A new way to handle large data: MSR sketching

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[3]Insitut Pasteur, Paris - France

Penn State, September 2025

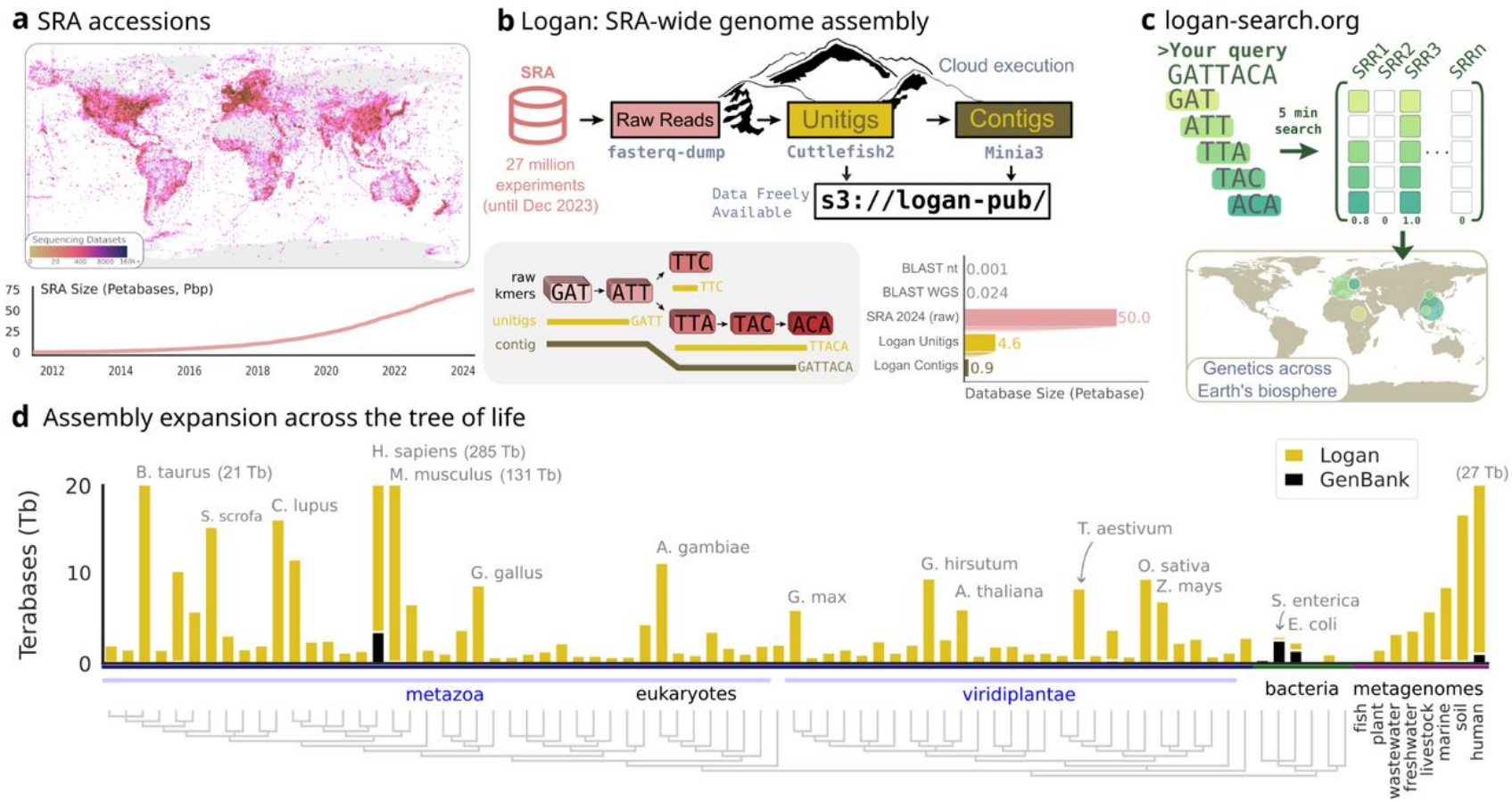
About me: postdoc, since Feb. 2025

Institut Pasteur, Paris

Rayan Chikhi
Institut Pasteur, Paris
Focus: massive genomics

My postdoc : Index & Search the Logan database

The Logan project

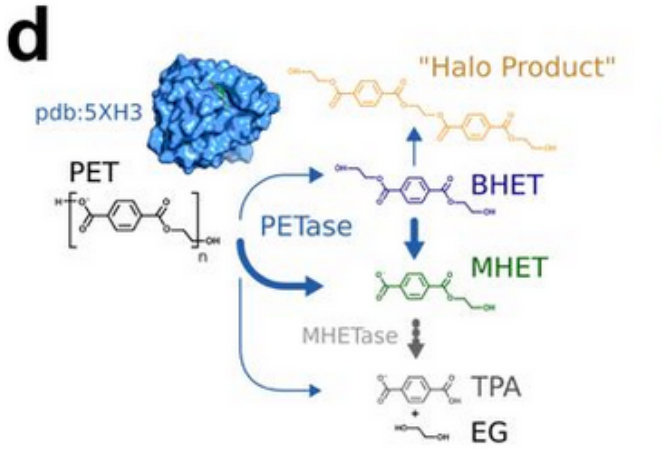


Logan: Planetary-Scale Genome Assembly Surveys Life's Diversity, *biorXiv*, 2025

The Logan project: exciting example

PAST SUCCESS - STARTUP

Plastivores: Plastic-Degrading Super-Microbes and Enzymes



- 213 known PETases

The Logan project: exciting example

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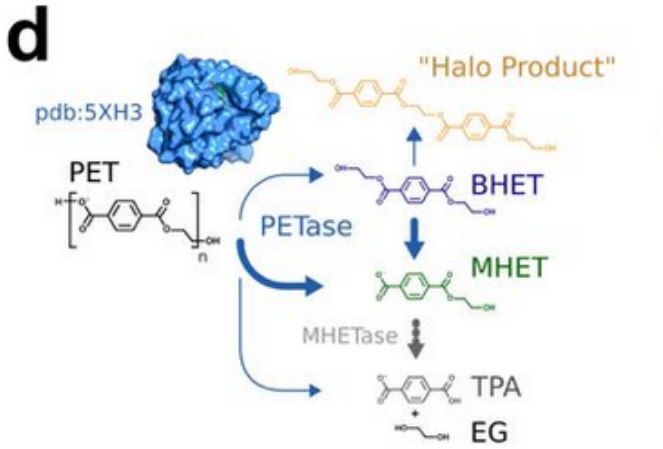

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- Let's look in Logan for homologs

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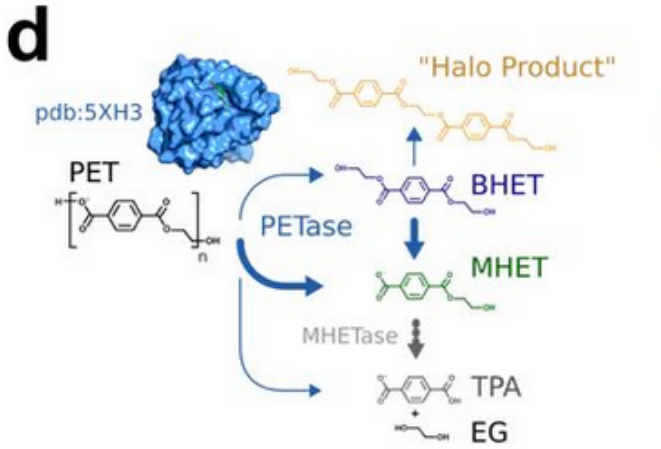
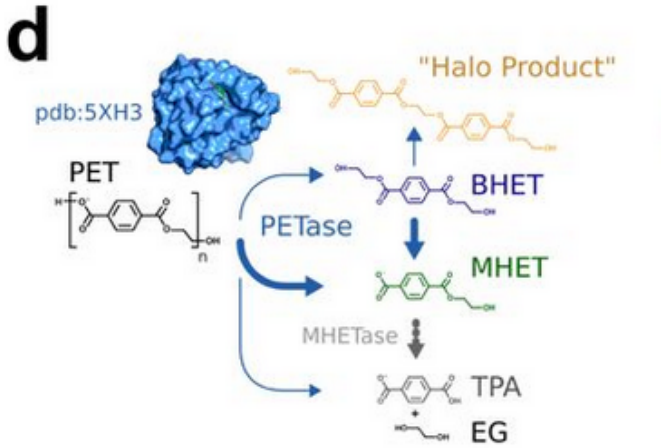


- 213 known PETases
- Let's look in Logan for homologs
- Result: 215M distinct sequences

The Logan project: exciting example

PAST SUCCESS - STARTUP

Plastivores: Plastic-Degrading Super-Microbes and Enzymes



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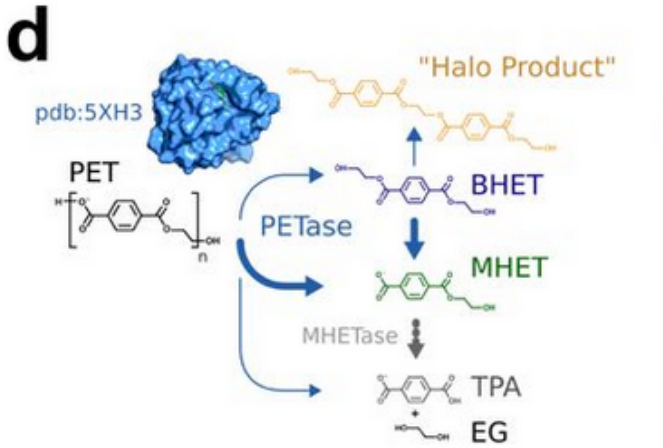
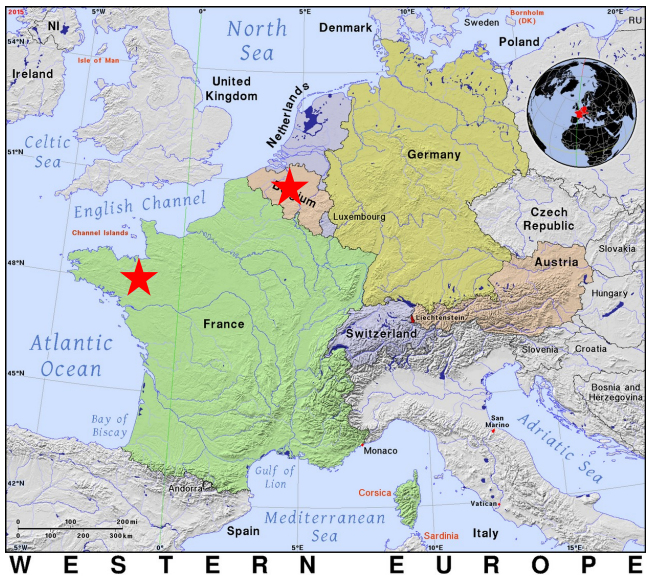


- 213 known PETases
- Let's look in Logan for homologs
- Result: 215M distinct sequences
- Some of them best than previously known PETases
- My job: improving speed/cost of the search

About me: Ph.D., 2021-2024

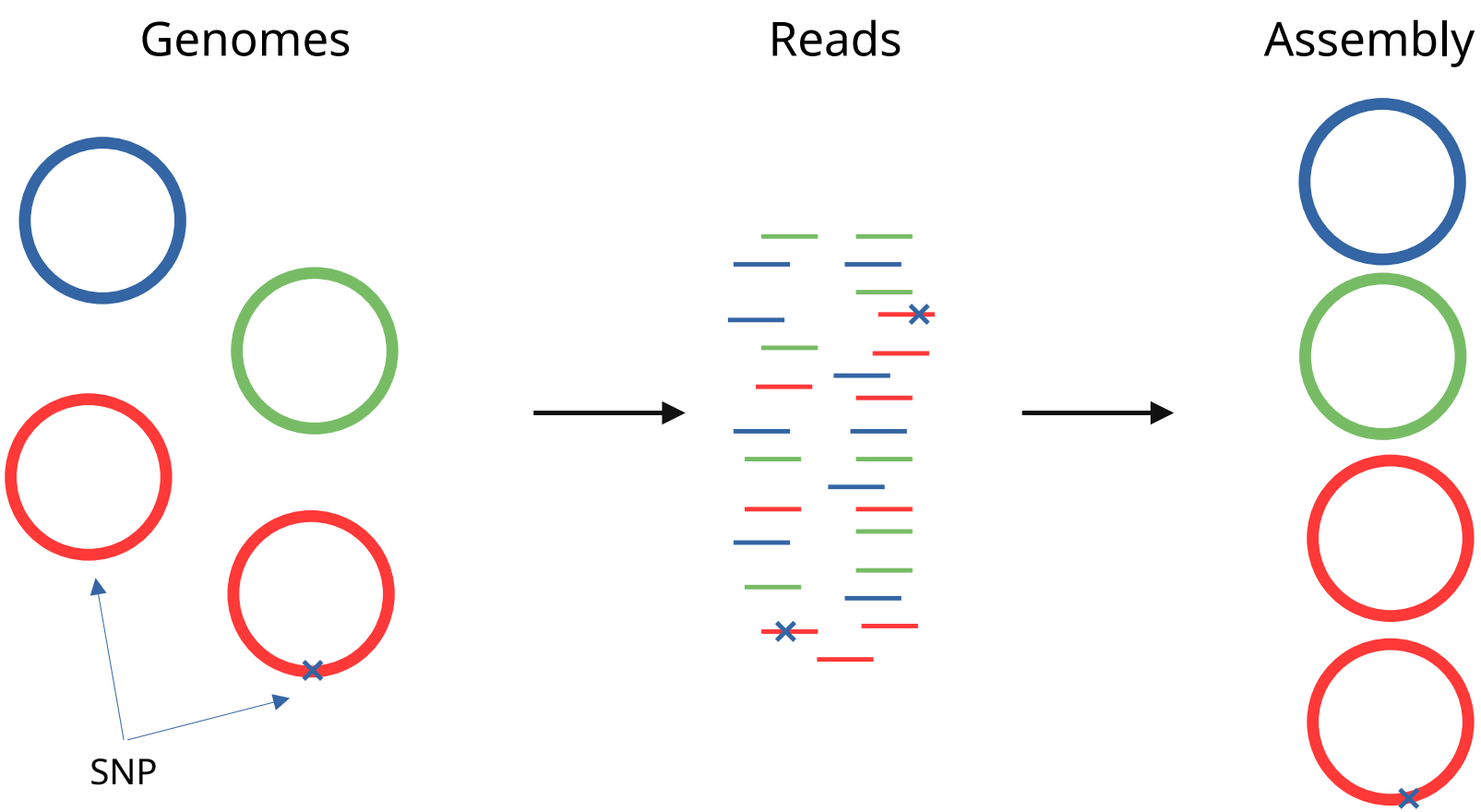


Jean-François Flot
Université Libre de Bruxelles
Focus: assembling wild genomes

Dominique Laveneir
Université de Rennes
Focus: computational methods

My Ph.D. : Haplotype assembly from long reads

Focus of my Ph.D.: Metagenome assembly



(Meta)genome assembly is a big computation

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- Assembling a human gut metagenome (HiFi, 250Gpb)

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metaFlye
4 days, 256GB RAM

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(Meta)genome assembly is a big computation

- Assembling a human gut metagenome (HiFi, 250Gpb)

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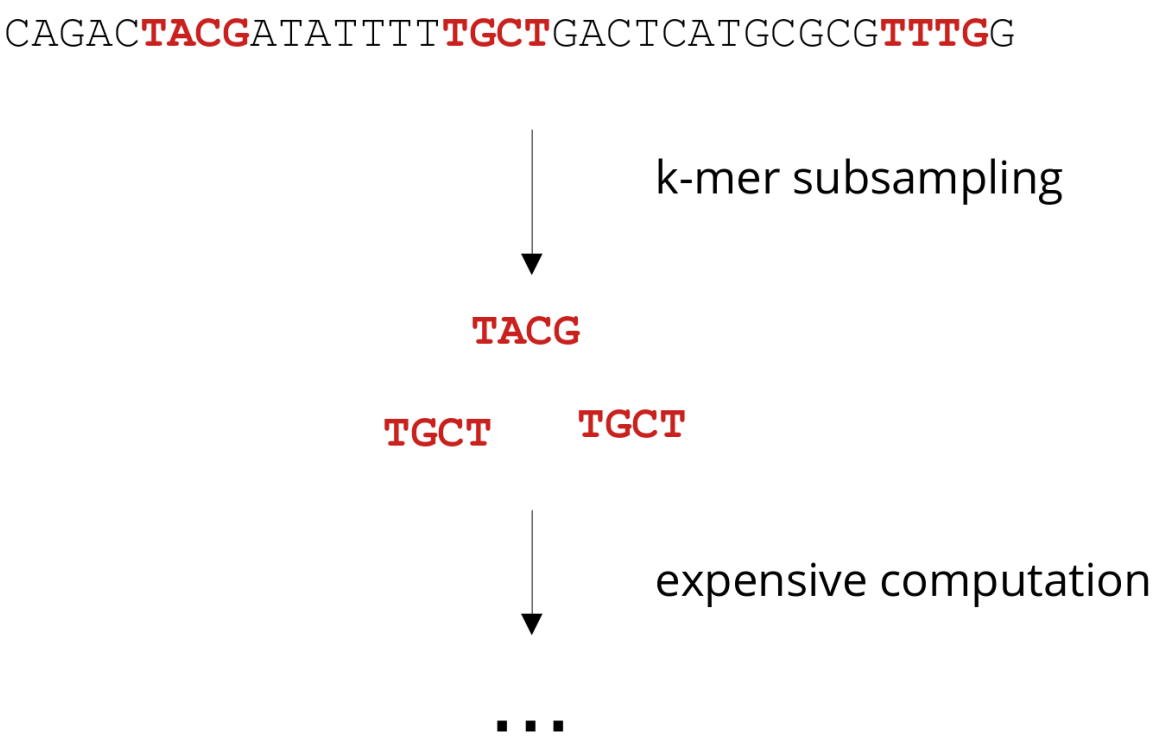
4 days, 256GB RAM

hifiasm_meta
11 days, 454GB RAM

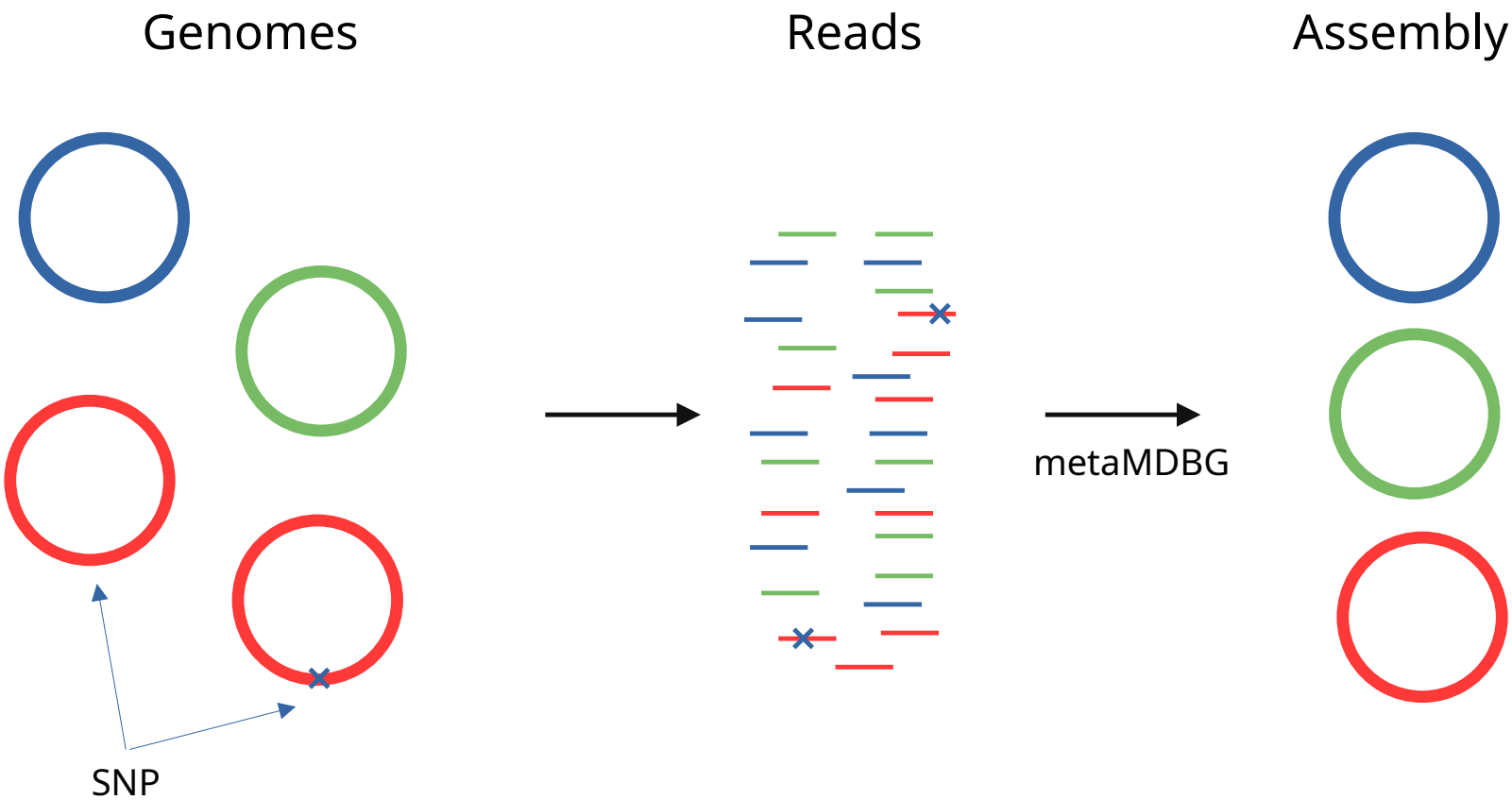
metaMDBG
19h, 10G RAM

metaMDBG: the trick is sketching input reads



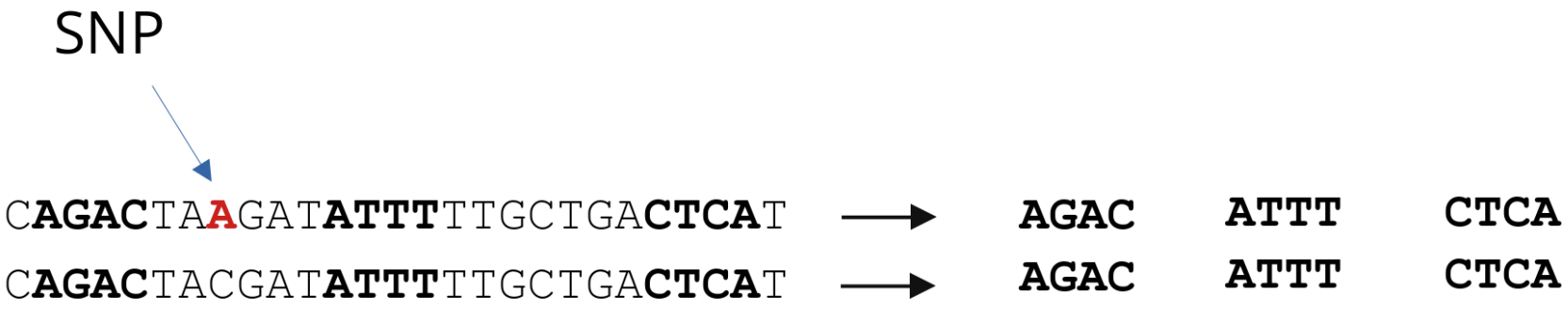
- minimizers, FracMinHash, seed-chain, strobemers...
- minimap2, Mash, BLAST, **metaMDBG**...

metaMDBG loses strain diversity



- metaMDBG is very fast, but some variants are lost!

k-mer sketching loses SNPs



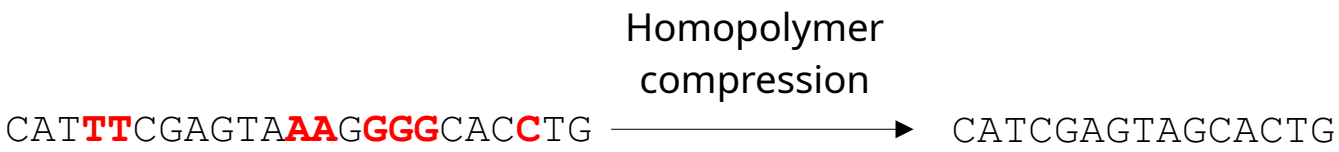
k-mer sketching loses SNPs

- Is k-mer subsampling really the only way to sketch sequences ?

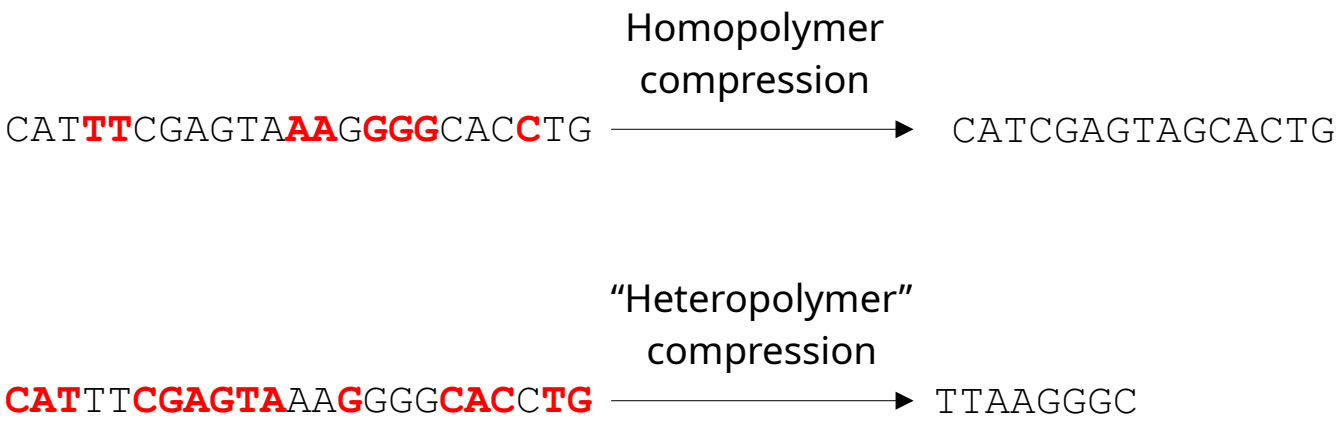
k-mer sketching loses SNPs

- Is k-mer subsampling really the only way to sketch sequences ?
- Blassel, Luc & Medvedev, Paul & Chikhi, Rayan. (2022). *Mapping-friendly sequence reductions: Going beyond homopolymer compression.* iScience.

Generalizing Homopolymer Compression



Generalizing Homopolymer Compression



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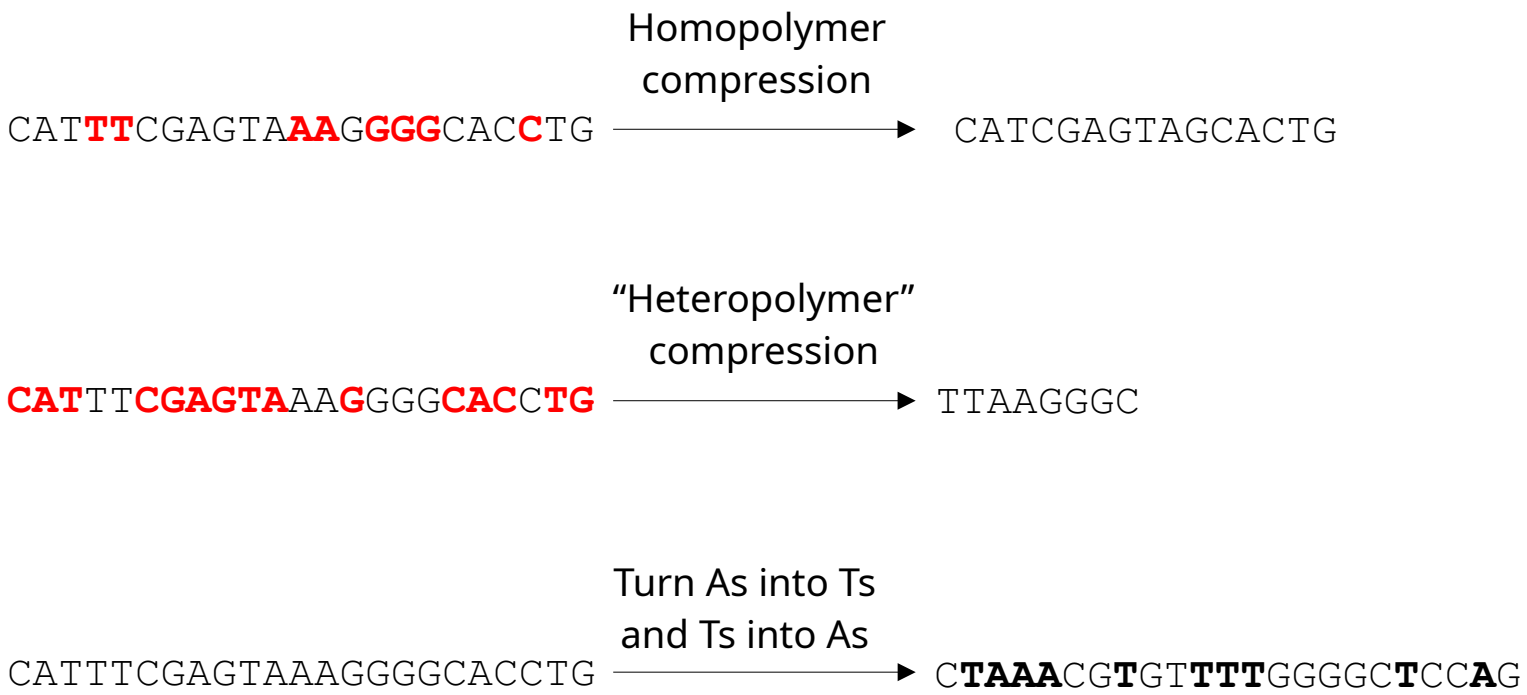

Generalizing Homopolymer Compression

			compression
CATTTCGAGTAAAGGGGCACCTG	Homopolymer compression →	CATCGAGTAGCACTG	0.75
CATTTCGAGTAAAGGGGCACCTG	"Heteropolymer" compression →	TTAAGGGC	0.25
CATTTCGAGTAAAGGGGCACCTG	Turn As into Ts and Ts into As →	CTAAACGTGTTTGGGGCTCCAG	1.0

Mapping-friendly Sequence Reductions: an example

$$f:\{A,C,G,T\}^{10}\rightarrow\{A,C,G,T,\emptyset\}$$

$$f(10-mer)\rightarrow A \quad if \quad hash(10-mer)\in[0,0.05]$$
$$f(10-mer)\rightarrow C \quad if \quad hash(10-mer)\in[0.05,0.1]$$
$$f(10-mer)\rightarrow G \quad if \quad hash(10-mer)\in[0.1,0.15]$$
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sequence `CAGTATGGATACAGATGGAGATATCATCGAGTAGGGGCACTGTACCAGAG`

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sequence **CAGTATGGAT**ACAGATGGAGATATCATCGAGTAGGGGCACTGTACCAGAG

hash(**CAGTATGGAT**)= 0.0023

f(**CAGTATGGAT**)= A

sketch A

Mapping-friendly Sequence Reductions: an example

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sequence CAGTATGGATACAGATGGAGATATCATCGAGTAGGGGCACTGTACCAGAG

hash(AGTATGGATA)= 0.624

f(AGTATGGATA)= $\emptyset$

sketch A

Mapping-friendly Sequence Reductions: an example

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sequence CA**GTATGGATAC**AGATGGAGATATCATCGAGTAGGGGCACTGTACCAGAG

hash(**GTATGGATAC**)= 0.124

f(**GTATGGATAC**)= G

sketch A G

Mapping-friendly Sequence Reductions: an example

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sequence CAG**TATGGATACA**GATGGAGATATCATCGAGTAGGGGCACTGTACCAGAG

hash(**TATGGATACA**)= 0.88

f(**TATGGATACA**)= $\emptyset$

sketch A G

Mapping-friendly Sequence Reductions: an example

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sequence CAGT**ATGGATACAG**ATGGAGATATCATCGAGTAGGGGCACTGTACCAGAG

hash(**ATGGATACAG**)= 0.32

f(**ATGGATACAG**)= $\emptyset$

sketch A G

Mapping-friendly Sequence Reductions: an example

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sequence CAGTA**TGGATACAGA**TGGAGATATCATCGAGTAGGGGCACTGTACCAGAG

hash(**TGGATACAGA**)= 0.19

f(**TGGATACAGA**)= T

sketch A G T

Mapping-friendly Sequence Reductions: an example

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sequence CAGTAT**GGATACAGAT**GGAGATATCATCGAGTAGGGGCACTGTACCAGAG

hash(**GGATACAGAT**)= 0.214

f(**GGATACAGAT**)= $\emptyset$

sketch A G T

Mapping-friendly Sequence Reductions: an example

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$$f(10-mer)\rightarrow A \quad if \quad hash(10-mer)\in[0,0.05]$$
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sequence CAGTATG**GATACAGATG**GAGATATCATCGAGTAGGGGCACTGTACCAGAG

hash(**GATACAGATG**)= 0.678

f(**GATACAGATG**)= $\emptyset$

sketch A G T

Mapping-friendly Sequence Reductions: an example

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sequence CAGTATGG**ATACAGATGG**AGATATCATCGAGTAGGGGCACTGTACCAGAG

hash(**ATACAGATGG**)= 0.669

f(**ATACAGATGG**)= $\emptyset$

sketch A G T

Mapping-friendly Sequence Reductions: an example

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sequence CAGTATGGATACAGATGGAGATATCATCGAGTAGGGGCAC**TGTACCAGAG**

hash(**TGTACCAGAG**)= 0.06

f(**TGTACCAGAG**)= C

sketch A G T T C C G T C

Mapping-friendly Sequence Reductions: homopolymer compression

$$f:\{A,C,G,T\}^2 \rightarrow \{A,C,G,T,\emptyset\}$$

$f(AA)\rightarrow\emptyset$	$f(CA)\rightarrow A$	$f(GA)\rightarrow A$	$f(TA)\rightarrow A$
$f(AC)\rightarrow C$	$f(CC)\rightarrow\emptyset$	$f(GC)\rightarrow C$	$f(TC)\rightarrow C$
$f(AG)\rightarrow G$	$f(CG)\rightarrow G$	$f(GG)\rightarrow\emptyset$	$f(TG)\rightarrow G$
$f(AT)\rightarrow T$	$f(CT)\rightarrow T$	$f(GT)\rightarrow T$	$f(TT)\rightarrow\emptyset$

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sequence ACGTTG

sketch

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sequence **AC**GTTG

sketch C

Mapping-friendly Sequence Reductions: homopolymer compression

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$f(AT)\rightarrow T$	$f(CT)\rightarrow T$	$f(GT)\rightarrow T$	$f(TT)\rightarrow\emptyset$

sequence ACGTTG

sketch CG

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$f(AT)\rightarrow T$	$f(CT)\rightarrow T$	$f(GT)\rightarrow T$	$f(TT)\rightarrow\emptyset$

sequence ACGTTG

sketch CGT

Mapping-friendly Sequence Reductions: homopolymer compression

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sequence ACG**TT**G

sketch CGT

Mapping-friendly Sequence Reductions: homopolymer compression

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$f(AT)\rightarrow T$	$f(CT)\rightarrow T$	$f(GT)\rightarrow T$	$f(TT)\rightarrow\emptyset$

sequence ACGT**TG**

sketch CGT G

Mapping-friendly Sequence Reductions: definition

$$l \in \mathbb{N}$$

$$f : \{A, C, G, T\}^l \rightarrow \{A, C, G, T, \emptyset\}$$

$$\forall\, kmer \in \{A, C, G, T\}^l, rc(f(kmer)) = f(rc(kmer))$$

Mapping-friendly Sequence Reductions: key parameters

$$f:\{A,C,G,T\}^{10}\rightarrow\{A,C,G,T,\emptyset\}$$

order (l)

$$f(10-mer)\rightarrow A \quad if \quad hash(10-mer)\in[0,0.05]$$
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compression ratio (c)

sequence CAGTATGGATACAGATGGAGATATCATCGAGTAGGGGCACTGTACCAGAG

sketch A G T T C C G T C

MSRs=Mapping-friendly Sequence Reductions

- MSR reductions are mapping-friendly

- original sequences align $\iff$ reduced sequences align

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- Key property of MSRs

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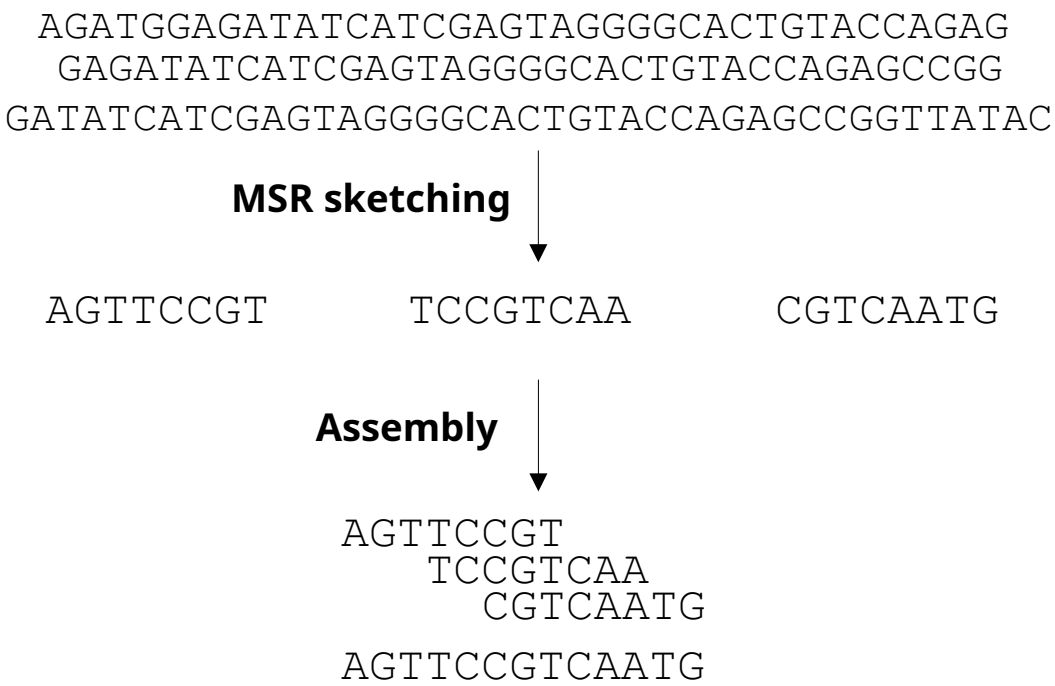
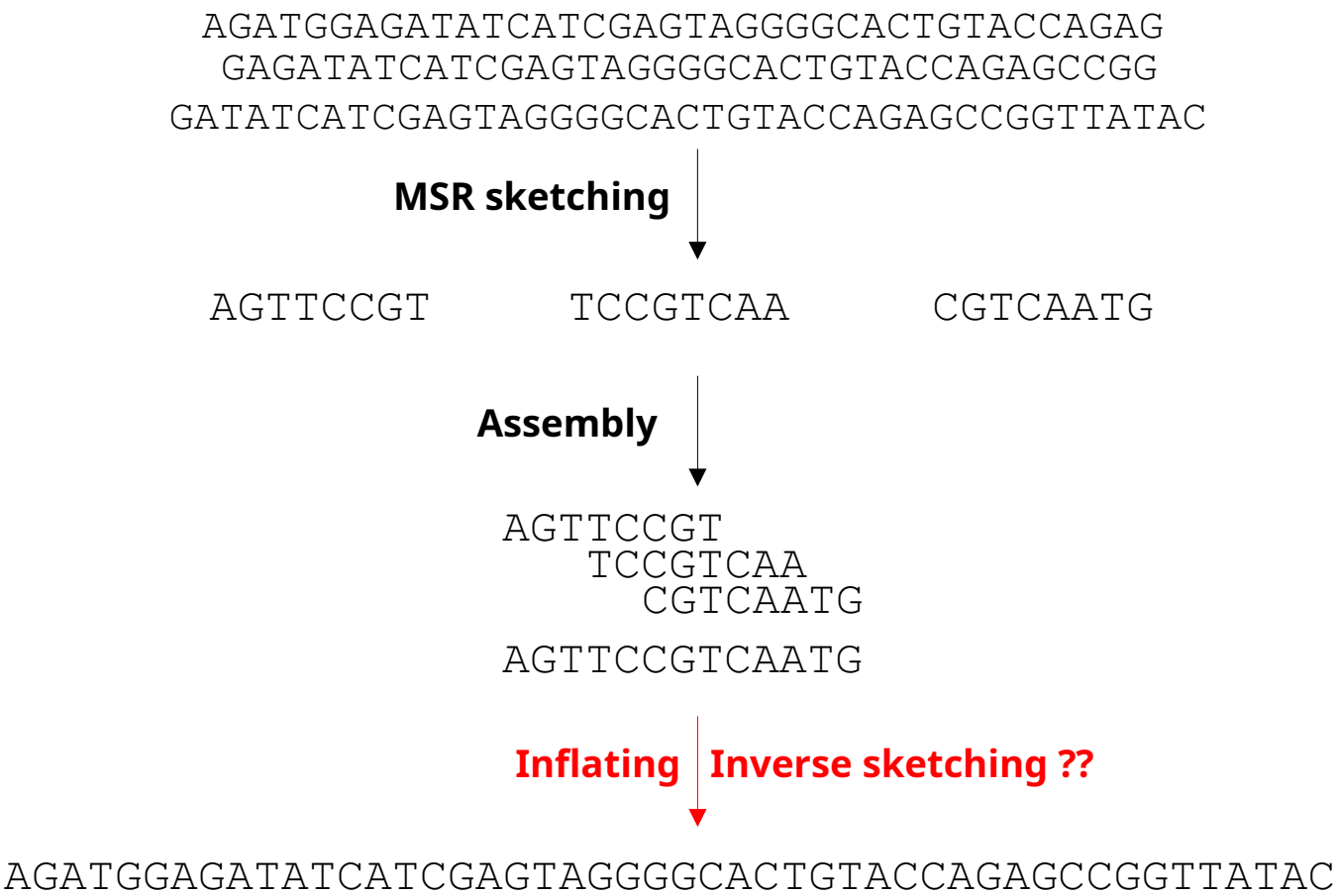
- original sequences align $\iff$ reduced sequences align
- Key property of MSRs
- Let's compress massively and assemble!

Assembling using MSR sketches



Assembling using MSR sketches



Inflating a reduced assembly

- Keep a record while compressing

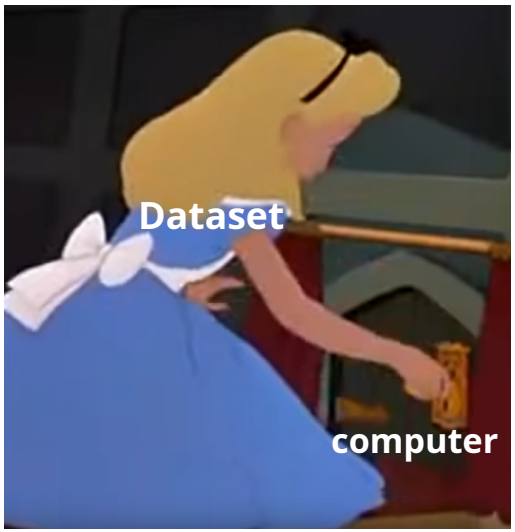
sequence CAGTATGGATACAGATGGAGATATCATCGAGTAGGGGCACTGTACCAGAG

sketch _____**AG**_____**A**_____**G**_____**C**_____**A**_

record {AGAG → ATGGATACAGATGGAGATATCATCG,
GAGC → AGTATGGATACAGATGGAGATATCATCGAGTAGGGGC,
AGCA → GATGGAGATATCATCGAGTAGGGGCACTGTAC}

The Alice assembler: assembling with MSR

Input dataset is too big



1. sketch reads

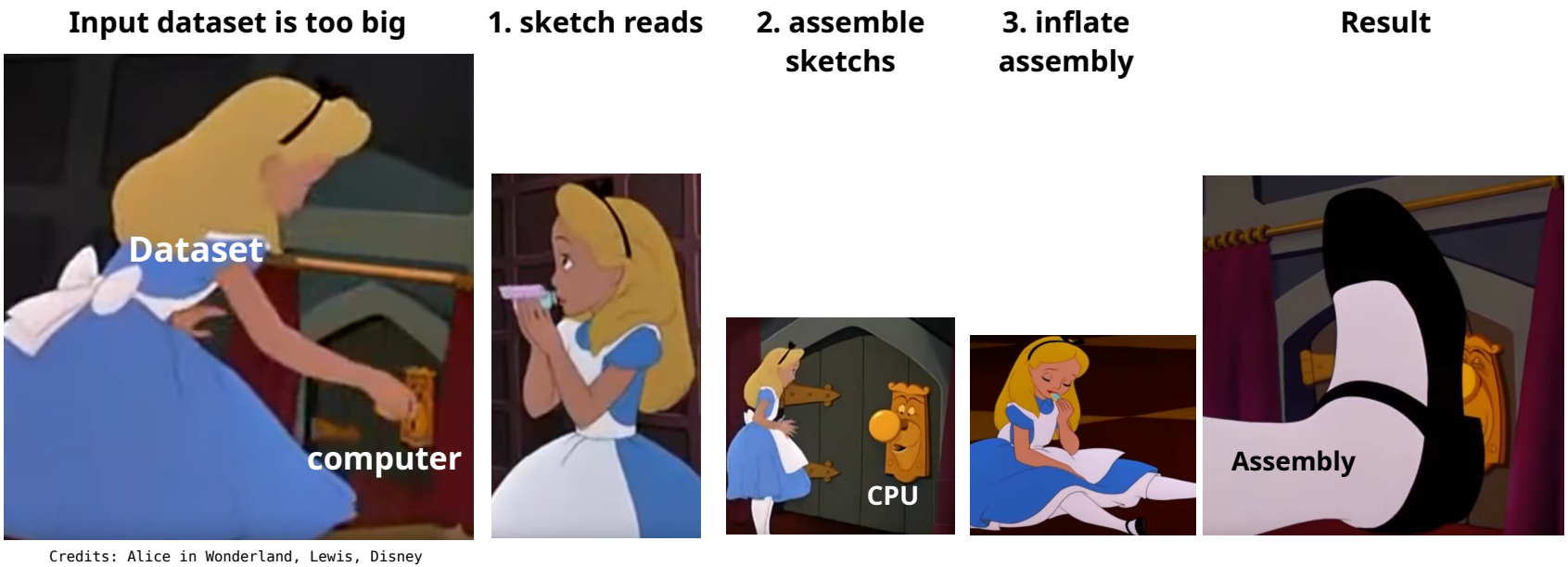
2. assemble sketchs

3. inflate assembly

Result

Credits: Alice in Wonderland, Lewis, Disney

The Alice assembler: assembling with MSR



Credits: Alice in Wonderland, Lewis, Disney

- Function f: chaotic hash function
- Any assembler for step 2., by default BCALM2+tip-clipping
- `github.com/rolandfaure/alice-asm`

MSRs keep SNPs

$$f:\{A,C,G,T\}^{10}\rightarrow\{A,C,G,T,\emptyset\}$$

$$f(10-mer)\rightarrow A \quad if \quad hash(10-mer)\in[0,0.05]$$
$$f(10-mer)\rightarrow C \quad if \quad hash(10-mer)\in[0.05,0.1]$$
$$f(10-mer)\rightarrow G \quad if \quad hash(10-mer)\in[0.1,0.15]$$
$$f(10-mer)\rightarrow T \quad if \quad hash(10-mer)\in[0.15,0.2]$$
$$f(10-mer)\rightarrow \emptyset \quad if \quad hash(10-mer)>0.2$$

sequence1 **CAGTATGGAT**ACAGATGGAGATATCATCGAGTAGGGGCACTGTACCAGAG

sketch1 A

sequence2 **CAGTATGGAT**ACAGATGGAGATAT**G**ATCGAGTAGGGGCACTGTACCAGAG

sketch2 A

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sequence1	C**AGTATGGATA**CAGATGGAGATATCATCGAGTAGGGGCACTGTACCAGAG
sketch1	A
sequence2	C**AGTATGGATA**CAGATGGAGATAT**G**ATCGAGTAGGGGCACTGTACCAGAG
sketch2	A

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sequence1 CA**GTATGGATAC**AGATGGAGATATCATCGAGTAGGGGCACTGTACCAGAG

sketch1 A G

sequence2 CA**GTATGGATAC**AGATGGAGATAT**G**ATCGAGTAGGGGCACTGTACCAGAG

sketch2 A G

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sequence1 CAGTATGGATACAG**ATGGAGATAT**CATCGAGTAGGGGCACTGTACCAGAG

sketch1 A G T

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sequence1	CAGTATGGATACAGA**TGGAGATATC**ATCGAGTAGGGGCACTGTACCAGAG
sketch1	A G T T
sequence2	CAGTATGGATACAGA**TGGAGATATG**ATCGAGTAGGGGCACTGTACCAGAG
sketch2	A G T

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sequence1	CAGTATGGATACAGATGGAGATATCATCGAGTAGGGGCACTGTACCAGAG
sketch1	A G T T
sequence2	CAGTATGGATACAGATGGAGATATGATCGAGTAGGGGCACTGTACCAGAG
sketch2	A G T G

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sequence1	CAGTATGGATACAGATG**GAGATATCAT**CGAGTAGGGGCACTGTACCAGAG
sketch1	A G T T C
sequence2	CAGTATGGATACAGATG**GAGATATGAT**CGAGTAGGGGCACTGTACCAGAG
sketch2	A G T G

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sequence1	CAGTATGGATACAGATGG**AGATATCATC**GAGTAGGGGCACTGTACCAGAG
sketch1	A G T T C
sequence2	CAGTATGGATACAGATGG**AGATATGATC**GAGTAGGGGCACTGTACCAGAG
sketch2	A G T G

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sequence1	CAGTATGGATACAGATGGAGATATCATCGAGTAGGGGCACTGTACCAGAG
sketch1	A G T T C C G T C
sequence2	CAGTATGGATACAGATGGAGATATGATCGAGTAGGGGCACTGTACCAGAG
sketch2	A G T G A C G T C

MSRs keep and amplify SNPs

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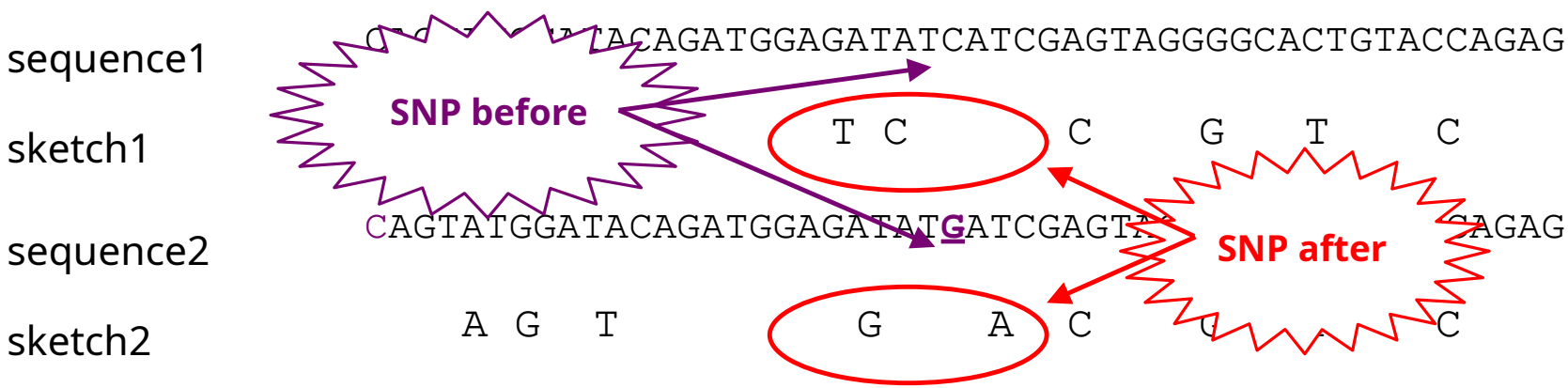

MSRs keep and amplify SNPs

- A SNP affects l l-mers
- Each l-mer outputs a base with probability c
- Probability that a SNP disappears in the sketch:

$$\sum_{i=0}^{l}\left(\binom{l}{i} c^i \cdot (1-c)^{l-i}\right)^2 \cdot \frac{1}{4^i} \approx (1-c)^{2l}$$

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	k-mer subsampling	MSR
c=0.1	0.81	10^{-10}
c=0.01	0.98	0.13

Table: Probability that a SNP disappears in sketch, using l=101

The Alice assembler: results

- Zymobiomics Gut Microbiome Standard with 5 strains of *E.coli*

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Genome fraction (%)

	metamdbg	alice
Escherichia_coli_B1109	78.408	92.039
Escherichia_coli_B3008	36.411	99.968
Escherichia_coli_B766	95.647	95.641
Escherichia_coli_JM109	38.211	96.334
Escherichia_coli_b2207	37.335	95.495

Measured using metaQUAST

- Strains are not collapsed

The Alice assembler: results

- Assembling a human gut metagenome (HiFi sequencing)

Flye
4d, 256G RAM

hifiasm_meta
11d, 454G RAM

metaMDBG
19h, 10G RAM

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- Assembling a human gut metagenome (HiFi sequencing)

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11d, 454G RAM

metaMDBG
19h, 10G RAM

Alice
5h, 10G RAM

The dark side of MSR: errors

- Distance between errors $\approx$ Original distance * compression ratio c
- original sequences align $\iff$ reduced sequences align **not completely true**

Potential applications and future MSRs

- MSRs are wild and unexplored

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- MSRs are wild and unexplored
- Alignment? SNP calling? Indexing? Whole genome operations (e.g. pangenome graph building)?
- Changing the MSR itself: error rate? Biology-informed MSR?