Alignment of whole genomes using MUMmer

Presentation in Algorithms in Bioinformatics (TÖ111F autumn 2014)

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Motivation

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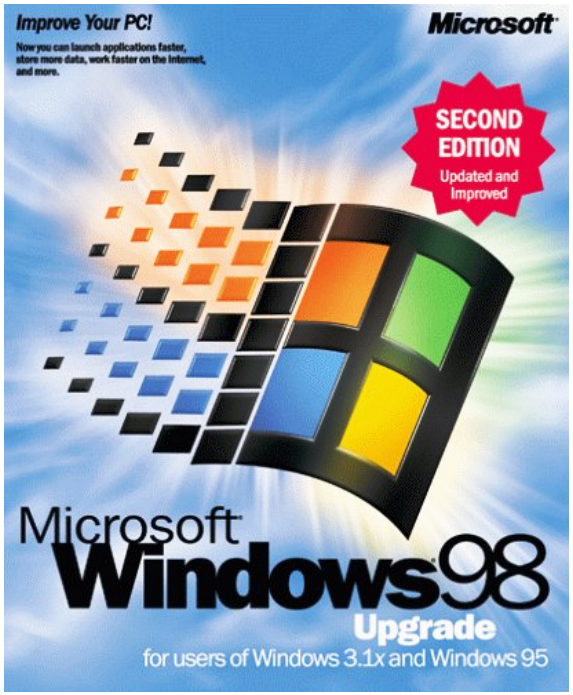

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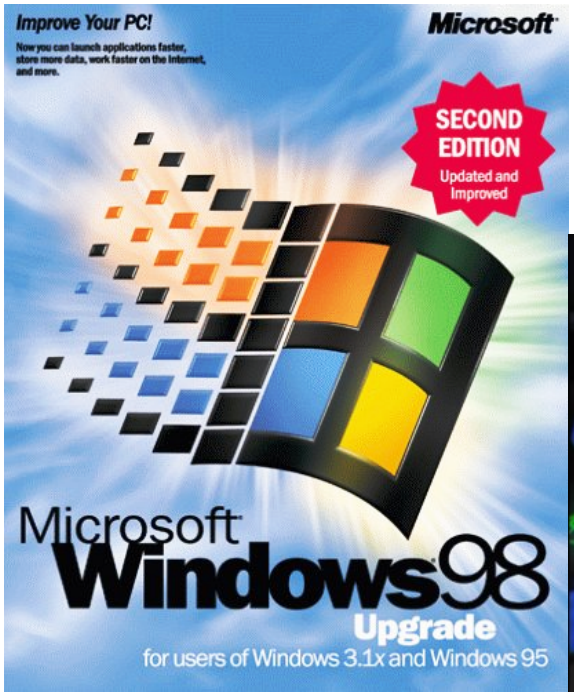

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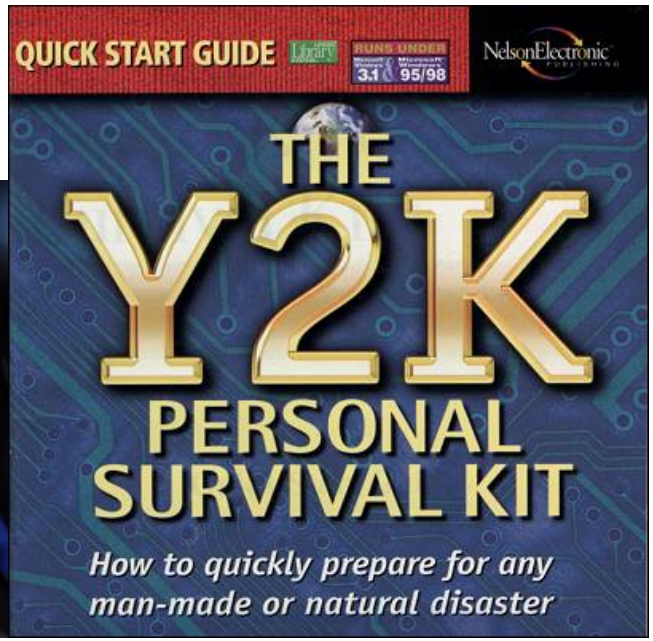

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But at that very same time in bioinformatics...

- The number of sequenced genomes was very limited but increasing very fast.
- Whenever a new genome is sequenced, one could ask himself:
  - How does this genome align to the other genomes we have sequenced?

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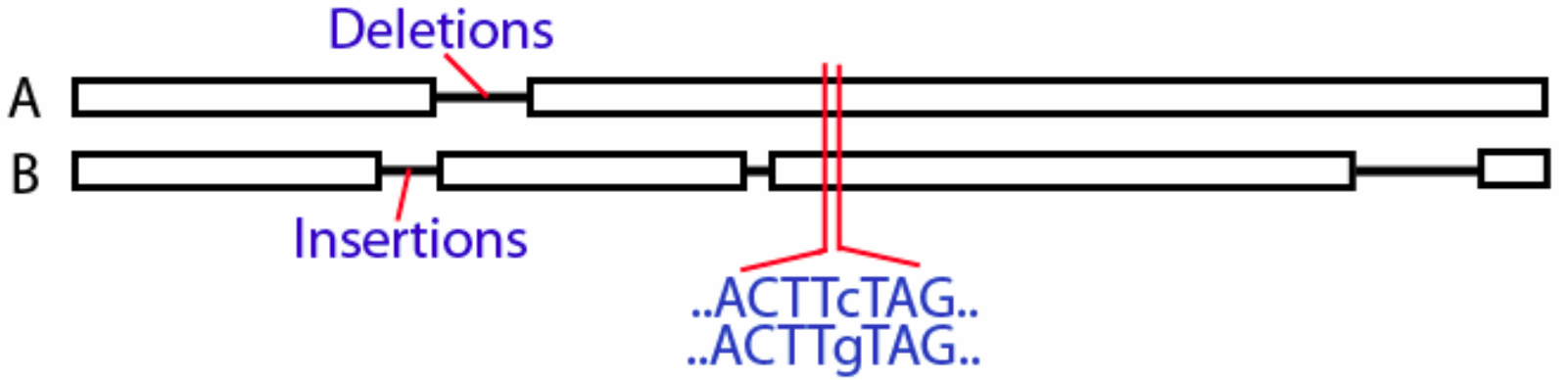
Problem:

- We had algorithms that were made for single gene sequences.
- But, they won't work well with whole genomes.
- It's simple: Size matters.
  - Take up way too much memory or
  - Have unacceptable computational time

Problem description

In Two genomes, A and B. Both could be very large (possibly over 1 Mbp)

Out Align the two genomes using insertions and deletions (or for short, indels) to maximize the matches.



Introduction to MUMmer

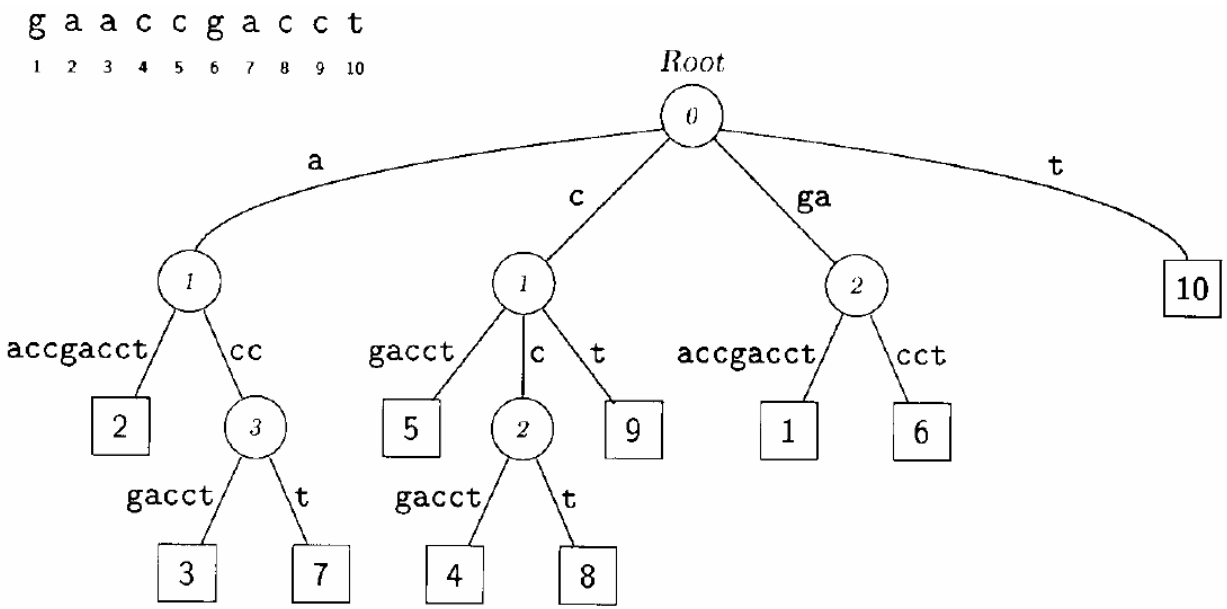
MUMmer:

- Was published in 1999.
- Is a system used to align whole genome sequences.
- Uses suffix trees as a data structure.
- Idea: Finding large chunks of exact matches on both genomes in linear time.
- Doesn't guarantee the optimal solution, just a good one.

Step 1: Creating a suffix tree

A suffix tree stores all possible suffixes in a tree.

- Square nodes are leaves.
  - Store information about the starting position of the suffix.
- Circular nodes are internal nodes.
  - Store information about the length of the shared prefix.



Creating a suffix tree takes $O(n)$ time and space.

Step 2: MUM decomposition

Let us first define what a MUM is

Definition

A subsequence is a MUM (Maximal Unique Matches) if and only if:

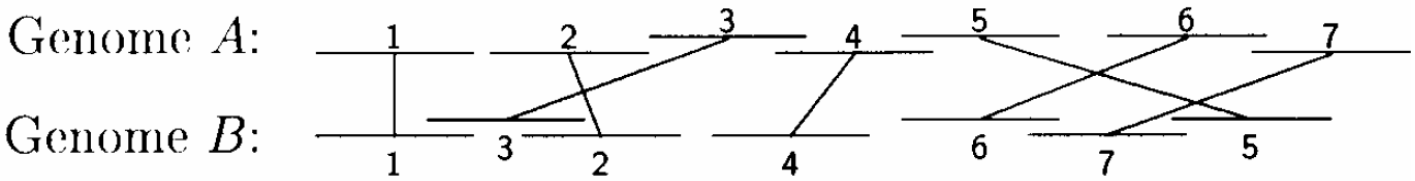
- The subsequence has an exact match on both genomes
- It is not a subsequence of another matched sequence
- It is unique

Example

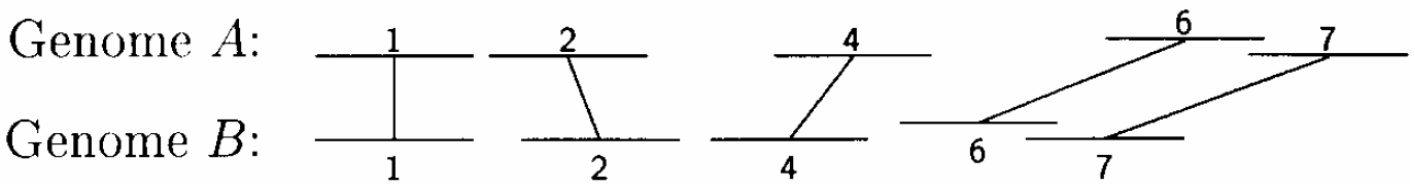
```
tcgatcGACGATCGCGGCCGTAGATCGAATAACGAGAGAGCATAAcgactta
gcattaGACGATCGCGGCCGTAGATCGAATAACGAGAGAGCATAAtccagag
```

Step 3: Sorting the matches found in the MUM alignment

Once we have found the MUMs, we enumerate them like this:

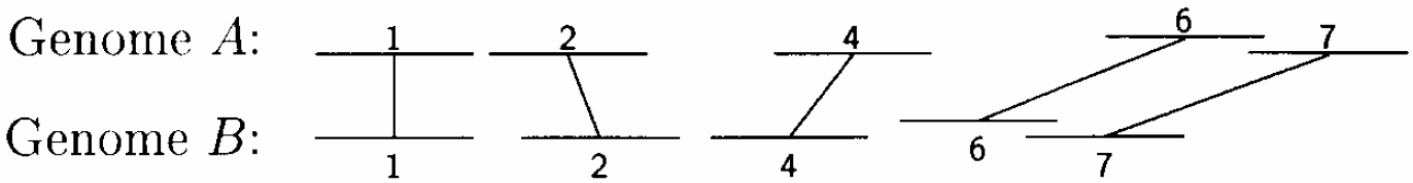


Problem: We cannot align all MUMs because they aren't in the same order in both genomes.
Solution: Align as many MUMs as we can:



Step 4: Closing the gaps

Everything in between the MUMs is called **gaps**.



- To find alignment for the gaps we can use any alignment algorithm.
- MUMmer uses the Smith-Waterman algorithm.

Diving deeper

How do we go from use suffix trees to find MUMs?

Example

In Two genomes

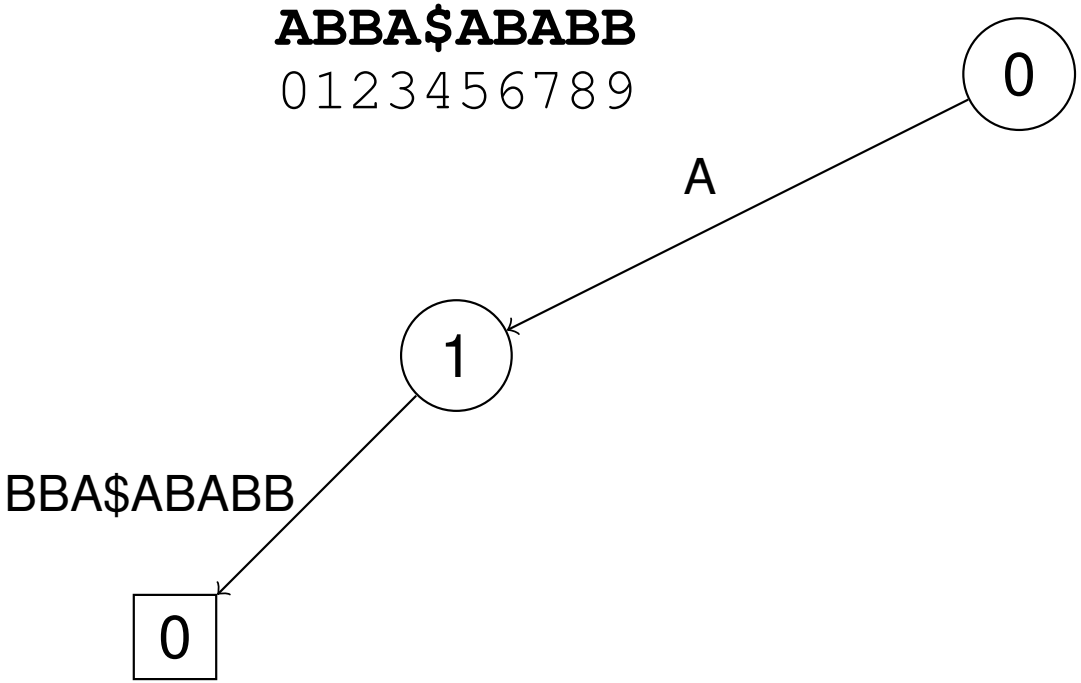
Genome A: `ABBA`

Genome B: `ABABB`

Out List of all MUMs.

Combined string: `ABBA$ABABB`

Creating a suffix tree



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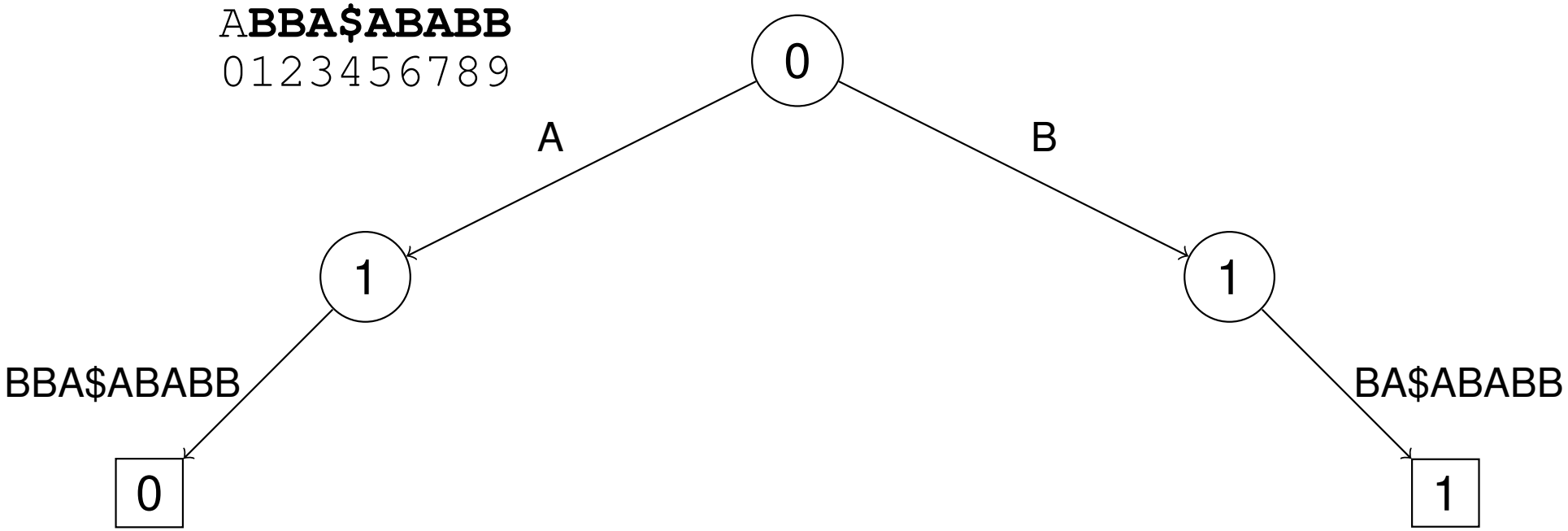

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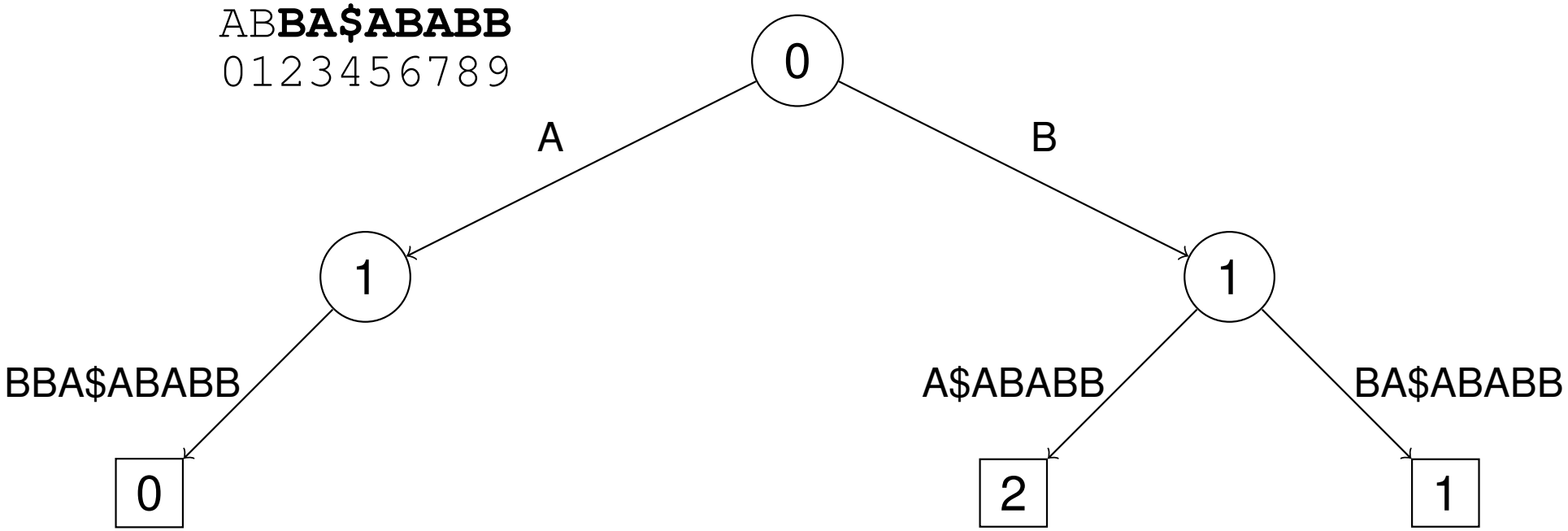

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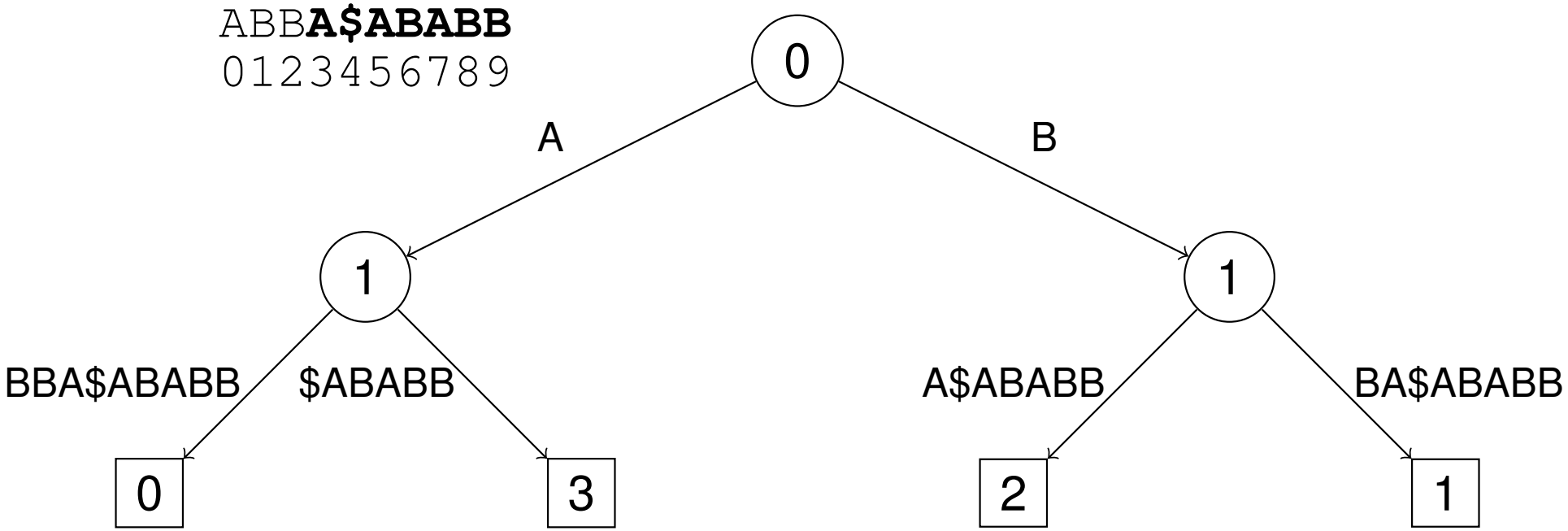

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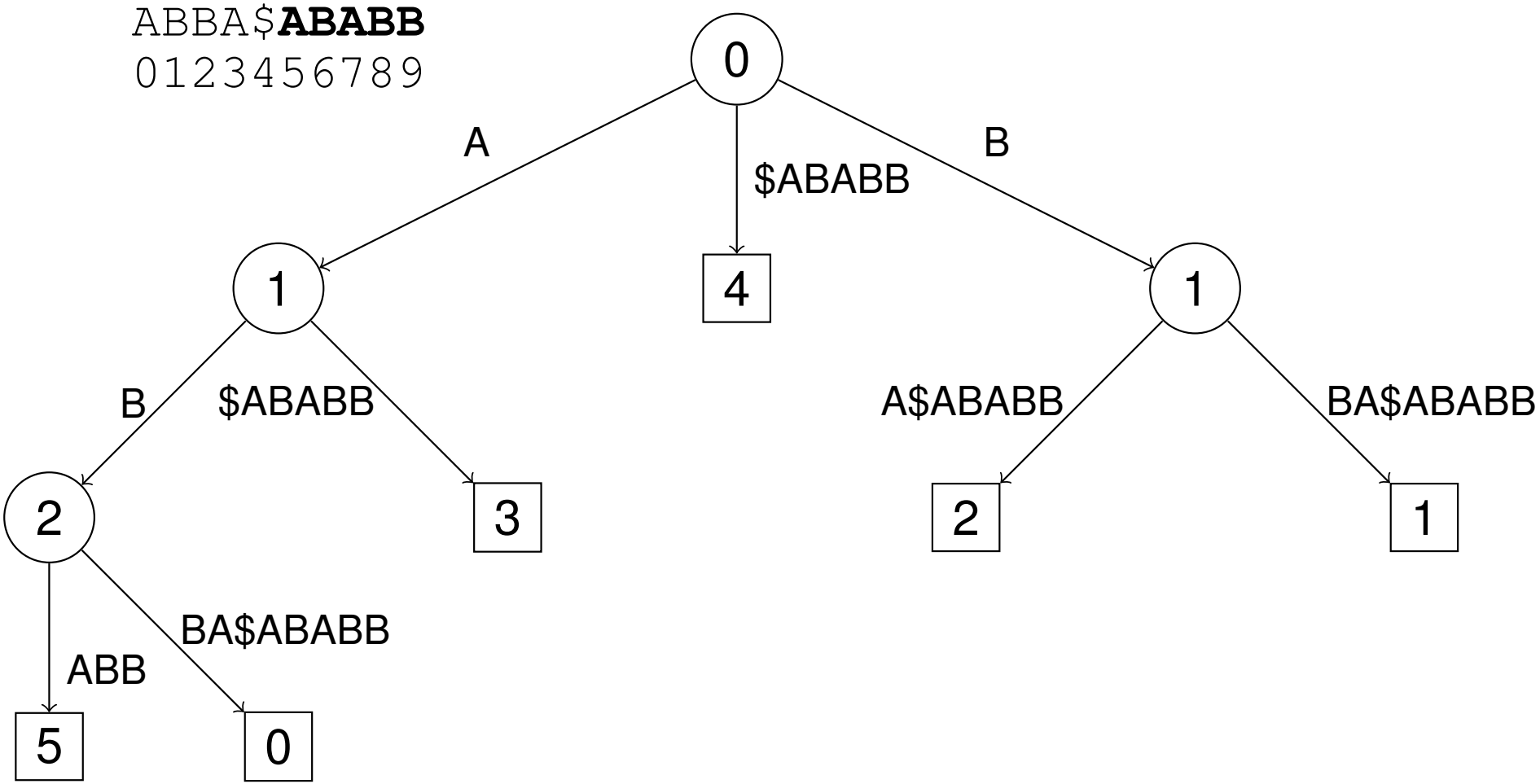

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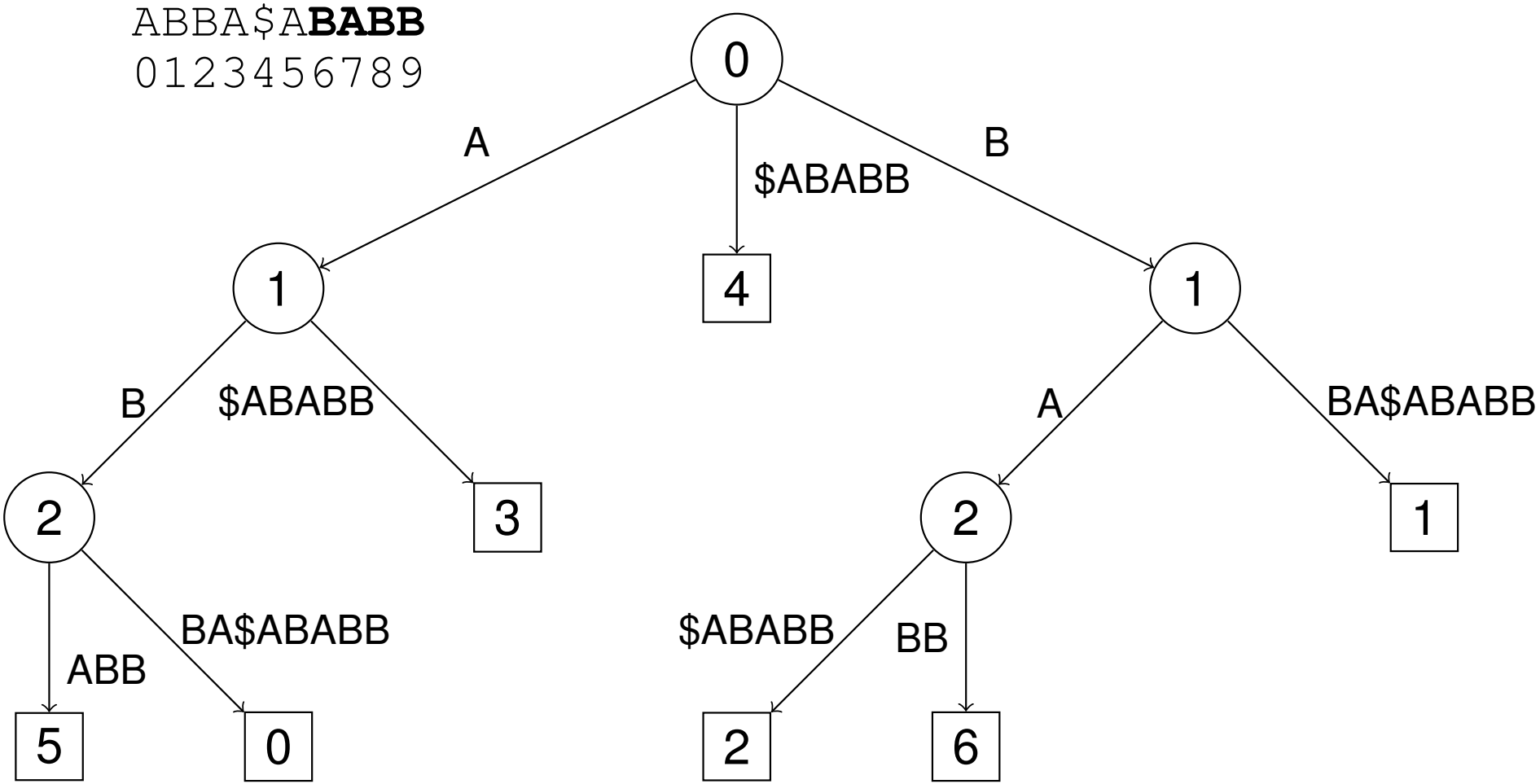

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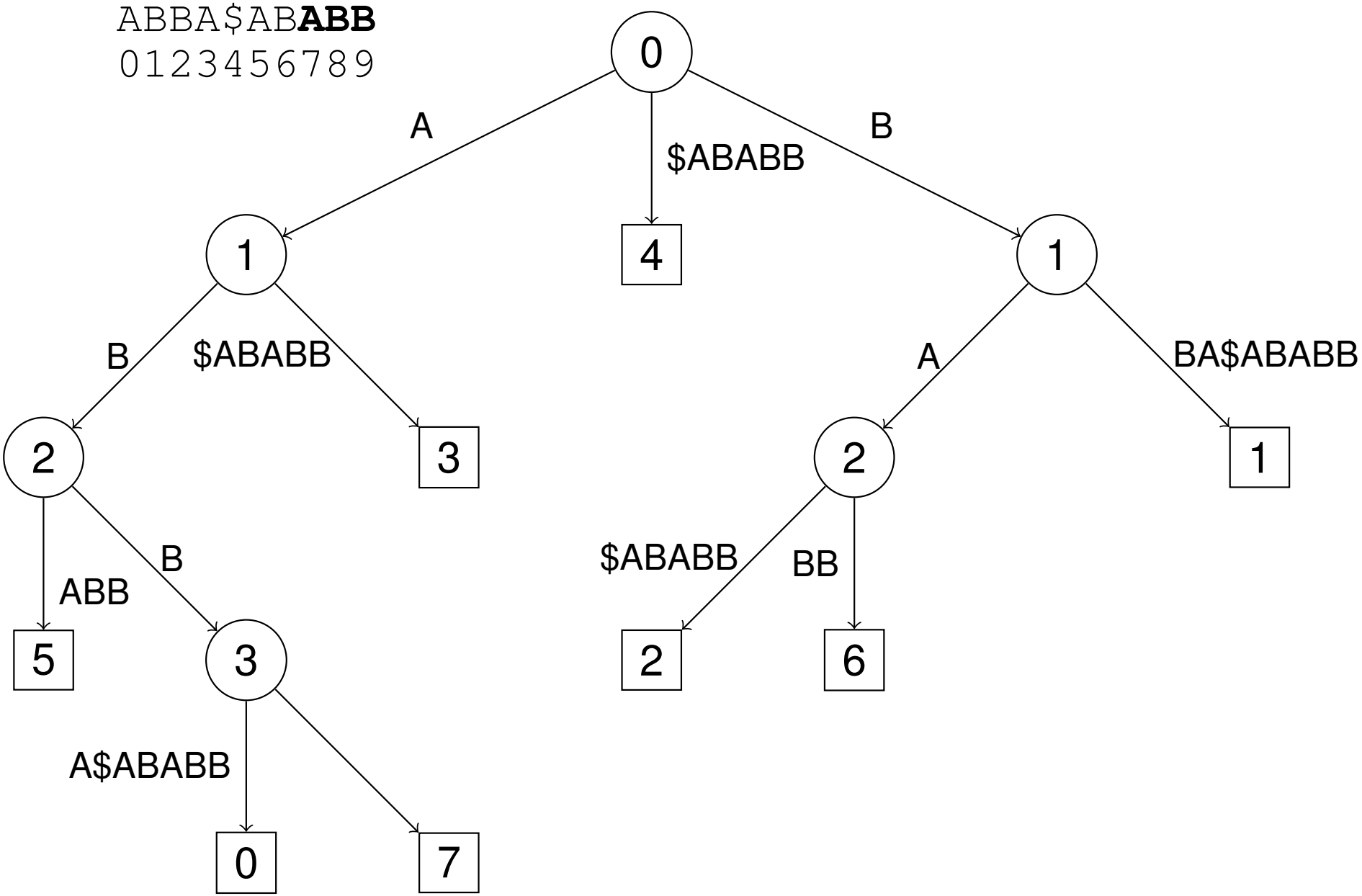

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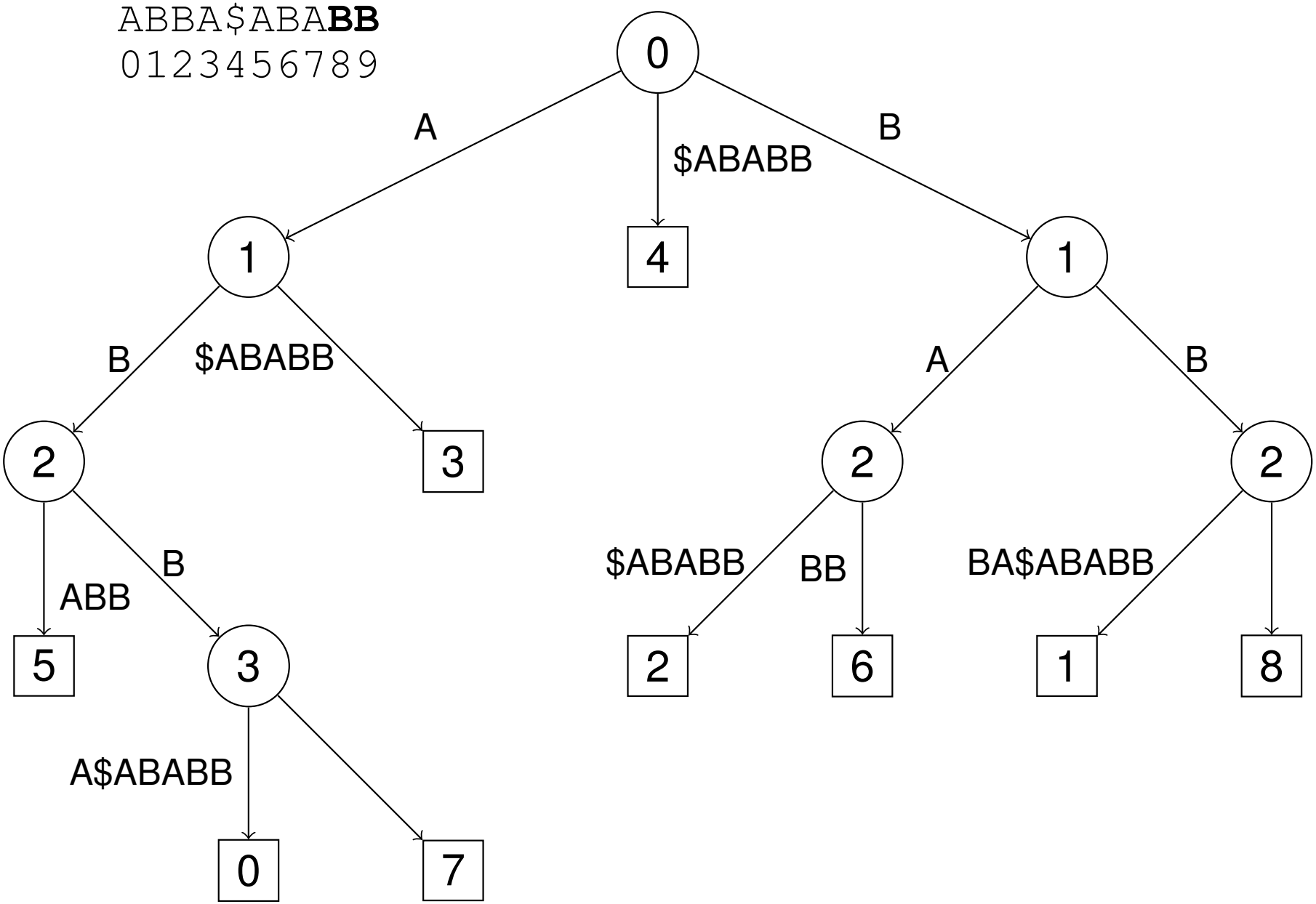

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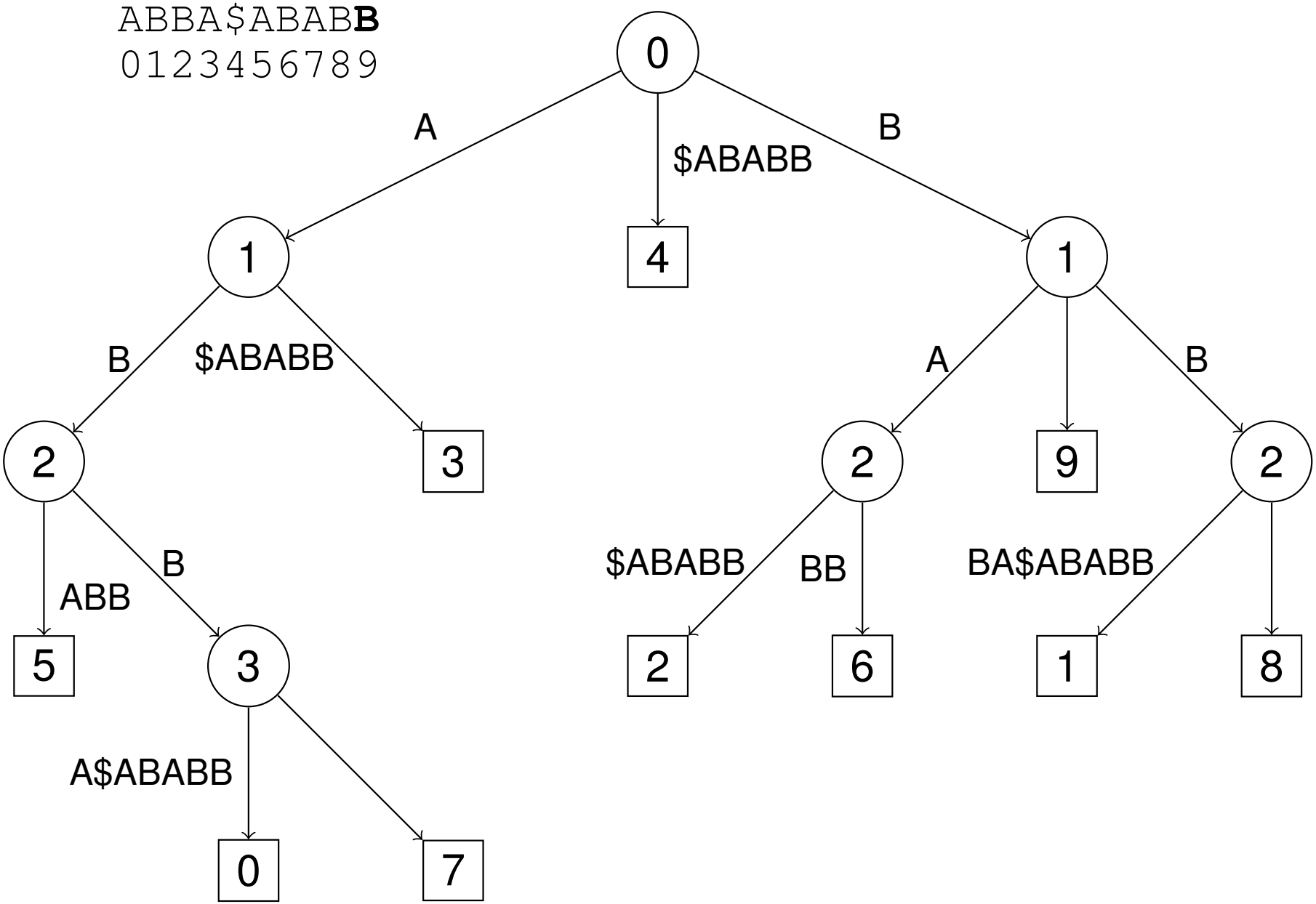


Finding MUMs from suffix tree

Let's recall what condition MUMs had to have:

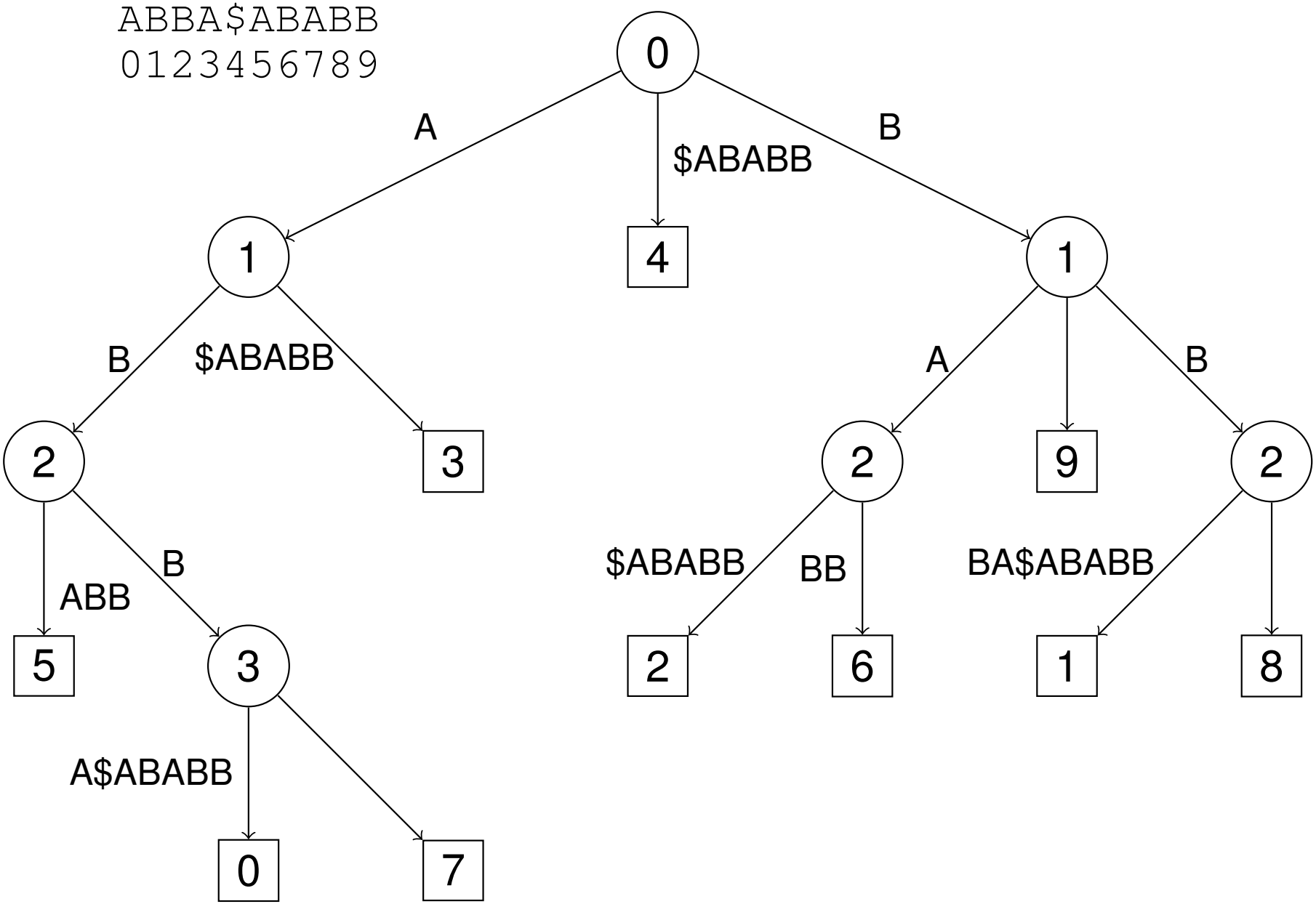
1. Exact matches on both genomes.
2. Surrounded by mismatches.
3. Unique.

We can achieve conditions 1 and 3 by searching the tree for a internal node with:

- Exactly two leafs.
- Both leaves start on each side of the dollar sign.

We'll need to check for condition 2 afterwards.

Finding potential MUMs



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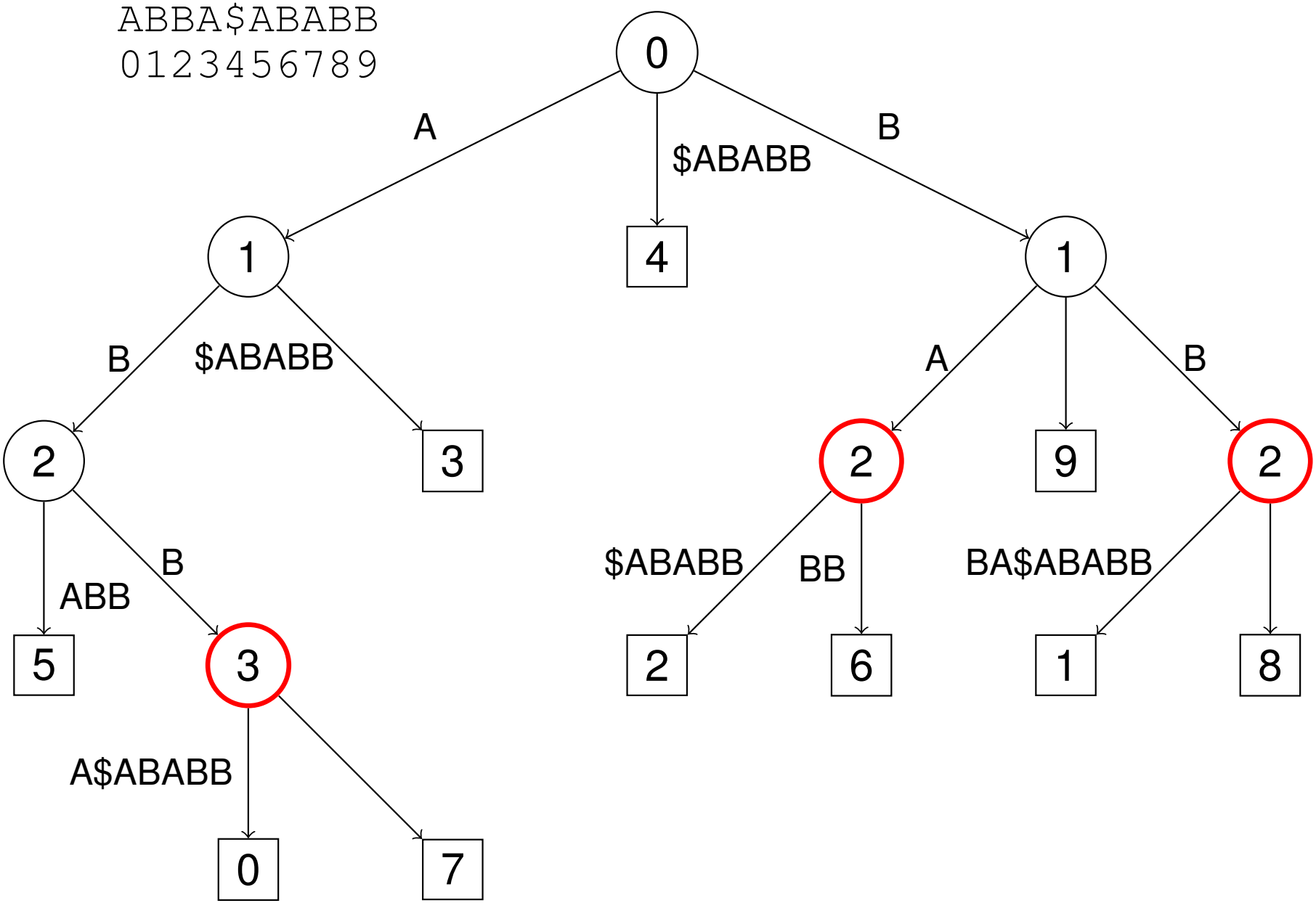

Potential MUMs to MUMs

We have the following potential MUMs:

- `ABB` at starting positions 0 and 7.
- `BA` at starting positions 2 and 6.
- `BB` at starting positions 1 and 8.

Our string: `ABBA$ABABB`. Let's check if condition 2 is satisfied

- `ABB` achieves condition 2 (it's surrounded by mismatches).
- `BA` achieves condition 2 as well.
- `BB` does NOT achieve condition 2. In both cases it is preceded by a `A`.

Resulting MUMs: **`ABB`** and **`BA`**.

Results and conclusion

MUMmer was put to the test on various genomes:

- Two strains of tuberculosis (bacteria) that are >99% identical
  - 5 seconds to create the suffix tree.
  - 45 seconds to sort the MUMs.
  - 5 seconds to generate alignments of the gaps.

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So in conclusion:

- If the two genomes are very similar, MUMs sequences will...:
  - ...be long and cover most of the genome.
  - ...rarely be a random match. Therefore few or no errors.
  - ...make the algorithm run fast (almost linear time)
- If the genomes are very different, MUMs sequences will...:
  - ...be short and cover a small part of the genome.
  - ...often be a random match. Therefore many errors.
  - ...make the algorithm run slow.

MUMmer 3

- MUMmer 3 is the latest version of MUMmer
- It was released in 2004 and is open-source.
- Requires less than half the memory and more than twice as fast than the initial MUMmer.
- Most notable features added since the initial MUMmer:
  - You can allow tolarence for mismatches when finding MUMs.
  - Can handle non-unique MUMs.
  - All sorts of visualization tools.

Thank you!

Feel free to ask any questions.