Searching massive amounts of sequencing data using K-mers and graphs

Finlay Maguire

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FCS, Dalhousie

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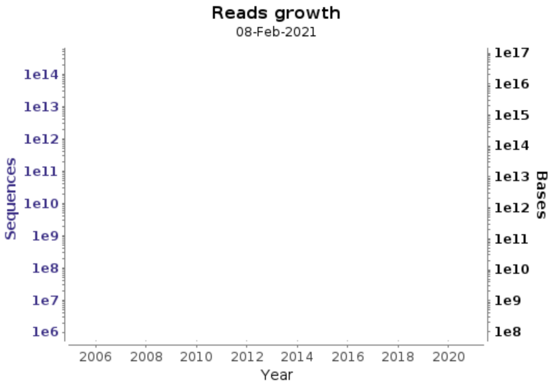
- Outline the two main strategies for k-mer indexing: colour aggregative and k-mer aggregative
- Describe the core algorithm used by BlastFrost (colour aggregative) and BIGSI (k-mer aggregative)

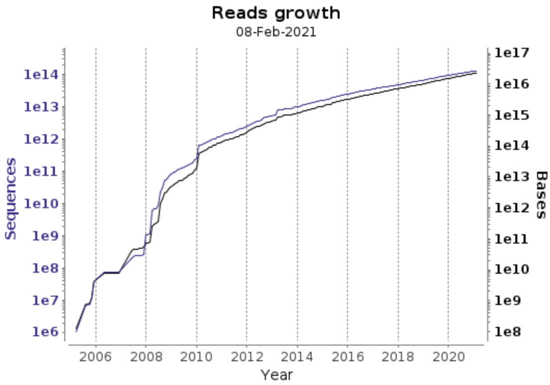
Massive datasets?

Sequencing Data Explosion



European Nucleotide Archive: Read Data

Sequencing Data Explosion



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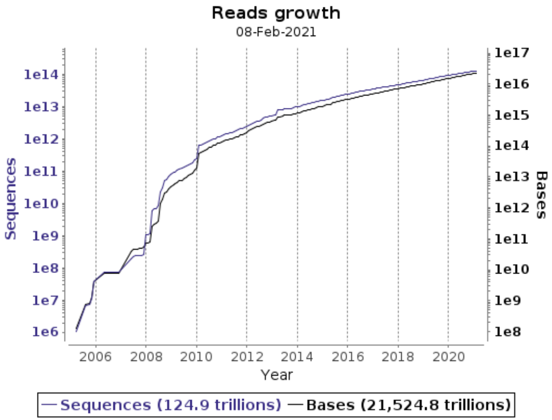

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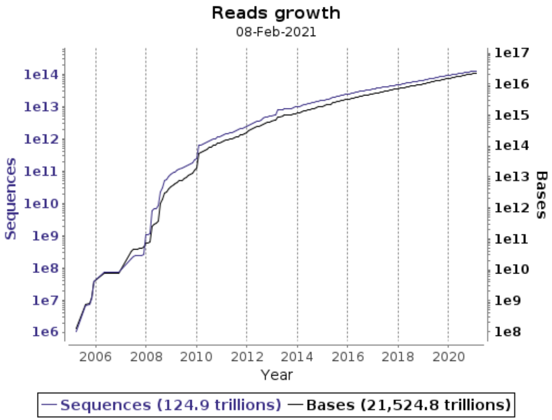

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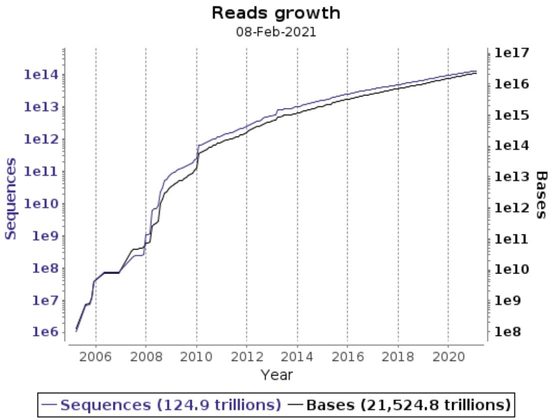

European Nucleotide Archive: Read Data

- Uncompressed at 2-bits per base:
- 5,381.2 TB (without any metadata or accession information)

Searching all this data: surveillance of colistin resistance

Countries reporting plasmid-mediated colistin resistance encoded by *mcr-1*

Data source: Al-Tawfiq, J. A., Laxminarayan, R. & Mendelson, M. How should we respond to the emergence of plasmid-mediated colistin resistance in humans and animals? Int. J. Infect. Dis. (2016). doi:10.1016/j.ijid.2016.11.415

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Searching all this data: surveillance of colistin resistance

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Animals | Humans | Animals and humans | Animals and environment | Animals, humans and environment

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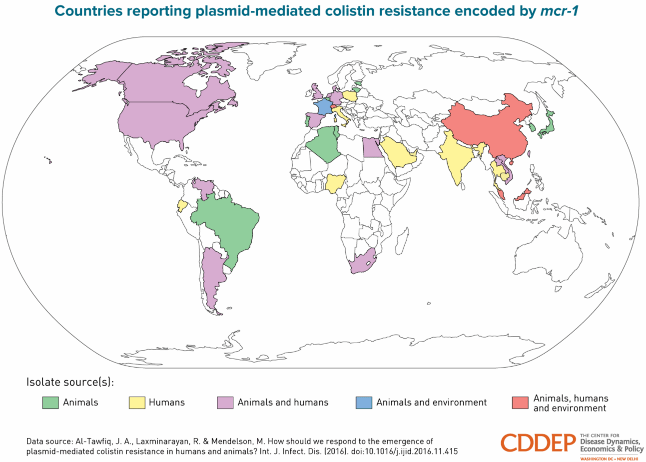

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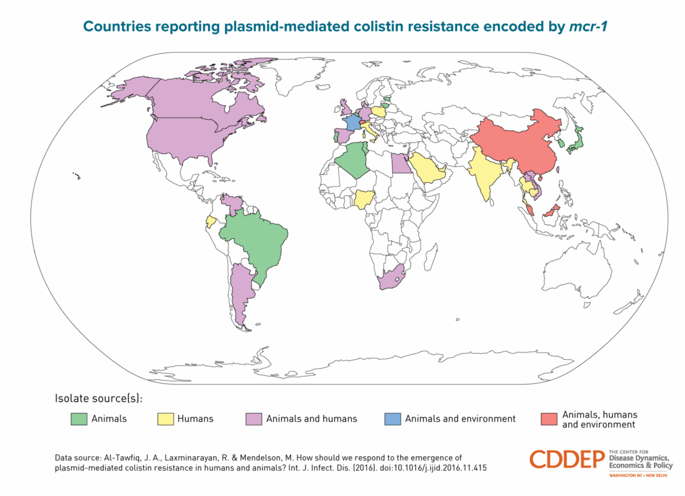

- Which genome and metagenome read sets from all over the world contain MCR-1?

Formal Problem

- $\mathcal{D}$ is a collection of n sets of reads

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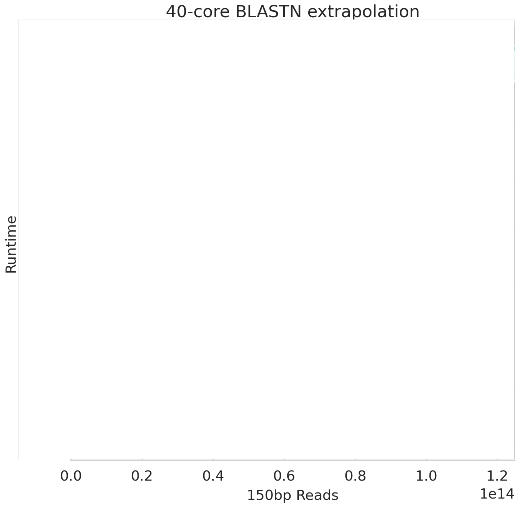
- Identify which sets of reads in $\mathcal{D}$ contain S

Just use BLAST?



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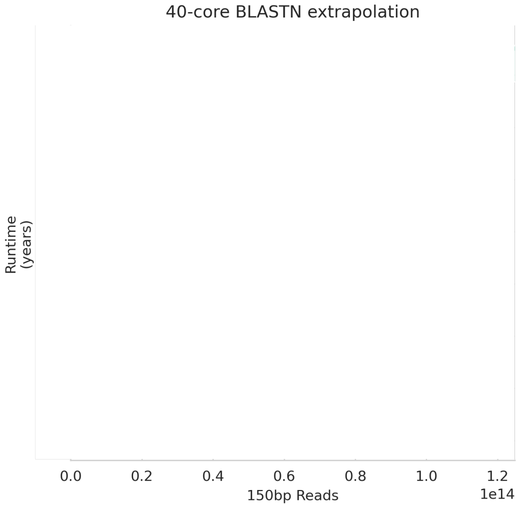

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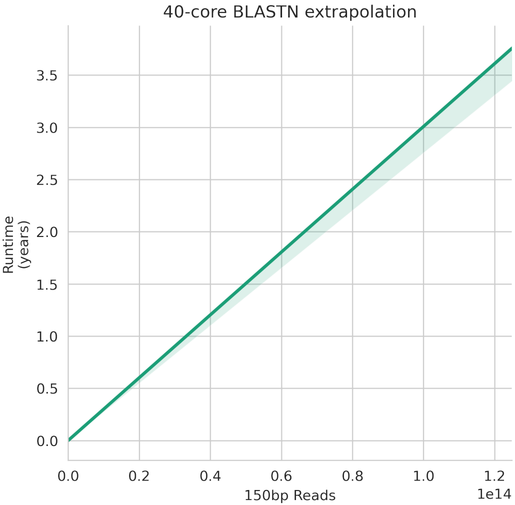

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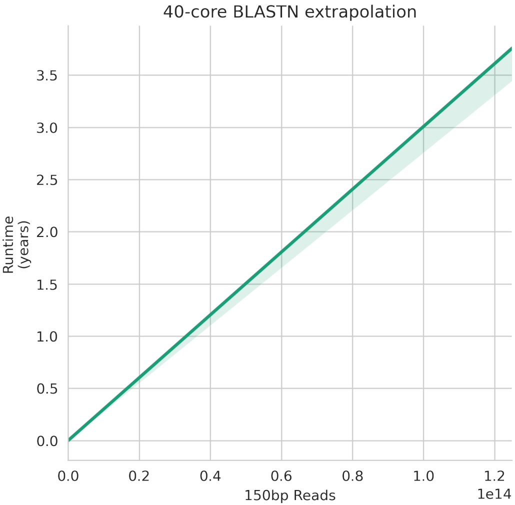
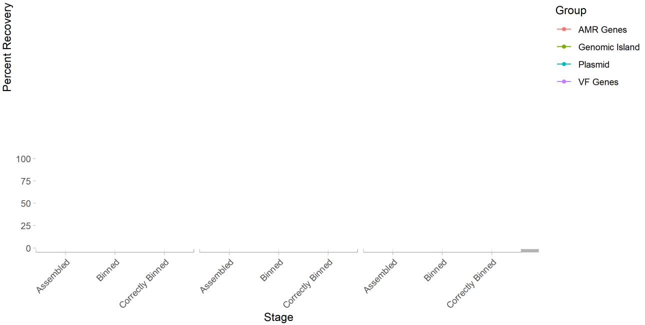


- By the end, there will be $\sim 3x$ more data than at the start.

What about only using assembled data?



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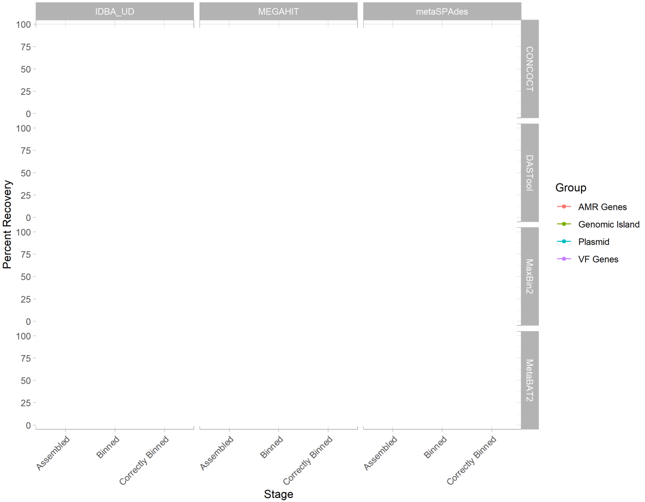

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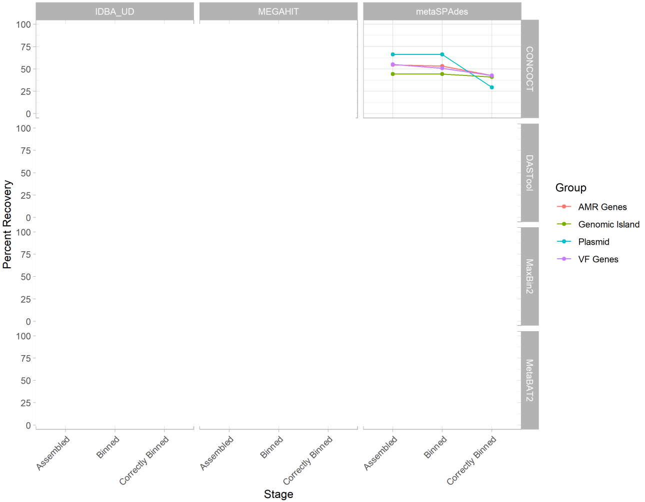

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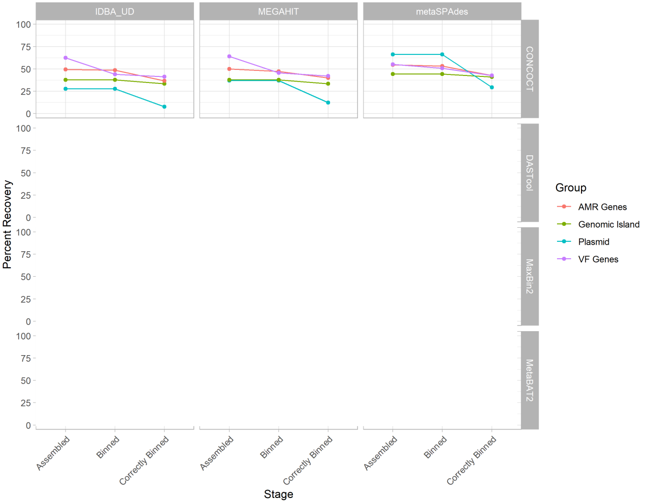

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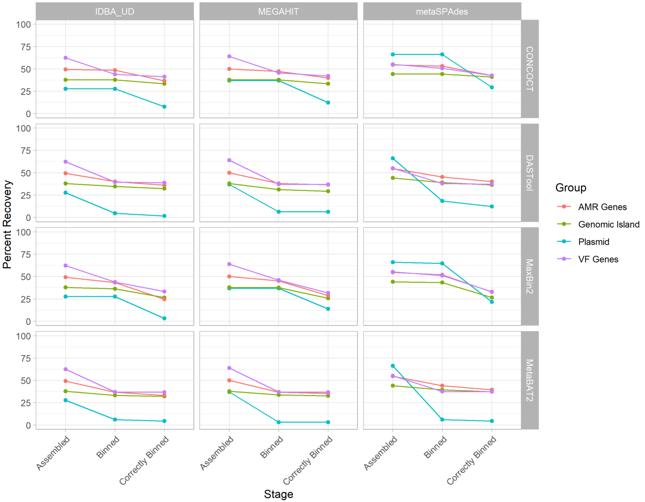

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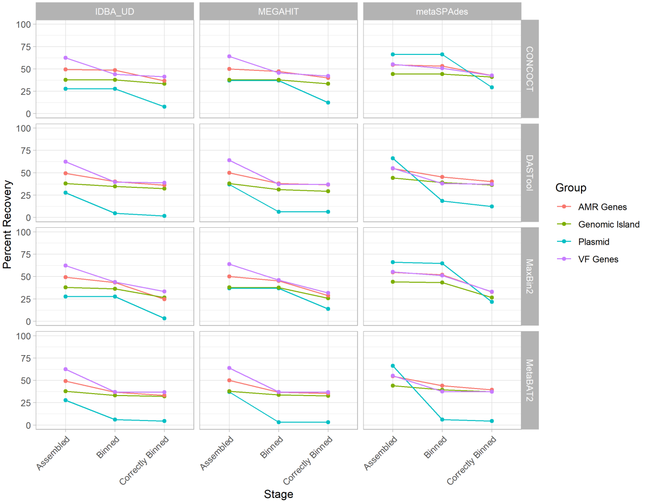

- No matter the method, assembly causes loss of information.

Let’s complicate but actually simplify this problem

k-mers!

Sequence Sets

k-mers!

Sequence Sets

AGCTCA

GGCTCA

k-mers!

Sequence Sets

AGCTCA

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Decompose to K-mers

k-mers!

Sequence Sets
AGCTCA
GGCTCA
Decompose to K-mers
AGC
GCT
CTC
TCA
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CTC
TCA

k-mers!


Sequence Sets
Decompose to K-mers
K-mer Counts
AGCTCA
GGCTCA
AGC
GCT
CTC
TCA
GGC
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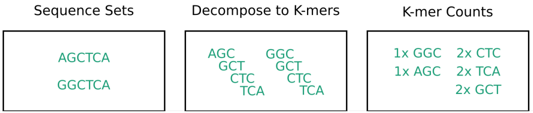
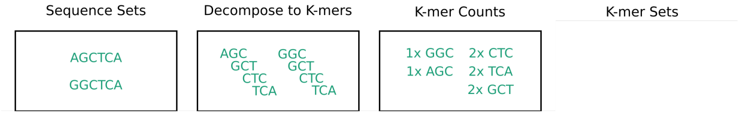
CTC
TCA

k-mers!



Sequence Sets
AGCTCA
GGCTCA
Decompose to K-mers
AGC GCT CTC TCA
GGC GCT CTC TCA
K-mer Counts
1x GGC
1x AGC
2x CTC
2x TCA
2x GCT

k-mers!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K-mer Sets

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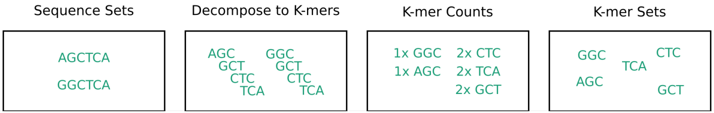
Sequence Sets
AGCTCA
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Decompose to K-mers
AGC GGC
GCT GCT
CTC CTC
TCA TCA
K-mer Counts
1x GGC 2x CTC
1x AGC 2x TCA
2x GCT
K-mer Sets
GGC CTC
TCA
AGC GCT

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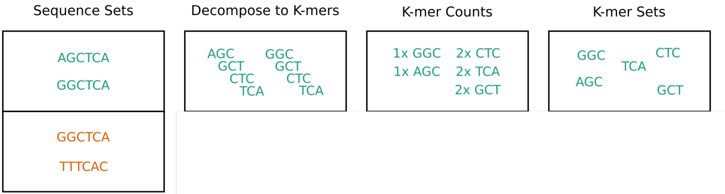

Sequence Sets
AGCTCA
GGCTCA
GGCTCA
TTTCAC
Decompose to K-mers
AGC
GCT
CTC
TCA
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GCT
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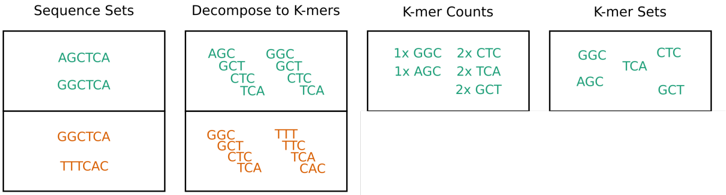
k-mers!



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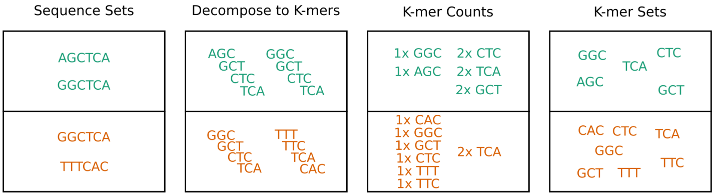
k-mers!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Formal Problem: querying the set of sets of k-mers

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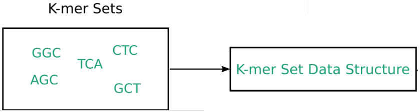
- Identify which sets of ~~reads~~ k-mers in $\mathcal{D}$ contain S
- Bonus: also applicable to anything you can decompose into k-mers e.g., assembled sequences and long-reads

Algorithms to query a set of k-mer sets

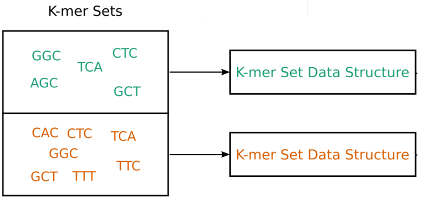
Components of a solution

K-mer Sets

Components of a solution



Components of a solution



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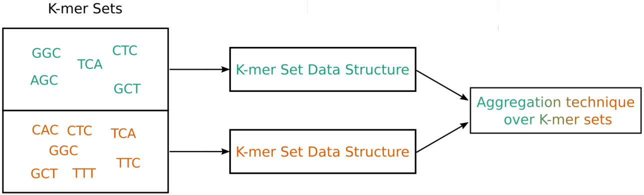

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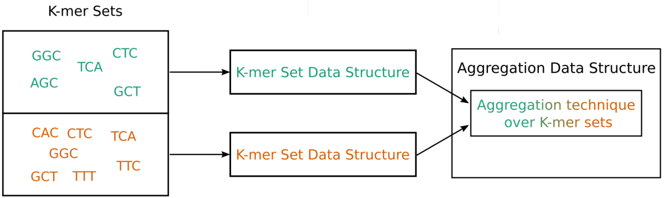

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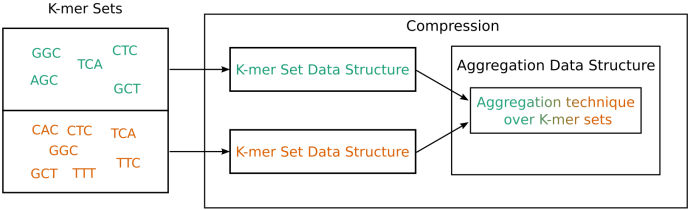

Indexing a single set of k-mers

K-mer Set Data Structure: de Bruijn graphs

sequence ATGGAAGTCGCGGAATC

homolog.us/Tutorials/book4/p2.1.html

K-mer Set Data Structure: de Bruijn graphs

sequence ATGGAAGTCGCGGAATC

7mers

homolog.us/Tutorials/book4/p2.1.html

K-mer Set Data Structure: de Bruijn graphs

sequence	**ATGGAAGTCGCGGAATC**
7mers	ATGGAAG

homolog.us/Tutorials/book4/p2.1.html

K-mer Set Data Structure: de Bruijn graphs

sequence	ATGGAAGTCGCGGAATC
7mers	ATGGAAG TGGAAGT

homolog.us/Tutorials/book4/p2.1.html

K-mer Set Data Structure: de Bruijn graphs

sequence ATGGAAGTCGCGGAATC

7mers

```
ATGGAAG
 TGGAAGT
  GGAAGTC
   GAAGTCG
    AAGTCGC
     AGTCGCG
      GTCGCGG
       TCGCGGA
        CGCGGAA
         GCGGAAT
          CGGAATC
```

homolog.us/Tutorials/book4/p2.1.html

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sequence **ATGGAAGTCGCGGAATC**

7mers

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de Bruijn graph

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de Bruijn graph

$\boxed{\text{ATGGAAG}}$

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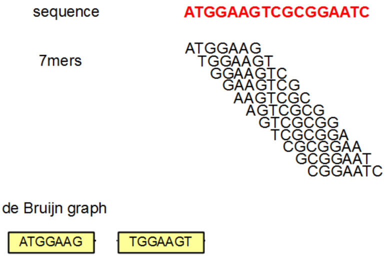

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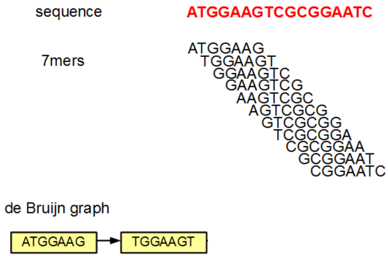

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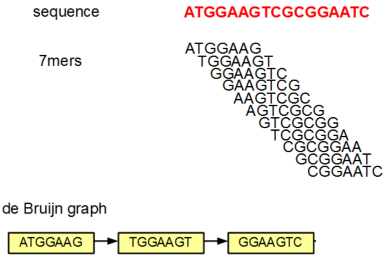

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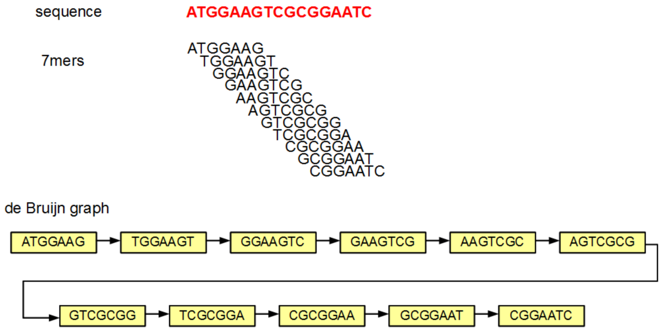

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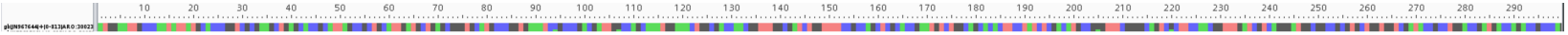
de Bruijn graph collapses diversity: NDM



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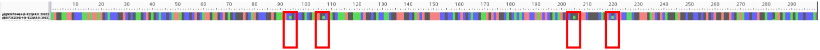

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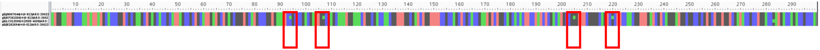

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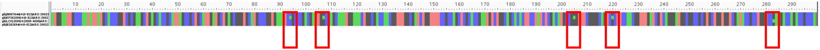

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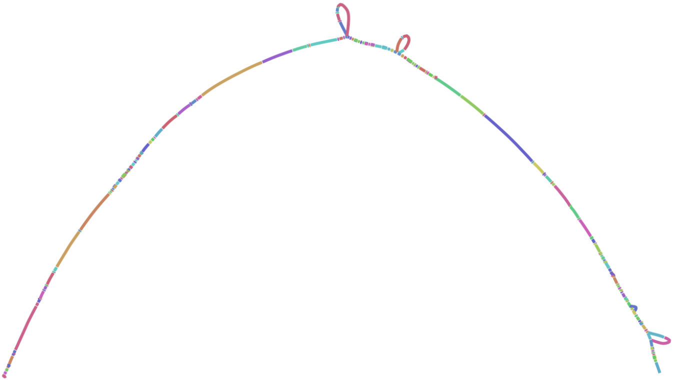
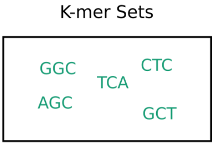


K-mer Set Data Structure: Bit-Vector



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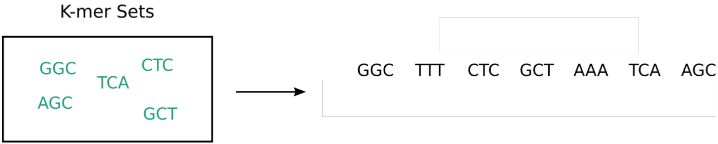

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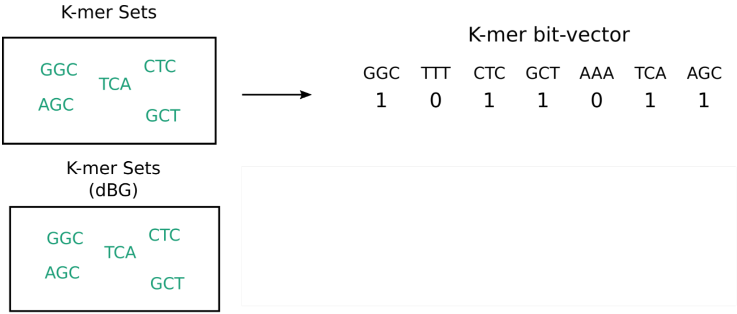

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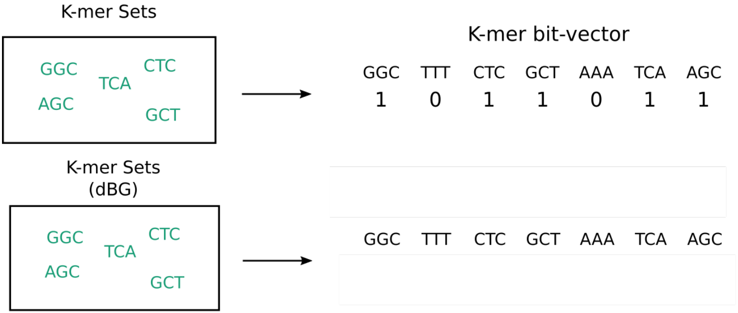

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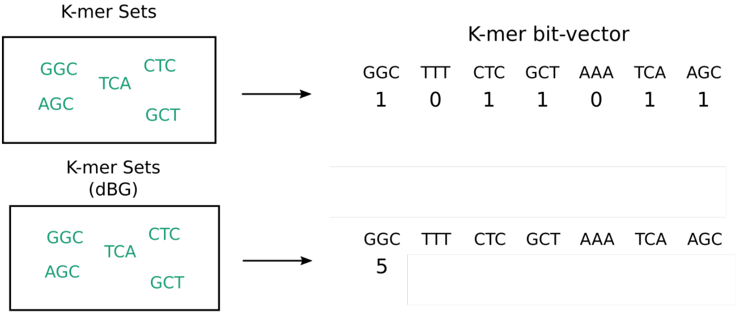

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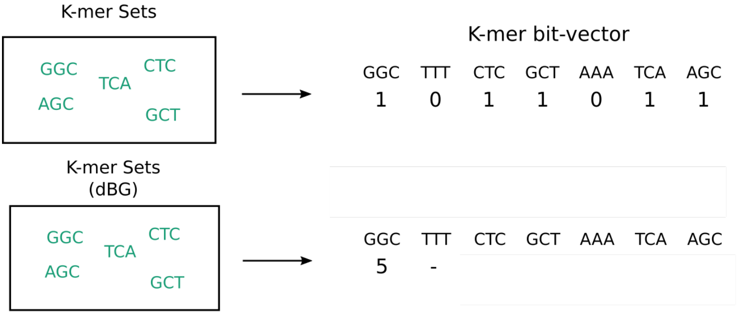

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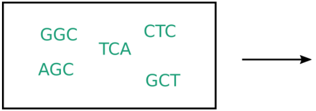
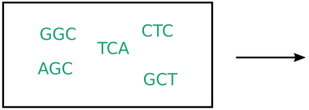
K-mer Sets



K-mer bit-vector

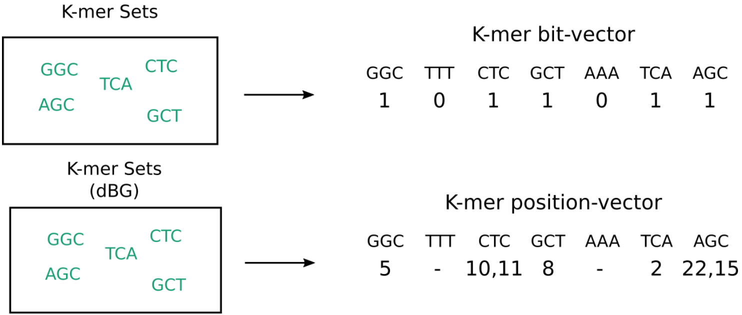
GGC	TTT	CTC	GCT	AAA	TCA	AGC
1	0	1	1	0	1	1

K-mer Sets
(dBG)



GGC	TTT	CTC	GCT	AAA	TCA	AGC
5	-	10,11	8	-	2	22,15

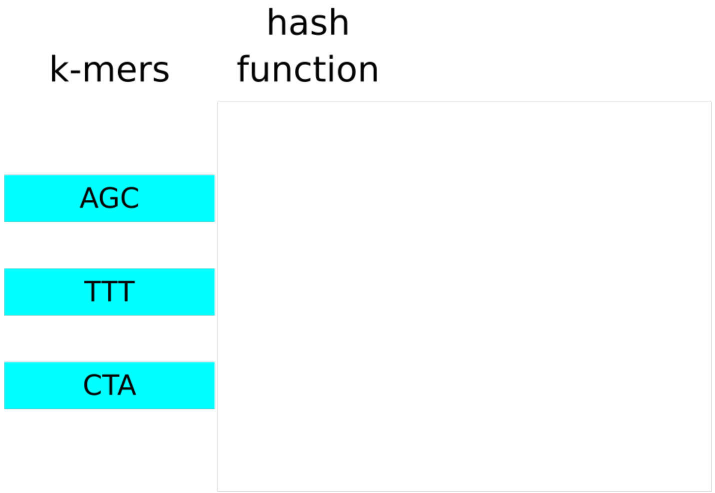
K-mer Set Data Structure: Bit-Vector



K-mer Set Data Structure: making bit-vectors more efficient

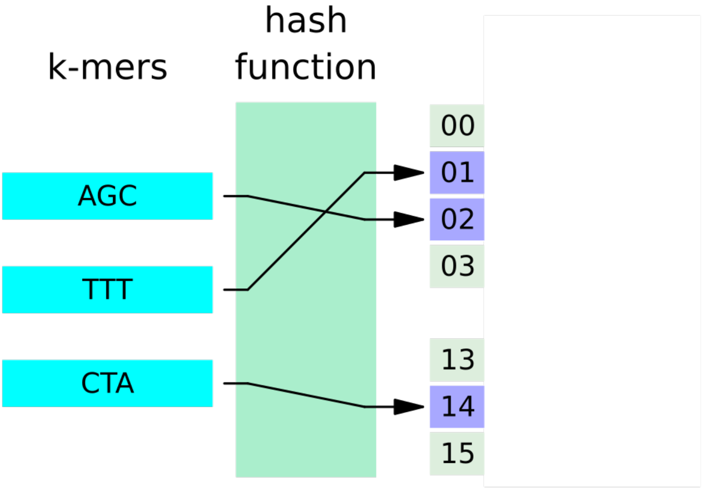
Adapted from *wikimedia.org/wiki/File:Hash_table_3_1_1_0_1_0_0_SP.svg*

K-mer Set Data Structure: making bit-vectors more efficient



Adapted from `wikimedia.org/wiki/File:Hash_table_3_1_1_0_1_0_0_SP.svg`

K-mer Set Data Structure: making bit-vectors more efficient



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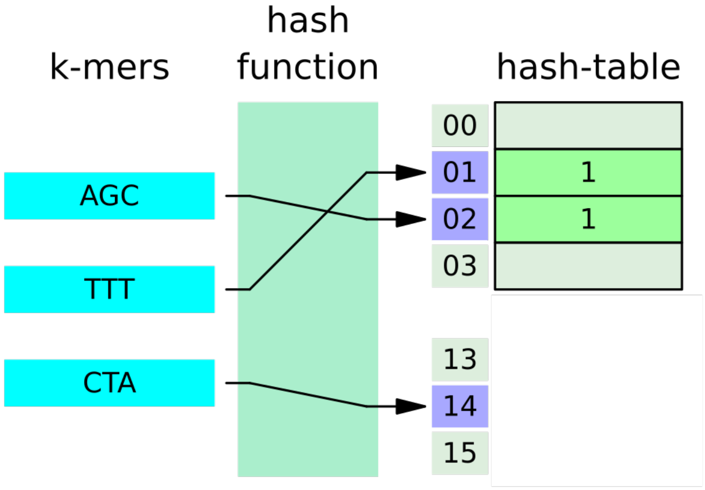
K-mer Set Data Structure: making bit-vectors more efficient



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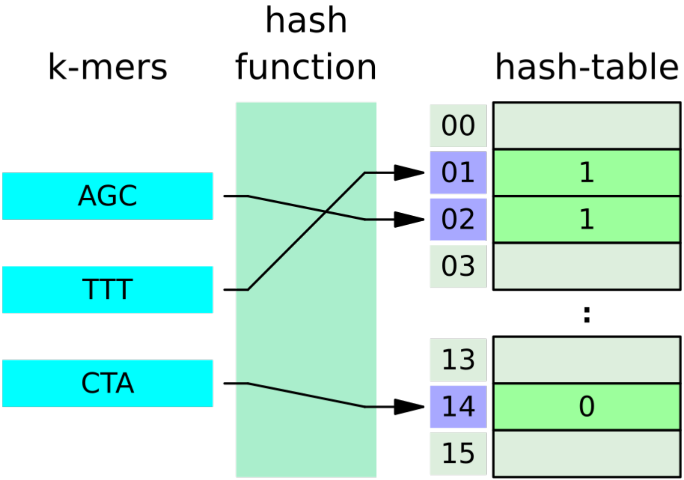
K-mer Set Data Structure: making bit-vectors more efficient



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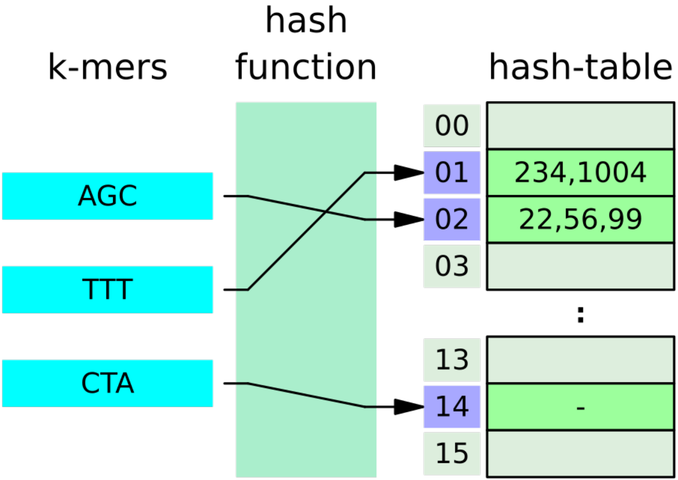
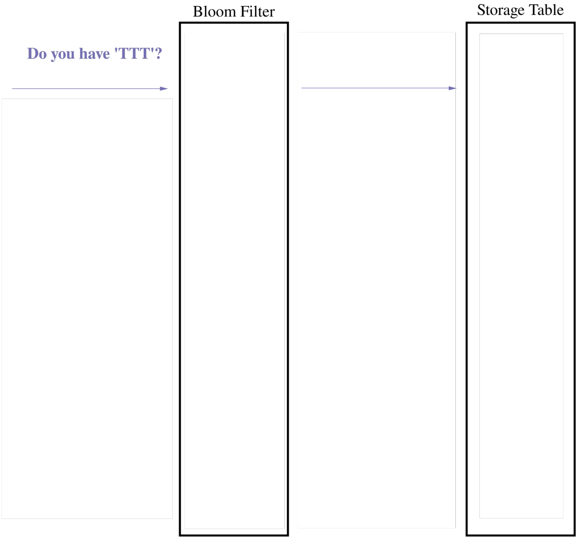
K-mer Set Data Structure: making bit-vectors more efficient



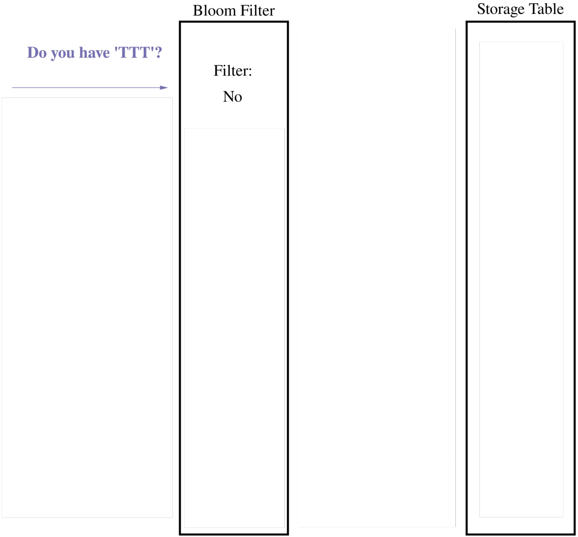
Adapted from `wikimedia.org/wiki/File:Hash_table_3_1_1_0_1_0_0_SP.svg`

K-mer Set Data Structure: bloom filters



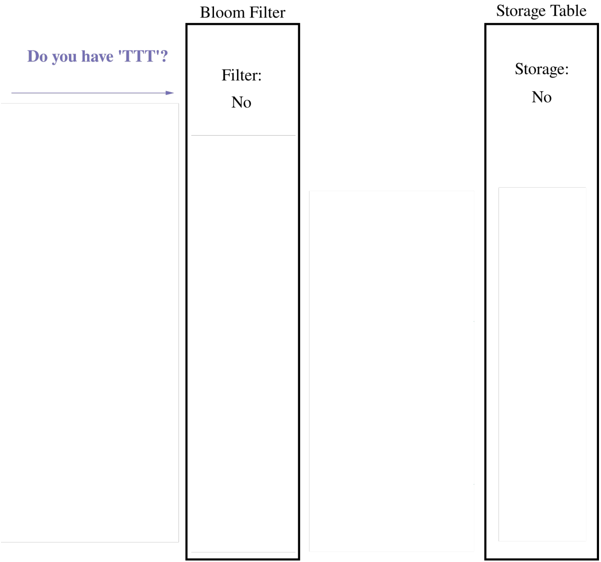
Adapted from *wikimedia.org/wiki/File:Bloom_filter_speed.svg*

K-mer Set Data Structure: bloom filters



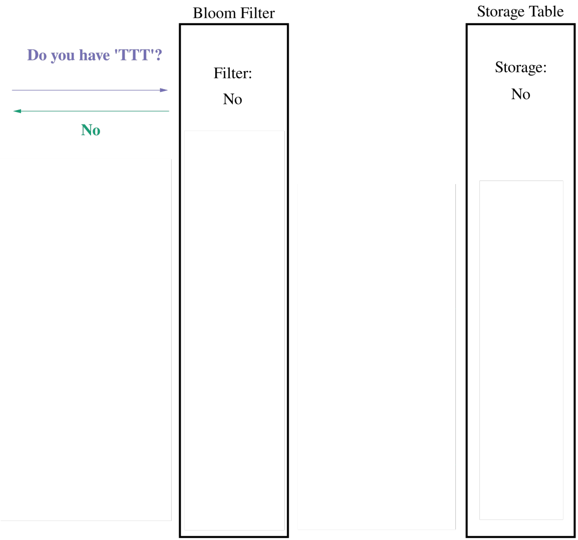
Adapted from *wikimedia.org/wiki/File:Bloom_filter_speed.svg*

K-mer Set Data Structure: bloom filters



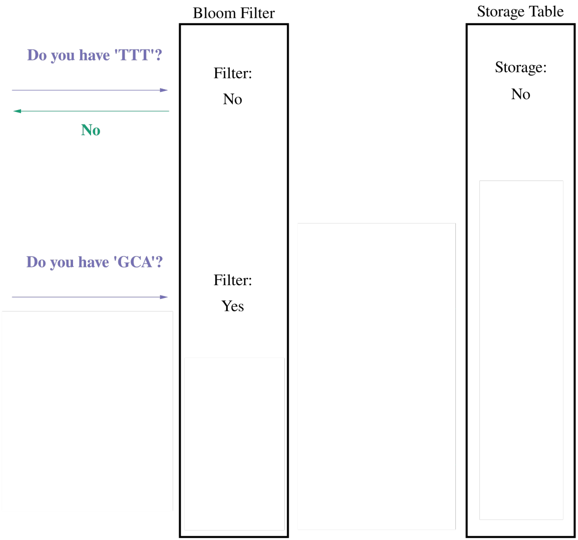
Adapted from `wikimedia.org/wiki/File:Bloom_filter_speed.svg`

K-mer Set Data Structure: bloom filters



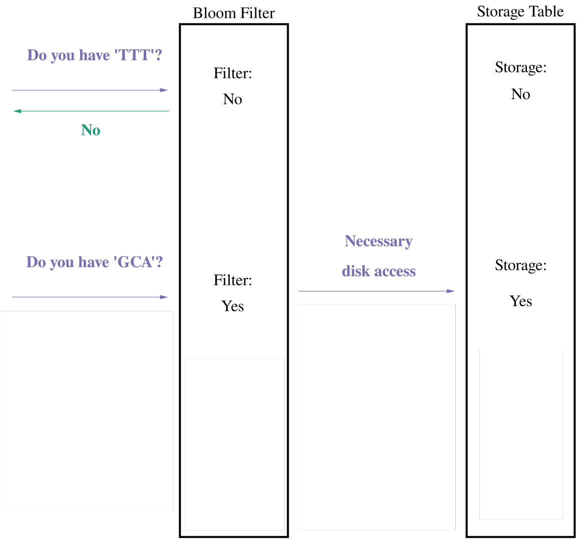
Adapted from `wikimedia.org/wiki/File:Bloom_filter_speed.svg`

K-mer Set Data Structure: bloom filters



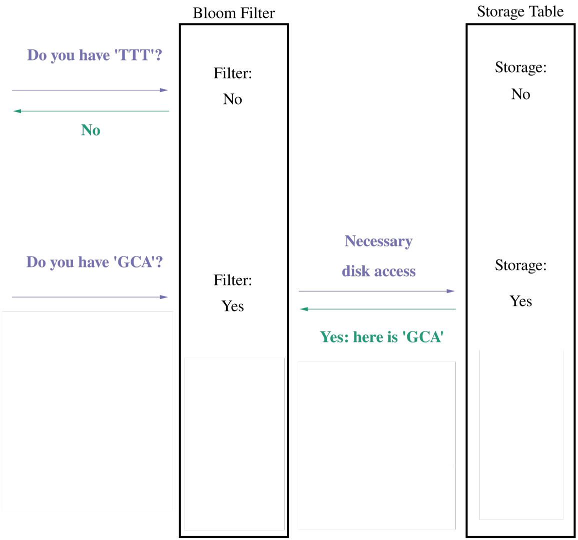
Adapted from `wikimedia.org/wiki/File:Bloom_filter_speed.svg`

K-mer Set Data Structure: bloom filters



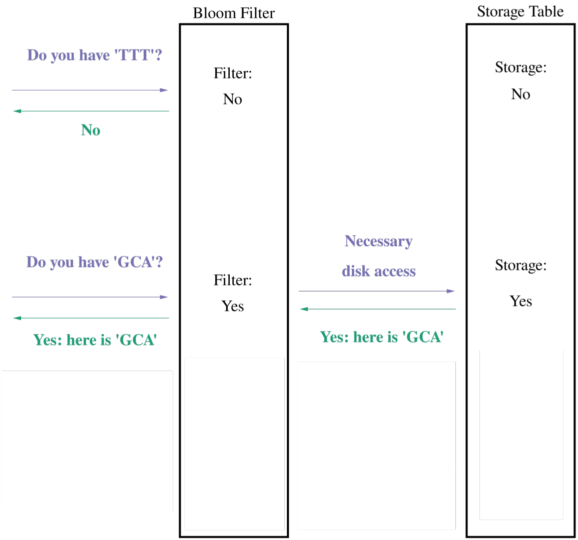
Adapted from `wikimedia.org/wiki/File:Bloom_filter_speed.svg`

K-mer Set Data Structure: bloom filters



Adapted from `wikimedia.org/wiki/File:Bloom_filter_speed.svg`

K-mer Set Data Structure: bloom filters



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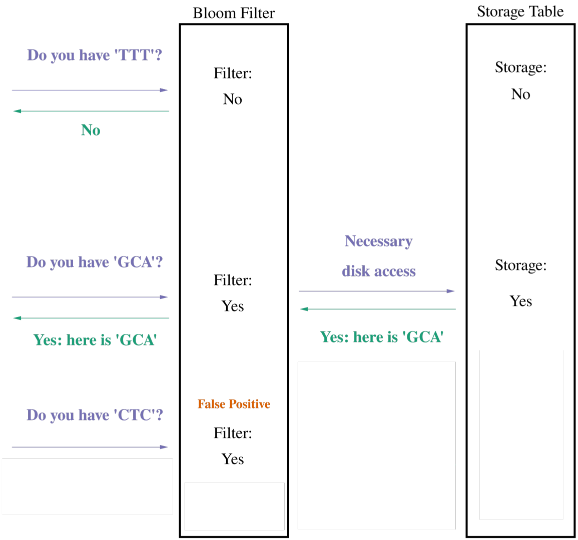
K-mer Set Data Structure: bloom filters



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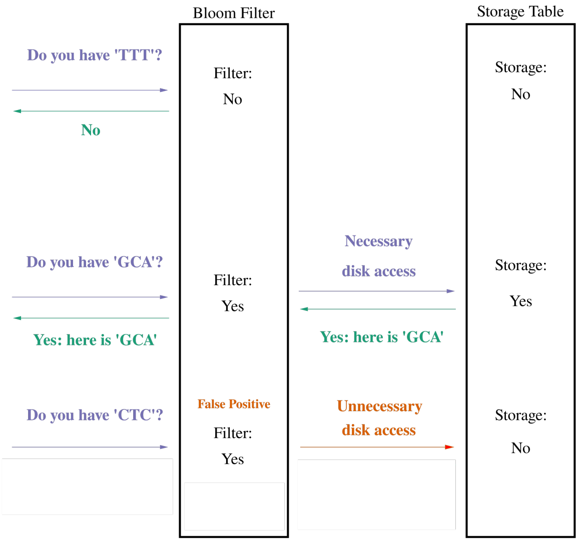
K-mer Set Data Structure: bloom filters



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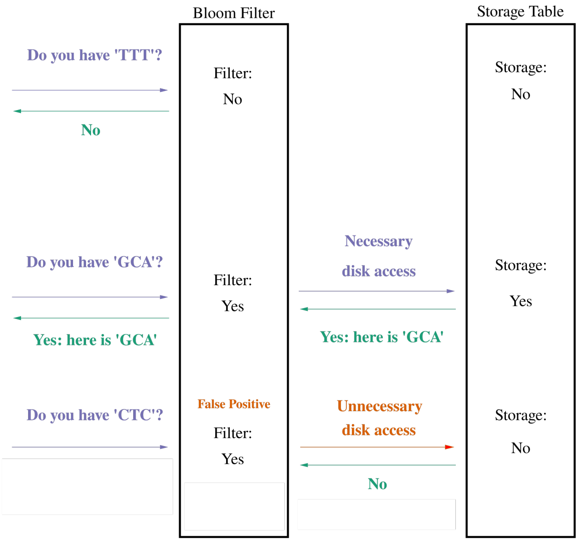
K-mer Set Data Structure: bloom filters



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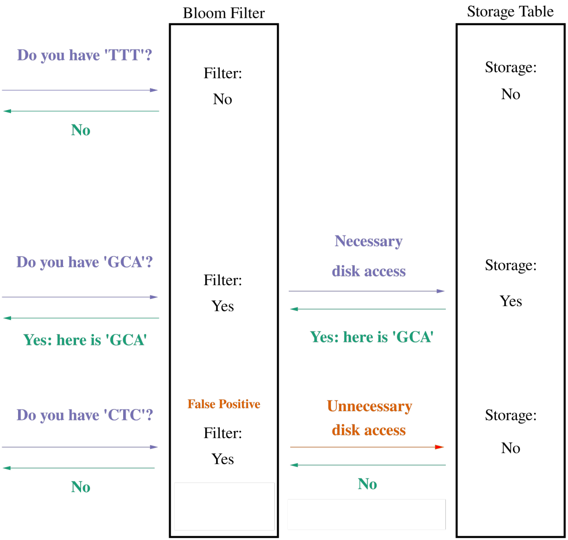
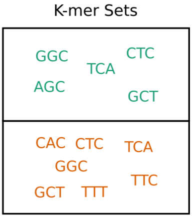
K-mer Set Data Structure: bloom filters



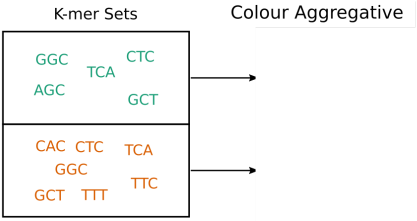
Adapted from `wikimedia.org/wiki/File:Bloom_filter_speed.svg`

How do we index across sets of k-mers?

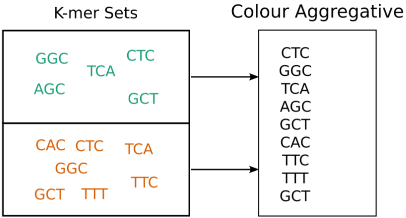
Two possible approaches: colour or k-mer aggregative



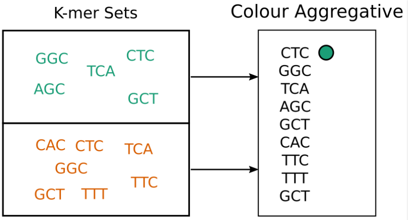
Two possible approaches: colour or k-mer aggregative



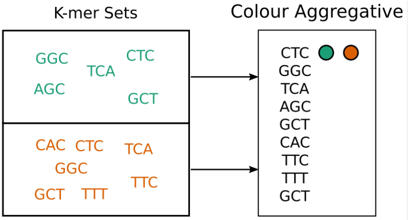
Two possible approaches: colour or k-mer aggregative



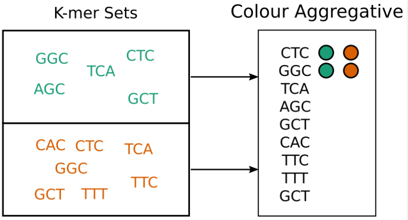
Two possible approaches: colour or k-mer aggregative



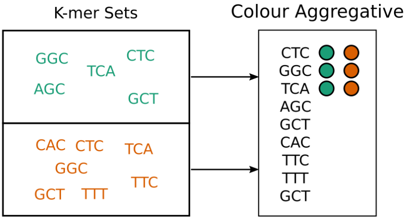
Two possible approaches: colour or k-mer aggregative



Two possible approaches: colour or k-mer aggregative



Two possible approaches: colour or k-mer aggregative



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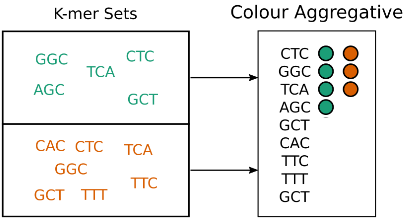
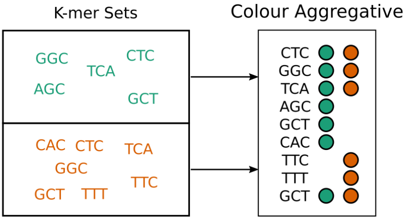
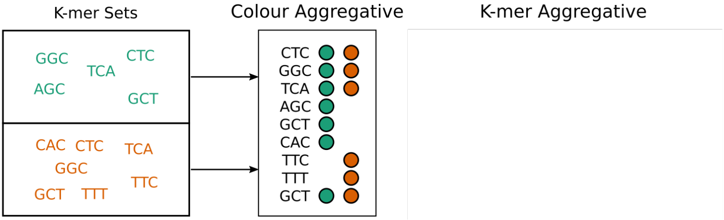


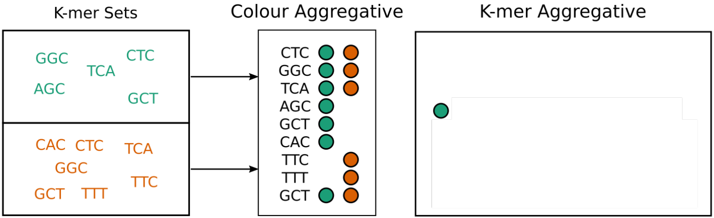
Two possible approaches: colour or k-mer aggregative



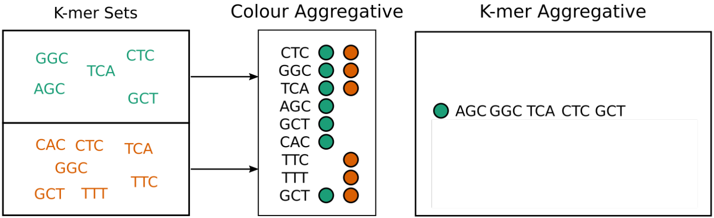
Two possible approaches: colour or k-mer aggregative



Two possible approaches: colour or k-mer aggregative



Two possible approaches: colour or k-mer aggregative



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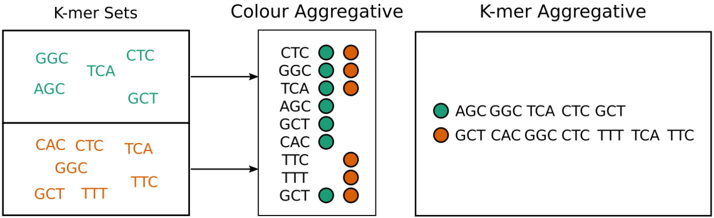

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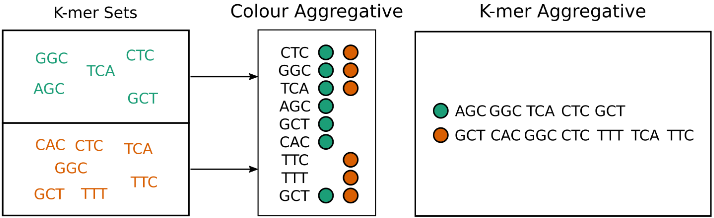
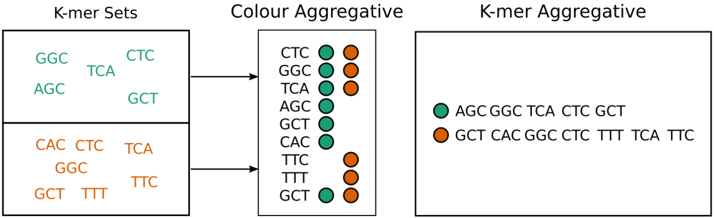


- Colour aggregative: k-mer -> sample(s)

Two possible approaches: colour or k-mer aggregative

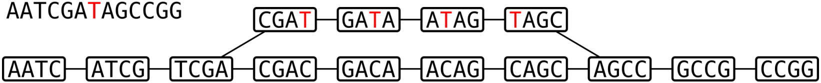


- Colour aggregative: k-mer -> sample(s)
- K-mer aggregative: sample -> k-mer(s)

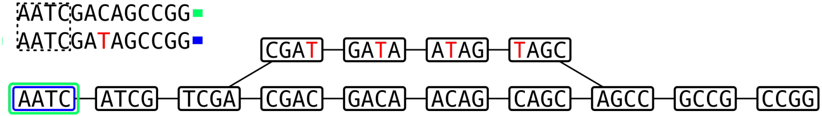
Colour aggregative methods

Coloured de Bruijn graph

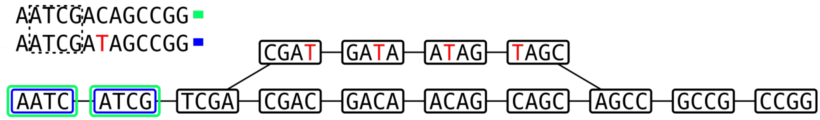
AATCGACAGCCGG
AATCGATAGCCGG



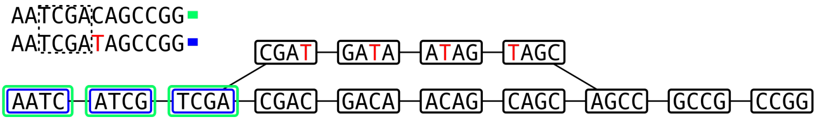
Coloured de Bruijn graph



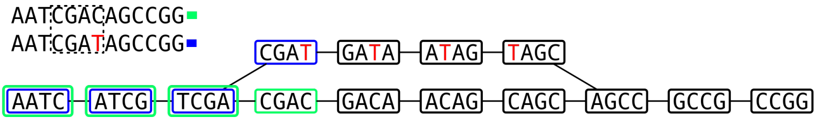
Coloured de Bruijn graph



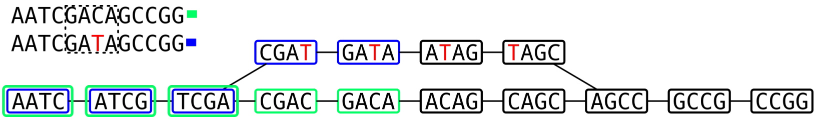
Coloured de Bruijn graph



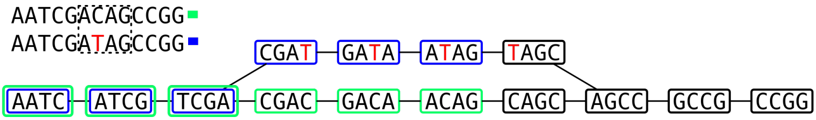
Coloured de Bruijn graph



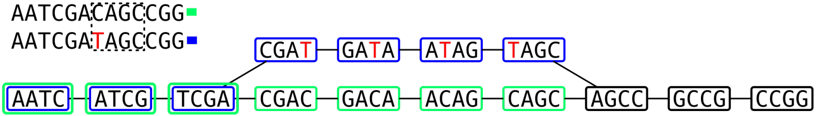
Coloured de Bruijn graph



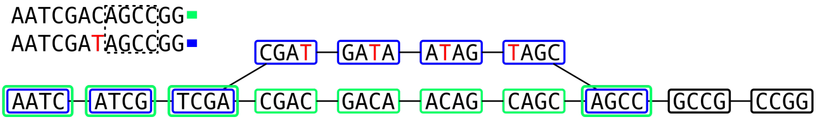
Coloured de Bruijn graph



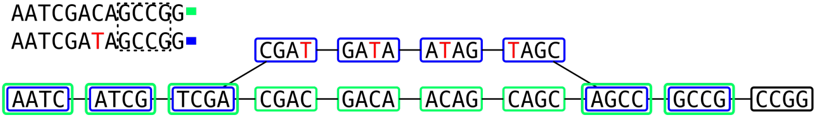
Coloured de Bruijn graph



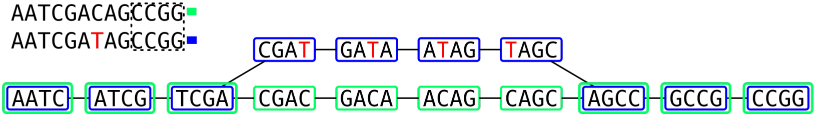
Coloured de Bruijn graph



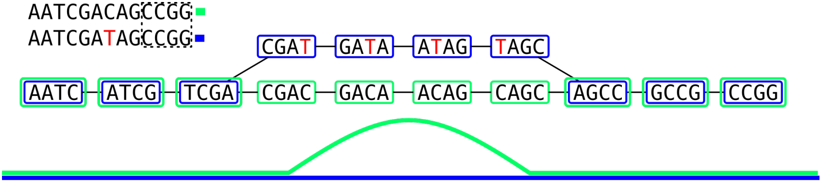
Coloured de Bruijn graph



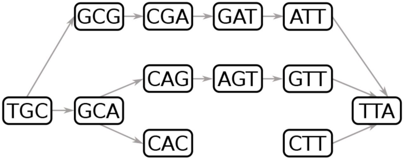
Coloured de Bruijn graph



Coloured de Bruijn graph

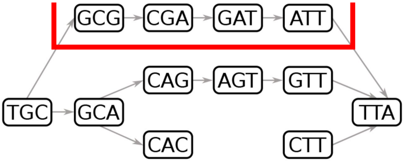


Succinct/Compacted coloured de Bruijn graphs



[Holley and Melsted, 2019]

Succinct/Compacted coloured de Bruijn graphs

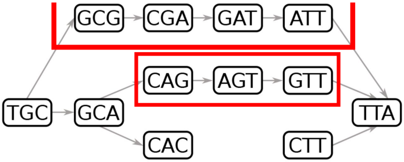


(a)

(b)

[Holley and Melsted, 2019]

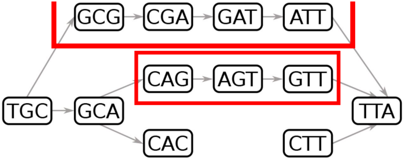
Succinct/Compacted coloured de Bruijn graphs



(a)

(b)

[Holley and Melsted, 2019]

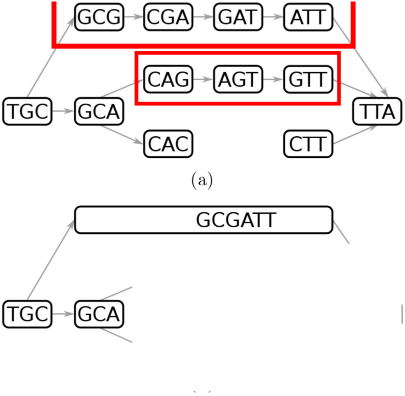


(a)

(b)

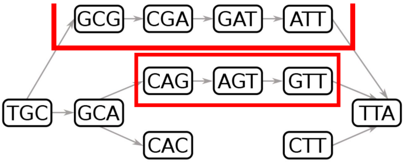
[Holley and Melsted, 2019]

Succinct/Compacted coloured de Bruijn graphs

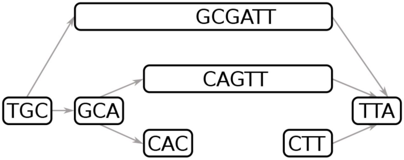


[Holley and Melsted, 2019]

Succinct/Compacted coloured de Bruijn graphs



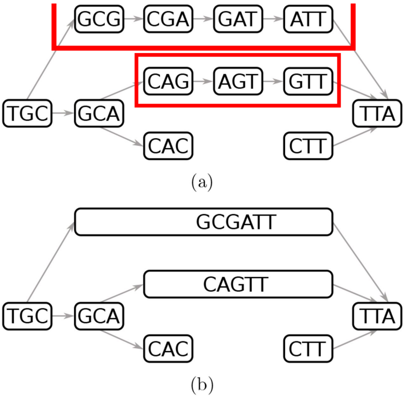
(a)



(b)

[Holley and Melsted, 2019]

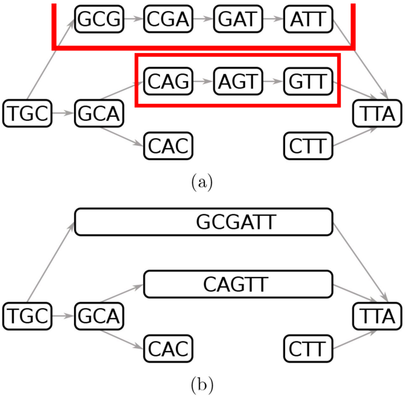
Succinct/Compacted coloured de Bruijn graphs



[Holley and Melsted, 2019]

- Compact maximal non-branching paths into untigs

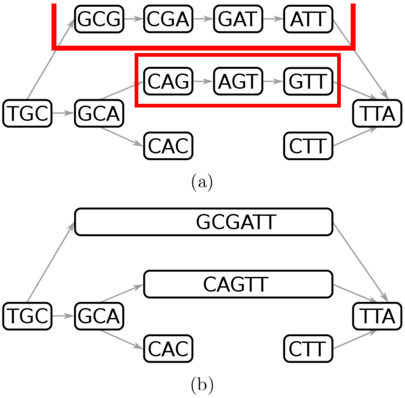
Succinct/Compacted coloured de Bruijn graphs



[Holley and Melsted, 2019]

- Compact maximal non-branching paths into untigs
- Use probabilistic data structures e.g. bloomfilters, minhash sketches, minimisers

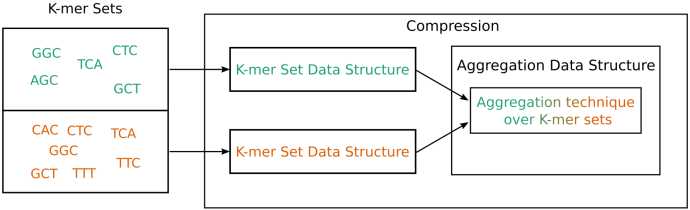
Succinct/Compacted coloured de Bruijn graphs



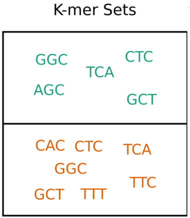
[Holley and Melsted, 2019]

- Compact maximal non-branching paths into untigs
- Use probabilistic data structures e.g. bloomfilters, minhash sketches, minimisers
- AKA make things more approximate but smaller!

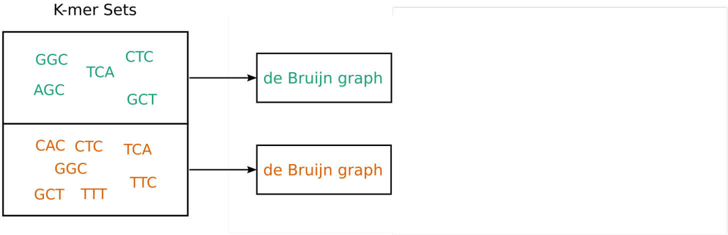
BlastFrost


K-mer Sets
GGC
TCA
CTC
AGC
GCT
CAC
CTC
TCA
GGC
TTC
GCT
TTT
Compression
K-mer Set Data Structure
K-mer Set Data Structure
Aggregation Data Structure
Aggregation technique
over K-mer sets

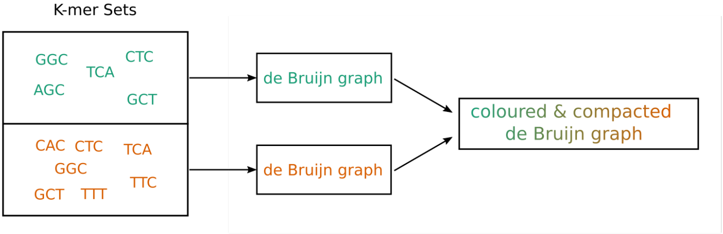
BlastFrost



BlastFrost

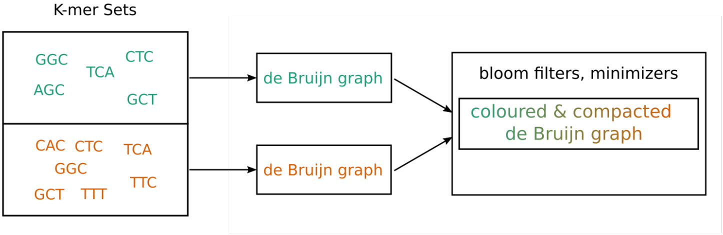

K-mer Sets
GGC
TCA
CTC
AGC
GCT
CAC
CTC
TCA
GGC
TTC
GCT
TTT
de Bruijn graph
de Bruijn graph

BlastFrost

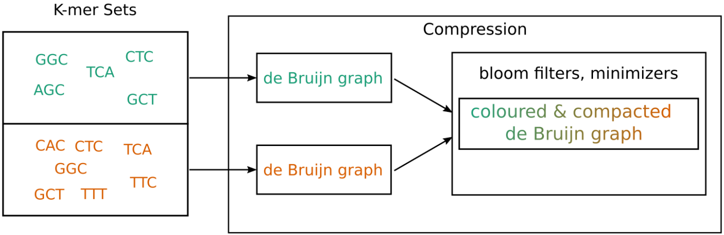


K-mer Sets
GGC
TCA
CTC
AGC
GCT
CAC
CTC
TCA
GGC
TTC
GCT
TTT
de Bruijn graph
de Bruijn graph
coloured & compacted
de Bruijn graph

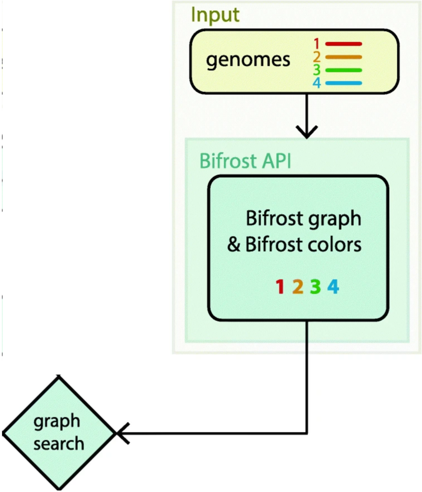
BlastFrost


K-mer Sets
GGC
TCA
CTC
AGC
GCT
CAC
CTC
TCA
GGC
TTC
GCT
TTT
de Bruijn graph
de Bruijn graph
bloom filters, minimizers
coloured & compacted
de Bruijn graph

BlastFrost


K-mer Sets
GGC
TCA
CTC
AGC
GCT
CAC
CTC
TCA
GGC
TTC
GCT
TTT
Compression
de Bruijn graph
de Bruijn graph
bloom filters, minimizers
coloured & compacted
de Bruijn graph

BlastFrost: Similar but for bigger sequences!



[Luhmann et al., 2020]

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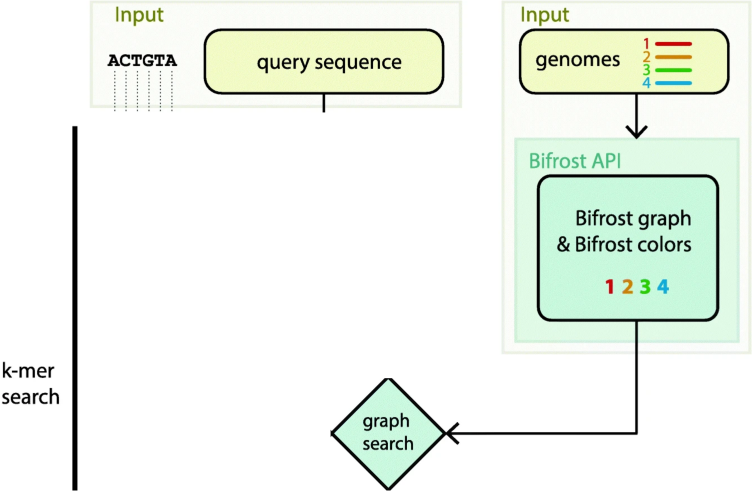

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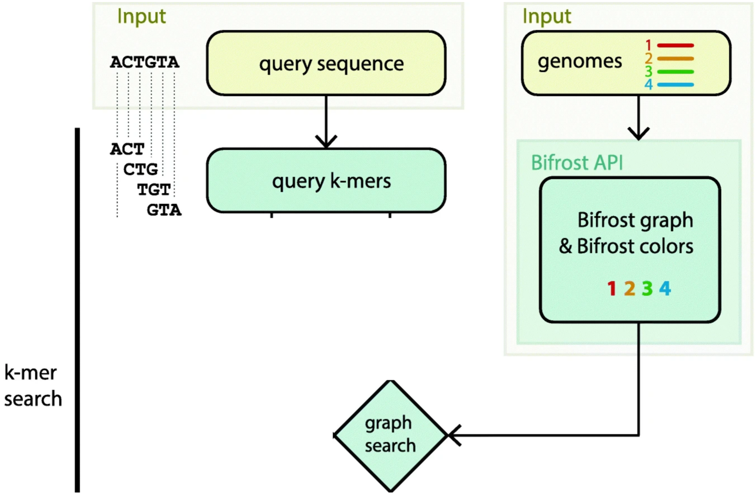

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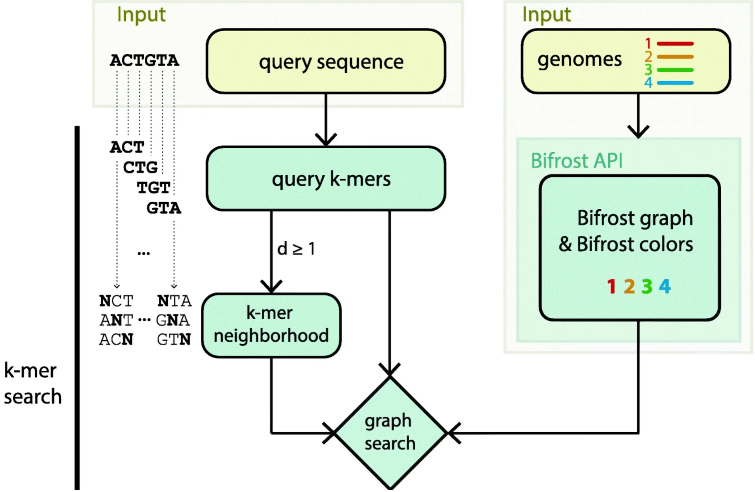

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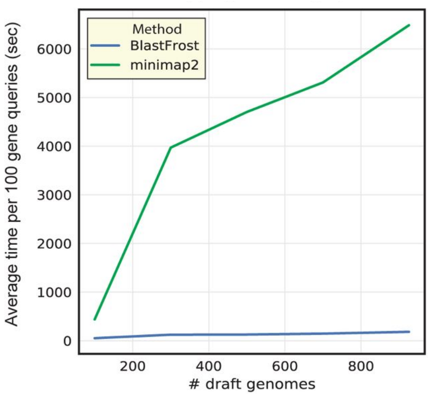
BlastFrost scaling



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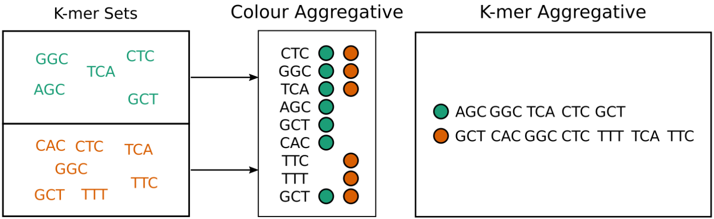
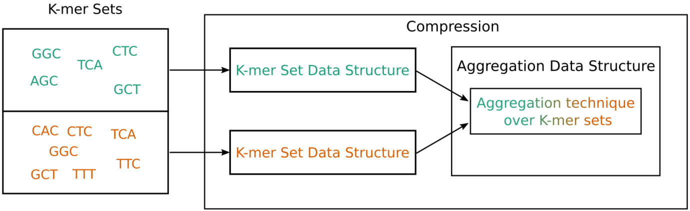
K-mer aggregative methods

Index based on sample -> k-mer(s)



BIGSI



[Bradley et al., 2019]

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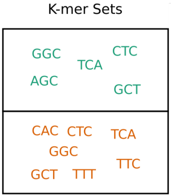

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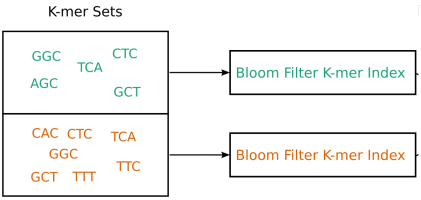

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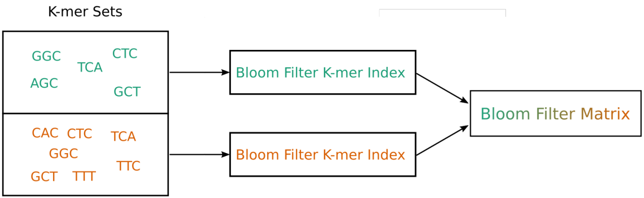

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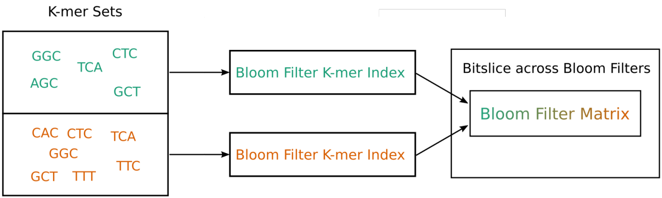

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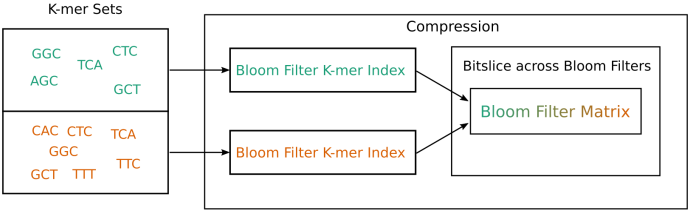
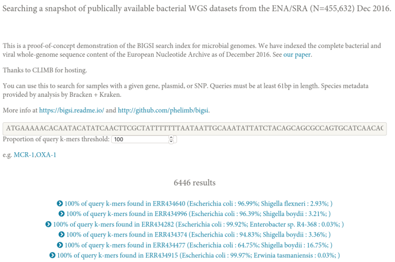


[Bradley et al., 2019]

BIGSI indexing of ENA



Searching a snapshot of publically available bacterial WGS datasets from the ENA/SRA (N=455,632) Dec 2016.

This is a proof-of-concept demonstration of the BIGSI search index for microbial genomes. We have indexed the complete bacterial and viral whole-genome sequence content of the European Nucleotide Archive as of December 2016. See our paper.

Thanks to CLIMB for hosting.

You can use this to search for samples with a given gene, plasmid, or SNP. Queries must be at least 61bp in length. Species metadata provided by analysis by Bracken + Kraken.

More info at https://bigsi.readme.io/ and http://github.com/phelimb/bigsi.

ATGAAAAACACAATACATATCAACTTCGCTATTTTTTTAATAATTGCAAATATTATCTACAGCAGCGCCAGTGCATCAACAC

Proportion of query k-mers threshold: 100

e.g. MCR-1,OXA-1

6446 results

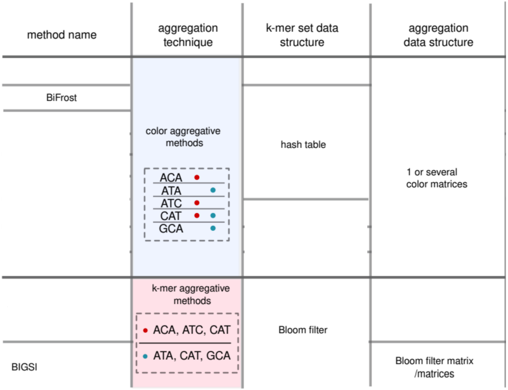
- 100% of query k-mers found in ERR434640 (Escherichia coli : 96.99%; Shigella flexneri : 2.93%;)
- 100% of query k-mers found in ERR434996 (Escherichia coli : 96.39%; Shigella boydii : 3.21%;)
- 100% of query k-mers found in ERR434282 (Escherichia coli : 99.92%; Enterobacter sp. R4-368 : 0.03%;)
- 100% of query k-mers found in ERR434374 (Escherichia coli : 94.83%; Shigella boydii : 3.36%;)
- 100% of query k-mers found in ERR434477 (Escherichia coli : 64.75%; Shigella boydii : 16.75%;)
- 100% of query k-mers found in ERR434915 (Escherichia coli : 99.97%; Erwinia tasmaniensis : 0.03%;)

[Bradley et al., 2019]

- Indexing all bacterial, viral and parasitic reads in ENA (500,000 sets, 170TB of data)
- 1.5TB index that be queried near instantaneously

Which method?

Many Options



[Marchet et al., 2021]

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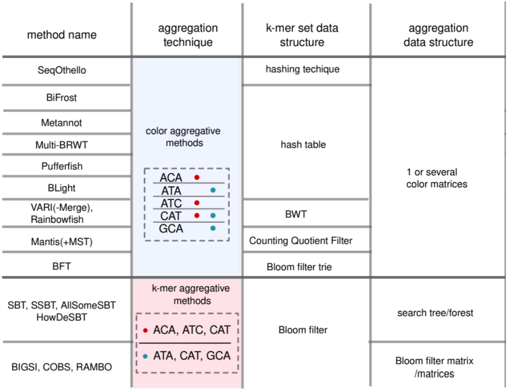

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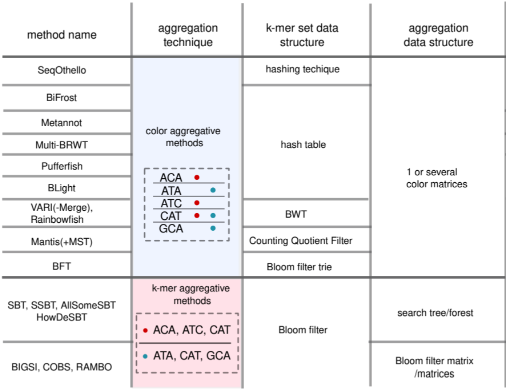

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- It depends: complexity, sequence length, query length

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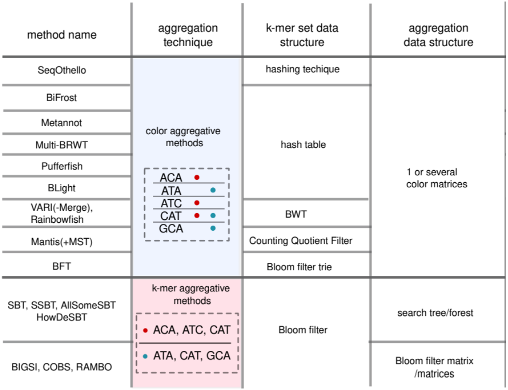

[Marchet et al., 2021]

- It depends: complexity, sequence length, query length
- What features you need e.g., inserting new sets, space vs time trade-offs

Summary

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    - BIGSI creates a big matrix of bloom filters where each column is a sample
- Active field and choosing best method is very data and task specific

Questions?

Bradley, P., Den Bakker, H. C., Rocha, E. P., McVean, G., and Iqbal, Z. (2019).
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BioRxiv, page 695338.

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BioRxiv.

Marchet, C., Boucher, C., Puglisi, S. J., Medvedev, P., Salson, M., and Chikhi, R. (2021).
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Genome Research, 31(1):1–12.