Alignment of whole genomes using MUMmer

Presentation in Algorithms in Bioinformatics (TÖ111F)

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Motivation

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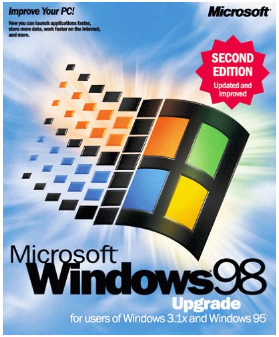
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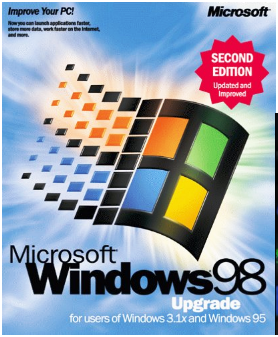
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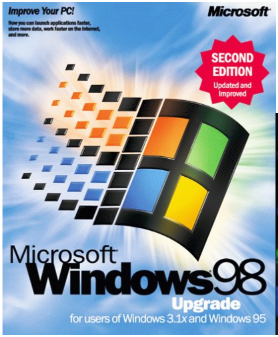

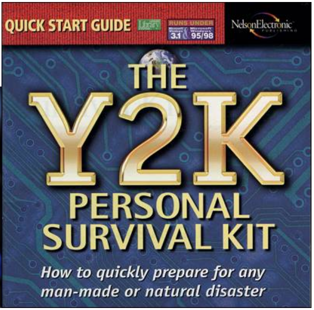
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Meanwhile at that particular time in bioinformatics...

- The number of sequenced genomes was very low but increasing very fast.
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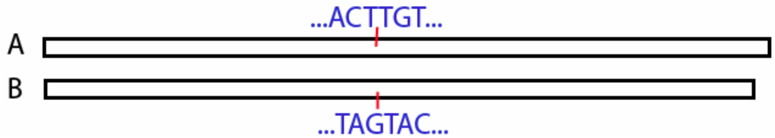
Problem:

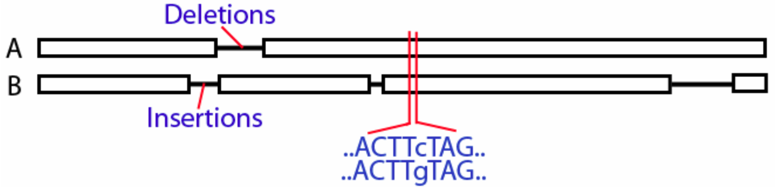
- We had algorithms that were made for single gene sequences.
- They didn't work well with whole genomes.
- It's simple: Size matters.
  - Require way too much memory or
  - take extremely long time to compute.

Problem description

In Two genomes, A and B. Both could be very large (millions of nucleotides)



Out Align the two genomes to maximize the number of matches using insertions and deletions.



Introduction to MUMmer

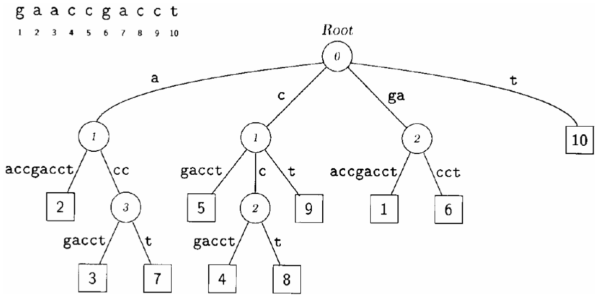
MUMmer:

- Was published in 1999.
- Is a system used to align whole genome sequences.
- Idea: Find 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

MUM is a abbreviation for Maximal Unique Matches.

Definition

A sequence is a MUM if and only if:

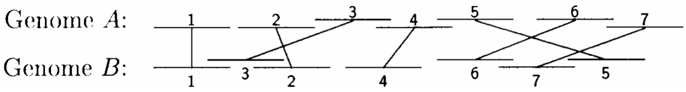
- The sequence has an exact match on both genomes
- and it is not a subsequence of another matched sequence
- and it is unique

Example

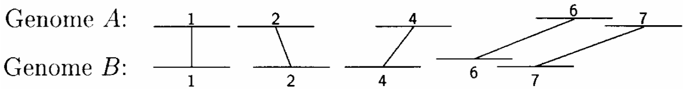
```
tcgatcGACGATCGCGGCCGTAGATCGAATAACGAGAGAGCATAAcgactta
gcattaGACGATCGCGGCCGTAGATCGAATAACGAGAGAGCATAAtccagag
```

Step 3: Sorting the matches found in the MUM alignment

We enumerate the found MUMs like this:

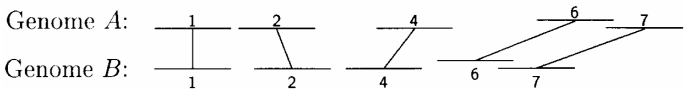


Problem: We cannot align all MUMs because they aren't in the same order in both genomes.
Solution: Align as many MUMs as we can:



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 suffix trees to finding MUMs?

Example

In Two genomes

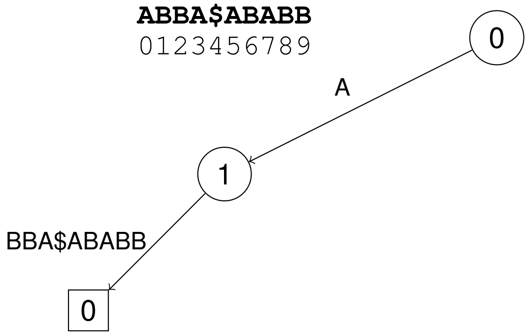
Genome A: `ABBA`

Genome B: `ABABB`

Out List of all MUMs.

Combined string: `ABBA$ABABB`

Creating a suffix tree



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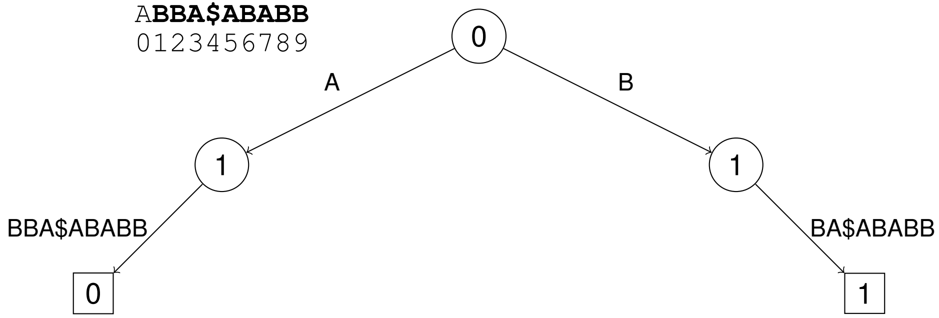

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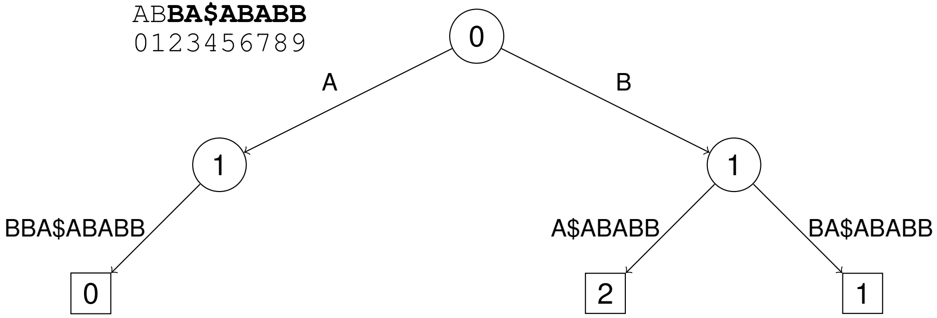

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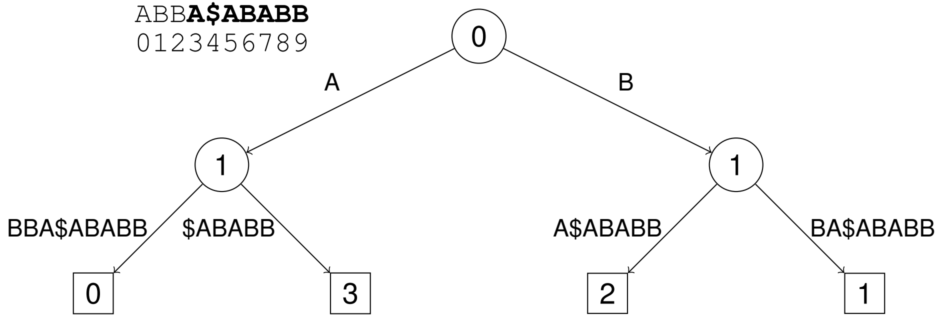

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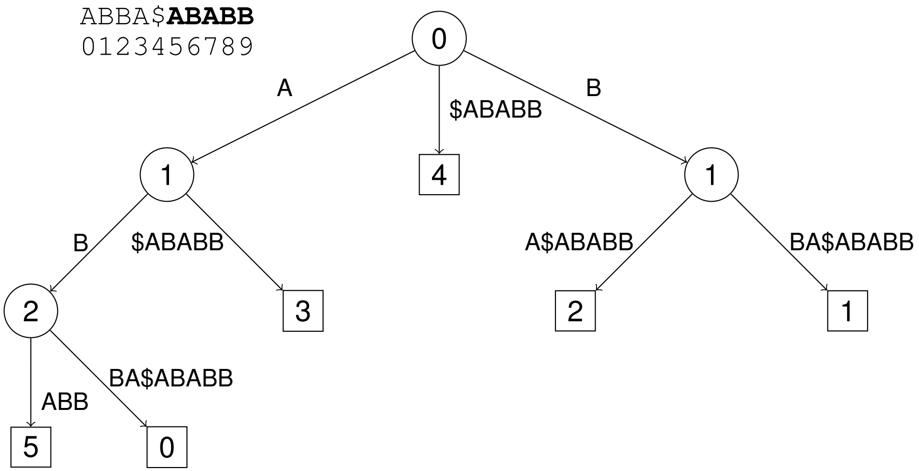
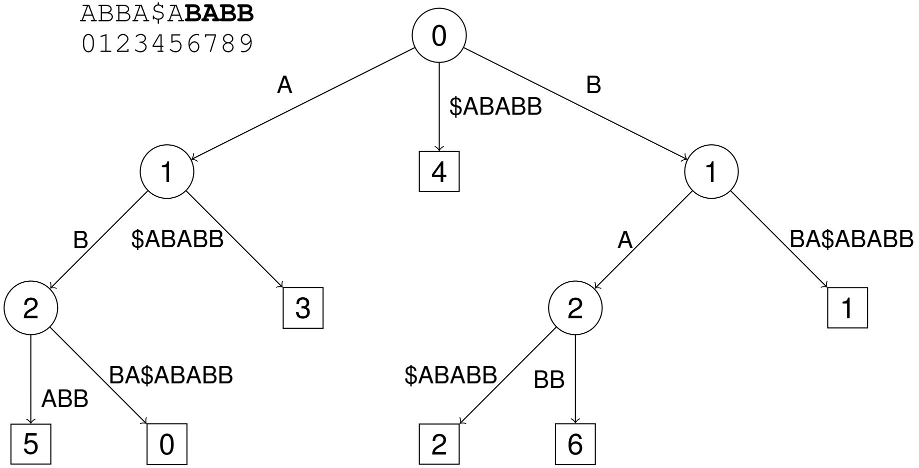


Creating a suffix tree

ABBA$A**BABB**
0123456789



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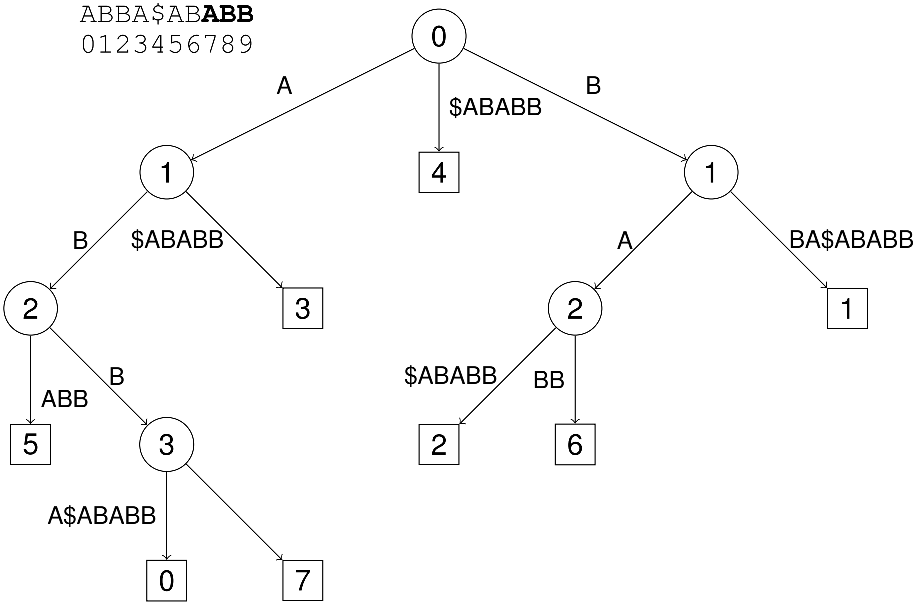

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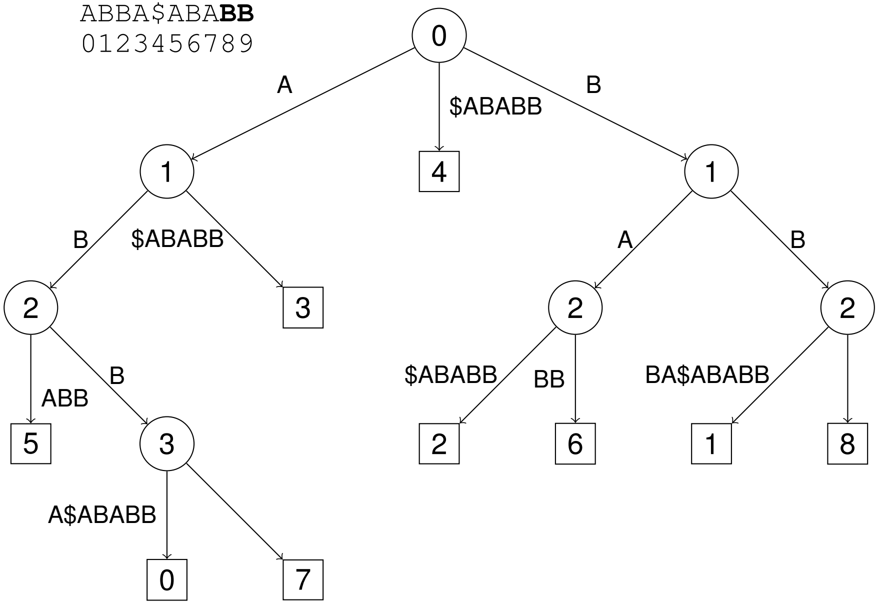

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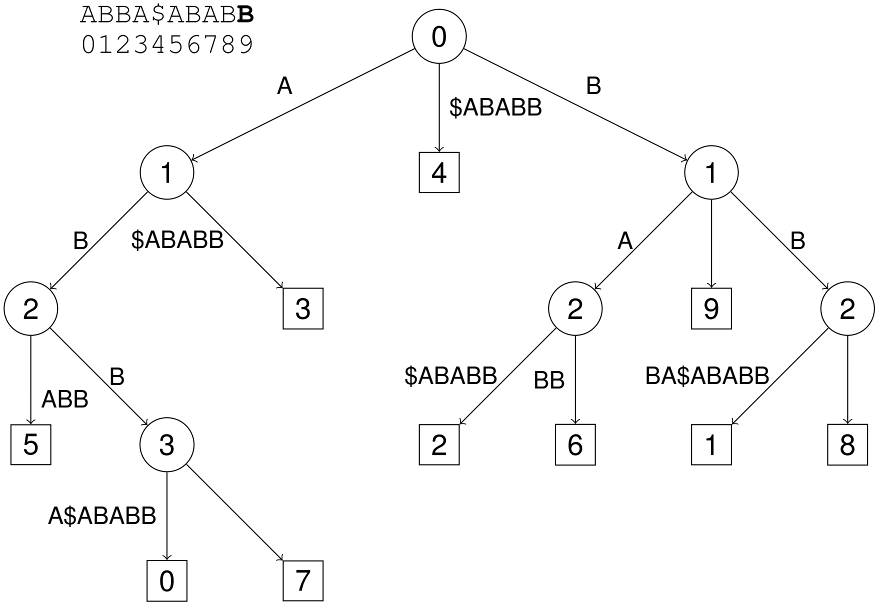


Finding MUMs from suffix tree

Let's recall what condition MUMs had to have:

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

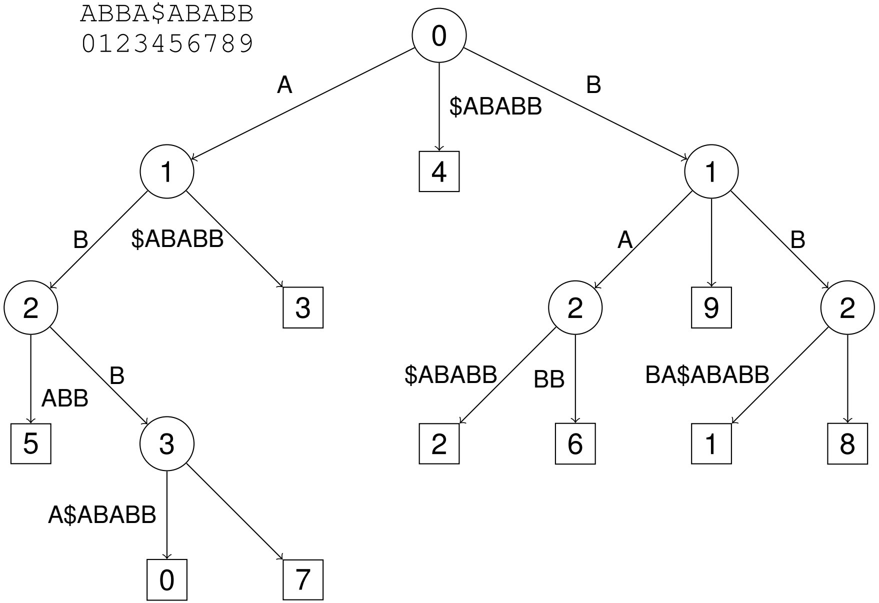
We can satisfy conditions 1 and 3 by searching the tree for a internal node with:

- Exactly two leafs.
- Both leaves' starting positions are on each side of the dollar sign.

We'll need to check for condition 2 afterwards.

Finding potential MUMs

```
ABBA$ABABB
0123456789
```



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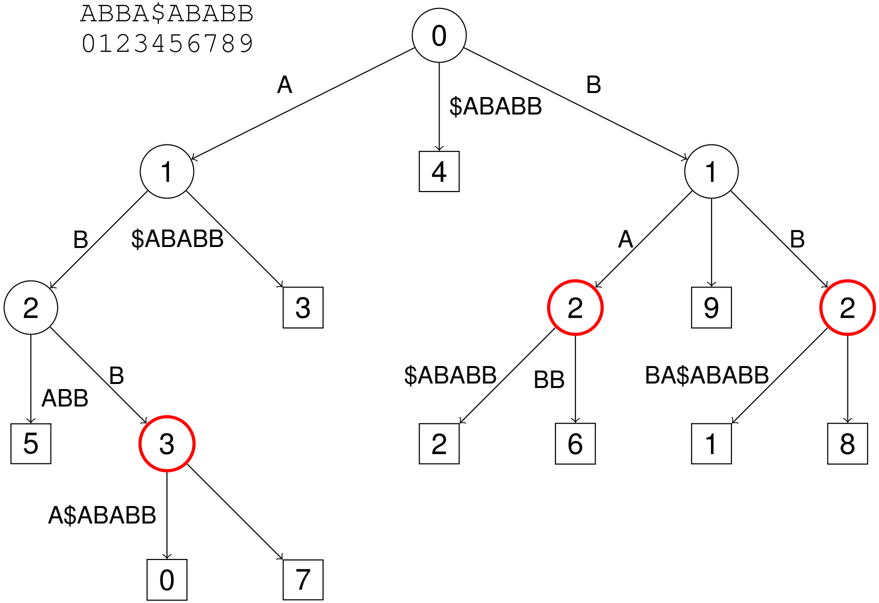

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We have the following potential MUMs:

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

- `ABB` satisfies condition 2.
- `BA` satisfies condition 2.
- `BB` does NOT satisfy condition 2.

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

Results and conclusion

- Two strains of tuberculosis that are >99% identical
  - 5 seconds to create the suffix tree.
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- If the two genomes are very similar, MUM sequences will...
  - ...be long and cover most of the genome.
  - ...rarely be a random match.
  - ...make the algorithm run fast.
- If the genomes are very different, MUM sequences will...
  - ...be short and cover a small part of the genome.
  - ...often be a random match.
  - ...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 memory and is a lot faster 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.

Original papers:
`http://mummer.sourceforge.net/MUMmer.pdf` by Arthur L. Delcher, Simon Kasif, Robert D. Fleischmann, Jeremy Peterson, Owen White and Steven L. Salzberg.

and

`http://mummer.sourceforge.net/MUMmer3.pdf` by Stefan Kurtz, Adam Phillippy, Arthur L. Delcher, Michael Smoot, Martin Shumway, Corina Antonescu and Steven L. Salzberg.