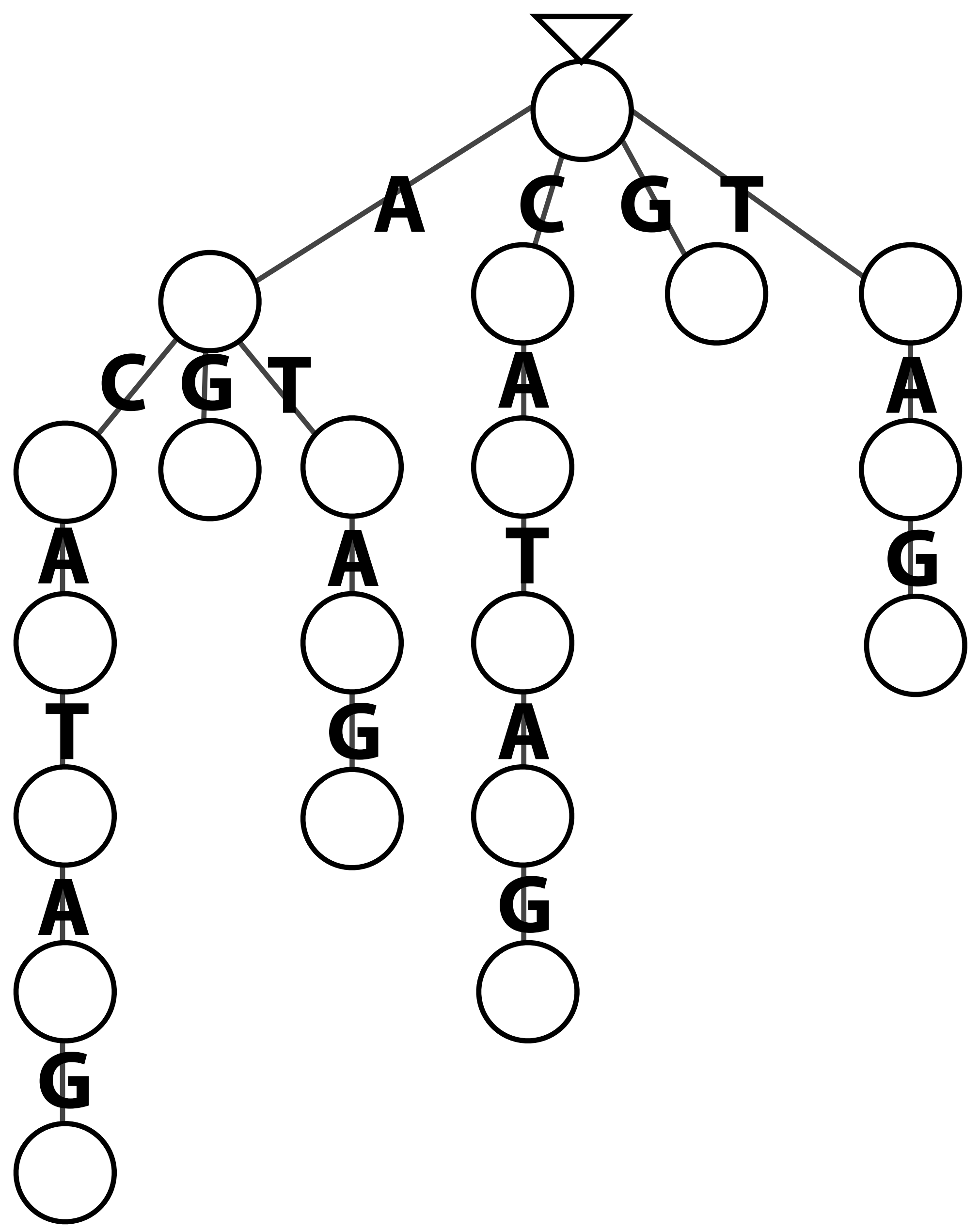


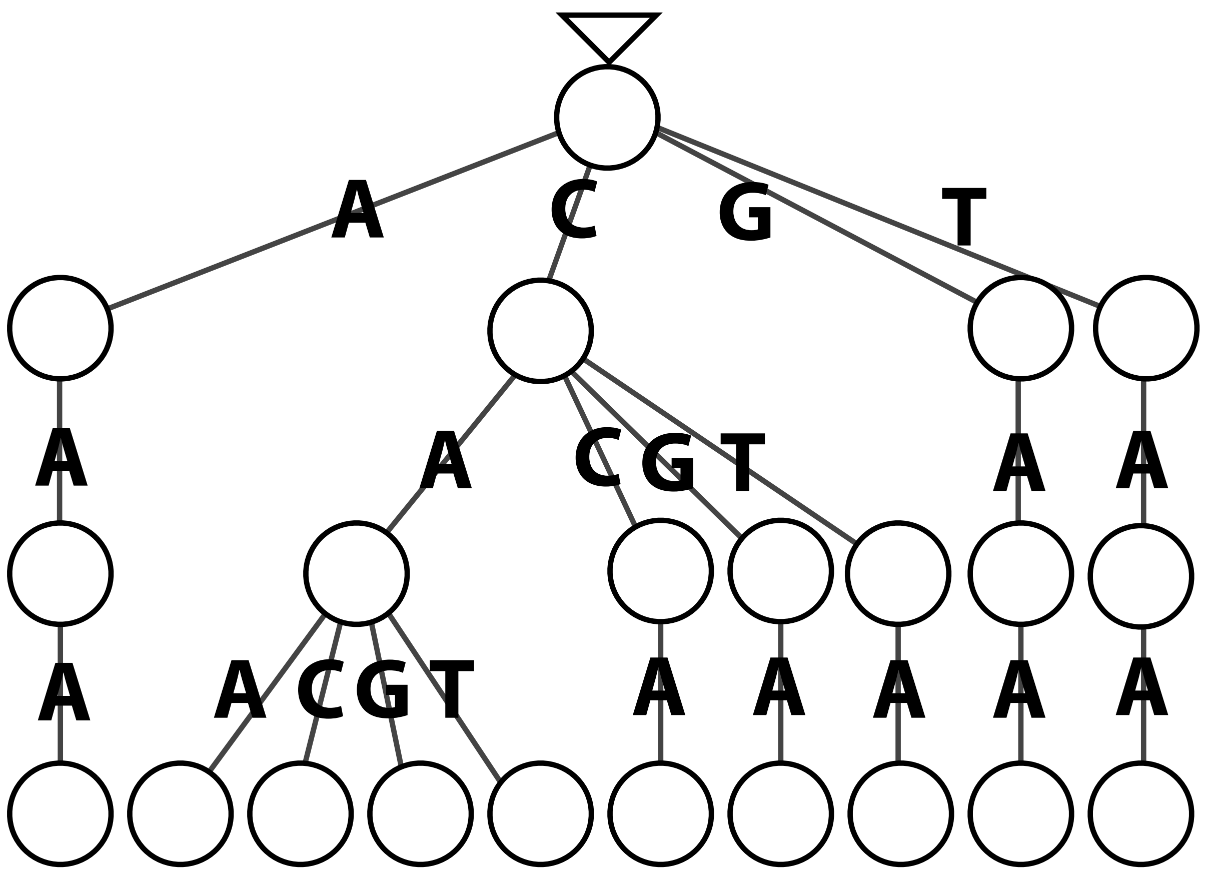
Light blue nodes match P exactly. Others have 1 mismatch.

Trie for neighborhood within 1 mismatch of *P* = CAA

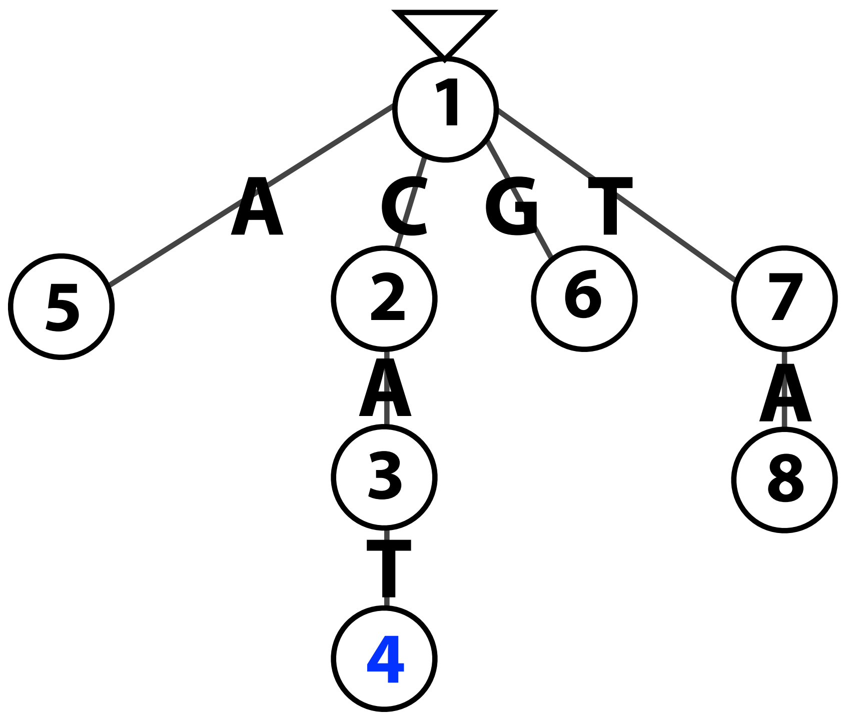
Co-traversal: pruning

We can think of the tree we're exploring as being the *intersection* of these two trees...





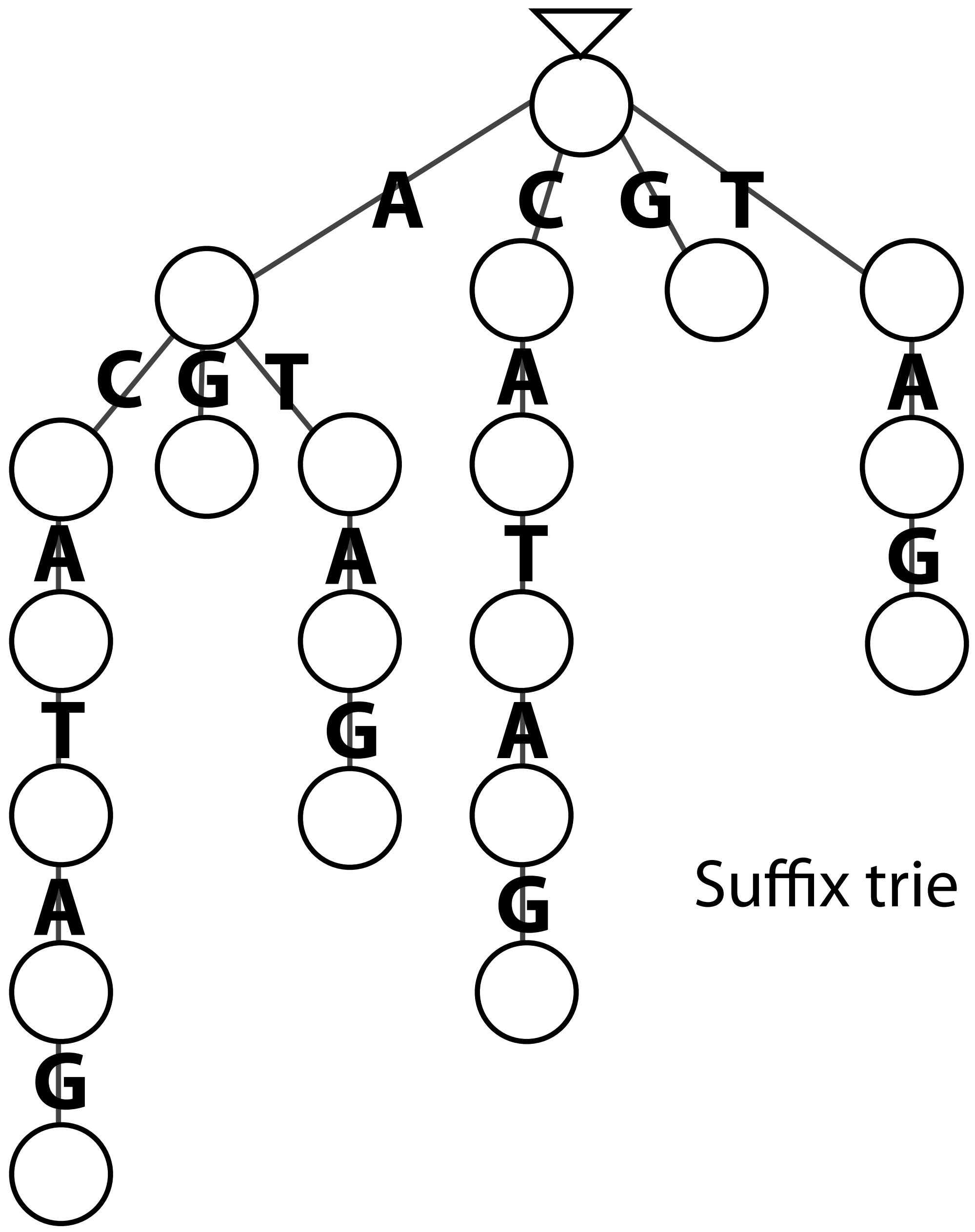
Co-traversal: pruning



Suffix trie of *T* = ACATAG $\cap$ Trie for neighborhood within 1 mismatch of *P* = CAA

Co-traversal: indexing

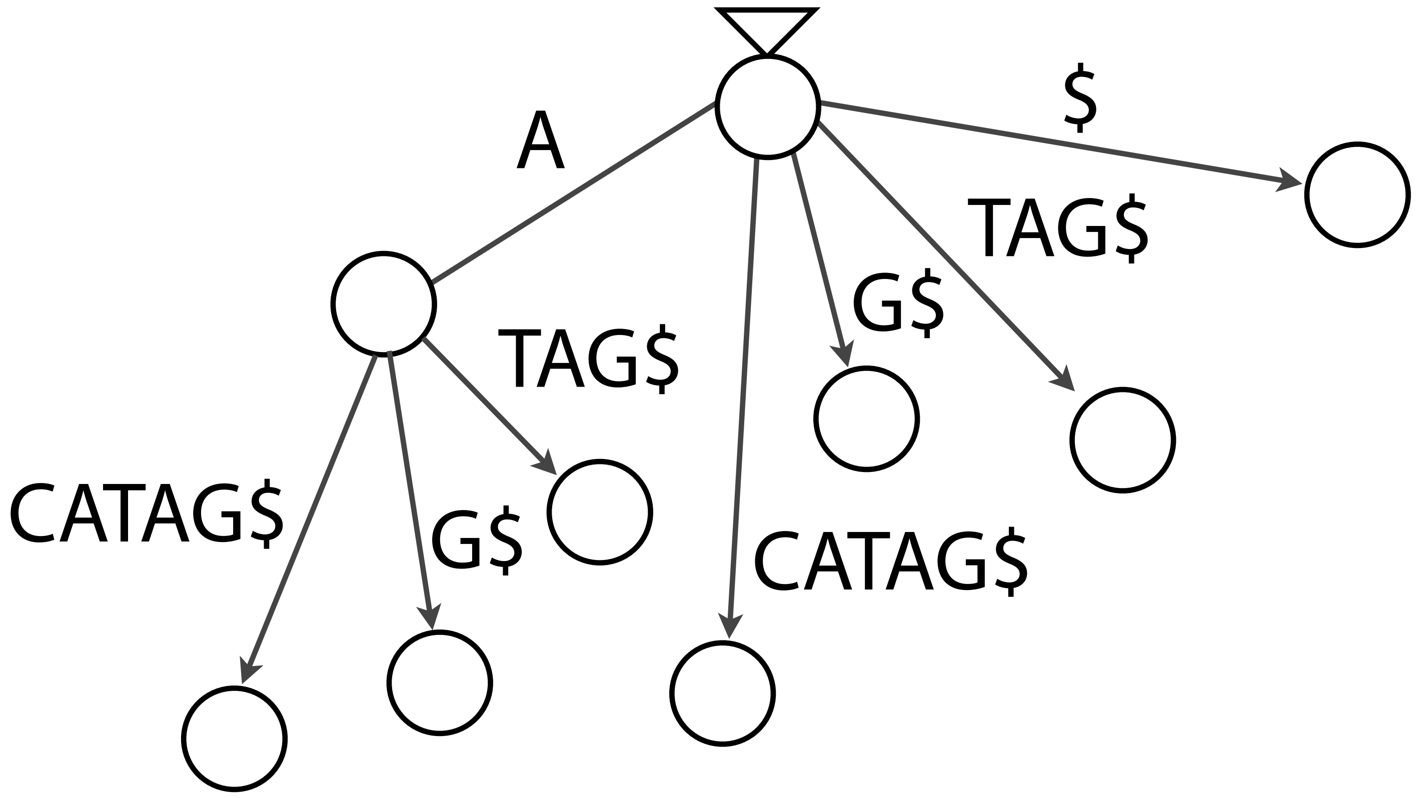
Co-traversal uses the shape of the suffix trie, but we don't want to actually build it. It's $O(m^2)$ space. What's an alternative?



Suffix trie of T = ACATAG

Co-traversal: indexing

Alternative 1: Replace suffix trie with suffix tree



Suffix tree of *T* = ACATAG$

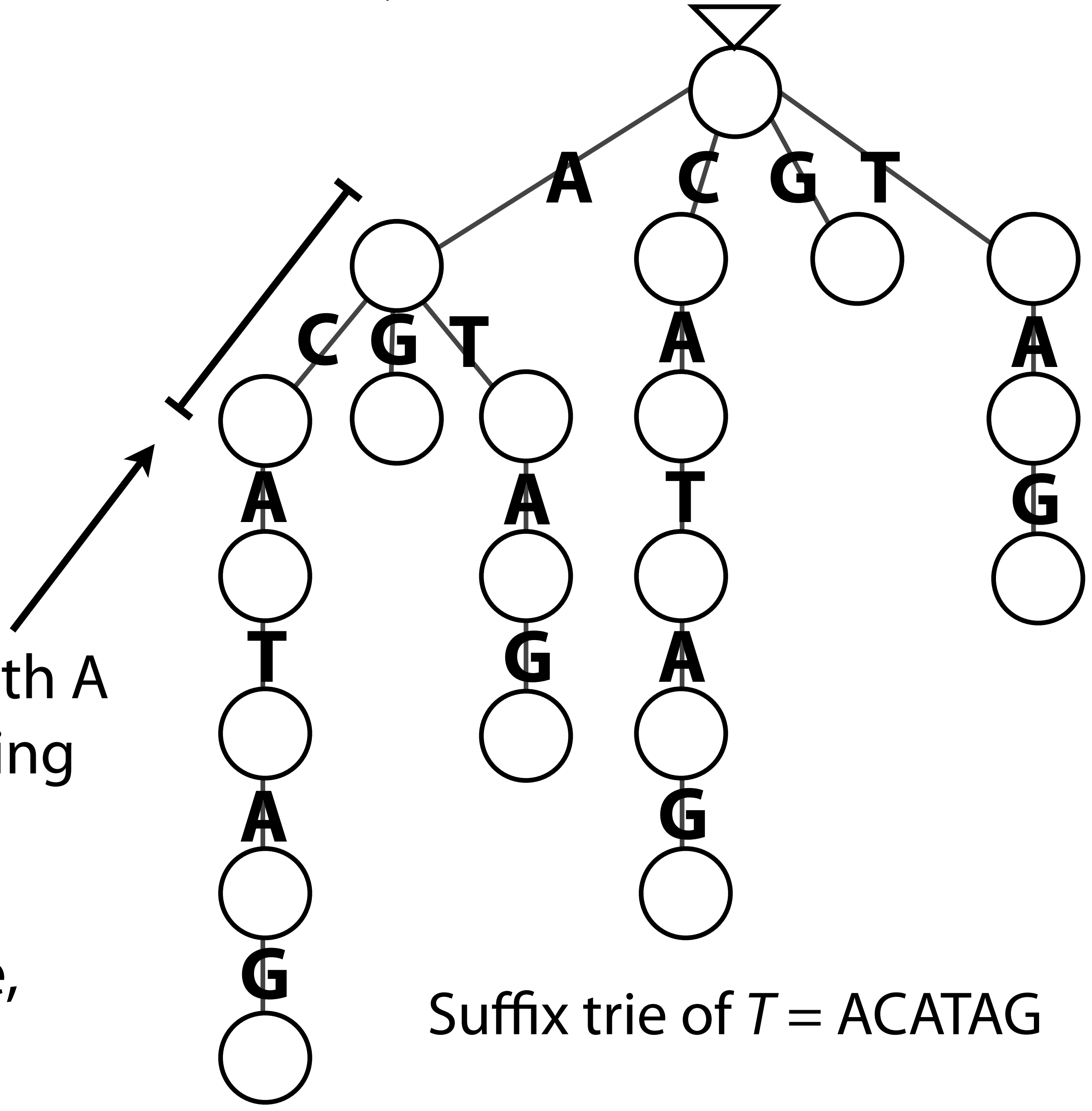
Co-traversal: indexing

Alternative 2: Replace suffix trie with suffix array

6	$
0	A C A T A G $
4	A G $
2	A T A G $
1	C A T A G $
5	G $
3	T A G $

If we know range of SA elements with A as a prefix, additional binary searching gives range with AC as a prefix

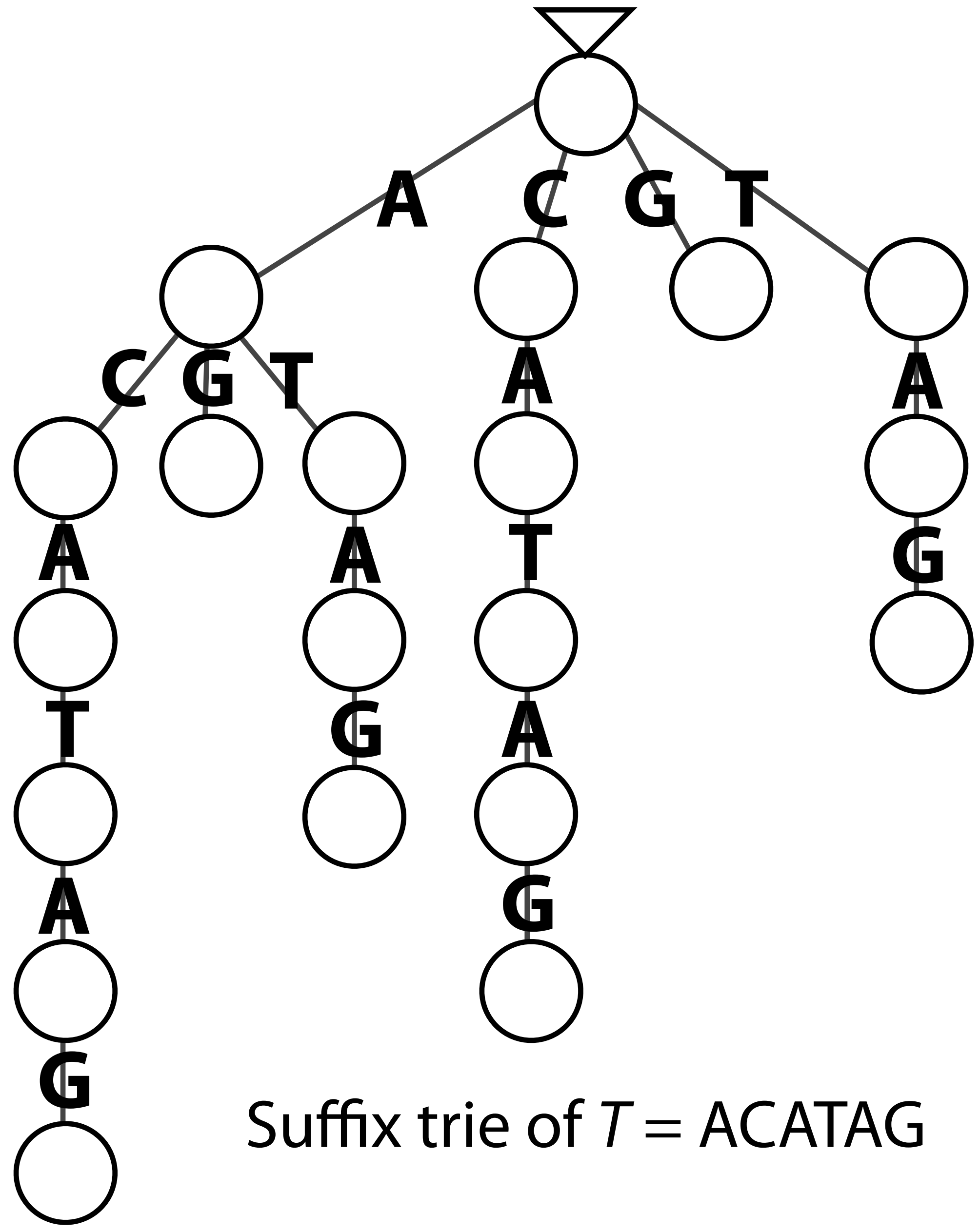
Even if we don't *build* suffix trie/tree, suffix array allows us to *traverse* it



Suffix trie of *T* = ACATAG

Co-traversal: indexing

Alternative 3: Replace suffix trie with FM Index



Suffix trie of *T* = ACATAG

Similar argument as suffix array, using LF Mapping instead of binary search

To traverse suffix trie, we need to build FM Index of *T'* = reverse(*T*)

Why?

Typical FM Index matches successively longer *suffixes* of *P*. If we want to match successively longer *prefixes*, we have to reverse *T* before building FM Index.

Alignment summary

Exact matching with naive algorithm and Boyer-Moore

Online versus offline

Inverted indexes using substrings

Approximate matching: pigeonhole, q-gram lemma

Suffix indexes:

- Suffix Trie & Tree: querying, naive building
- Suffix Array: querying with binary search, accelerants
- FM Index: querying with LF mapping

Dynamic programming: edit distance, global alignment, local alignment

Combining dynamic-programming alignment with indexes; co-traversal