HowDeSBT and Simka wedding:
What has been done and what we plan to do?

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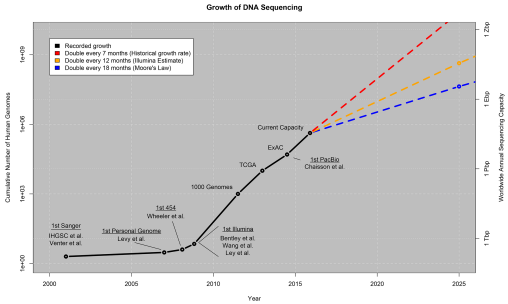
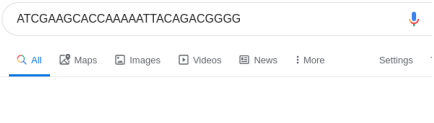
DSB meeting
4 February 2020

High production of sequencing data



Stephens *et al.*

- Non-indexed datasets
- Query only the metadata, not the sequences content

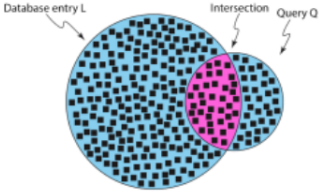


Query a sequence of interest?

Given experiment sets, and a sequence of interest, which dataset contains this sequence?

In terms of k-mers:

A query Q matches an experiment L if at least a fraction θ of Q's k-mers are present in L.



k-mers based indexing: general processing

- k-mers counting for each dataset
  - dealing with sequencing errors
- indexing each set of k-mers (using AMQ for example)
  - with or without the counting information, depending on the data structure used
- merging each index in one
  - with possible adjustments to optimize storage and query

Example: SBT, HowDeSBT, BIGSI ...

Common to all methods: k-mers counting

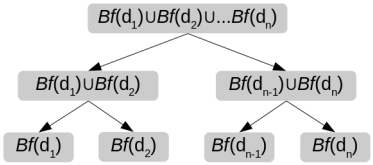
Dealing with sequencing errors

- Usually, k-mer counters use simple error correction (throw out k-mers whose abundance are below a hard threshold)

- low abundance k-mer: not necessarily an error (under-represented sequence)
- metagenomics, transcriptomics, cancer genomics (Griffith *et al.*)

HowDeSBT[1]: main idea

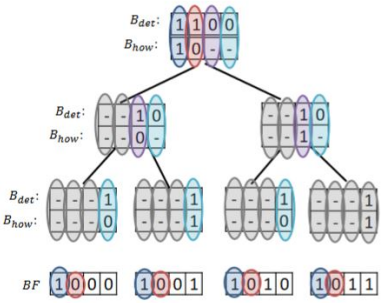
- Indexing datasets using their k-mers content
- Bloom filters as a basic structure
- Final index based on Sequence Bloom Tree (Solomon and Kingsford)



- One leaf = one experiment.
- Internal node represents k-mers in its subtree.
- Root node is the union of each BF in the tree.

[1] Harris and Medvedev

HowDeSBT: data structure

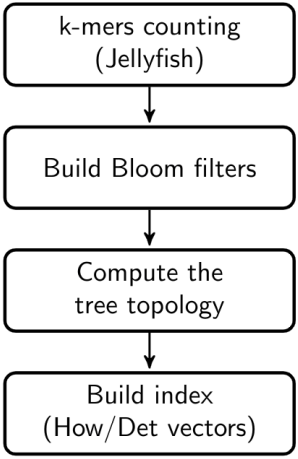


Medvedev, DSB 2019

Two binary vectors by node:

- B_{det} : Bit is **det**ermined in the subtree?
- B_{how} : If **det**, **how** is it determined? (0/1)

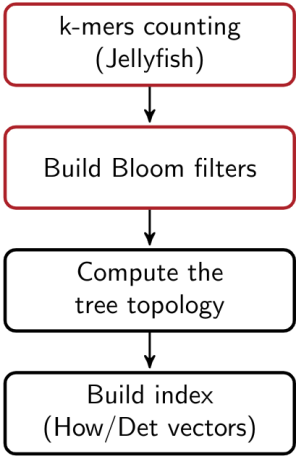
HowDeSBT: pipeline



What we want to do?

- Include particular error handling
- At the same time: can computation times and memory footprint be improved?

HowDeSBT: pipeline



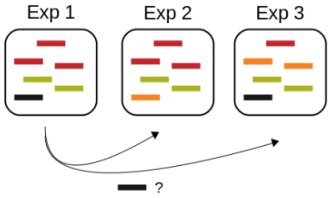
What we want to do?

- Include particular error handling
- At the same time: can computation times and memory footprint be improved?

- Focus on the two first steps

How to improve errors handling?

- Leverage information across samples
- e.g. For a k-mer seen less than N times, check the count in the other datasets.



- Verification only in datasets with compatible metadata

How? Help from Simka (Benoit *et al.*)

- *de novo* comparative metagenomics tool.
- Compute ecological distances between samples using k-mers decomposition.

	A	**B**	**C**	**D**
A	0	0.2	0.1	0.4
B	0.2	0	0.6	0.3
C	0.1	0.6	0	0.5
D	0.4	0.3	0.5	0

k-mers matrix

- After modifications, we can obtain a count table with datasets in columns and k-mers in lines.

	A	B	C	D
ACGT	12	16	7	1
ACTG	1	0	0	0
CTGA	8	1	8	0
GATA	21	10	21	20
TCGA	12	0	0	4
TCGT	0	1	0	1

k-mers matrix

- Leverage information across samples:
  - easily applicable with this kind of matrix
- Add this new errors handling feature in Simka
- Many ways to do it

Count table

	A	B	C	D
ACGT	12	16	7	1
ACTG	**1**	0	0	0
CTGA	8	**1**	8	0
GATA	21	10	21	20
TCGA	12	0	0	4
TCGT	0	**1**	0	**1**

Binary matrix

	A	B	C	D
ACGT	1	1	1	1
CTGA	1	**1**	1	0
GATA	1	1	1	1
TCGA	1	0	0	1
TCGT	0	**1**	0	**1**

Simka: How it works ? - Reminder

- Minimizers & super-k-mers (KMC 2, Deorowicz *et al.*)

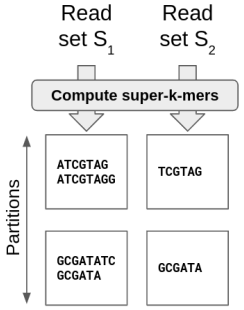
- super-k-mers: merged overlapping k-mers that share the same minimizer.

2 minimizers, 2 super-k-mers with $k = 6$ **and** $m = 3$

CTCATCGAC, TGCACGTTC

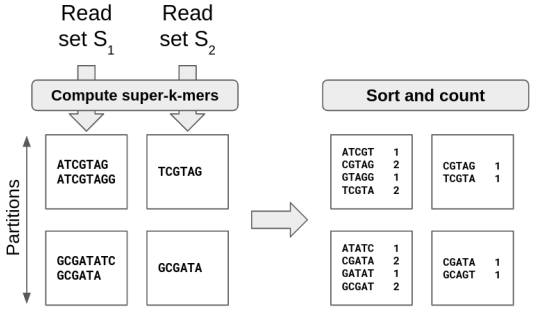
How it works: Counting (GATB-DSK)

- Step 1: Compute super-k-mers from each dataset and store them into partitions according their minimizers.



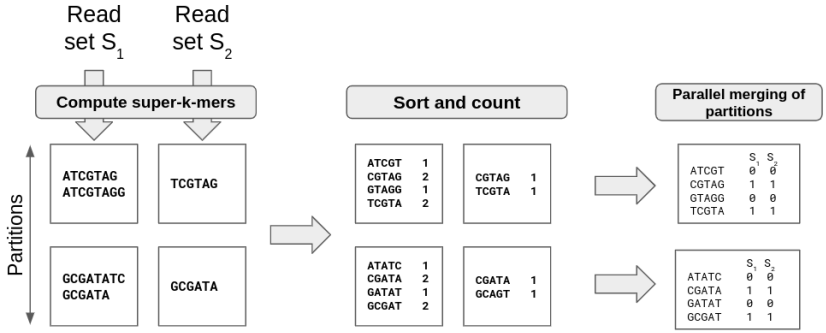
How it works: Counting (GATB-DSK)

- Step 2: In each partition, split super-k-mers into k-mers and sort them. The count is given by identical consecutive k-mers.



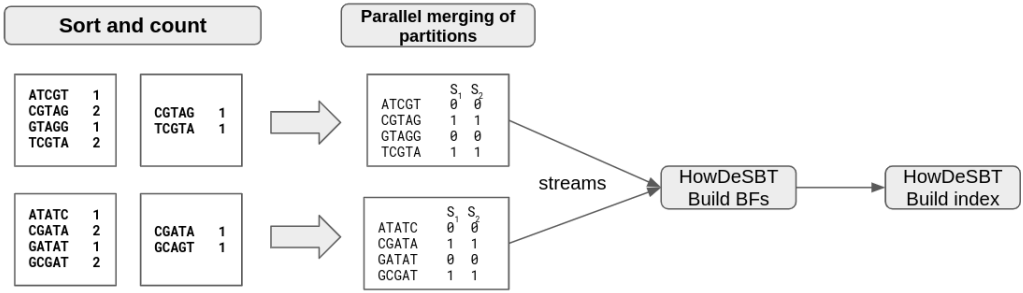
How it works: Counting (GATB-DSK)

- Step 3: Merge equivalent partitions between datasets to obtain sub-matrices.



Simka-HowDeSBT: Current implementation

- Merge between datasets and stream each lines to build Bloom filters with HowDeSBT.



- https://github.com/tlemane/Simka-HowDeSBT

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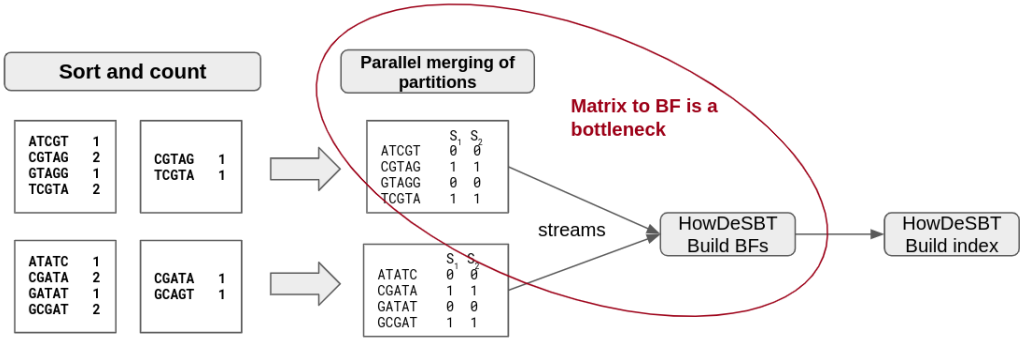
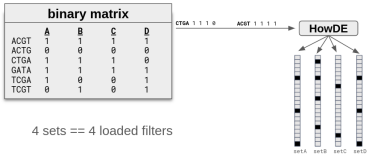


- `https://github.com/tlemane/Simka-HowDeSBT`

Matrix to Bloom filters

- Currently two possibilities:
  - Stream each line to HowDeSBT
  - Binary matrix on disk

In both cases: requires to have as many open filters in memory as there are data sets



4 sets == 4 loaded filters

Solutions ?

- Store matrix on disk:
  - Multiple passes
  - Transposition
- Build Bloom filters on files:
  - too many files open at the same time with large number of datasets

Can we do better?

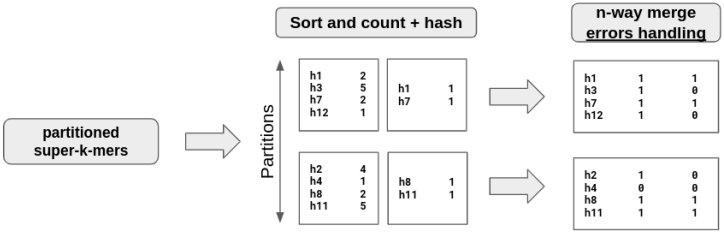
- Currently, Simka gives textual k-mers counted to HowDeSBT which builds Bloom filters

- Modify early steps of Simka to build directly Bloom filters.
  - One possibility: **hash instead of k-mers**

Hash instead of k-mers (not yet implemented)

Hash instead of k-mers

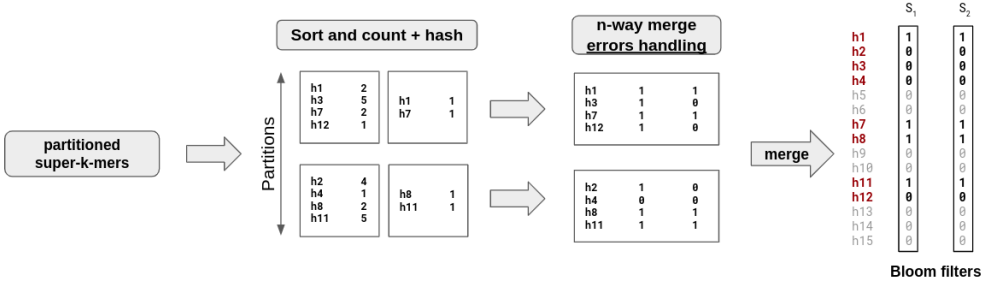
- hash k-mers at step 2 → obtain sorted hash values in partitions



Hash instead of k-mers (not yet implemented)

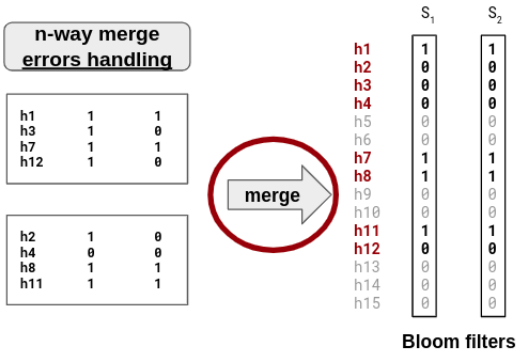
Merging sub-matrices

Set missing hash values to 0 → Bloom filters



Hash instead of k-mers (not yet implemented)

- Obtain directly Bloom filters but with one more merge



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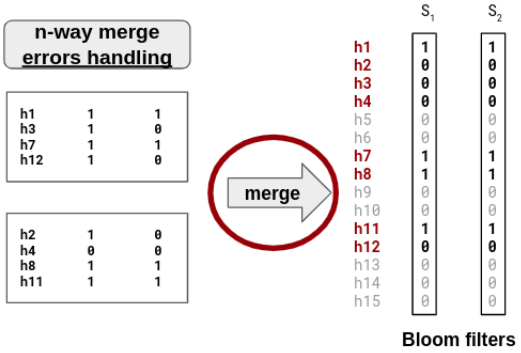
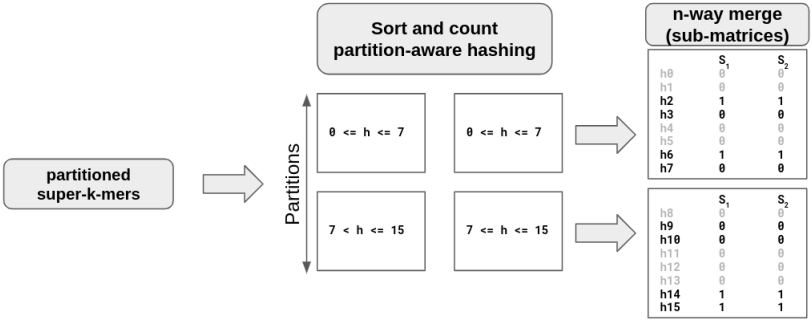


- **Can we avoid this second merge?**

Partition-aware hashing

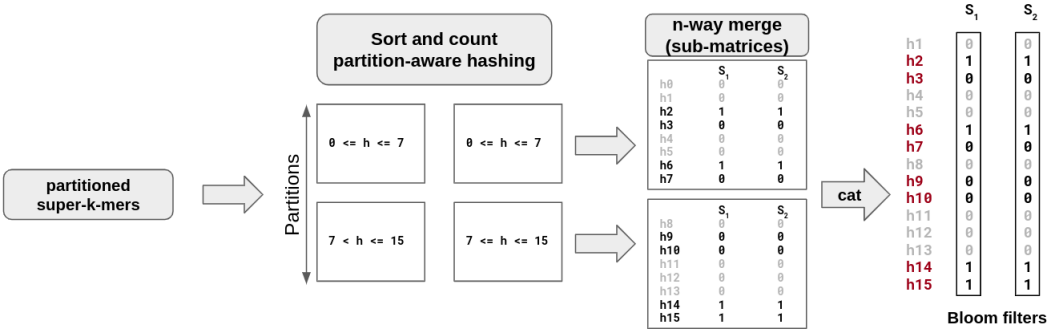
Define hash space according to the partition

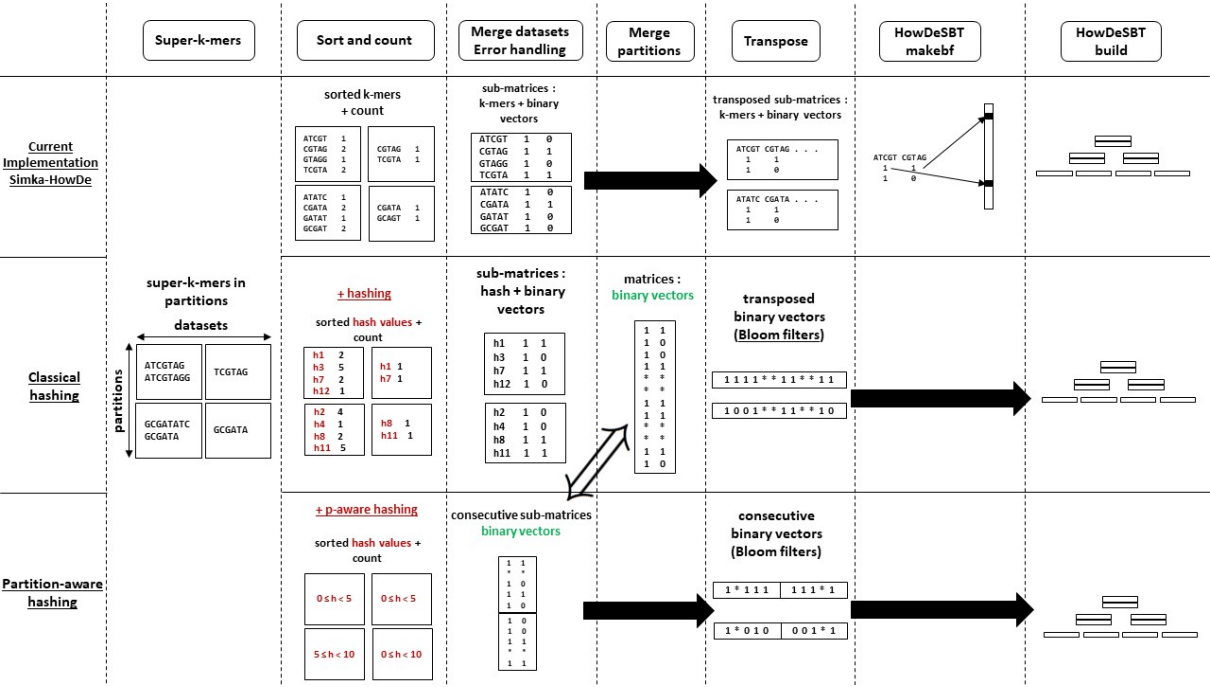
Requires to compute minimizers at query to select the right hash space



Partition-aware hashing

- Merging step becomes concatenation




Super-k-mers
Sort and count
Merge datasets
Error handling
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sorted k-mers + count
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Classical hashing
super-k-mers in partitions
datasets
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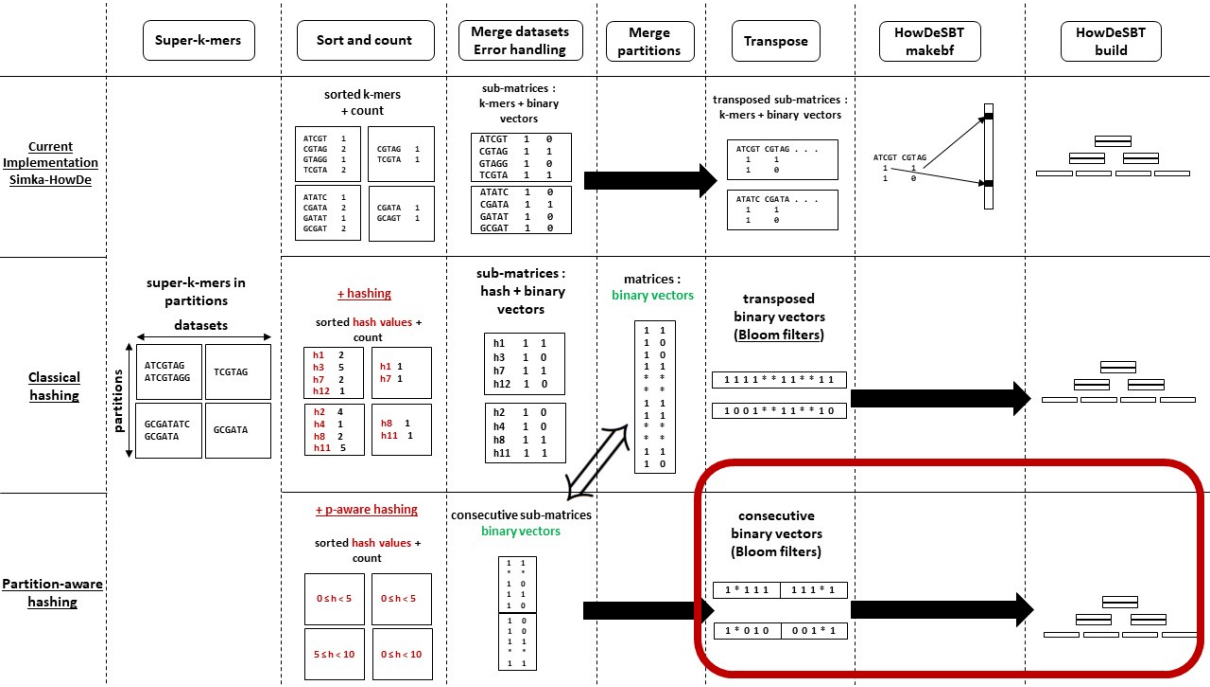
ATCGTAG
ATCGTAGGG
TCGTAG
GCGATATC
GCGATA
GCGATA
+ hashing
sorted hash values + count
sub-matrices : hash + binary vectors
matrices : binary vectors
transposed binary vectors (Bloom filters)
1 1 1 1 * * 1 1 * * 1 1
1 0 0 1 * * 1 1 * * 1 0
Partition-aware hashing
+ p-aware hashing
sorted hash values + count
0 ≤ h < 5
0 ≤ h < 5
5 ≤ h < 10
0 ≤ h < 10
consecutive sub-matrices
binary vectors
consecutive binary vectors (Bloom filters)
1 * 1 1 1
1 1 1 * 1
1 * 0 1 0
0 0 1 * 1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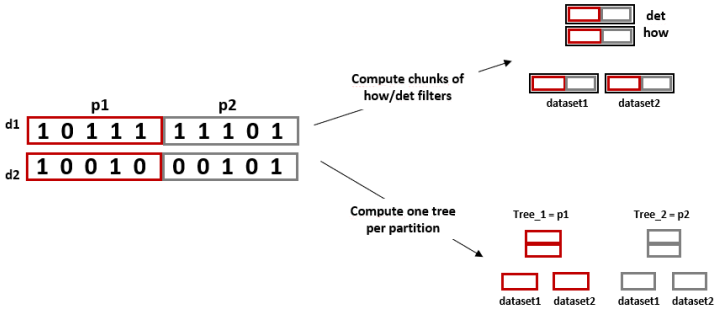
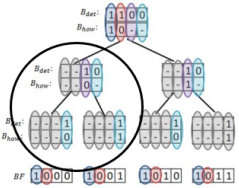
Can the tree computation be parallelized?





Simka-HowDeSBT: What we plan to do?

- **Build one global tree vs one tree per partition?**
  - Are there any issues with building one tree per partition?
    - Storage?
    - Query efficiency?
  - In the case of tree per partition: classical hashing $\Leftrightarrow$ partition-aware hashing

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    - Consideration relative to the tree topology computation

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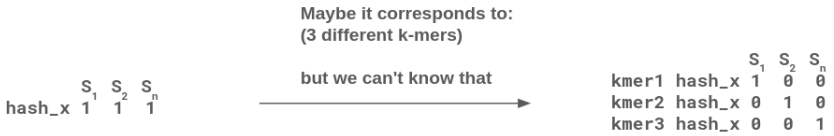
- **What about collisions?**
- **Implementation**

S1

	p0	p1	p2
	n k-mers	**n k-mers**	**n k-mers**
index ⇔ hash value	[0, 33[	[33, 66[	[66, 100[
	100-bits Bloom filter		

	p0	p1	p2
	x k-mers	**y k-mers**	**z k-mers**
index ⇔ hash value	[0, 40[	[40, 50[	[50, 100[
	100-bits Bloom filter		

S2



Solution: using oversized hash function