Simka: fast kmer-based method for estimating the similarity between numerous metagenomic datasets

Gaëtan Benoit

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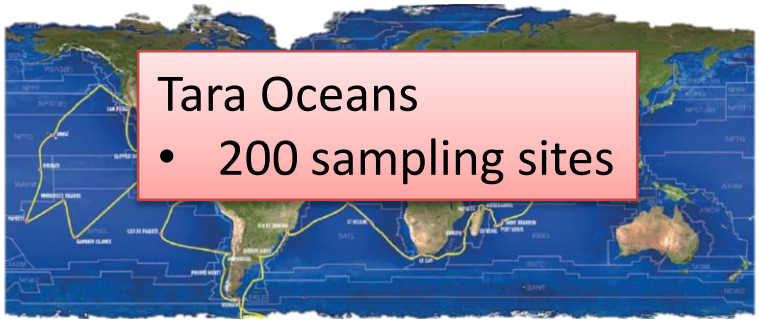
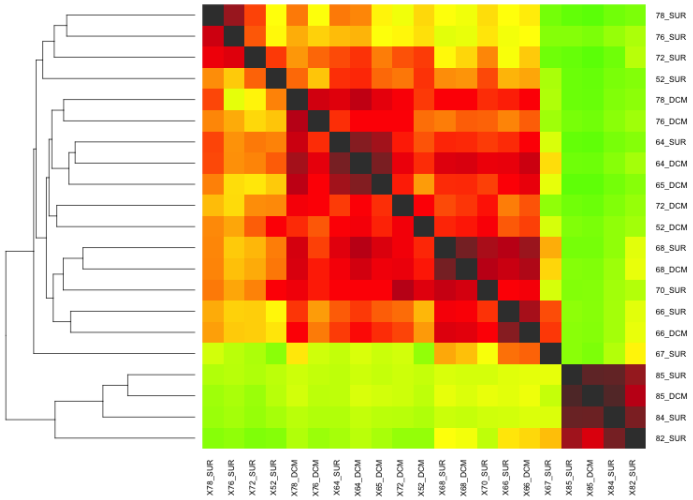
24/09/2015

Context



N metagenomic samples

Whole genome sequencing



Similarity heatmap N^2

De novo comparative metagenomics

fasta fasta … fasta

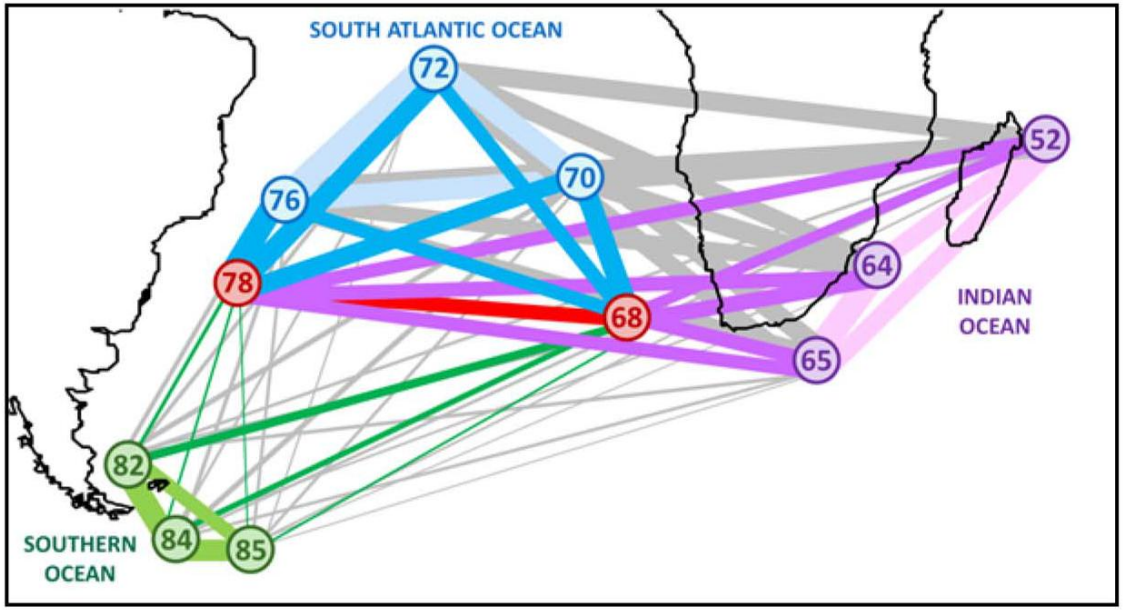
N MetaG datasets

Tara Oceans
- > 1000 datasets
- > 100 millions reads each

De novo comparative metagenomics

- Sea water
  - < 5% assembled reads
  - < 10% known species

- Compare **environmental data** and **genomic contents**
  - Environmental characteristics of Agulhas rings affect interocean plankton transport. Villar *et al.* Science 2015

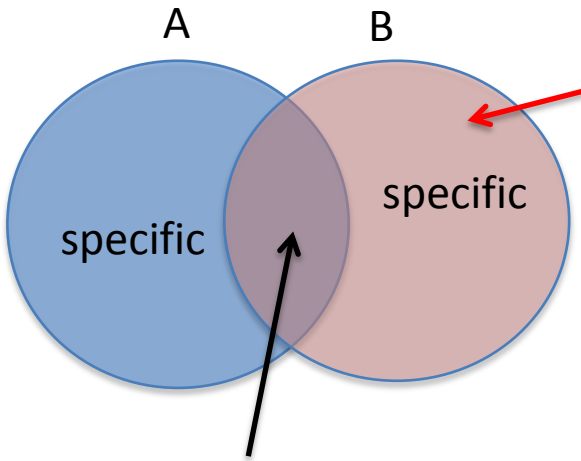


Similarities on
- Barcodes
- WGS

→same conclusions

Similarity between 2 samples

Idea: Similarity is given by the **size of the intersection**



100M reads

✖ Would require **months** of computation

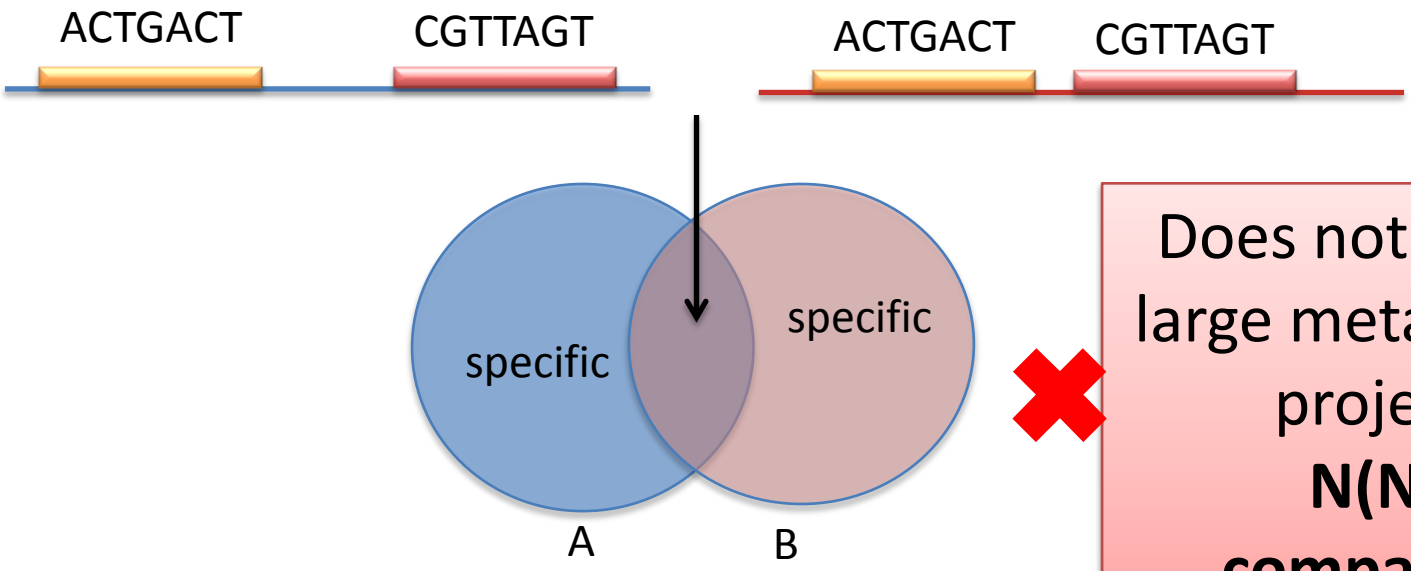
Intersection = number of **similar reads**

Similar: alignment score > 90%
(Blast-like approaches, all-vs-all sequence alignment)

State of the art

Commet (Maillet *et al.* IEEE BIBM 2014)

- "**similar**": share at least ***t*** non-overlapping ***kmers*** (words of size k)
- Example: t=2:



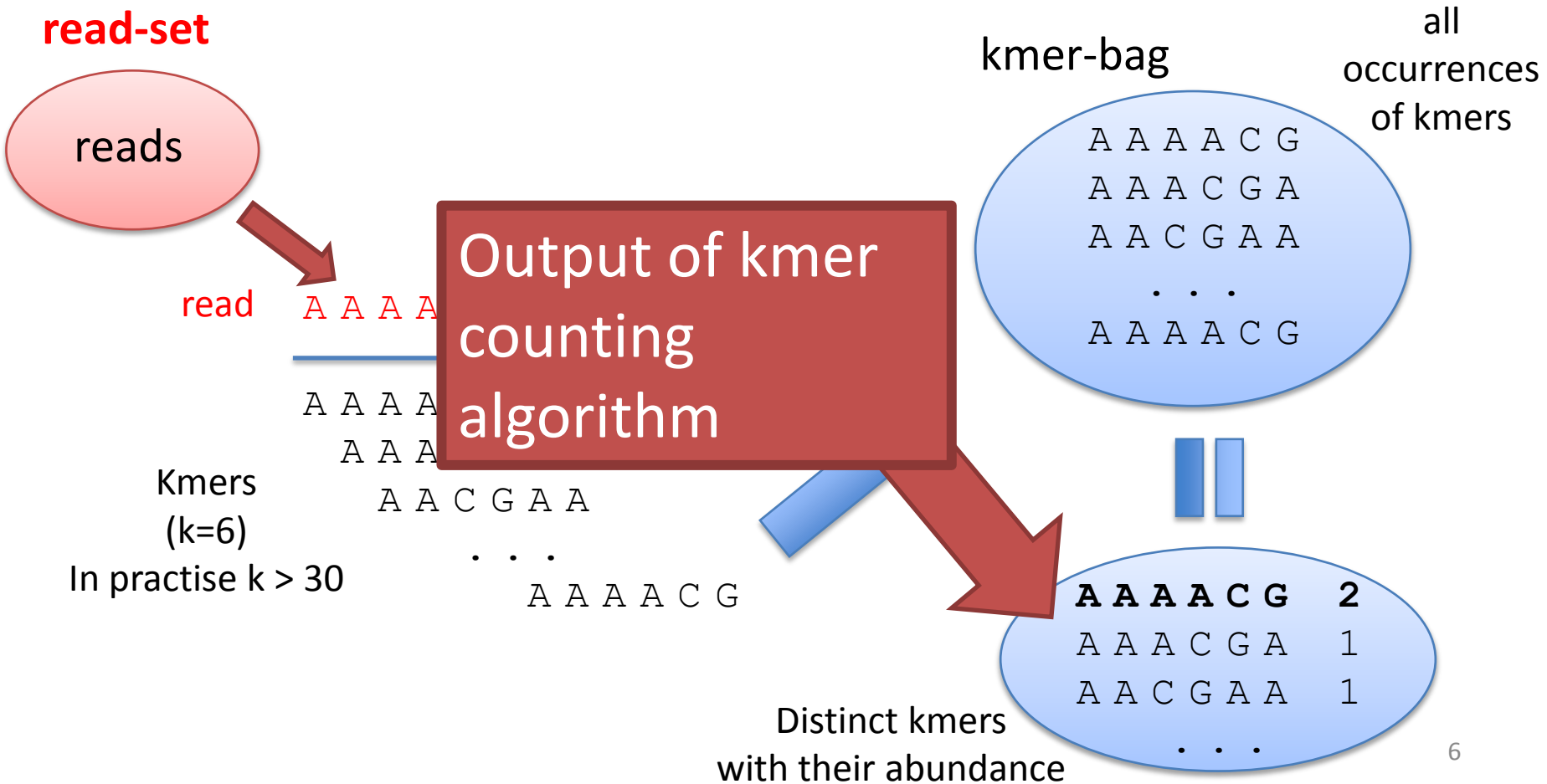
Does not scale on large metagenomic projects : **N(N-1) comparisons**

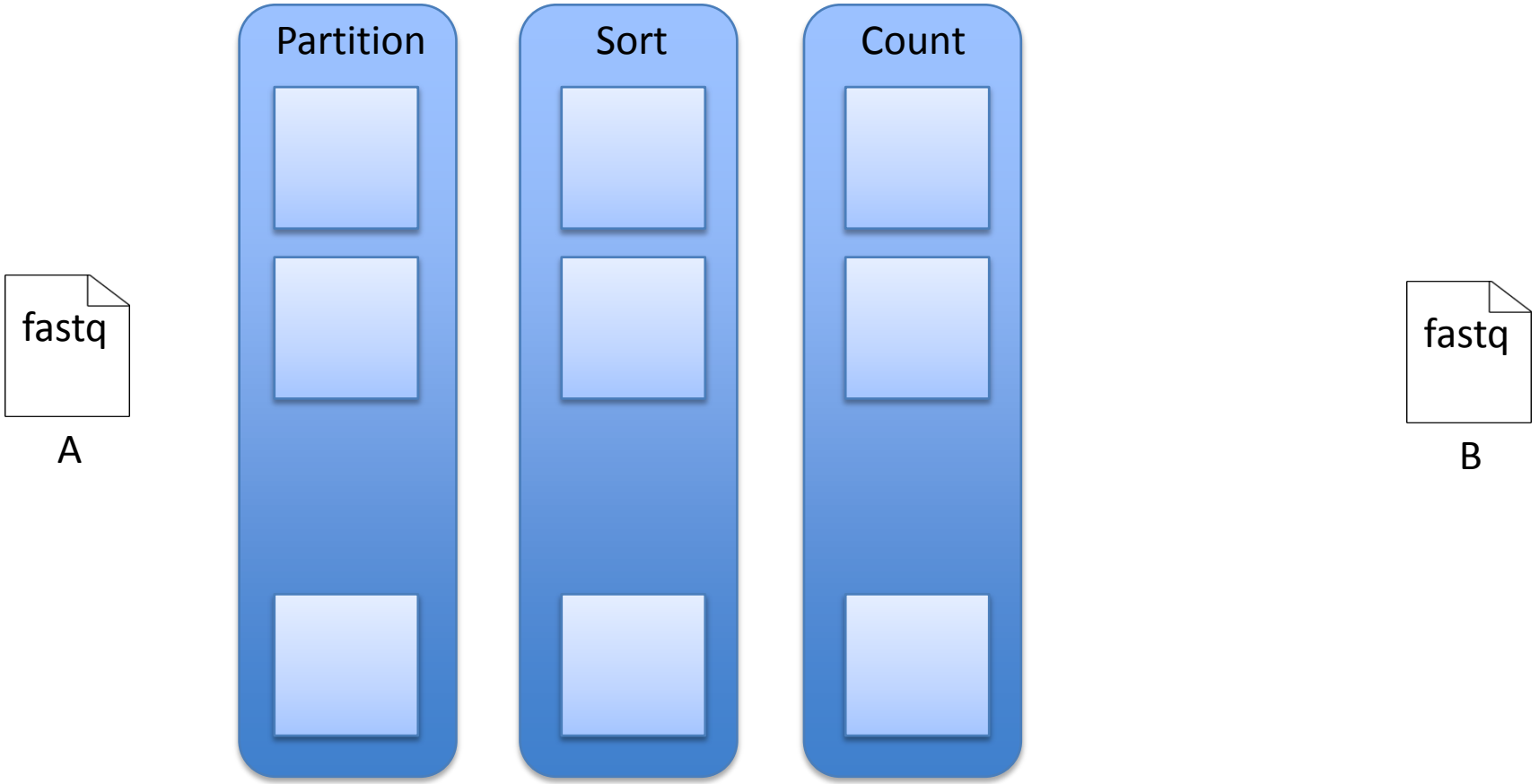
- Computes one intersection in **few hours**
  - Alignment free method
  - Only **indexing** and **querying kmers**

Simka: comparing numerous datasets

New representation of datasets

- **Not** viewed as a **read-set** anymore
- But as a **bag** of its **overlapping kmers**



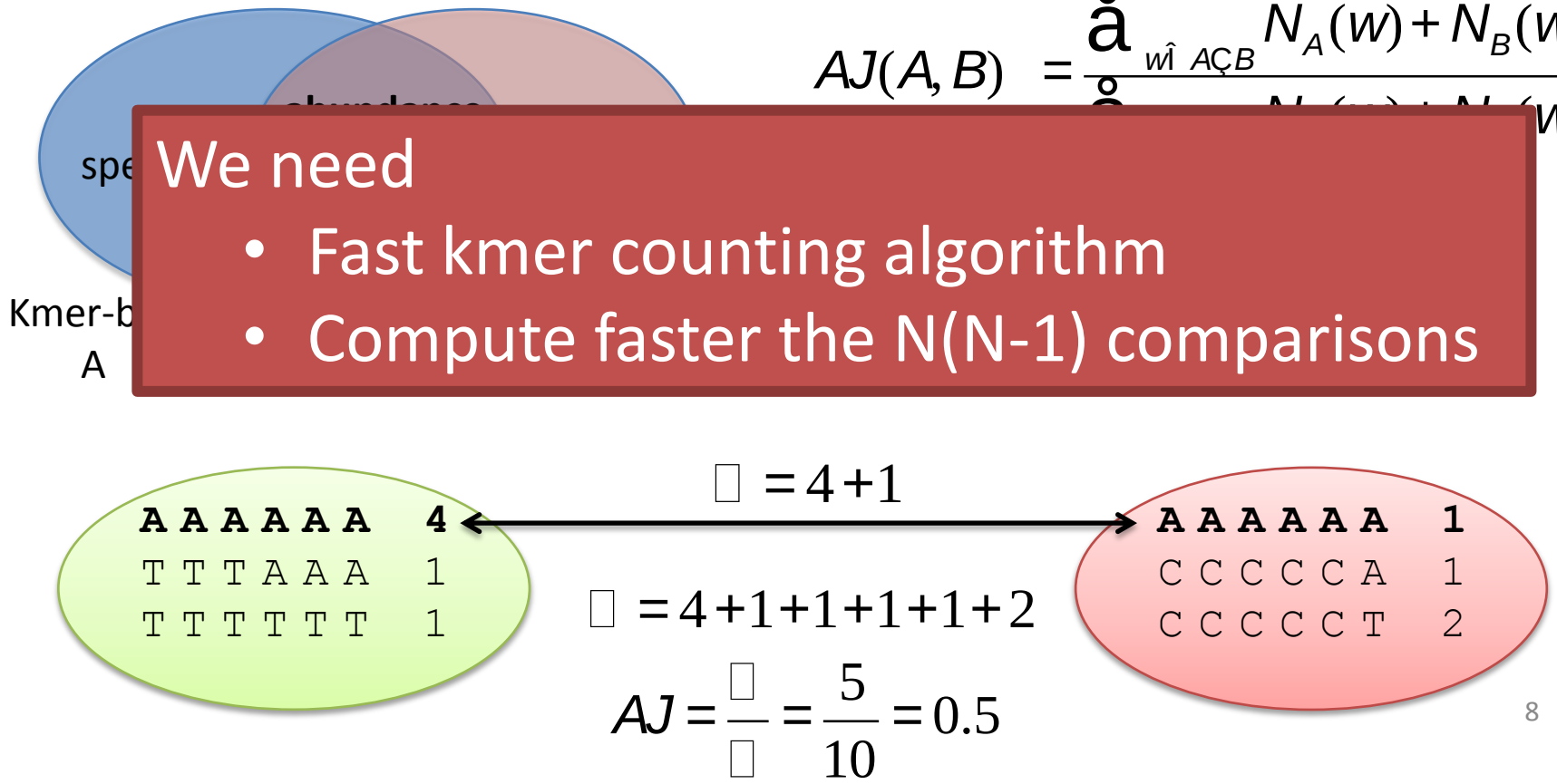

Partition
Sort
Count
fastq
A
fastq
B

Simka: comparing numerous datasets

New similarity function

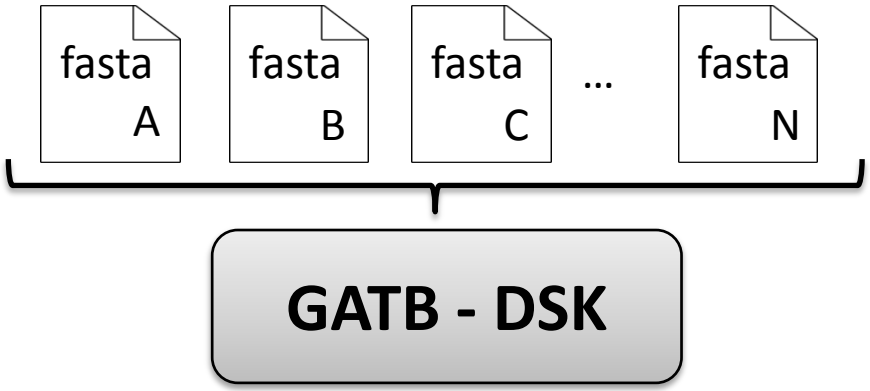
- Pairwise similarity measure based on **shared kmers**

Abundance-based Jaccard similarity



Multiset kmer counting

- Count the kmers of N datasets **simultaneously**
  - Based on KMC2 algorithm (Deorowicz *et al.* Bioinformatics 2015)
  - Available in GATB library (Drezen et al. Bioinformatics 2014)



	A	B	C	…	N
ACGATC	0	4	5 2	…	0

Its abundance in each dataset

- We can now count the kmers of large datasets quickly
- Compute all the intersections simultaneously

Simka algorithm

- Example with 3 datasets on **Abundance-based Jaccard similarity**

$$AJ(i,j) = \frac{\sum_{w \in i \cap j} N_i(w) + N_j(w)}{\sum_{w \in i \cup j} N_i(w) + N_j(w)} = \frac{n(i,j)}{u(i,j)}$$

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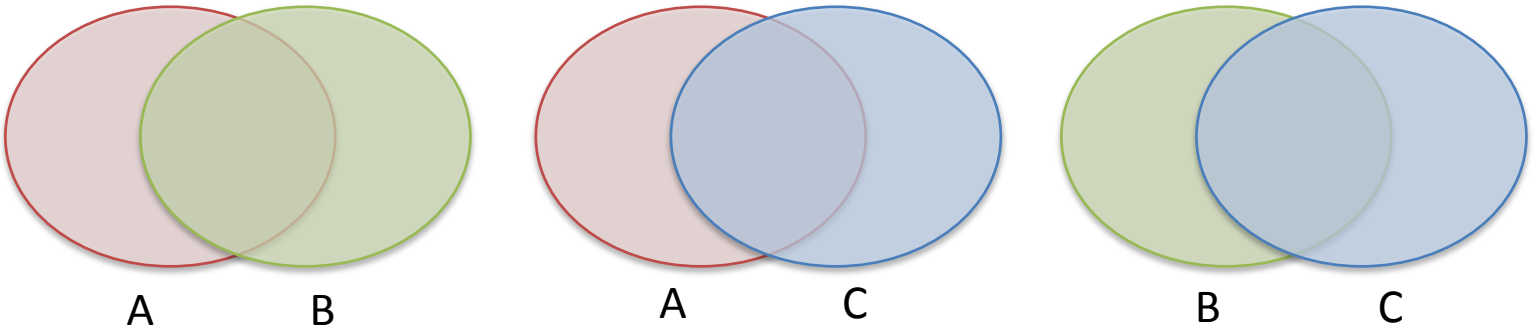
For each pair(i, j)

Kmer shared by A, B and C

	A	B	C
ACGATC	4	2	8



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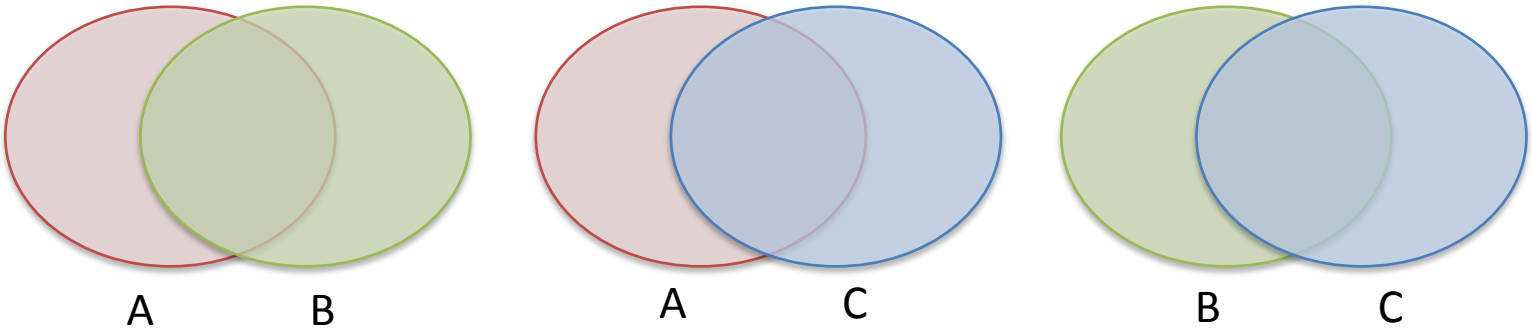

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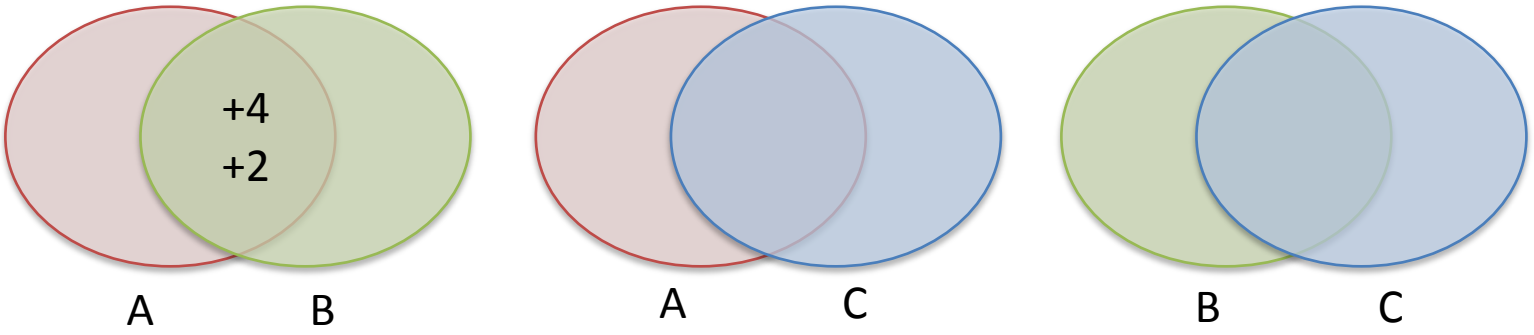

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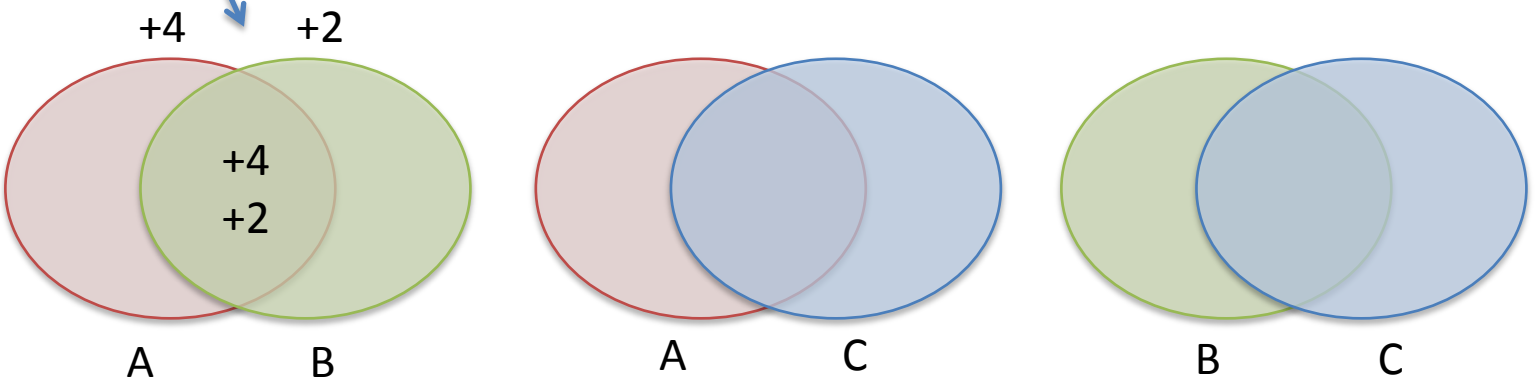

AJ(A,B) = 6/6 = 1

Simka algorithm

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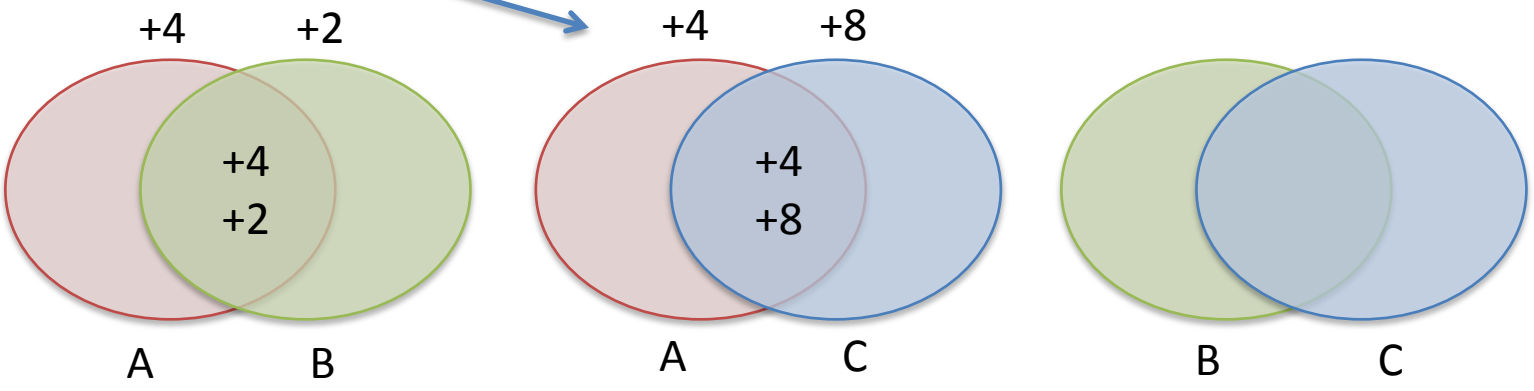

AJ(A,B) = 6/6 = 1

AJ(A,C) = 12/12 = 1

Simka algorithm

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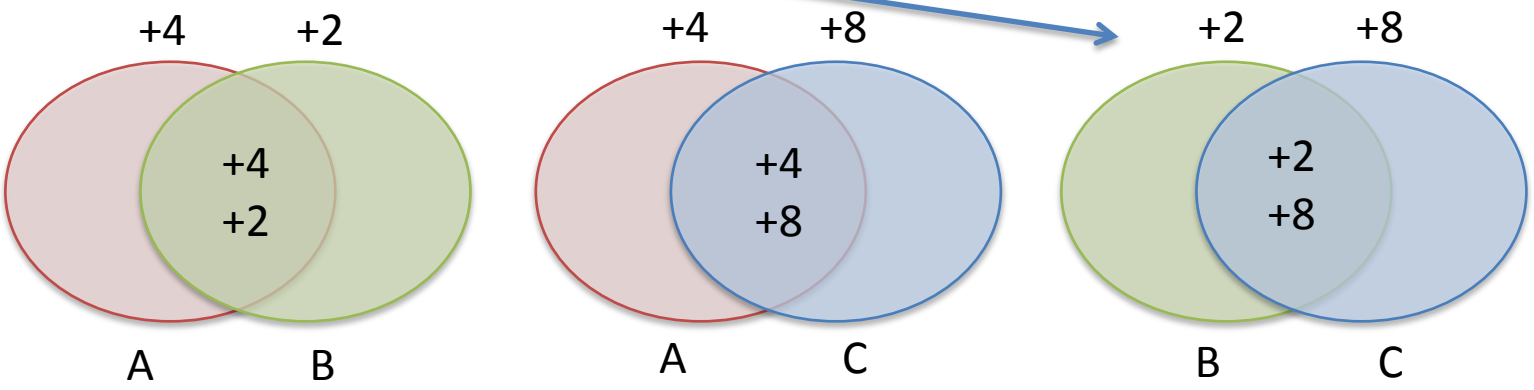

Simka algorithm

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Kmer specific to A

	A	B	C
ACGATC	6	0	0

For each pair(i, j)

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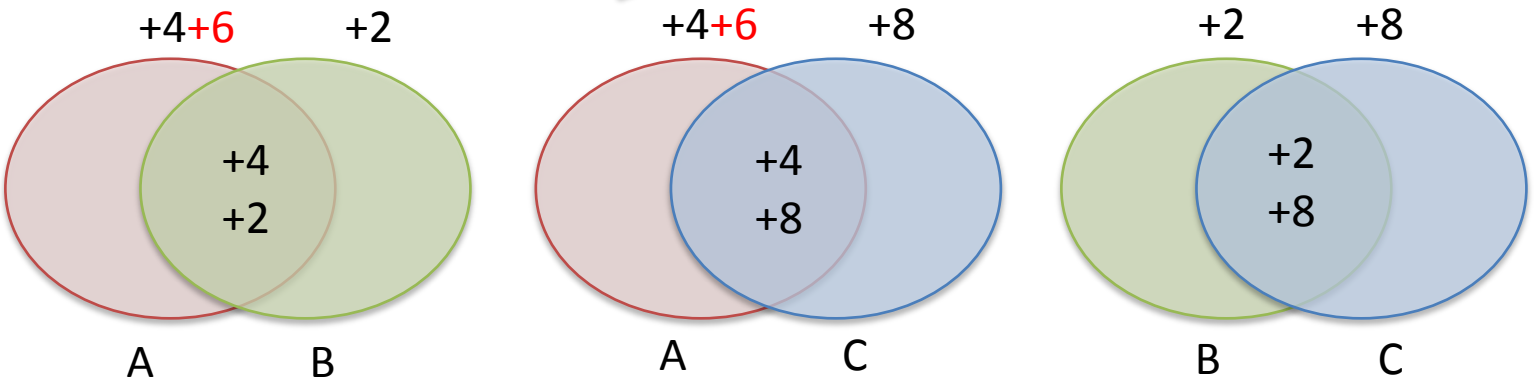
Update union **u[i,j] += Ni + Nj**



AJ(A,B) = 6/12 = 0.5

AJ(A,C) = 12/18 = 0.66

AJ(B,C) = 10/10 = 1

Simka algorithm

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N(N-1)

For each pair(i, j)

If kmer is shared **Ni > 0 and Nj > 0**

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Kmer specific to A

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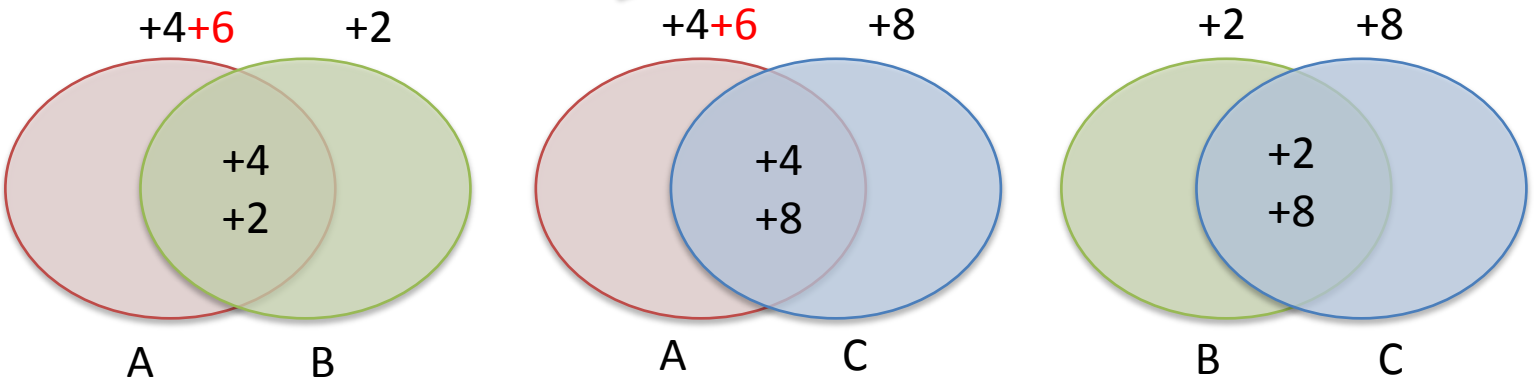
ACGATC	6	0	0



AJ(A,B) = 6/12 = 0.5

AJ(A,C) = 12/18 = 0.66

AJ(B,C) = 10/10 = 1

Execution time

On 21 Tara samples, 2.1G reads, 210GB data

- Commet (state of the art)
  - On cluster (one node)
    - **A few weeks**

- Simka
  - On cluster (one node): **3h**
    - Counting kmers: 75%
    - Update unions/intersections **N(N-1)**: 25%
  - On standard computer: 10h
    - 4 GB memory, 4 cores

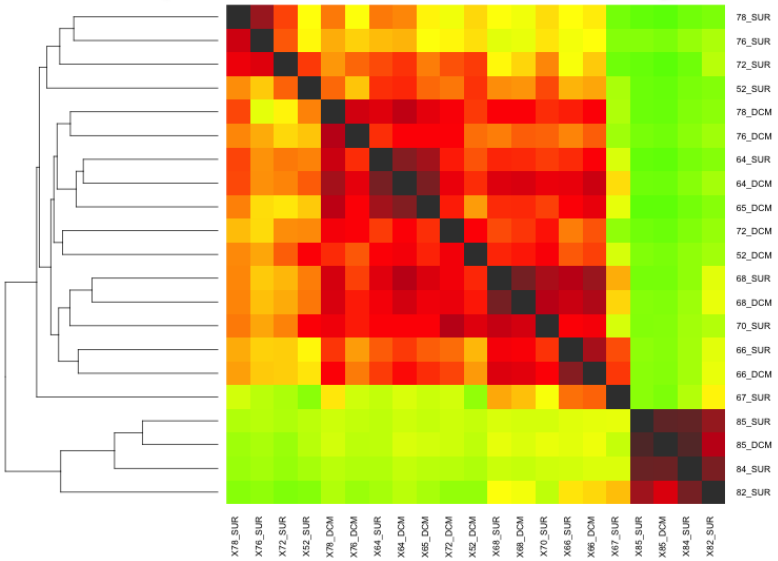
Representation of similarity

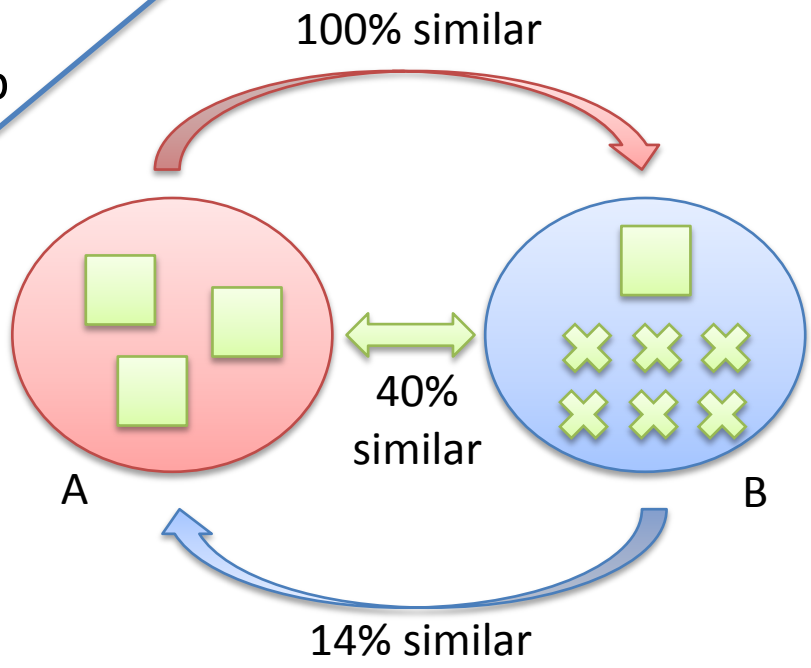
$$AJ_{sym}(i,j) = \frac{\sum_{w \in i \cap j} N_i(w) + N_j(w)}{\sum_{w \in i \cup j} N_i(w) + N_j(w)}$$

$$AJ_{asym}(i,j) = \frac{\sum_{w \in i \cap j} N_i(w)}{\sum_{w \in i} N_i(w)}$$

Hierarchical clustering

Heatmap

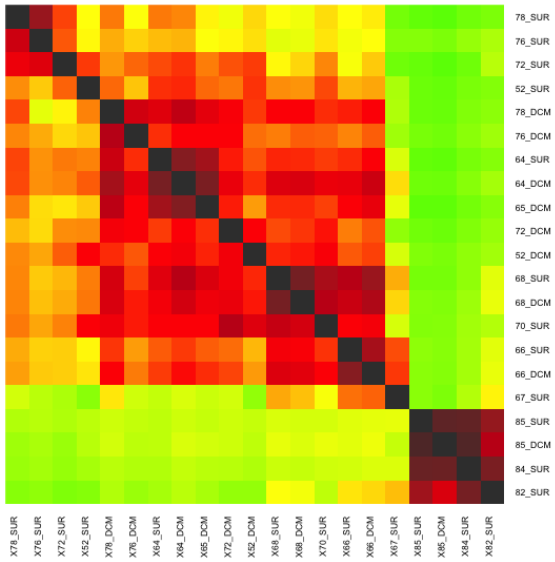




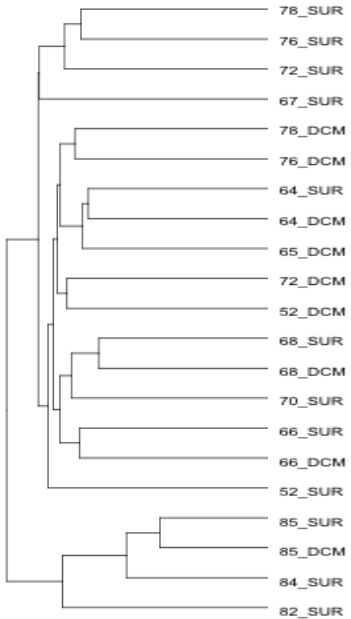
Asymmetry can shows information about diversity

Results

Two things to compare with Commet



Heatmap
absolute similarity

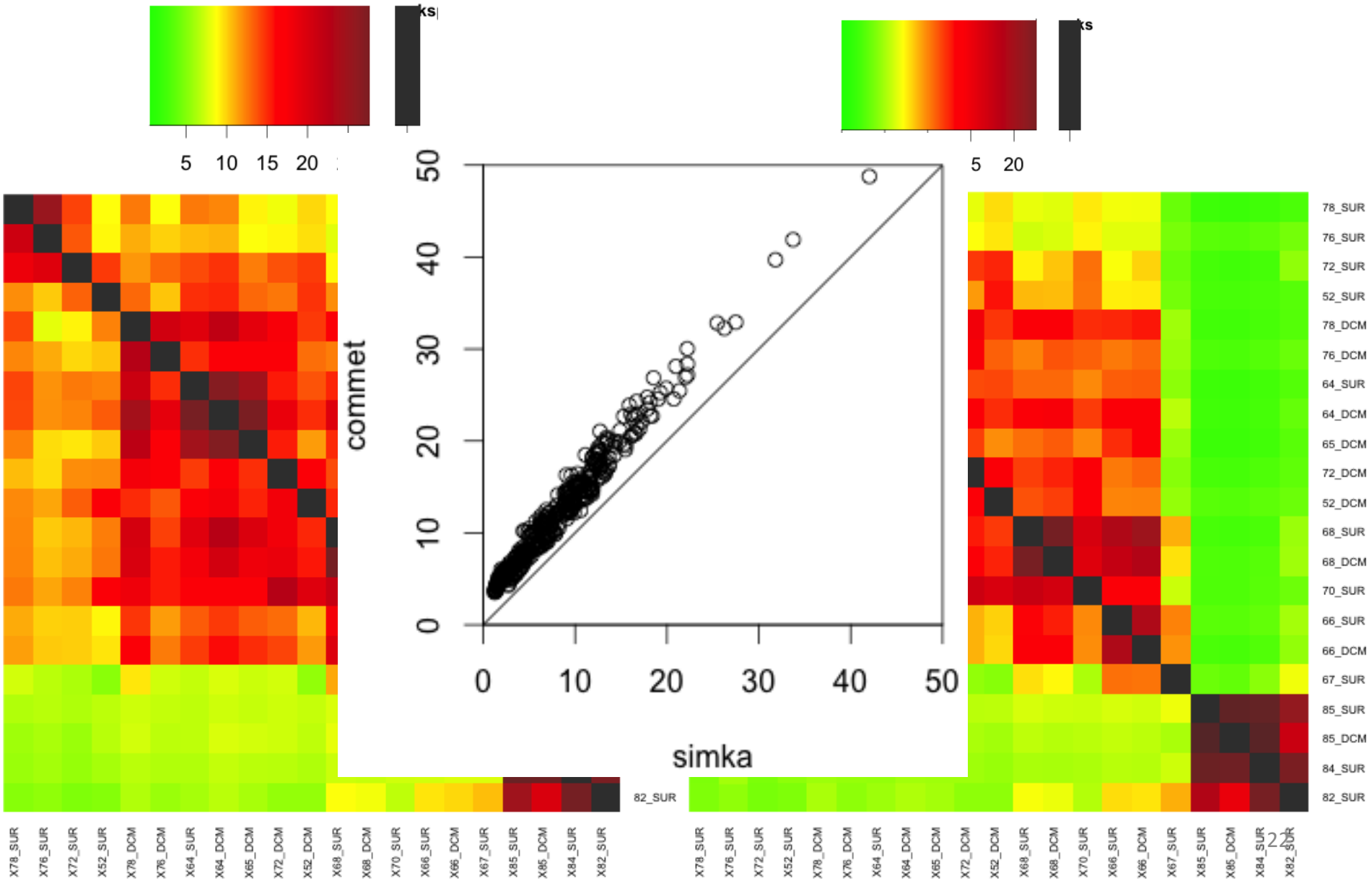


Hierarchical clustering
relative similarity

On 21 datasets from Tara Oceans

Commet (k=33)

Simka (k=31)



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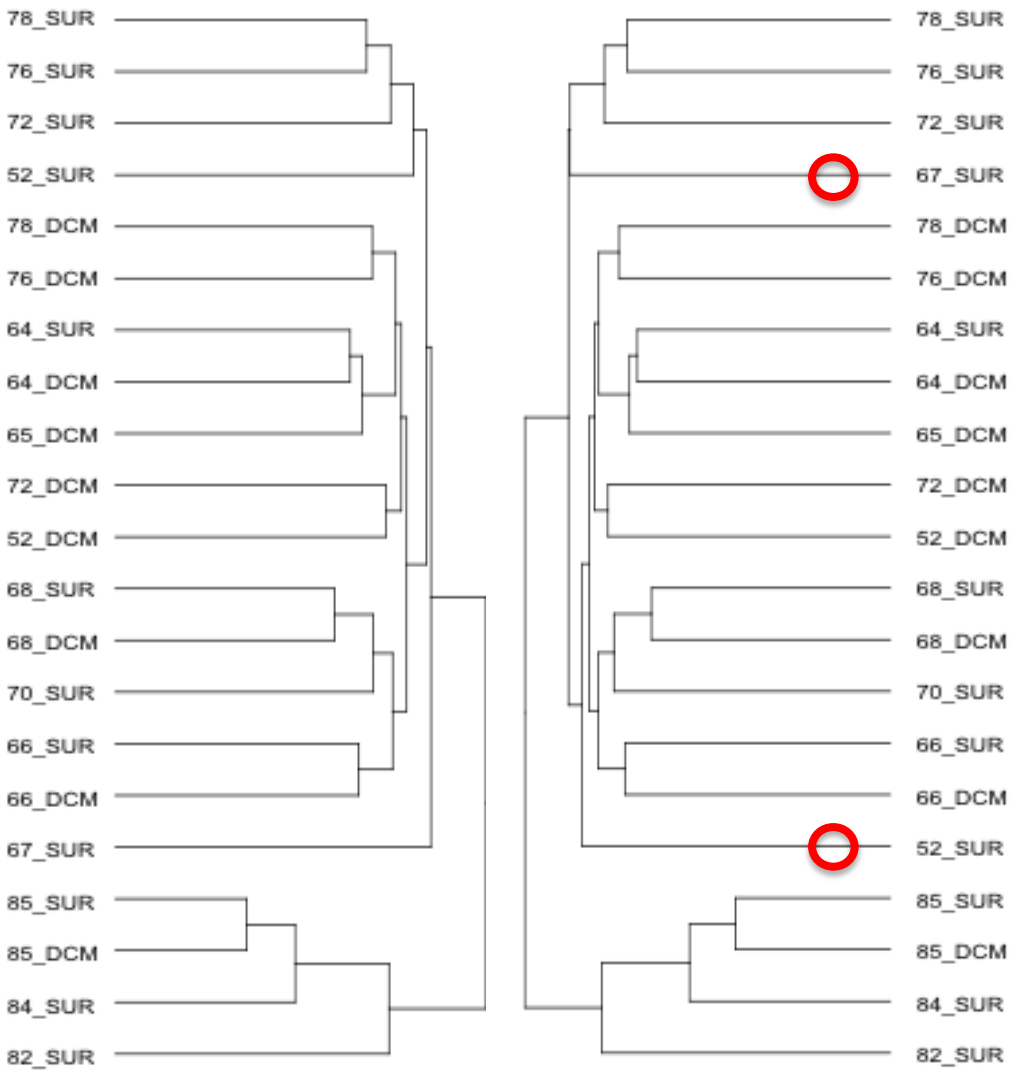


Other measures provided

- Transform the **abundance vectors** to get new measures
  - From **abundance** to **presence/absence**

	A	B	C
ACGATC	0	4	2

To boolean vector

	A	B	C
ACGATC	0	1	1

Jaccard similarity:

$$J_{sym}(A,B) = \frac{|A \cap B|}{|A \cup B|} \qquad J_{asym}(A,B) = \frac{|A \cap B|}{|A|}$$

  - Filtering potentially erroneous kmers
    - Discard kmer if **specific** (D=1) and **unique** (Ni=1)

	A	B	C
ACGATC	0	1	0

✖

	A	B	C
ACGATC	0	1	1

✔

	A	B	C
ACGATC	0	0	8

✔

Conclusion

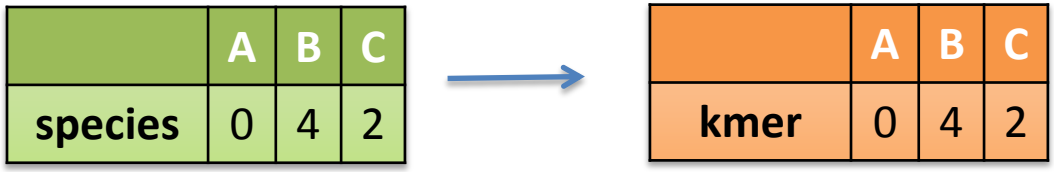
- Simka
  - New pairwise similarity functions based on **shared kmers**
  - Provides measures based on **abundance** and **presence/absence**
  - Results close to read-based methods
  - Fast and low memory thanks to the GATB library
    - Execution time (21 Tara samples, 2.1G reads, 210GB data)
      - Commet (state of the art): **few weeks**
      - Simka
        - On cluster: **3h**
        - On standard computer: 10h

GATB
www.gatb.inria.fr

Simka
www.gatb.fr/software/simka

Perspectives

- Add similarity measures well used in ecology (Ex: Bray Curtis)



- Bootstrapping
  - Test the robustness of Simka
    - Are there differences between using 100M or 10M reads?
    - Provides similarity matrix with confidence intervals
      - Sim(A, B) = 23% **±0.6%**
  - Add confidence levels to dendrogram

- Simka Potara
  - For cluster and cloud
  - MapReduce model
  - Process huge amount of data
    - **130 Tara samples** (13G reads, 1.3TB data) compared in **< 1 day**

Acknowledgements

PHD Supervisor

Claire Lemaitre
Pierre Peterlongo
Dominique Lavenier

GATB devs

Erwan Drezen
Guillaume Rizk

Commet

Nicolas Maillet

Partners

INRA

Stéphane Robin
Sophie Schbath
Mahendra Mariadassou
Julien Chiquet
Julie Aubert
Sarah Ouadah
Emilie Lebarbier

CEA

Olivier Jaillon
Jean-Marc Aury
Eric Pelletier
Thomas Vannier

Founded

ANR Hydrogen