ETH zürich

Scalable Annotated Genome Graphs for Representing Sequence Data

Mikhail Karasikov

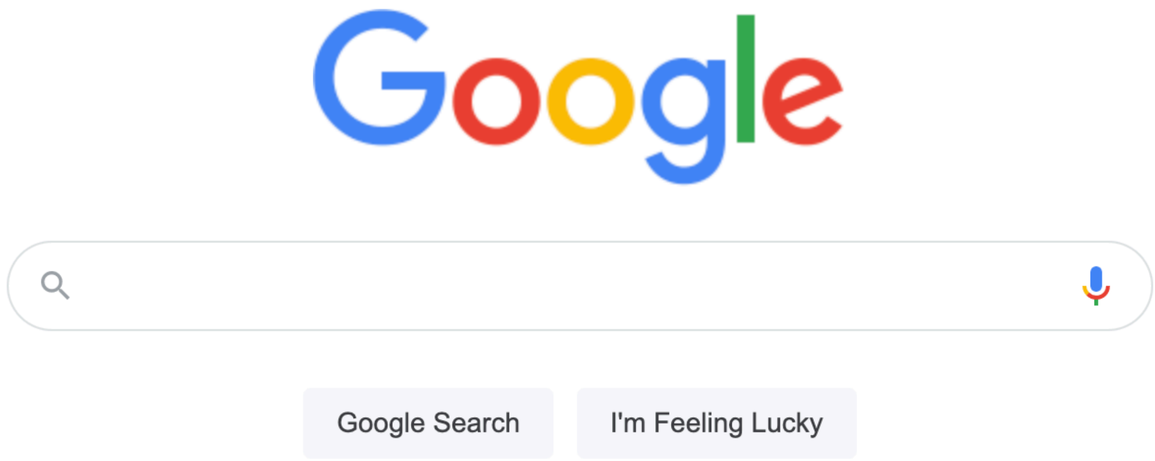
Doctoral examination

10 July 2023 (Zurich, Switzerland)

Committee:

Prof. Dr. Gunnar Rätsch
Prof. Dr. Jean-Philippe Vert
Prof. Dr. Ewan Birney
Dr. Rayan Chikhi

What we want



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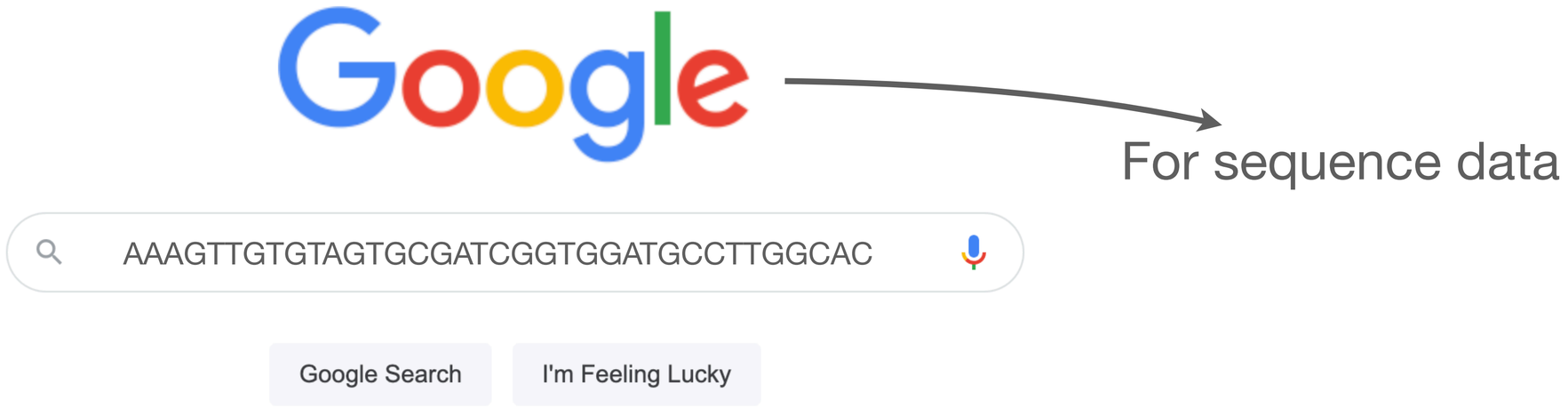
Google
For sequence data
AAAGTTGTGTAGTGCGATCGGTGGATGCCTTGGCAC
Google Search
I'm Feeling Lucky

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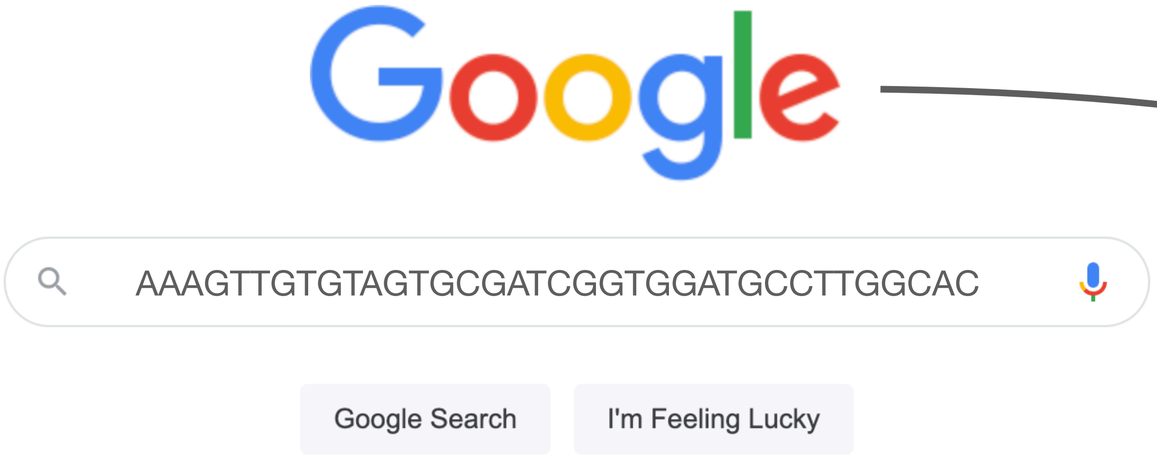


For sequence data

ENA European Nucleotide Archive

UK 10K

HMP

GENOME 10K

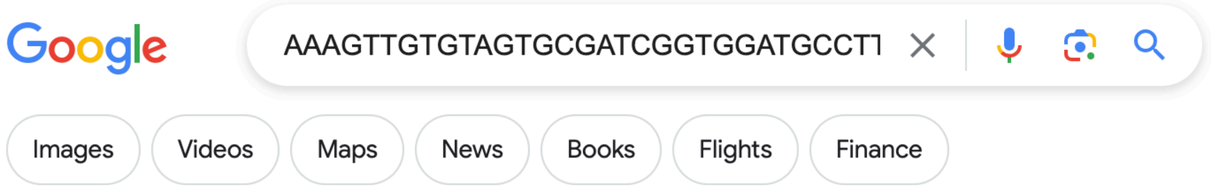
european genome-phenome archive

NCBI SRA

MetaSUB

• • •

Existing search engines do not work (yet)



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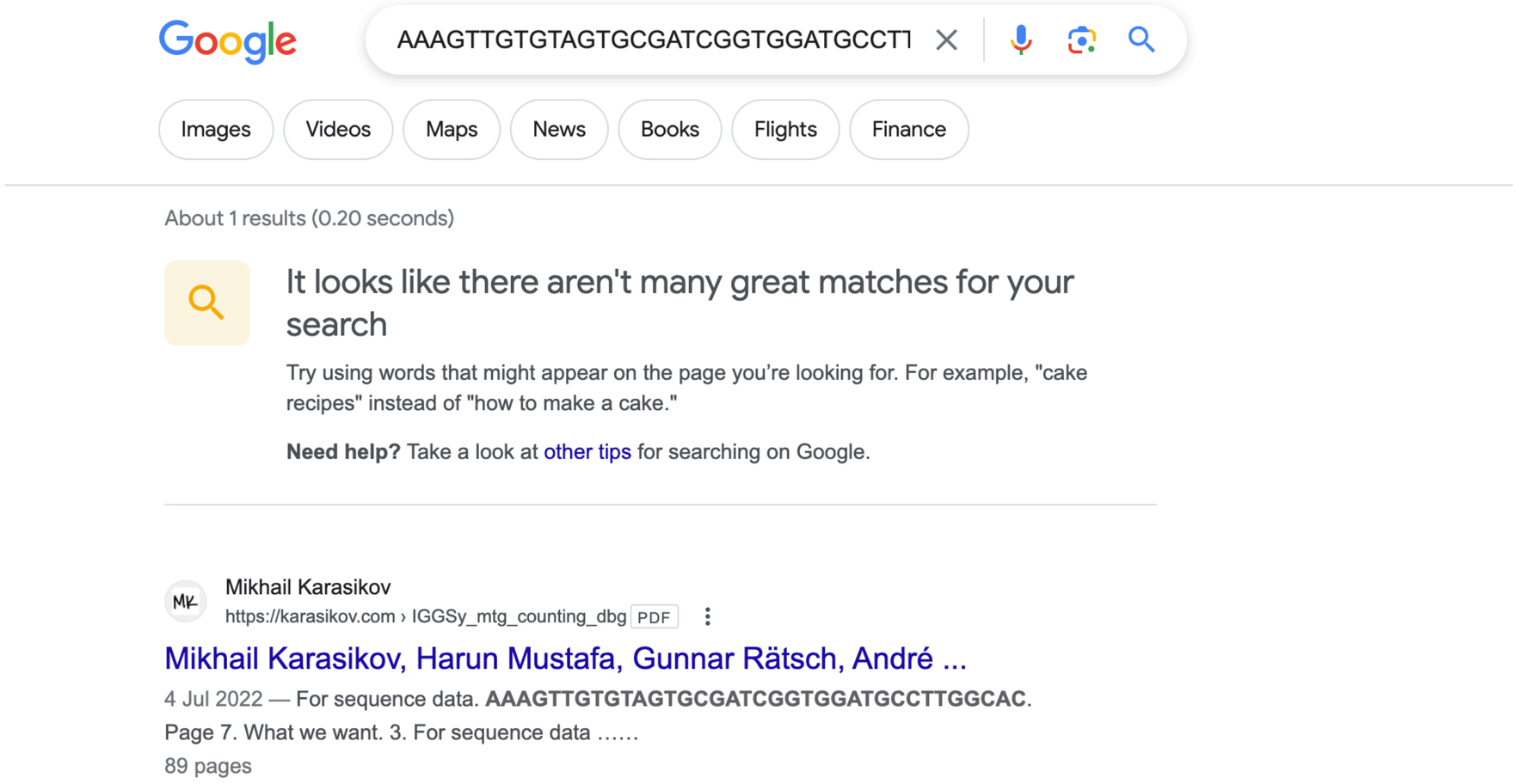

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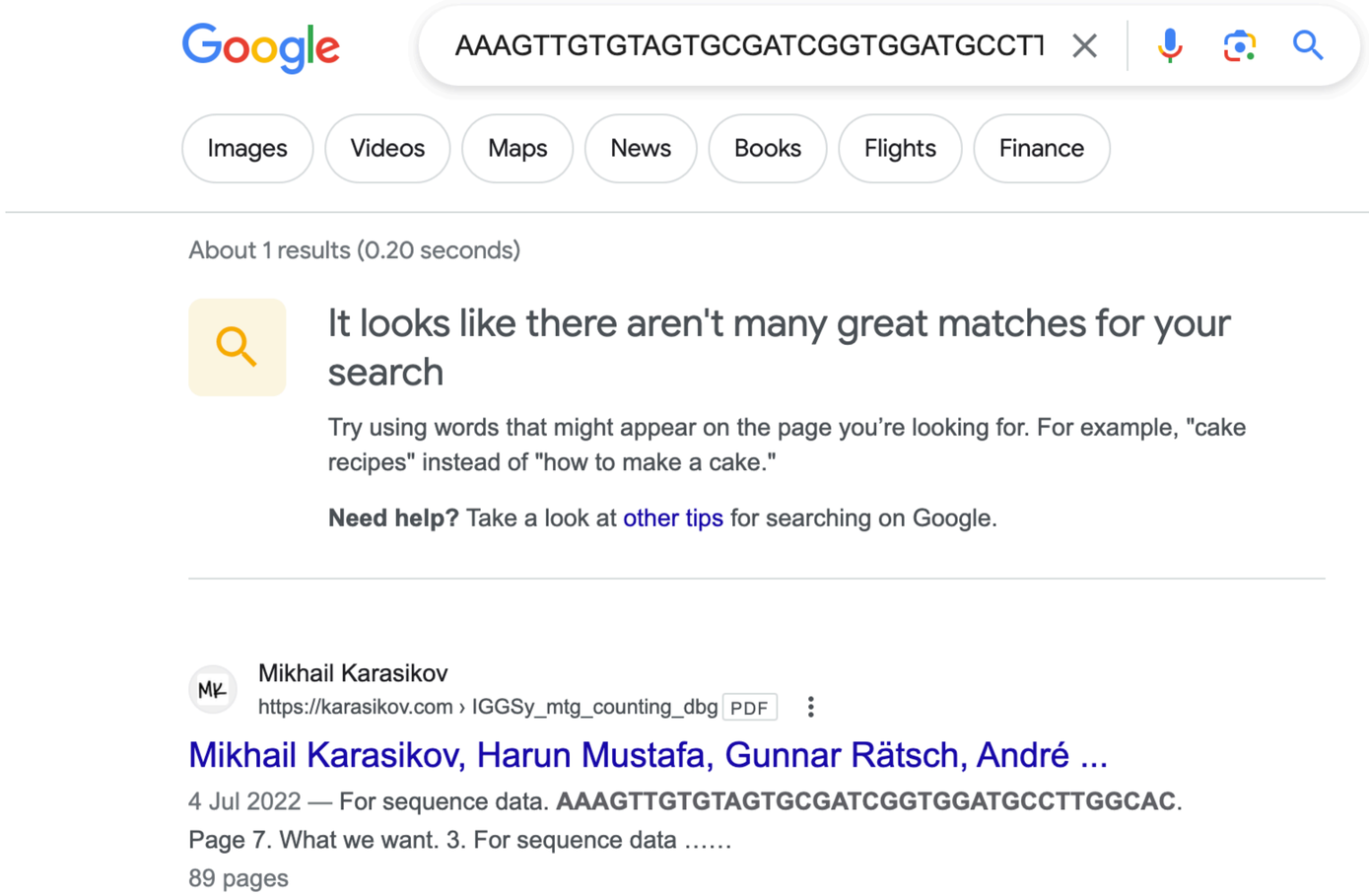
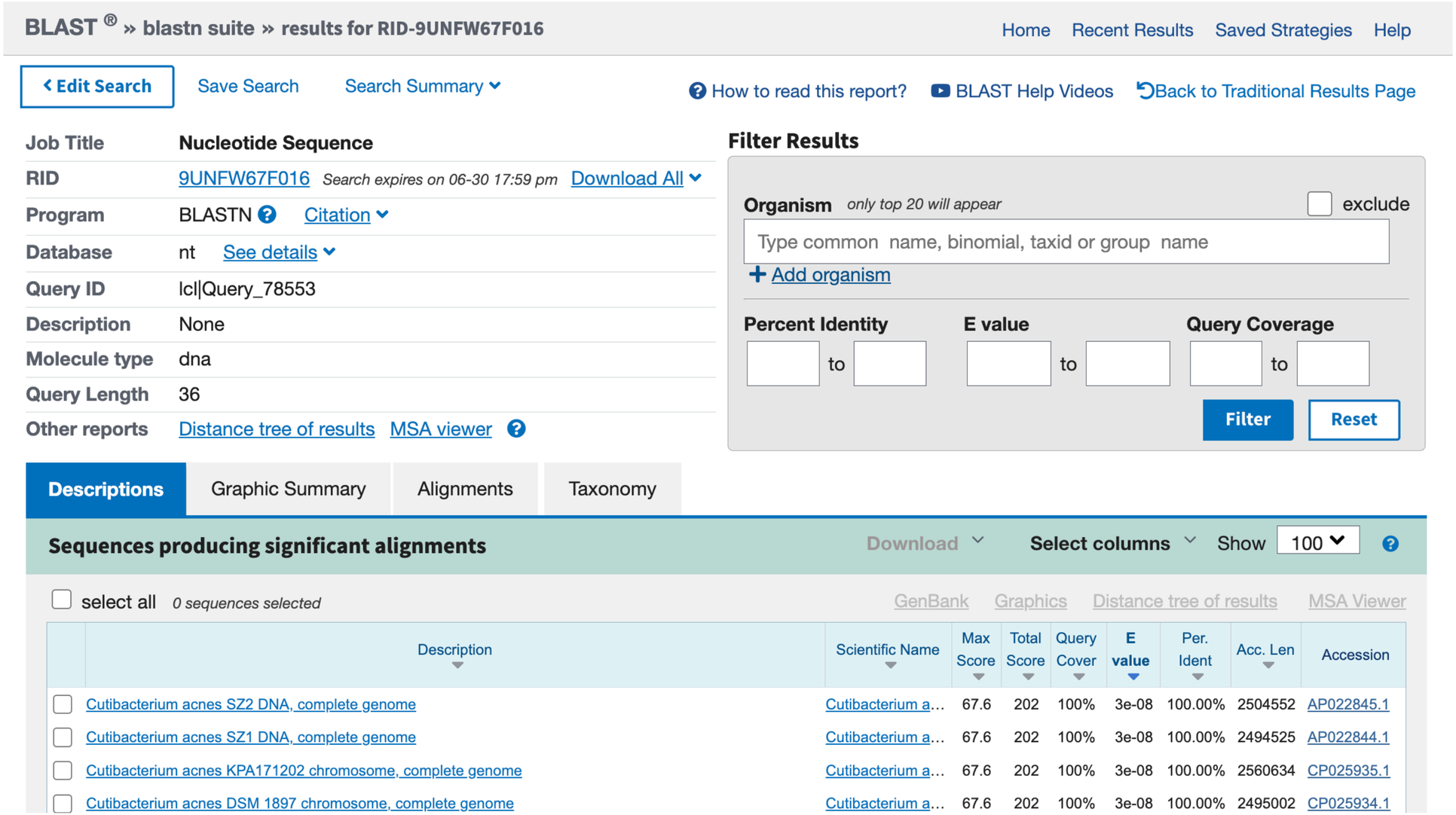


BLAST finds reference sequences



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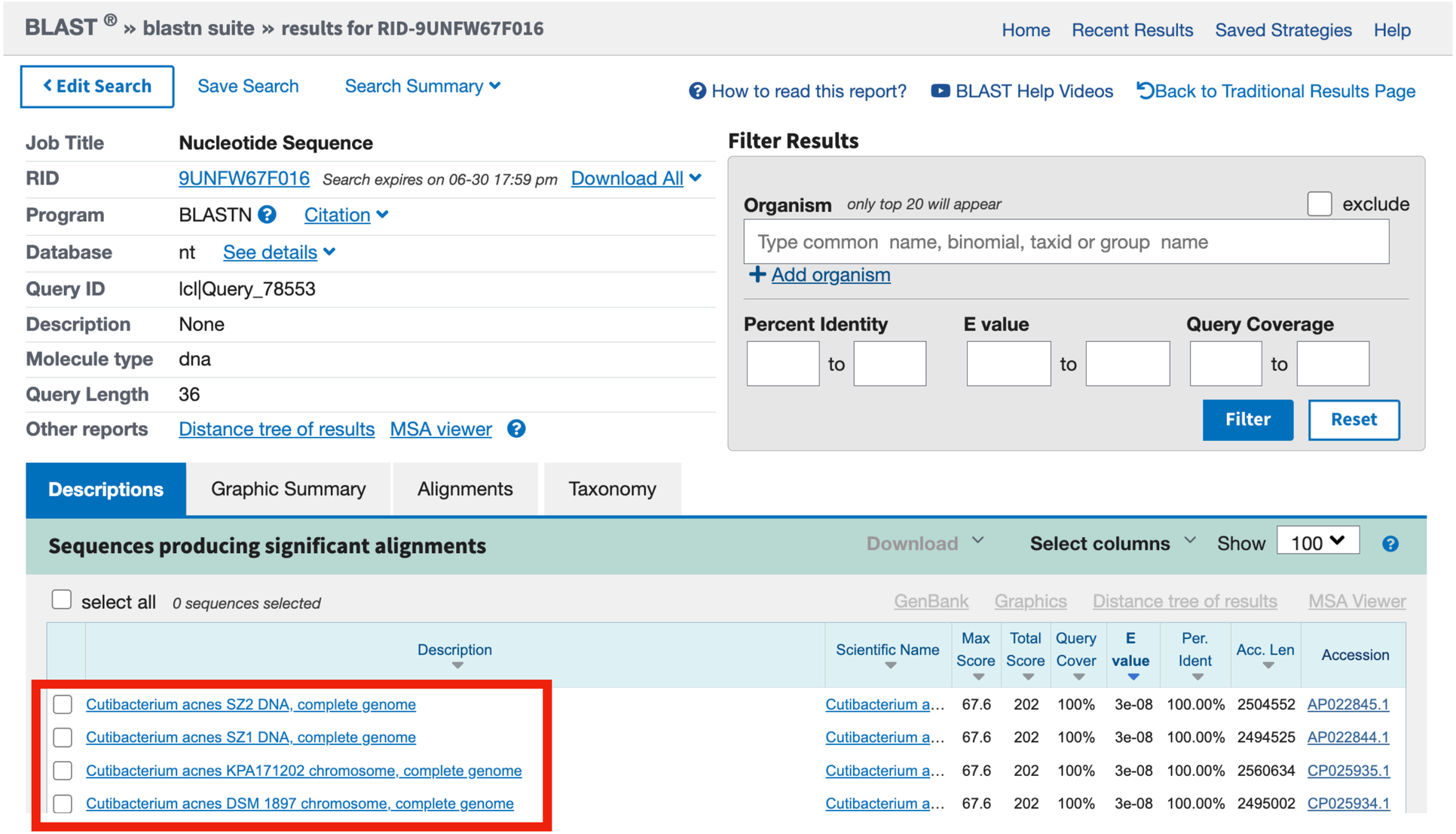
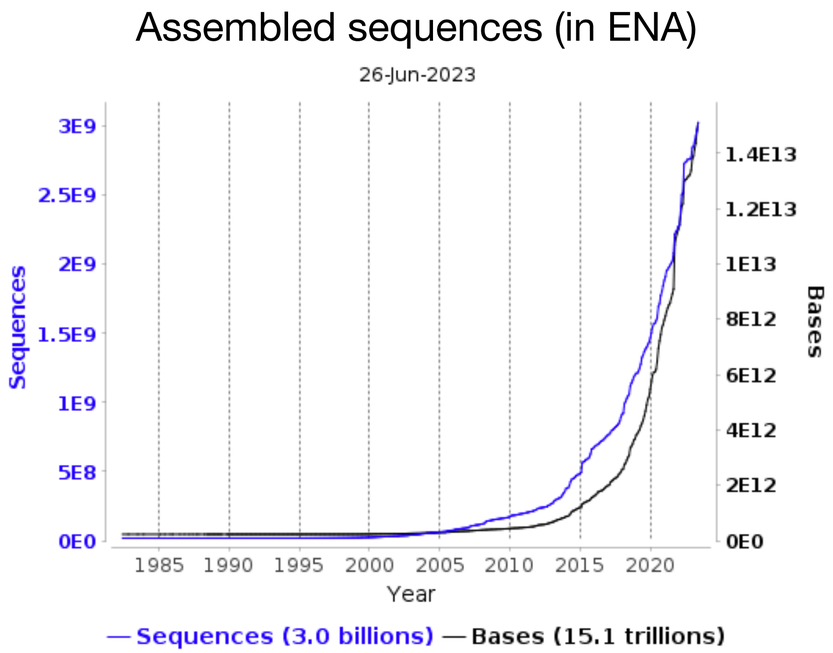


assembled sequences

Growth of sequence archives

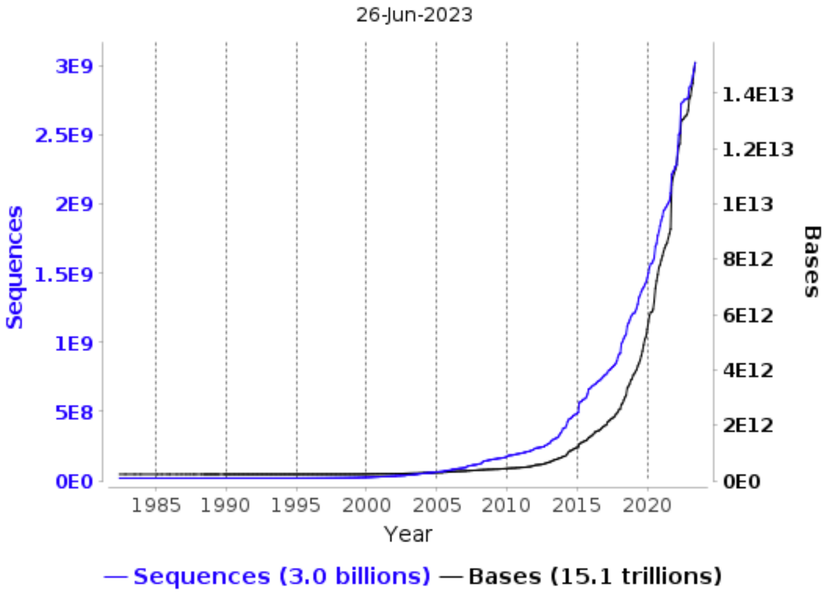


ENA
European Nucleotide Archive

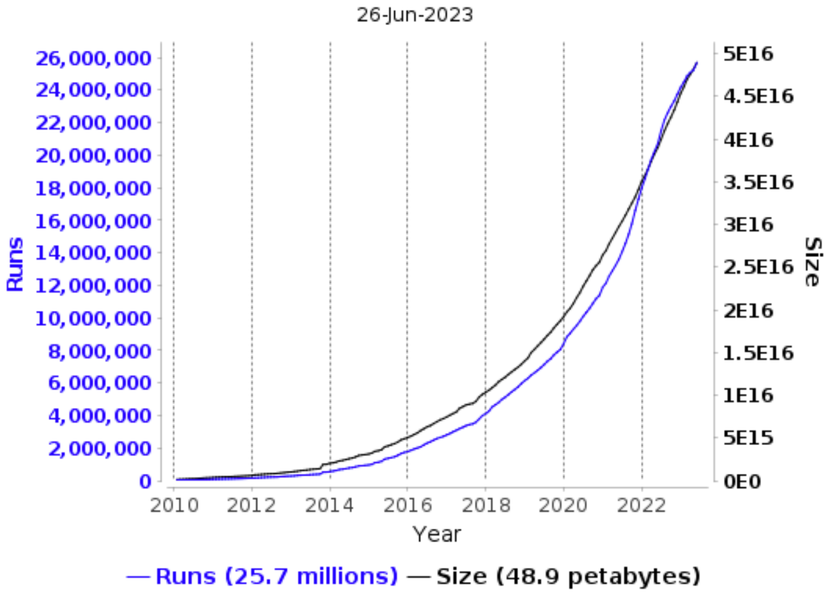
Data source: https://www.ebi.ac.uk/ena/browser/about/statistics

Growth of sequence archives

Assembled sequences (in ENA)



Raw reads (in ENA)



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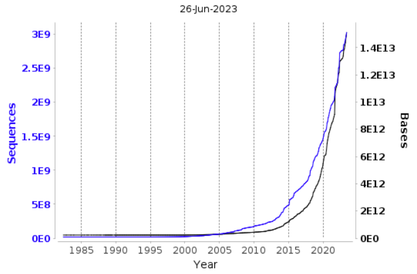

15 Tbp

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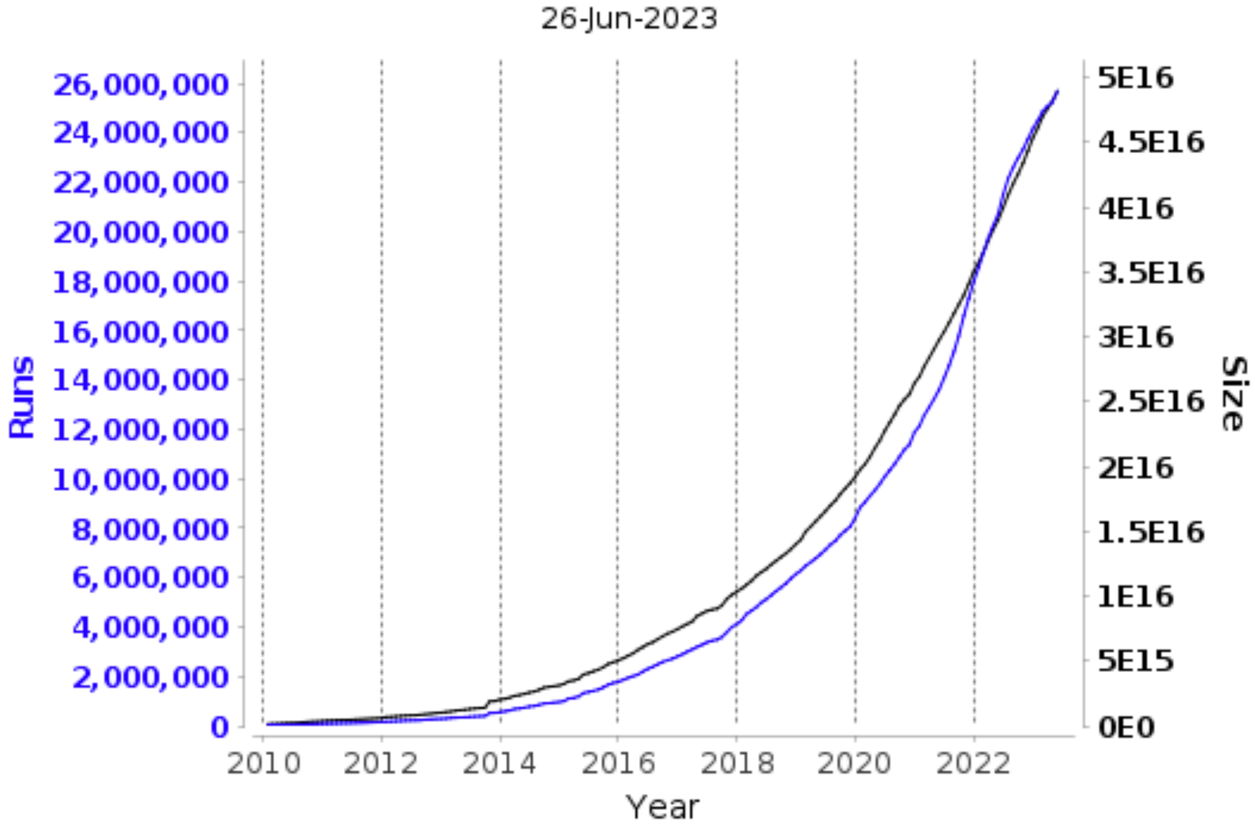

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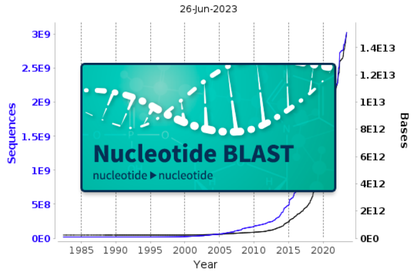

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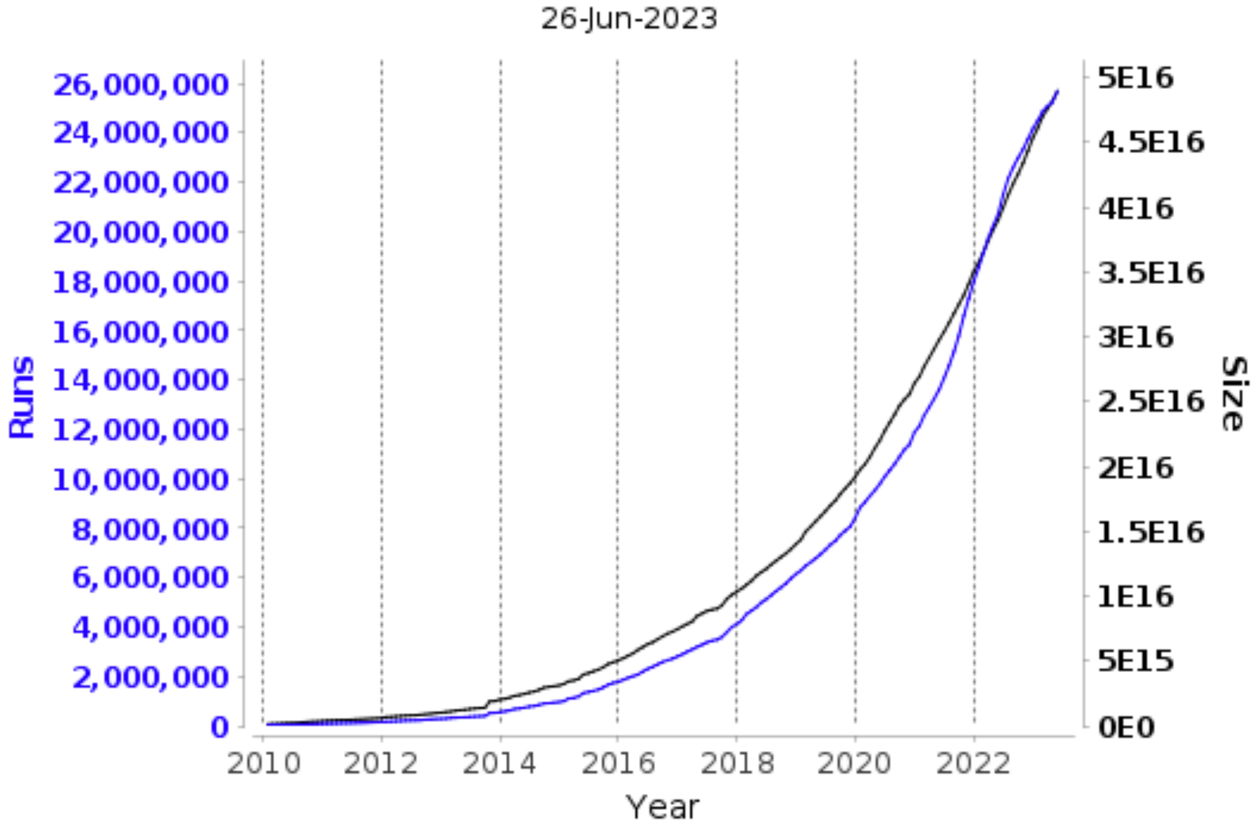

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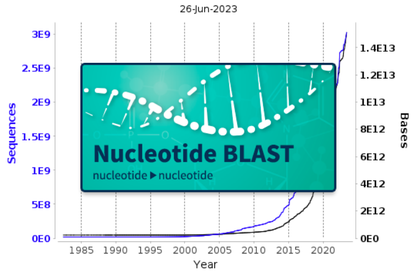

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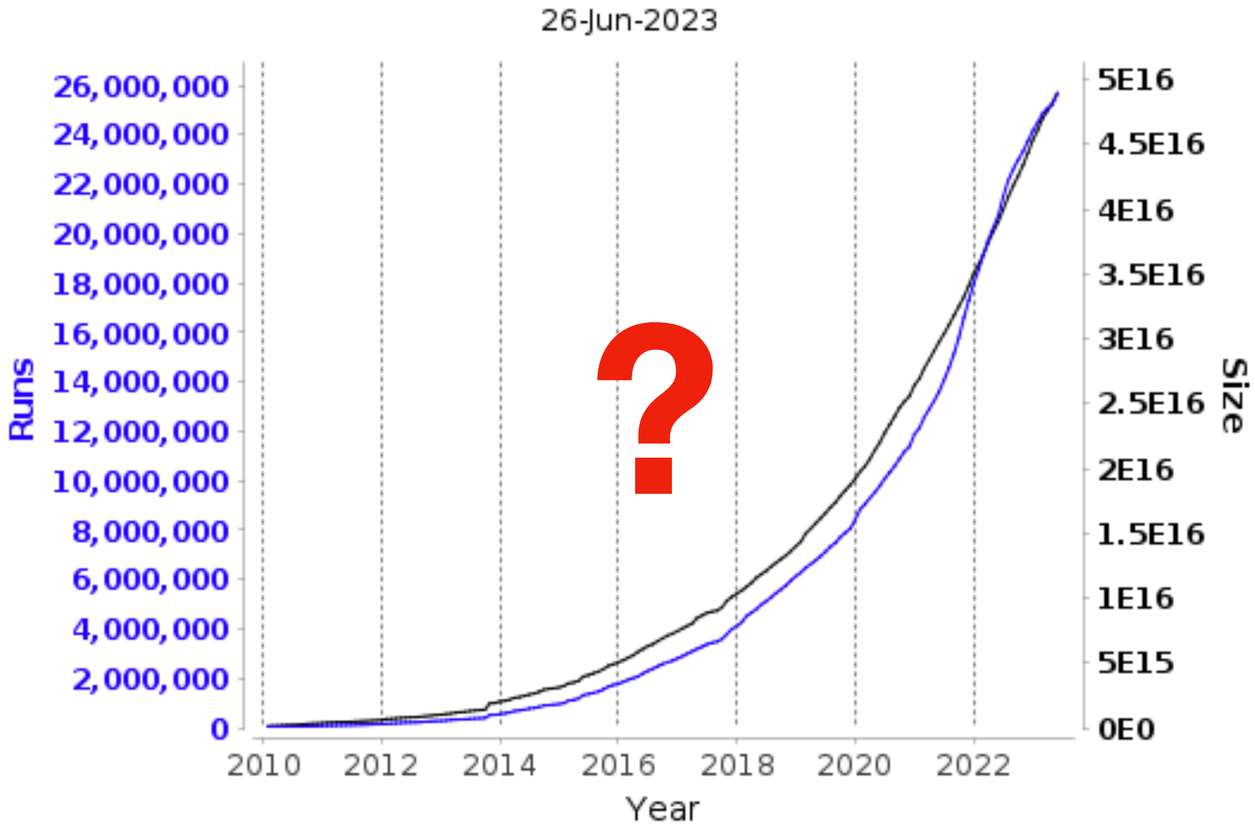

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Indexing sequences

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  - enormous amount of data (> 50 PB)
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  De Bruijn graph

Background

De Bruijn graphs have been introduced to the field by Pevzner in 1989

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```
ACTAGCTAGCTAG
```

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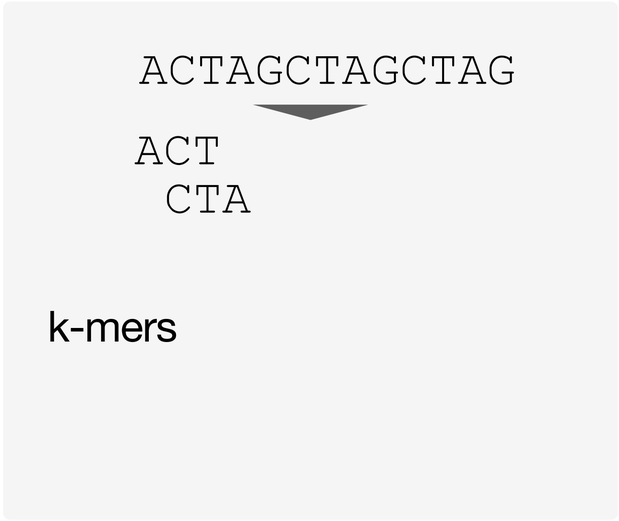

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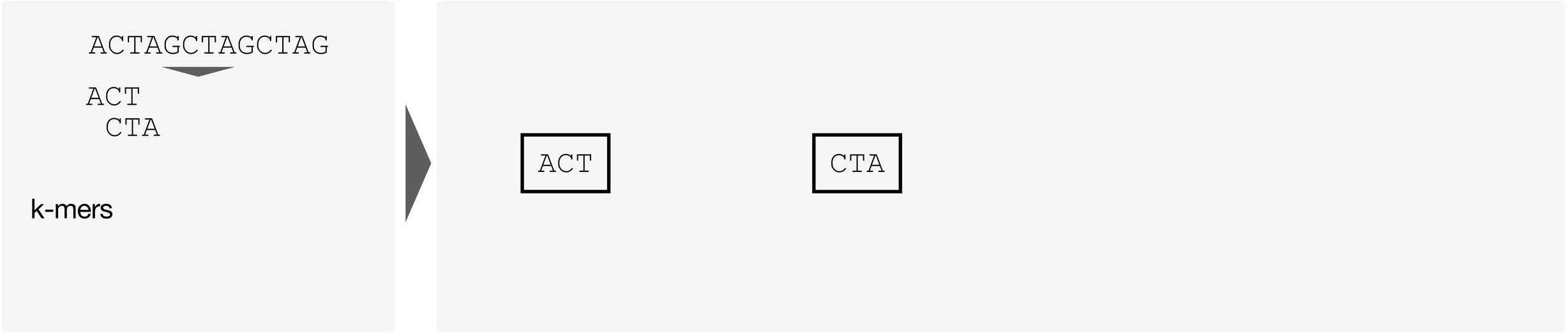

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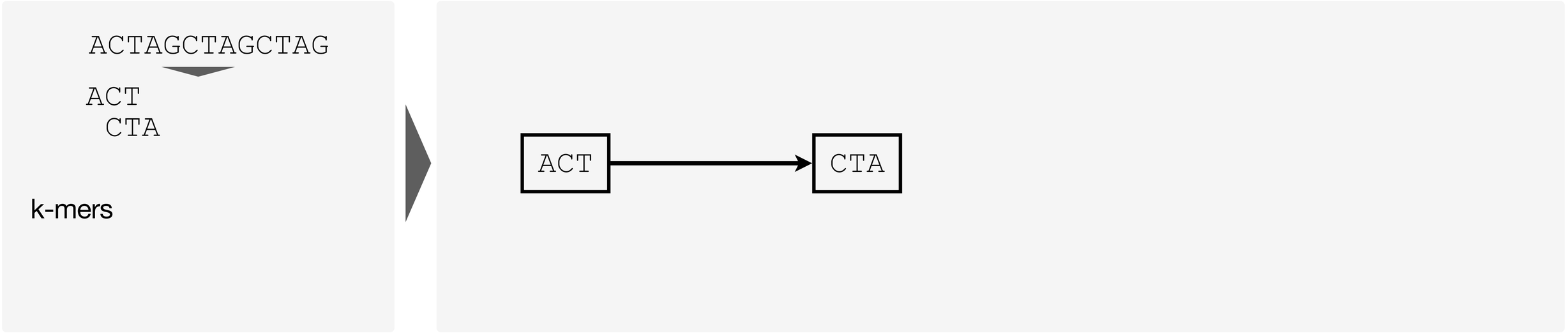

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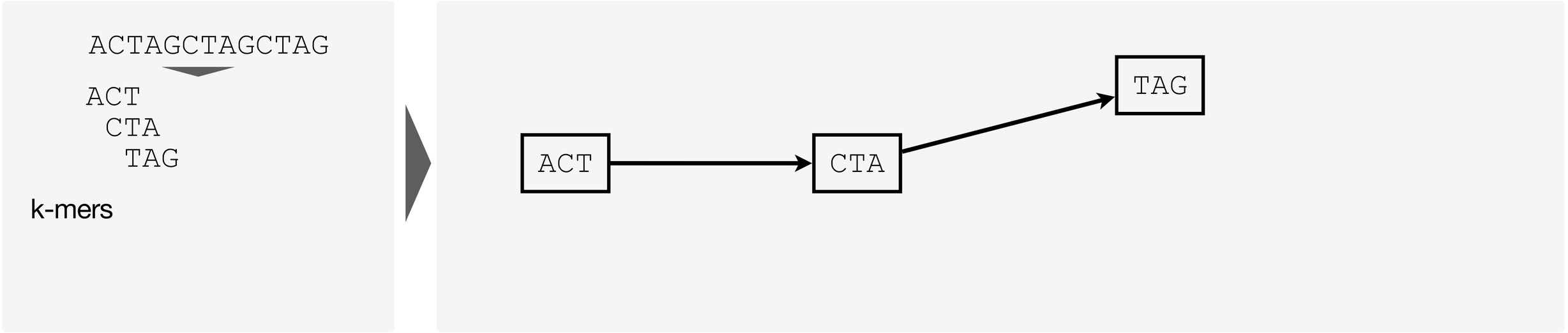

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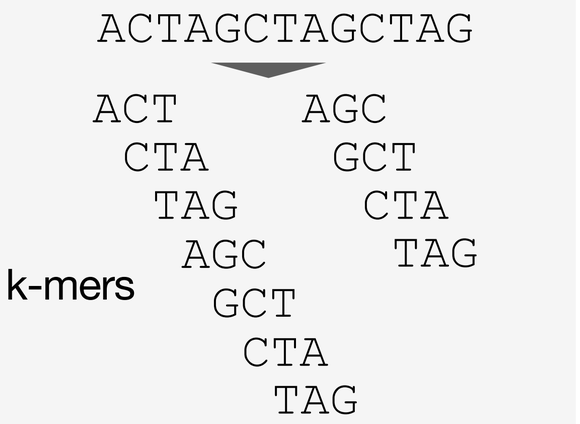

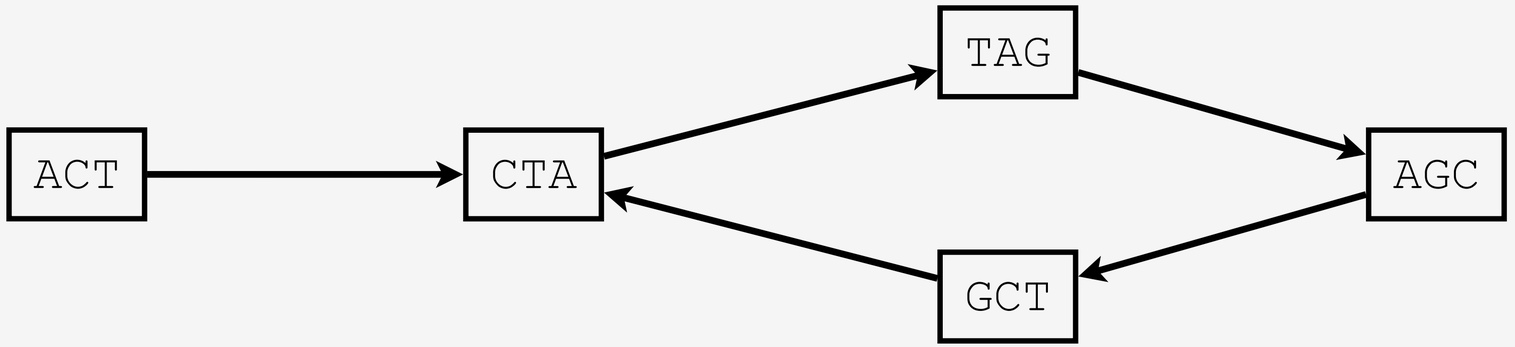

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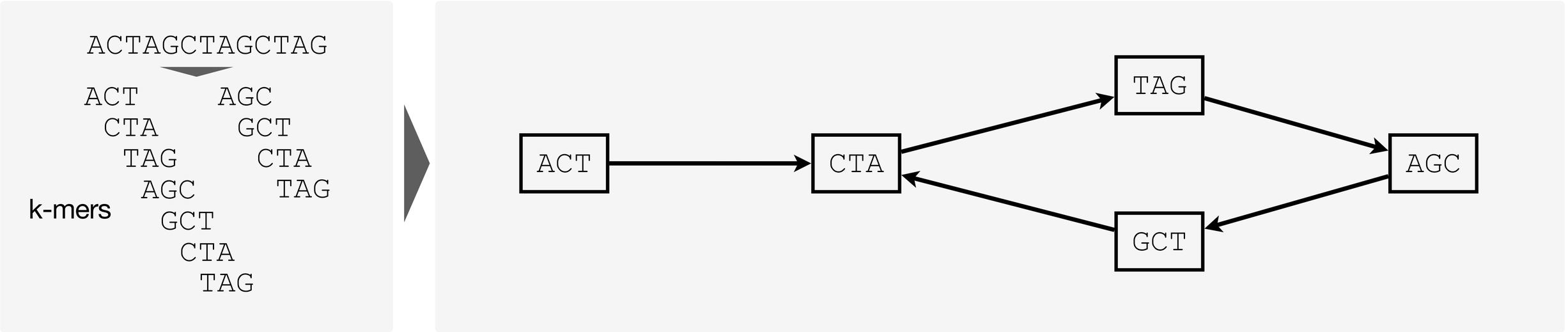

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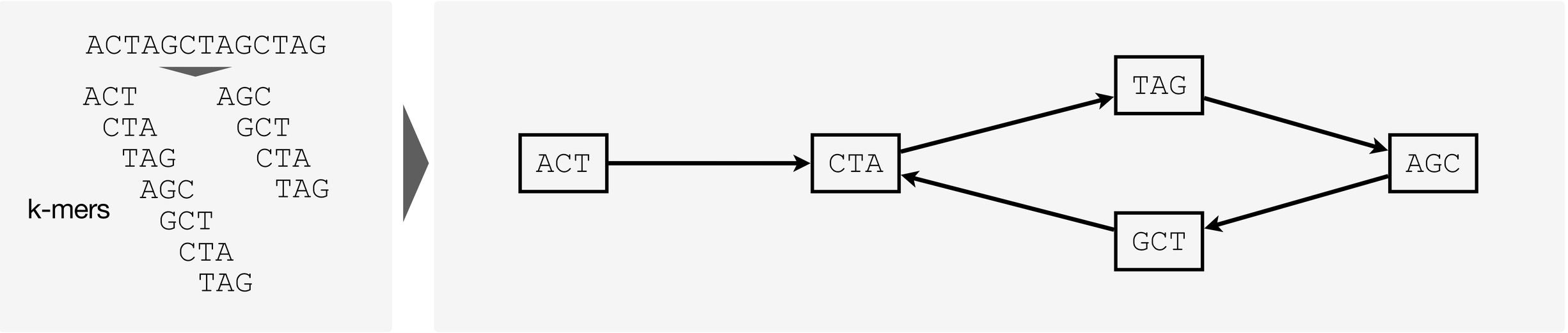

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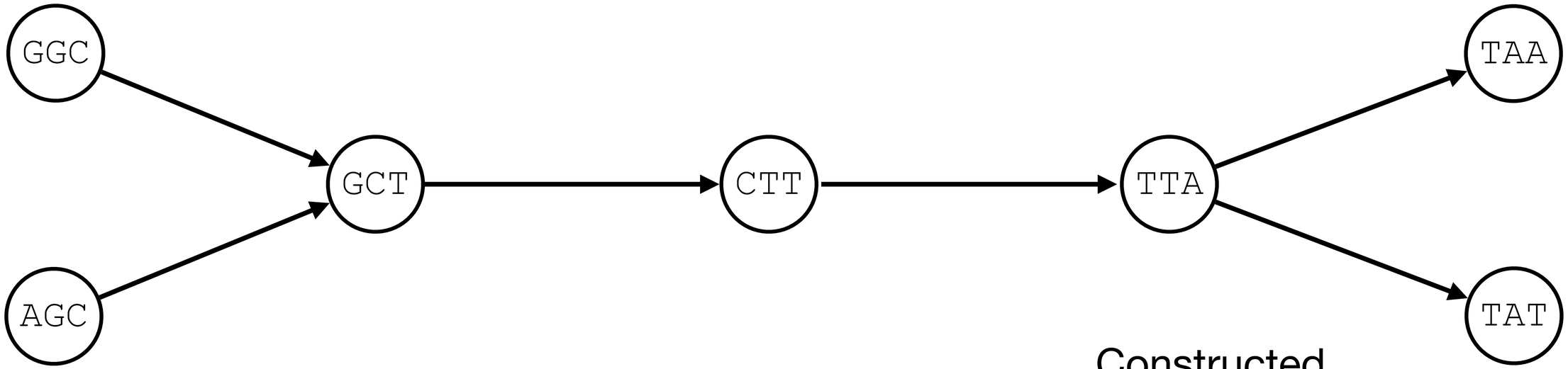
  - [Pevzner, 1989]
  - [Idury, Waterman, 1995]
  - [Pevzner, Tang, Waterman, 2001]
  - [Zerbino, Birney, 2008]

Background

Annotated De Bruijn graphs



Constructed
from sequences

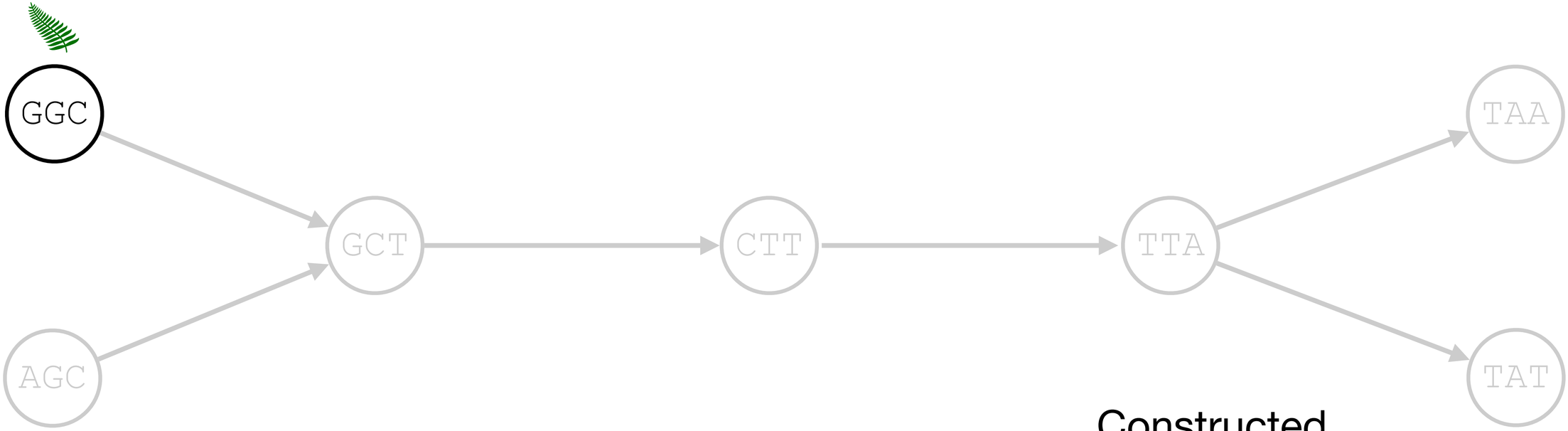
L1: GGCTTAT

L2: AGCTTAA

L3: TTAA

Background

Annotated De Bruijn graphs



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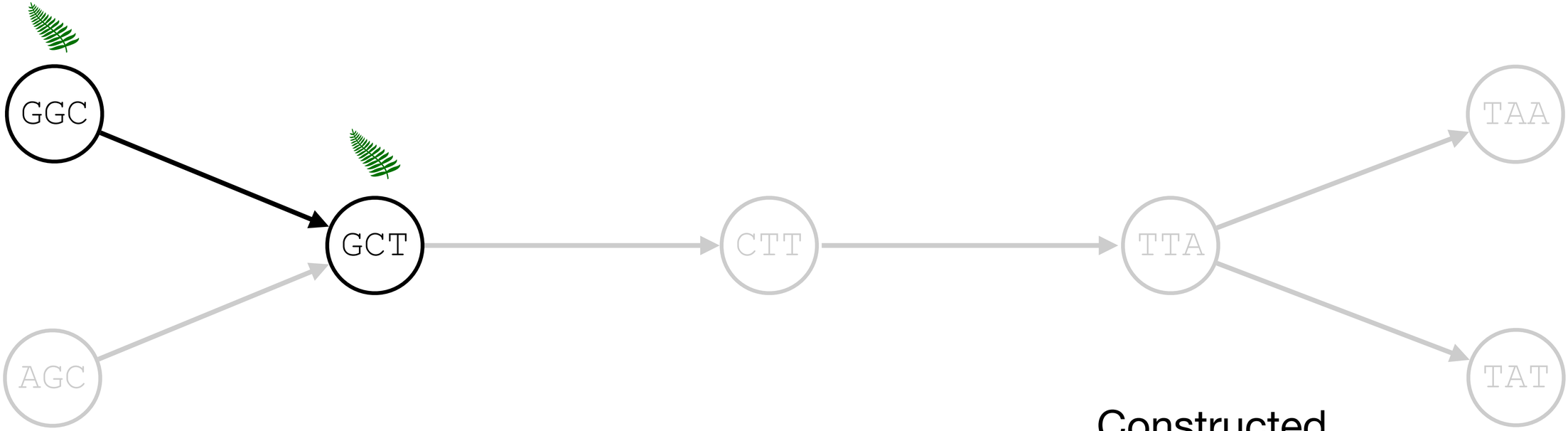

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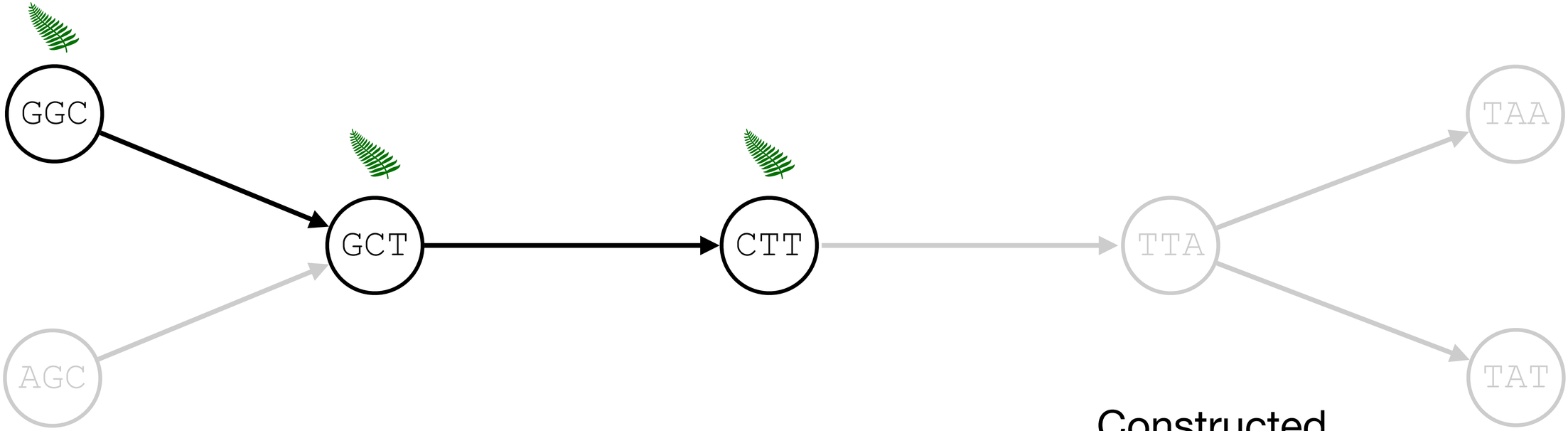

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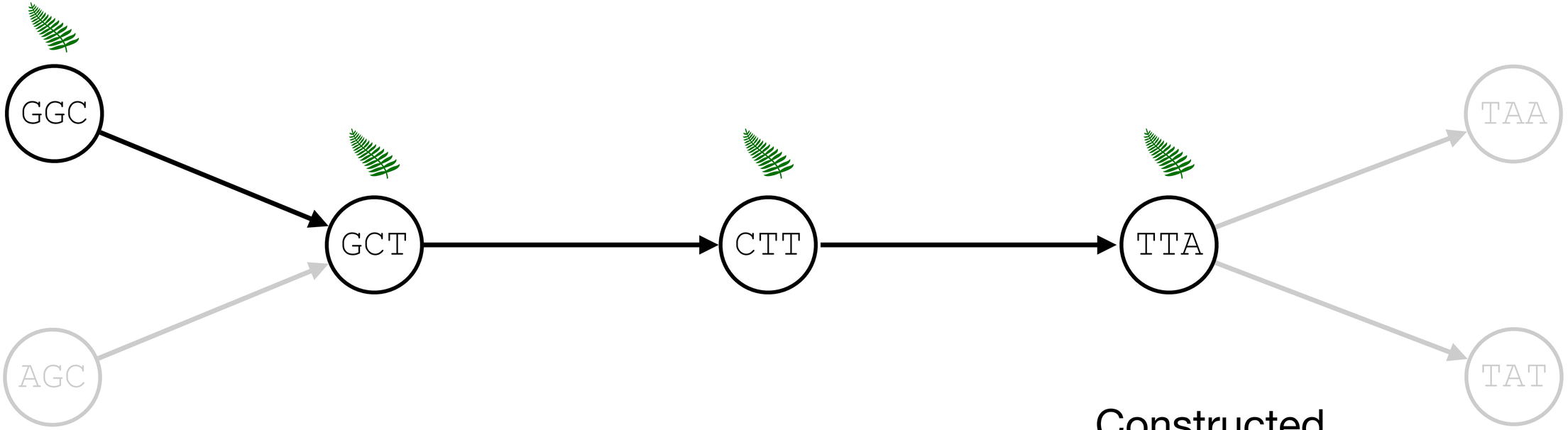

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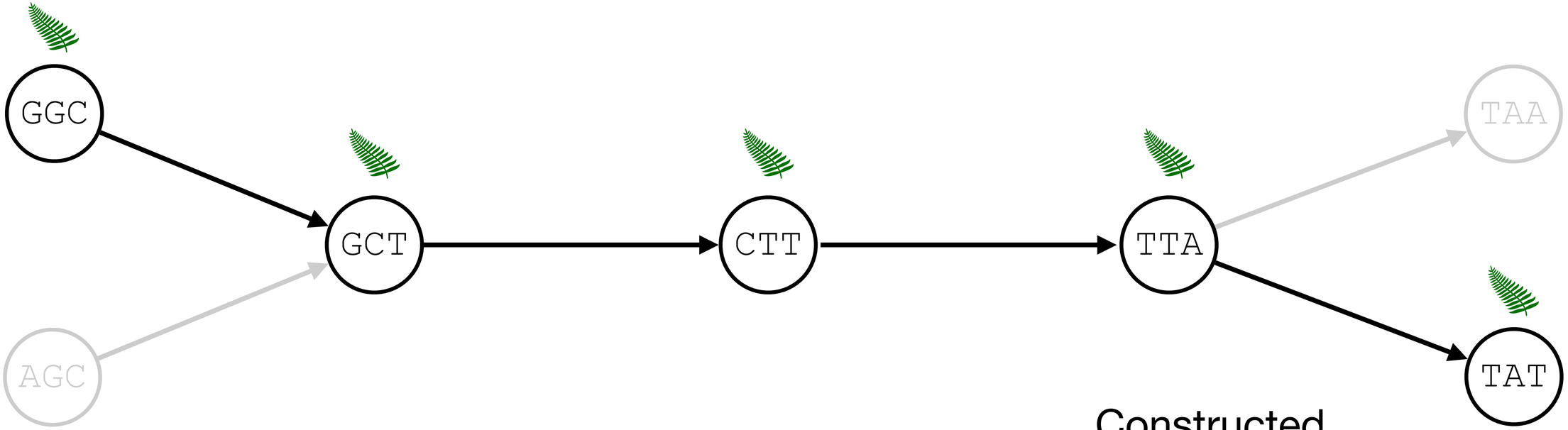

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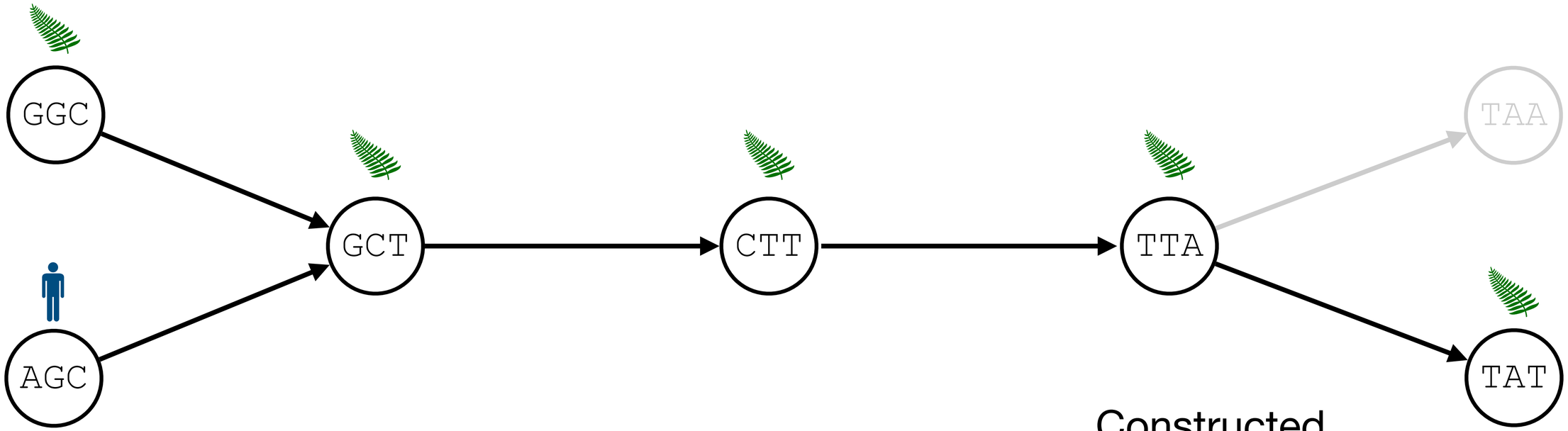

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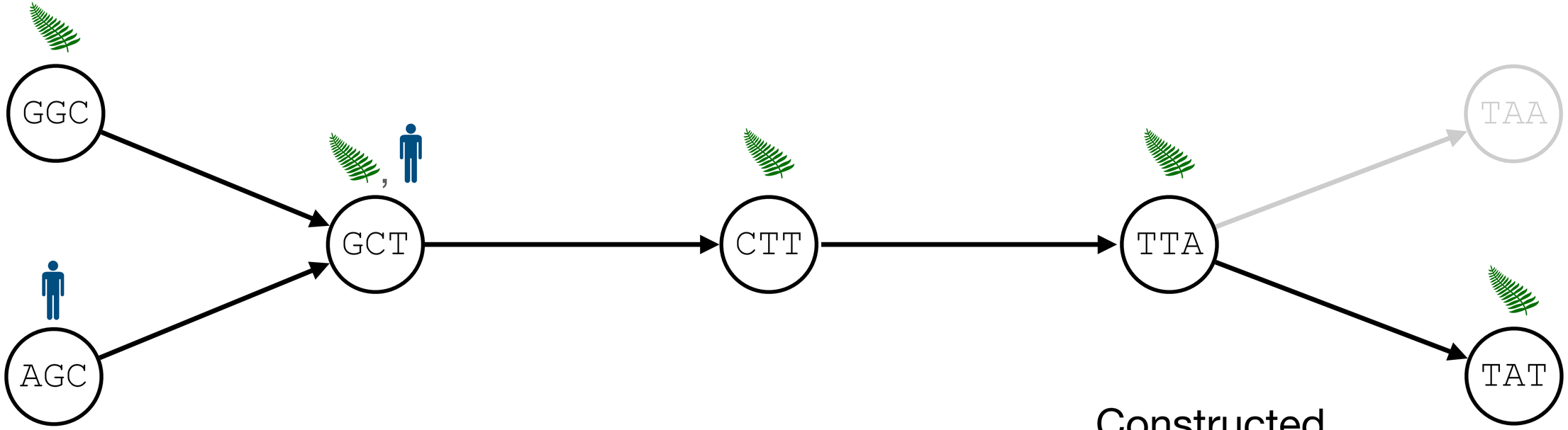

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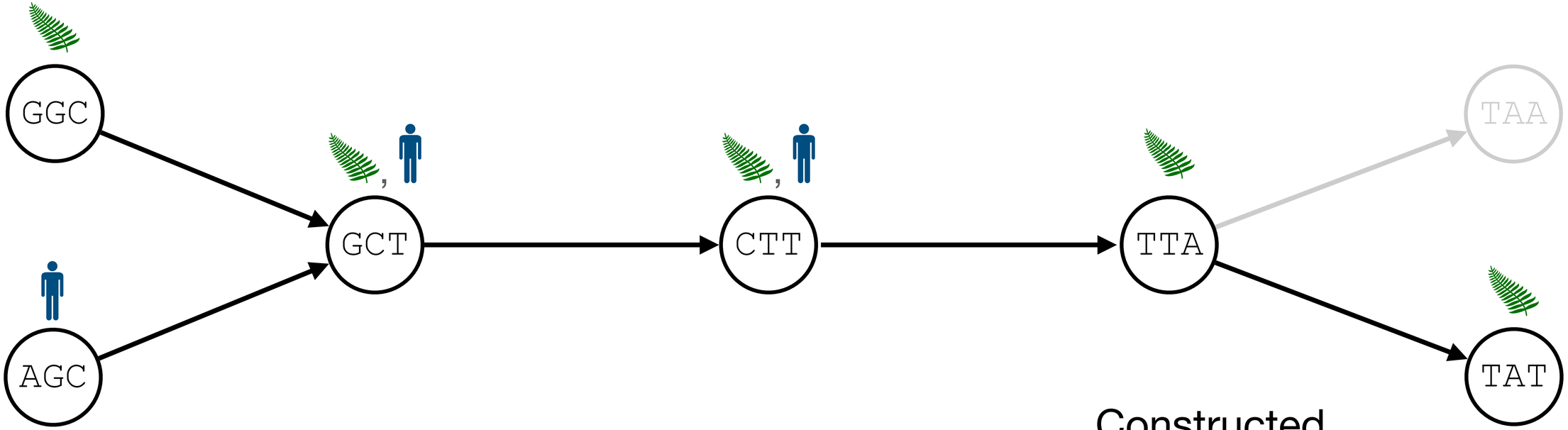

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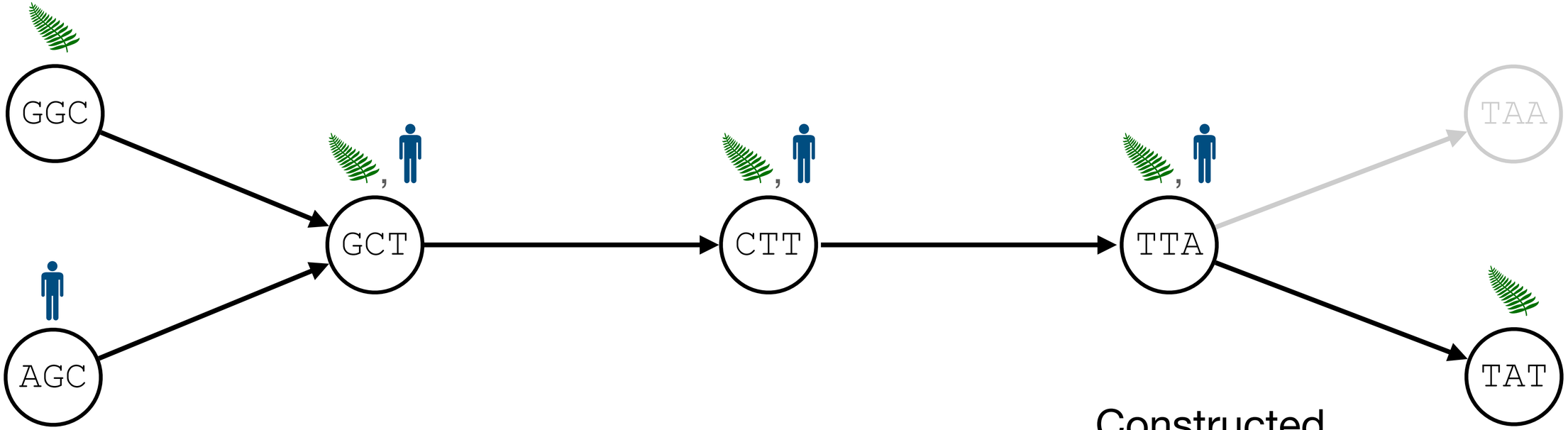

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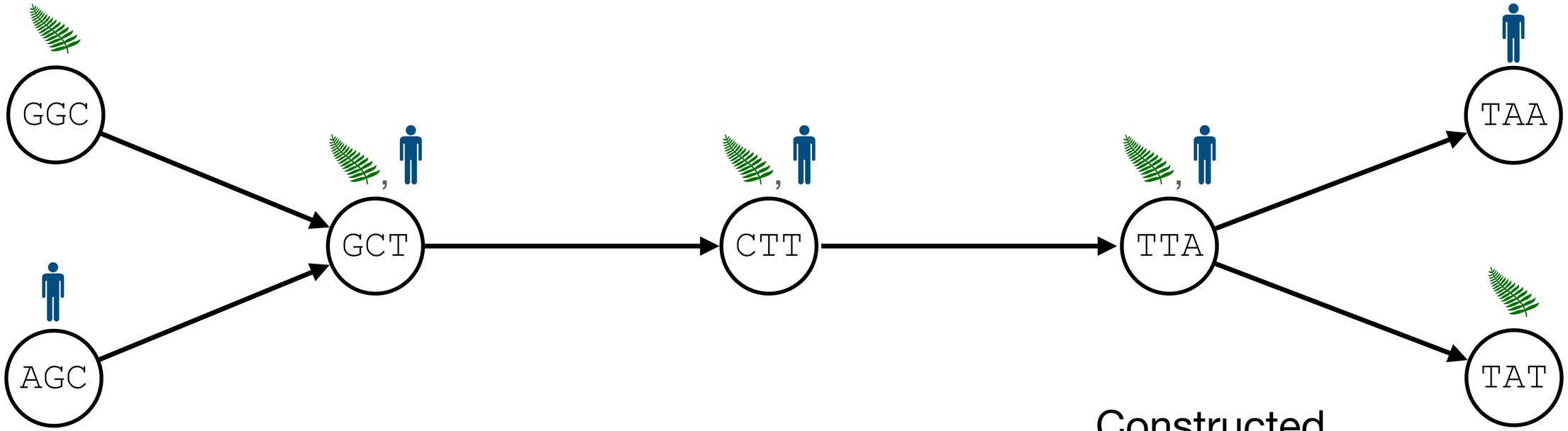

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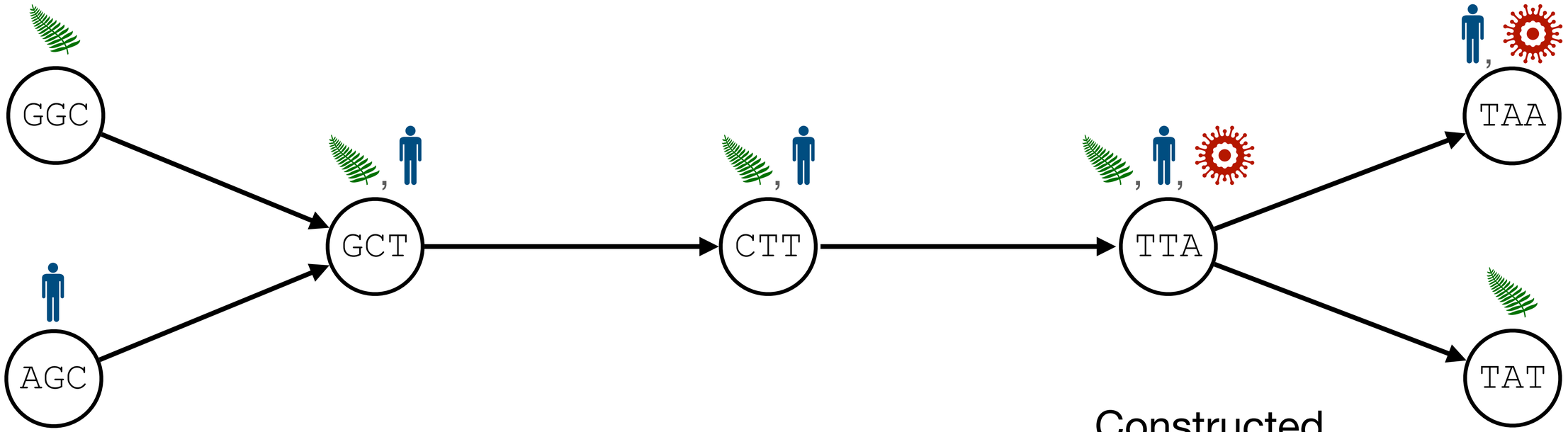

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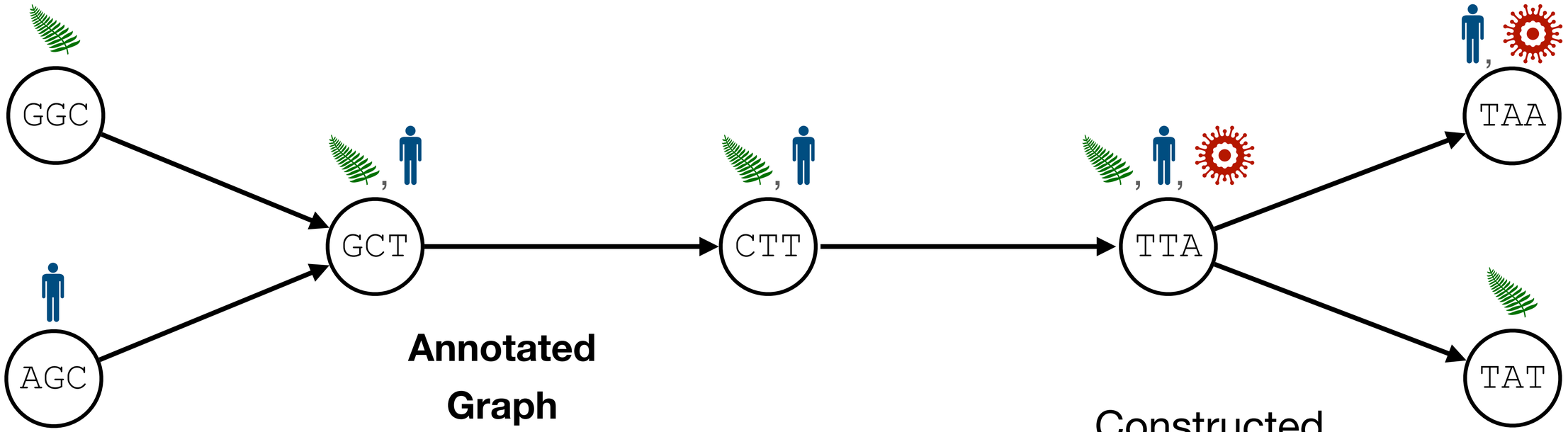

Annotated Graph

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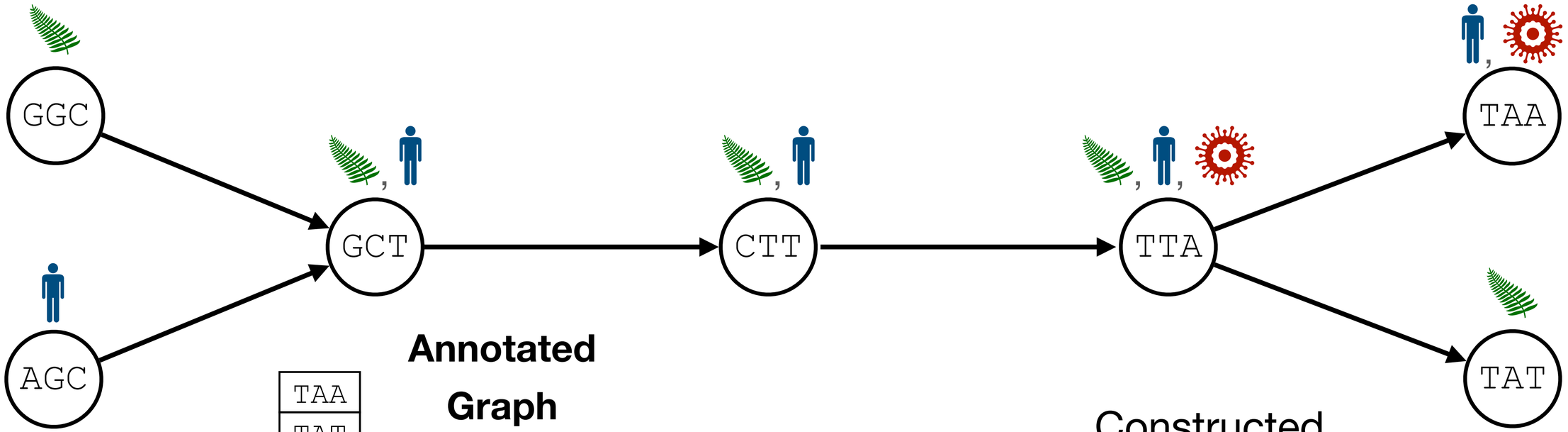

Annotated Graph

TAA
TAT
GCT
AGC
GGC
CTT
TTA

k-mer dictionary

Constructed from sequences

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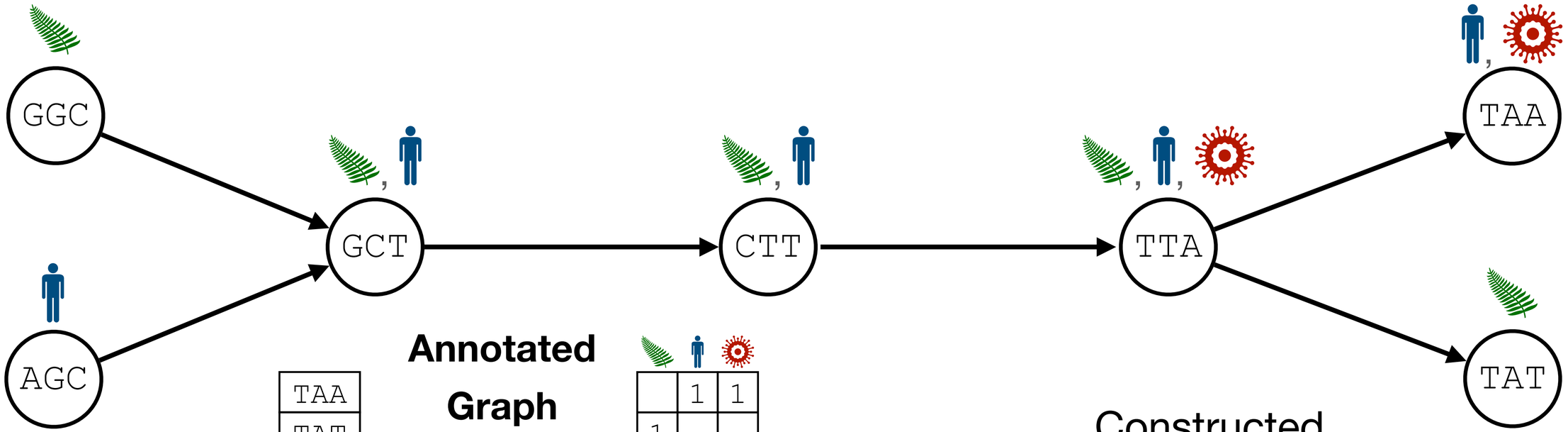

TAA
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GCT
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GGC
CTT
TTA

k-mer dictionary

Annotated Graph

	1	1
1		
1	1	
	1	
1		
1	1	
1	1	1

graph annotation

Constructed from sequences

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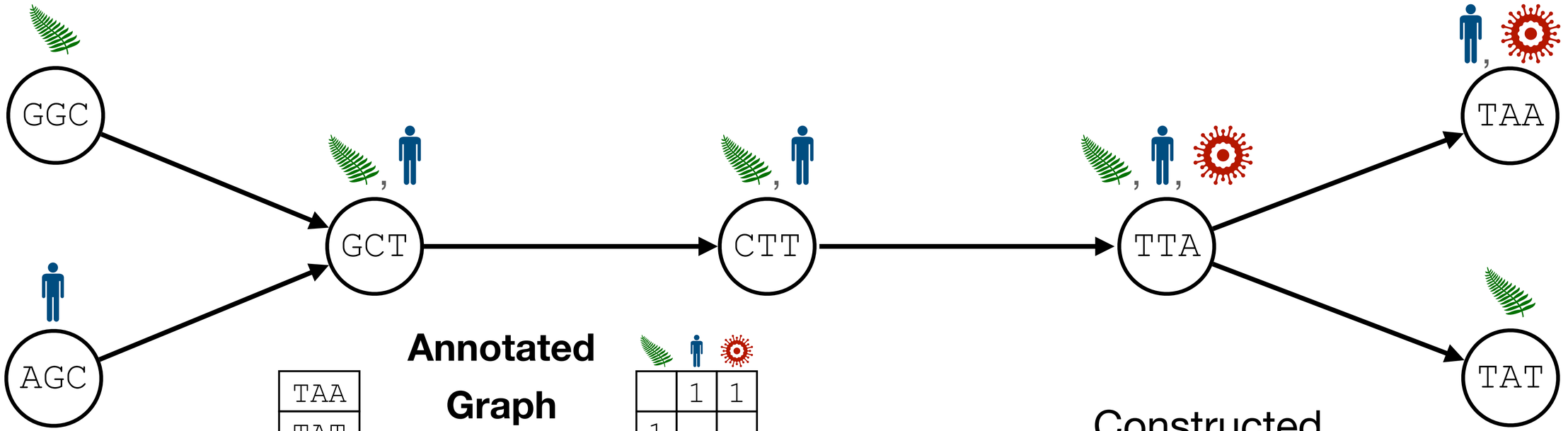
Background

Annotated De Bruijn graphs

- [Iqbal, Caccamo, Turner, Flicek, McVean, 2012]
- [Muggli *et al.*, 2017]



Annotated Graph

TAA
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GCT
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k-mer dictionary

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1		
1	1	
	1	
1		
1	1	
1	1	1

graph annotation

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Indexing workflow

```
>smp_1
ACGTAC
ACGC
CGTAC
```

```
>smp_2
ACGAA
ACGTAC
ACG
```

```
>smp_3
ACGTA
GTACT
ACGAT
```

...

```
>smp_m-1
ACGAACA
ACGCACA
CGCAC
```

```
>smp_m
ACGCGAA
CGCGA
ACGCGA
```

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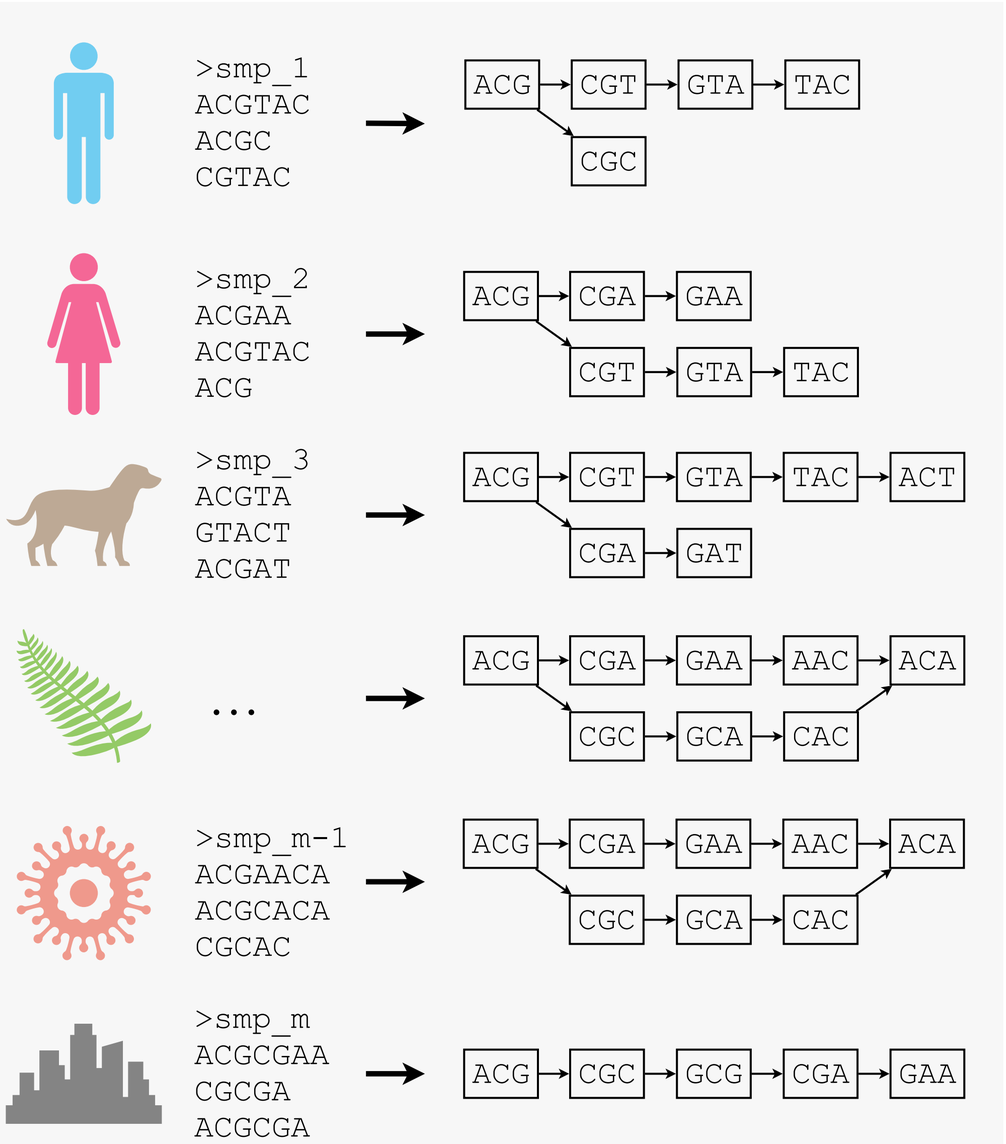

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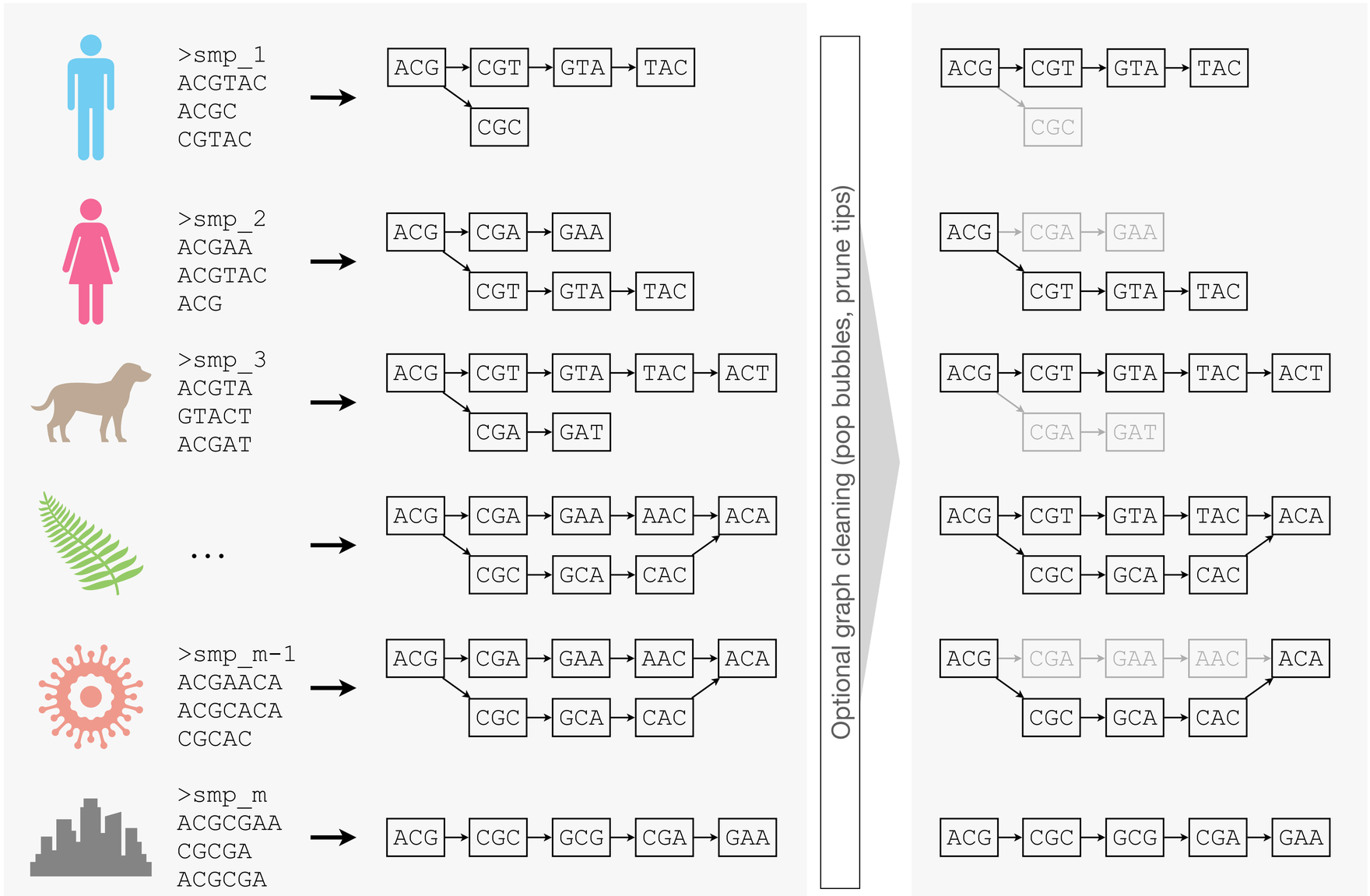

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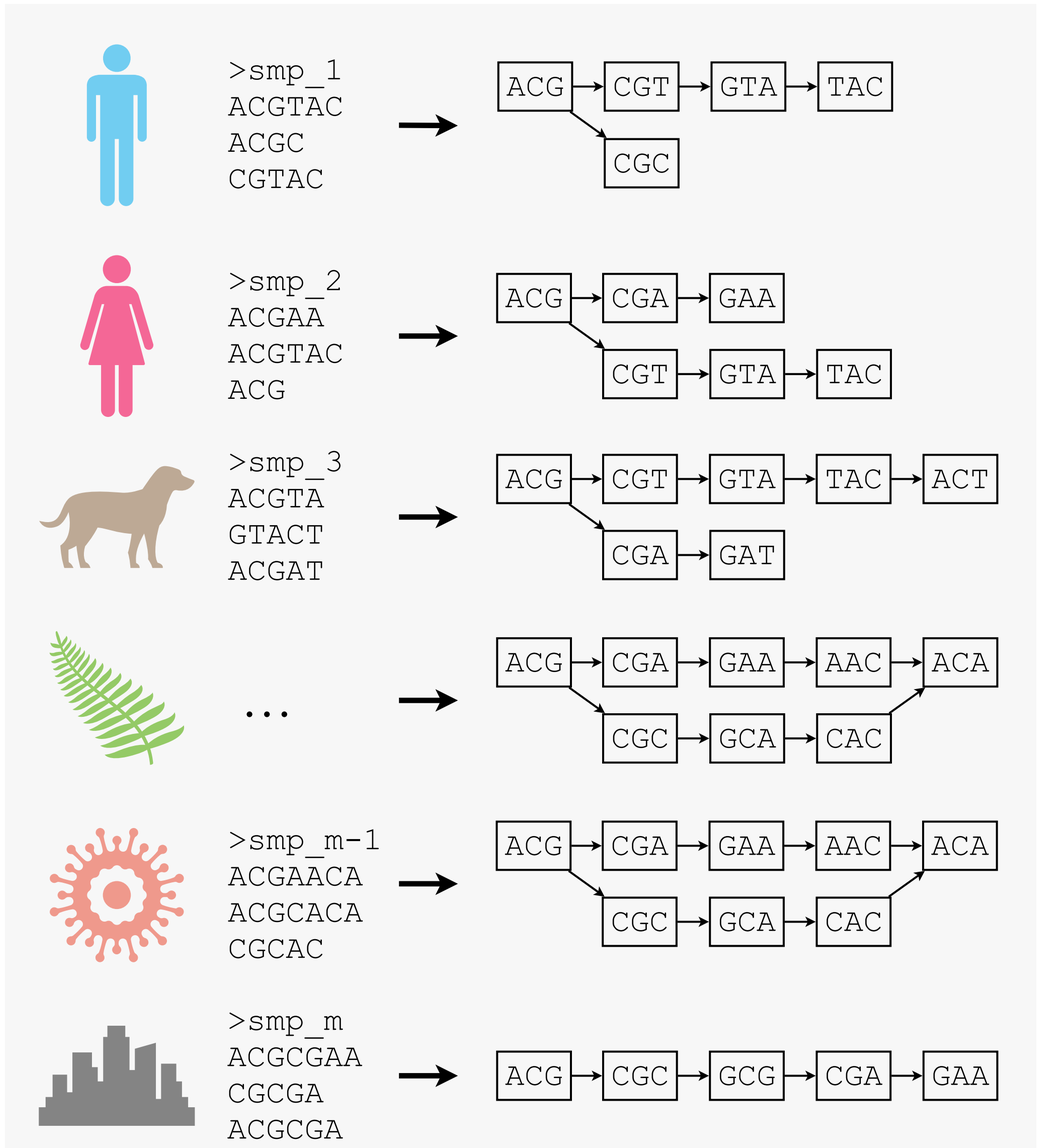
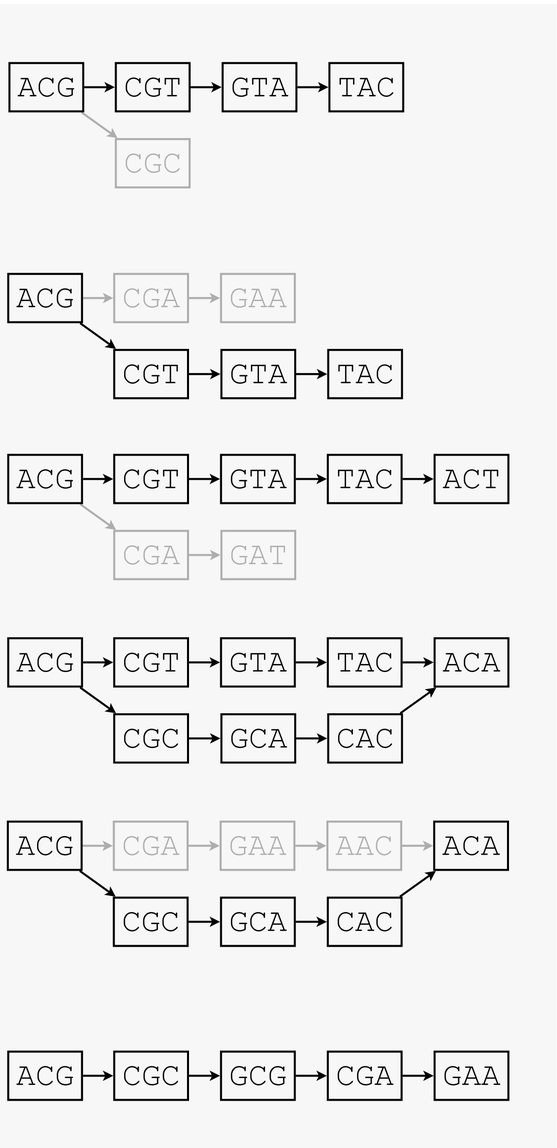
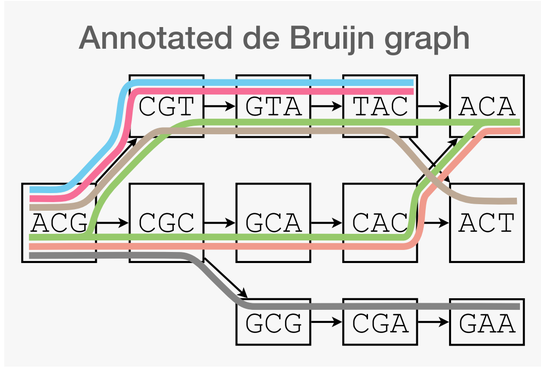


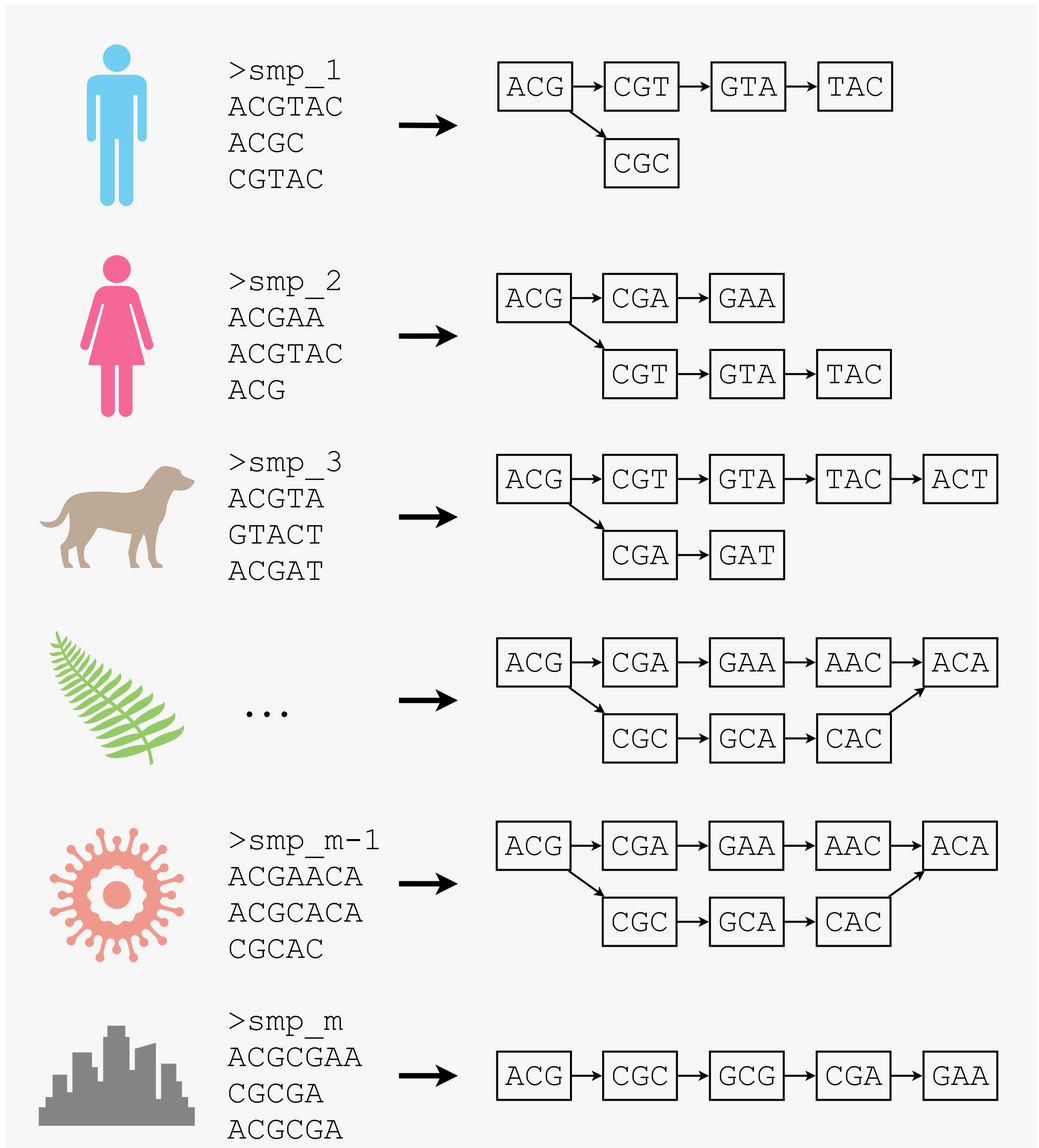
Optional graph cleaning (pop bubbles, prune tips)



Merge into a joint graph



Indexing workflow



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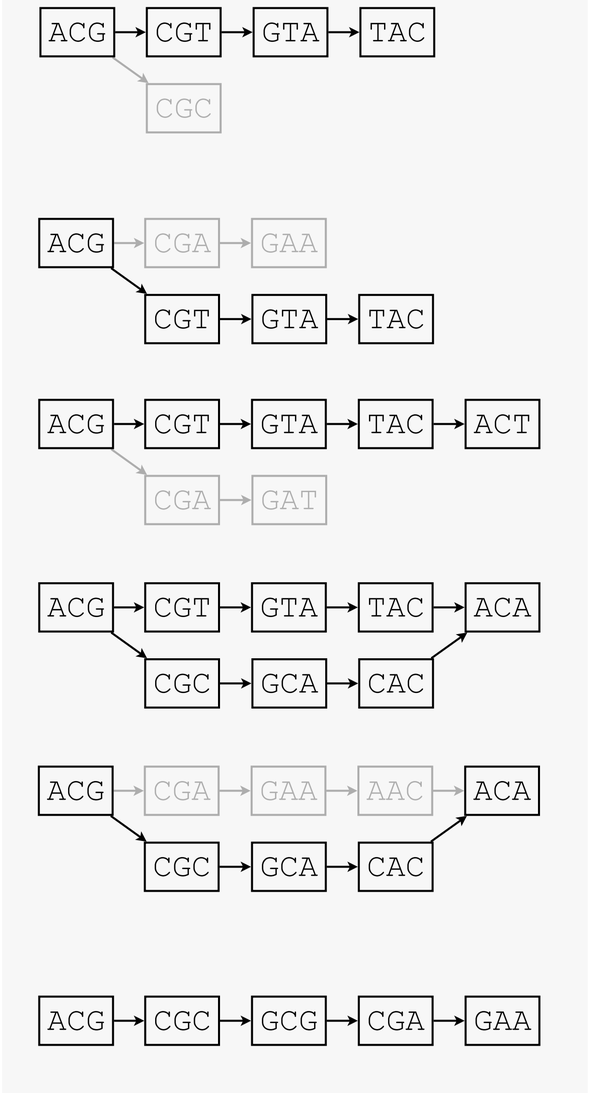
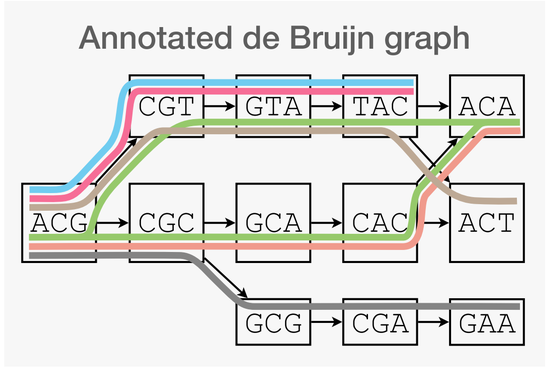
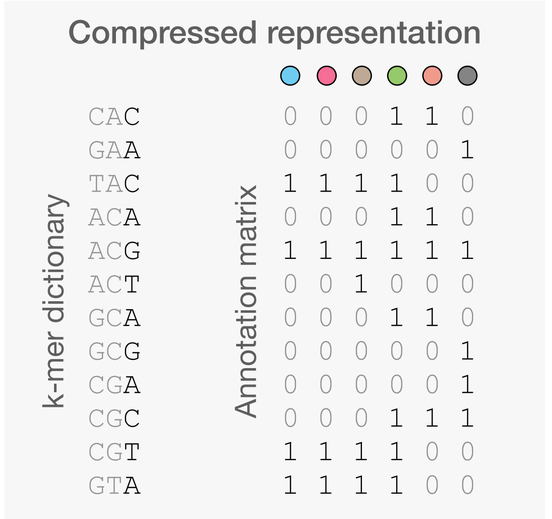


Merge into a joint graph





Indexing workflow

MetaGraph

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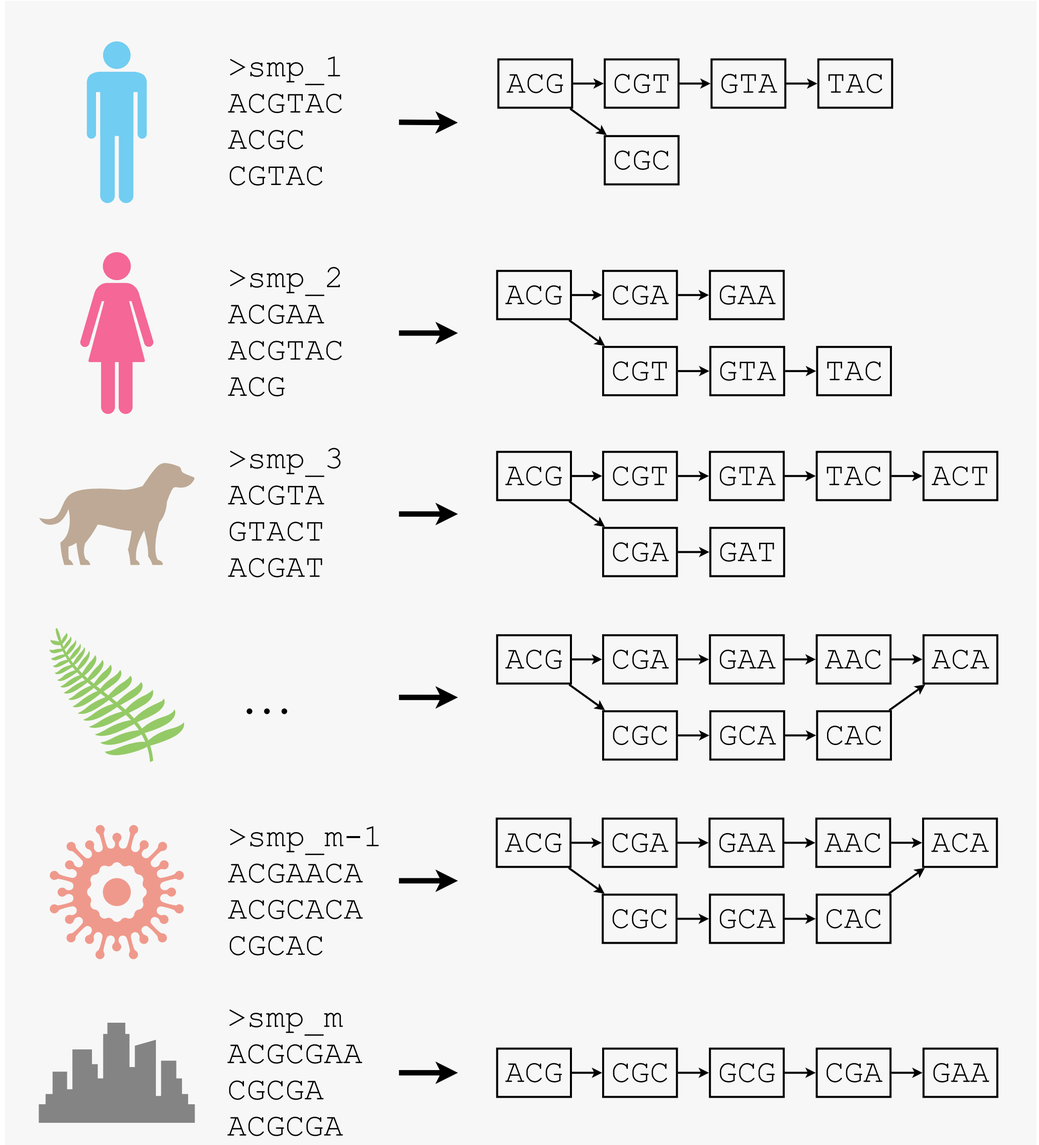
Mikhail Karasikov, Harun Mustafa, Daniel Danciu, Marc Zimmermann, Christopher Barber, Gunnar Rätsch, André Kahles

doi: https://doi.org/10.1101/2020.10.01.322164



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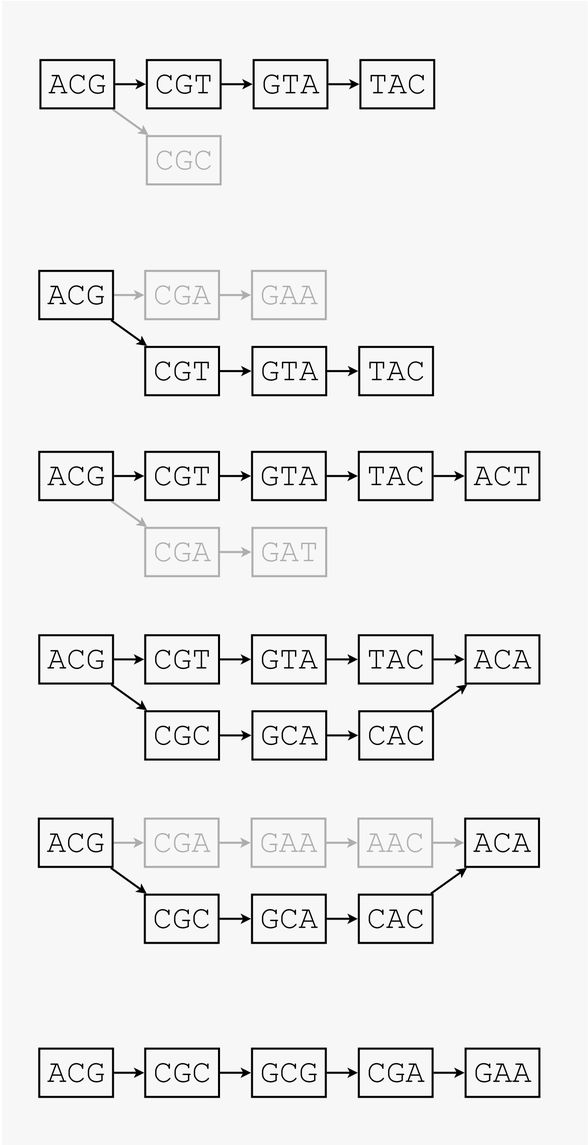

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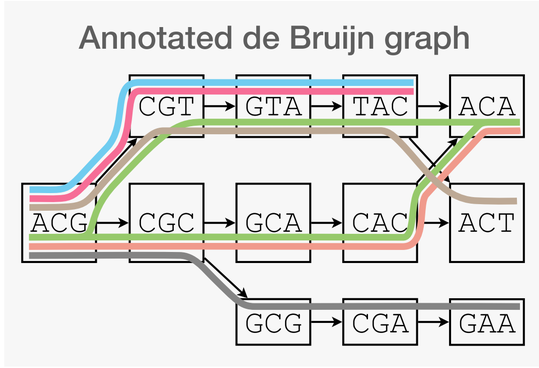

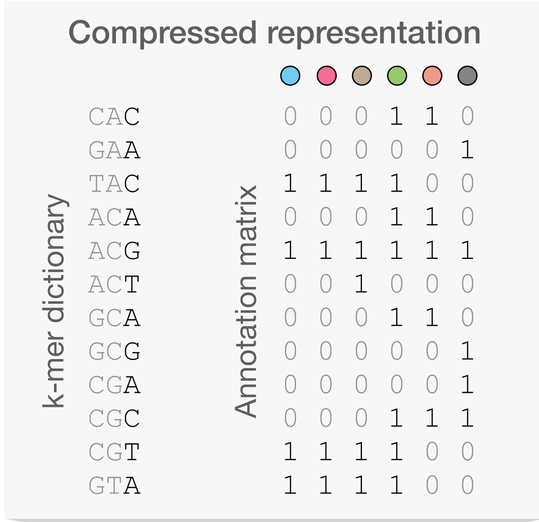

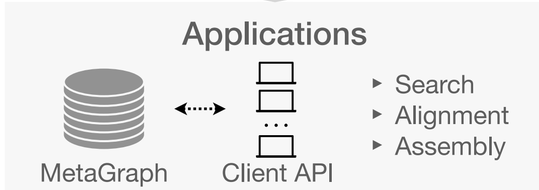

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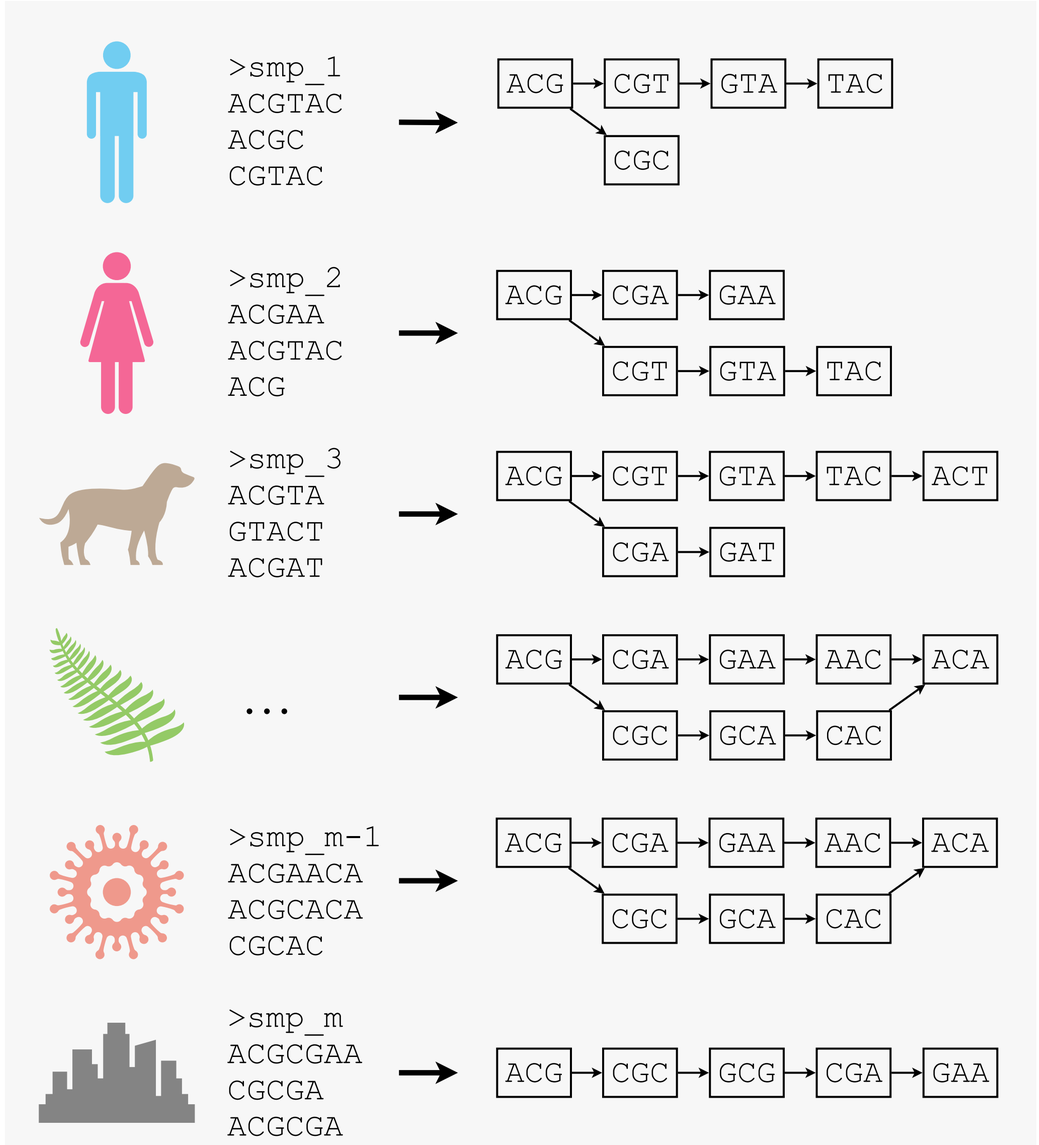

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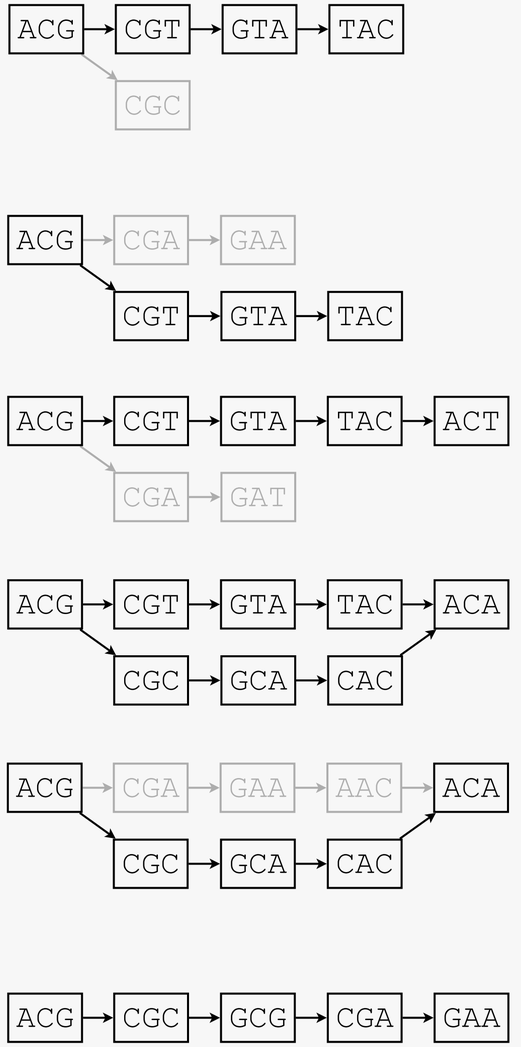

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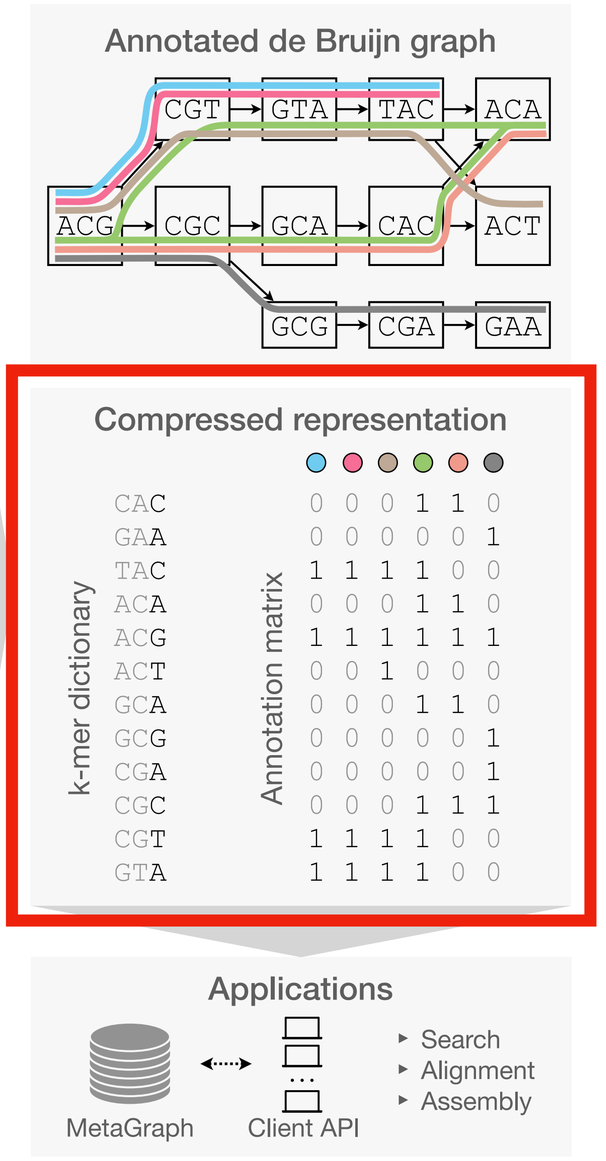

Indexing workflow

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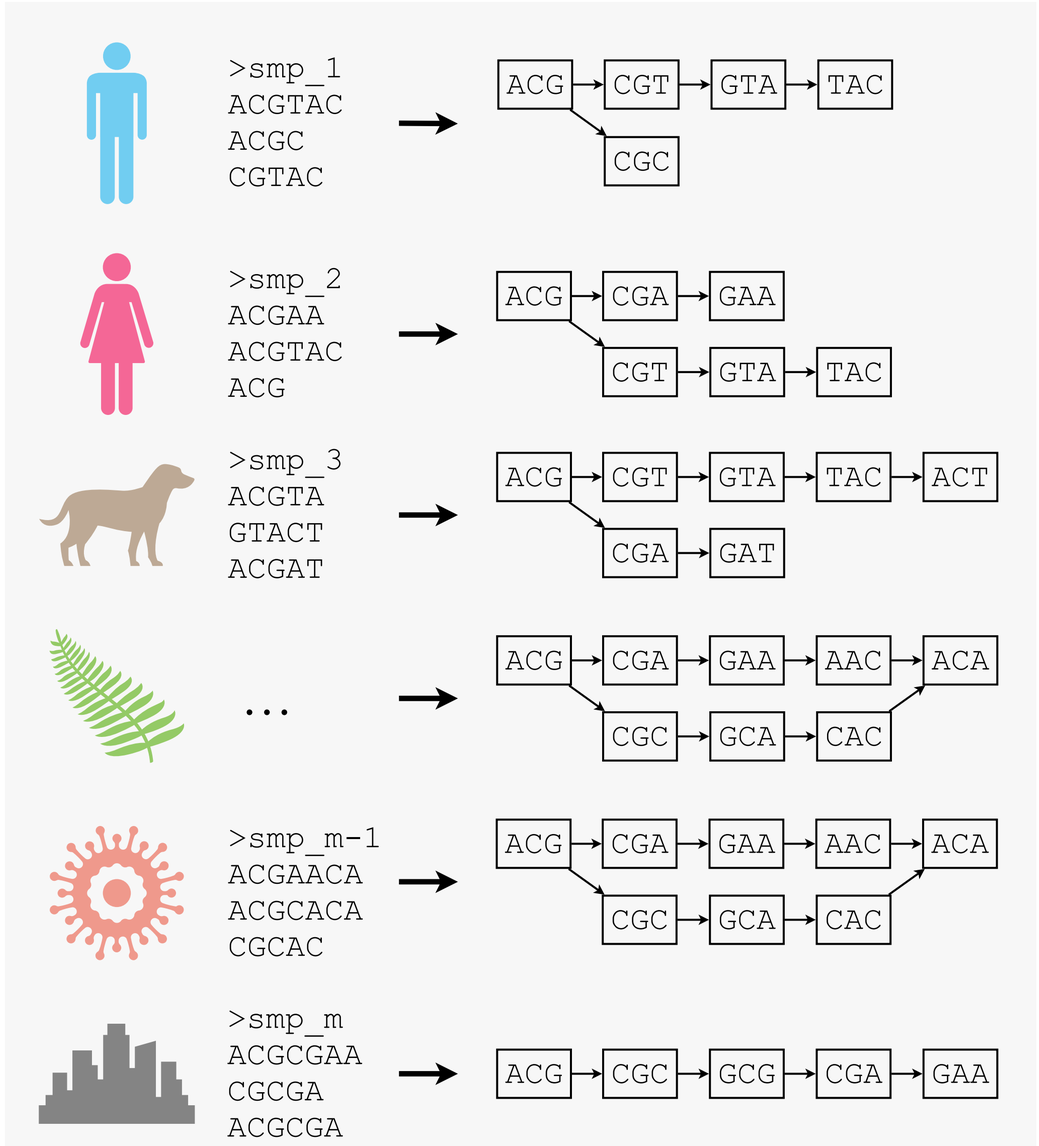

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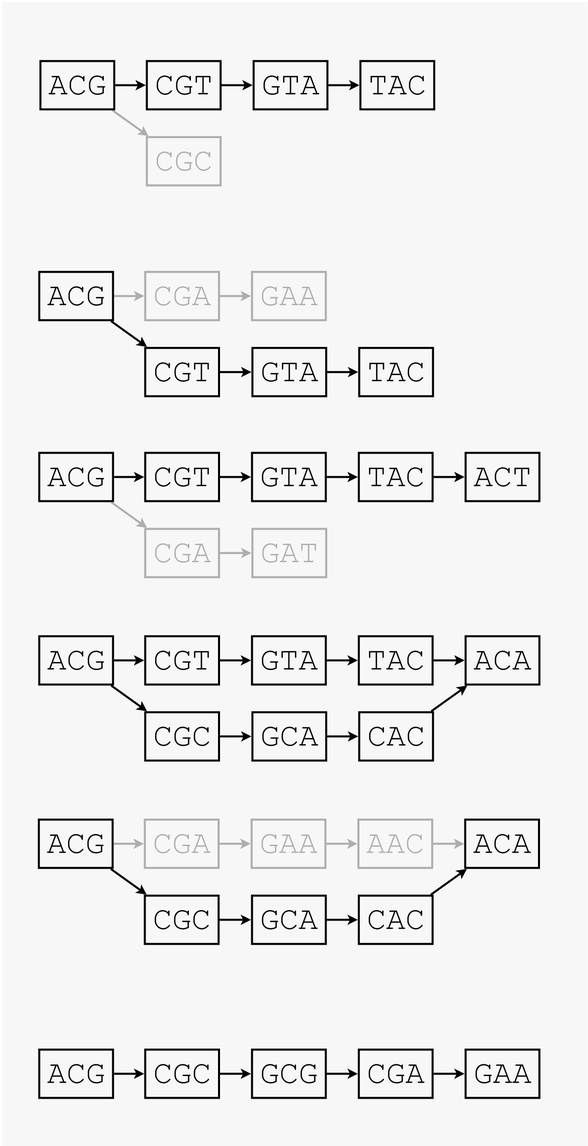

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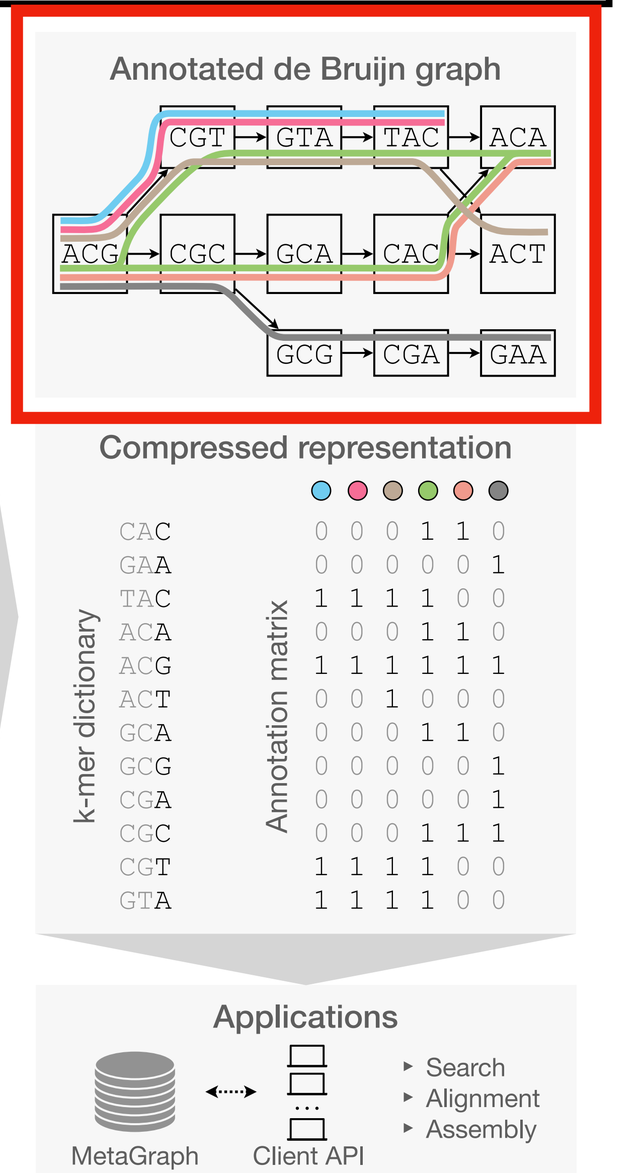

Sequence search

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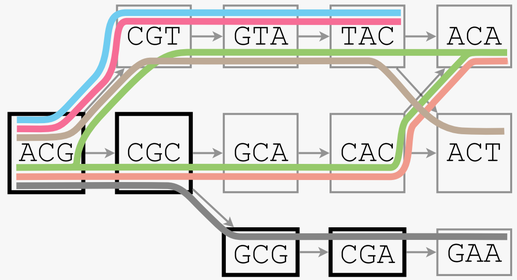
```
>query
ACGCGAT
```



k-mer matching

Sequence search

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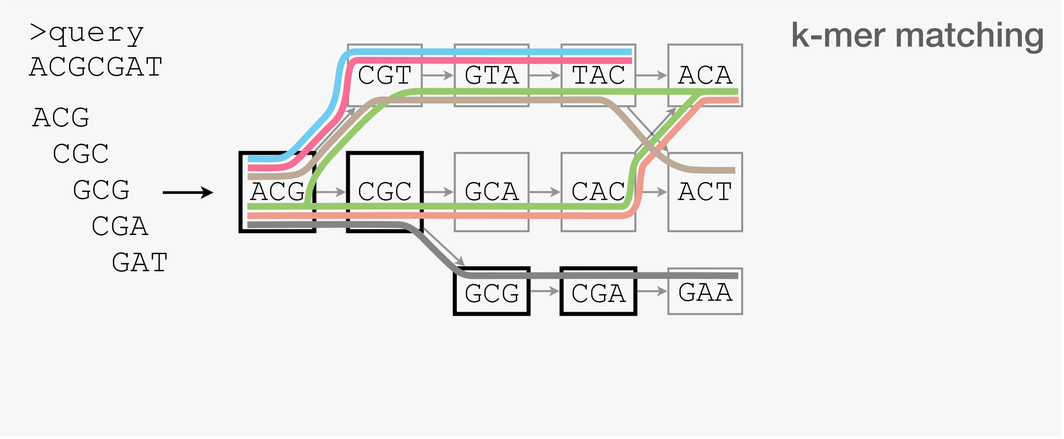

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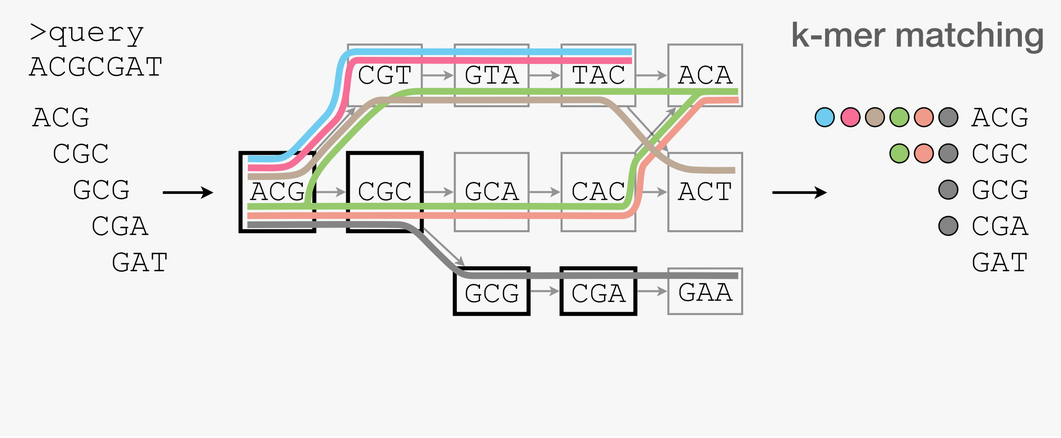

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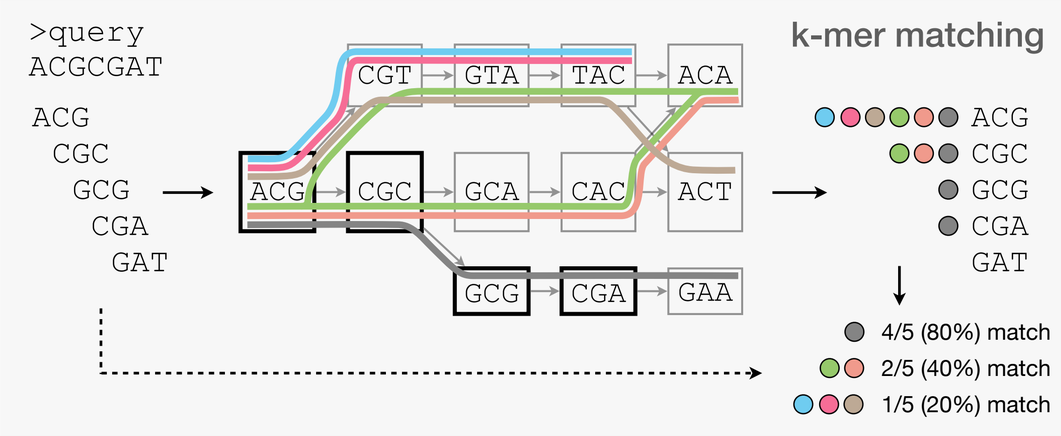

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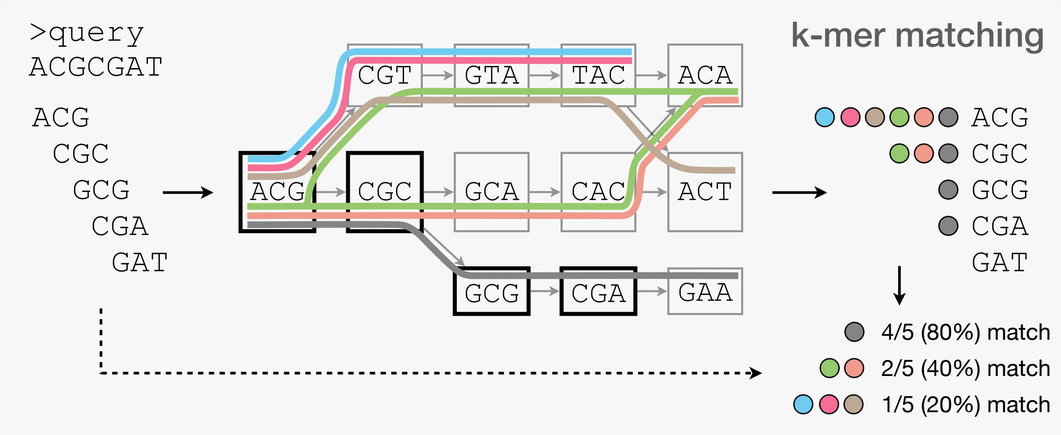

- SBT [Solomon, Kingsford, 2016]
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- Mantis [Pandey *et al.*, 2018]

Sequence search

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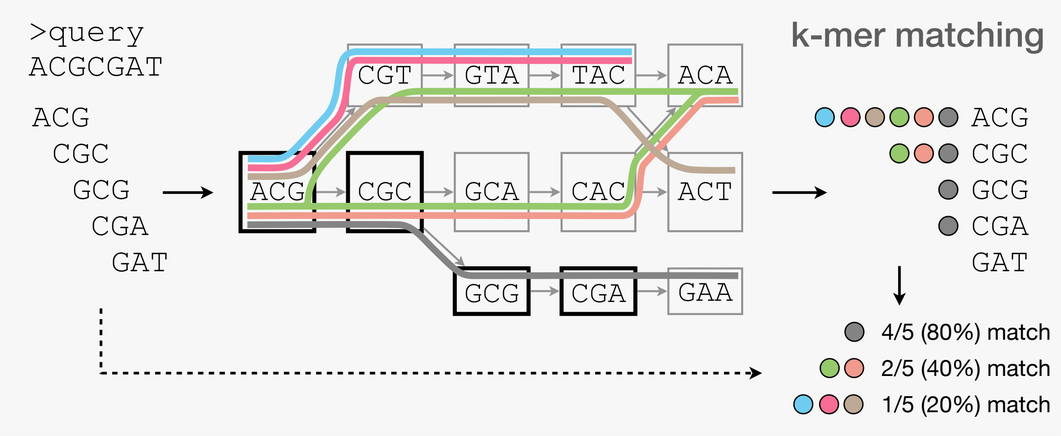

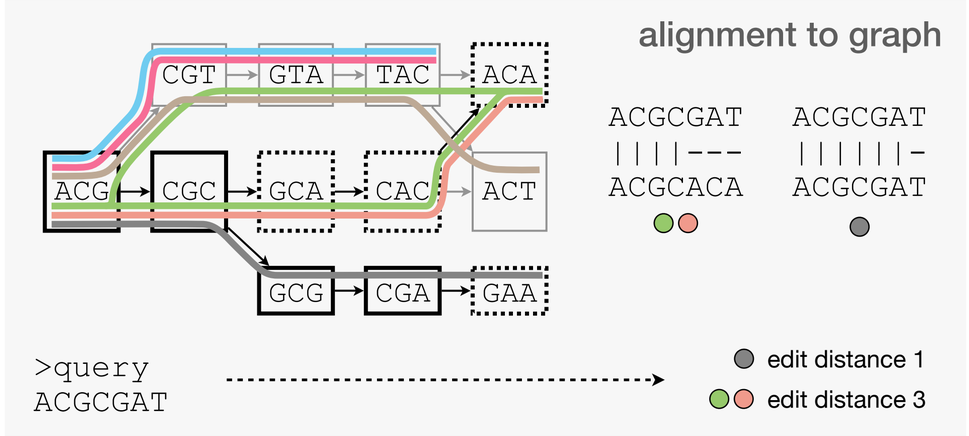

- SBT [Solomon, Kingsford, 2016]
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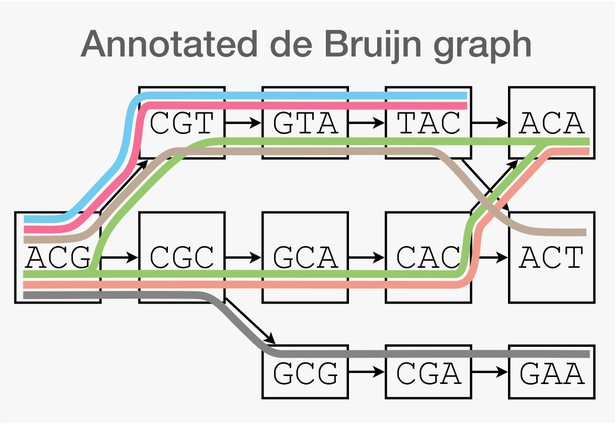
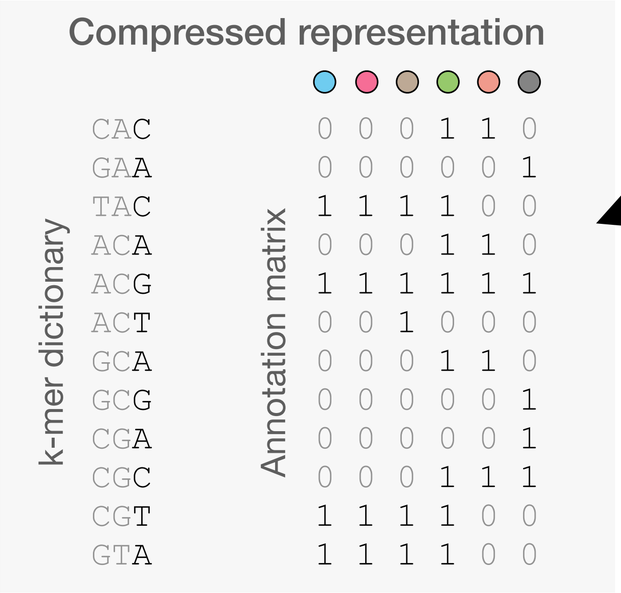
- Mantis [Pandey *et al.*, 2018]

- [Lee, Grasso, Sharlow, 2002]
- deBGA [Liu, Guo, Brudno, Wang, 2016]
- SPAligner [Dvorkina *et al.*, 2020]
- AStarix [Ivanov *et al.*, 2020]
- [Schulz *et al.*, 2021]
- MetaGraph-MLA [Mustafa *et al.*, 2022]

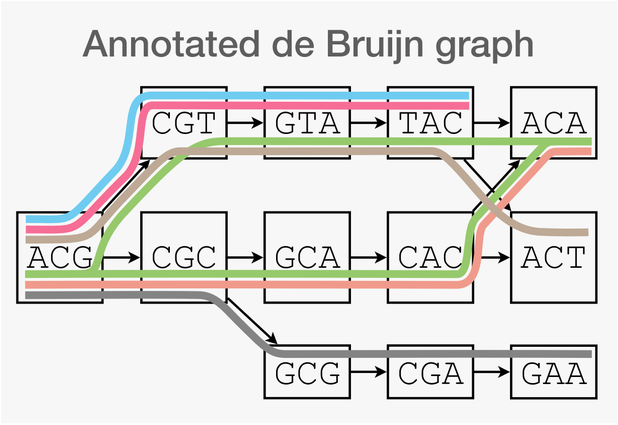
Representing annotated De Bruijn graphs

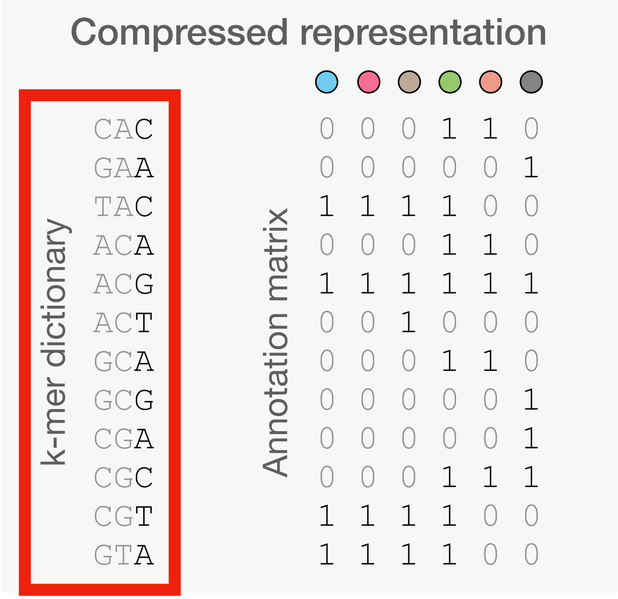




Must be efficiently **queryable**

Representing annotated De Bruijn graphs

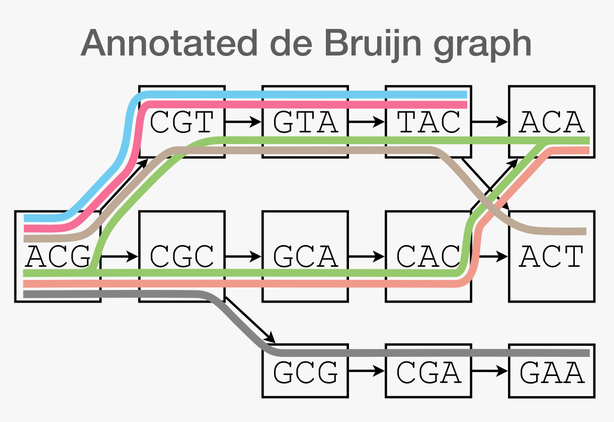


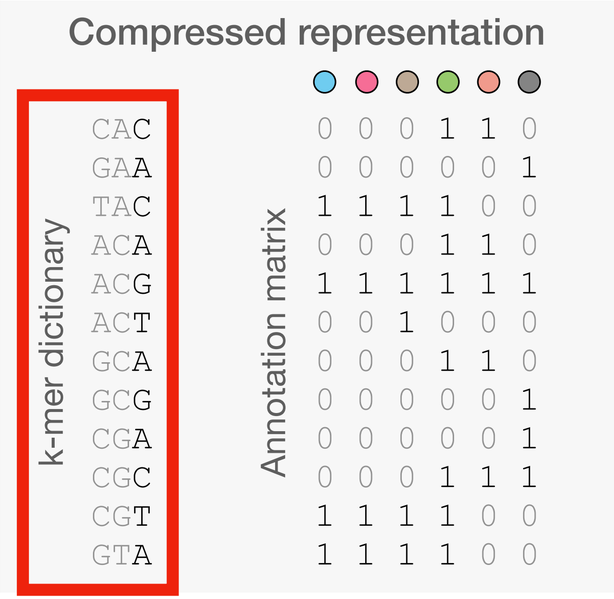


Representing graph

- Hash table
- Indicator set bit vector [Conway *et al.*, 2011]
- BOSS table [Bowe *et al.*, 2012]

Representing annotated De Bruijn graphs





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  - ✓ ~2–3 bits per k-mer for DNA
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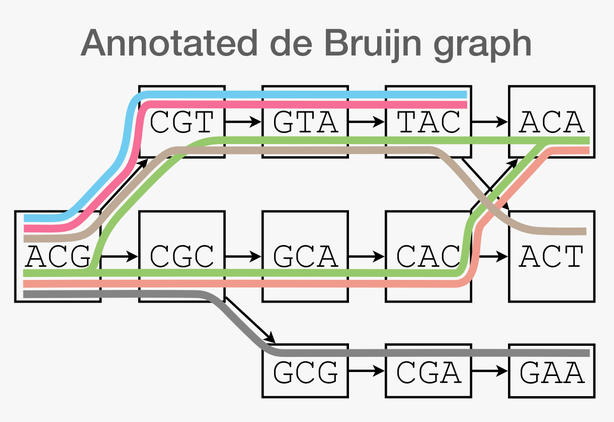

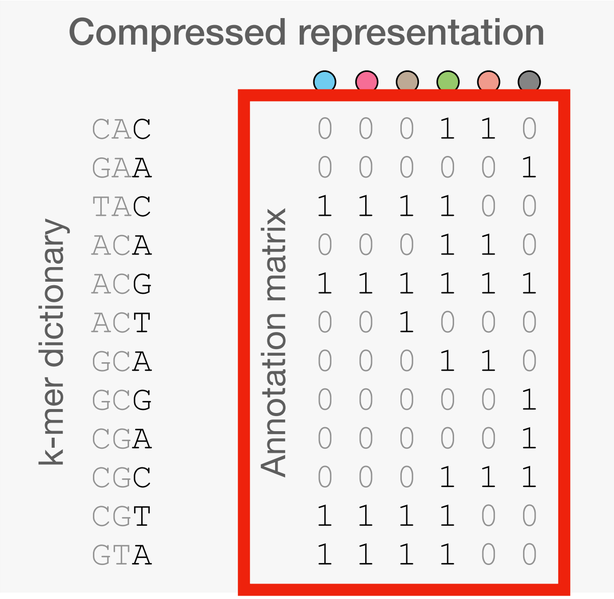

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Representing annotation

- Column-major sparse representation
- RowFlat (employed in VARI [Muggli *et al.*, 2017])
- Rainbowfish [Almodaresi *et al.*, 2017]
- Rainbow-MST [Almodaresi *et al.*, 2019]

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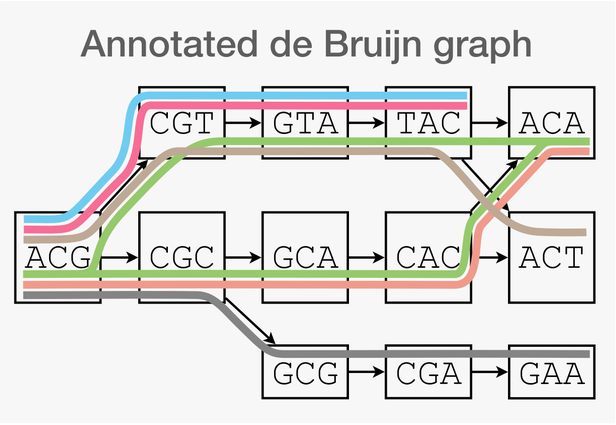

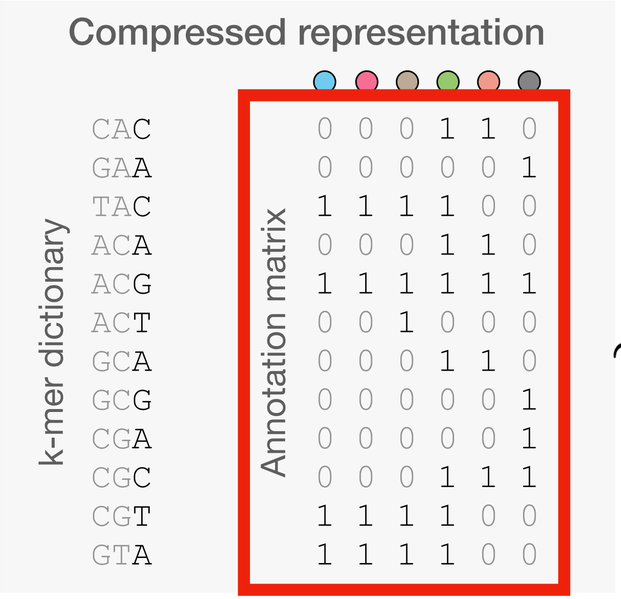

$\sim 10^{11}$

$\sim 10^{6}$

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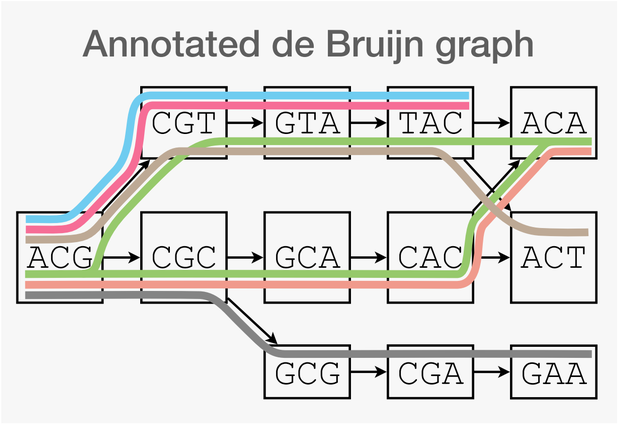

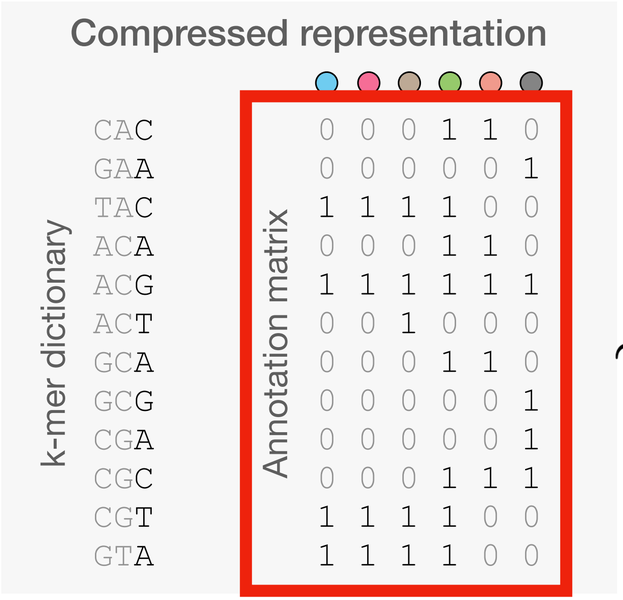

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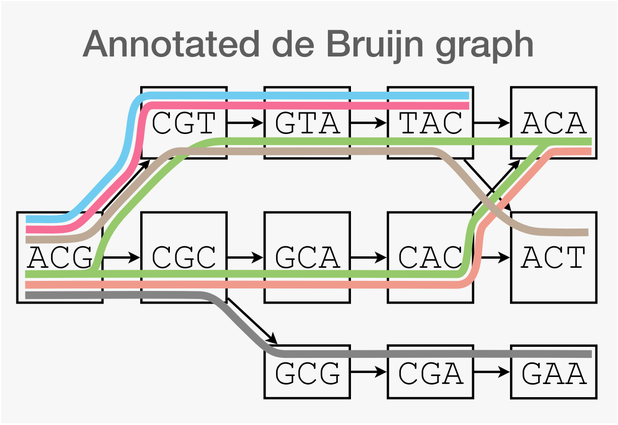
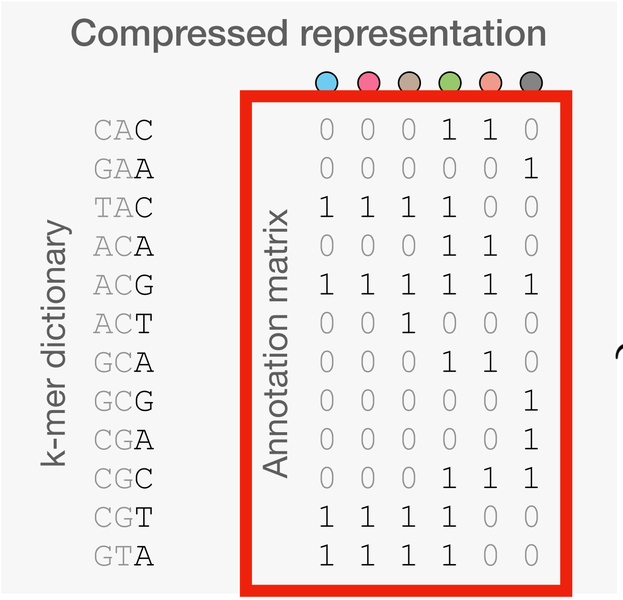
Challenge:
Represent huge-scale annotations

Representing graph annotations





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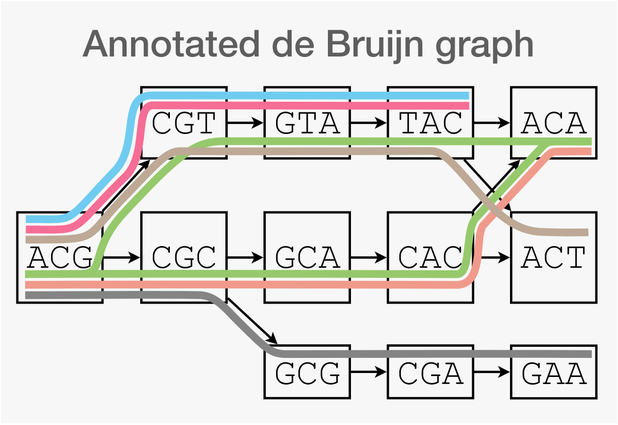
$\sim 10^{6}$

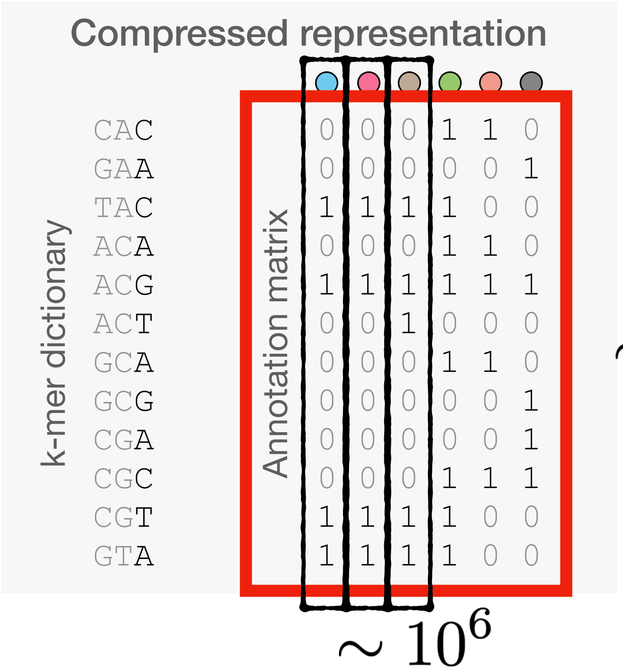
Challenge:
Represent huge-scale annotations

Typical properties

1. high sparsity

Representing graph annotations



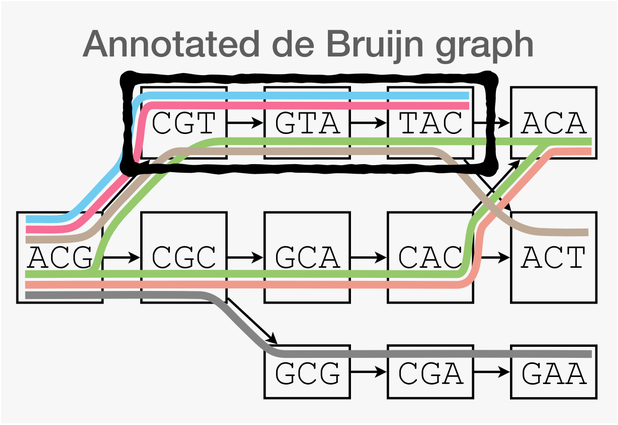


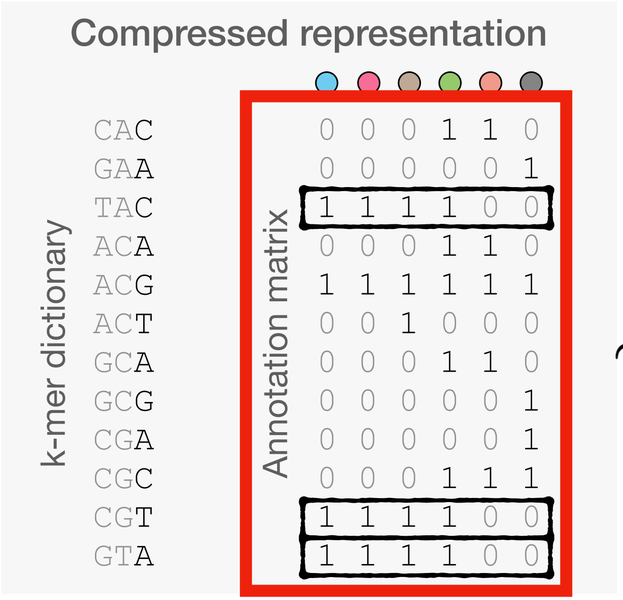
Challenge:
Represent huge-scale annotations

Typical properties

1. high sparsity
2. similarity of **columns**

Representing graph annotations





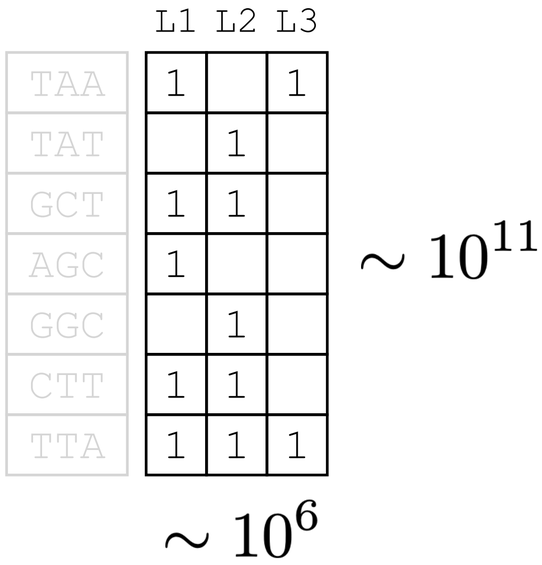
Challenge:
Represent huge-scale annotations

Typical properties

1. high sparsity
2. similarity of **columns**
3. similarity of **rows**

Annotation representations

1. Column-major sparse representation



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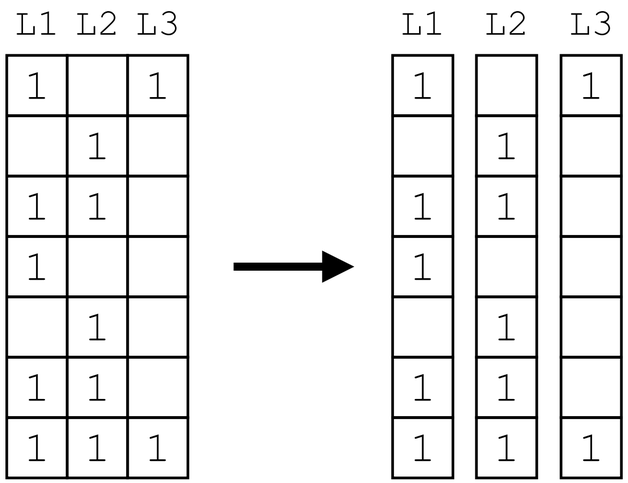
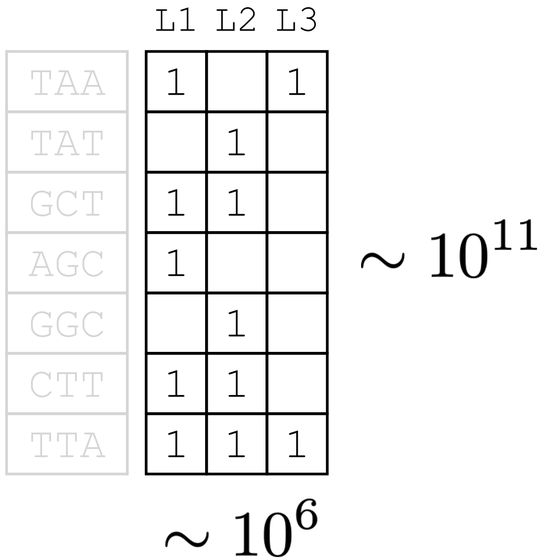
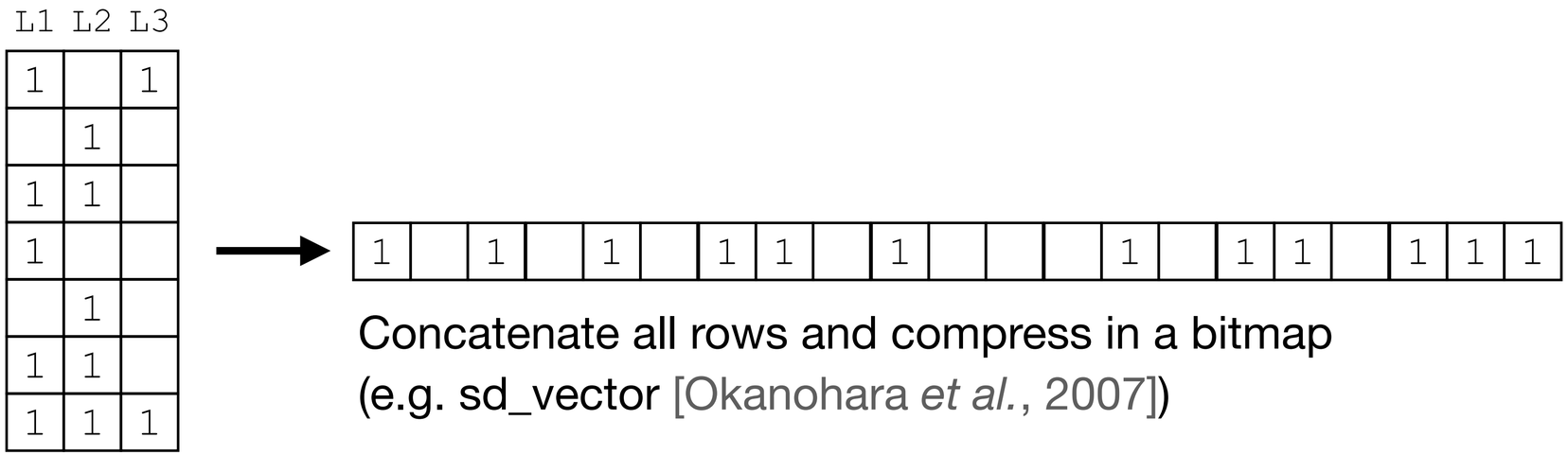




Columns are stored as **compressed bitmaps**
(e.g. sd_vector [Okanohara *et al.*, 2007])

Annotation representations

1. Column-major sparse representation
2. RowFlat (employed in VARI [Muggli *et al.*, 2017])



Annotation representations

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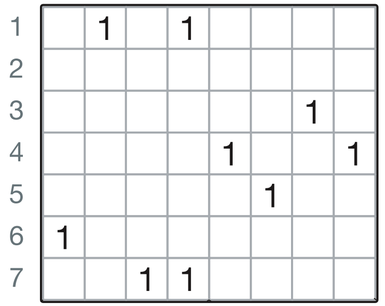

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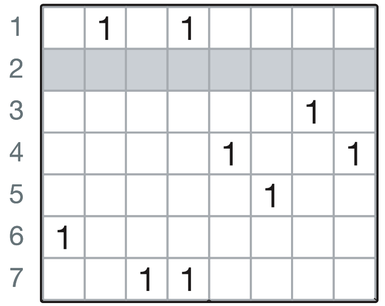

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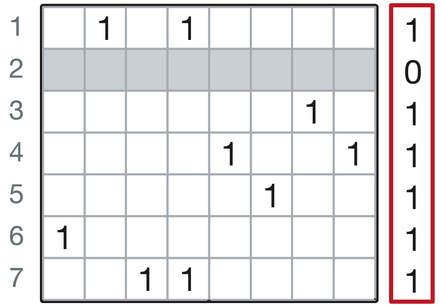

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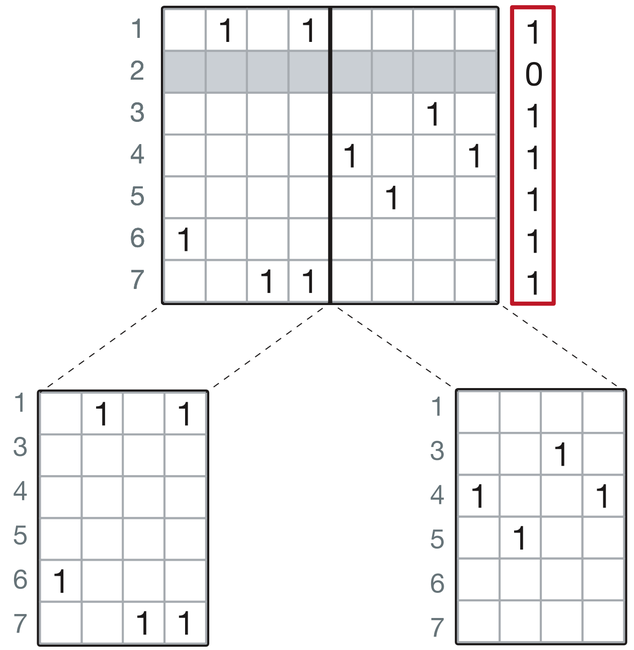

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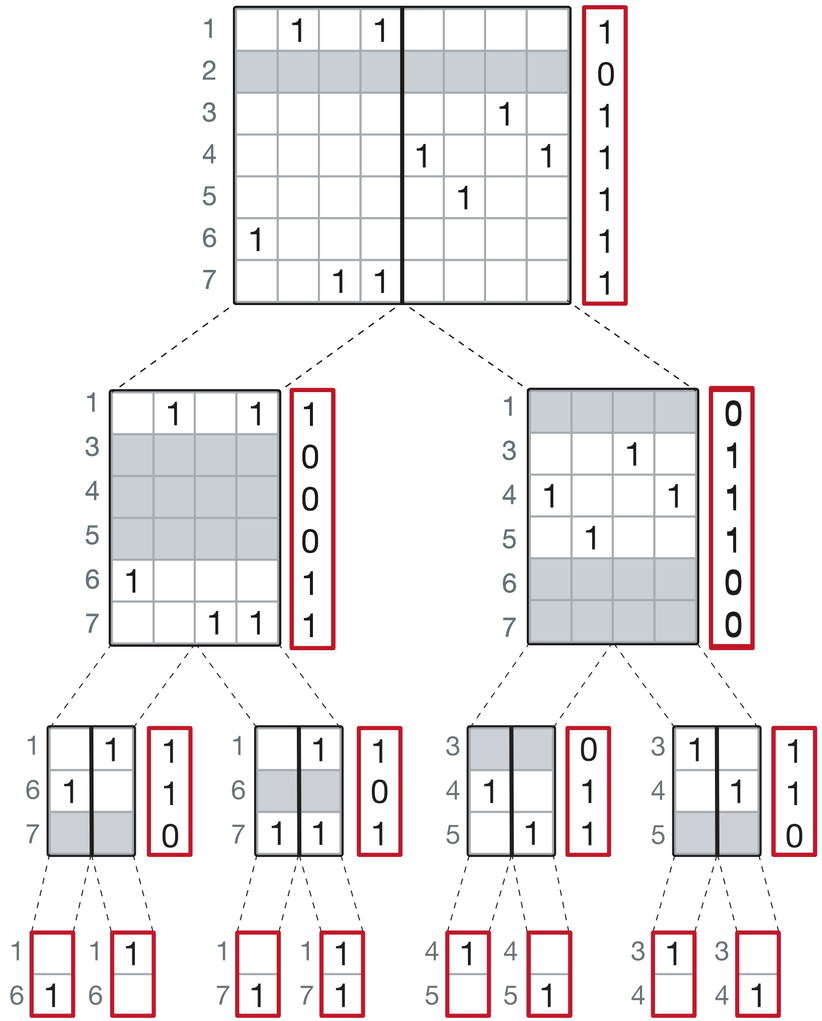

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Sparse Binary Relation Representations for Genome Graph Annotation

Mikhail Karasikov, Harun Mustafa, Amir Joudaki, Sara Javadzadeh-No, Gunnar Rätsch & André Kahles

Conference paper | First Online: 02 April 2019

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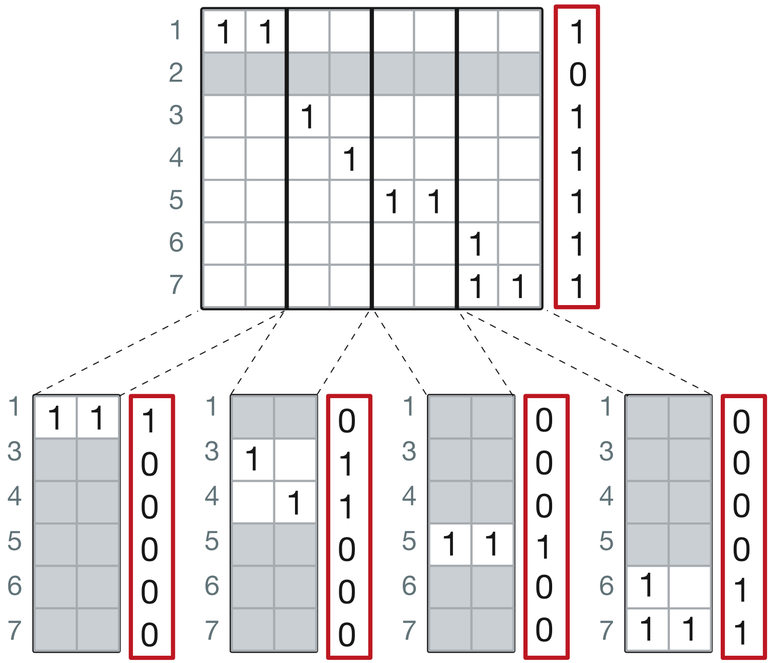

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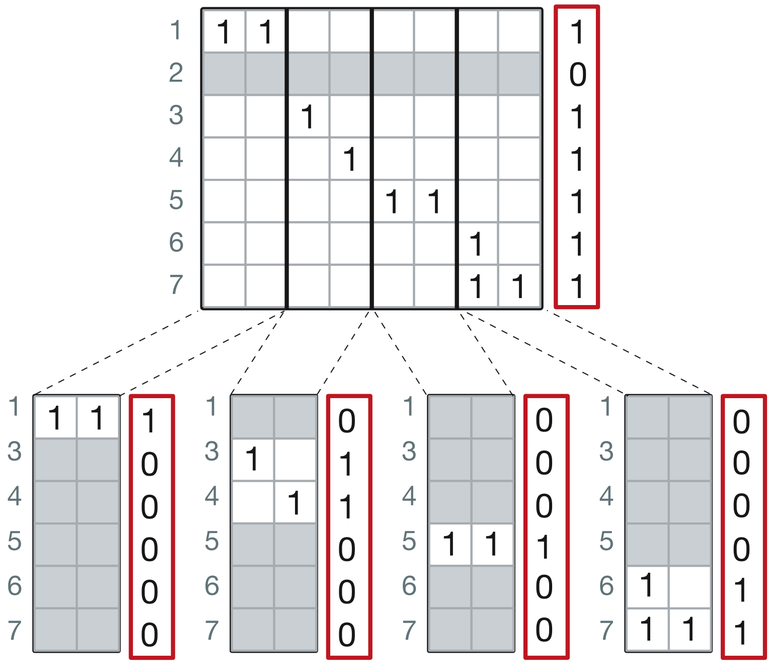

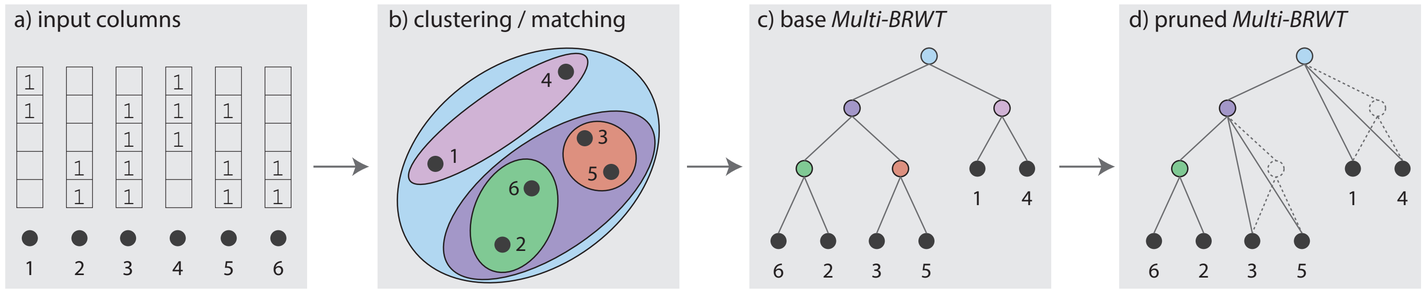

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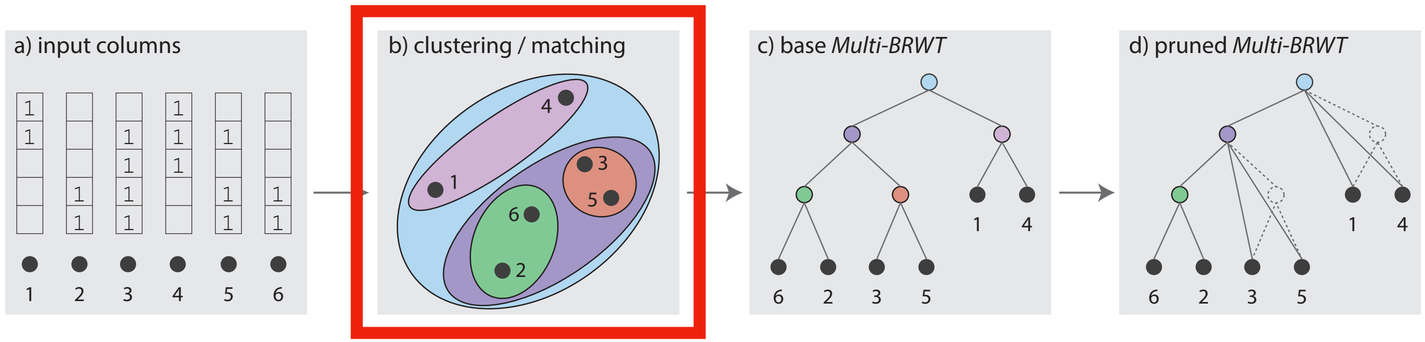

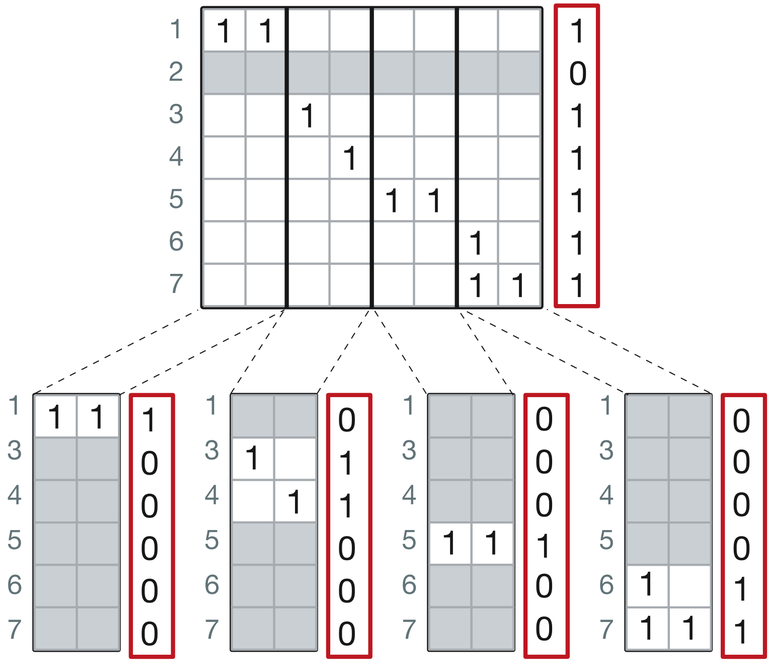

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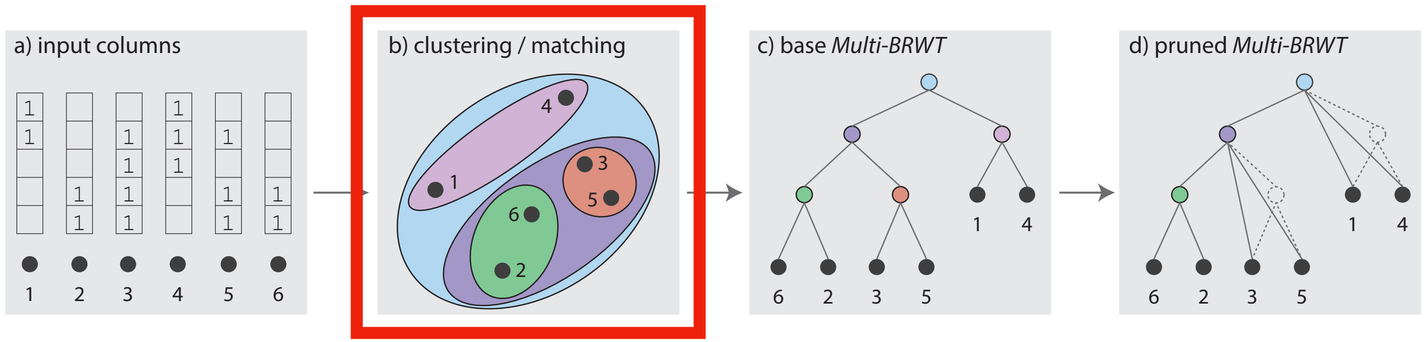
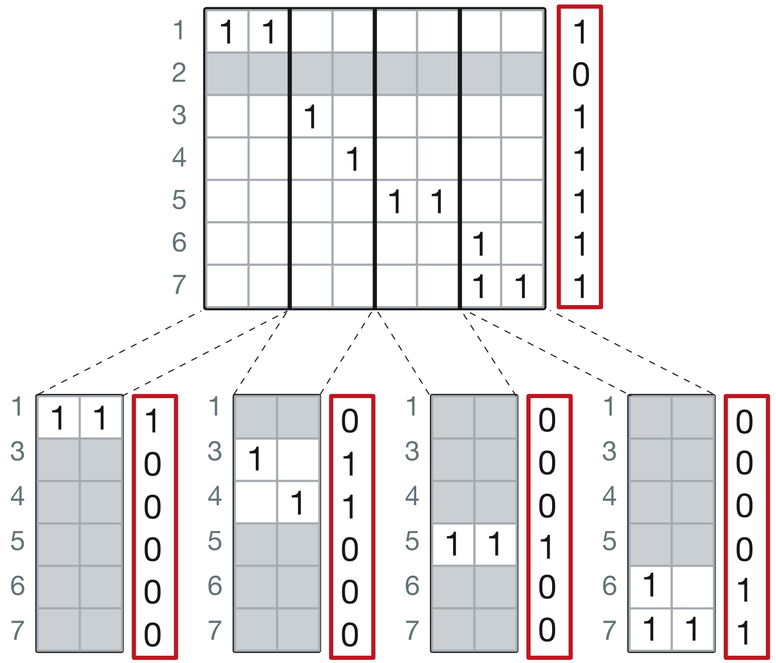


Non-trivial for >500,000 columns



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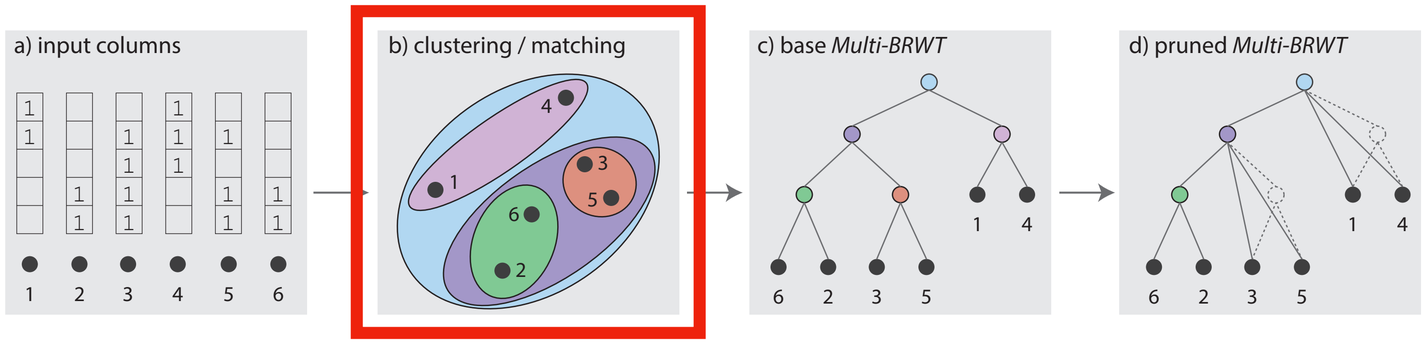

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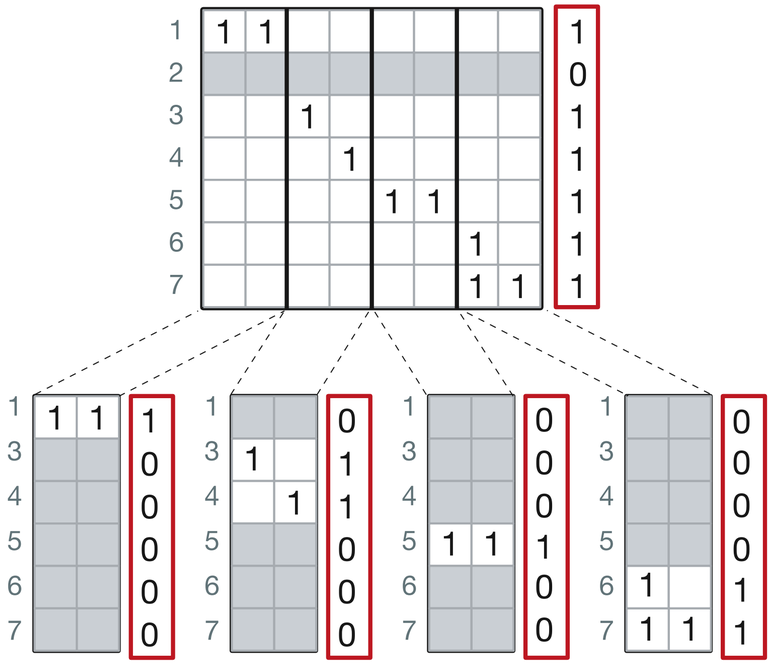
Use taxonomy



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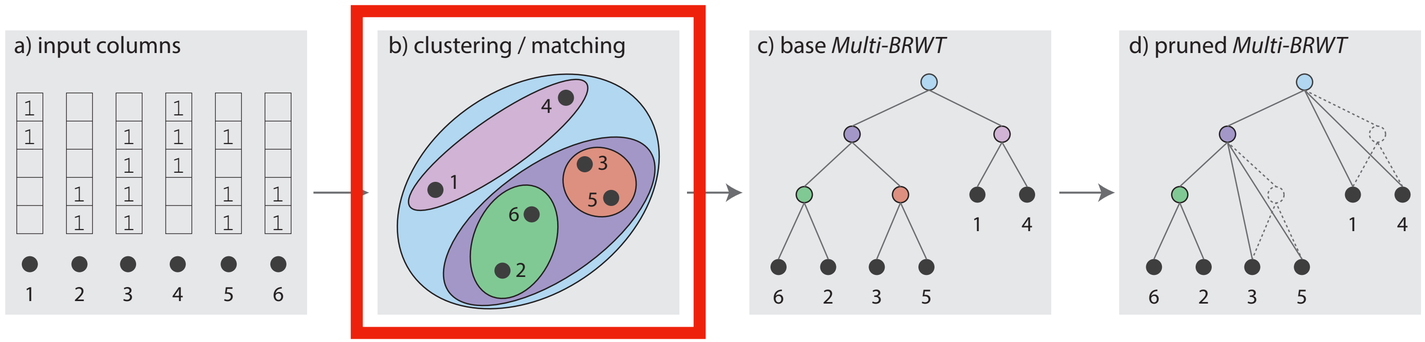

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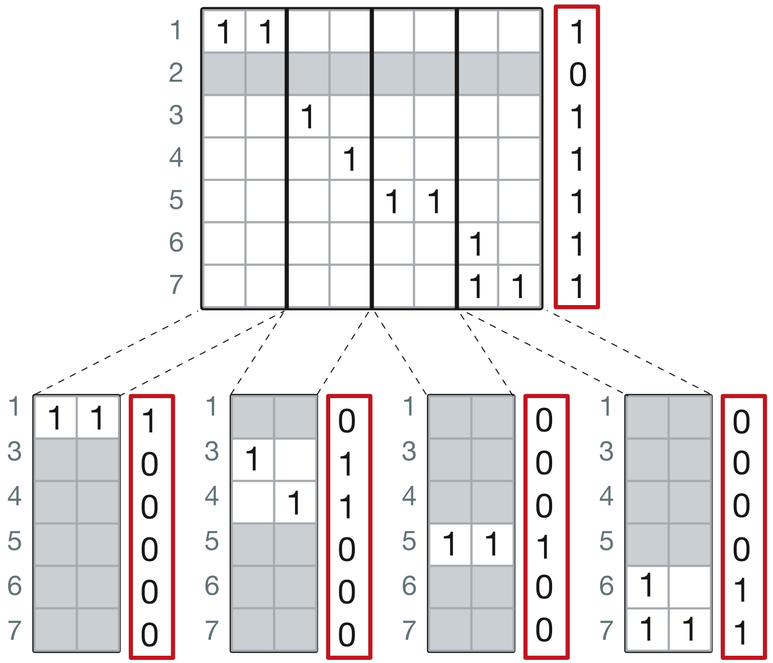
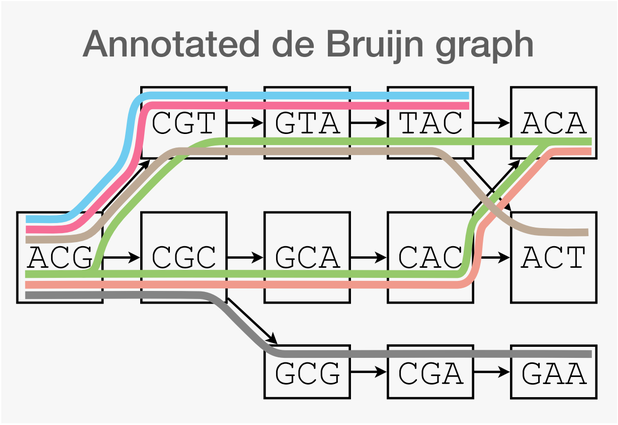


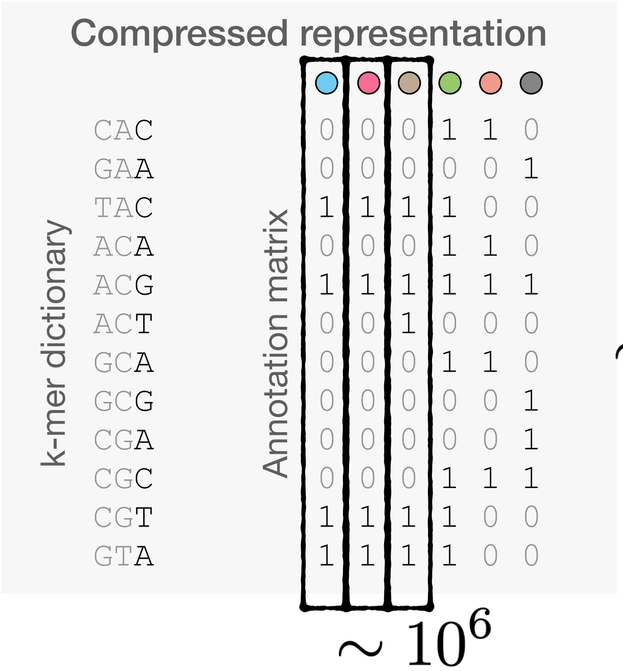
Efficient and Robust Search of Microbial Genomes via Phylogenetic Compression

Karel Břinda, Leandro Lima, Simone Pignotti, Natalia Quinones-Olvera, Kamil Salikhov, Rayan Chikhi, Gregory Kucherov, Zamin Iqbal, Michael Baym

doi: https://doi.org/10.1101/2023.04.15.536996 Posted April 18, 2023.

Representing graph annotations



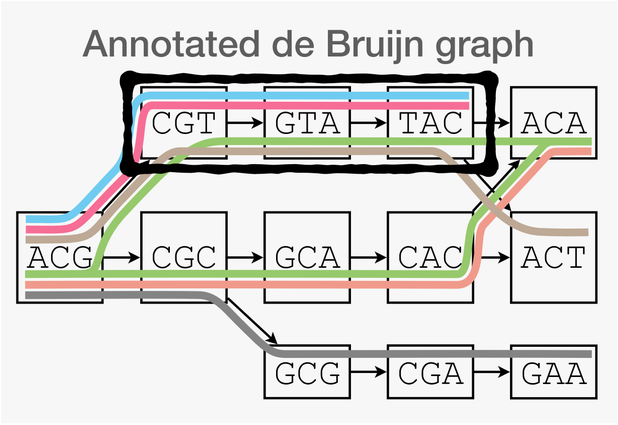


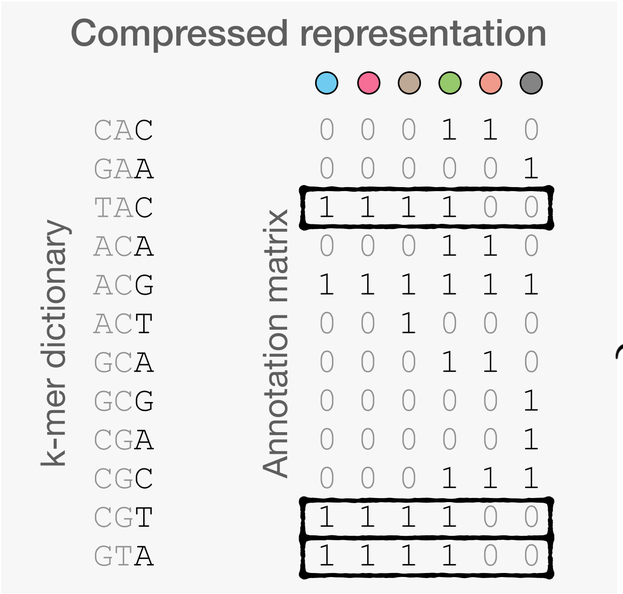
Challenge:
Represent huge-scale annotations

Typical properties

1. high sparsity
2. similarity of **columns** $\Rightarrow$ **Multi-BRWT**

Representing graph annotations





$\sim 10^{11}$

$\sim 10^{6}$

Challenge:
Represent huge-scale annotations

Typical properties

1. high sparsity
2. similarity of **columns** $\Rightarrow$ **Multi-BRWT**
3. similarity of **rows**
   - **adjacent nodes** have similar annotations

RowDiff

Delta compression

Bioinformatics, 37, 2021, i169–i176
doi: 10.1093/bioinformatics/btab330
ISMB/ECCB 2021
OXFORD

Topology-based sparsification of graph annotations

Daniel Danciu[1,2,†], Mikhail Karasikov[1,2,3,†], Harun Mustafa[1,2,3], André Kahles[1,2,3,*] and Gunnar Rätsch[1,2,3,4,*]

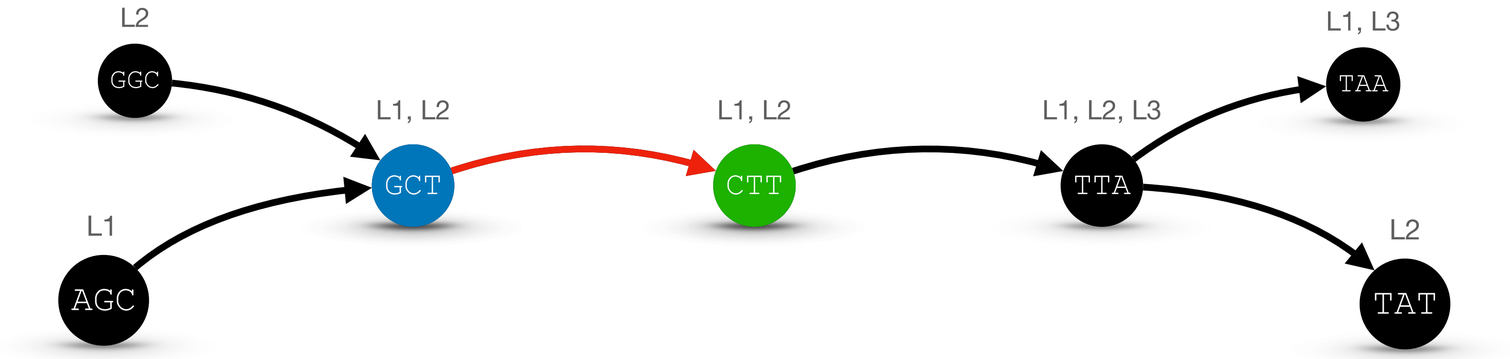
Idea:

- Store only **diffs**

$$L^{\delta}(v) := L(v) \oplus L(v_{\text{succ}})$$

XOR

	L1	L2	L3	
TAA	1		1	
TAT		1		
GCT	1	1		v
AGC	1			
GGC		1		
CTT	1	1		v_{succ}
TTA	1	1	1	



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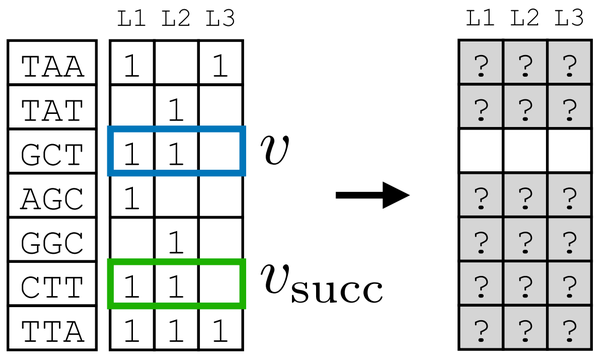

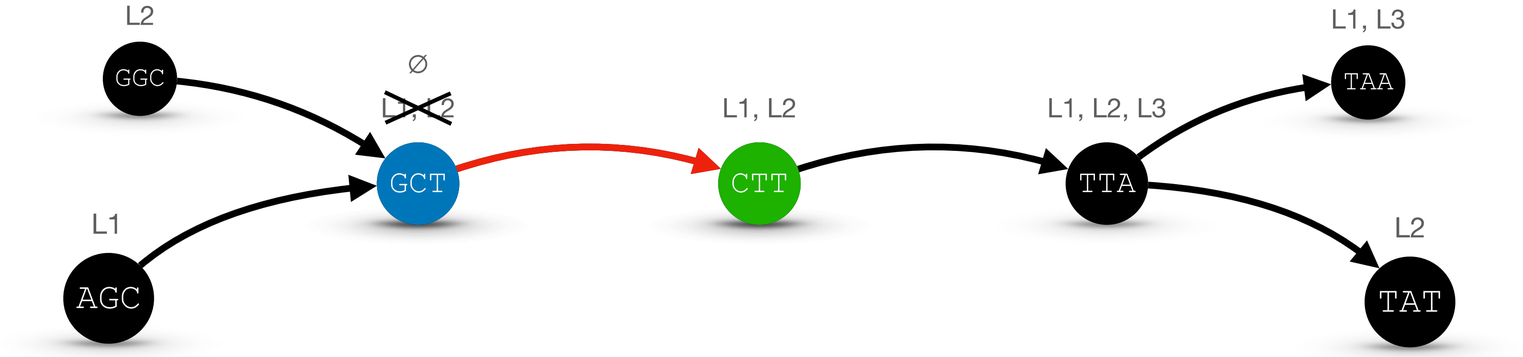

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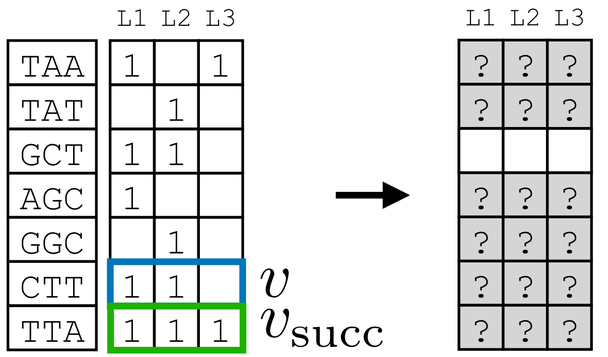

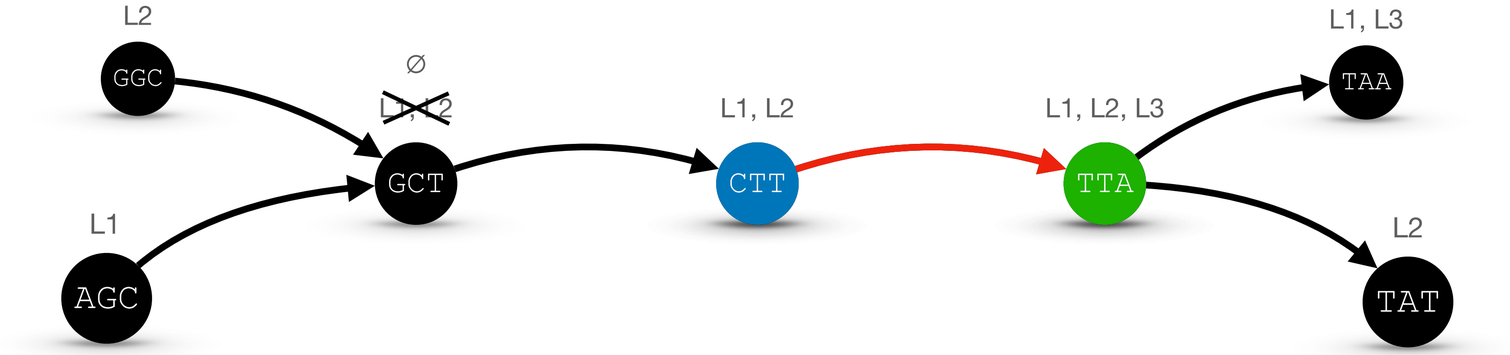

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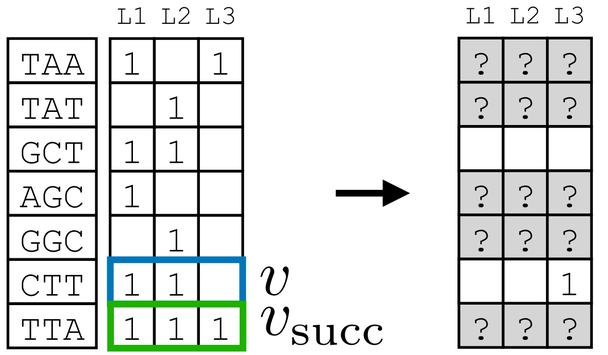

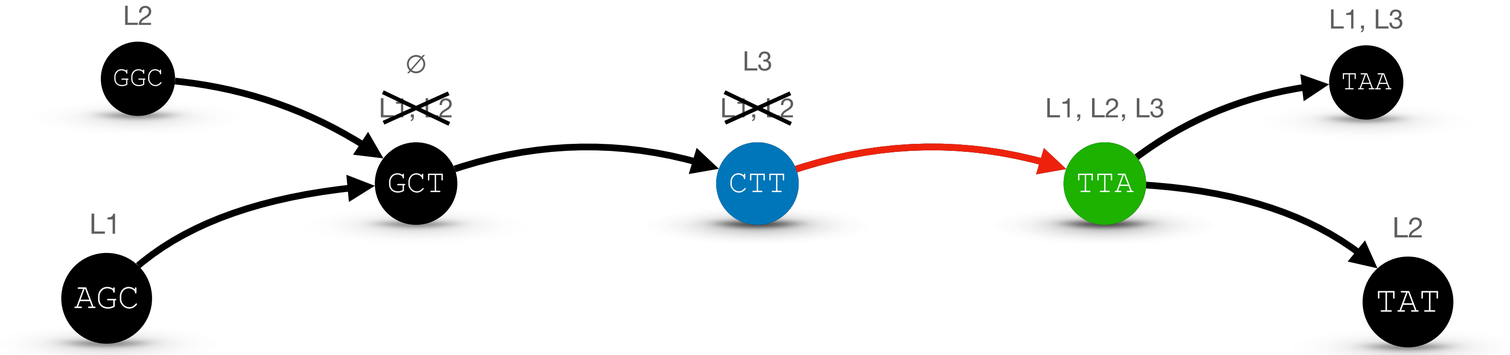

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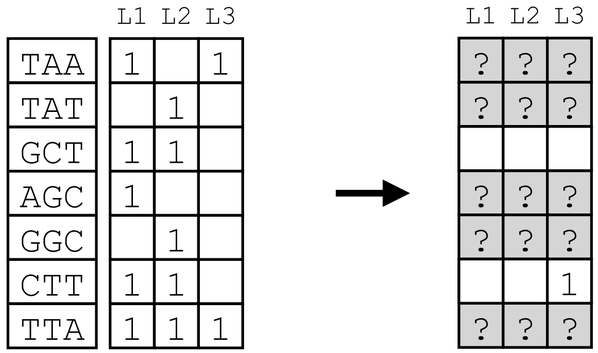

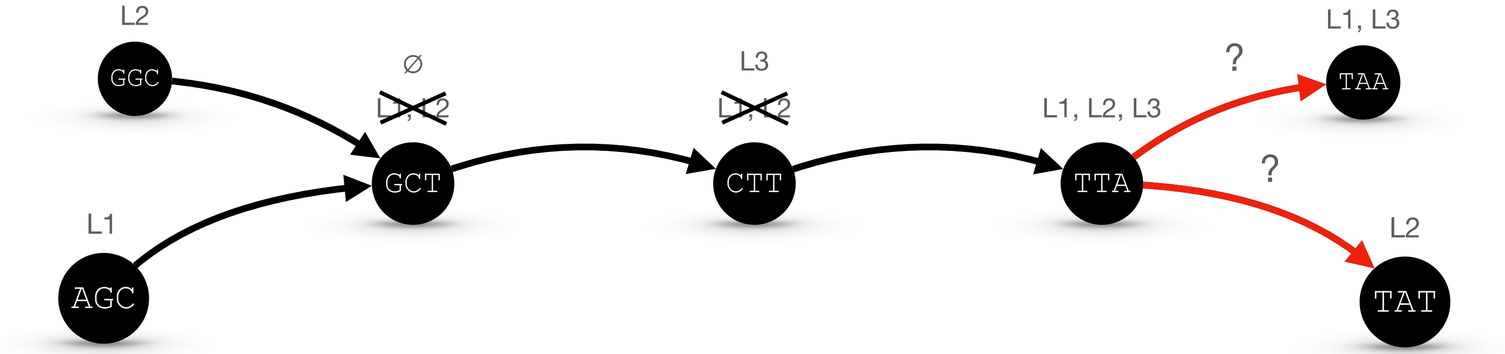

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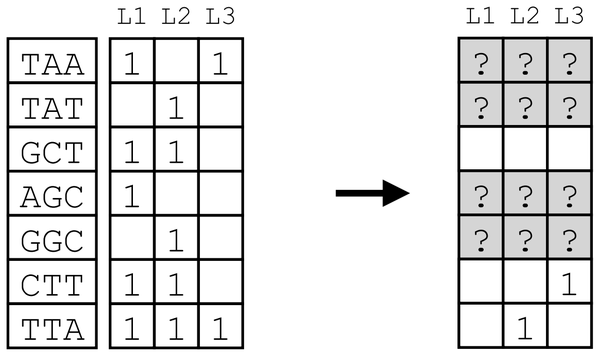

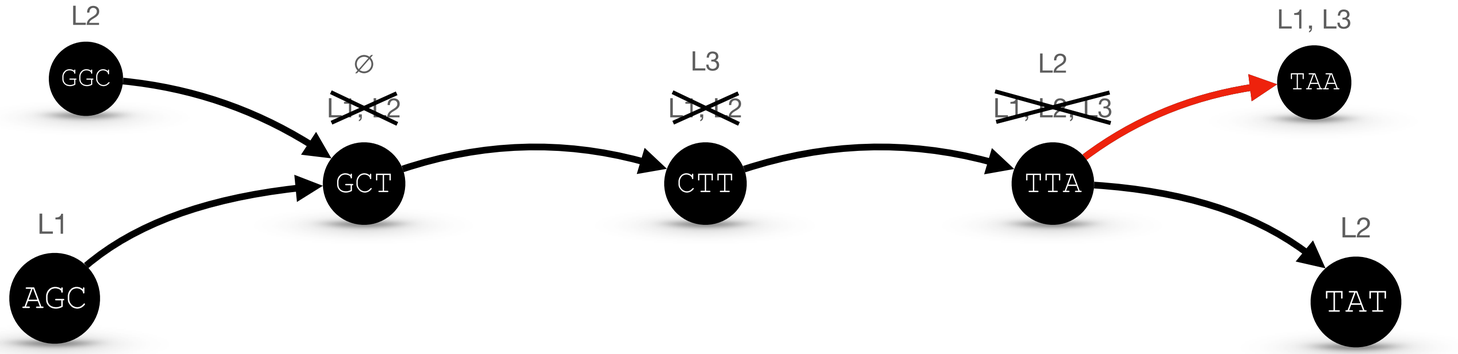

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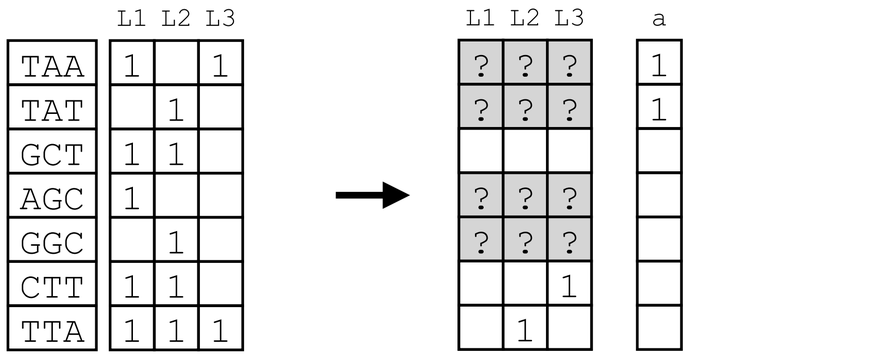

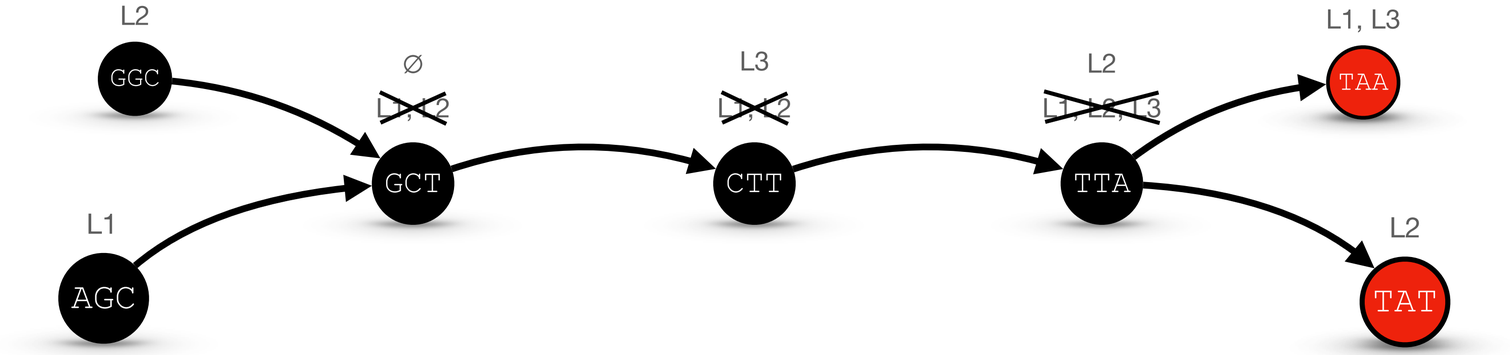

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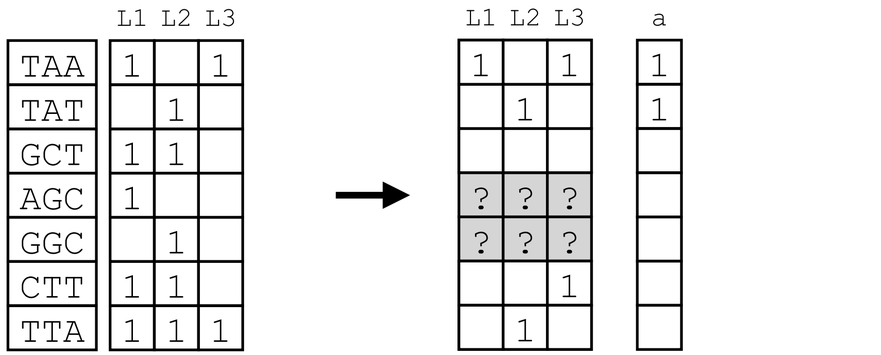

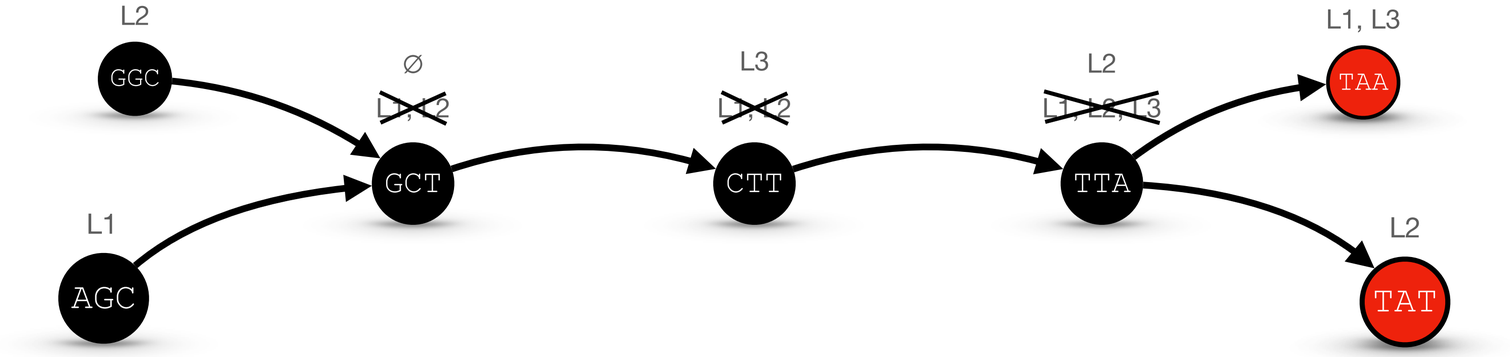

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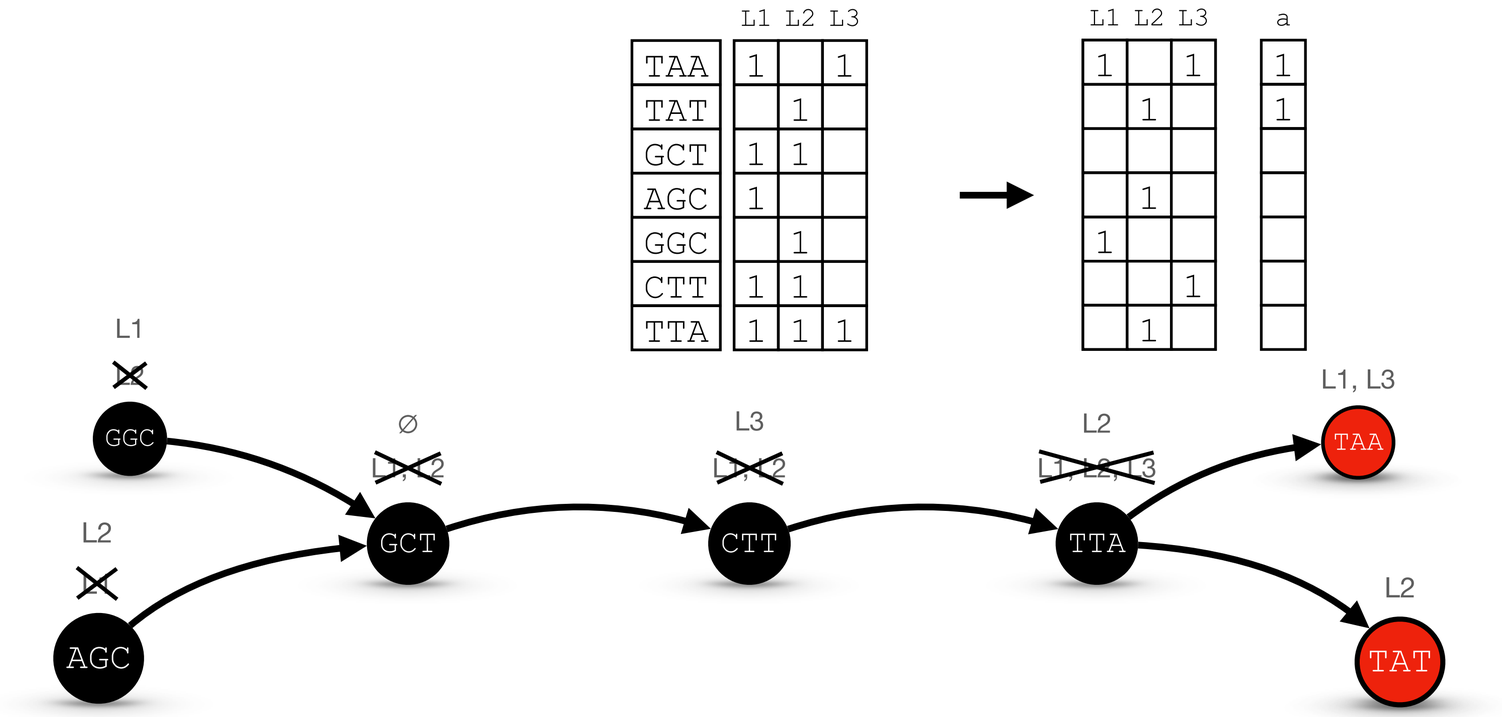

RowDiff effectively **transforms** the matrix:

- **makes it sparser**, and thus, more compressible
- **any representation scheme** can then be applied on top
- the overhead is very small (<1 bit per node)

RowDiff

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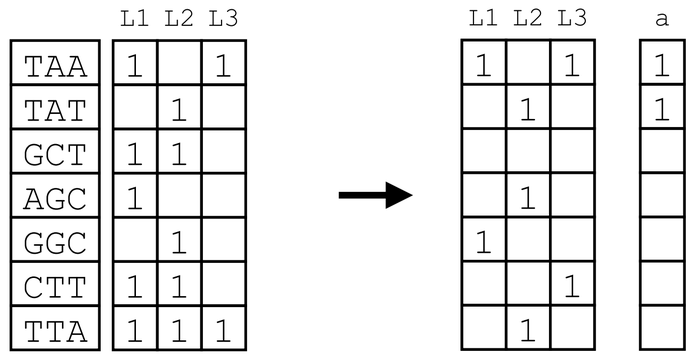
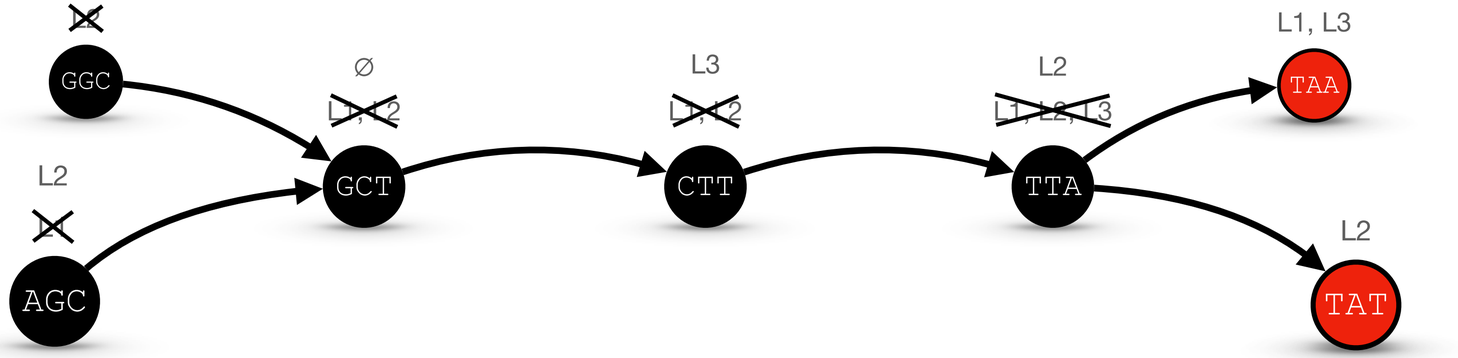
Idea:

- Store only **diffs**
  $L^{\delta}(v) := L(v) \oplus L(v_{\text{succ}})$

- Reconstruct
  $L(v) = L(v_{\text{succ}}) \oplus L^{\delta}(v)$

reconstruct recursively





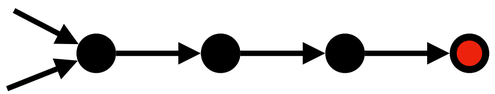
RowDiff effectively **transforms** the matrix:

- **makes it sparser**, and thus, more compressible
- **any representation scheme** can then be applied on top
- the overhead is very small (<1 bit per node)

RowDiff

Anchor nodes

1. **Each *sink* *node*** (with no outgoing edges) **must be anchored**



RowDiff

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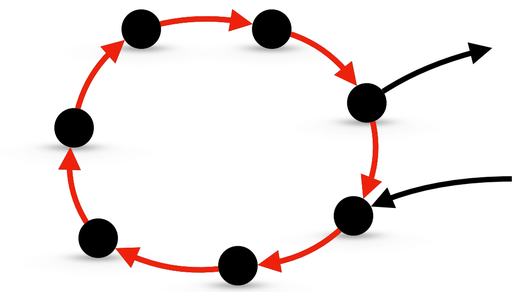
2. **Each *row-diff cycle*** must have **at least one anchor** node in it



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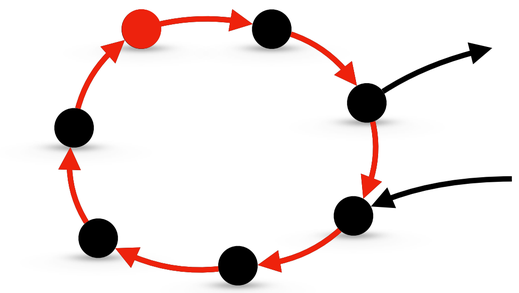

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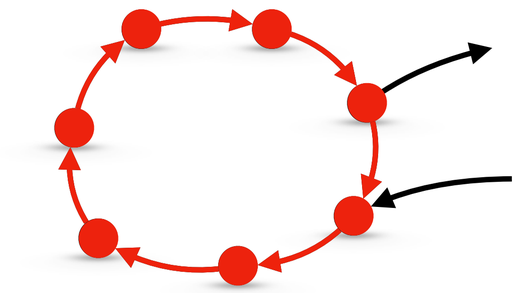

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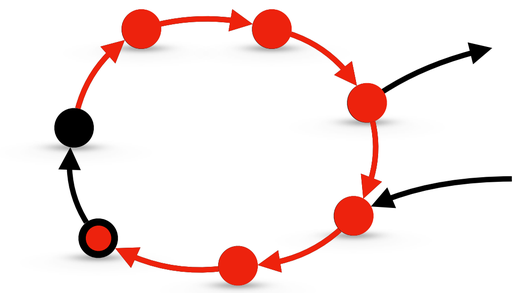

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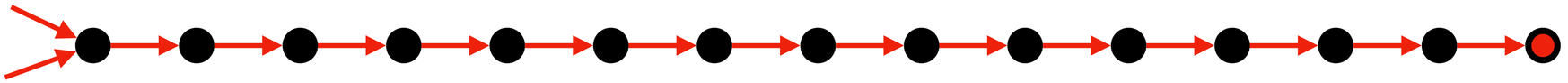

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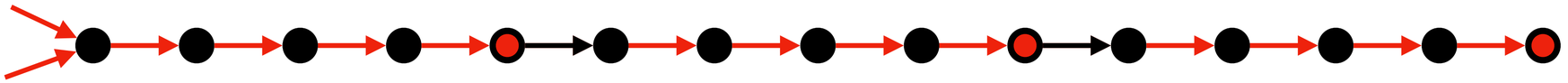
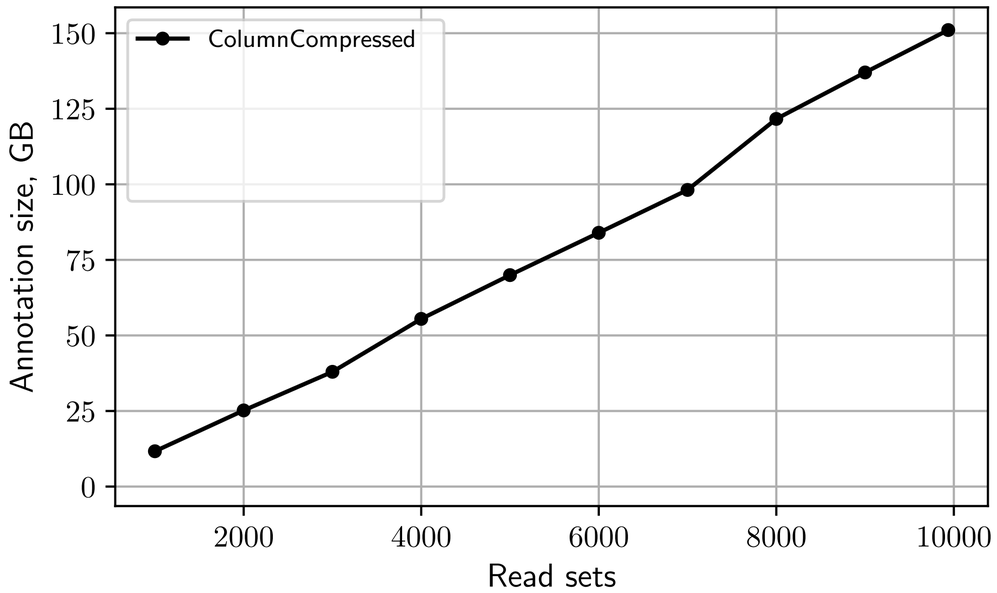


RowDiff: results

Indexing 10,000 (25 TB) human RNA-seq experiments from ENA [Almodaresi et al., 2019]



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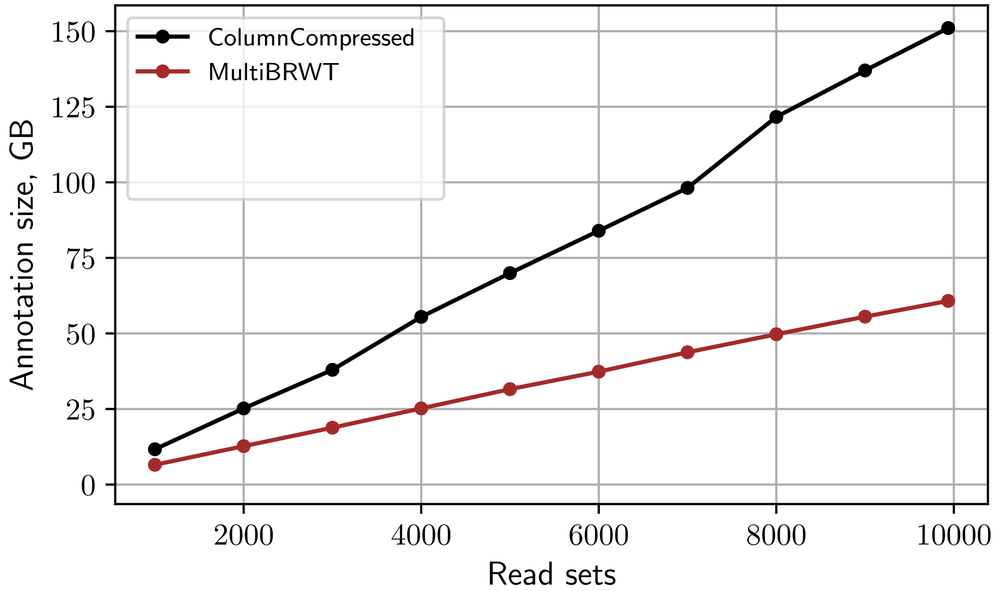

- **Multi-BRWT** exploits similarity of **columns**

RowDiff: results

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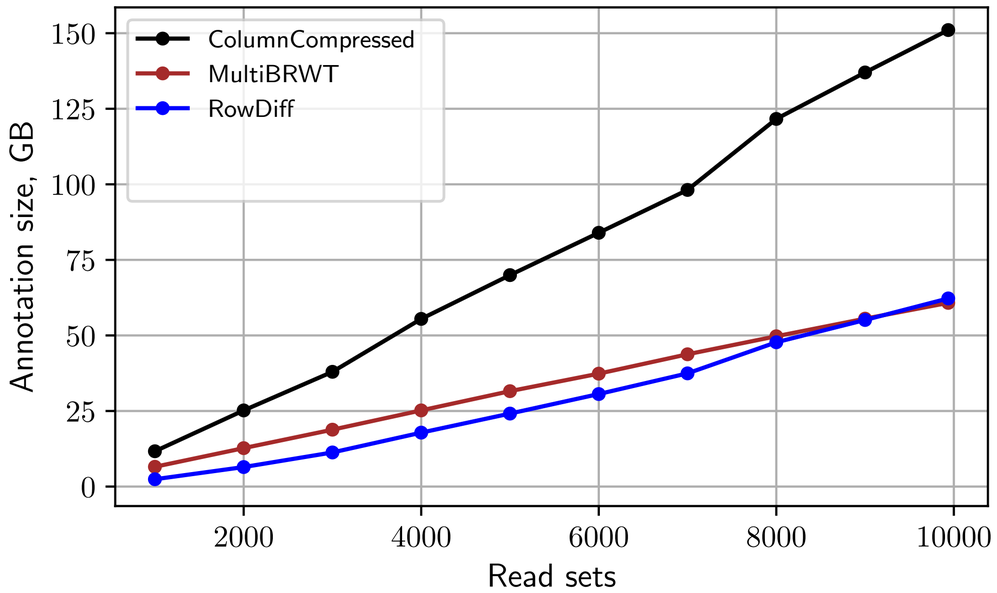

- **Multi-BRWT** exploits similarity of **columns**
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  - effectively transforms the matrix
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RowDiff: results

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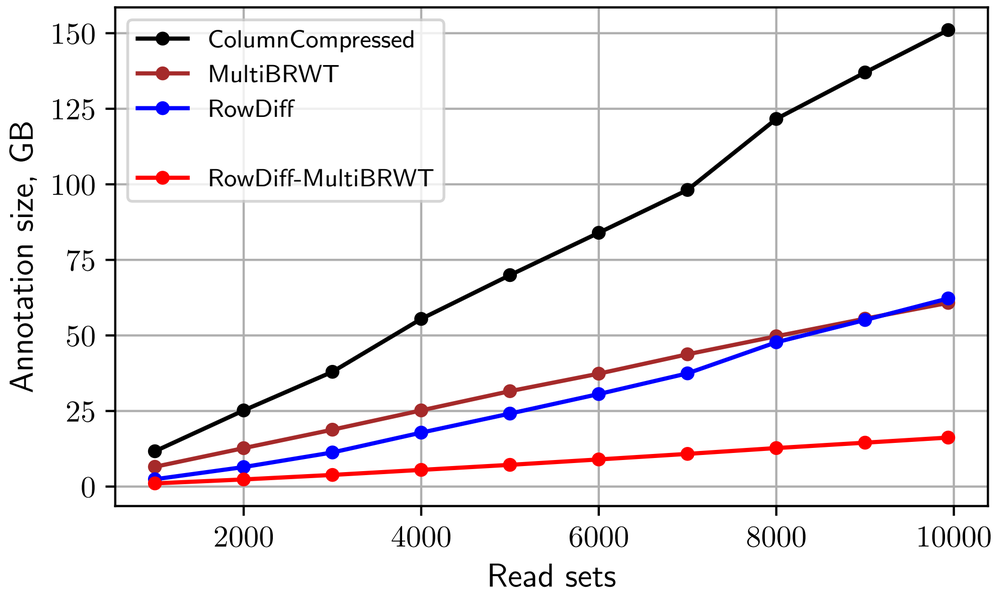

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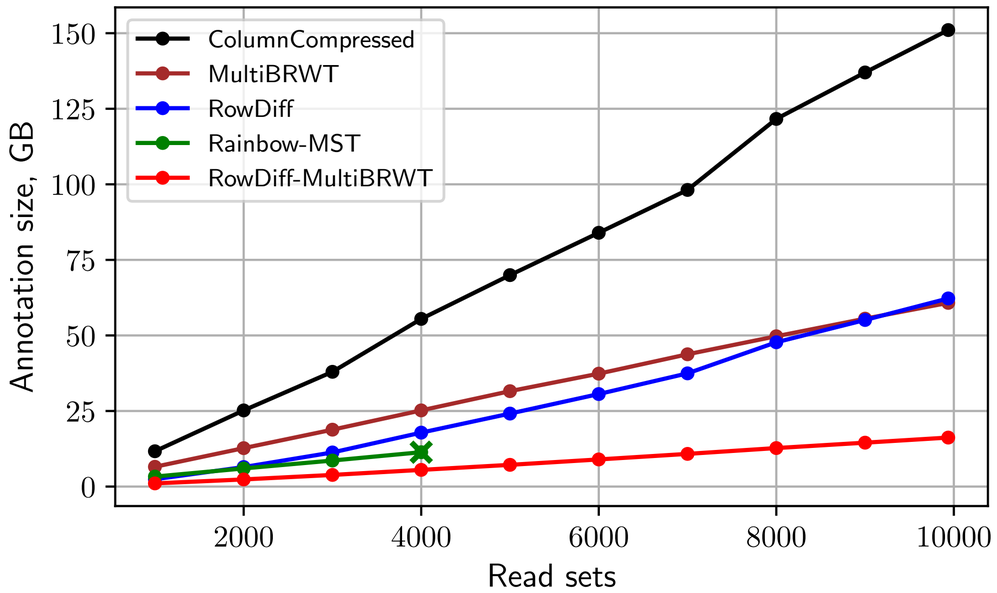
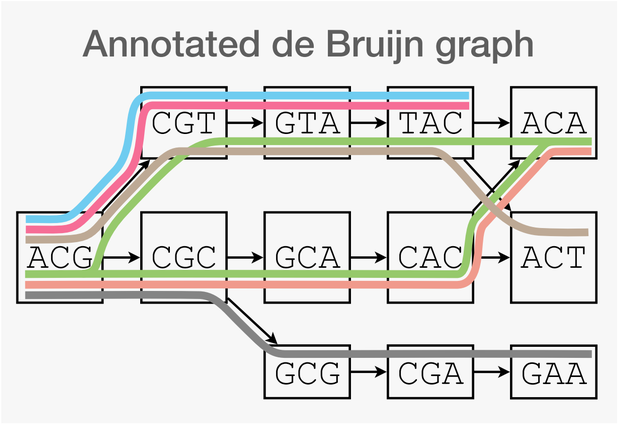
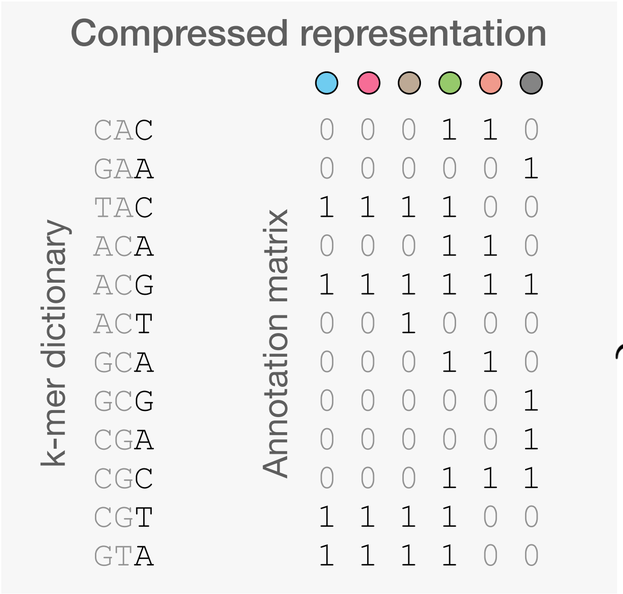


- **Multi-BRWT** exploits similarity of **columns**
- **RowDiff** exploits similarity of **rows**
  - effectively transforms the matrix
  - can be combined with any representation scheme
- When combined together, **outperform** the **state-of-the-art**

Representing graph annotations





$\sim 10^{11}$

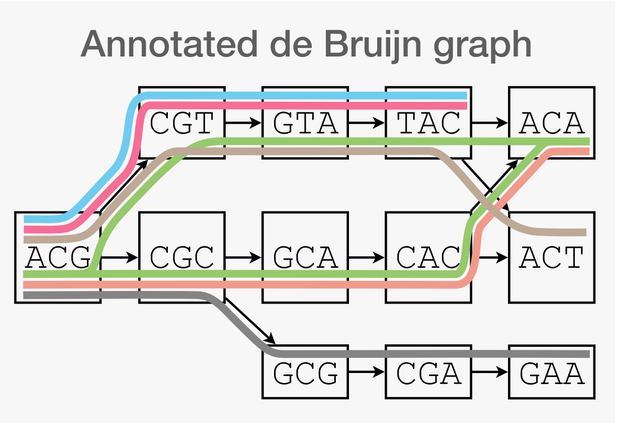
$\sim 10^{6}$

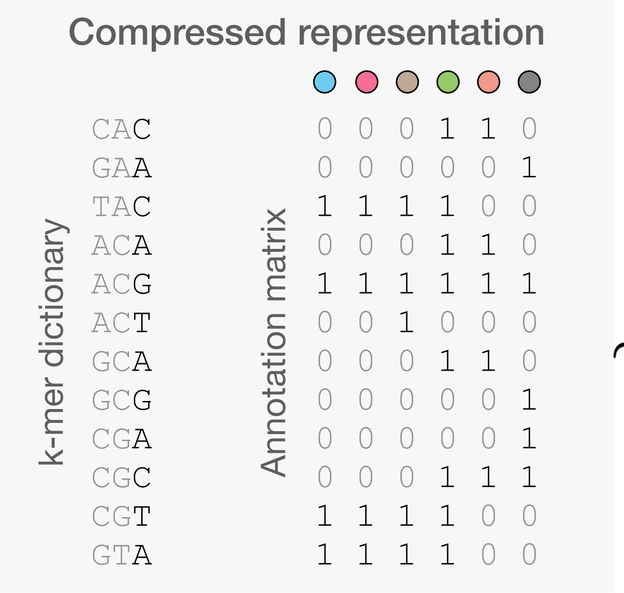
Challenge:
Represent huge-scale annotations

Typical properties

1. high sparsity
2. similarity of **columns** $\Rightarrow$ **Multi-BRWT**
3. similarity of **rows** $\Rightarrow$ **RowDiff**

Representing graph annotations





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✔

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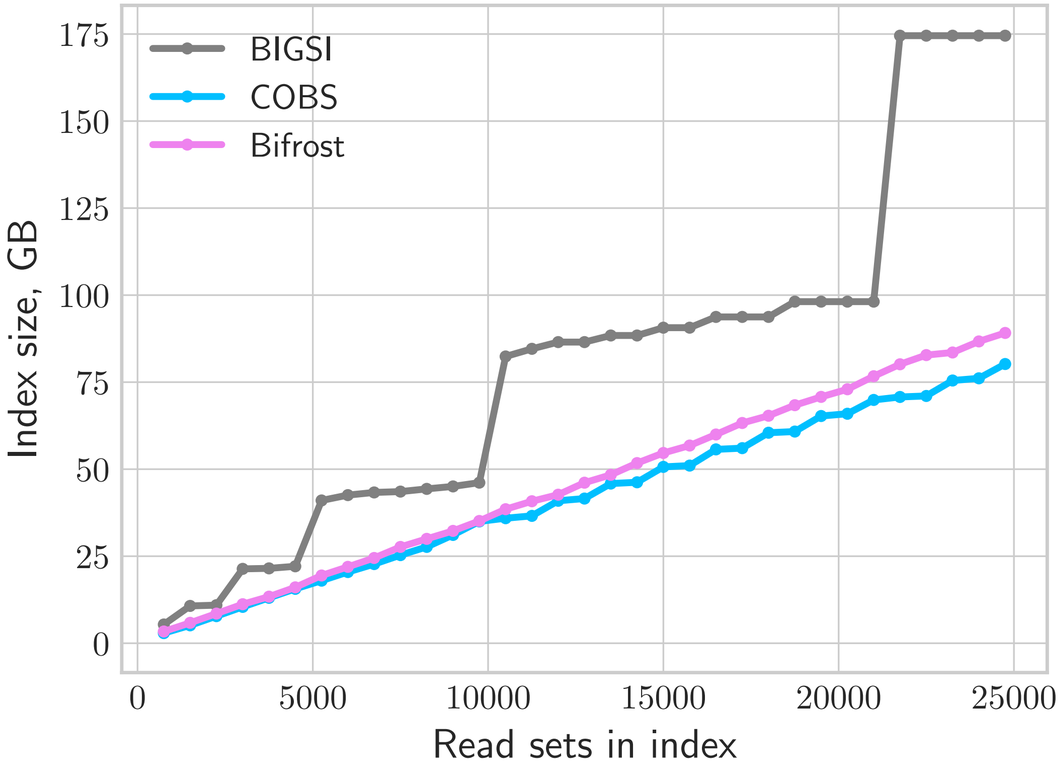
Scalability of MetaGraph

Indexing microbial samples (BIGSI [Bradley *et al.*, 2019] subsets)



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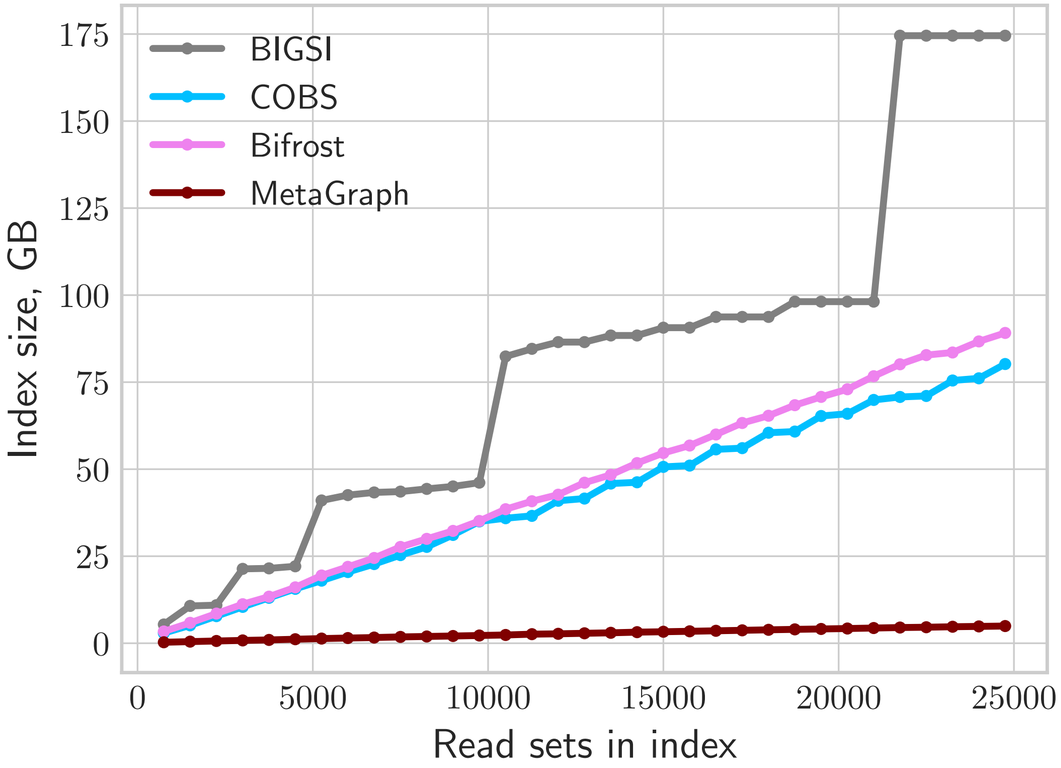

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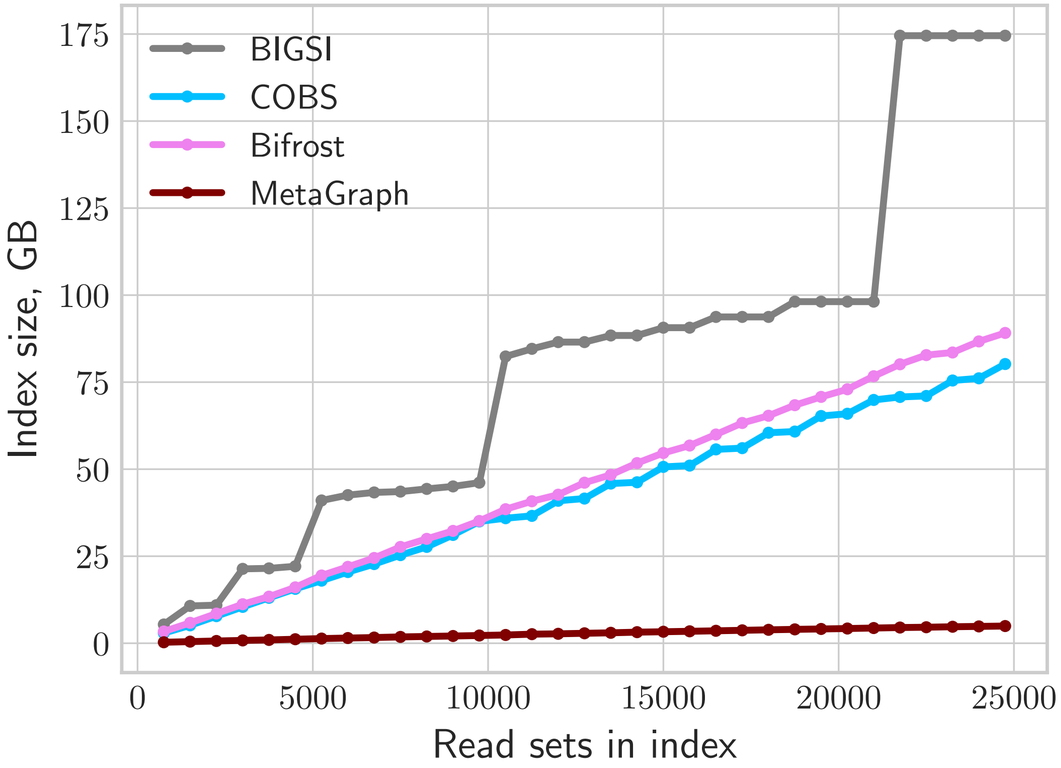
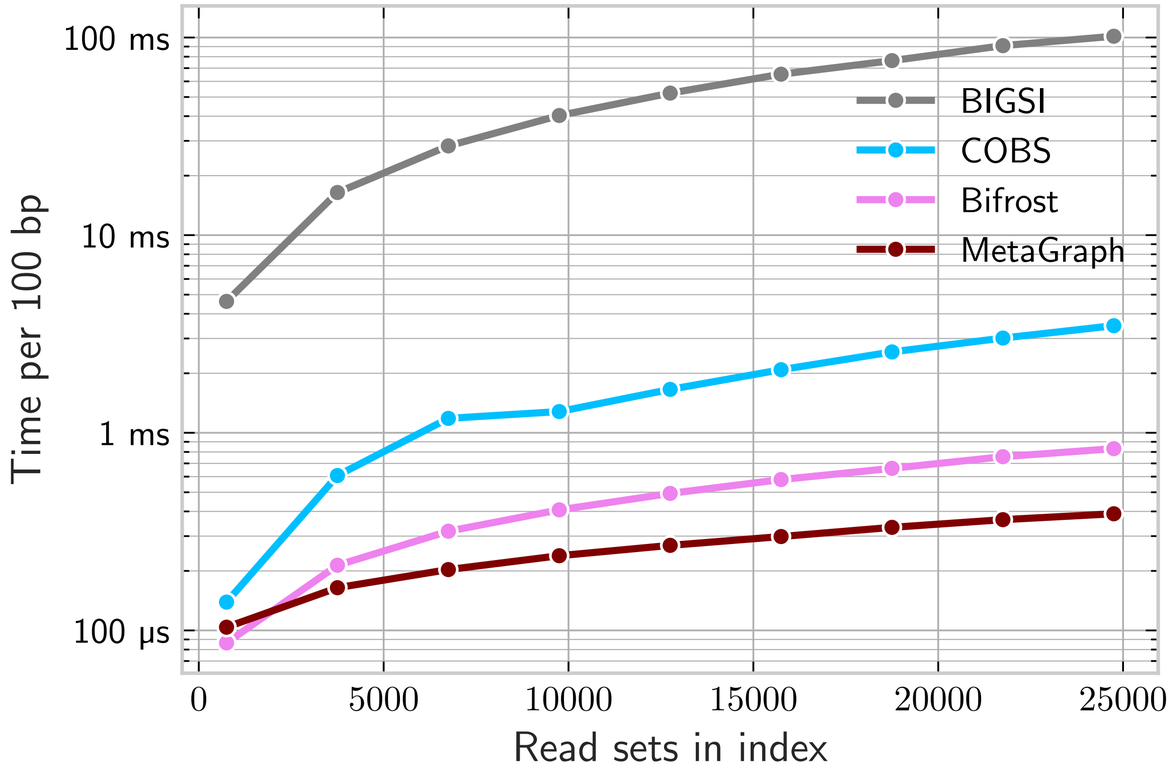


Querying DRR067889



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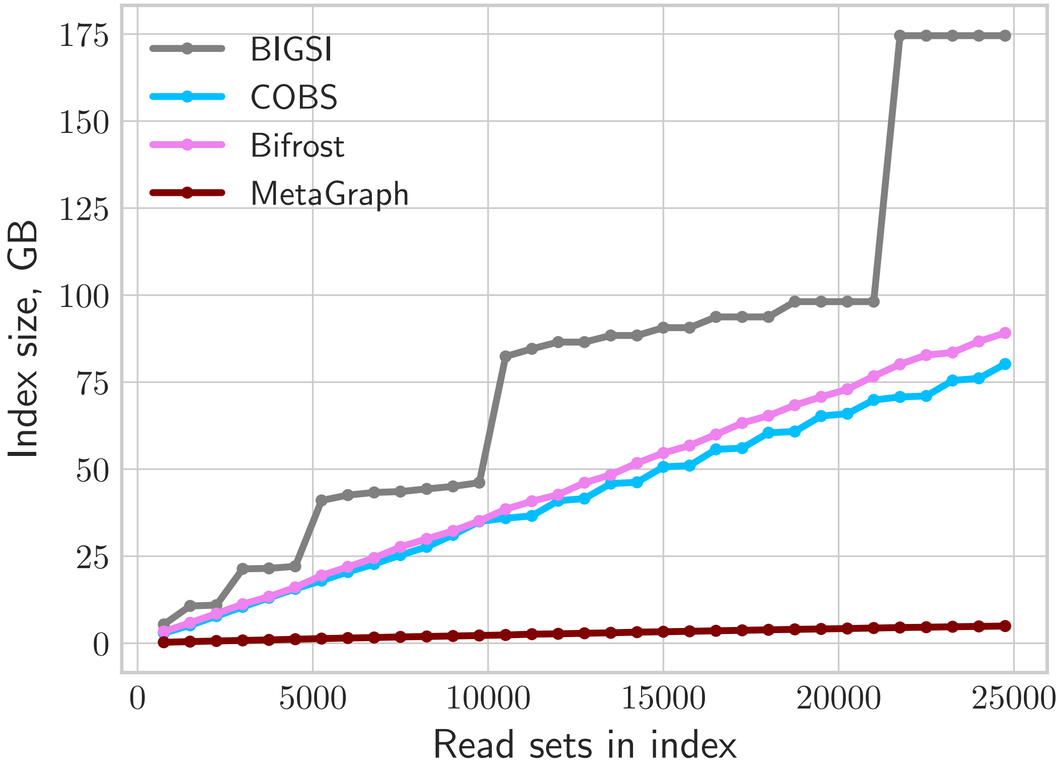

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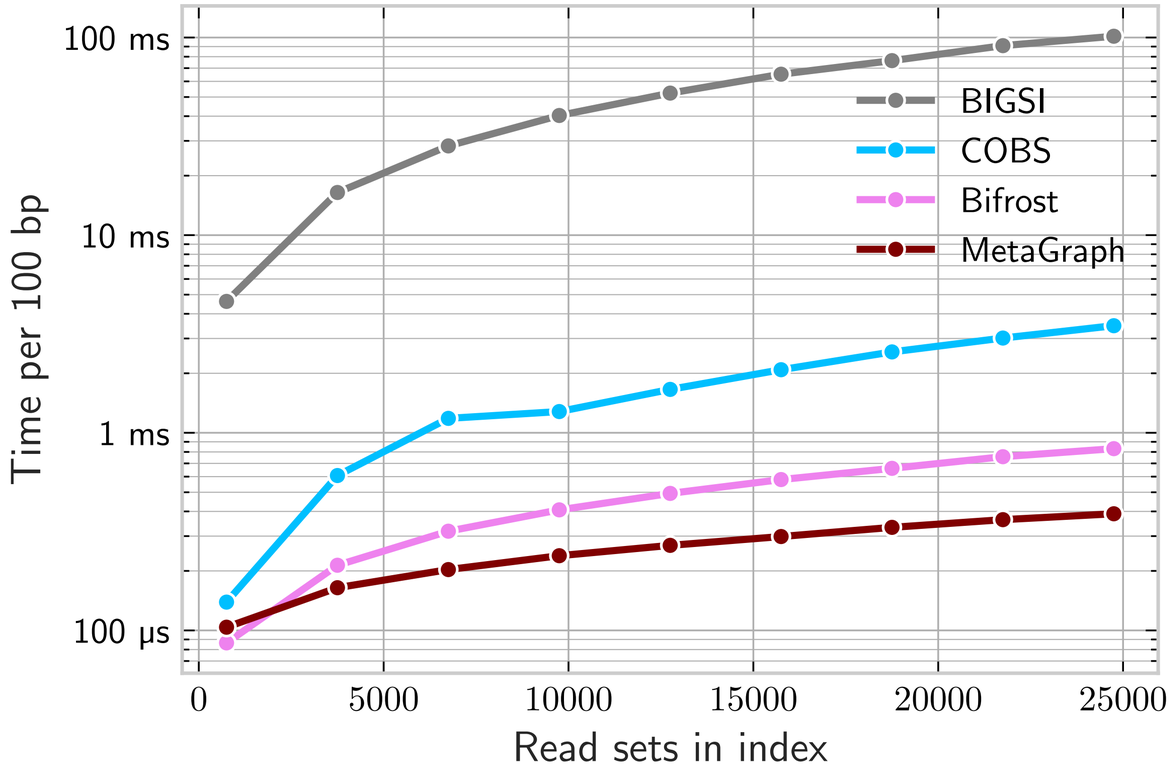
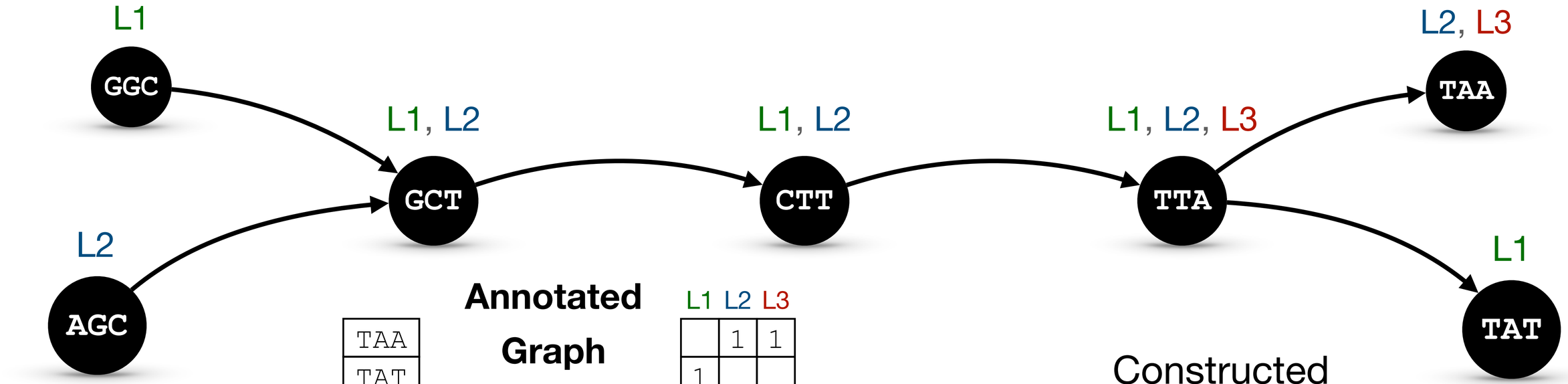


- Use of **succinct data structures** and efficient representation schemes
- Choice of **efficient algorithms** (e.g., batch operations)

From qualitative to quantitative

0. Representing **presence/absence**



Annotated Graph

TAA
TAT
GCT
AGC
GGC
CTT
TTA

k-mer dictionary

L1	L2	L3
	1	1
1		
1	1	
	1	
1		
1	1	
1	1	1

graph annotation

Constructed from sequences

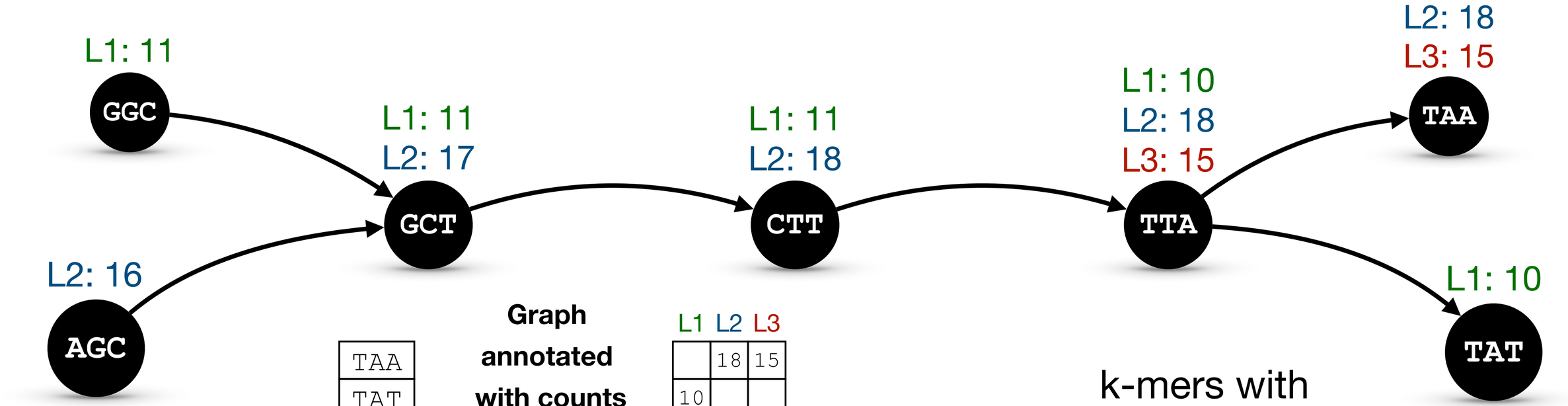
L1: GGCTTAT

L2: AGCTTAA

L3: TTAA

From qualitative to quantitative

1. Representing **k-mer abundances**



TAA
TAT
GCT
AGC
GGC
CTT
TTA

k-mer dictionary

Graph annotated with counts

L1	L2	L3
	18	15
10		
11	17	
	16	
11		
11	18	
10	18	15

graph annotation

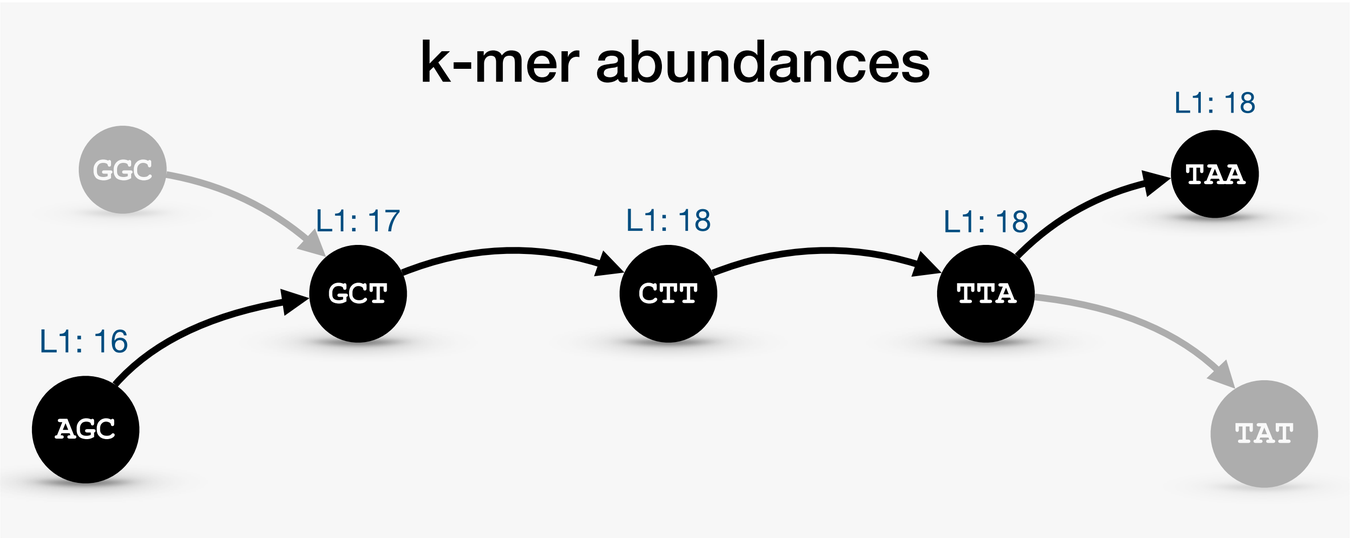
k-mers with multiplicities

L1: `GGC: 11, …`

L2: `AGC: 16, …`

L3: `TTA: 15, …`

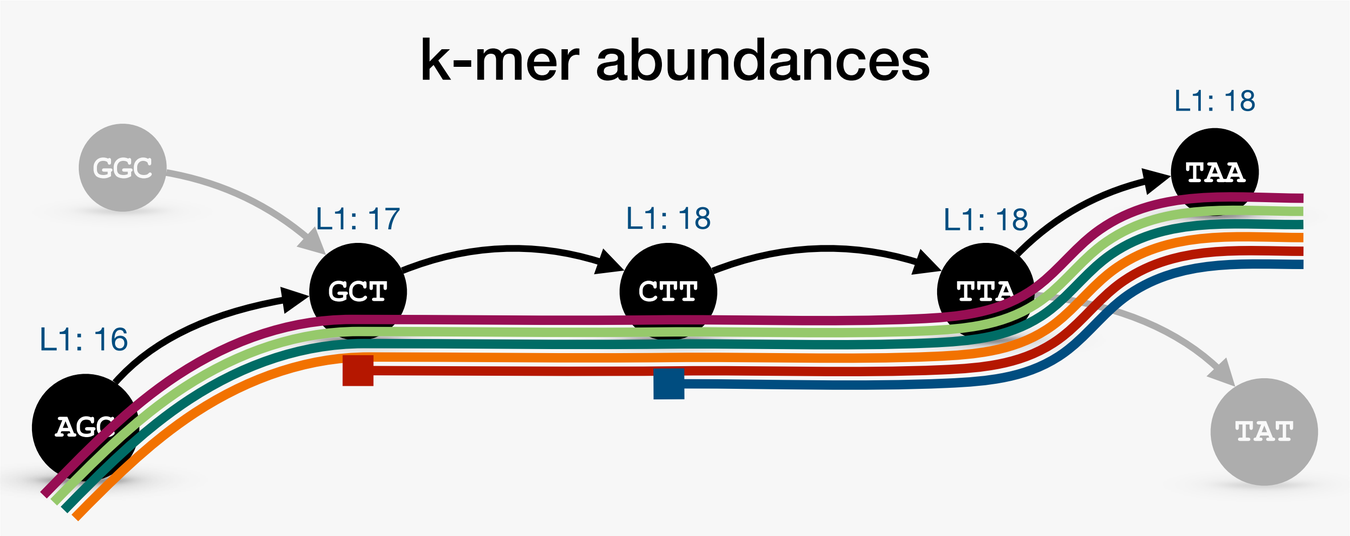
Exploiting regularities



Observe regularities:

Abundances of adjacent k-mers are often similar

Exploiting regularities



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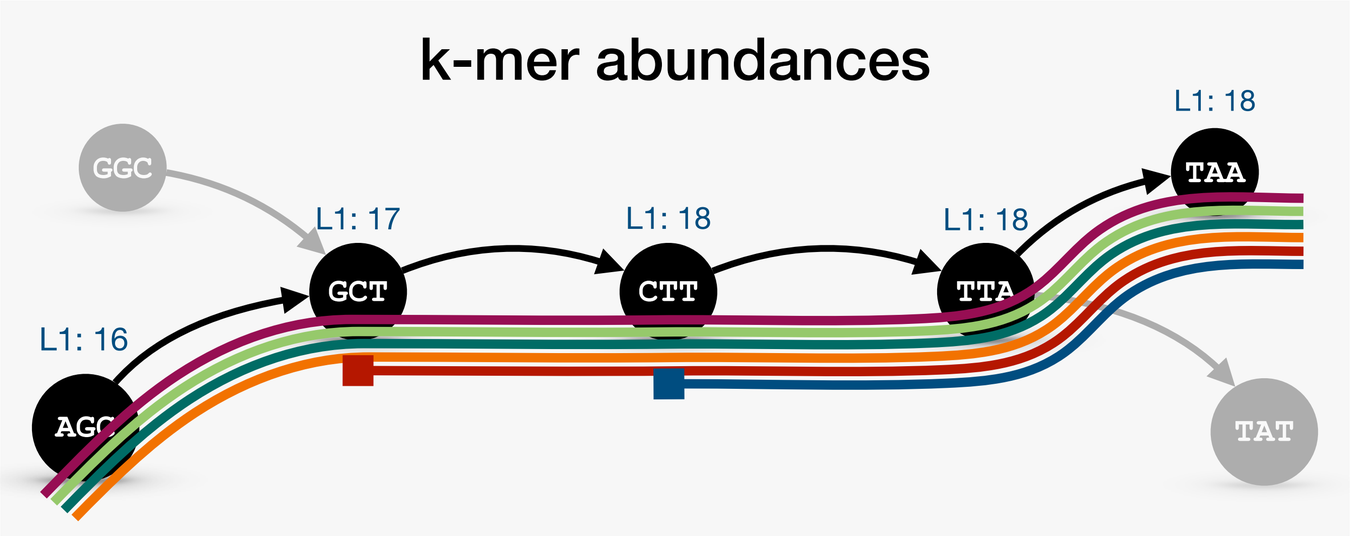


Observe regularities:

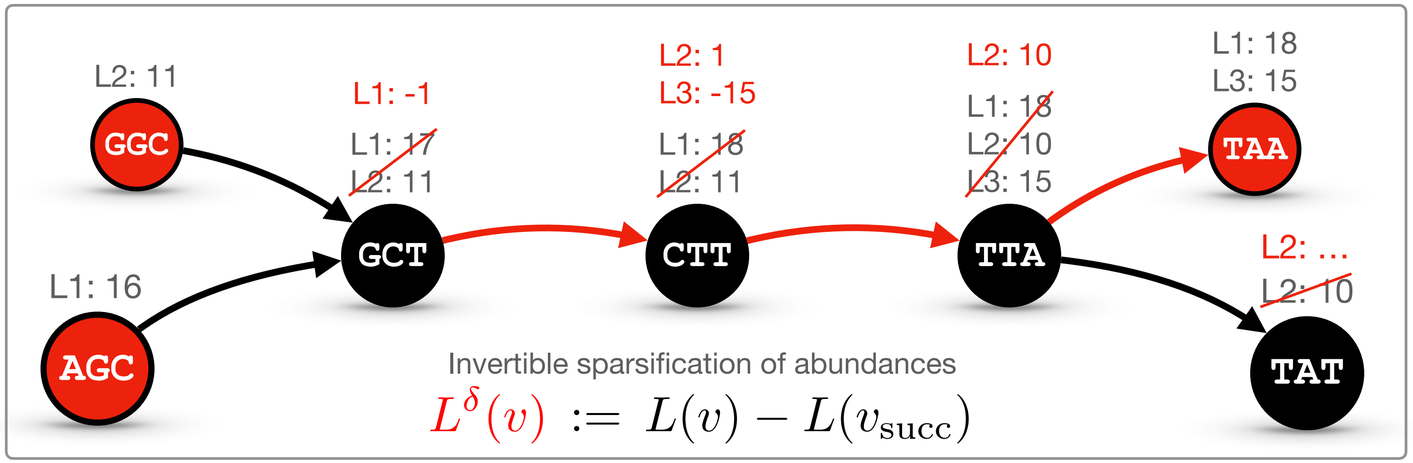
Abundances of adjacent k-mers are often similar

Idea:

Generalize the RowDiff scheme

Lossless Indexing with Counting de Bruijn Graphs
Mikhail Karasikov, Harun Mustafa, Gunnar Rätsch, André Kahles
Genome Res. 2022; doi: https://doi.org/10.1101/gr.276607.122

RowDiff for k-mer abundances



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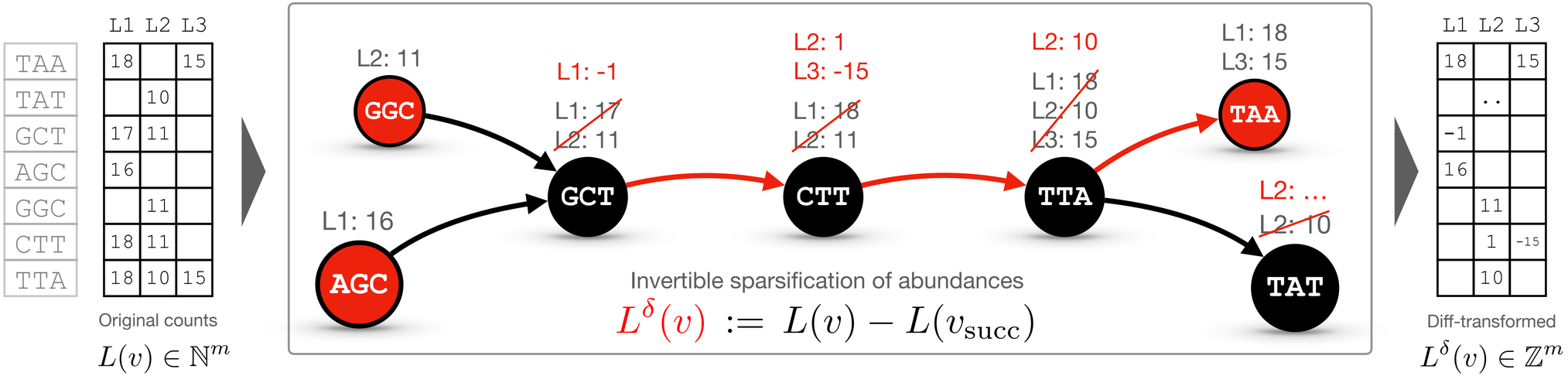

Indexing k-mer counts

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Indexing 2,586 human RNA-Seq read sets [Solomon, Kingsford, 2016].
Querying 100 random human transcripts (≈ 90 kbp).

Method	Index size	Peak RAM	Query time
REINDEER	59 GB	91 GB	56.5 sec
MetaGraph	**11 GB**	**11 GB**	**17.6 sec**

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Method	Index size	Peak RAM	Query time
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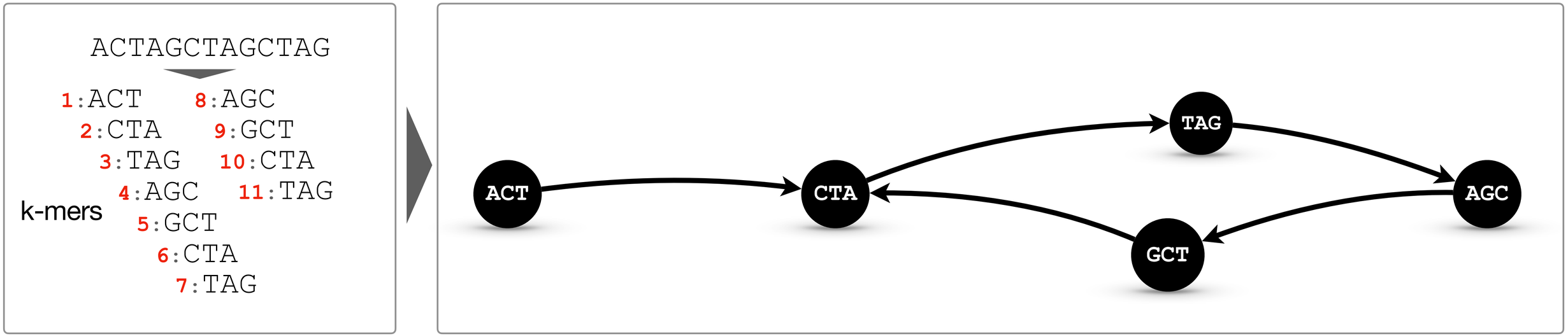
- **5x smaller** representations, uses **8x less RAM**
- **3x faster** to query

From qualitative to quantitative

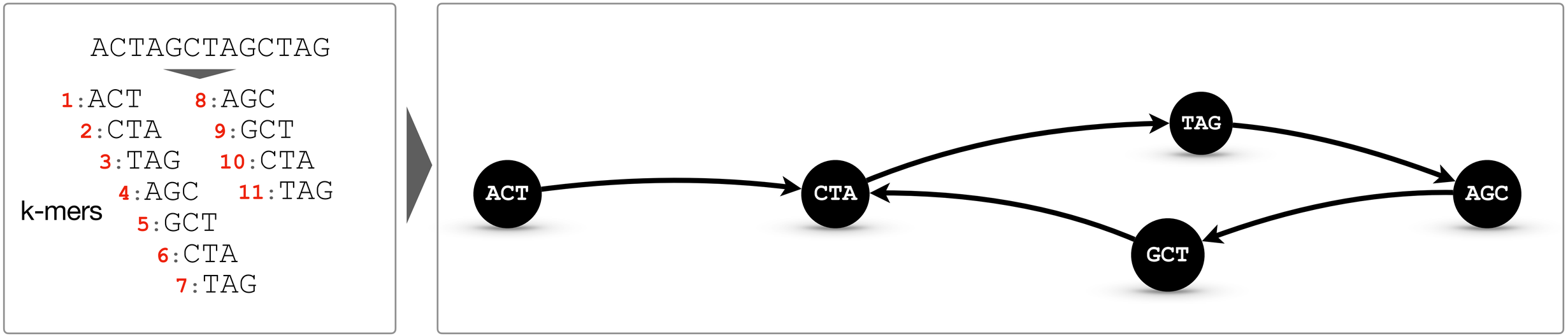
2. Representing **k-mer coordinates**



De Bruijn graph

From qualitative to quantitative

2. Representing **k-mer coordinates**

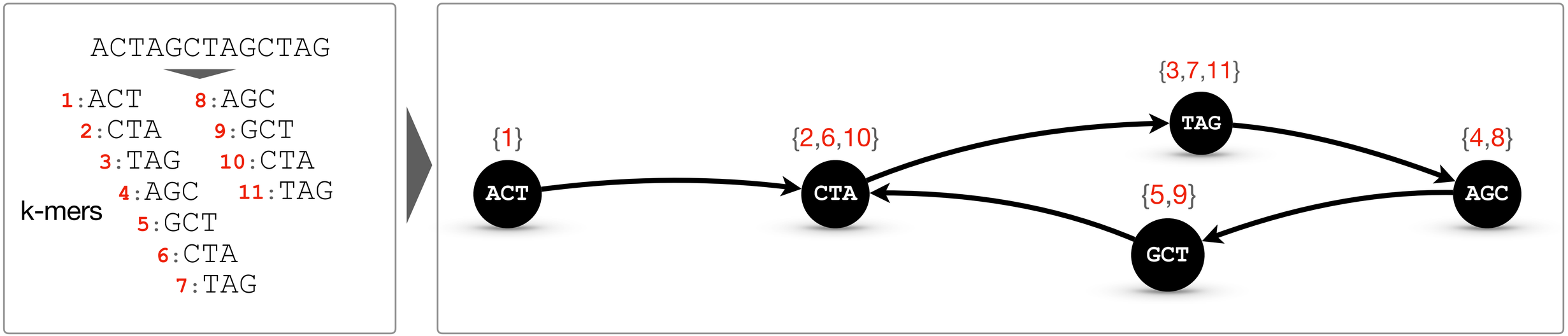


Not invertible representation

De Bruijn graph

From qualitative to quantitative

2. Representing **k-mer coordinates**



Invertible 👍

De Bruijn graph

with k-mer coordinates

From qualitative to quantitative

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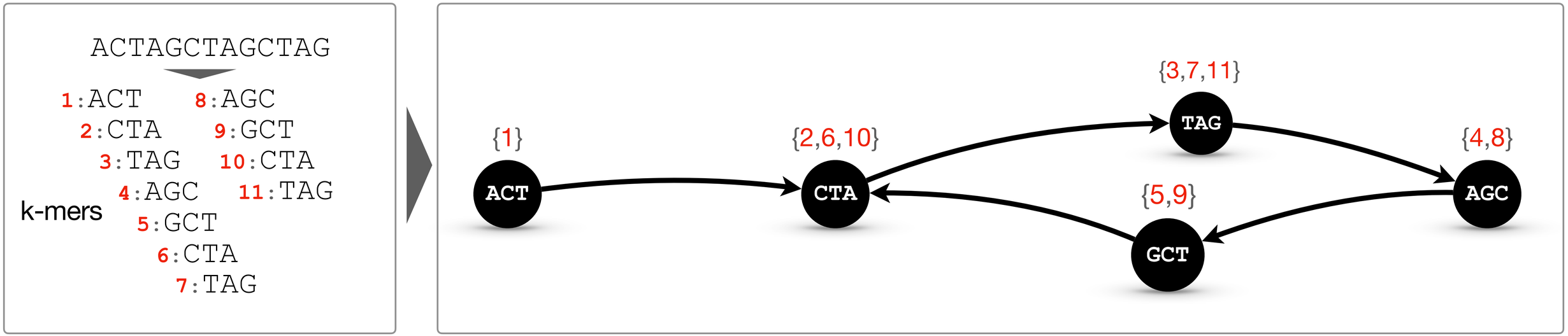

Encoding ***k-mer coordinates*** allows

- reconstructing original sequences

  (hence, **lossless sequence representation)**

De Bruijn graph

with k-mer coordinates

From qualitative to quantitative

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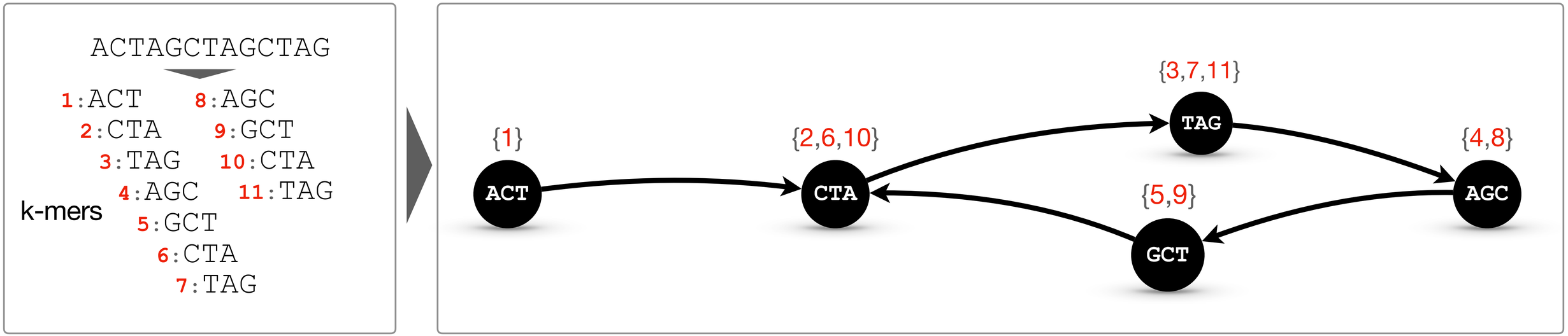

Encoding ***k-mer coordinates*** allows

- reconstructing original sequences
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- performing exact sequence alignment

De Bruijn graph

with k-mer coordinates

From qualitative to quantitative

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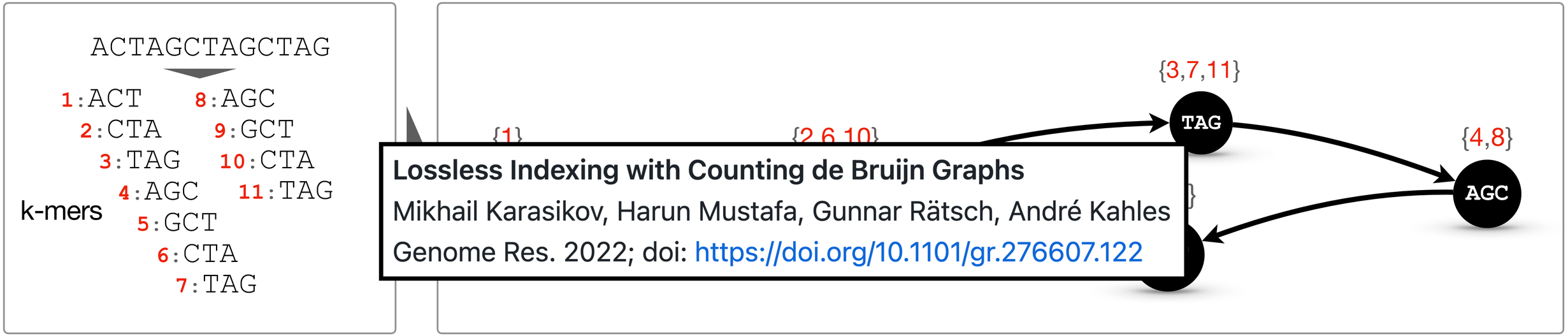

Encoding ***k-mer coordinates*** allows

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  (hence, **lossless sequence representation)**
- performing exact sequence alignment

De Bruijn graph

with k-mer coordinates

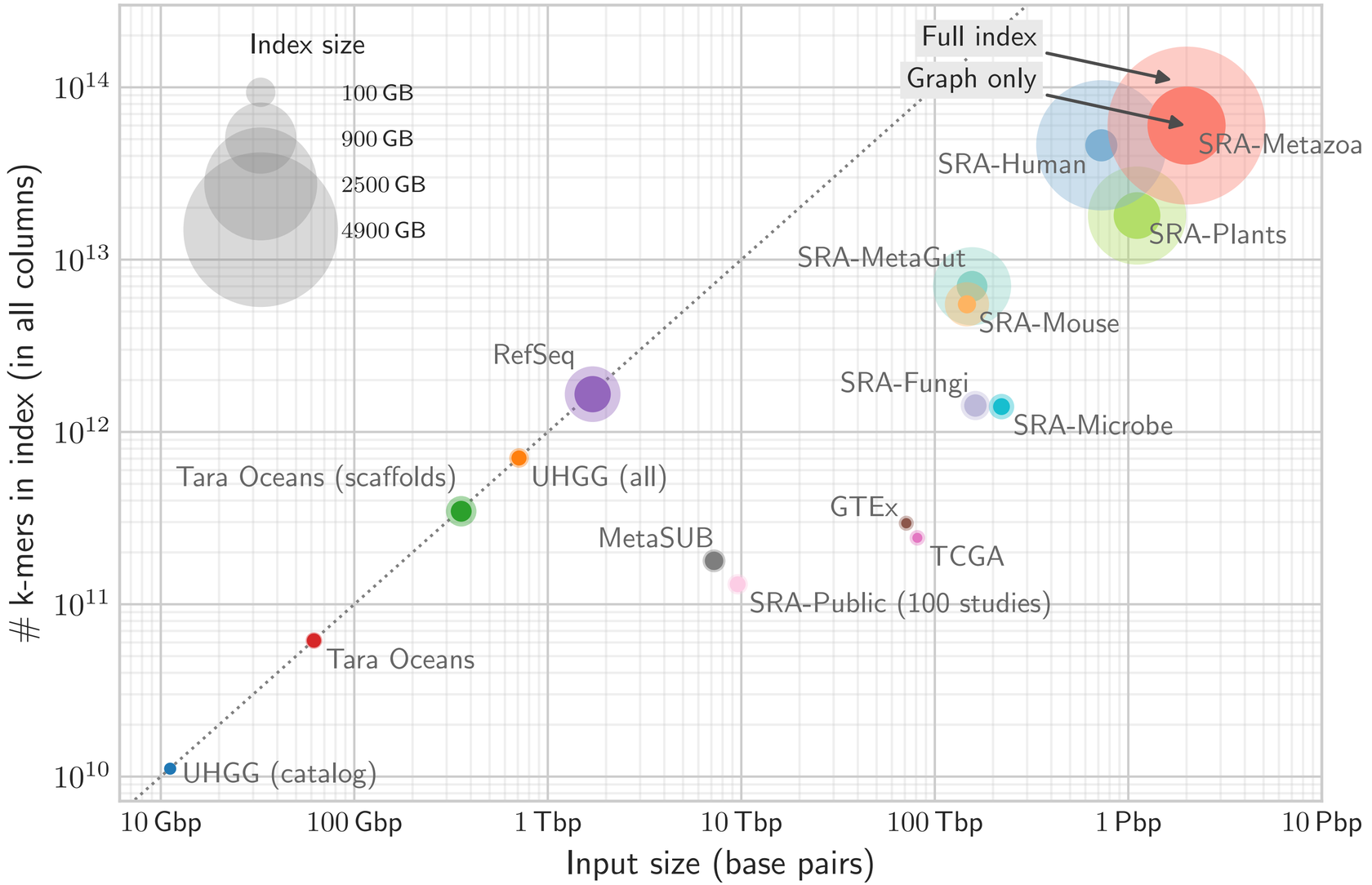
Indexing large sequence archives

Indexing at Petabase-scale

MetaGraph: Indexing and Analysing Nucleotide Archives at Petabase-scale

Mikhail Karasikov, Harun Mustafa, Daniel Danciu, Marc Zimmermann, Christopher Barber, Gunnar Rätsch, André Kahles

doi: https://doi.org/10.1101/2020.10.01.322164



Datasets: UHGG (Almeida *et al.*, 2020), Tara Oceans (Paoli, 2022), GTEx (Lonsdale *et al.*, 2013), TCGA (Kaiser, 2005), MetaSUB (Danko *et al.*, 2019), SRA-Microbe (Bradley *et al.*, 2019)

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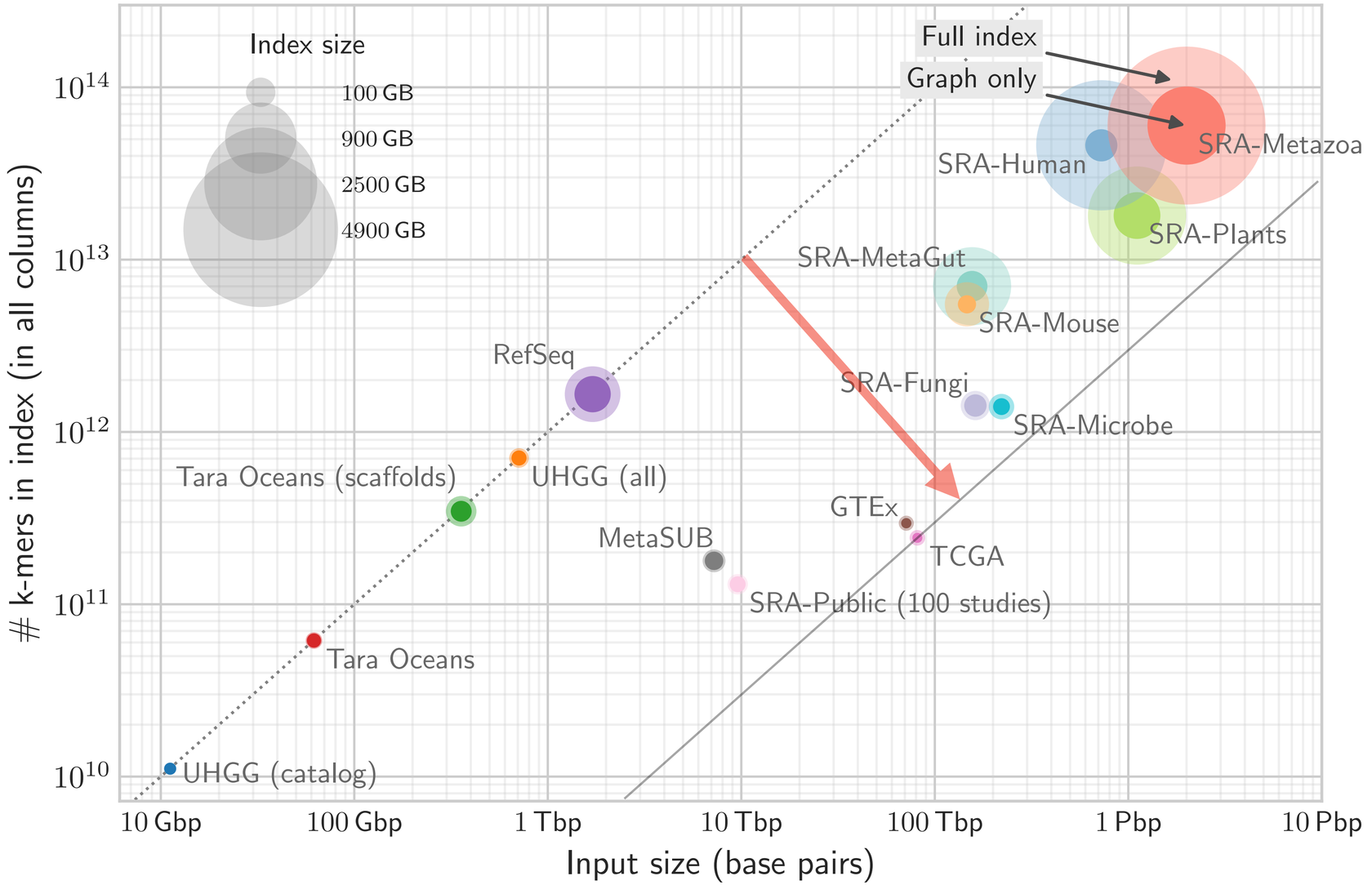

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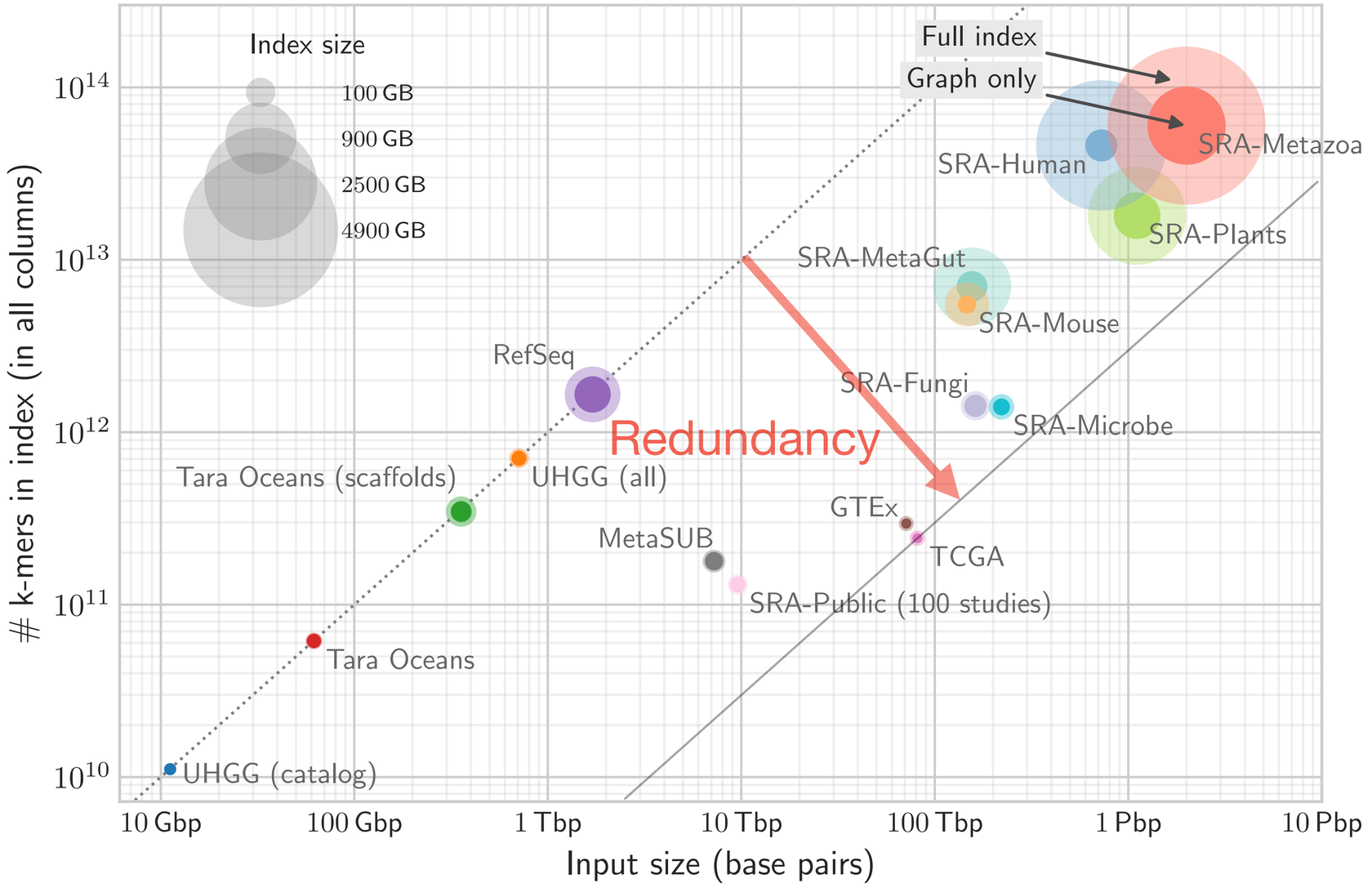

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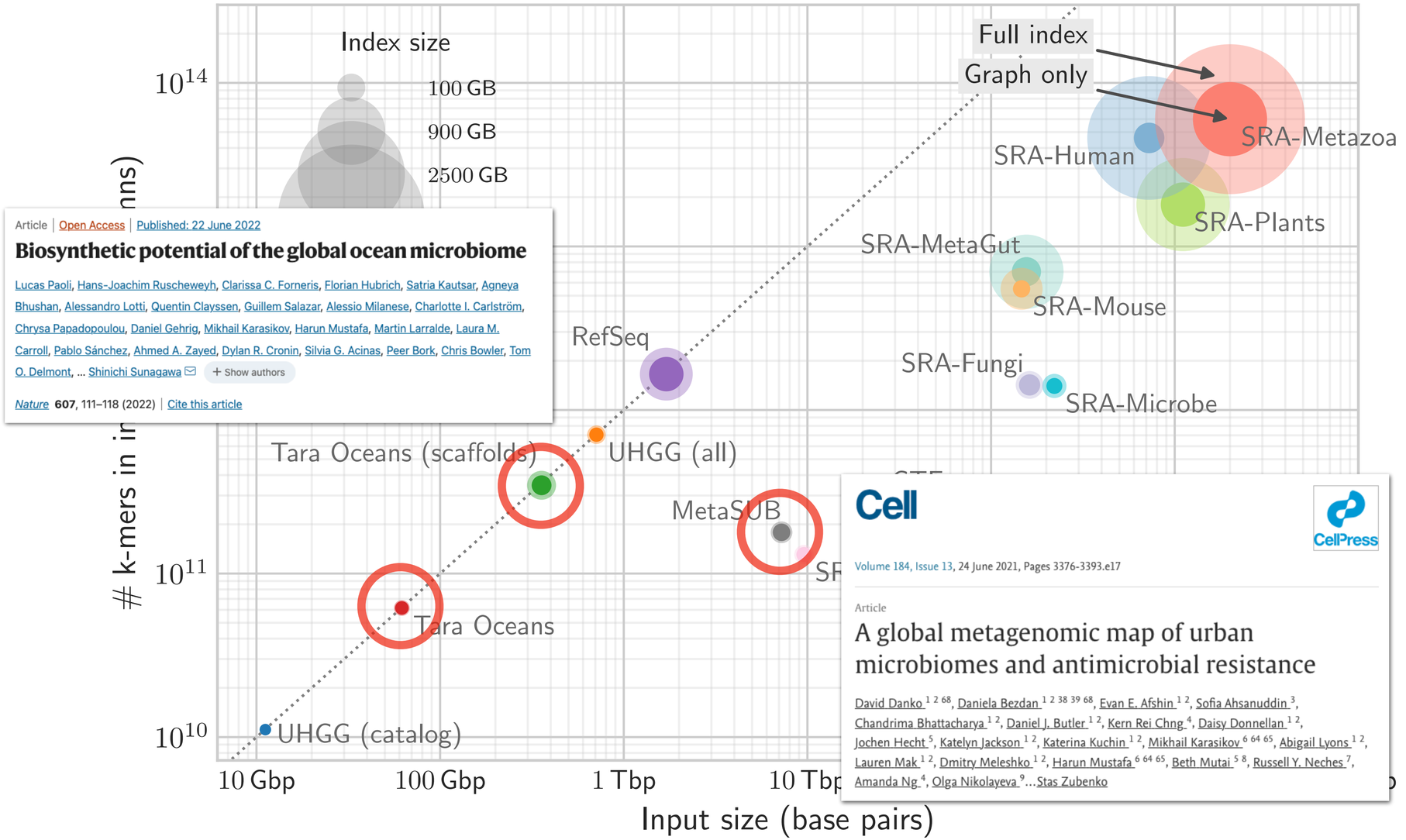

Article | Open Access | Published: 22 June 2022

Biosynthetic potential of the global ocean microbiome

Lucas Paoli, Hans-Joachim Ruscheweyh, Clarissa C. Forneris, Florian Hubrich, Satria Kautsar, Agneya Bhushan, Alessandro Lotti, Quentin Clayssen, Guillem Salazar, Alessio Milanese, Charlotte I. Carlström, Chrysa Papadopoulou, Daniel Gehrig, Mikhail Karasikov, Harun Mustafa, Martin Larralde, Laura M. Carroll, Pablo Sánchez, Ahmed A. Zayed, Dylan R. Cronin, Silvia G. Acinas, Peer Bork, Chris Bowler, Tom O. Delmont, ... Shinichi Sunagawa + Show authors

Nature **607**, 111–118 (2022) | Cite this article

Cell

CellPress

Volume 184, Issue 13, 24 June 2021, Pages 3376-3393.e17

Article

A global metagenomic map of urban microbiomes and antimicrobial resistance

David Danko [1 2 68], Daniela Bezdan [1 2 38 39 68], Evan E. Afshin [1 2], Sofia Ahsanuddin [3], Chandrima Bhattacharya [1 2], Daniel J. Butler [1 2], Kern Rei Chng [4], Daisy Donnellan [1 2], Jochen Hecht [5], Katelyn Jackson [1 2], Katerina Kuchin [1 2], Mikhail Karasikov [6 64 65], Abigail Lyons [1 2], Lauren Mak [1 2], Dmitry Meleshko [1 2], Harun Mustafa [6 64 65], Beth Mutai [5 8], Russell Y. Neches [7], Amanda Ng [4], Olga Nikolayeva [9]...Stas Zubenko

Datasets: UHGG (Almeida *et al.*, 2020), Tara Oceans (Paoli, 2022), GTEx (Lonsdale *et al.*, 2013), TCGA (Kaiser, 2005), MetaSUB (Danko *et al.*, 2019), SRA-Microbe (Bradley *et al.*, 2019)

Indexing at Petabase-scale

MetaGraph: Indexing and Analysing Nucleotide Archives at Petabase-scale

Mikhail Karasikov, Harun Mustafa, Daniel Danciu, Marc Zimmermann, Christopher Barber, Gunnar Rätsch, André Kahles

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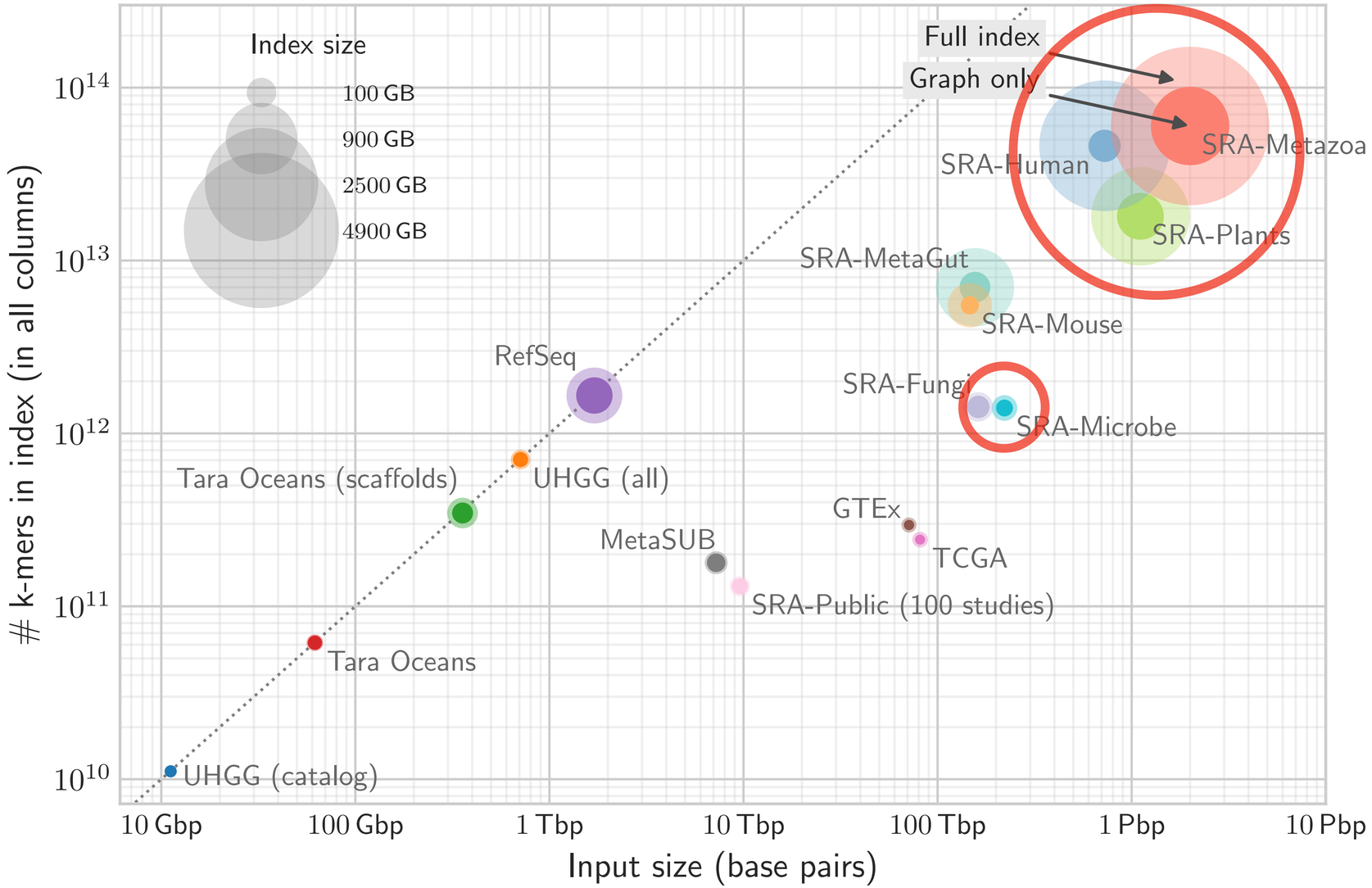

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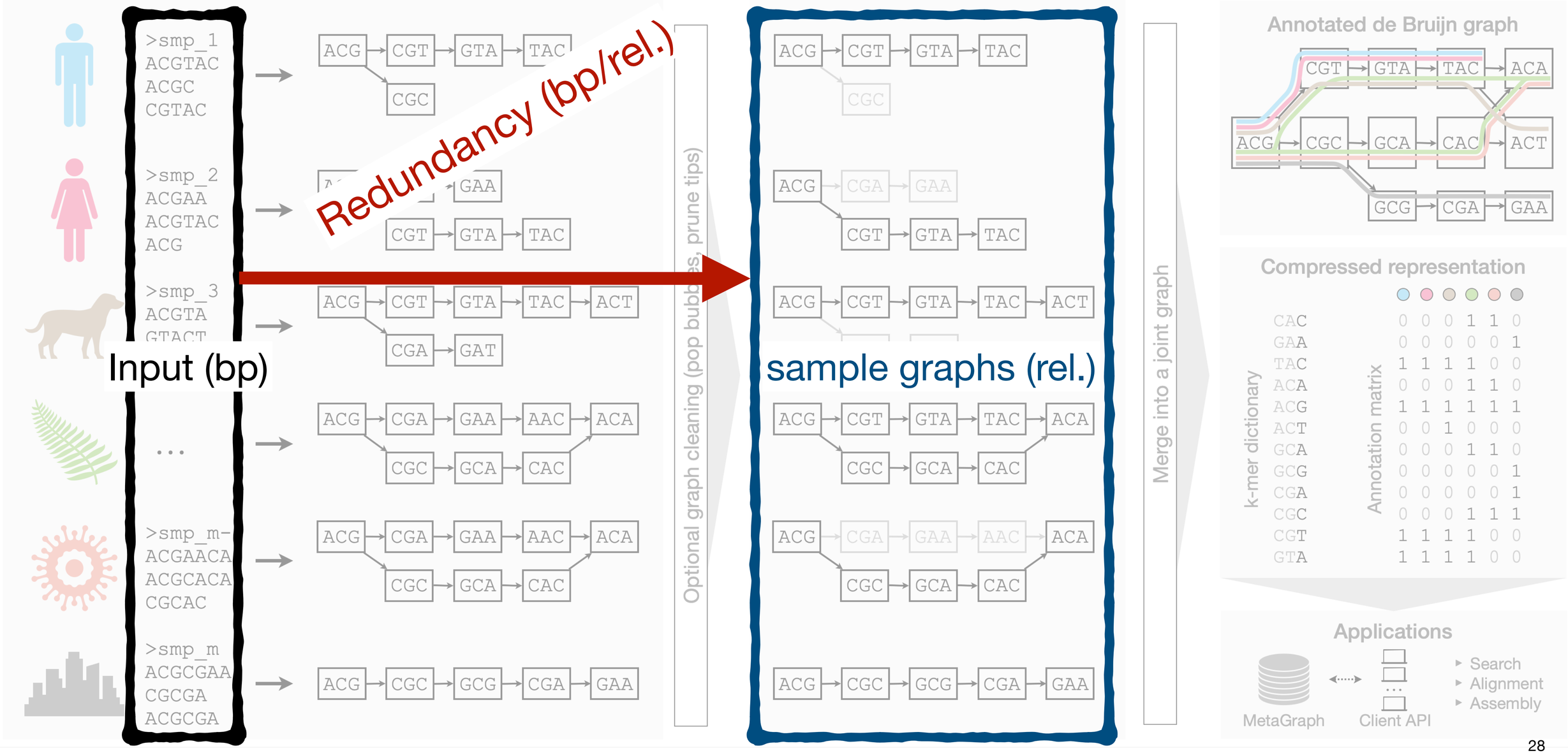

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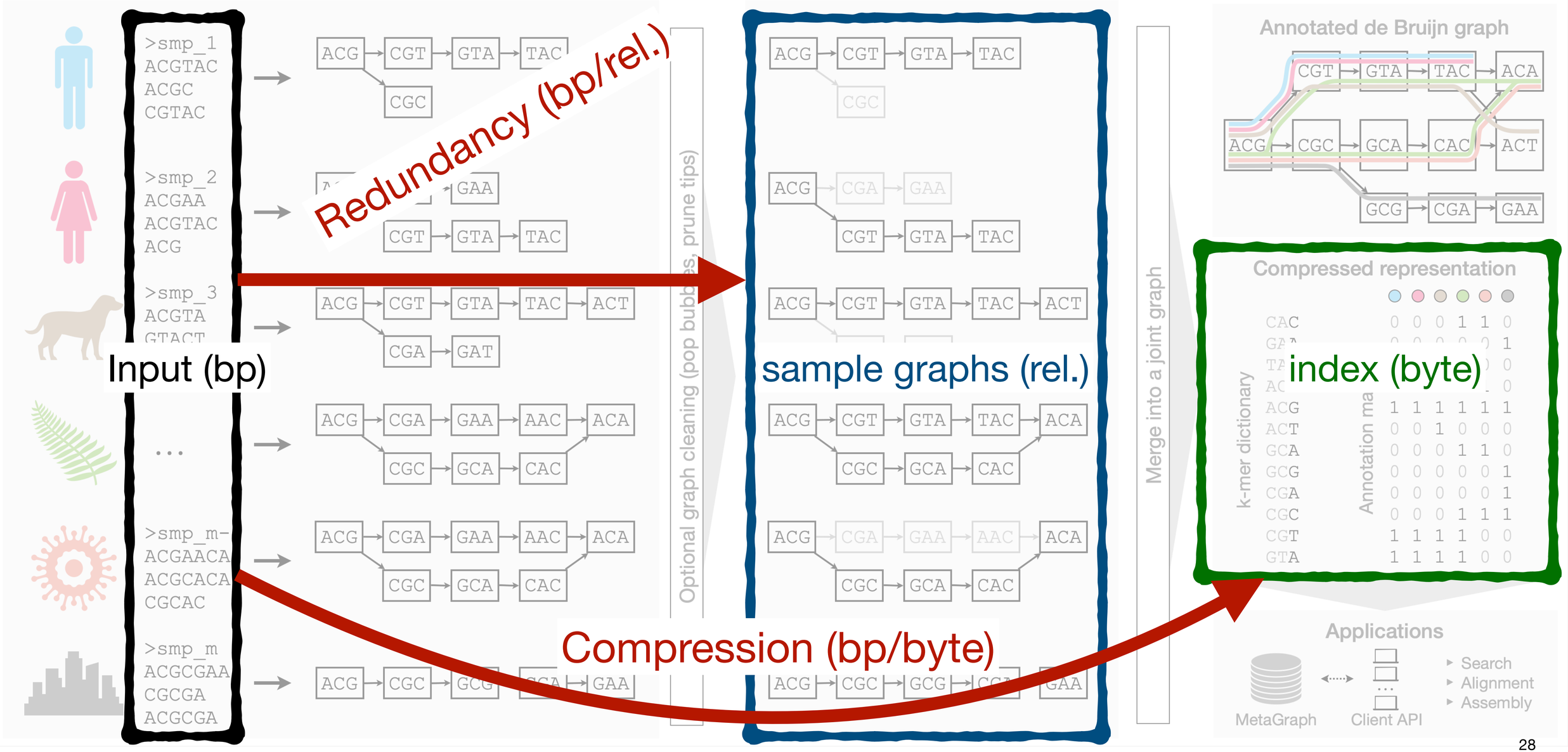

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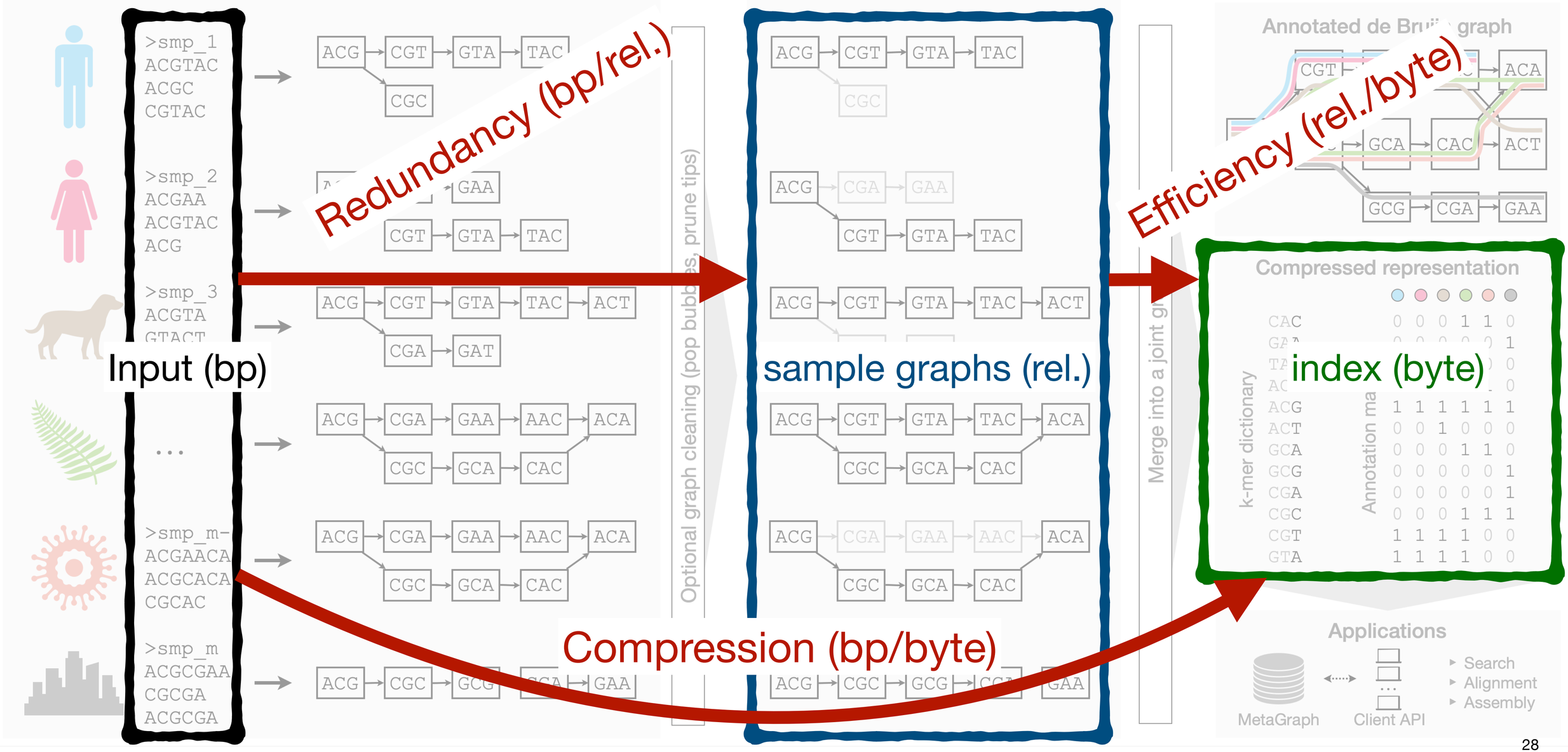

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Assembled seq.	UHGG (catalog)	0.01	4,644	3.2 GB	3.5	1.0	3.5
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	SRA-Plants	1,109.2	531,714	1,844.1 GB	602	61.5	9.8
	SRA-Human	725.4	436,494	3,402.1 GB	213	15.7	13.5
	SRA-Metazoa (Mouse)	146.6	57,938	291.6 GB	503	26.6	18.9
	SRA-Metazoa (1k studies)	118.8	67,391	302.7 GB	393	33.5	11.7
	SRA-Metazoa	1,999.5	805,239	5.1 TB*	390*	33.3	11.7*

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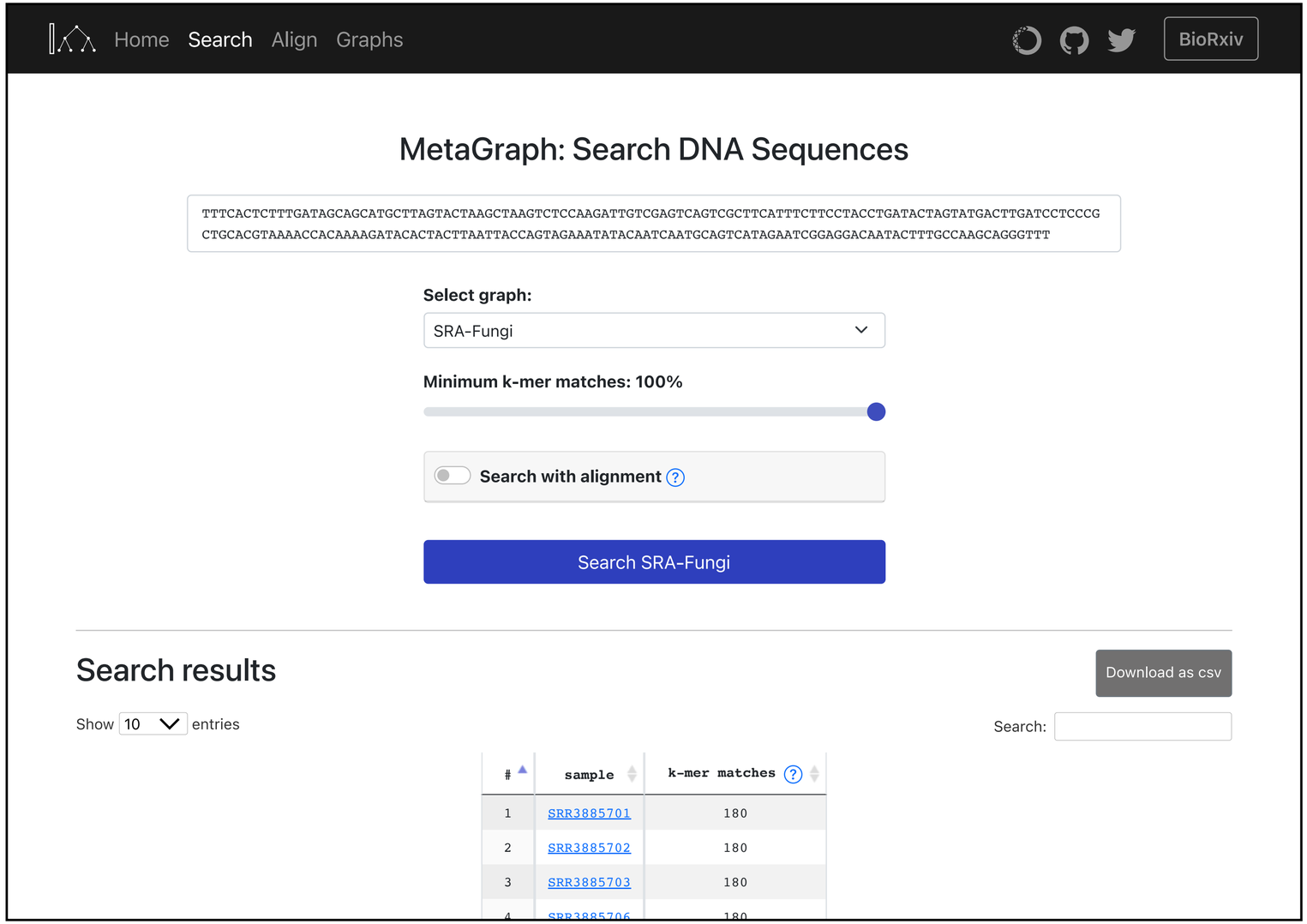
  - effective query cost for SRA-Public (23M samples): **$2.8** per **1 Mbp** of query
  - **600x cheaper** than Serratus
  - indexing cost: only 2.2 cents per sample

MetaGraph Online



metagraph.ethz.ch/search

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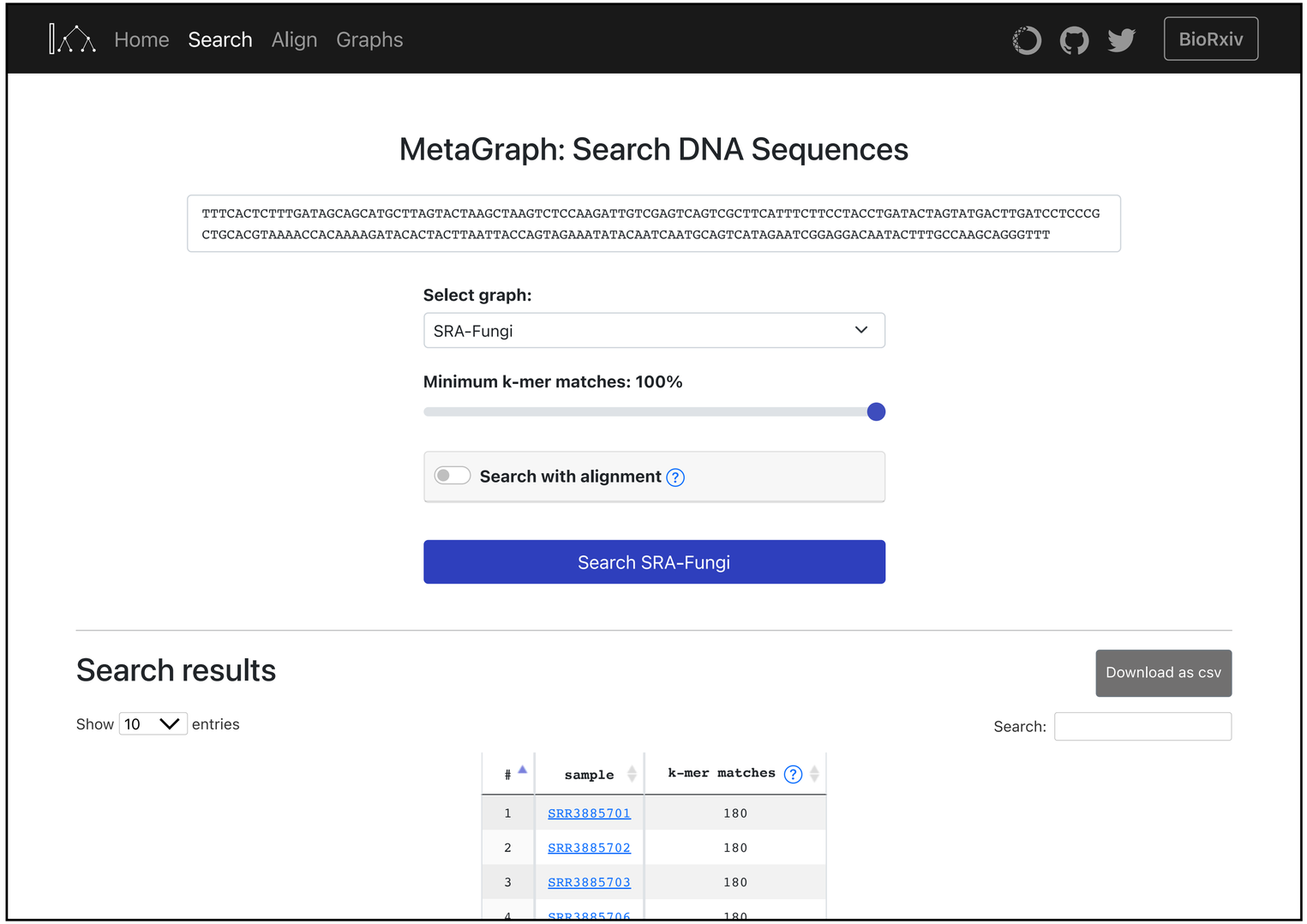

metagraph.ethz.ch/search

Python Client API

```
In [1]: from metagraph.client import GraphClient

        SRV = "metagraph.ethz.ch"
        PORT = 12345
        g1 = GraphClient(SRV, PORT, api_path="/metasub")
        g2 = GraphClient(SRV, PORT, api_path="/refseq")
```

```
In [2]: query = "GGCTAACTACGTGCCAGCAGCCGCGGTAATAC"
        g1.search(query, align=True)
```

Out [2]:

	sample	sequence	score
0	SRR2201245	GGCTAACTACGTGCCAGCAGCCGCGGTAATAC	64
1	ERR1732568	GGCTAACTACGTGCCAGCAGCCGCGGTAATAC	64
2	ERR847096	GGCTAACTACGTGCCAGCAGCCGCGGTAATAC	64
...	...	...	...

Conclusion

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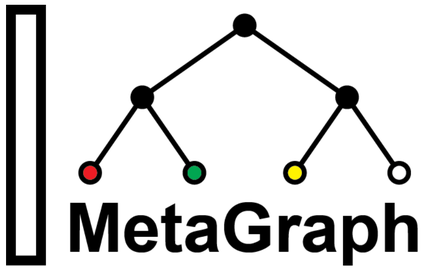

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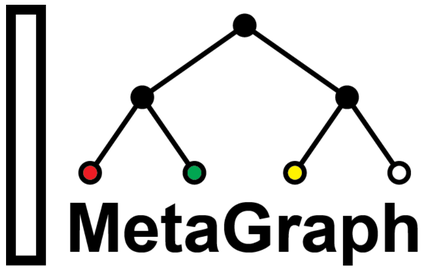

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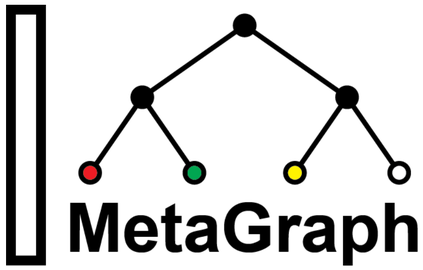

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Publications

Primary works

- Mikhail Karasikov, Harun Mustafa, Daniel Danciu, Marc Zimmermann, Christopher Barber, Gunnar Rätsch, and André Kahles. "MetaGraph: Indexing and Analysing Nucleotide Archives at Petabase-scale". In: *bioRxiv* (2020). DOI: 10.1101/2020.10.01.322164
- Mikhail Karasikov, Harun Mustafa, Gunnar Rätsch, and André Kahles. "Lossless indexing with counting de Bruijn graphs". In: *Genome Research* 32.9 (2022), pp. 1754–1764. DOI: 10.1101/gr.276607.122
- Mikhail Karasikov, Harun Mustafa, Amir Joudaki, Sara Javadzadeh-No, Gunnar Rätsch, and André Kahles. "Sparse binary relation representations for genome graph annotation". In: *Journal of Computational Biology* 27.4 (2020), pp. 626–639. DOI: 10.1089/cmb.2019.0324
- Daniel Danciu, Mikhail Karasikov, Harun Mustafa, André Kahles, and Gunnar Rätsch. "Topology-based sparsification of graph annotations". In: *Bioinformatics* 37.Supplement_1 (July 2021), pp. i169–i176. DOI: 10.1093/bioinformatics/btab330

Significant contributions

- David Danko et al. "A global metagenomic map of urban microbiomes and antimicrobial resistance". In: *Cell* 184.13 (2021), 3376–3393.e17. DOI: 10.1016/j.cell.2021.05.002
- Lucas Paoli, Hans-Joachim Ruscheweyh, Clarissa C. Forneris, Florian Hubrich, Satria Kautsar, Agneya Bhushan, Alessandro Lotti, Quentin Clayssen, Guillem Salazar, Alessio Milanese, Charlotte I. Carlström, Chrysa Papadopoulou, Daniel Gehrig, Mikhail Karasikov, Harun Mustafa, Martin Larralde, Laura M. Carroll, Pablo Sánchez, Ahmed A. Zayed, Dylan R. Cronin, Silvia G. Acinas, Peer Bork, Chris Bowler, Tom O. Delmont, Josep M. Gasol, Alvar D. Gossert, André Kahles, Matthew B. Sullivan, Patrick Wincker, Georg Zeller, Serina L. Robinson, Jörn Piel, and Shinichi Sunagawa. "Biosynthetic potential of the global ocean microbiome". In: *Nature* 607.7917 (2022), pp. 111–118. DOI: 10.1038/s41586-022-04862-3
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Outreach

Conferences

Talks:

- RECOMB 2019 (Washington, DC, USA) — presented by HM
- ISMB/ECCB 2021, HiTSeq COSI (online)
- RECOMB 2022 (La Jolla, California, USA)
- IGGSy 2022 (Ascona, Switzerland)
- JOBIM 2022 (Rennes, France) — **invited talk**

Poster:

- Biological Data Science - CSHL Meeting 2022 (Cold Spring Harbor, New York, USA)

Other talks

- MLSS 2020 (online)
- Zurich Seminars in Bioinformatics 2022 (Zurich, Switzerland)

Collaborations

- Tara Oceans (Sunagawa lab)
- **MetaSUB consortia** (C. Mason)
- Differential assembly (M. Huber)

Possible future applications

- Detection/confirmation of
  - novel splice junctions
  - **trans-splice junctions**
  - genomic variants (incl. structural variants)
  - novel sequence elements
  - gene fusions
  - phages in metagenomes
  - novel functional elements in metagenomes
  - pathogen pervasiveness (e.g. SARS CoV-II)
- Differential assembly
- Joint variant calling
- Large association studies on sequence elements

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