TwoPaCo: An efficient algorithm to build the compacted de Bruijn graph from many complete genomes

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Motivation

- More and more complete genomes
- Pan-genome: analysis within same species
- Mammalian-sized genomes are coming soon

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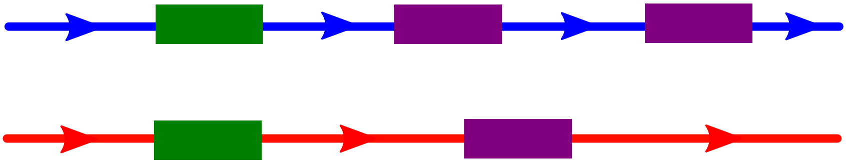
Key question: what is a handy data structure to represent genomes?

The simplest way: string(s) of characters.

The Linear Representation

Two genomes:



The Linear Representation

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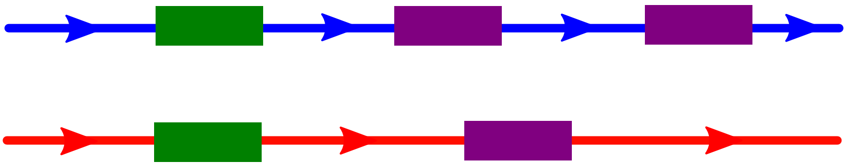
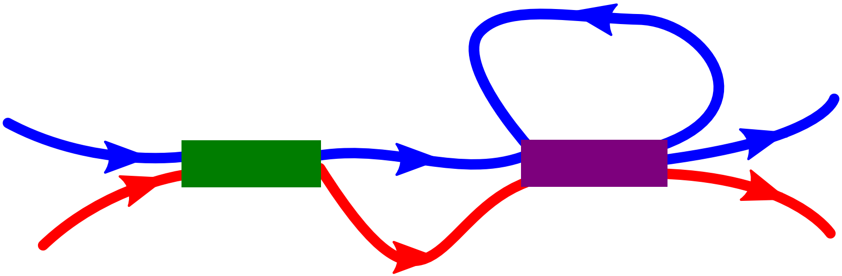


Issues:

- Homology between genomes?
- Duplications?
- Rearrangements?

Solution: a Graph Representation

What we want to see:



Why de Bruijn graph?

A simple object.

Demonstrated utility in:

- Assembly
- Read mapping
- Synteny identification

The de Bruijn Graph

$k = 2$

TGACGTC TGACTTC

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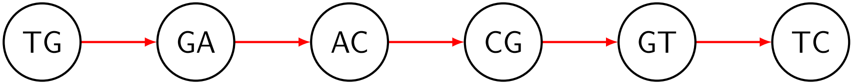
$$\begin{tikzcd} TG \arrow[r] & GA \arrow[r] & AC \arrow[r] & CG \arrow[r] & GT \arrow[r] & TC \end{tikzcd}$$

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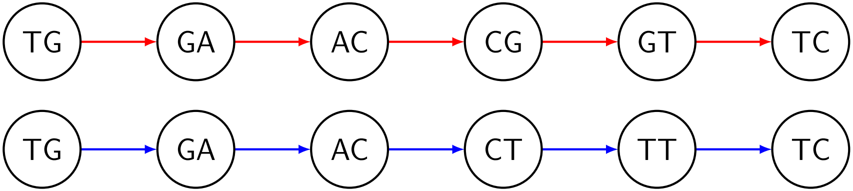

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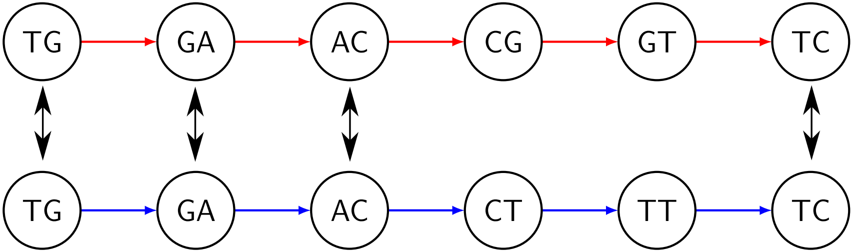

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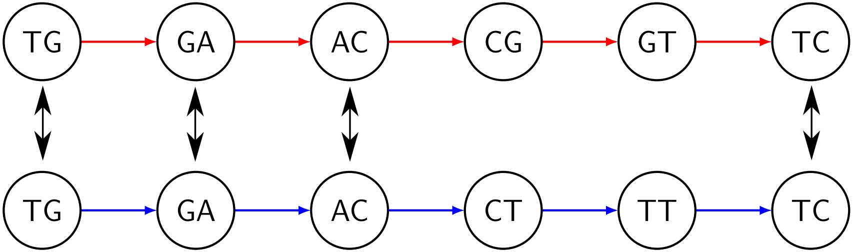
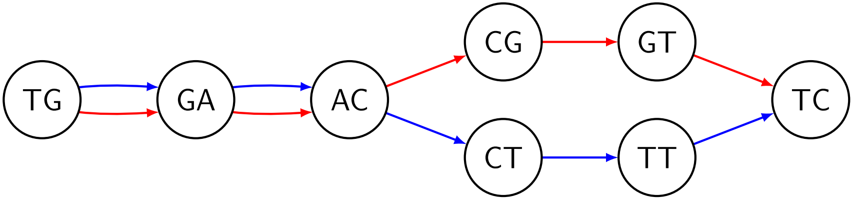
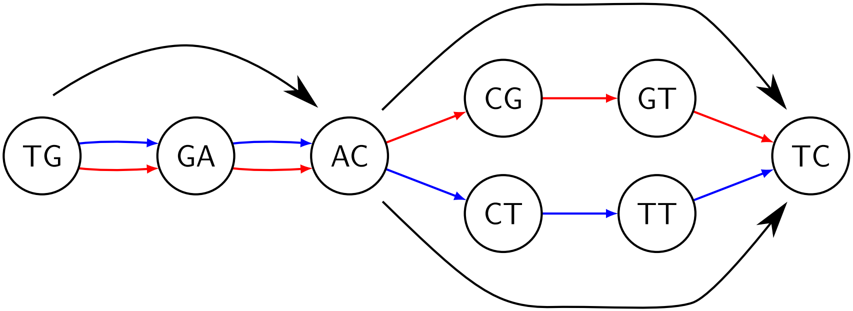




Compaction



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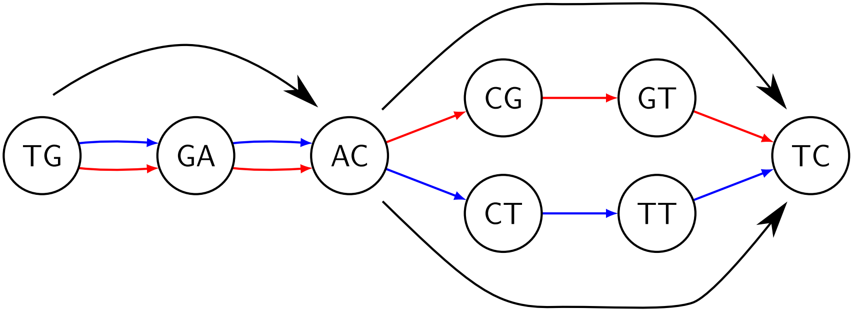
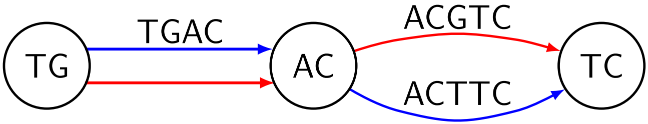


After compaction:



The Challenge

Construct the compacted graph from many large genomes **bypassing** the ordinary graph traverse.

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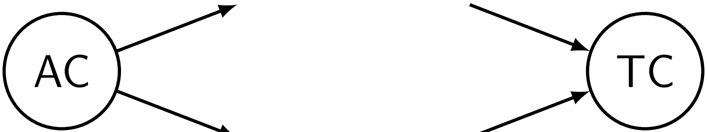
A recent advance: 7 Humans in 15 hours using 100 GB of RAM using a BWT-based algorithm by Baier *et al.*, 2015, Beller *et al.*, 2014.

Junctions

A vertex v is a **junction** if:

- v has ≥ 2 distinct outgoing or incoming edges:



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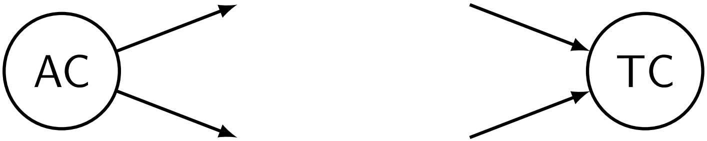

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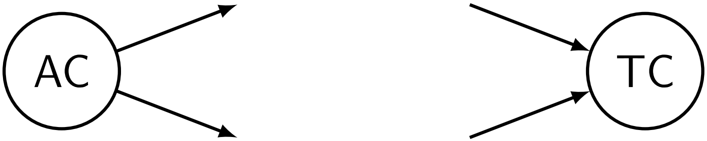

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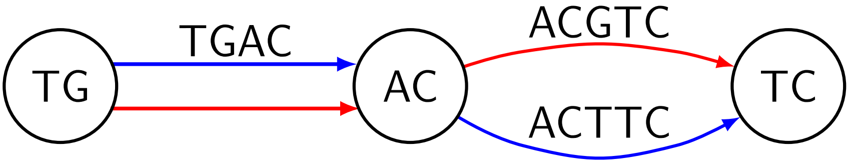
Facts:

- Junctions $=$ vertices of the compacted graph
- Compaction $=$ finding positions of junctions

Observations



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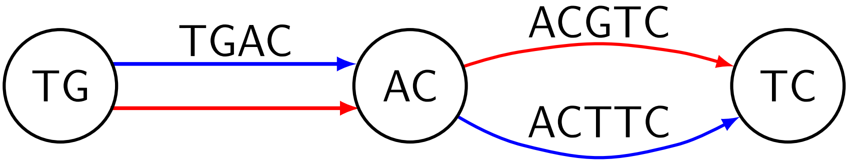

TG GA AC CG GT TC

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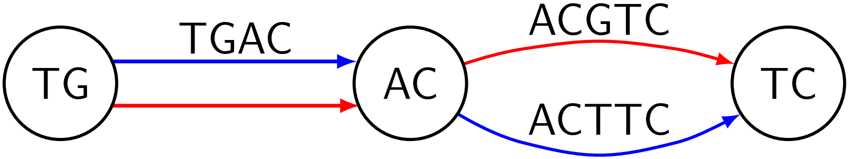

TG GA AC CG GT TC

TG $\rightarrow$ AC $\rightarrow$ TC

The Observation

The observation only works when we have complete genomes.

Once we know junctions, construction of the edges is simple.

We can simply traverse input strings and record junctions in the order they appear.

How to identify junctions?

The Naive Algorithm

A naive way:

- Store all $(k+1)$-mers (edges) in a hash table
- Consider each vertex one by one
- Query all possible edges from the table
- If found > 1 edge, mark vertex as a junction

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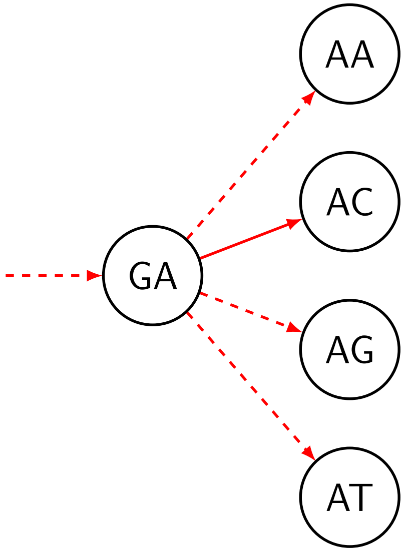
Problem: the hash table can be too large.

An Example

Hash table = { GA $\rightarrow$ AC }



What is the Bloom filter

A probabilistic data structure representing a set

Properties:

- Occupies fixed space
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Is GA $\rightarrow$ AC in the set? Yes.

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- Occupies fixed space
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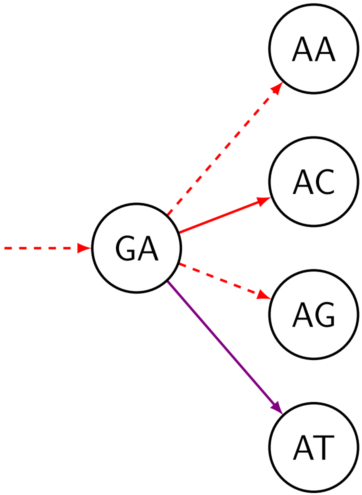
Example: Bloom Filter $=$ { GA $\rightarrow$ AC }

Is GA $\rightarrow$ AC in the set? Yes.

Is GA $\rightarrow$ AT in the set? **Maybe** no.

An Example

Bloom Filter = { GA → AC, GA → AT }



The purple edge is a false positive.

The Two Pass Algorithm

How to eliminate false positives?

The Two Pass Algorithm

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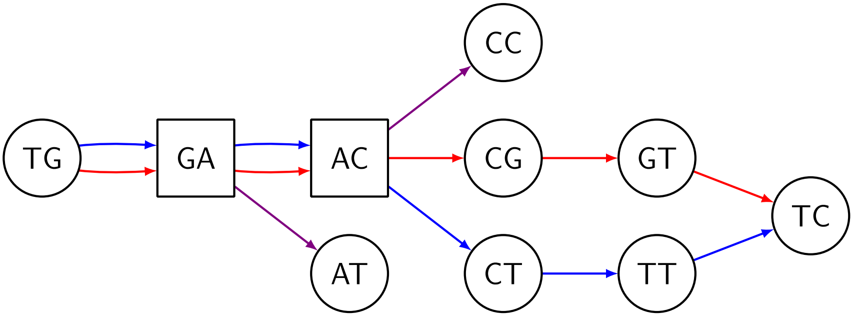
Two-pass algorithm:

1. Use the Bloom filter to identify **junction candidates**
2. Use the hash table, but store **only edges that touch candidates**

An Example: the First Step

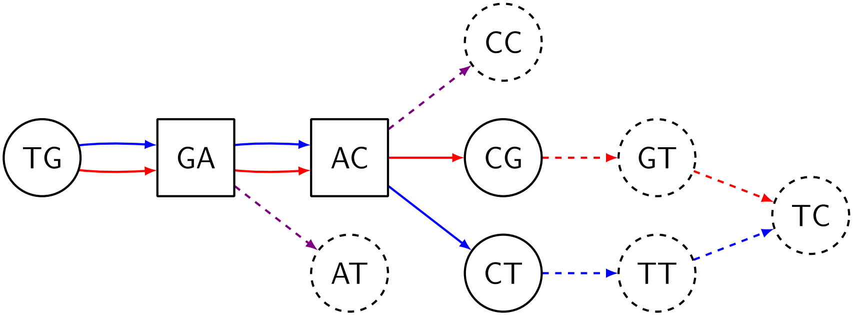
Here edges stored in the Bloom filter, purple ones are false positives:



Junction candidates: GA & AC

An Example: the Second Step

Edges stored in the hash table. We kept only edges touching junction candidates:



Junction: AC

Results

Datasets:

- 7 humans: 5 versions of the reference + 2 haplotypes of NA12878 from 1000 Genomes
- 93 simulated humans (FIGG)
- 8 primates available in UCSC genome browser

Results

Running time (minutes) & memory usage (GBs).

# genomes	BWT-based	TwoPaCo	
	1 thread	1 thread	15 threads
Humans			
7, $k = 25$	867 (100.30)	436 (4.40)	63 (4.84)
7, $k = 100$	807 (46.02)	317 (8.42)	57 (8.75)
43+7, $k = 25$	-	-	705 (69.77)
43+7, $k = 100$	-	-	927 (70.21)
93+7, $k = 25$	-	-	1383 (77.42)
Primates			
8, $k = 25$	-	914 (34.36)	111 (34.36)
8,$k = 100$	-	756 (56.06)	101 (61.68)

Conclusion & Future Work

Advantages of the algorithm:

- Fast
- Small memory footprint
- Can handle large inputs

Drawbacks:

- Less applicable for large k

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Take home message: it is easy to construct the compacted de Bruijn graph for complete genomes.

Conclusion & Future Work

Can potentially facilitate:

- Visualization
- Synteny mining (Sibelia)
- Structural variations analysis
- ...

Acknowledgments

Personal:

- Son Pham
- Daniel Lemire

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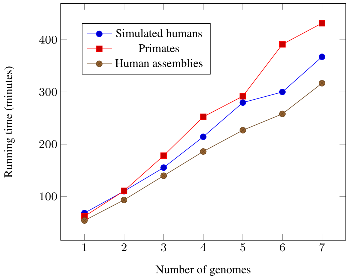
- DBI-1356529
- CCF-1439057
- IIS-1453527
- IIS-1421908

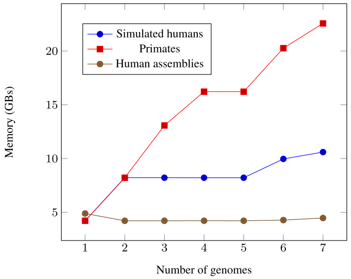
Thank you for your attention!

Input Size vs. Performance

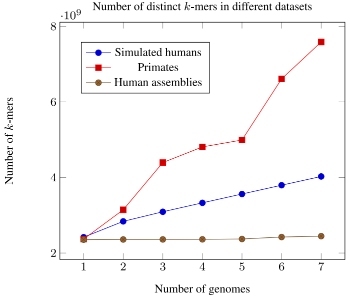
Running time



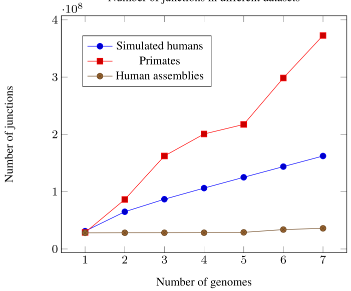
Maximum memory consumption



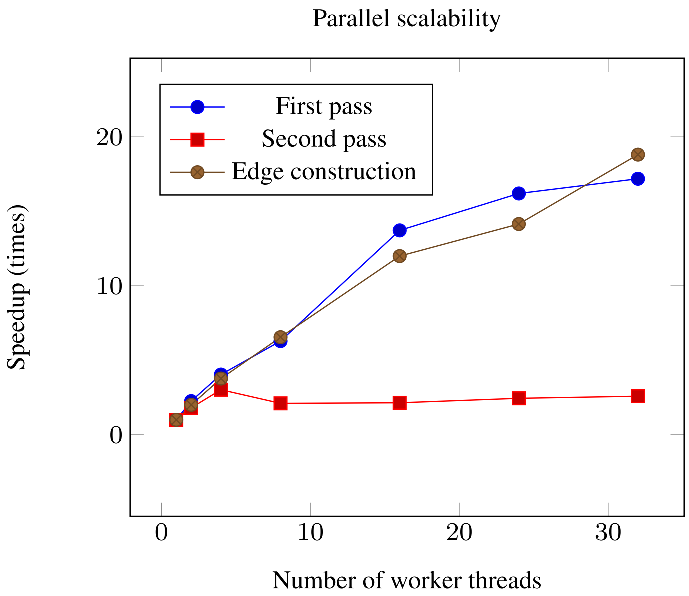
Number of distinct k-mers in different datasets



Number of junctions in different datasets



Parallel Scalability



Splitting

Table 1: The minimal number of rounds it takes to compress the graph without exceeding a given memory threshold.

Memory threshold	Used memory	Bloom filter size	Running time	Rounds
10	8.62	8.59	259	1
8	6.73	4.29	434	3
6	5.98	4.29	539	4
4	3.51	2.14	665	6