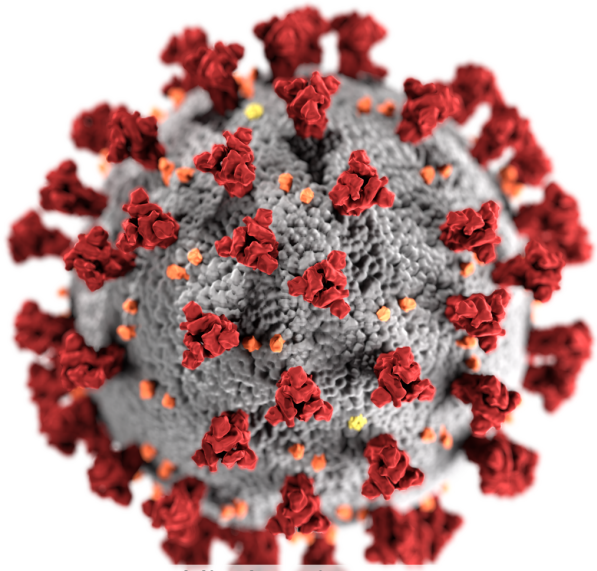
Compressed indexing of (ultra) large viral alignments

M. Salson, T. Baudeau, A. Boddaert, A. B. Gueye, L. Bulteau,
Y. Hernandez--Courbevoie, C. Marchet, N. Pan, S. Will, Y. Ponty

Characterising SARS-CoV-2 RNA structure



Public domain CDC

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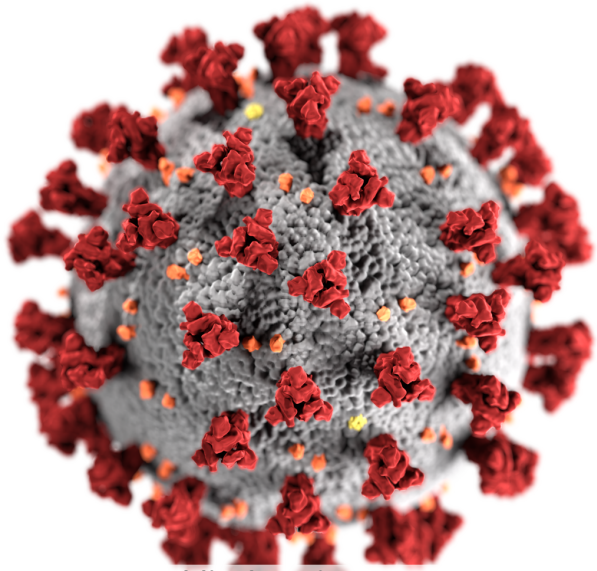

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RNA virus
30 kbp genome

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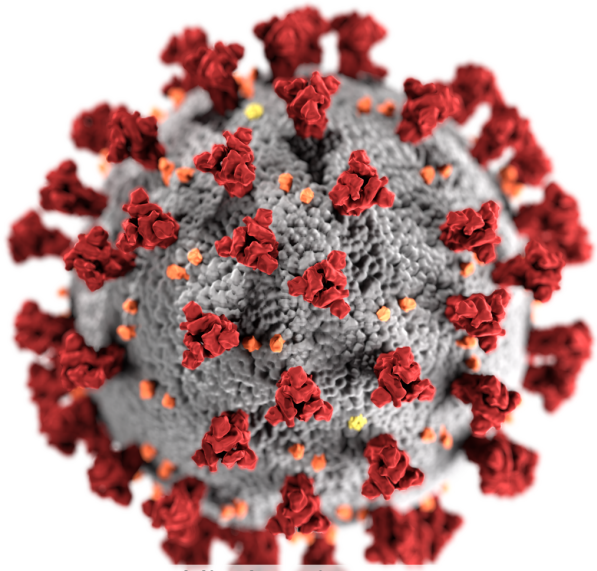

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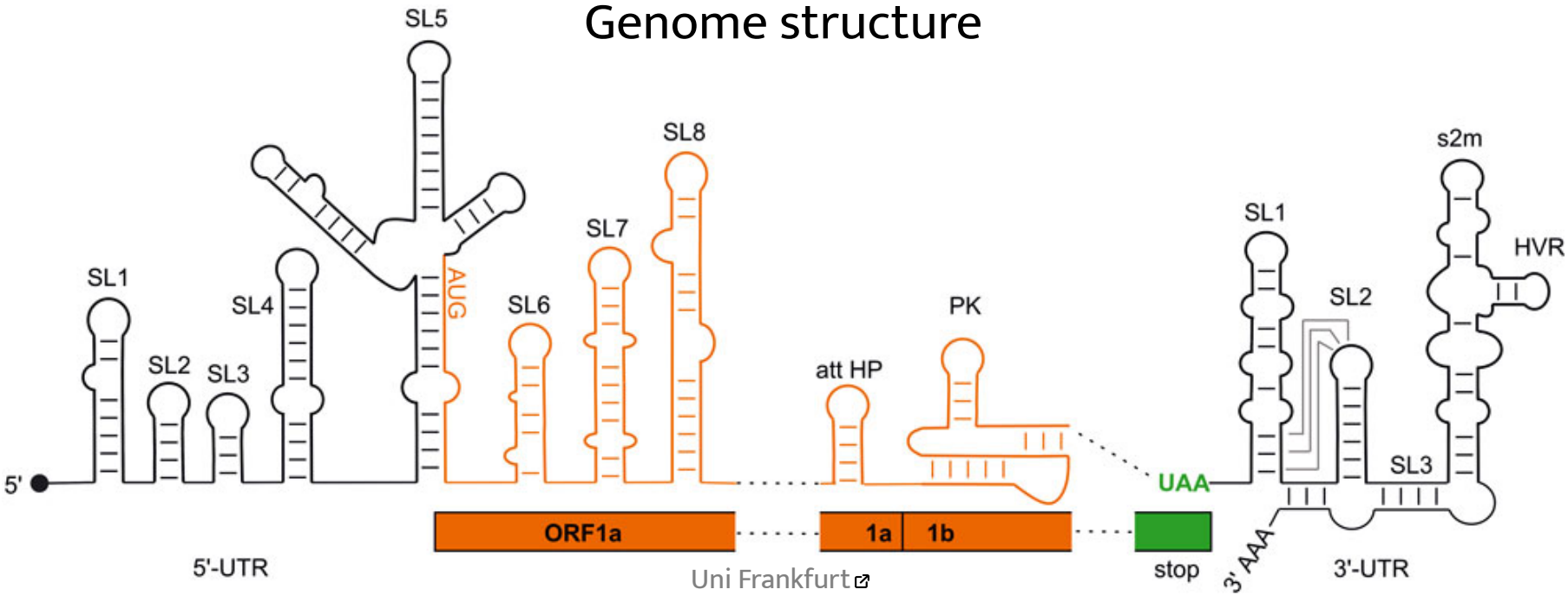
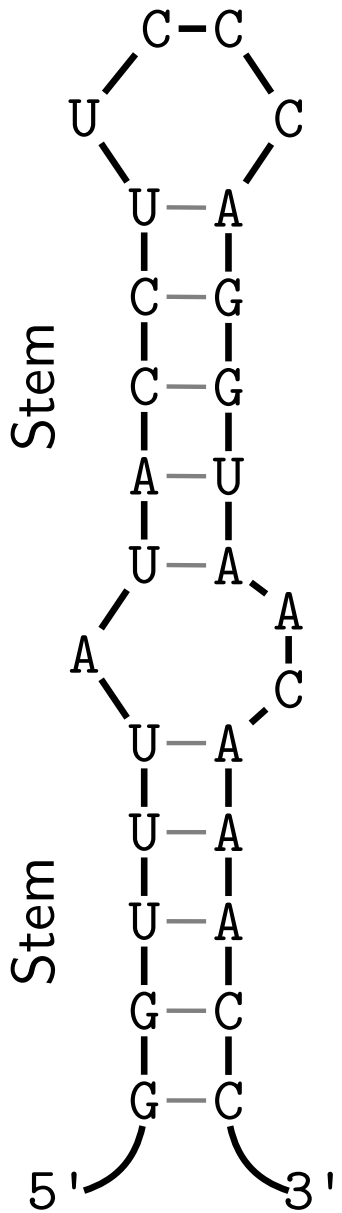
RNA virus
30 kbp genome

Genome structure



Uni Frankfurt

Covariations are a clue to identify stems



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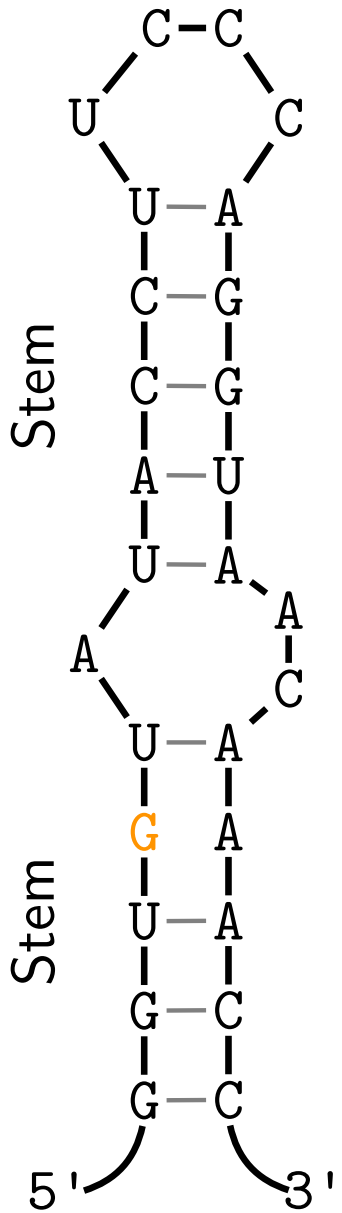

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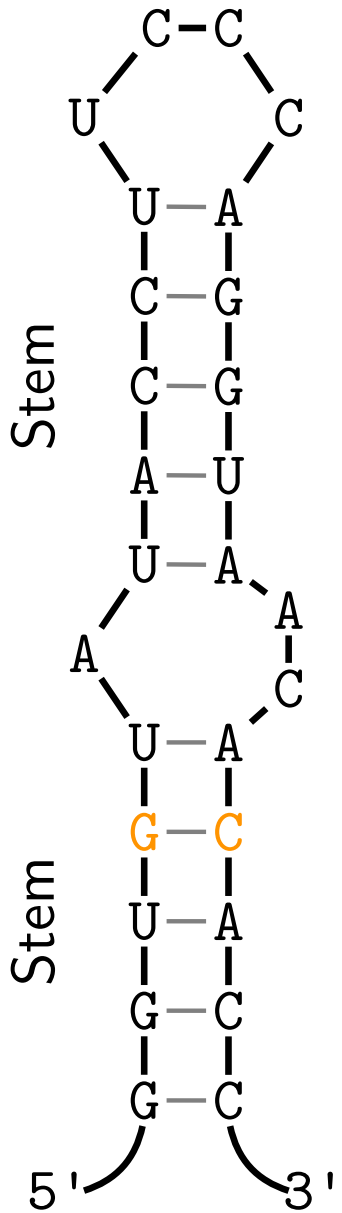

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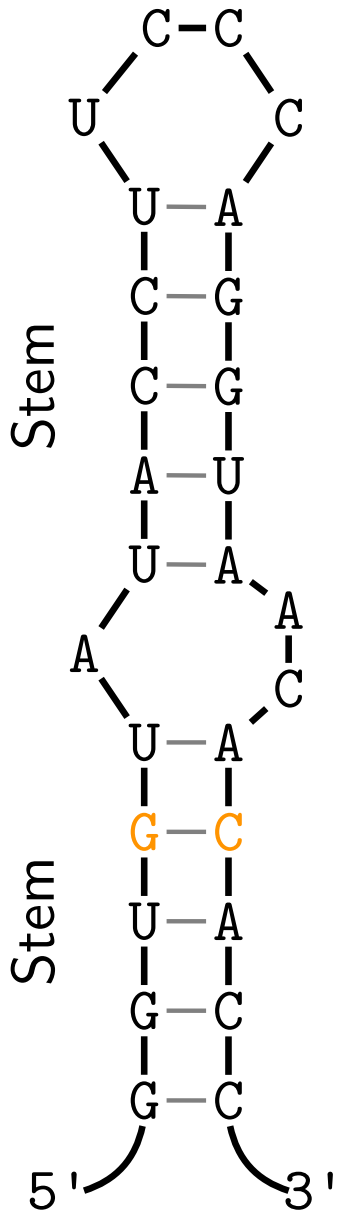

GGUUUAUACCUUCCCAGGUAACAAACC

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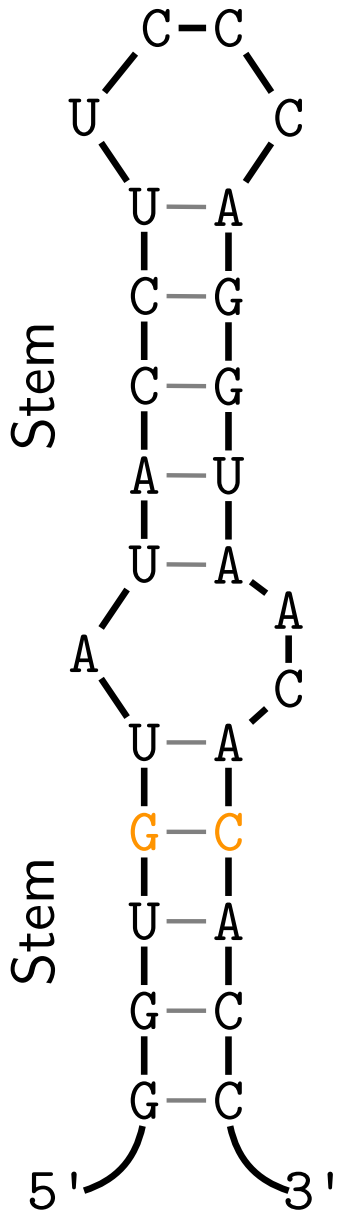

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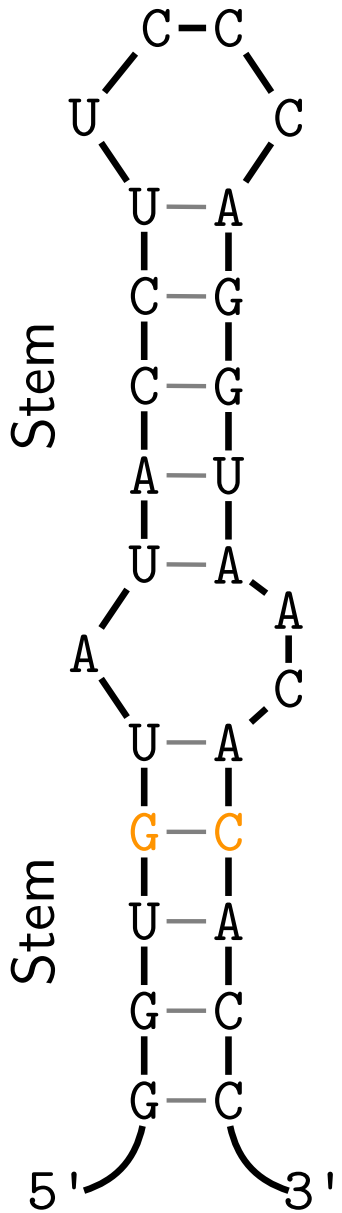

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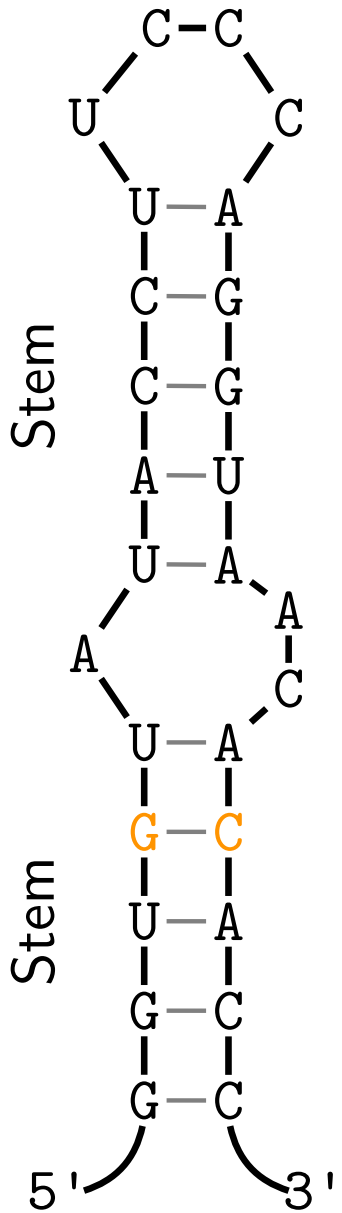

GGUUUAUACCUUCGCAGGUAACAAACC
GGUGUAUACCUUCCCAGGUAACACACC
GGUUUAUACCUUCCCAGGUAACAAACC
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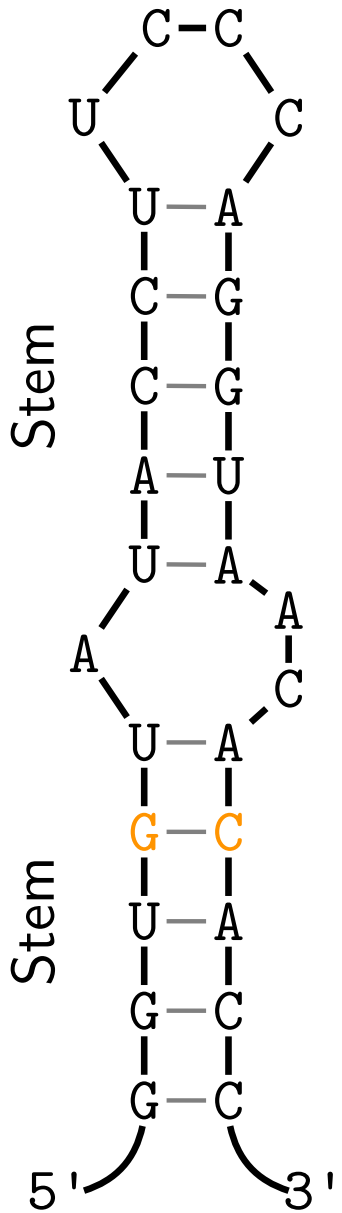


```
GGUUUAUACCUUCGCAGGUAACAAACC
GGUGUAUACCUUCCCAGGUAACACACC
GGUUUAUACCUUCCCAGGUAACAAACC
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```

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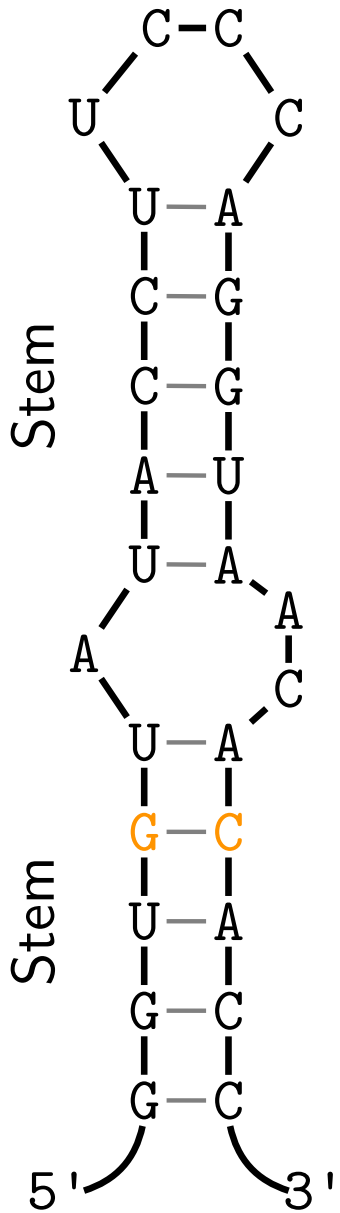

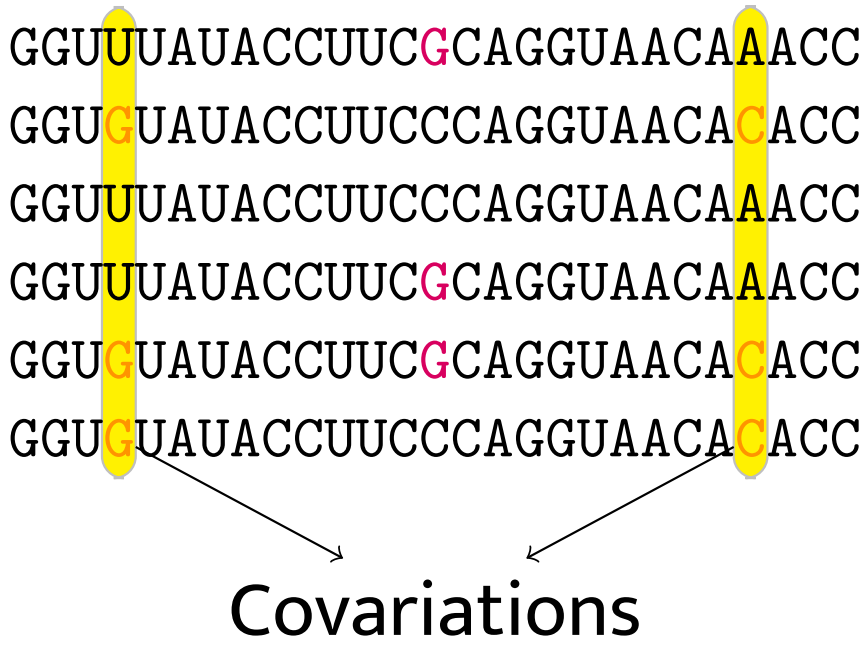

Identifying covariations through conservation scores

U	A
G	C
U	A
U	A
G	C
G	C

6 compatible pairs

U	A
G	A
G	A
U	C
G	C
U	C

2 compatible pairs

The conservation score of a pair of columns depends on the number of compatible pairs

See RNAalifold (Bernhart et al, 2008)

With n columns of size s, this could be computed in $\Theta(sn^2)$

Lots of data to identify covariations in SARS-CoV-2

3,079,138

genomes

On NCBI Virus, as of 26 Nov 2024

Awesome! But that's quite a MSA...

Assuming we can build it...

Computing conservations scores on millions of genomes

Let's assume we have a MSA of 1M SARS-CoV-2

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  $\rightarrow$ 450 M pairs of columns

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- That's 30k columns of 1Mbp
- We need to consider every pair of columns
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More generally, getting any kind of information from a 1Mbp column is inefficient

A self-index for multiple sequence alignement (MSA)

GGUUUAUACCUUCGCAGGUAACAAACC
GGUGUAUACCUUCCCAGGUAACACACC
GGUUUAUACCUUCCCAGGUAACAAACC
GGUUUAUACCUUCGCAGGUAACAAACC
GGUGUAUACCUUCGCAGGUAACACACC
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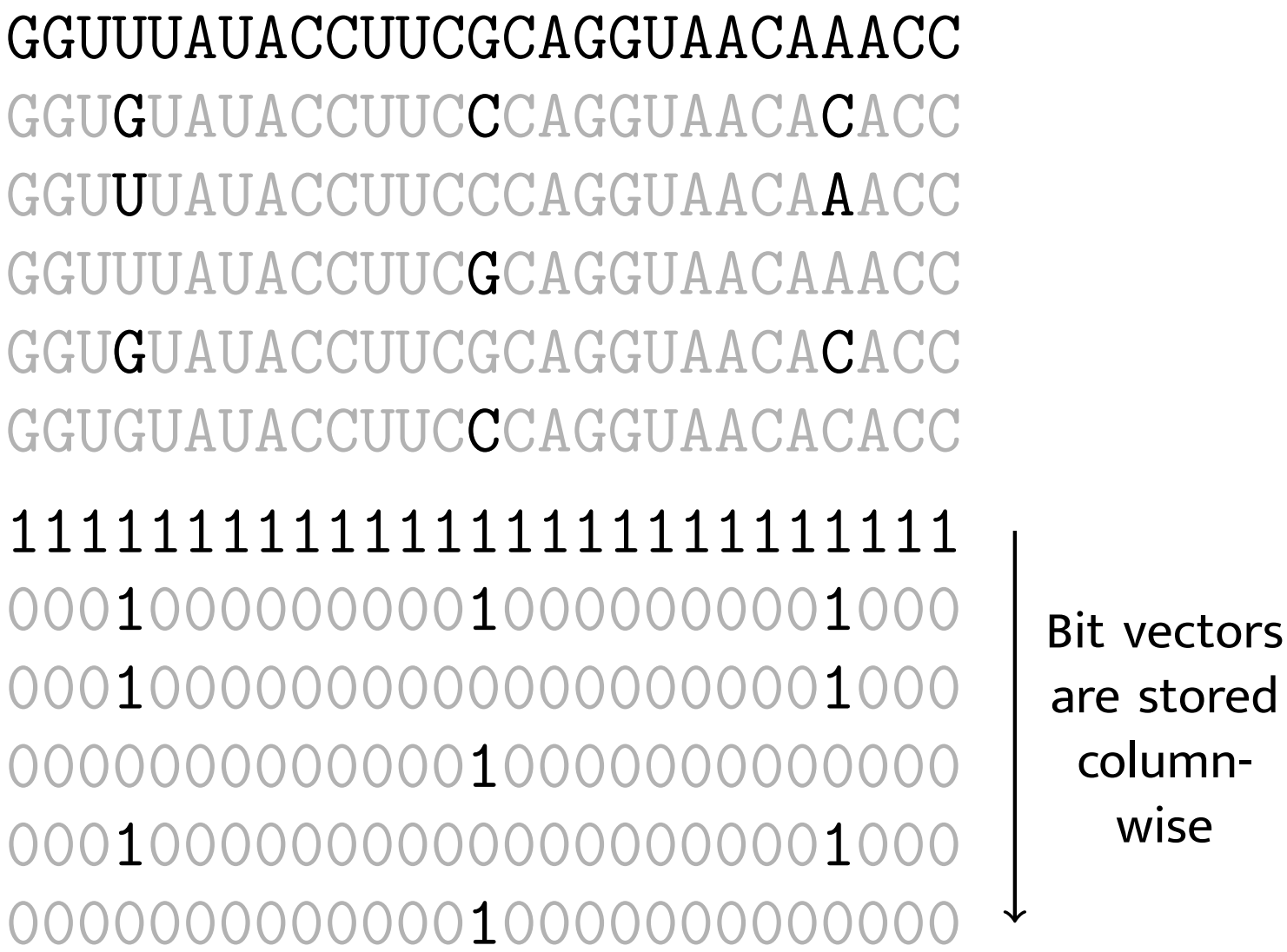

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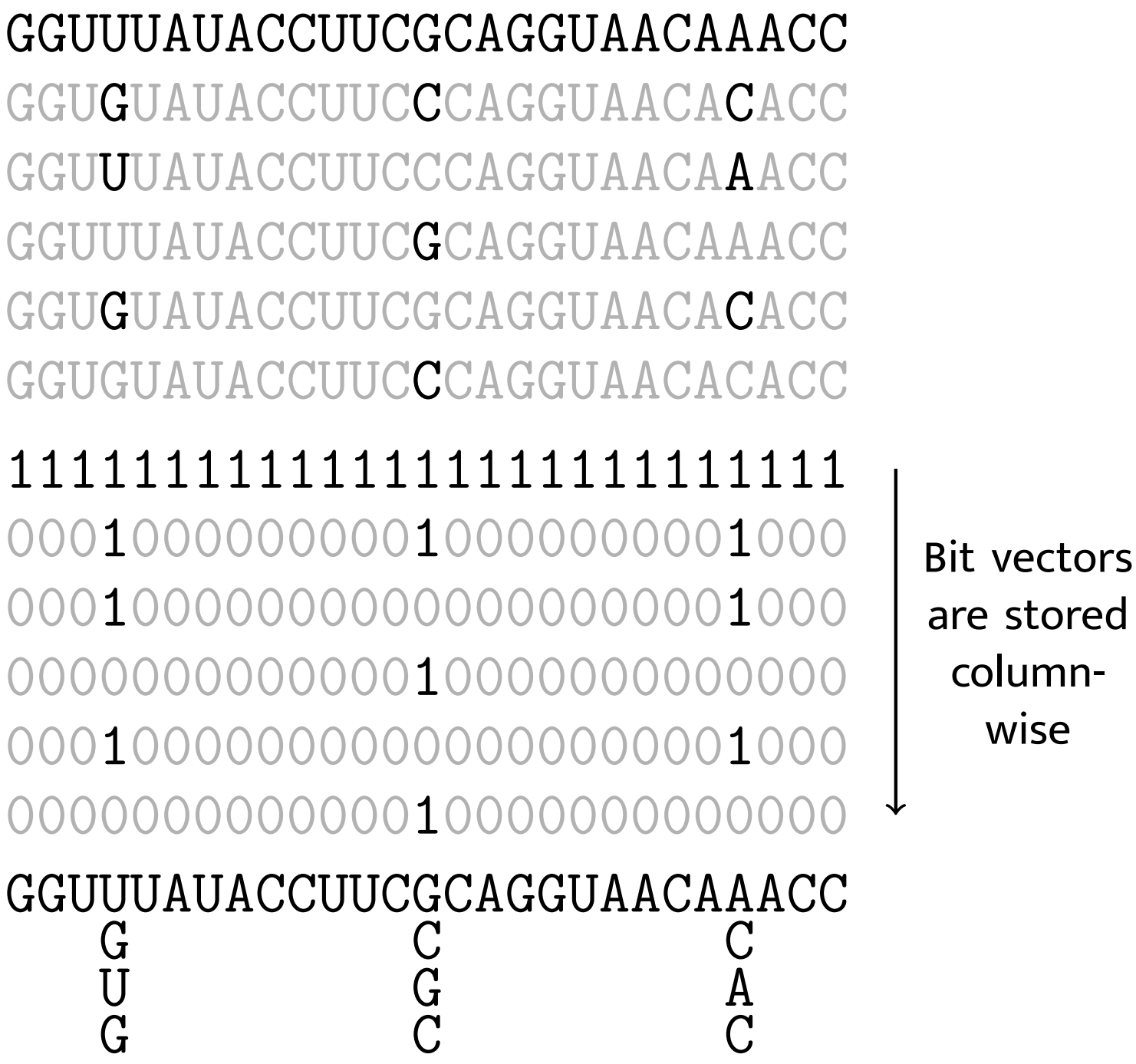

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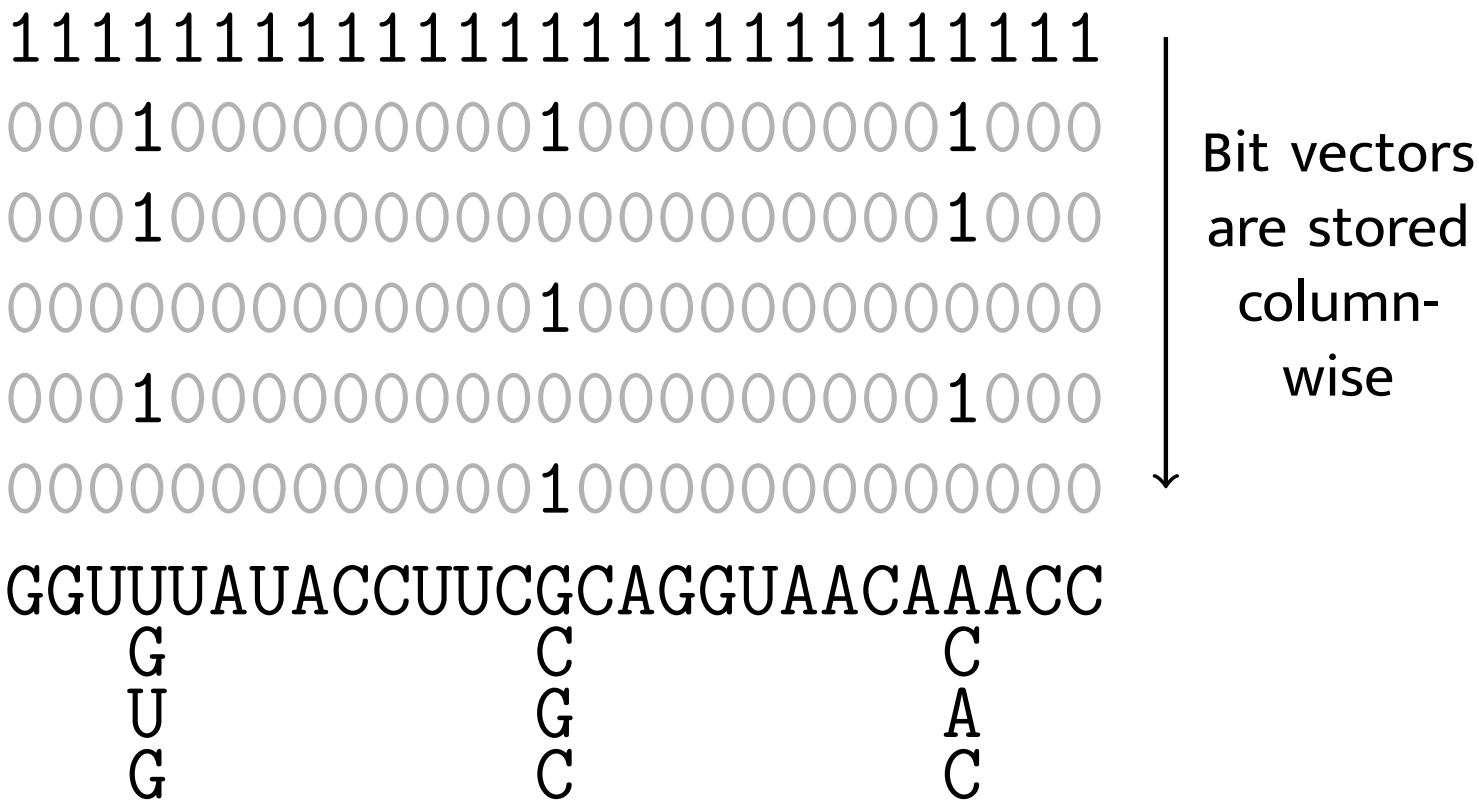
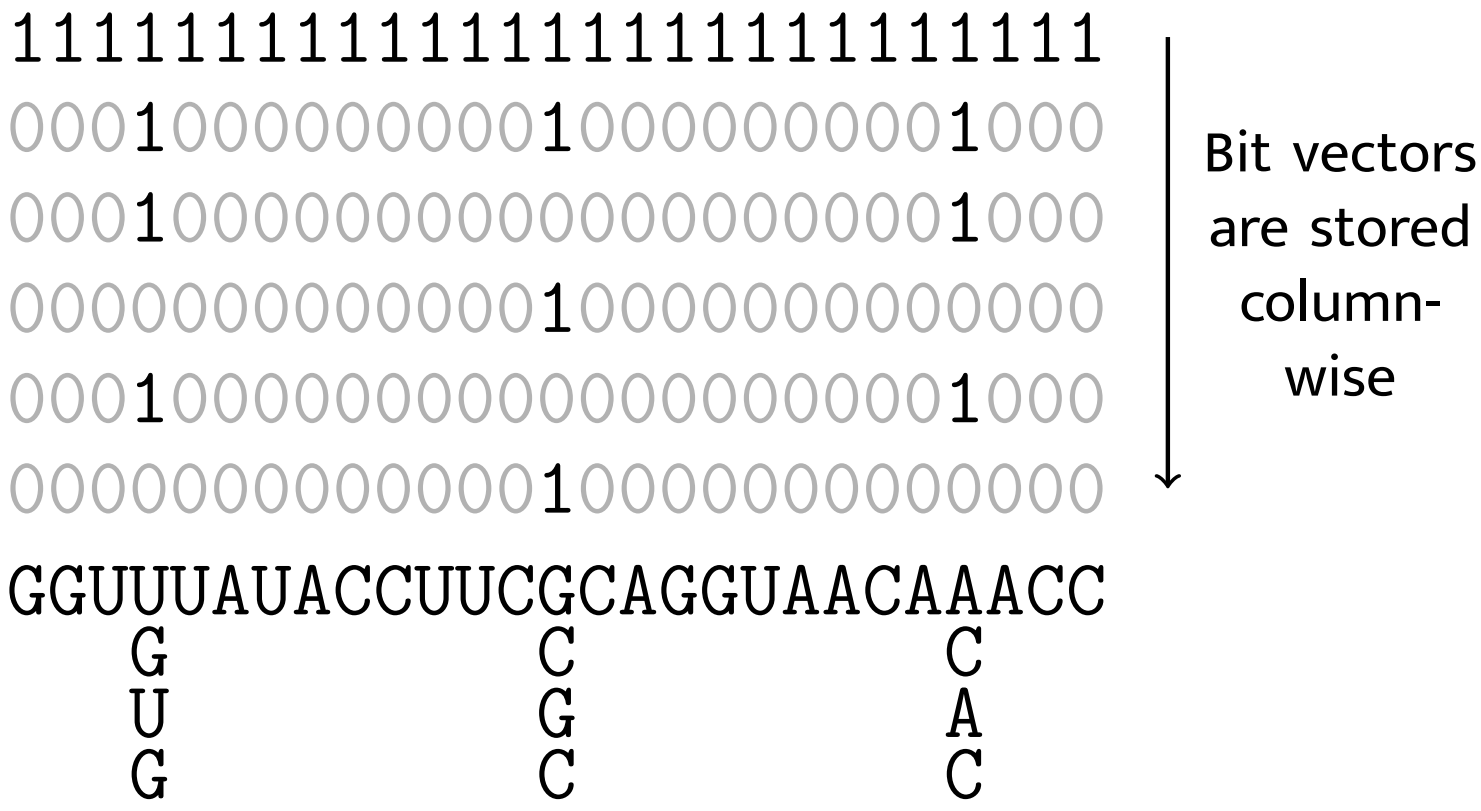


A self-index for multiple sequence alignement (MSA)

r_i : number of runs of an identical letter in column i of the MSA

r_i: number of 1s in the bit vector of column i



A self-index for multiple sequence alignement (MSA)

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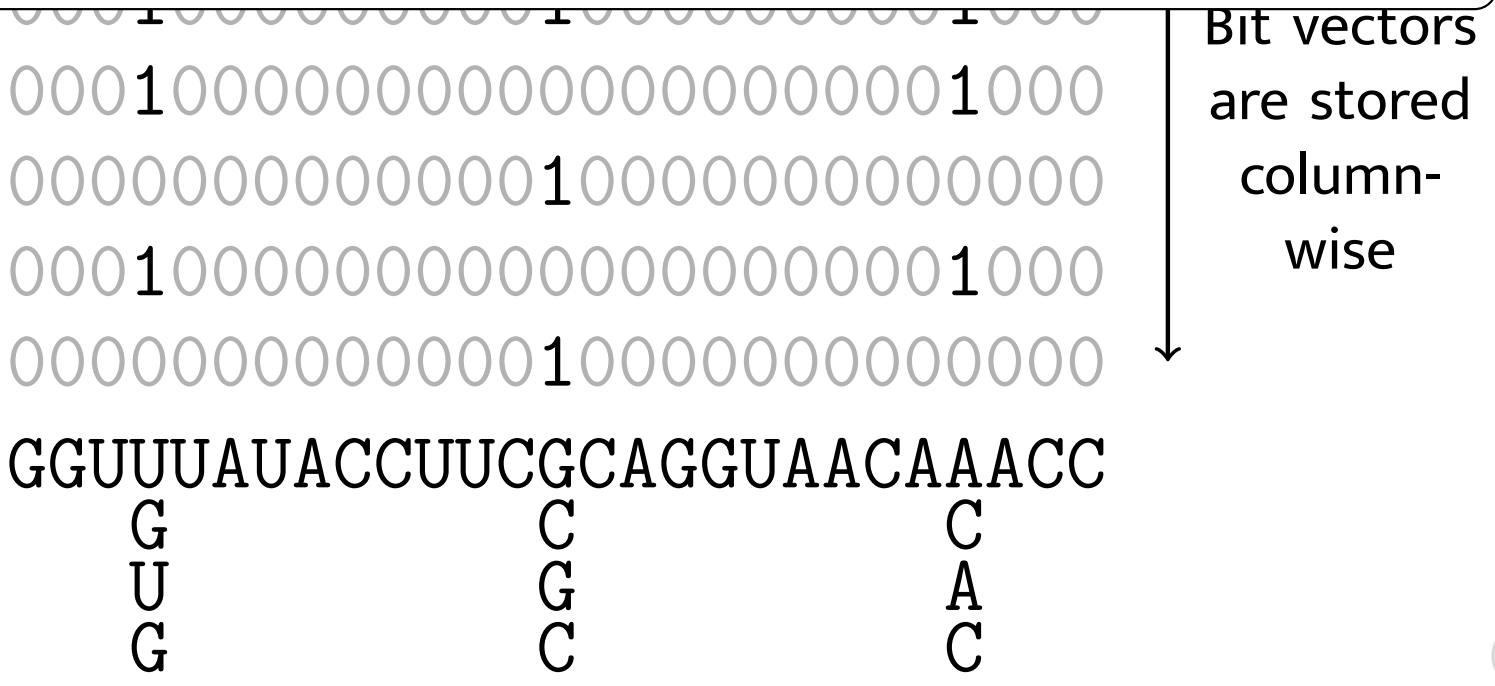
The fewer runs, the more we compress



`rank` and `select` for querying our self-index for MSA

`rank`/`select` are fundamental operations on bit vectors

`rank`(B, i): nb of 1s in $B[O \ldots i]$
`select`(B, i): position of the i-th 1 in B

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1

0

0

0

1

0

1

0

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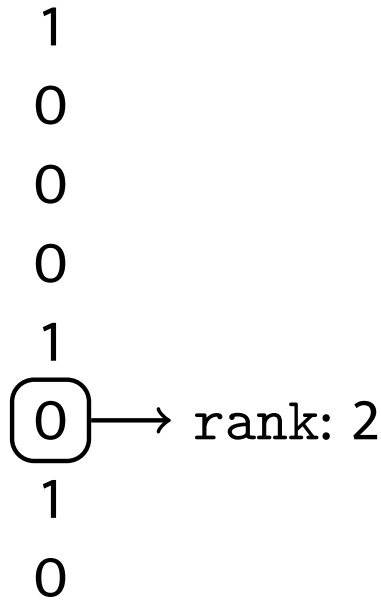

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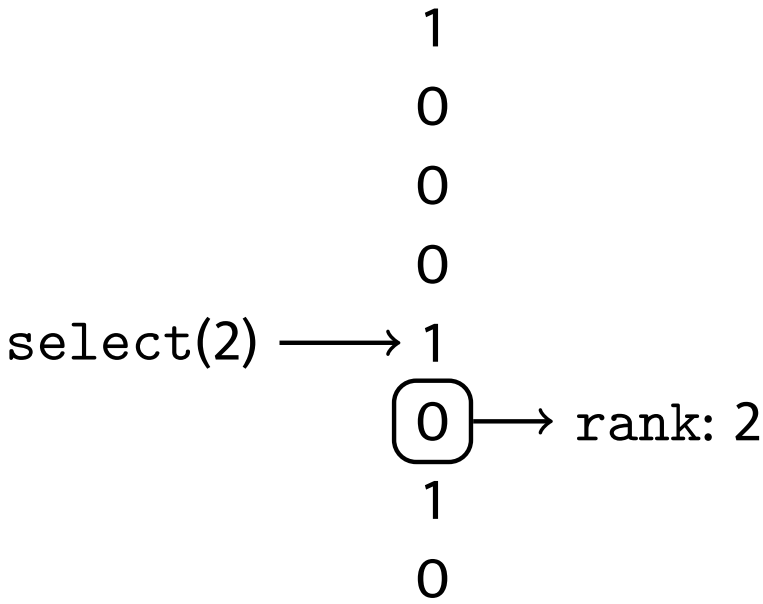

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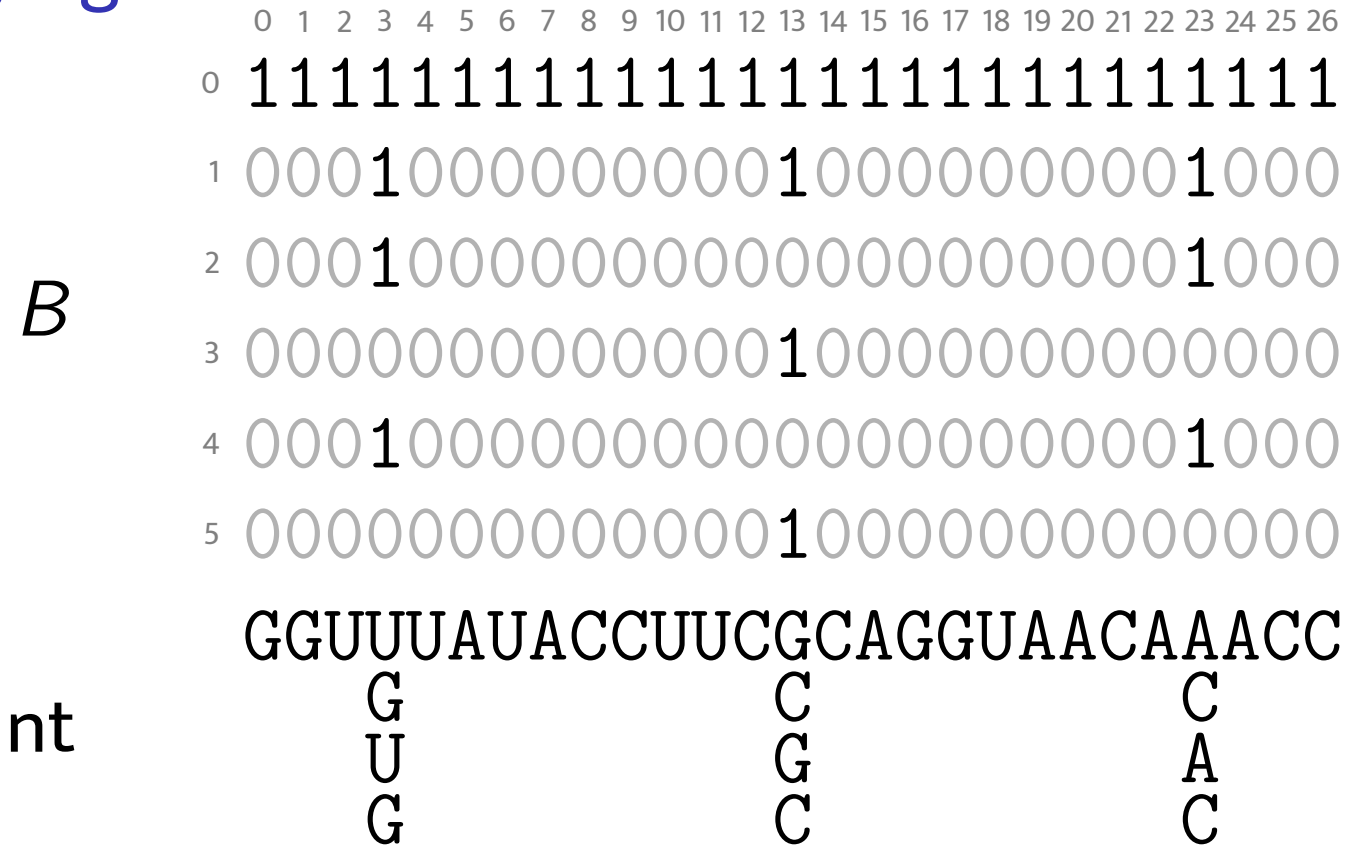
Compressed bit-vectors can support constant-time `rank`/`select` operations

See eg. Gog et al, 2014

Querying CREMSA



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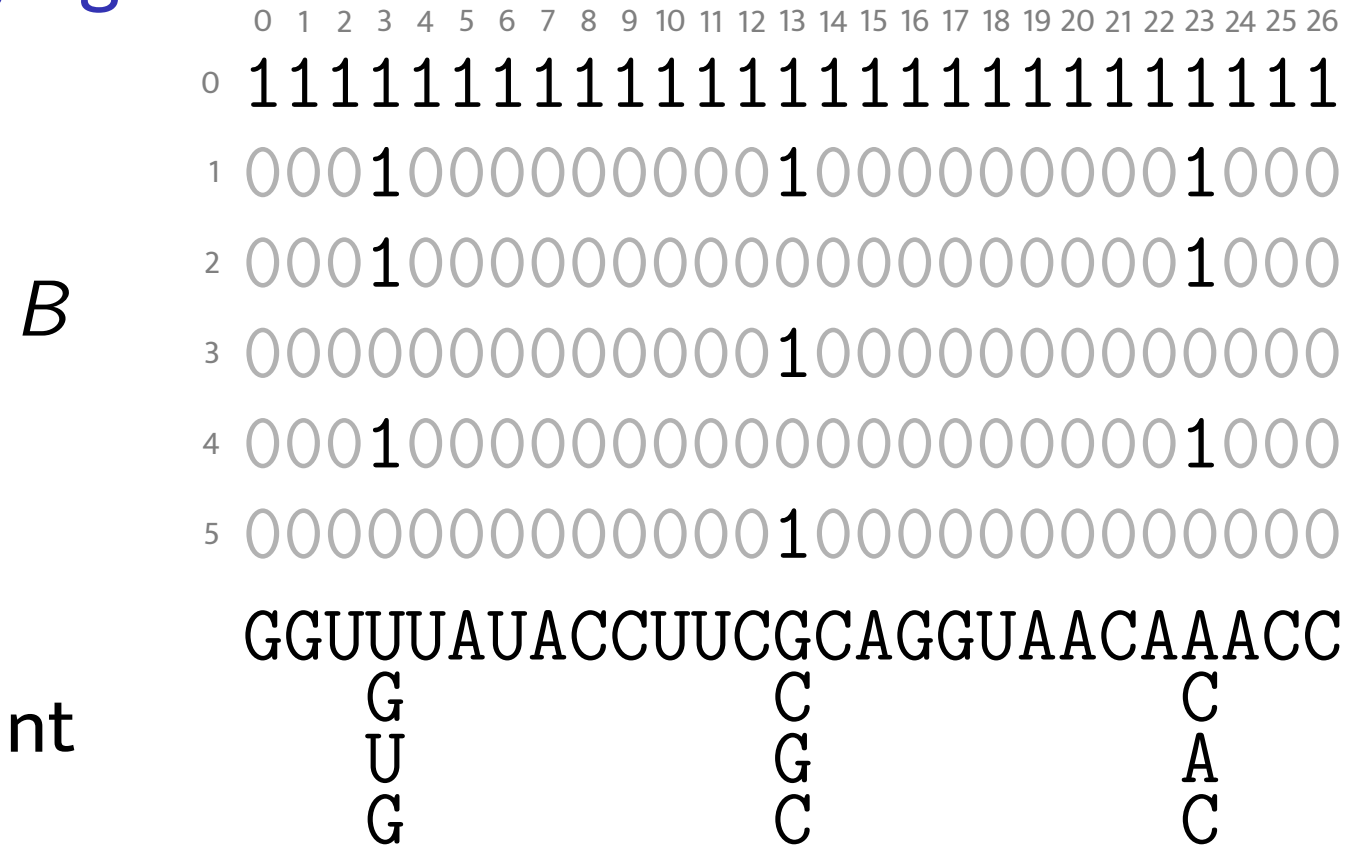
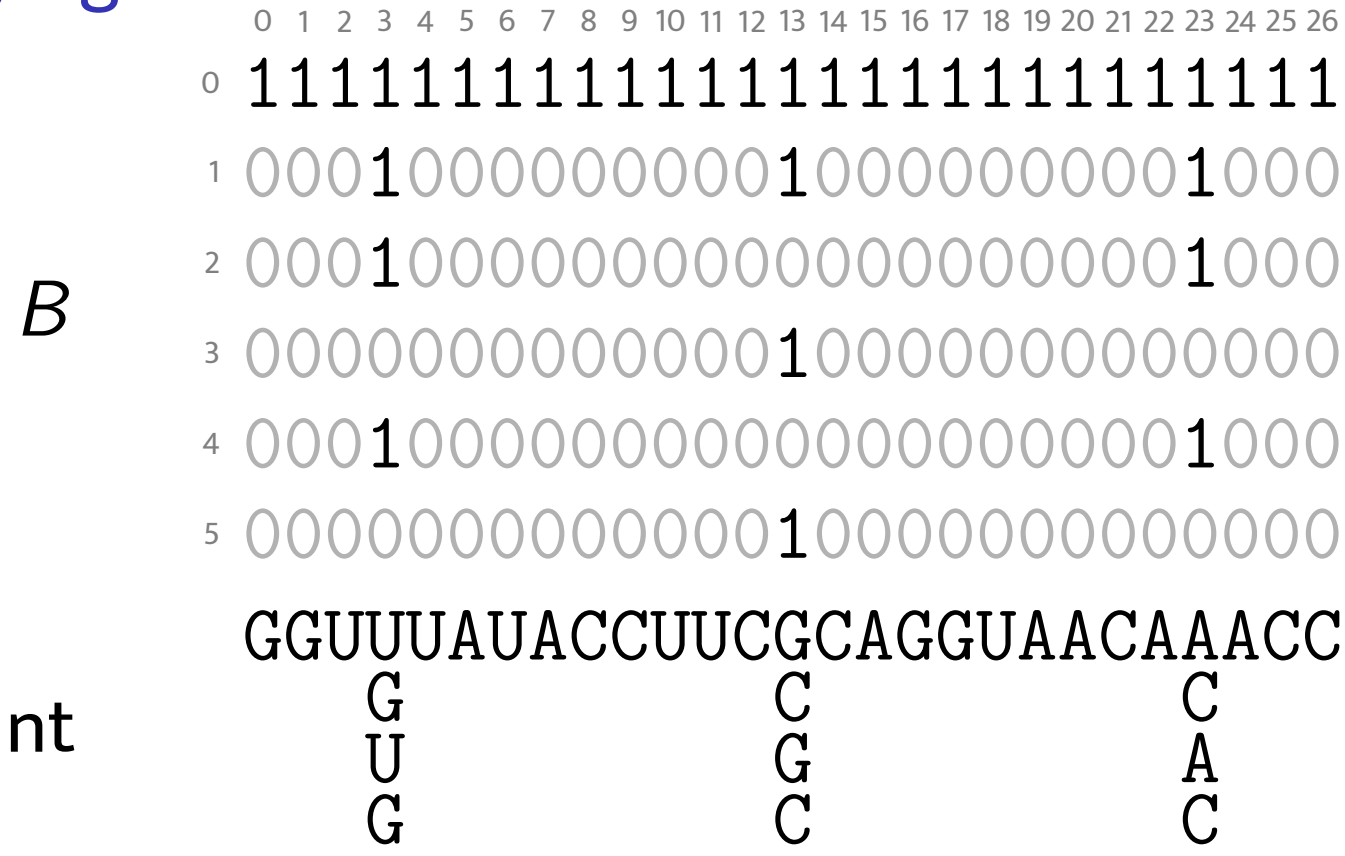


Accessing $s_i[j]$

Querying CREMSA



Accessing $s_i[j]$

$s_2[13]$?

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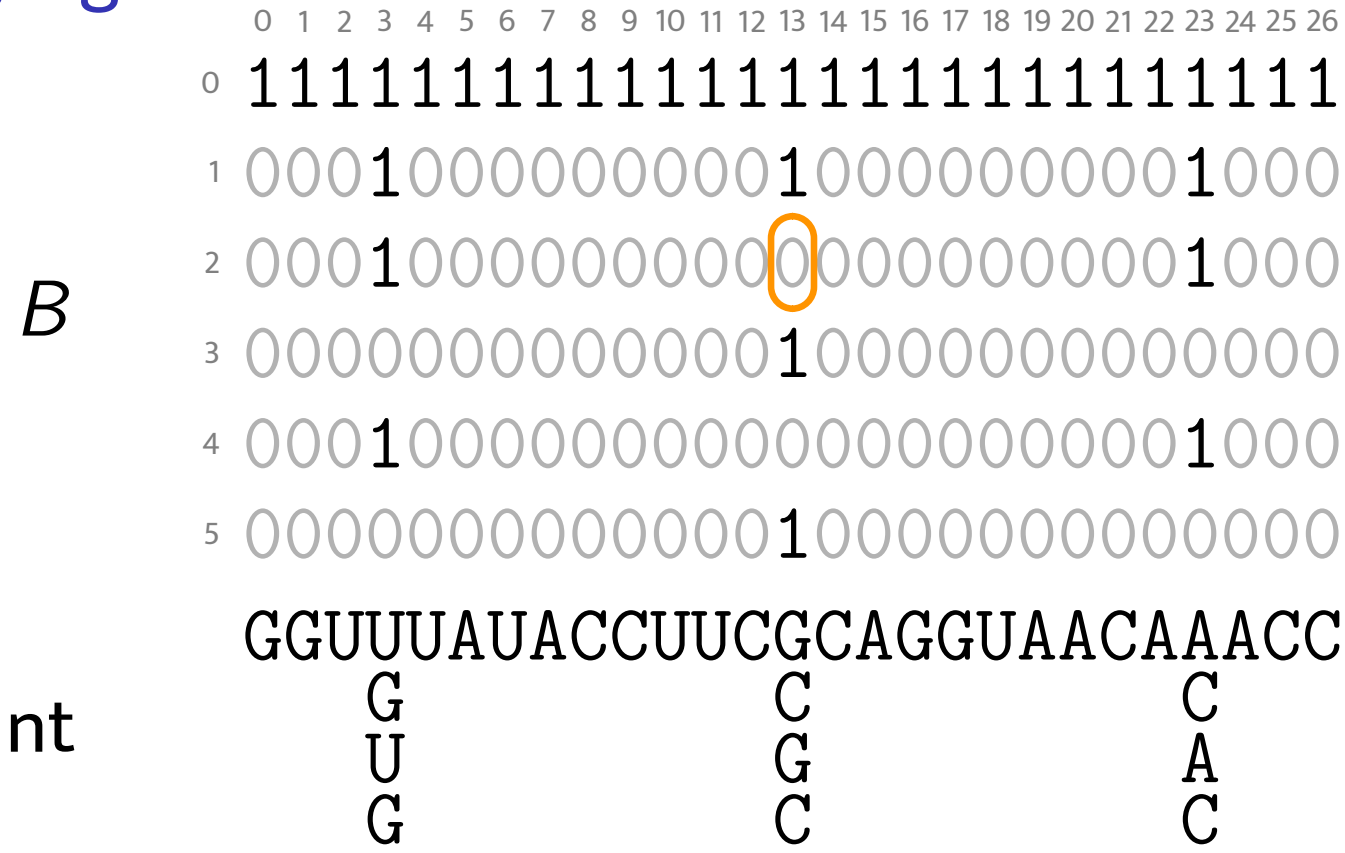

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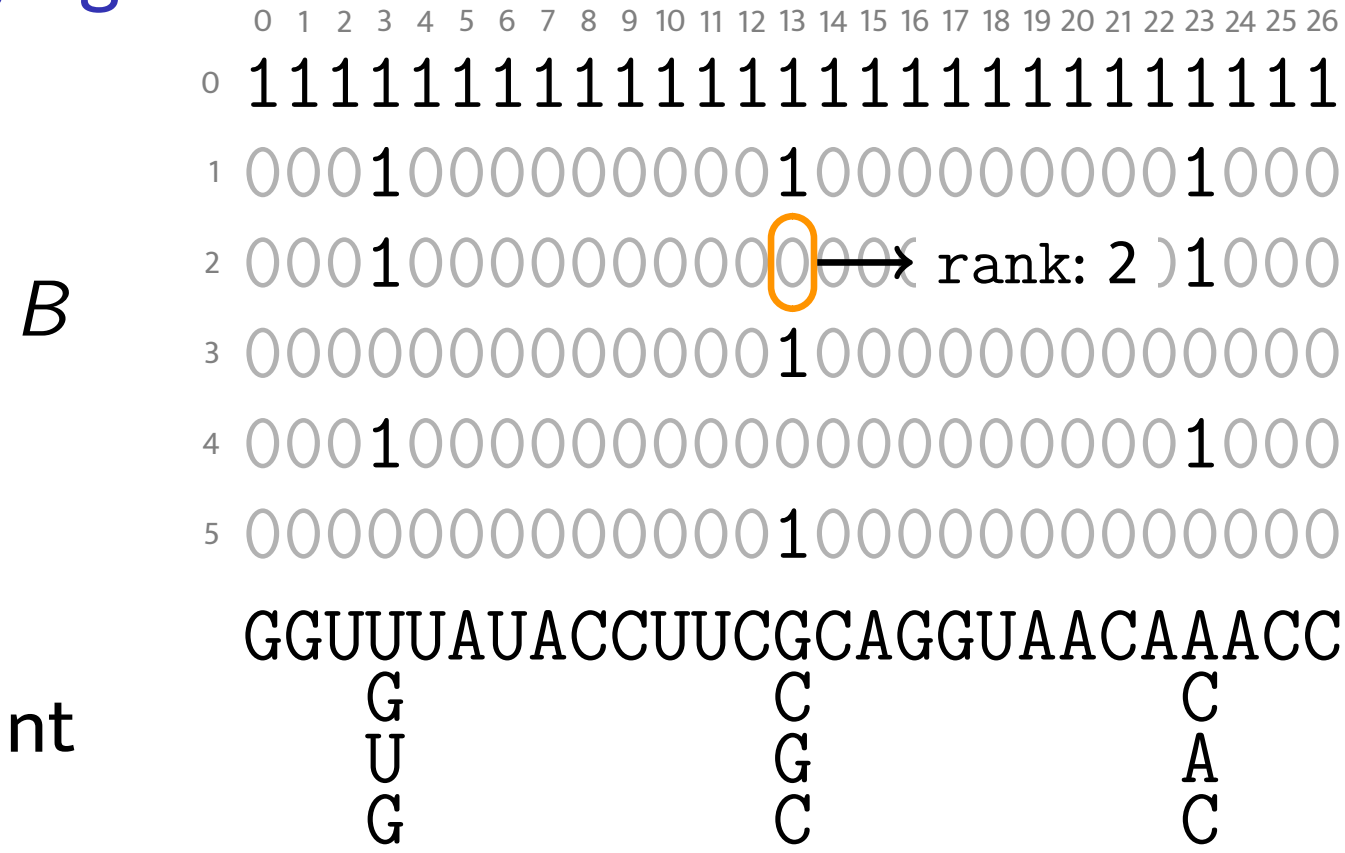

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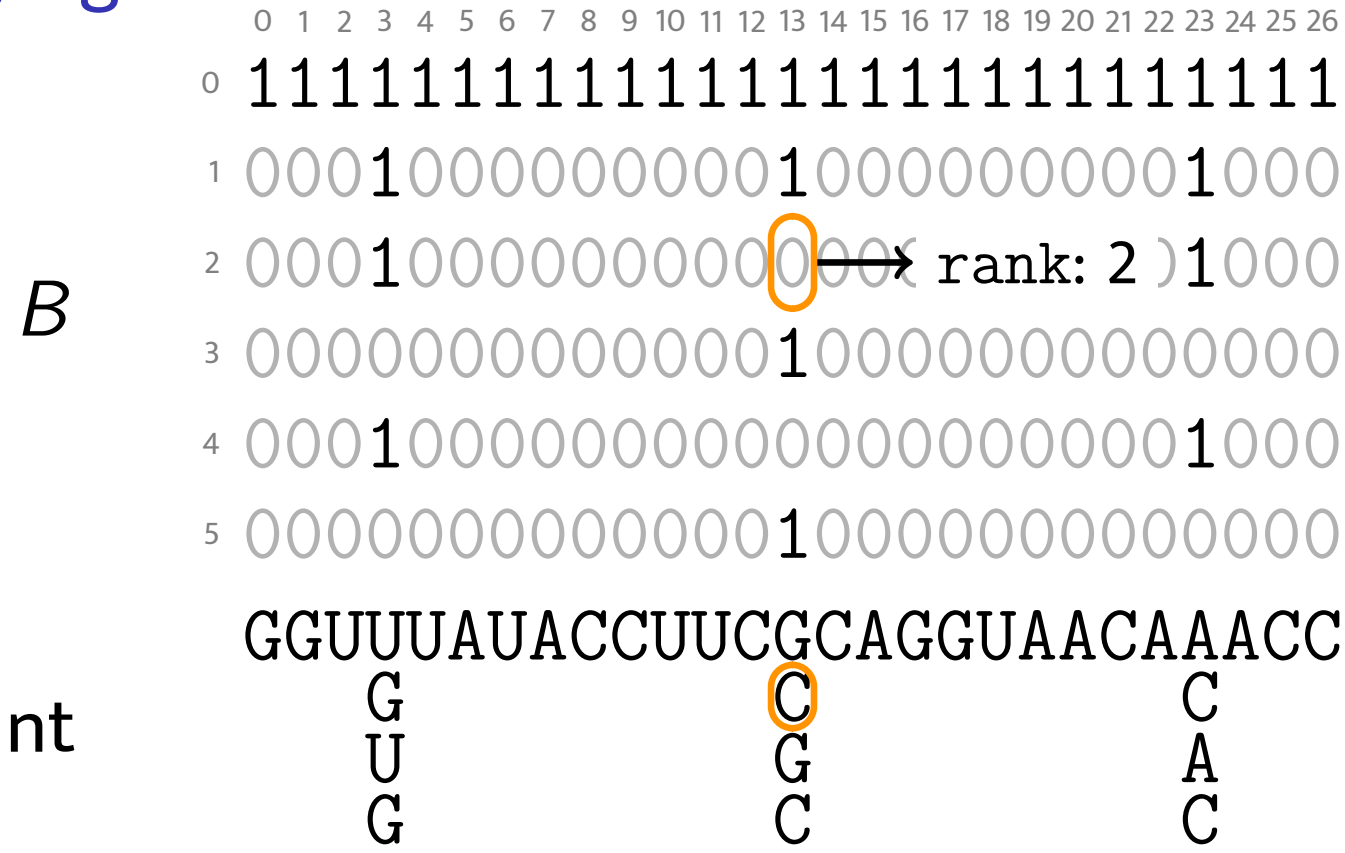

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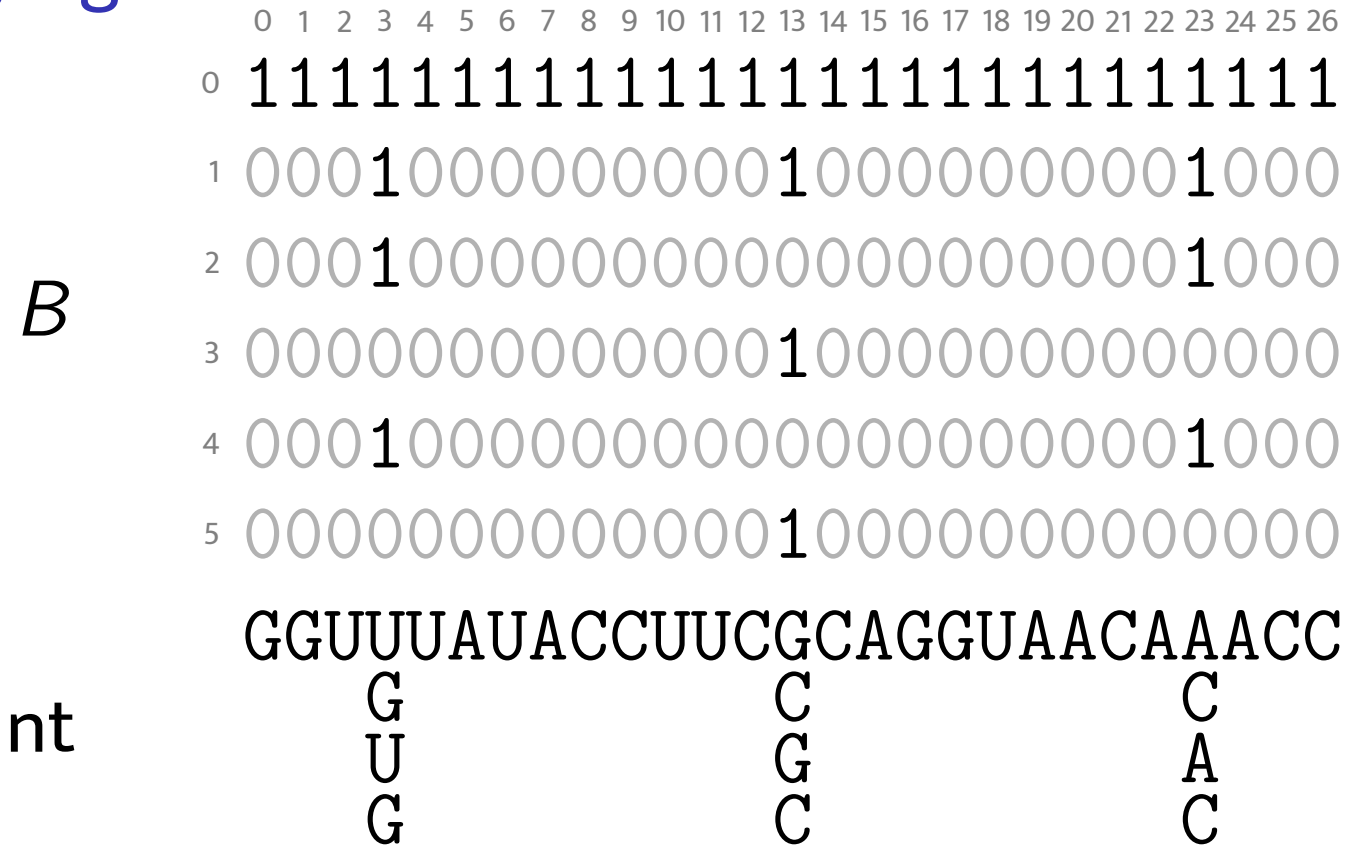
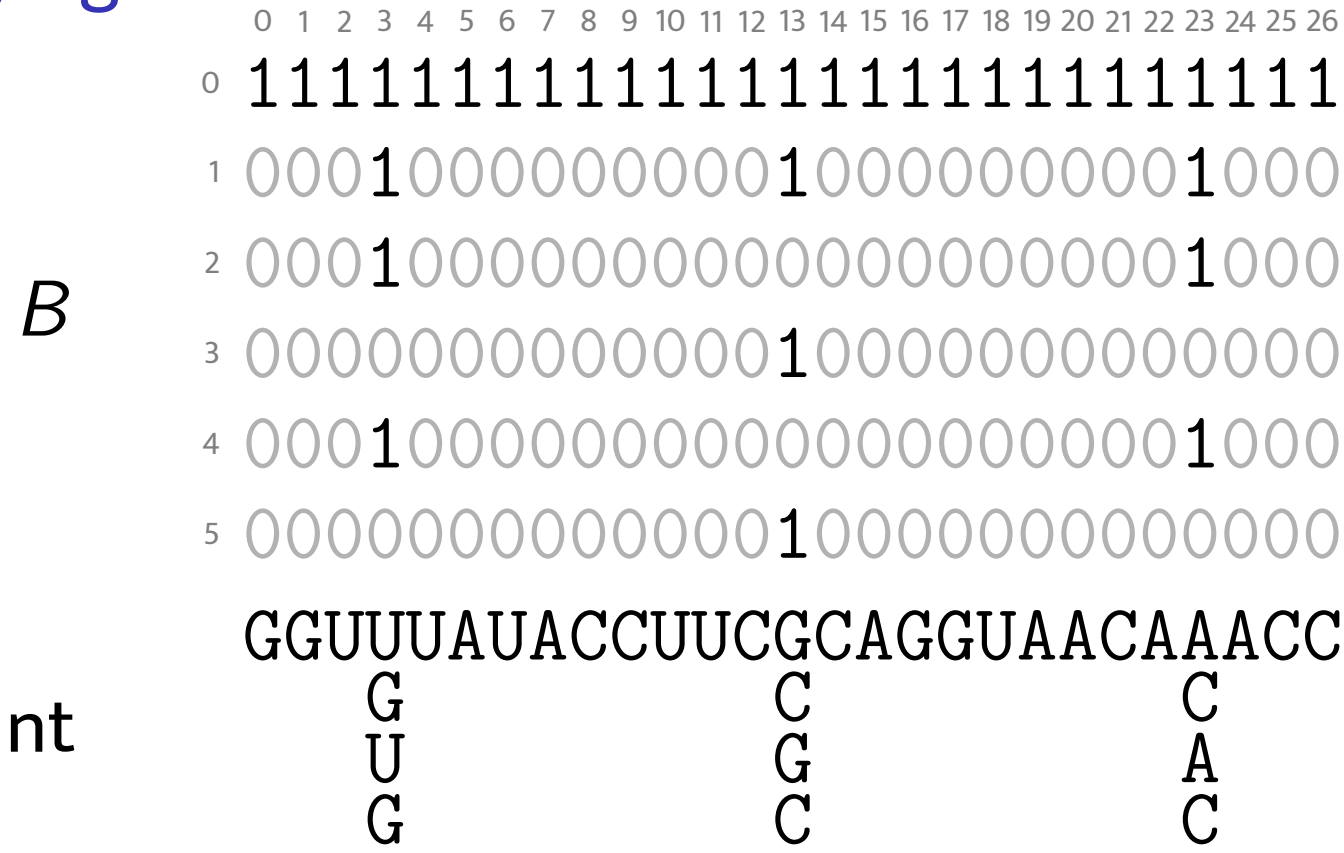


Accessing $s_i[j]$

$$s_i[j] = \mathsf{nt}_j[\mathtt{rank}(B_j, i)]$$

$$\Theta(1)$$

Querying CREMSA



Accessing $s_i[j]$ Counting nt in col. j

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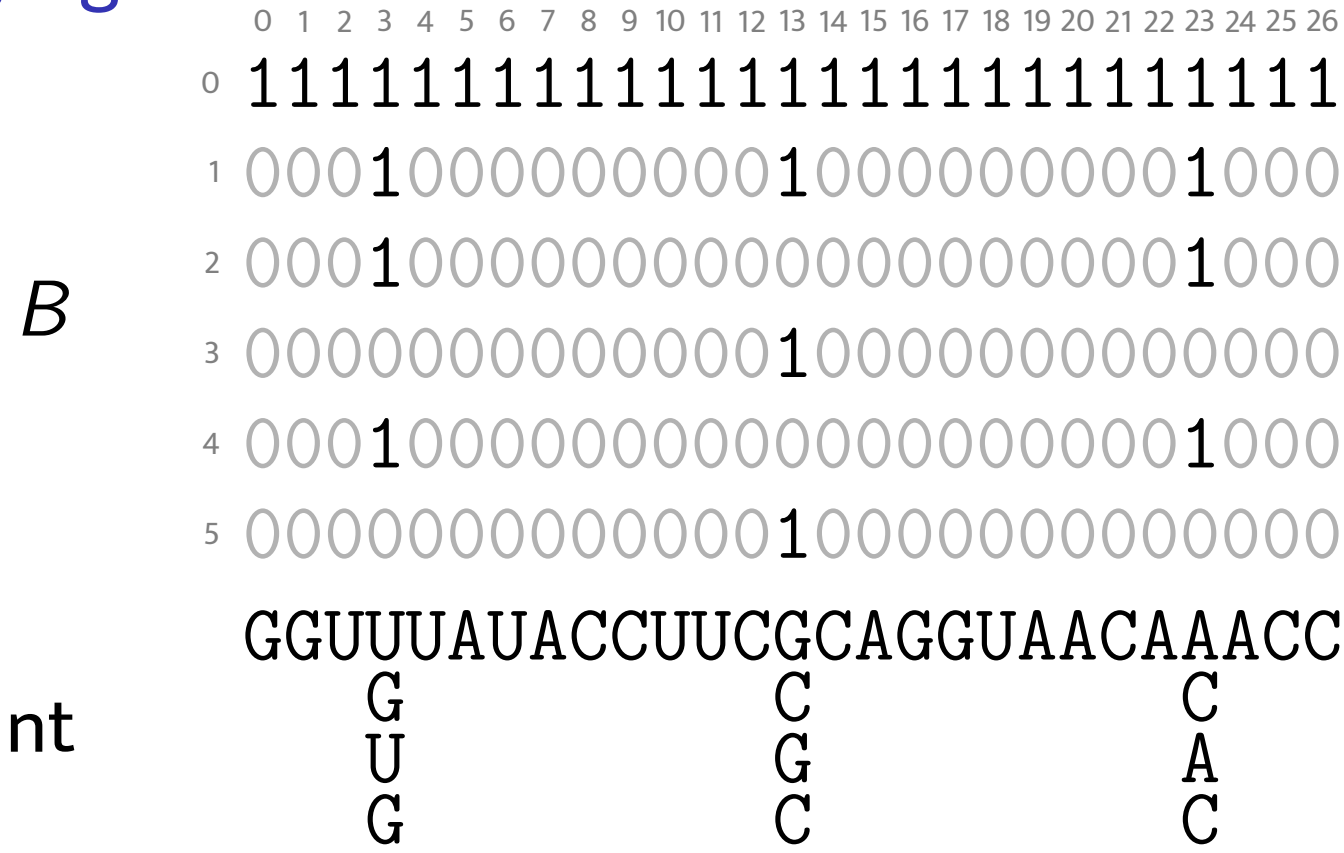

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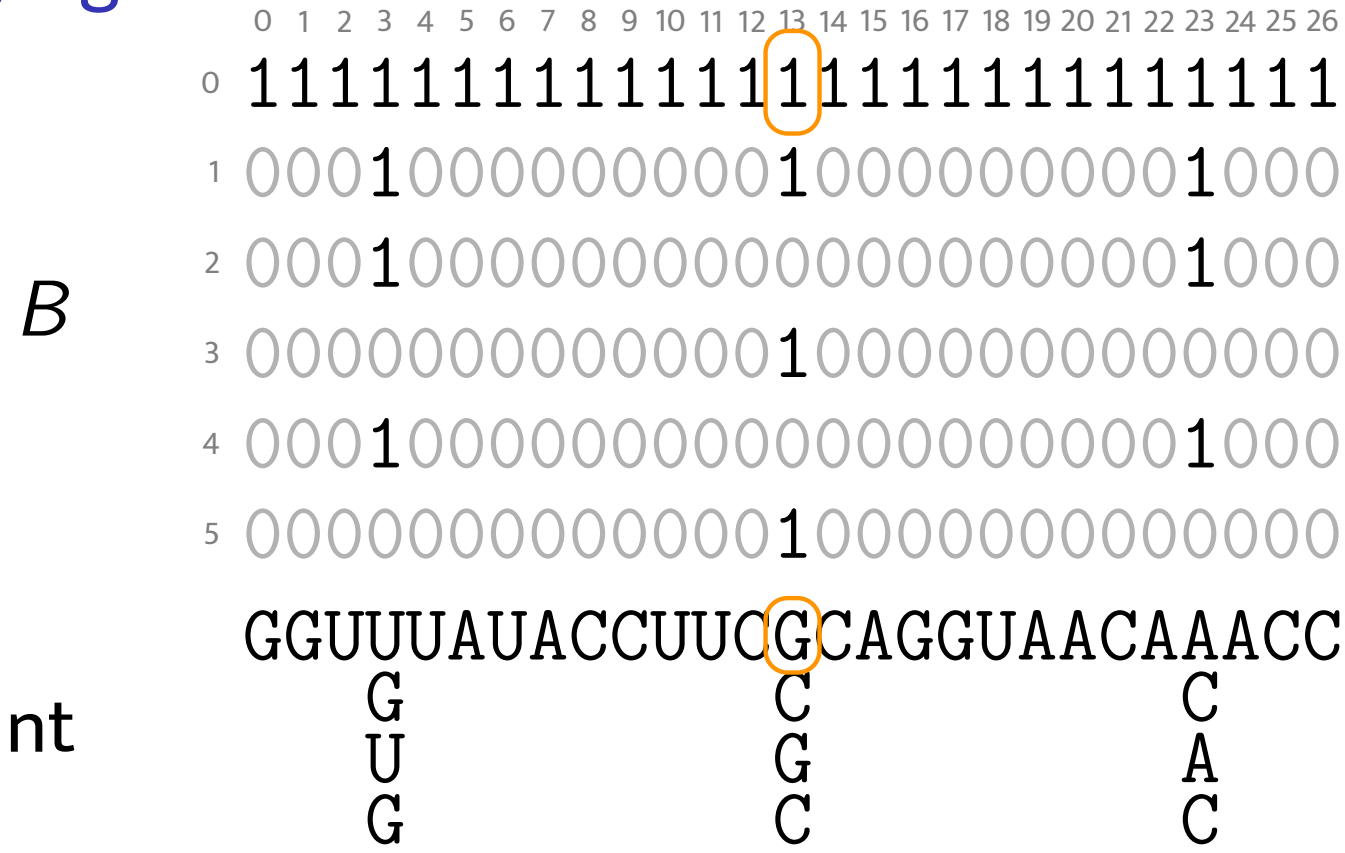
Counting nt in col. j

Iterating on 1s (with `select`) to compute the length of each run

Querying CREMSA



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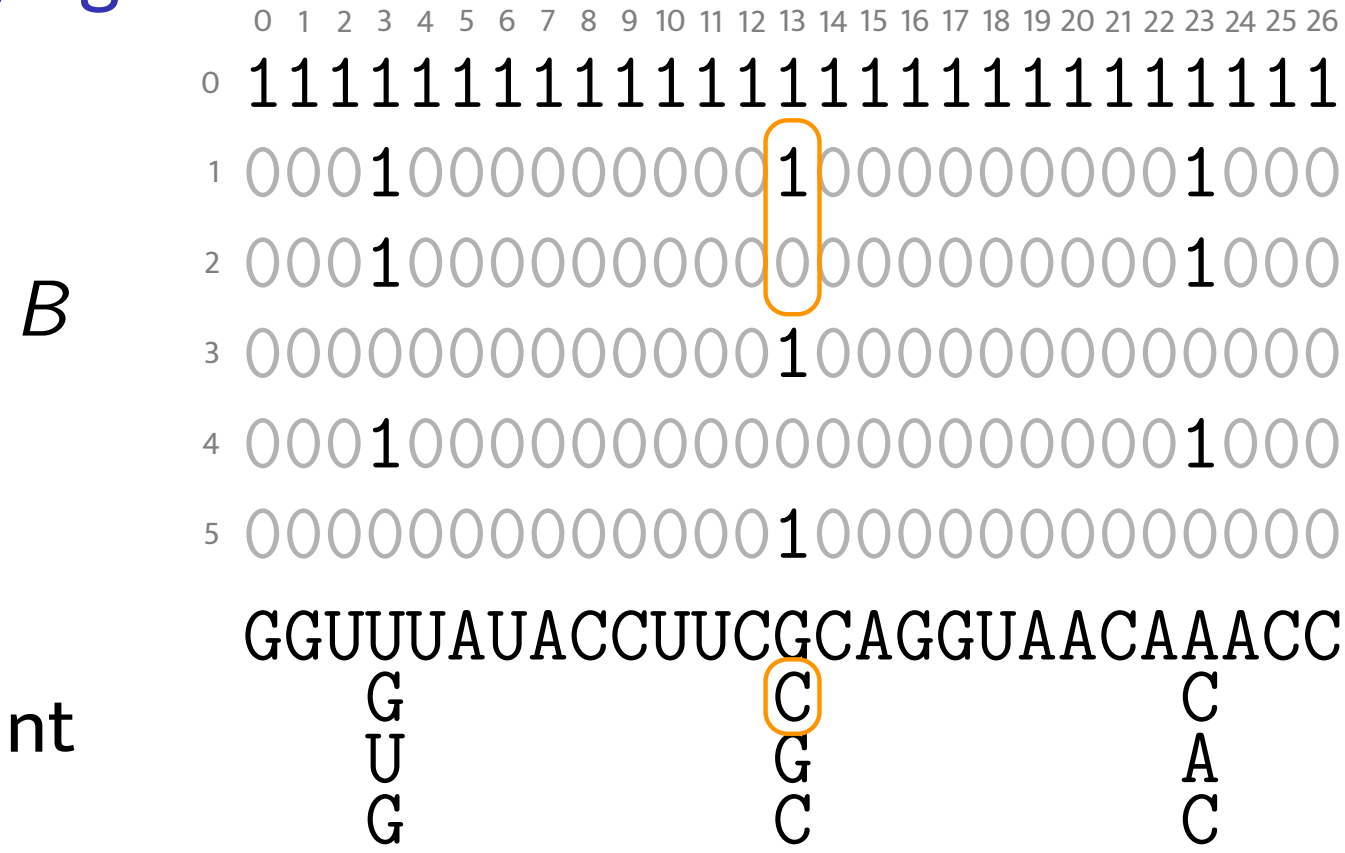
A	C	G	T
0	0	1	0

Querying CREMSA



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Iterating on 1s (with `select`) to compute the length of each run

A	C	G	T
0	2	1	0

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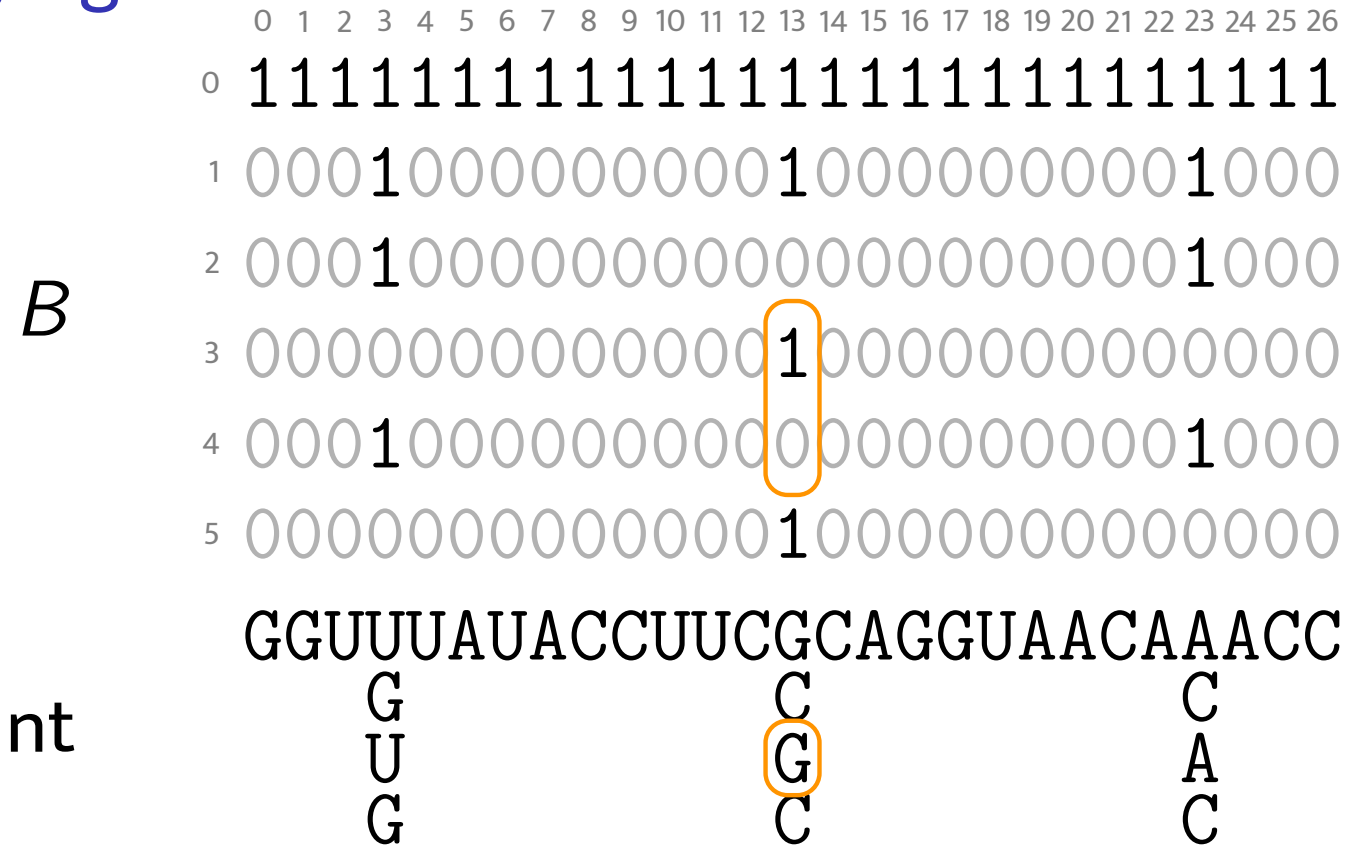

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$$\Theta(1)$$

Counting nt in col. j

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A	C	G	T
0	2	3	0

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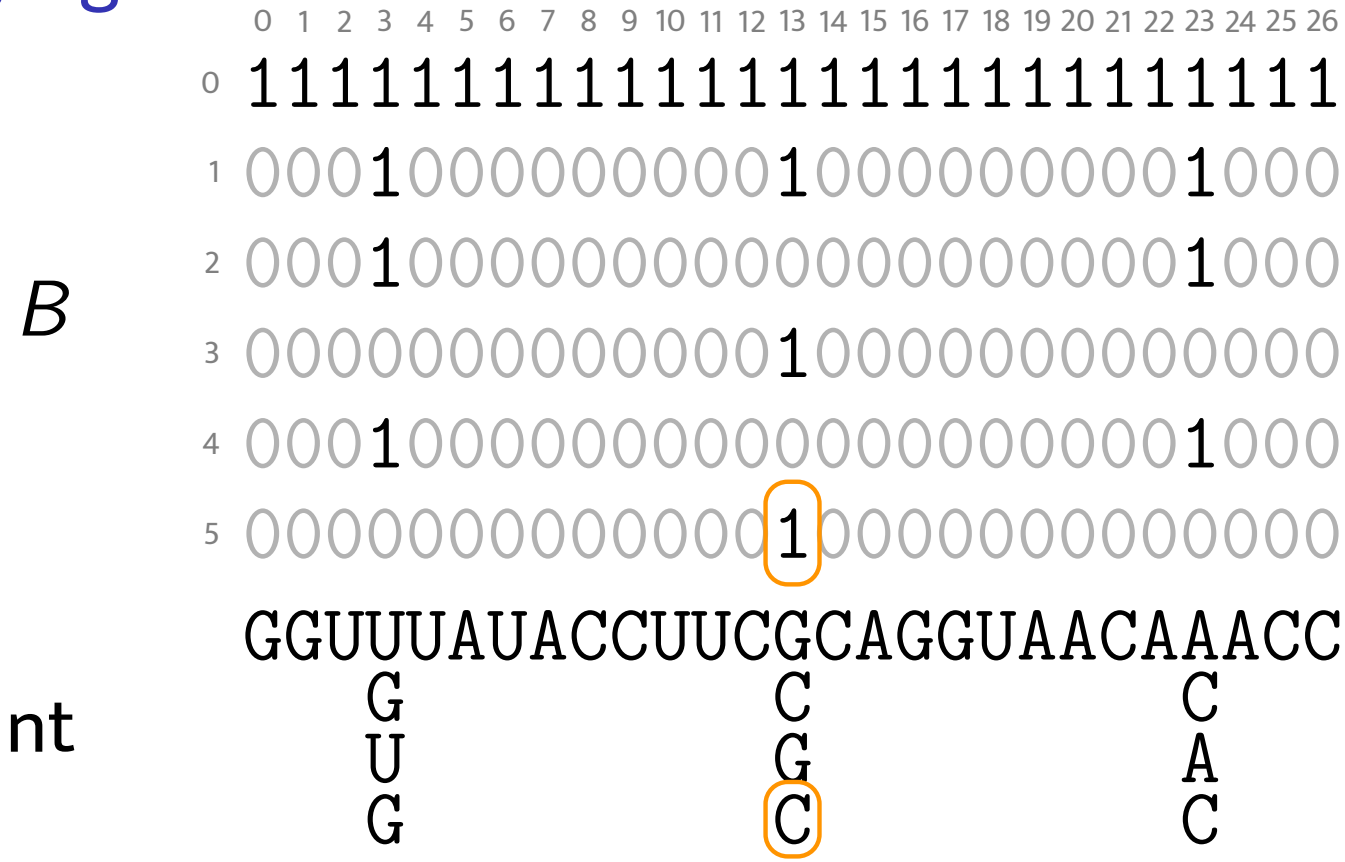

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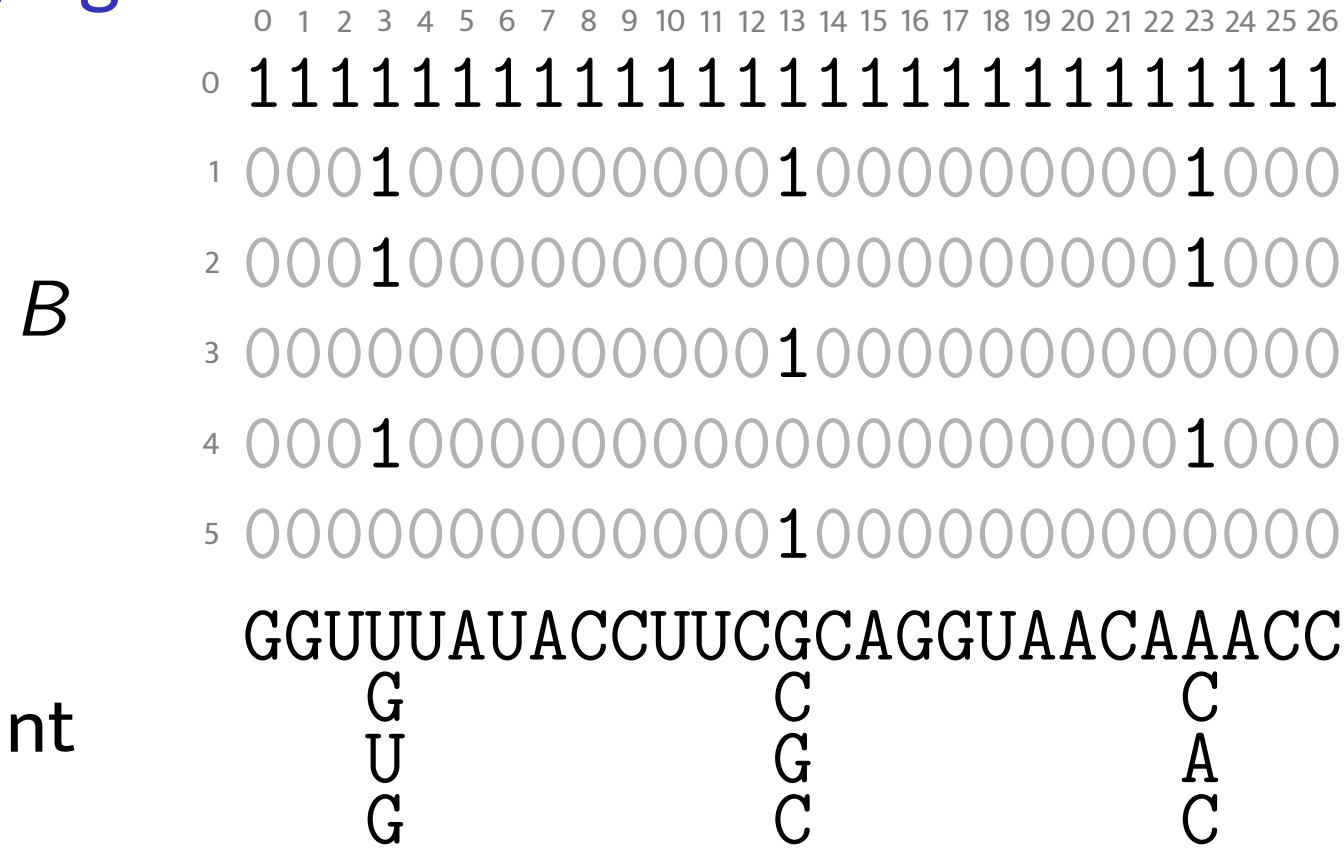
$\Theta(1)$

A	C	G	T
0	3	3	0

Querying CREMSA



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$$s_i[j] = \mathrm{nt}_j[\mathtt{rank}(B_j, i)]$$

$\Theta(1)$ $\Theta(r_j)$

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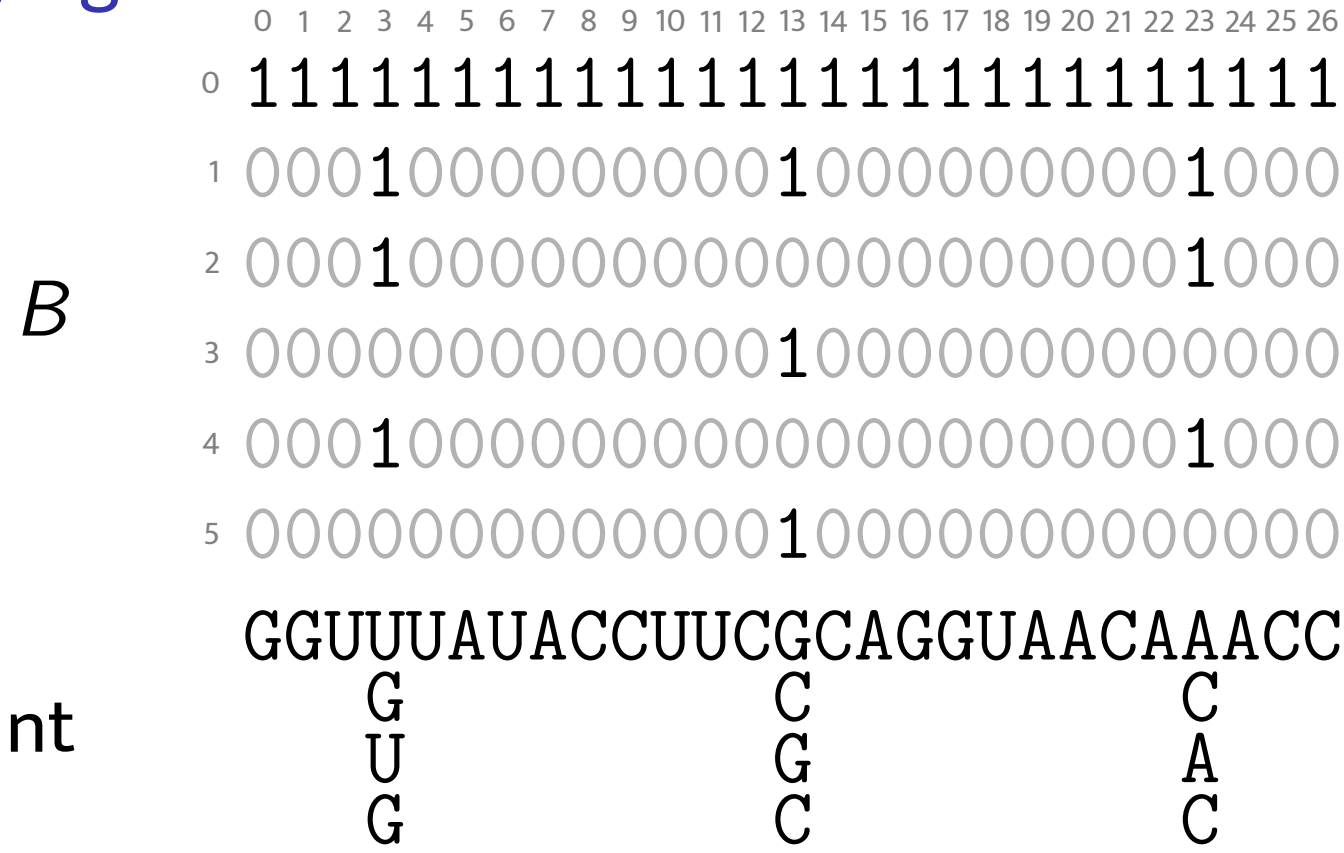

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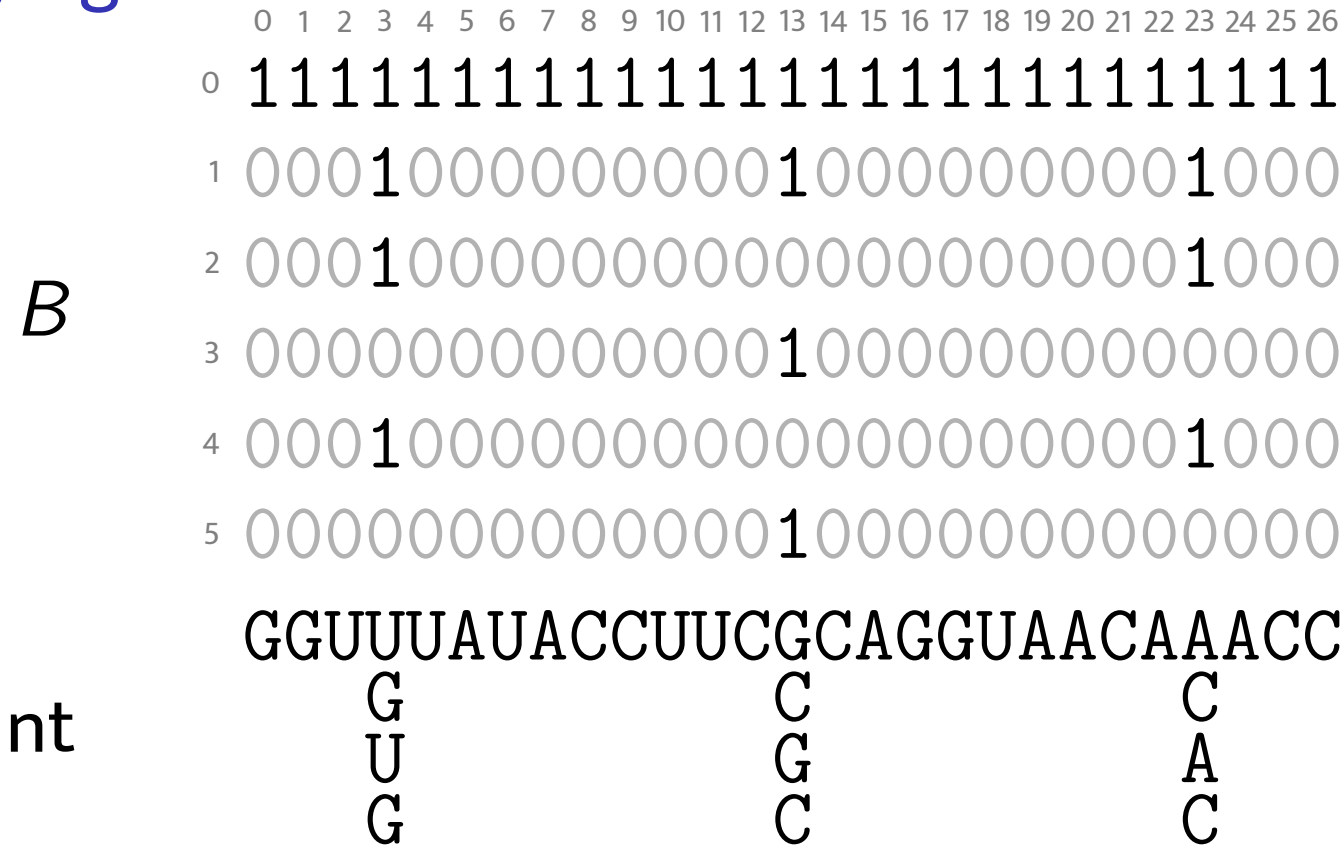

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$\Theta(1)$ $\Theta(r_j)$ $\Theta(\max(r_{j_1}, r_{j_2}))$

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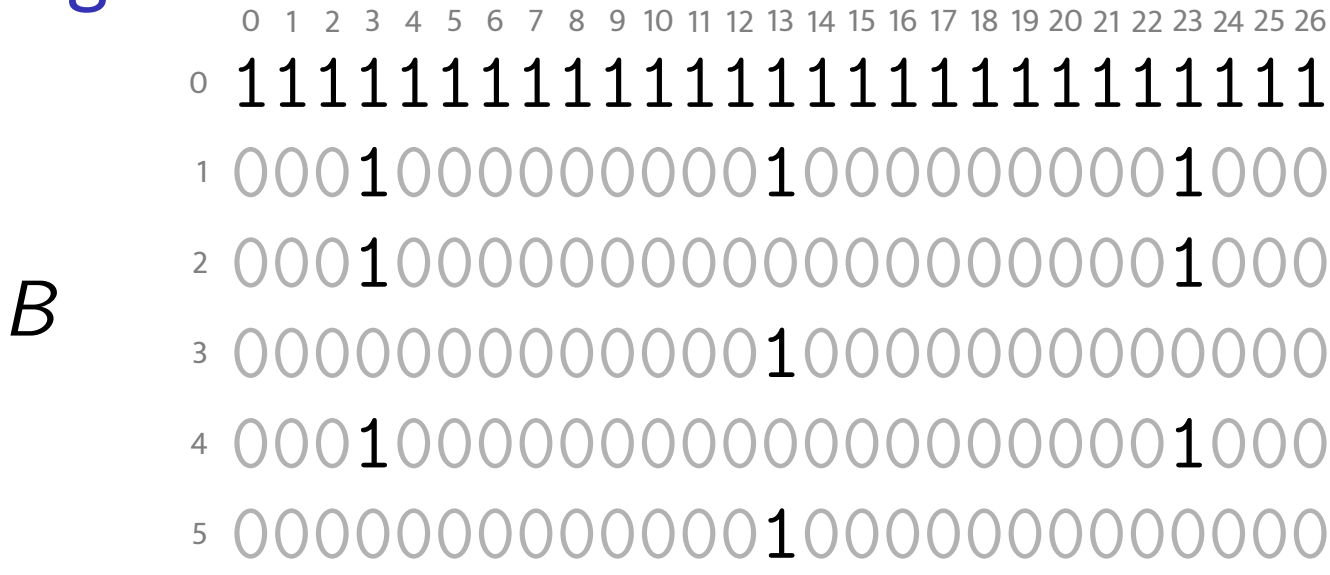

The fewer runs, the faster the queries

U G A
G C C

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Fewer/longer runs lead to a lighter **and** quicker index

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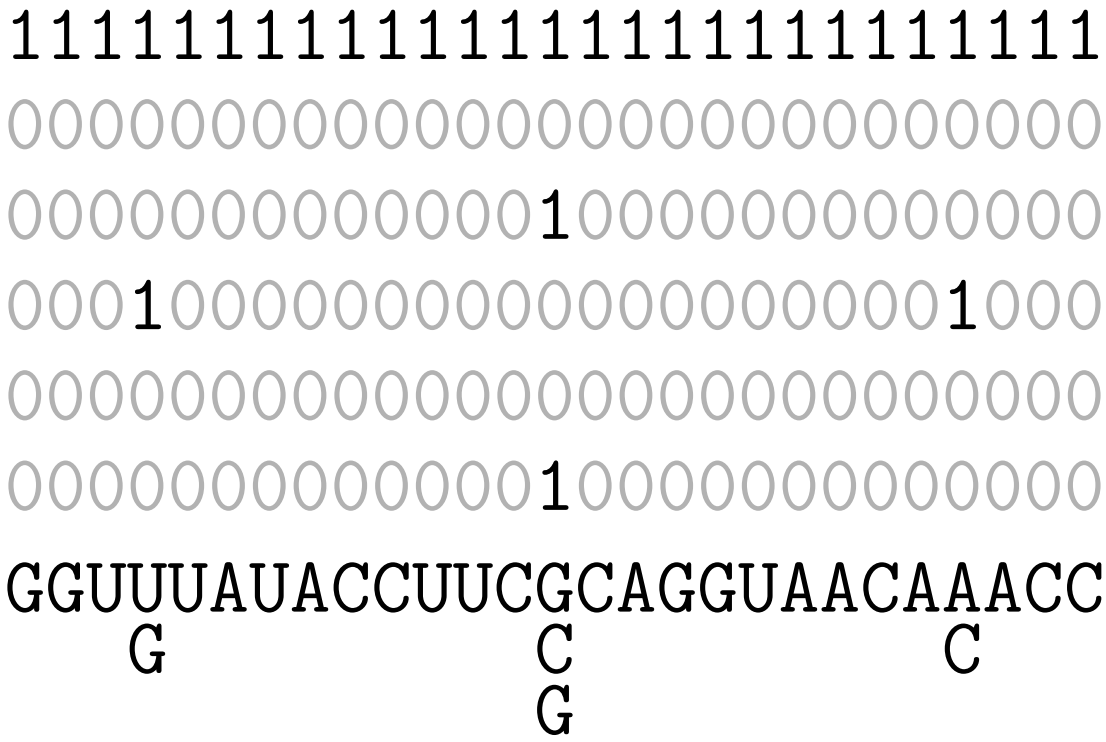
GGUUUAUACCUUCCCAGGUAACAAACC
GGUGUAUACCUUCCCAGGUAACACACC
GGUGUAUACCUUCCCAGGUAACACACC
GGUGUAUACCUUCGCAGGUAACACACC

Order of the sequences in the MSA matters

Fewer/longer runs lead to a lighter **and** quicker index



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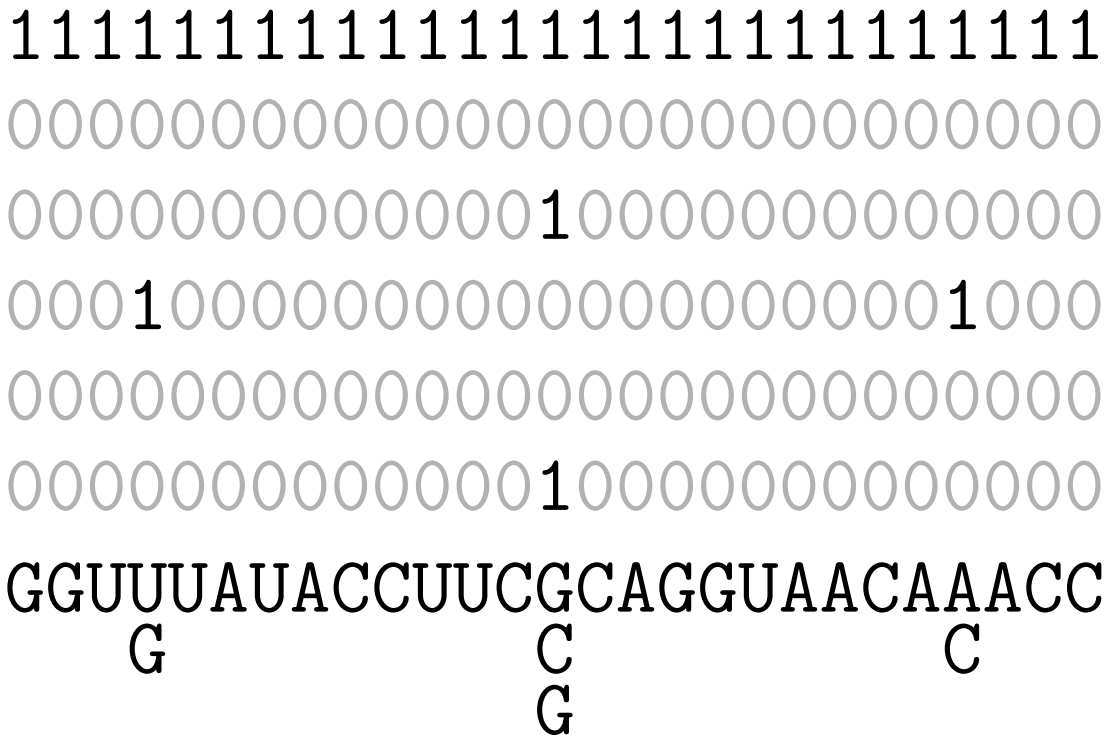

But finding the optimal order is NP-complete

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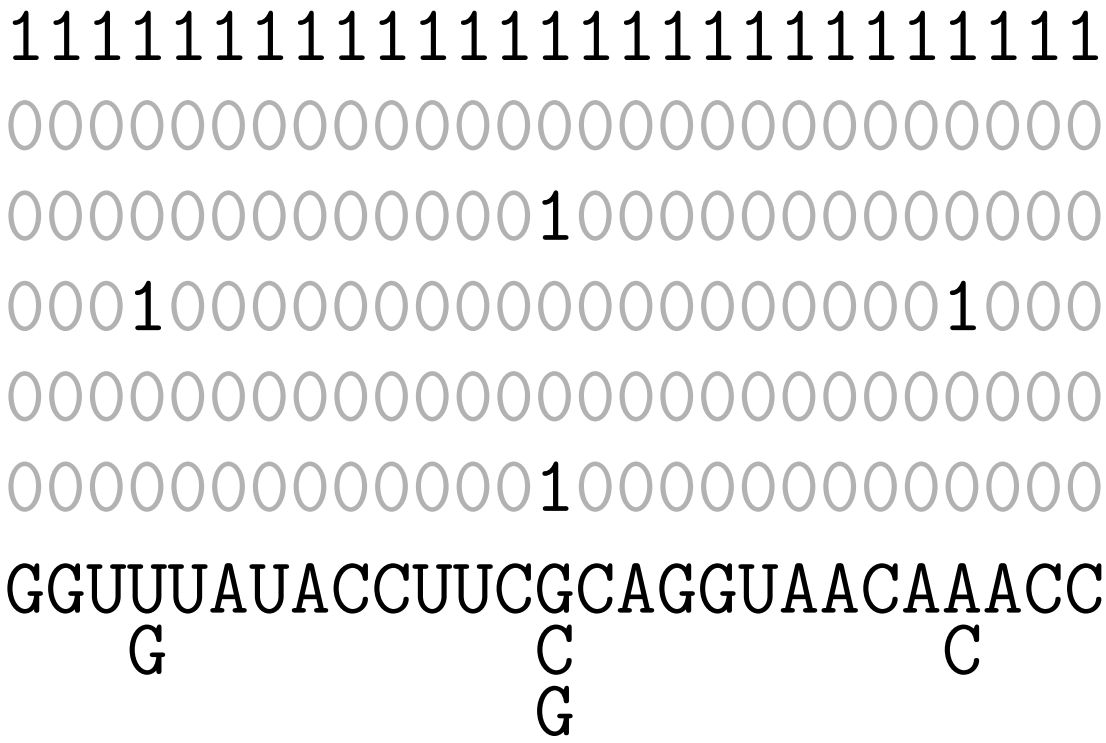

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Using known lineages offer good results in practice

CREMSA on 1M SARS-CoV-2 sequences

1,031,437 genomes

Downloaded in Dec 2023, deduplicated, removed those with $\geq$ 20 uncertain nucleotides

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Multiple sequence alignment

Using HAlign3, with 1.5 h CPU and **600 GB** of RAM. 36,000 columns

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Time	10 min
RAM	245 MB
Size on disk	53 MB

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	CREMSA	gzip	xz
Time	10 min	90 min	70 min
RAM	245 MB	2 MB	97 MB
Size on disk	53 MB	11,873 MB	33 MB

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Sorted input	28 MB		24 MB	
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Compressors

$\rightarrow \sim$ 6h for all the pairs of columns

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Not much (yet)

Only 251 pairs have a good conservation score

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Only 251 pairs have a good conservation score

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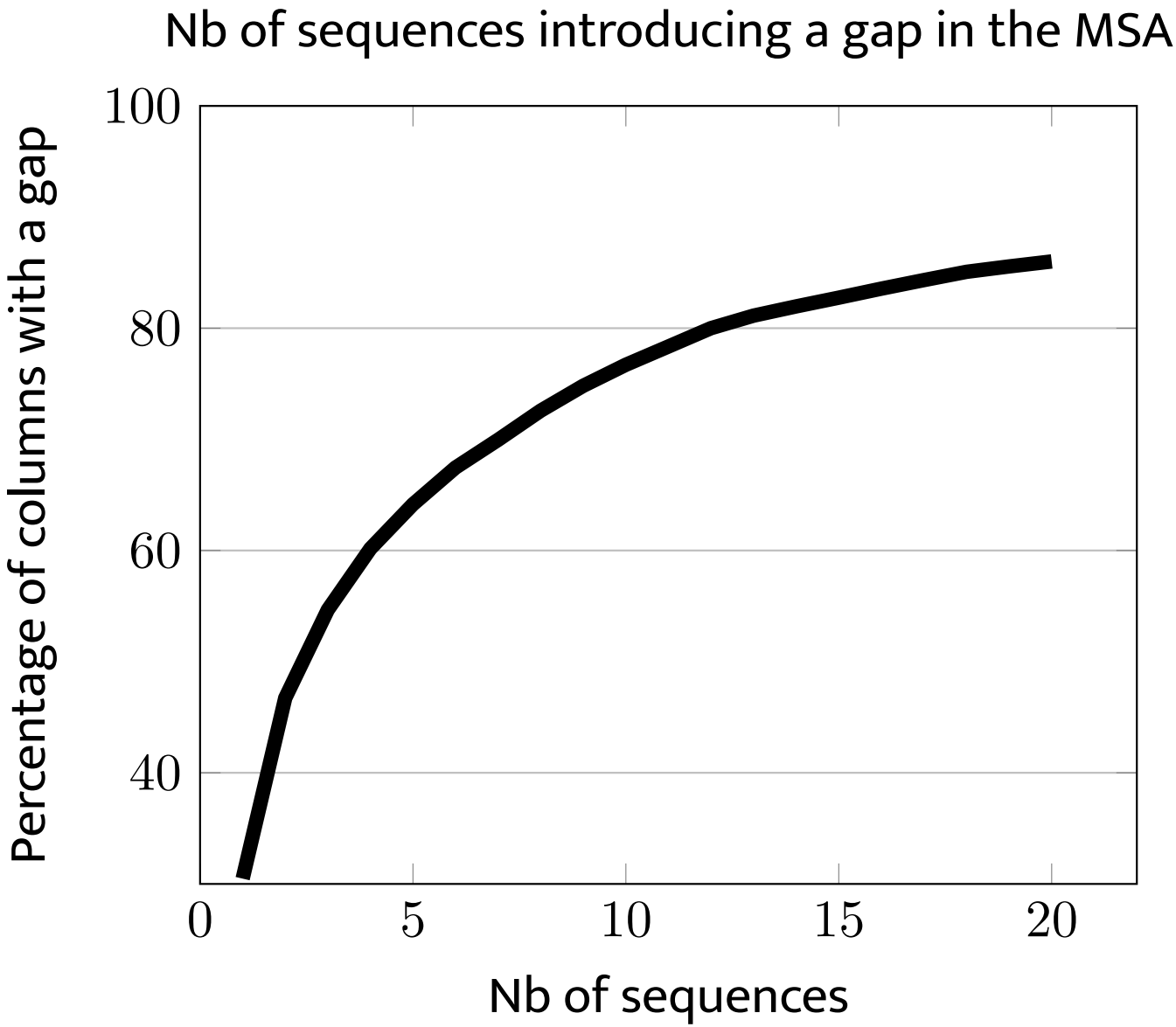
More data $\rightarrow$ more signal? **or** More data $\rightarrow$ more noise?

A few sequences introduce gaps in a column



CREMSA : Compressed indexing of (ultra) large viral alignments

https://gitlab.univ-lille.fr/mikael.salson/cremsa

CREMSA is fast and lightweight

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Reordering sequences save time and space

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Side note: anyone interested to design a **lightweight** method for multiple sequence aligments of highly similar sequences?

Announcement: Open Maître de conférences position in Lille

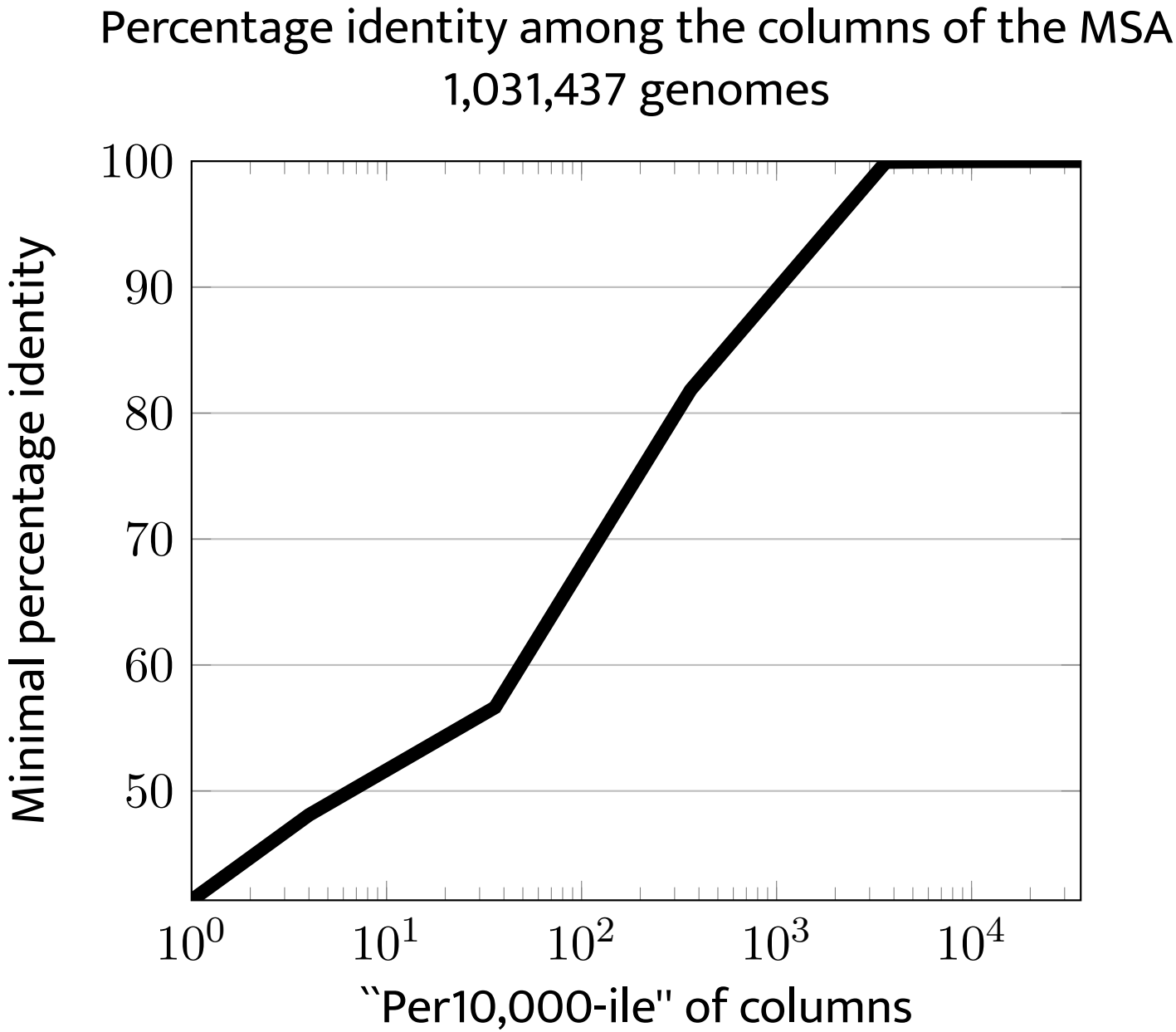
Maître de conférences position open in Bonsai (CRIStAL), Lille

Research themes in Bonsai

data structures, sequence algorithms, hash functions
oncohematology
non-ribosomal peptides
paleoproteomics
...

Contact me if interested: `mikael.salson@univ-lille.fr`

The 1M genomes are highly conserved



In practice *r* is tiny