P&S Genomics

Lecture 4: Read Mapping

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ETH Zürich

Spring 2023

24 March 2023

Agenda for Lecture 3

- What is Genome Analysis?
- What is Intelligent Genome Analysis?
- How we Analyze Genome?

Agenda for Today

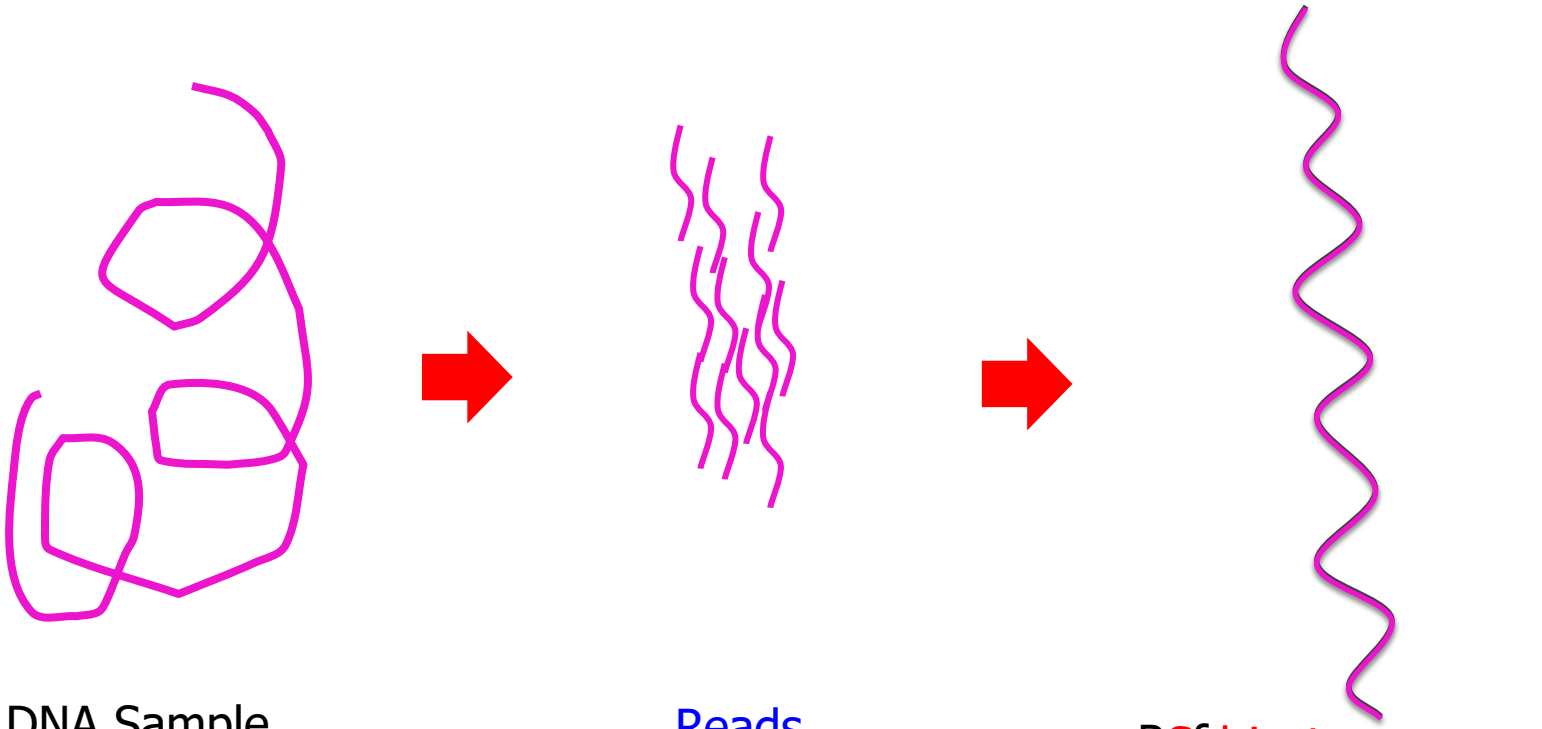
- What is Read Mapping?
- What Makes Read Mapper Slow?
- Algorithmic & Hardware Acceleration
  - Seed Filtering Technique
  - Pre-alignment Filtering Technique
  - Read Alignment Acceleration

Agenda for Today

- **What is Read Mapping?**
- What Makes Read Mapper Slow?
- Algorithmic & Hardware Acceleration
  - Seed Filtering Technique
  - Pre-alignment Filtering Technique
  - Read Alignment Acceleration

Read Mapping

Map reads to a known reference genome with some minor differences allowed

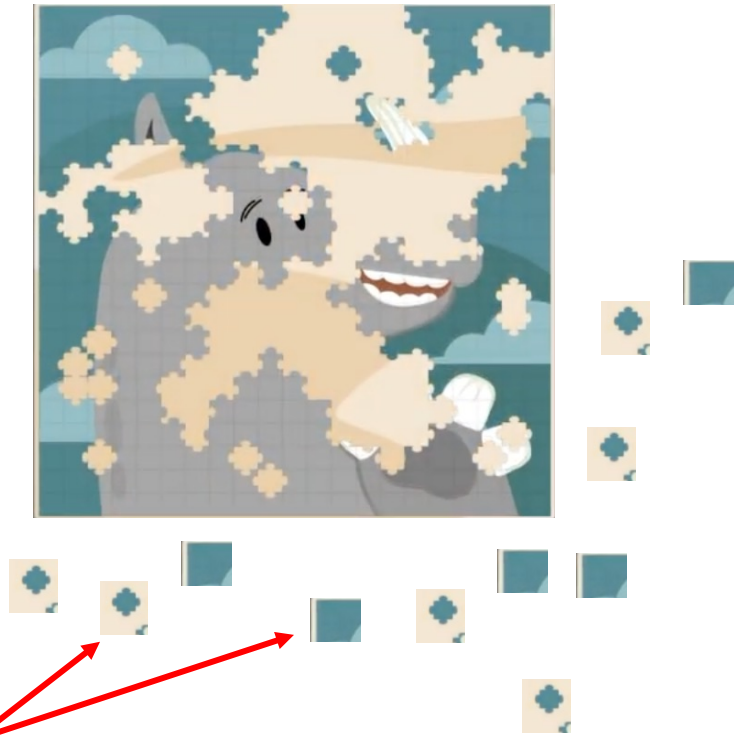


Solving the Puzzle

.FASTA file

Reference genome

.FASTQ file



Reads

https://www.pacb.com/smrt-science/smrt-sequencing/hifi-reads-for-highly-accurate-long-read-sequencing/

Cracking the 1st Human Genome Sequence

- **1990-2003:** The Human Genome Project (HGP) provides a complete and accurate sequence of all **DNA base pairs** that make up the human genome and finds 20,000 to 25,000 human genes.

3.2 x10^9 bases

13 years

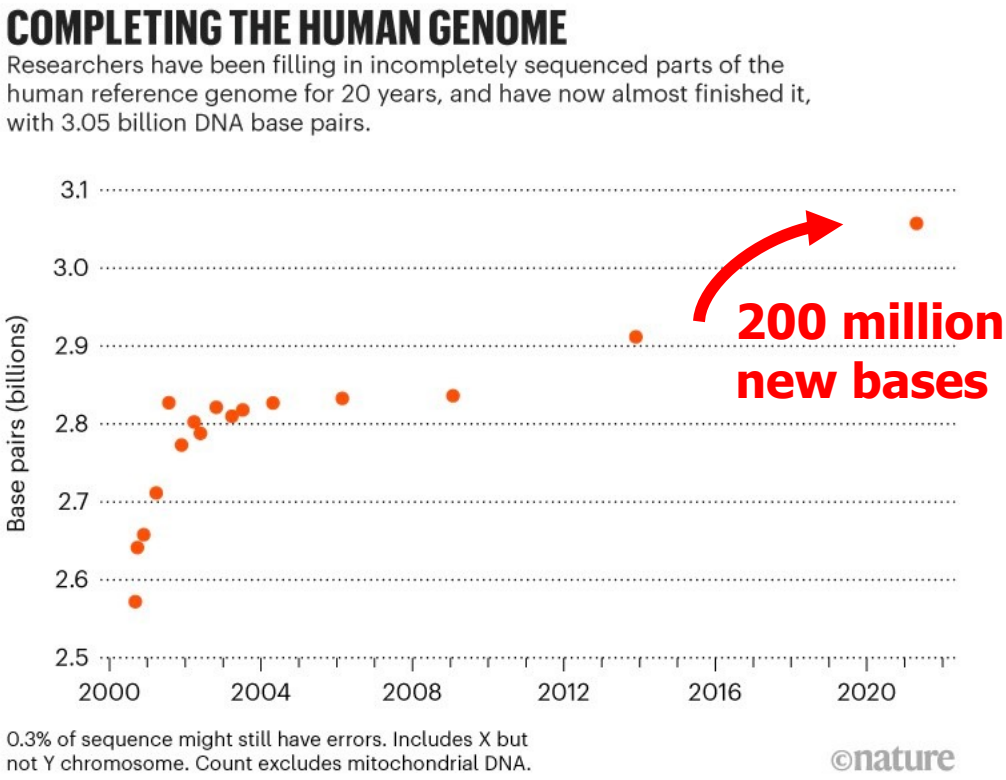
>3x10^9 $

Three Decades & Yet to be Complete!

The complete sequence of a human genome 27 May 2021

Sergey Nurk, Sergey Koren, Arang Rhie, Mikko Rautiainen, Andrey V. Bzikadze, Alla Mikheenko, Mitchell R. Vollger, Nicolas Altemose, Lev Uralsky, Ariel Gershman, Sergey Aganezov, Savannah J. Hoyt, Mark Diekhans, Glennis A. Logsdon, Michael Alonge, Stylianos E. Antonarakis, Matthew Borchers, Gerard G. Bouffard, Shelise Y. Brooks, Gina V. Caldas, Haoyu Cheng, Che
Philip C. Dishuck, Richard Durbin, Tatiana Dvorkina
Arkarachai Fungtammasan, Erik Garrison, Patrick G
Gabrielle A. Hartley, Marina Haukness, Kerstin How
Erich D. Jarvis, Peter Kerpedjiev, Melanie Kirsche, M
Valerie V. Maduro, Tobias Marschall, Ann M. McCartn
Eugene W. Myers, Nathan D. Olson, Benedict Paten,
Tamara Potapova, Evgeny I. Rogaev, Jeffrey A. Rosenf
Kishwar Shafin, Colin J. Shew, Alaina Shumate, Yumi
Jessica M. Storer, Aaron Streets, Beth A. Sullivan, Fra
Brian P. Walenz, Aaron Wenger, Jonathan M. D. Woo
Samantha Zarate, Urvashi Surti, Rajiv C. McCoy, Me
Rachel J. O'Neill, Winston Timp, Justin M. Zook, Mic
Adam M. Phillippy

doi: https://doi.org/10.1101/2021.05.26.445798

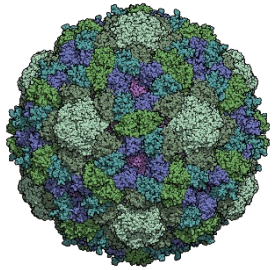


Obtaining the Human Reference Genome

- **GRCh38.p13**
- Description: Genome Reference Consortium Human Build 38 patch release 13 (GRCh38.p13)
- Organism name: [Homo sapiens (human)]
- Date: 2019/02/28
- 3,099,706,404 bases
- Compressed .fna file (964.9 MB)
- https://www.ncbi.nlm.nih.gov/assembly/GCF_000001405.39

```
>NC_000001.11 Homo sapiens chromosome 1, GRCh38.p13 Primary Assembly
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
….
```

How Long is DNA?



Phi X174 virus
5.386 Killo bp

E. coli O157:H7
5.44 Million bp

Homo Sapiens
3.2 Billion bp

Onion, Allium Cepa
16 Billion bp

Paris Japonica
149 Billion bp

Obtaining .FASTQ Files

- https://www.ncbi.nlm.nih.gov/sra/ERR240727

Full

Send to:

ERX215261: Whole Genome Sequencing of human TSI NA20754
1 ILLUMINA (Illumina HiSeq 2000) run: 4.1M spots, 818.7M bases, 387.2Mb downloads

Design: Illumina sequencing of library 6511095, constructed from sample accession SRS001721 for study accession SRP000540. This is part of an Illumina multiplexed sequencing run (9340_1). This submission includes reads tagged with the sequence TTAGGCAT.

Submitted by: The Wellcome Trust Sanger Institute (SC)

Study: Whole genome sequencing of (TSI) Toscani in Italia HapMap population
PRJNA33847 • SRP000540 • All experiments • All runs

Sample: Coriell GM20754
SAMN00001273 • SRS001721 • All experiments • All runs
Organism: Homo sapiens

Library:
Name: 6511095
Instrument: Illumina HiSeq 2000
Strategy: WGS
Source: GENOMIC
Selection: RANDOM
Layout: PAIRED
Construction protocol: Standard

Runs: 1 run, 4.1M spots, 818.7M bases, 387.2Mb

Run	# of Spots	# of Bases	Size	Published
ERR240727	4,093,747	818.7M	387.2Mb	2013-03-22

Let's learn
how to map a read

Read Mapping: A Brute Force Algorithm

Very expensive!

$O(m^2kn)$

m: read length
k: no. of reads
n: reference genome length

Read Mapping in 111 pages!

In-depth analysis of 107 read mappers (1988-2020)

Mohammed Alser, Jeremy Rotman, Dhrithi Deshpande, Kodi Taraszka, Huwenbo Shi, Pelin Icer Baykal, Harry Taegyun Yang, Victor Xue, Sergey Knyazev, Benjamin D. Singer, Brunilda Balliu, David Koslicki, Pavel Skums, Alex Zelikovsky, Can Alkan, Onur Mutlu, Serghei Mangul
"Technology dictates algorithms: Recent developments in read alignment"
Genome Biology, 2021
[Source code]

Alser *et al. Genome Biology* (2021) 22:249
https://doi.org/10.1186/s13059-021-02443-7

Genome Biology

REVIEW Open Access

Technology dictates algorithms: recent developments in read alignment

Mohammed Alser[1,2,3†], Jeremy Rotman[4†], Dhrithi Deshpande[5], Kodi Taraszka[4], Huwenbo Shi[6,7], Pelin Icer Baykal[8], Harry Taegyun Yang[4,9], Victor Xue[4], Sergey Knyazev[8], Benjamin D. Singer[10,11,12], Brunilda Balliu[13], David Koslicki[14,15,16], Pavel Skums[8], Alex Zelikovsky[8,17], Can Alkan[2,18], Onur Mutlu[1,2,3†] and Serghei Mangul[5*†]

Feedback From Our Community!

James Ferguson
@Psy_Fer_

This is awesome! I've got my evening reading sorted.

Stéphane Le Crom
@slecrom

Very complete article on the evolution of read alignment algorithms. #NGS #genomics

Svetlana Gorokhova
@SGorokhova

An impressive overview of read alignment methods over the last three decades

BContrerasMoreira @BrunoContrerasM · Sep 10

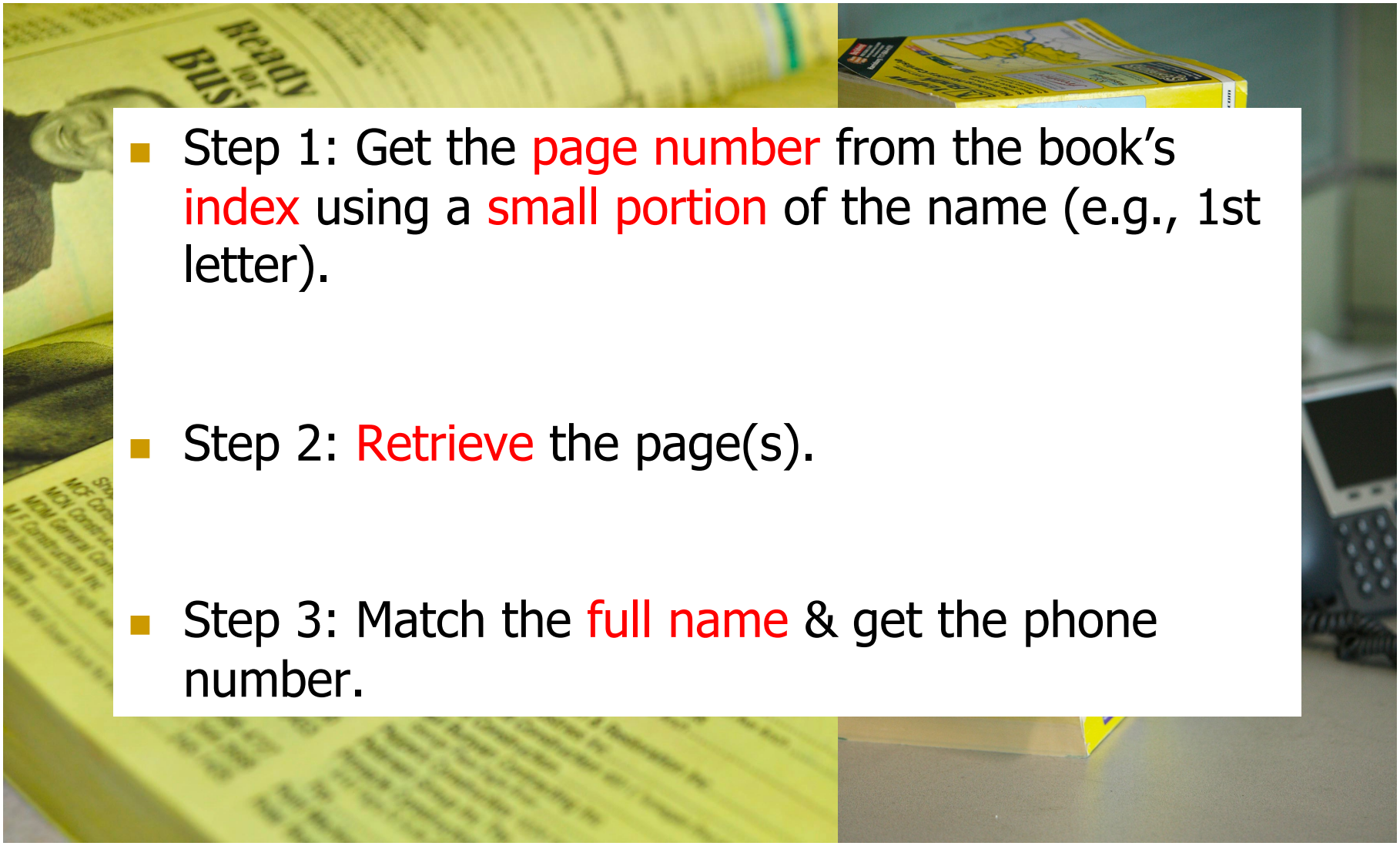
Replying to @mealser @GenomeBiology and 3 others

Buen hilo de repaso sobre la evolución de los algoritmos de alineamiento de secuencias a medida que ha mejorado la tecnología de secuenciación

https://twitter.com/mealser/status/1435223377644503040

Mapping a read is similar to querying the yellow pages!

Similar to Searching Yellow Pages!



- Step 1: Get the page number from the book's index using a small portion of the name (e.g., 1st letter).
- Step 2: Retrieve the page(s).
- Step 3: Match the full name & get the phone number.

Matching Each Read with Reference Genome

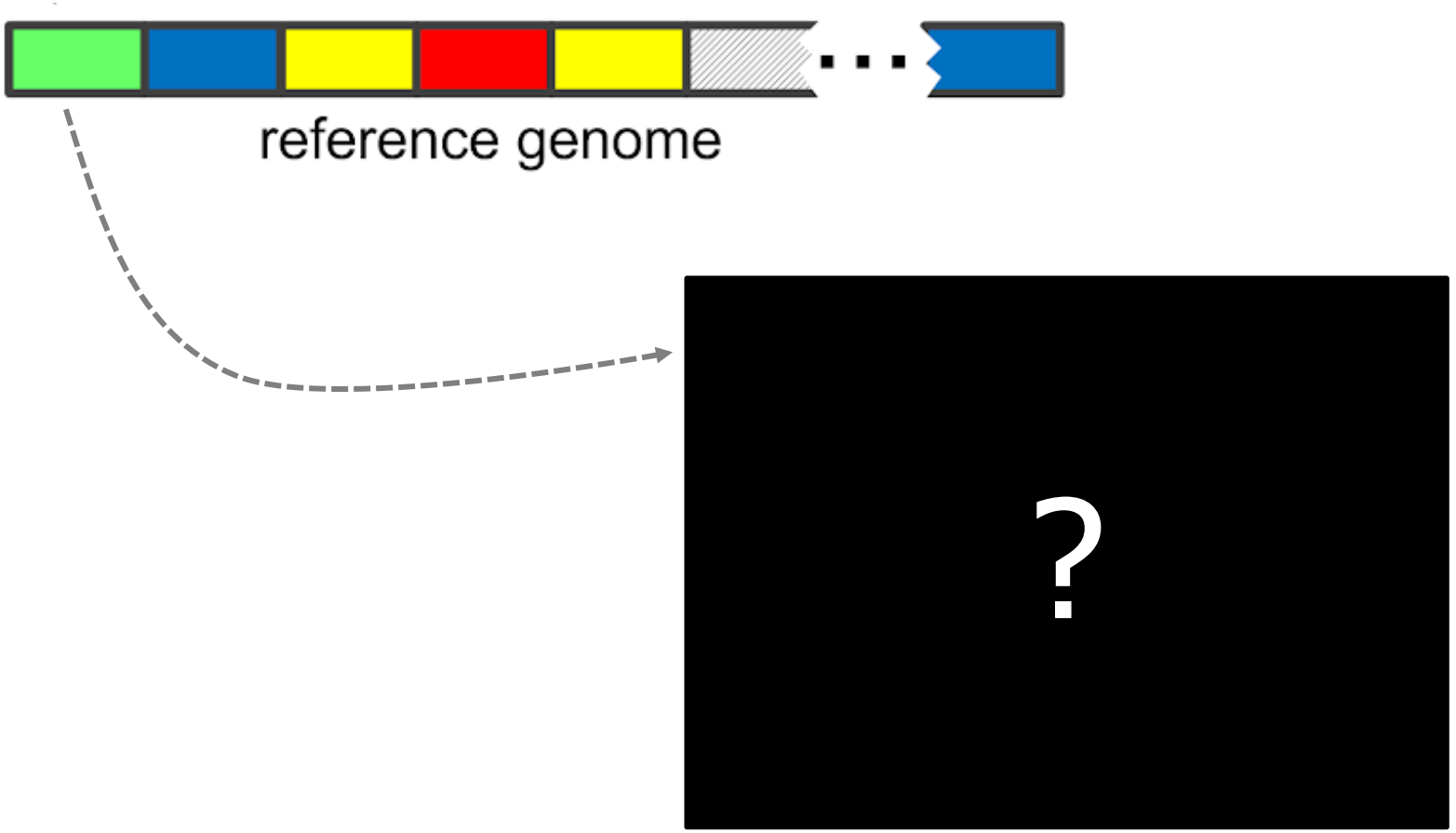
.FASTA file:

```
>NG_008679.1:5001-38170 Homo sapiens paired box 6 (PAX6)
ACCCTTCATTGACATTTAAACTCTGGGGCAGGTGAACGCGGCTGTCAGATCT
GCCACTTCCCCTGCCGAGCGGCGGTGAGAAGTGTGGGAACCGGCGCTGCCAGGCTCACCTGCCTCCCCGC
CCTCCGCTCCCAGGTAACCGCCCCCCCGGCCCGGCTCGGGGCCCGCGGGGCCTCTCCGCTG
CCAGCGACTGCTGTCCCCAAATCAAAGCCCGCCCCAAGTGGCCCCGGGGCTTGATTTTTGCTTTTAAAAG
GAGGCATACAAAGATGGAAGCGAGTTACTGAGGGAGGGATAGGAAGGGGGGTGGAGGAGGGACTTGTCTT
TGCCGAGTGTCAAAAGTAGCACTCCTAATCCAGTCCGGCCCT
GAGCTGGGAGTAGGGGGCGGGAGTCTGCTGCTGCTGTCTGCTAAAGCCACTCGCGACCGCGAAAAATGCA
GGAGGTGGGGACGCACTTTGCATCCAGACCTCCTCTGCATCGCAGTTCCGCTTGGGAAAG
TCCGTACCCGCGCCTAAAGACACCCTGCCGCGGGTCGGGCGAGGTGCAGCAGAAGTTTCCC
GCGGTTGCAAAGTGCAGATGGCTGGACCGCAACAAAGTCTAGAGATGGGGTTCGTTTCTCAGAAAGACGC
```

.FASTQ file:

```
@HWI-EAS209_0006_FC706VJ:5:58:5894:21141#ATCACG/1
TAATAAATCTTTAGATNNNNNNNNNTAG
+HWI-EAS209_0006_FC706VJ:5:58:5894:21141#ATCACG/1
efcfffffcfeefffcffffffddf`feed]`]_Ba_^__[YBBBBBBBBBRTT
```

Step 1: Indexing the Reference Genome

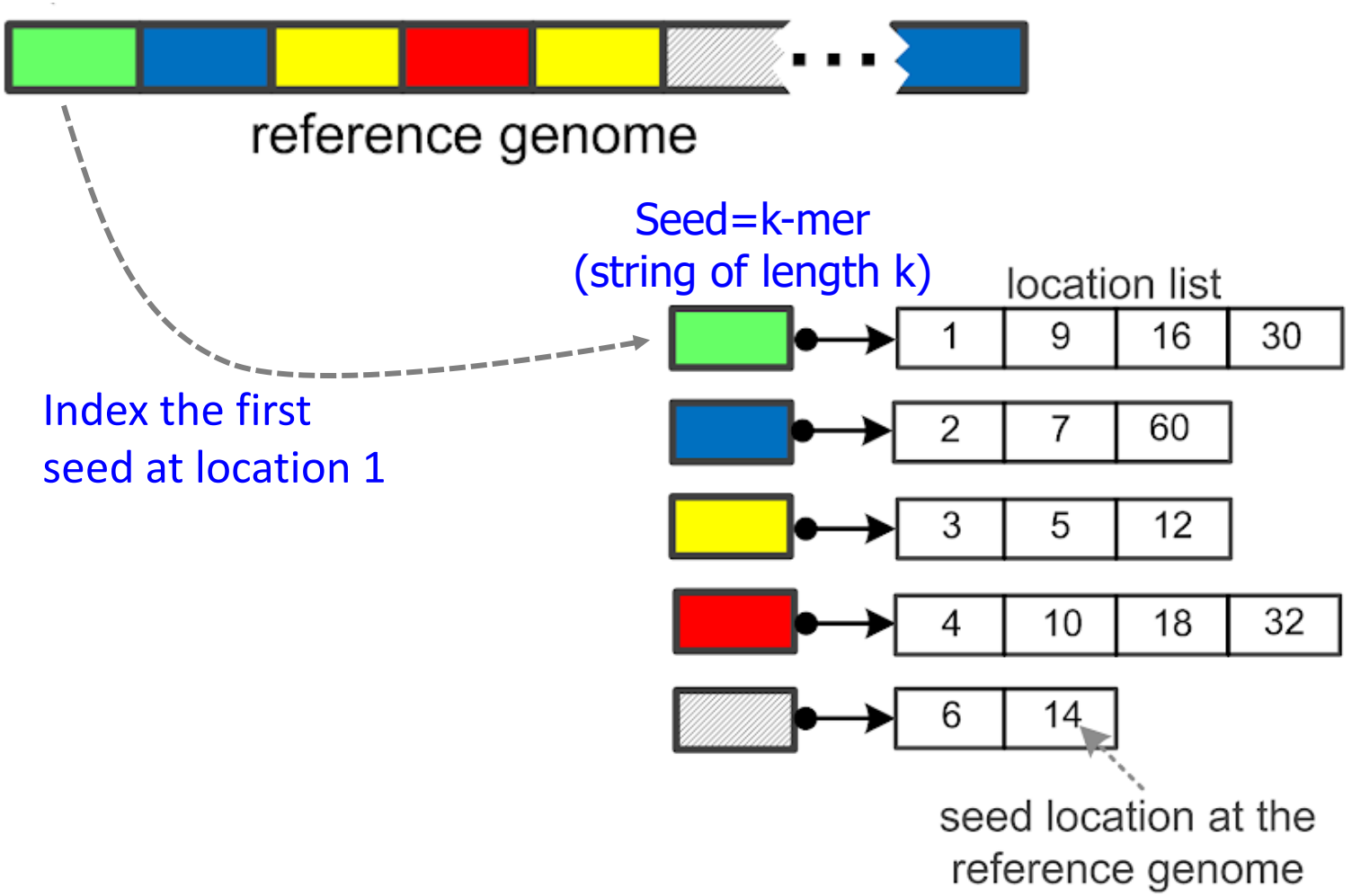


Popular Indexing Technique

Hashing is the most popular indexing technique for read mapping since 1988

Alser+, "Technology dictates algorithms: Recent developments in read alignment", Genome Biology, 2021

Step 1: Indexing the Reference Genome



Genome Index Properties

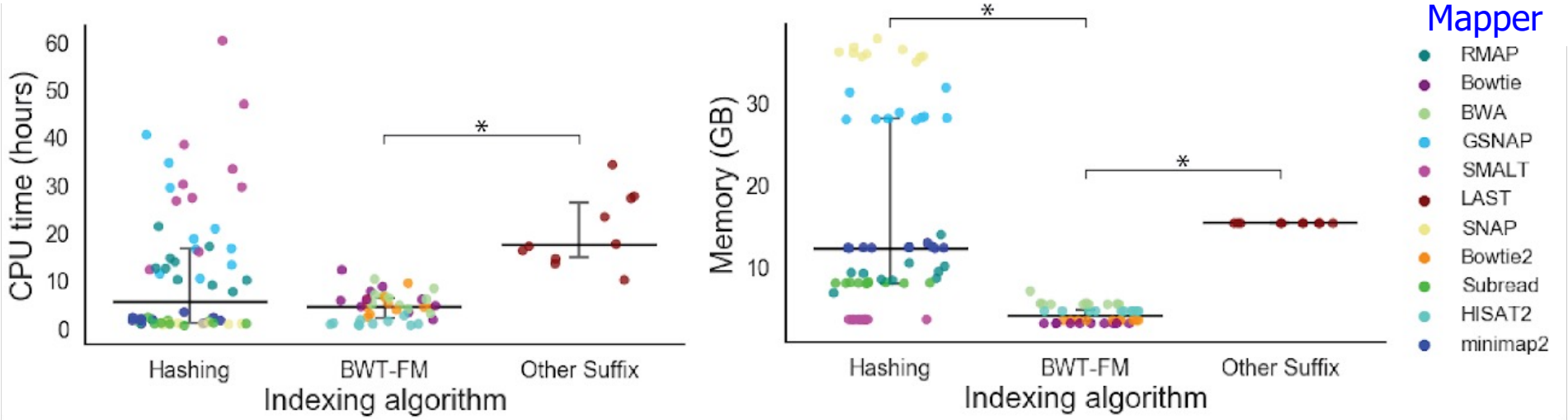
- The index is built only once for each reference.

- Seeds can be overlapping, non-overlapping, spaced, adjacent, non-adjacent, minimizers, compressed, …

Tool	Version	Index Size*	Indexing Time
mrFAST	2.2.5	16.5 GB	20.00 min
minimap2	0.12.7	7.2 GB	3.33 min
BWA-MEM	0.7.17	4.7 GB	49.96 min

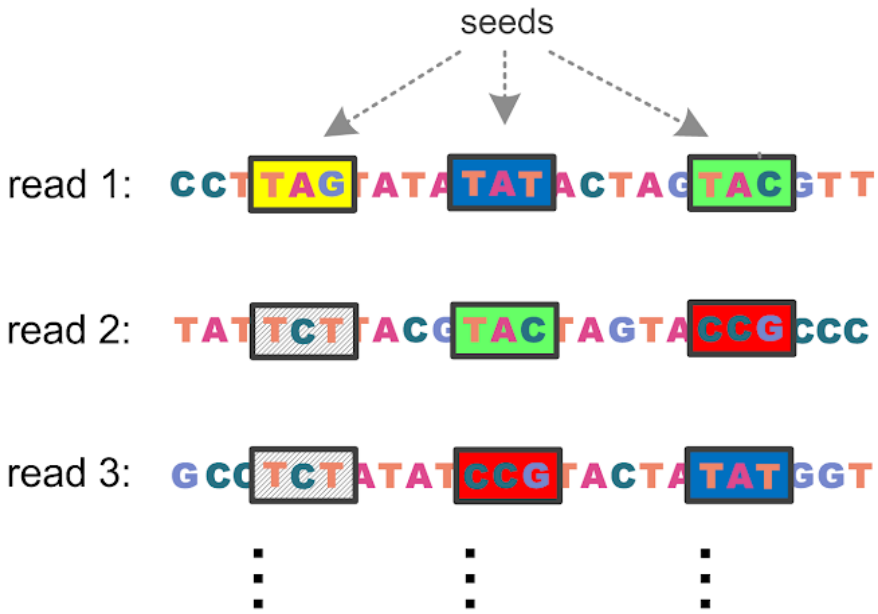
*Human genome = 3.2 GB

Performance of Human Genome Indexing

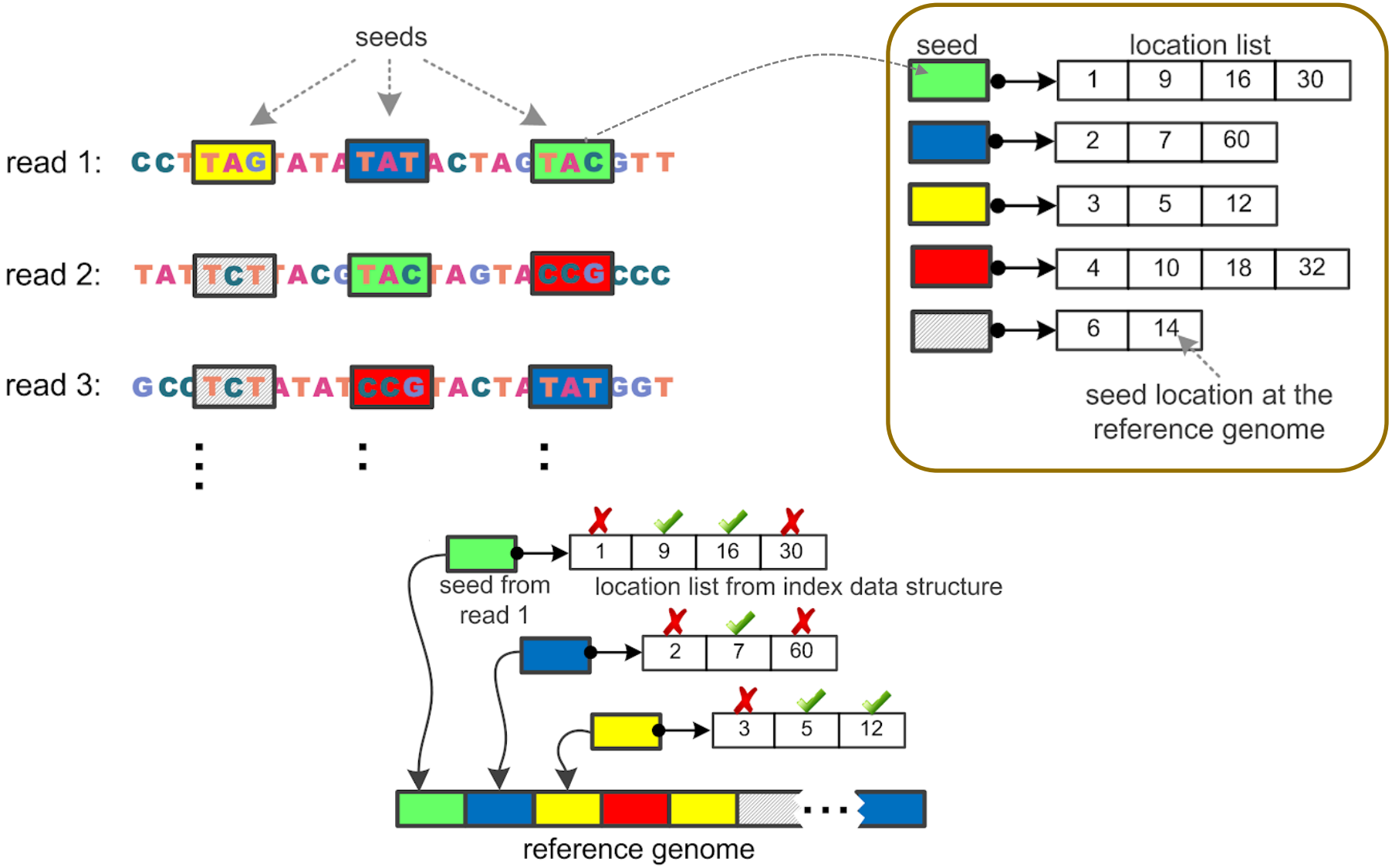


Alser+, "Technology dictates algorithms: Recent developments in read alignment", Genome Biology, 2021

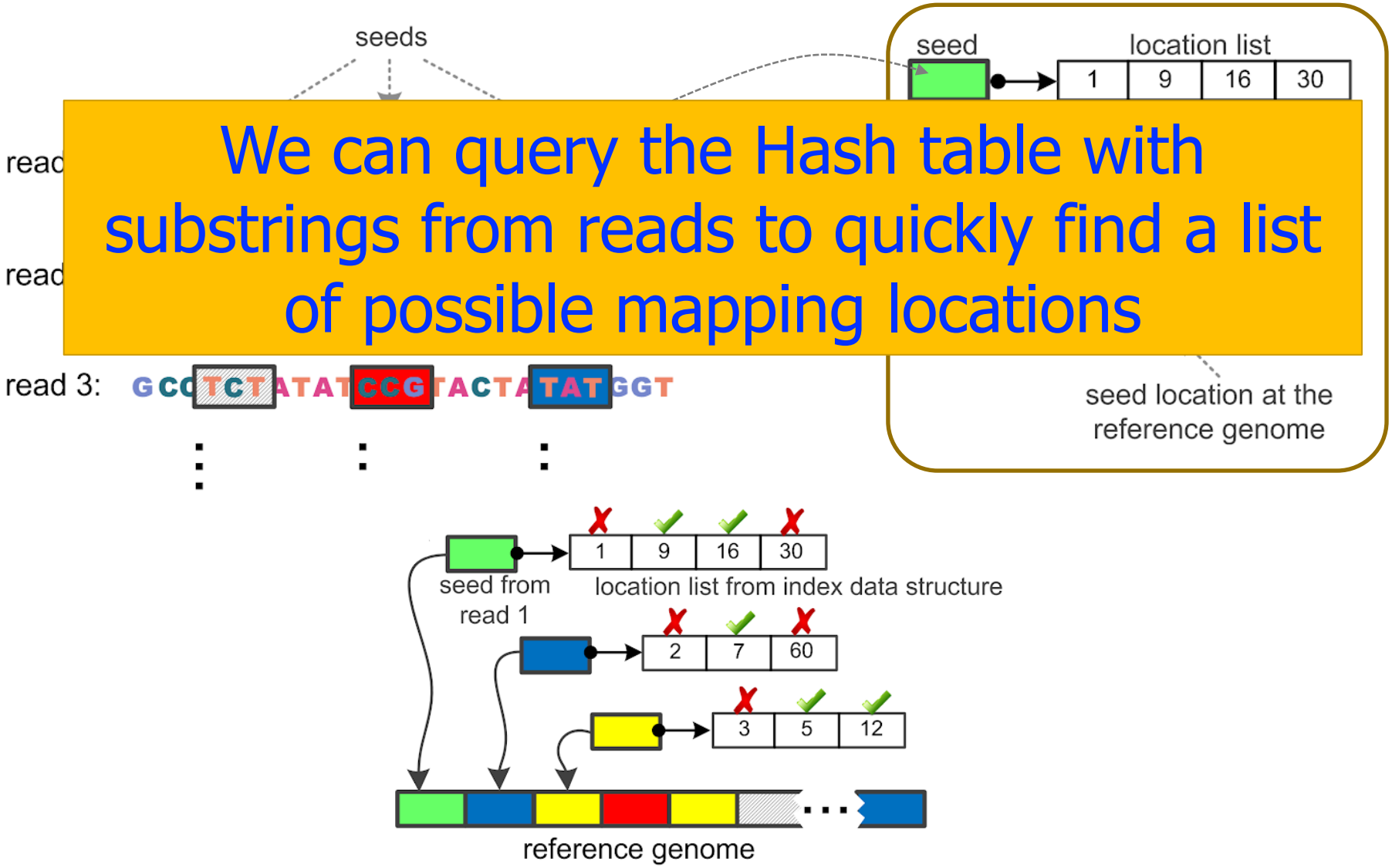
Step 2: Query the Index Using Read Seeds



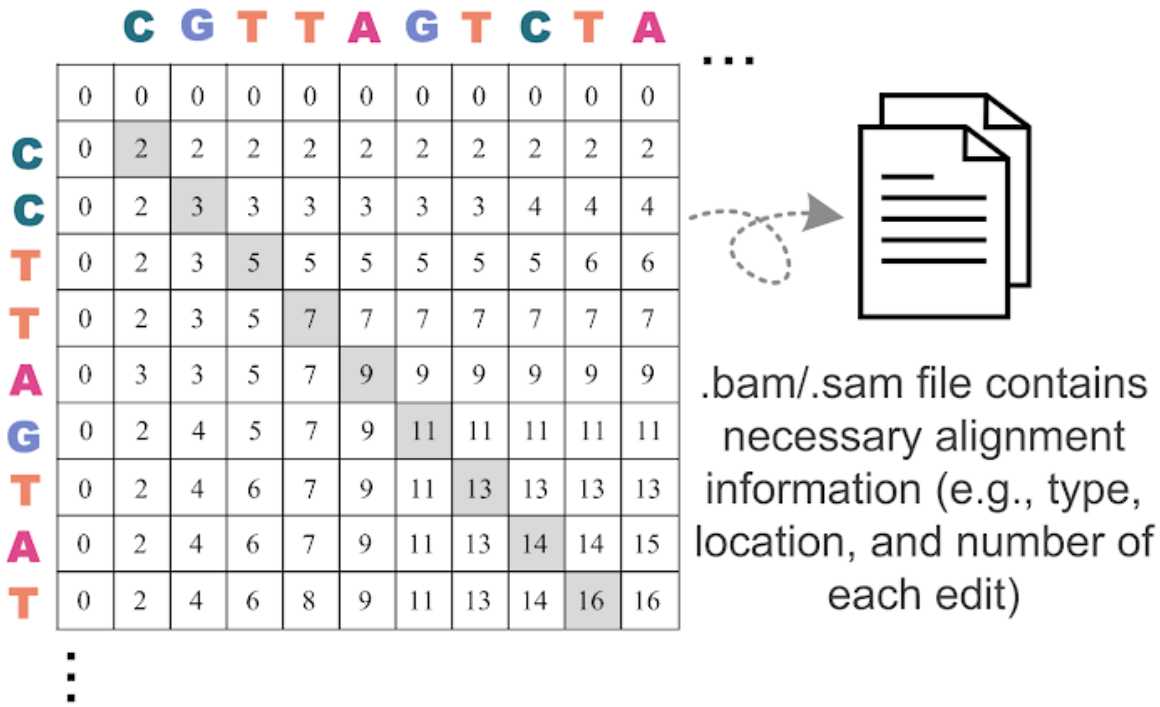
Step 2: Query the Index Using Read Seeds



Step 2: Query the Index Using Read Seeds



Step 3: Sequence Alignment (Verification)

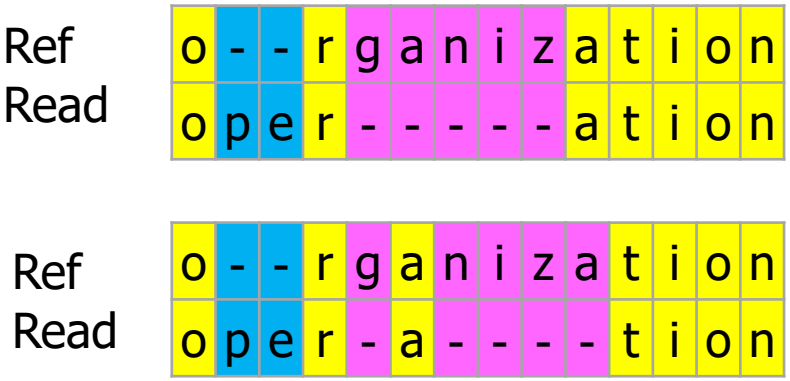


		C	G	T	T	A	G	T	C	T	A
	0	0	0	0	0	0	0	0	0	0	0
C	0	2	2	2	2	2	2	2	2	2	2
C	0	2	3	3	3	3	3	3	4	4	4
T	0	2	3	5	5	5	5	5	5	6	6
T	0	2	3	5	7	7	7	7	7	7	7
A	0	3	3	5	7	9	9	9	9	9	9
G	0	2	4	5	7	9	11	11	11	11	11
T	0	2	4	6	7	9	11	13	13	13	13
A	0	2	4	6	7	9	11	13	14	14	15
T	0	2	4	6	8	9	11	13	14	16	16

Step 3: Sequence Alignment (Verification)

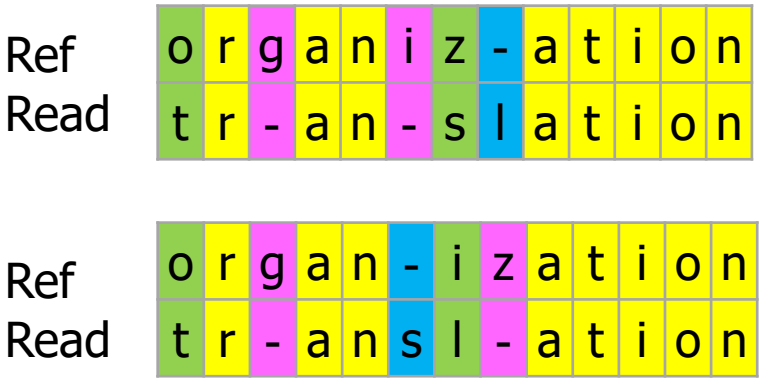
- **Edit distance** is defined as the minimum number of edits (i.e. insertions, deletions, or substitutions) needed to make the read exactly match the reference segment.

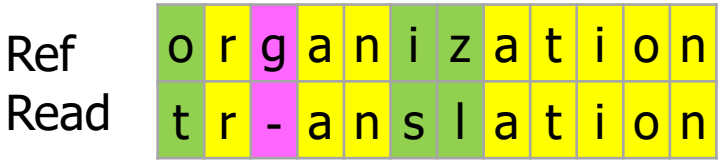
organization x operation



Edit distance = 7

organization x translation





Edit distance = 4

match
deletion
insertion
mismatch

Popular Algorithms for Sequence Alignment

Smith-Waterman remains

the most popular algorithm

since 1988

Hamming distance is

the second most popular technique

since 2008

Alser+, "Technology dictates algorithms: Recent developments in read alignment", Genome Biology, 2021

An Example of Hash Table Based Mappers

- + Guaranteed to find *all* mappings → very sensitive
- + Can tolerate up to *e* errors

nature genetics

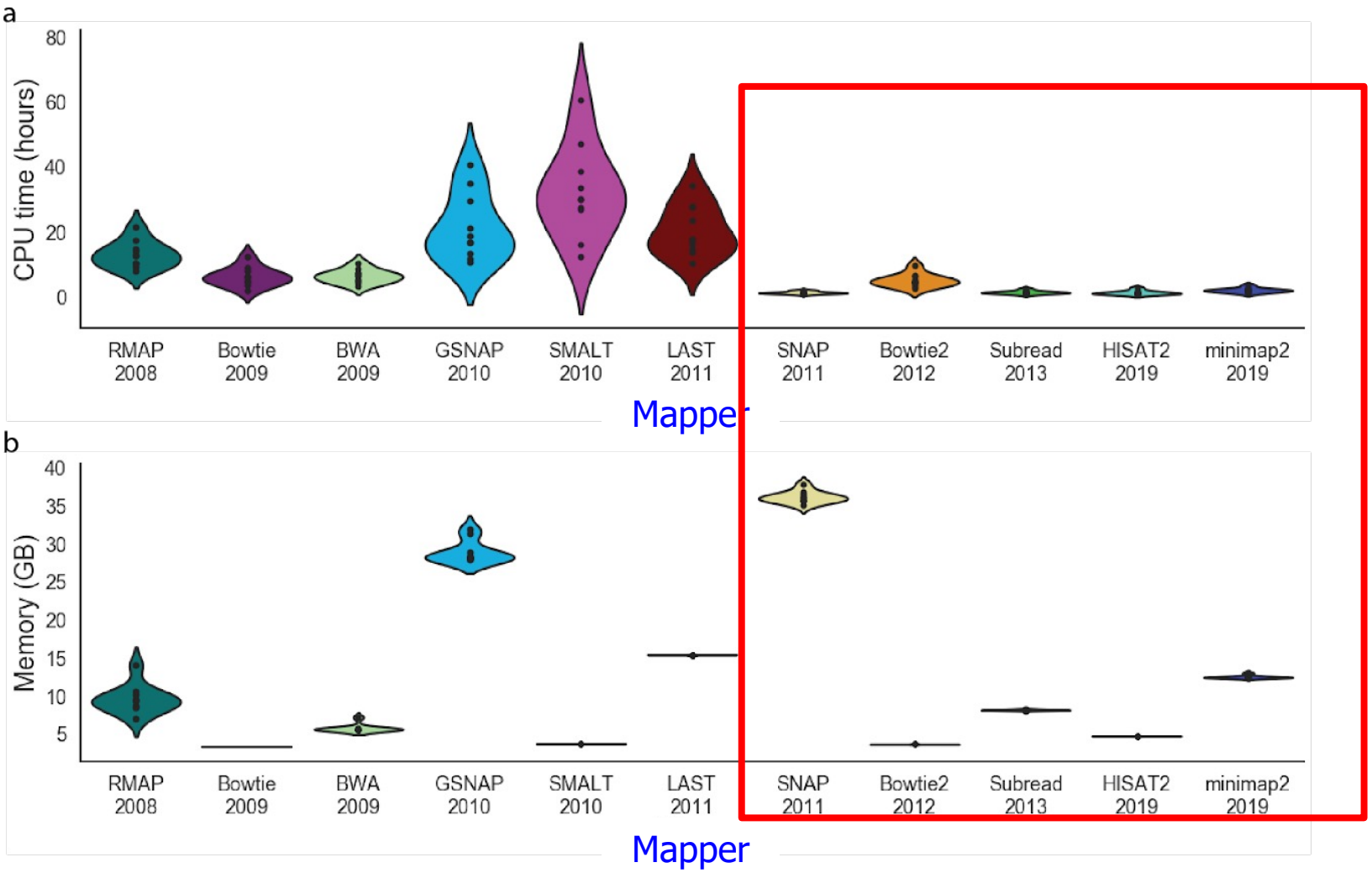
https://github.com/BilkentCompGen/mrfast

Personalized copy number and segmental duplication maps using next-generation sequencing

Can Alkan[1,2], Jeffrey M Kidd[1], Tomas Marques-Bonet[1,3], Gozde Aksay[1], Francesca Antonacci[1], Fereydoun Hormozdiari[4], Jacob O Kitzman[1], Carl Baker[1], Maika Malig[1], Onur Mutlu[5], S Cenk Sahinalp[4], Richard A Gibbs[6] & Evan E Eichler[1,2]

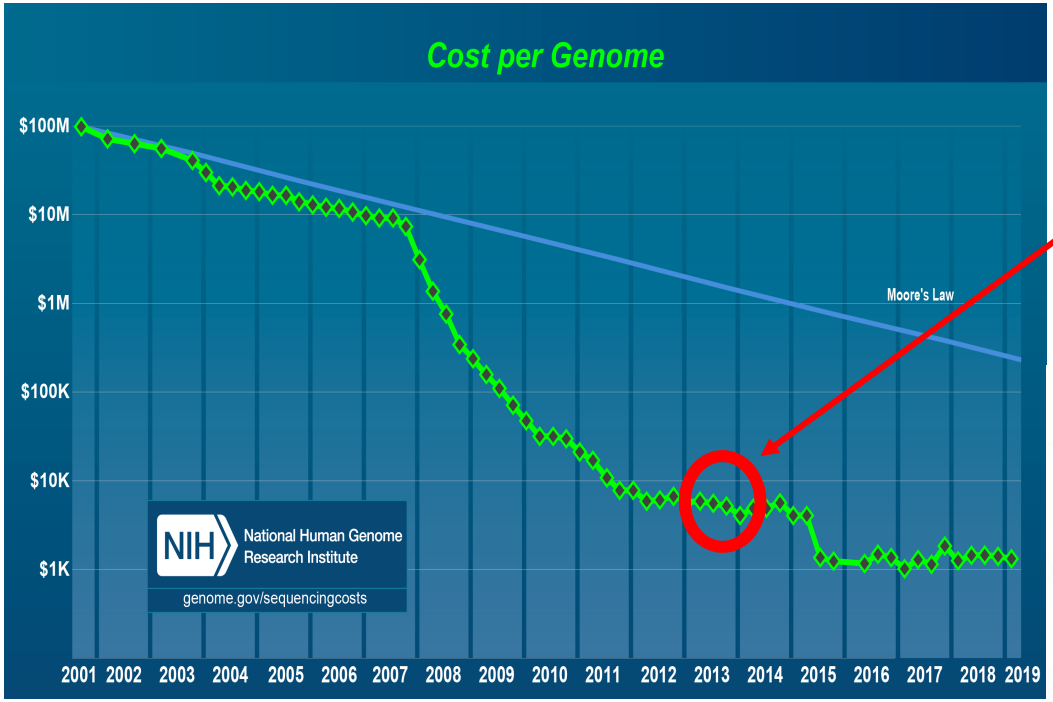
Alkan+, "Personalized copy number and segmental duplication maps using next-generation sequencing", Nature Genetics 2009.

Performance of Read Mapping

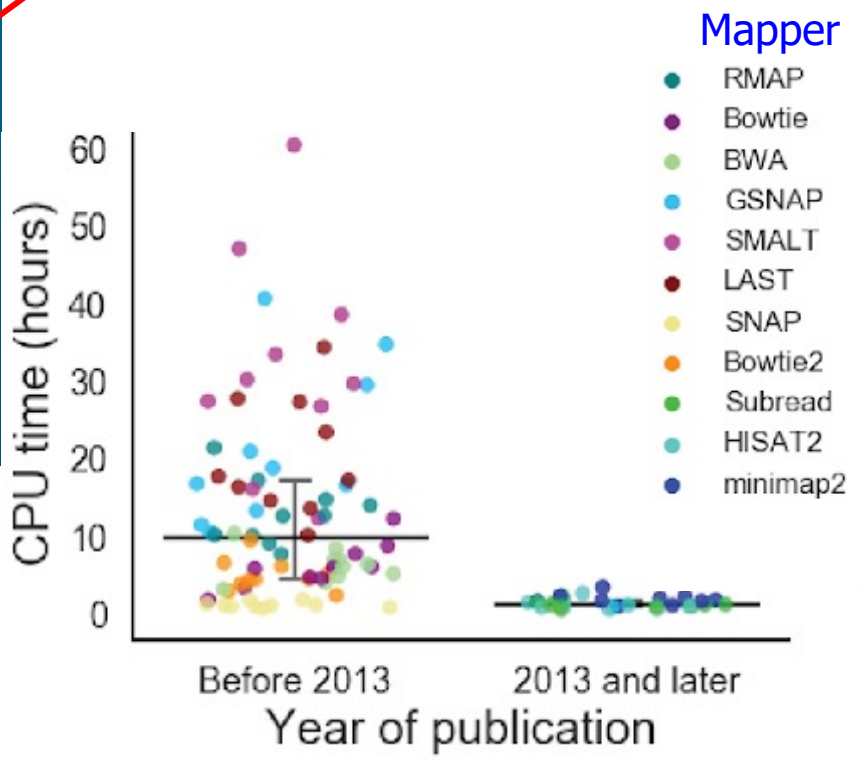


Alser+, "Technology dictates algorithms: Recent developments in read alignment", Genome Biology, 2021

The Need for Speed



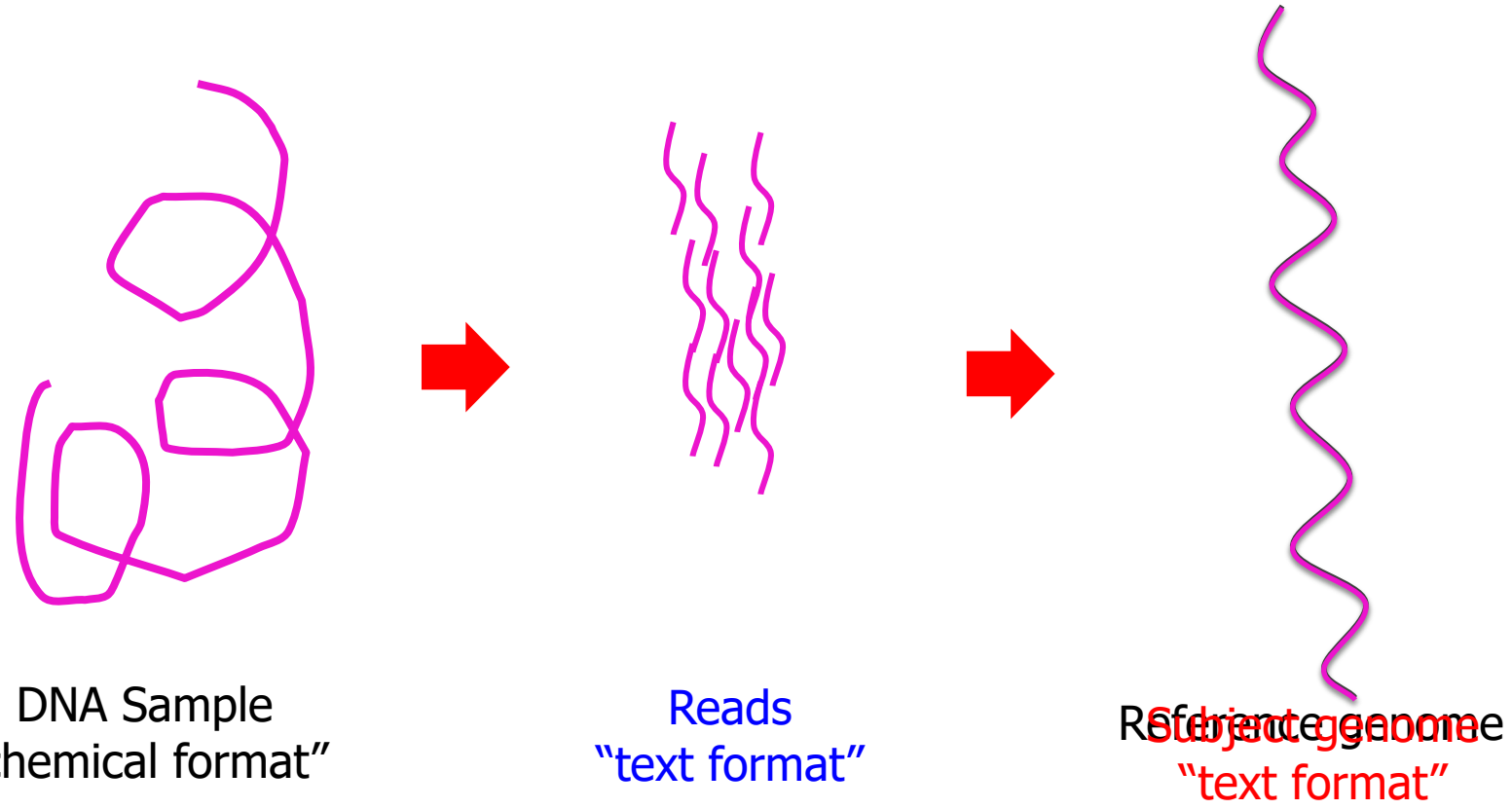
Did we realize the **need** for **faster** genome analysis?



Alser+, "Technology dictates algorithms: Recent developments in read alignment", Genome Biology, 2021

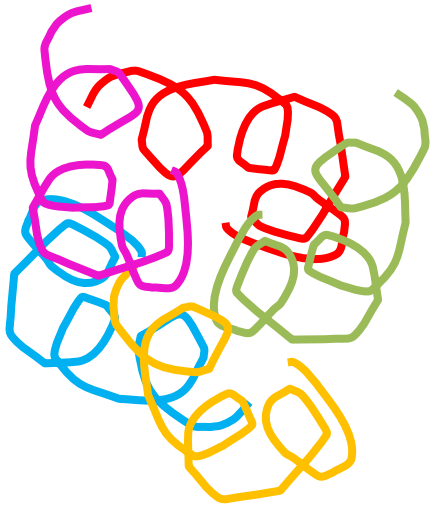
Read Mapping

Map reads to a known reference genome with some minor differences allowed

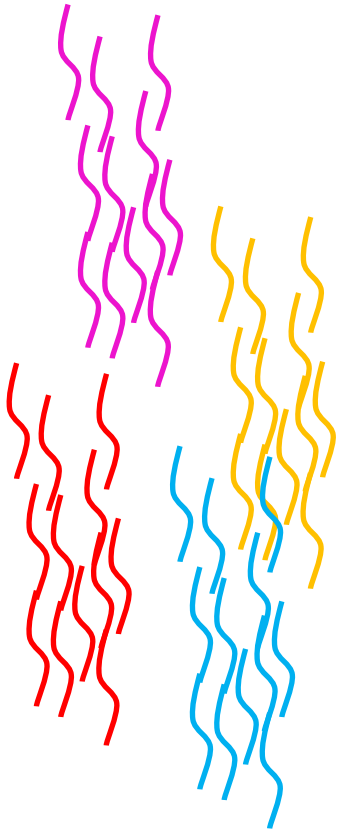


Metagenomics Analysis

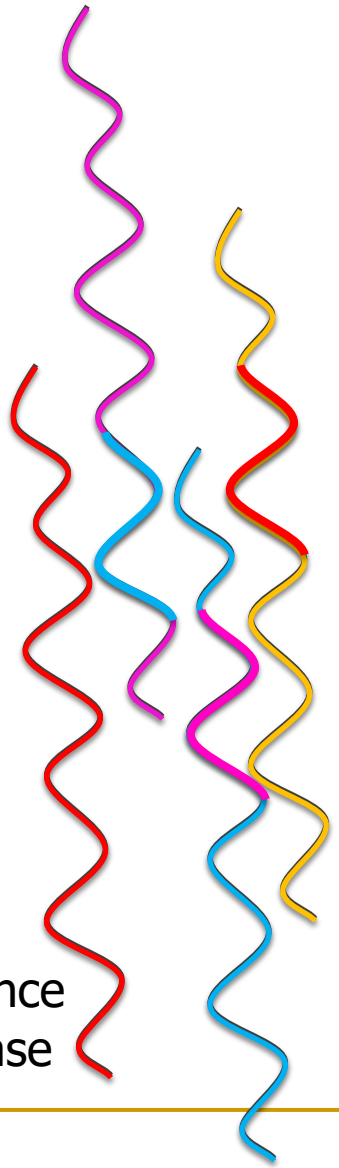
Reads from different unknown donors at sequencing time are mapped to many known reference genomes



genetic material recovered directly from environmental samples

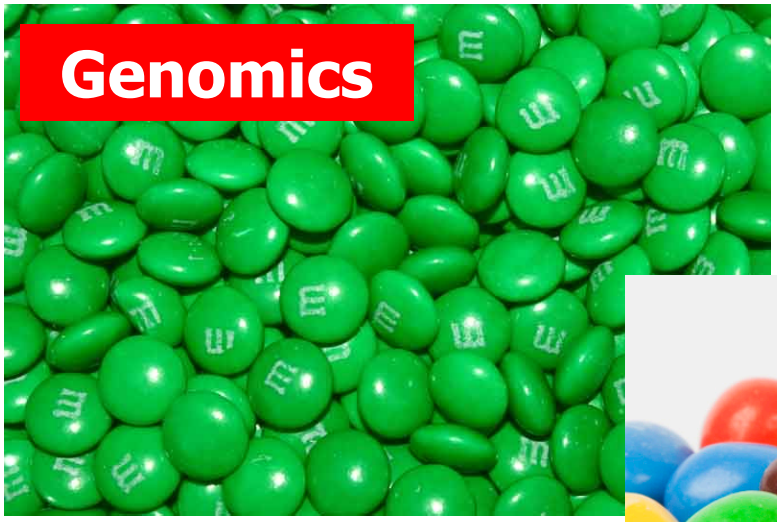


Reads
"text format"



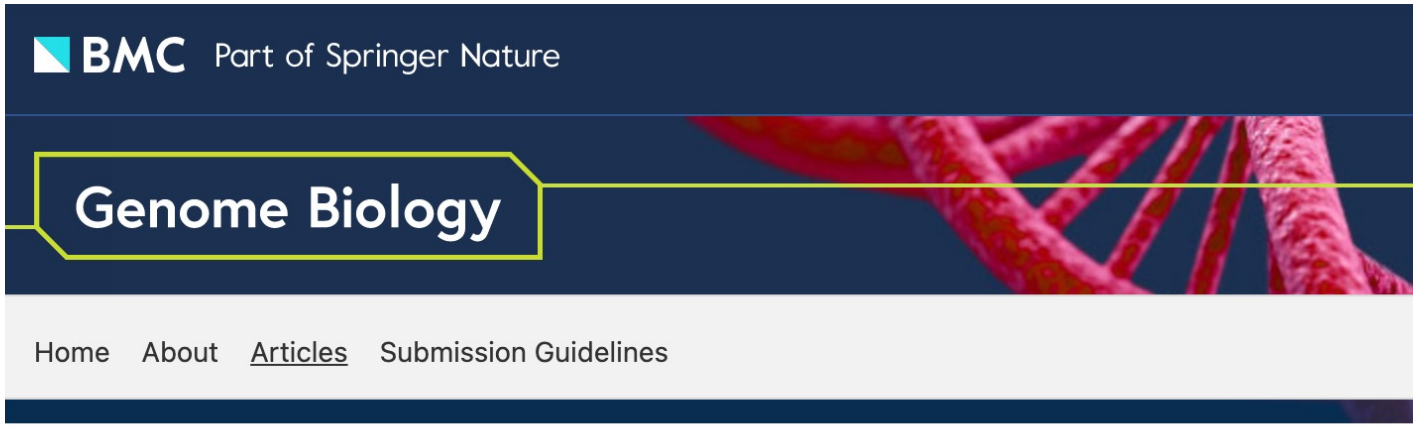
Reference Database

Genomics vs. Metagenomics



More on Metagenomic Profiling: Metalign

Nathan LaPierre, Mohammed Alser, Eleazar Eskin, David Koslicki, Serghei Mangul
"Metalign: efficient alignment-based metagenomic profiling via containment min hash"
Genome Biology, September 2020.
[Talk Video (7 minutes) at ISMB 2020]
[Source code]



Software | Open Access | Published: 10 September 2020

Metalign: efficient alignment-based metagenomic profiling via containment min hash

Nathan LaPierre, Mohammed Alser, Eleazar Eskin, David Koslicki & Serghei Mangul

Genome Biology **21**, Article number: 242 (2020) | Cite this article

Check Also CAMI II Paper

F. Meyer, A. Fritz, Z.L. Deng, D. Koslicki, A. Gurevich, G. Robertson, Mohammed Alser, and others

"Critical Assessment of Metagenome Interpretation - the second round of challenges"

bioRxiv, 2021

[Source Code]

Critical Assessment of Metagenome Interpretation - the second round of challenges

F. Meyer, A. Fritz, Z.-L. Deng, D. Koslicki, A. Gurevich, G. Robertson, M. Alser, D. Antipov, F. Beghini, D. Bertrand, J. J. Brito, C.T. Brown, J. Buchmann, A. Buluç, B. Chen, R. Chikhi, P.T. Clausen, A. Cristian, P.W. Dabrowski, A. E. Darling, R. Egan, E. Eskin, E. Georganas, E. Goltsman, M.A. Gray, L. H. Hansen, S. Hofmeyr, P. Huang, L. Irber, H. Jia, T. S. Jørgensen, S. D. Kieser, T. Klemetsen, A. Kola, M. Kolmogorov, A. Korobeynikov, J. Kwan, N. LaPierre, C. Lemaitre, C. Li, A. Limasset, F. Malcher-Miranda, S. Mangul, V. R. Marcelino, C. Marchet, P. Marijon, D. Meleshko, D. R. Mende, A. Milanese, N. Nagarajan, J. Nissen, S. Nurk, L. Oliker, L. Paoli, P. Peterlongo, V. C. Piro, J. S. Porter, S. Rasmussen, E. R. Rees, K. Reinert, B. Renard, E. M. Robertsen, G. L. Rosen, H.-J. Ruscheweyh, V. Sarwal, N. Segata, E. Seiler, L. Shi, F. Sun, S. Sunagawa, S. J. Sørensen, A. Thomas, C. Tong, M. Trajkovski, J. Tremblay, G. Uritskiy, R. Vicedomini, Zi. Wang, Zhe. Wang, Zho. Wang, A. Warren, N. P. Willassen, K. Yelick, R. You, G. Zeller, Z. Zhao, S. Zhu, J. Zhu, R. Garrido-Oter, P. Gastmeier, S. Hacquard, S. Häußler, A. Khaledi, F. Maechler, F. Mesny, S. Radutoiu, P. Schulze-Lefert, N. Smit, T. Strowig, A. Bremges, A. Sczyrba, A. C. McHardy

doi: https://doi.org/10.1101/2021.07.12.451567

bioRxiv
THE PREPRINT SERVER FOR BIOLOGY

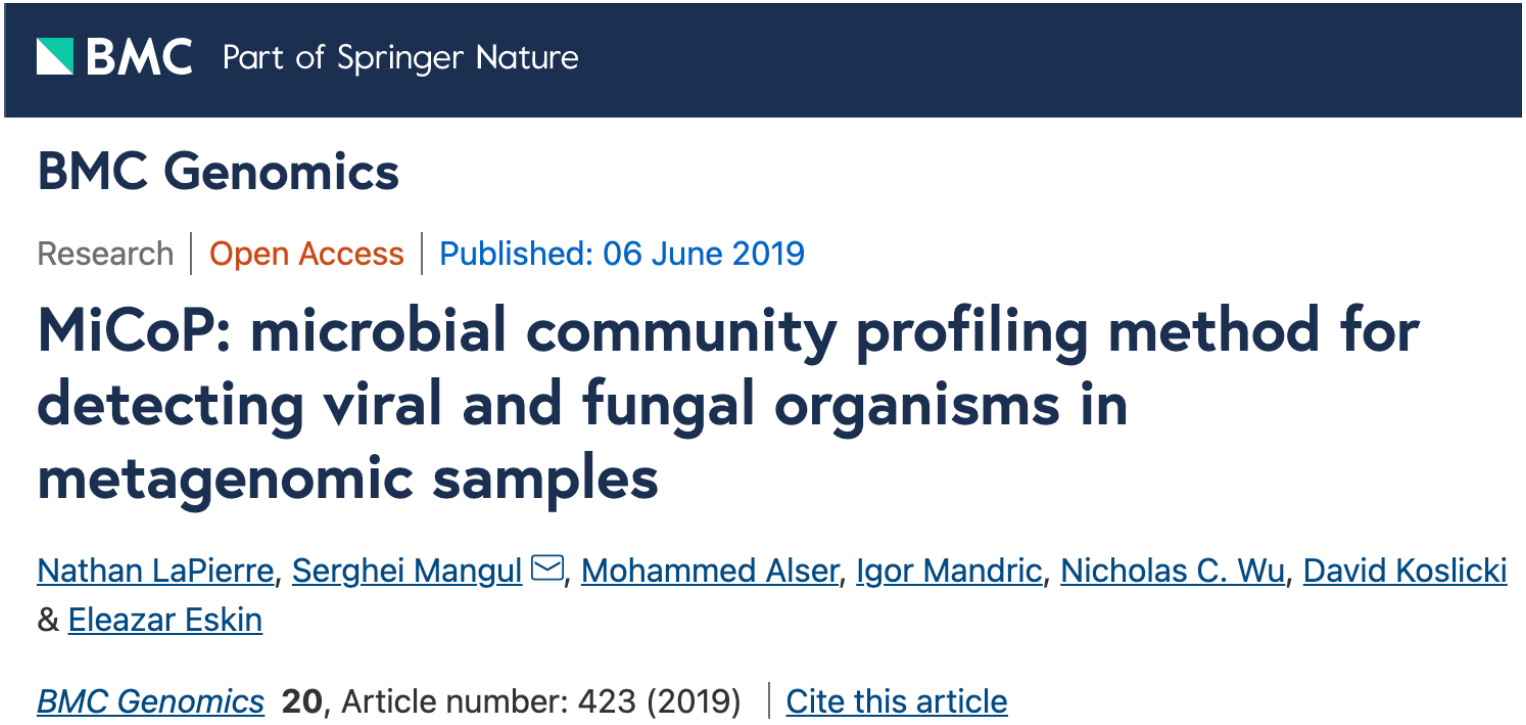
Check Also MiCoP

Nathan LaPierre, Serghei Mangul, Mohammed Alser, Igor Mandric, Nicholas C. Wu, David Koslicki & Eleazar Eskin

"MiCoP: microbial community profiling method for detecting viral and fungal organisms in metagenomic samples"

BMC Genomics, June 2019.

[Source code]



BMC Part of Springer Nature

BMC Genomics

Research | Open Access | Published: 06 June 2019

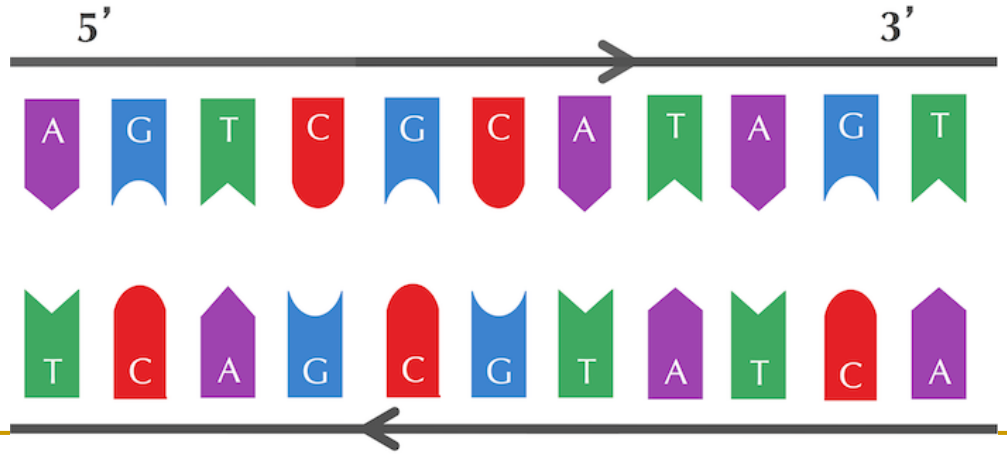
MiCoP: microbial community profiling method for detecting viral and fungal organisms in metagenomic samples

Nathan LaPierre, Serghei Mangul ✉, Mohammed Alser, Igor Mandric, Nicholas C. Wu, David Koslicki & Eleazar Eskin

BMC Genomics **20**, Article number: 423 (2019) | Cite this article

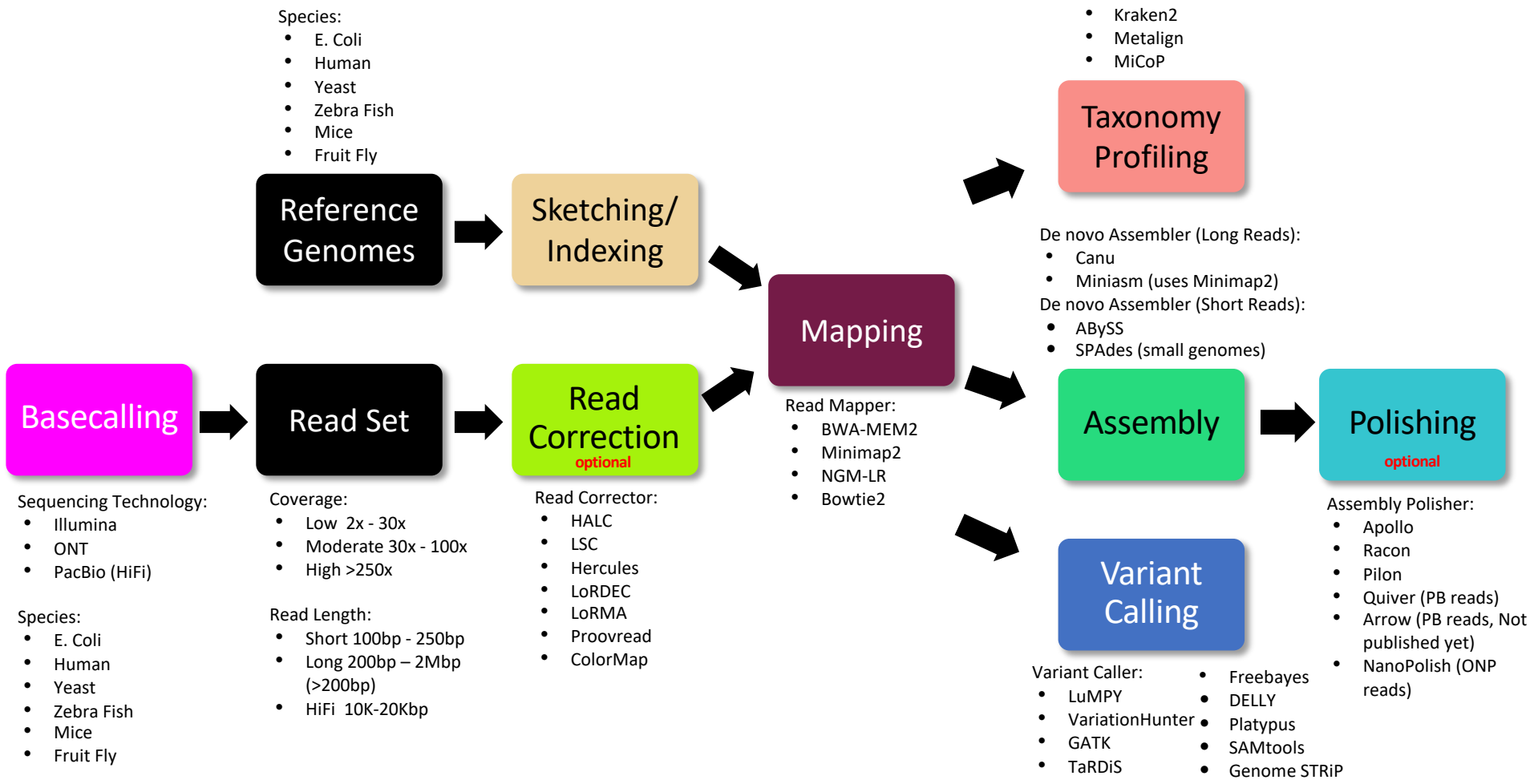
Challenges in Read Mapping

- Need to find many mappings of each read
- Need to tolerate variances/sequencing errors in each read
- Need to map each read very fast (i.e., performance is important, life critical in some cases)
- Need to map reads to both forward and reverse strands



https://www.bioinformaticsalgorithms.org/bioinformatics-chapter-1

Several Genome Analysis Pipelines



Revisiting the Puzzle

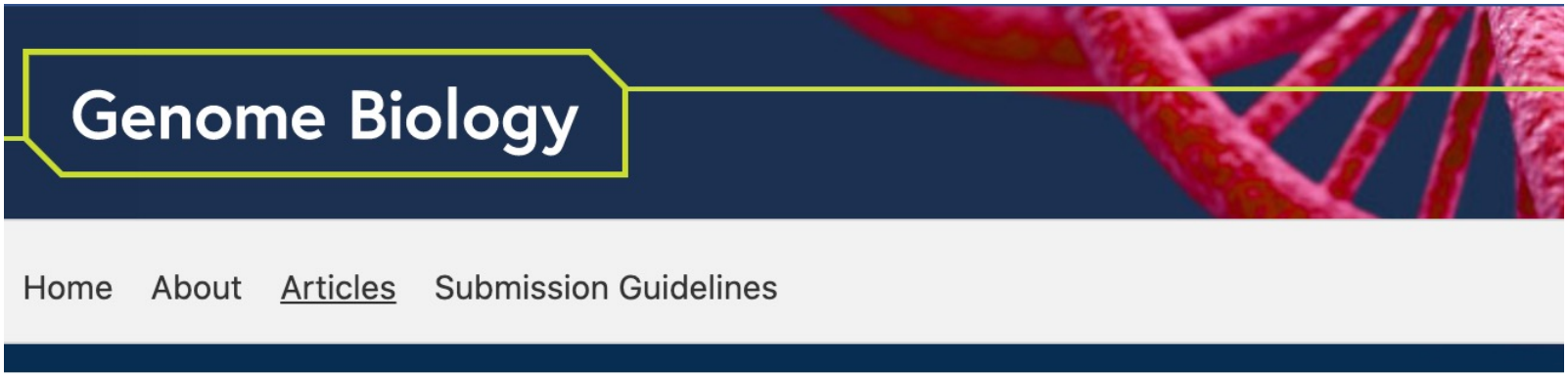
https://www.pacb.com/smrt-science/smrt-sequencing/hifi-reads-for-highly-accurate-long-read-sequencing/

Reference Genome Bias

"African pan-genome contains ~10% more DNA bases than the current human reference genome"

Sherman+, "Assembly of a pan-genome from deep sequencing of 910 humans of African descent" *Nature genetics*, 2019.

Time to Change the Reference Genome



Opinion | Open Access | Published: 09 August 2019

Is it time to change the reference genome?

Sara Ballouz, Alexander Dobin & Jesse A. Gillis

Genome Biology **20**, Article number: 159 (2019) | Cite this article

12k Accesses | **11** Citations | **45** Altmetric | Metrics

"Switching to a consensus reference would offer important advantages over the continued use of the current reference with few disadvantages"

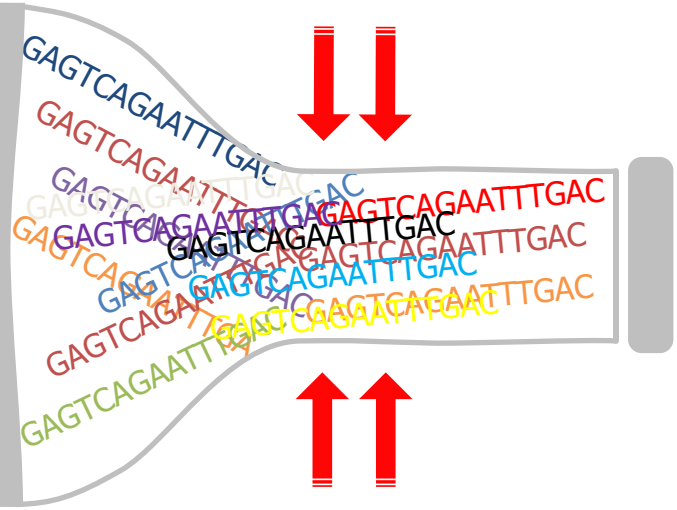
Analysis is Bottlenecked in Read Mapping!!

48 Human whole genomes

at 30× coverage

in about 2 days

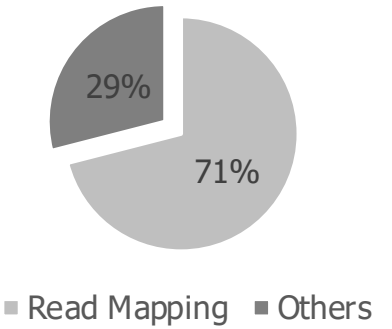
Illumina NovaSeq 6000



1 Human genome

32 CPU hours

on a 48-core processor



Goyal+, "Ultra-fast next generation human genome sequencing data processing using DRAGENTM bio-IT processor for precision medicine", *Open Journal of Genetics*, 2017.

Agenda for Today

- What is Read Mapping?
- **What Makes Read Mapper Slow?**
- Algorithmic & Hardware Acceleration
  - Seed Filtering Technique
  - Pre-alignment Filtering Technique
  - Read Alignment Acceleration

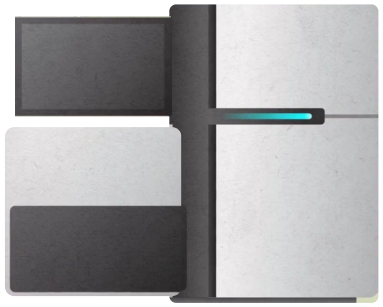
What makes read mapping a **bottleneck**?

A Tsunami of Sequencing Data

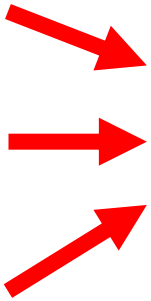
A Tera-scale increase in sequencing production in the past 25 years		
Genes & Operons	1990	**Kilo** = 1,000
Bacterial genomes	1995	**Mega** = 1,000,000
Human genome	2000	**Giga** = 1,000,000,000
Human microbiome	2005	**Tera** = 1,000,000,000,000
50K Microbiomes	2015	**Peta** = 1,000,000,000,000,000
what is expected for the next 15 years ? (a Giga?)		
200K Microbiomes	2020	**Exa** = 1,000,000,000,000,000,000
1M Microbiomes	2025	**Zetta** = 1,000,000,000,000,000,000,000
Earth Microbiome	2030	**Yotta** = 1,000,000,000,000,000,000,000,000

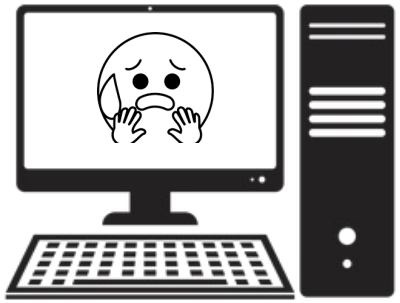
Source: @kyrpides

Lack of Specialized Compute Capability



Specialized Machine
for Sequencing



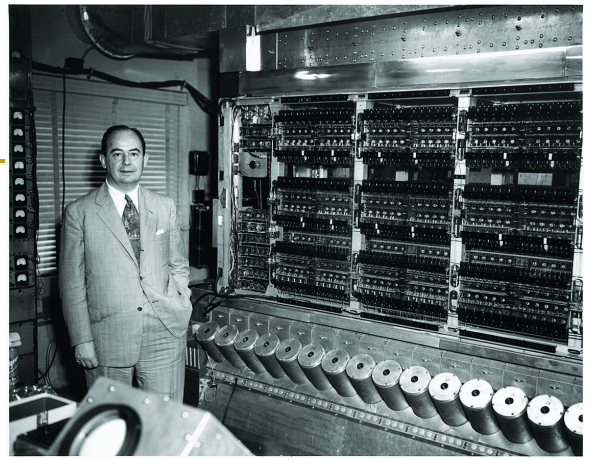


General-Purpose Machine
for Analysis

FAST

SLOW

Today's Computing Systems

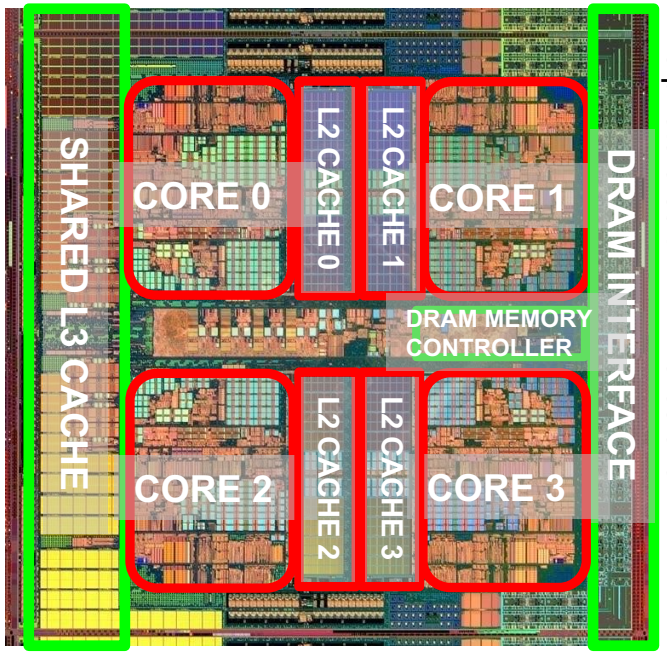


von Neumann model, 1945

where the **CPU** can **access data** stored in an off-chip main memory only through **power-hungry bus**

Storage (SSD/HDD)

Main Memory



*Die photo credit: AMD Barcelona

Microprocessor

Burks, Goldstein, von Neumann, "Preliminary discussion of the logical design of an electronic computing instrument," 1946.

The Problem

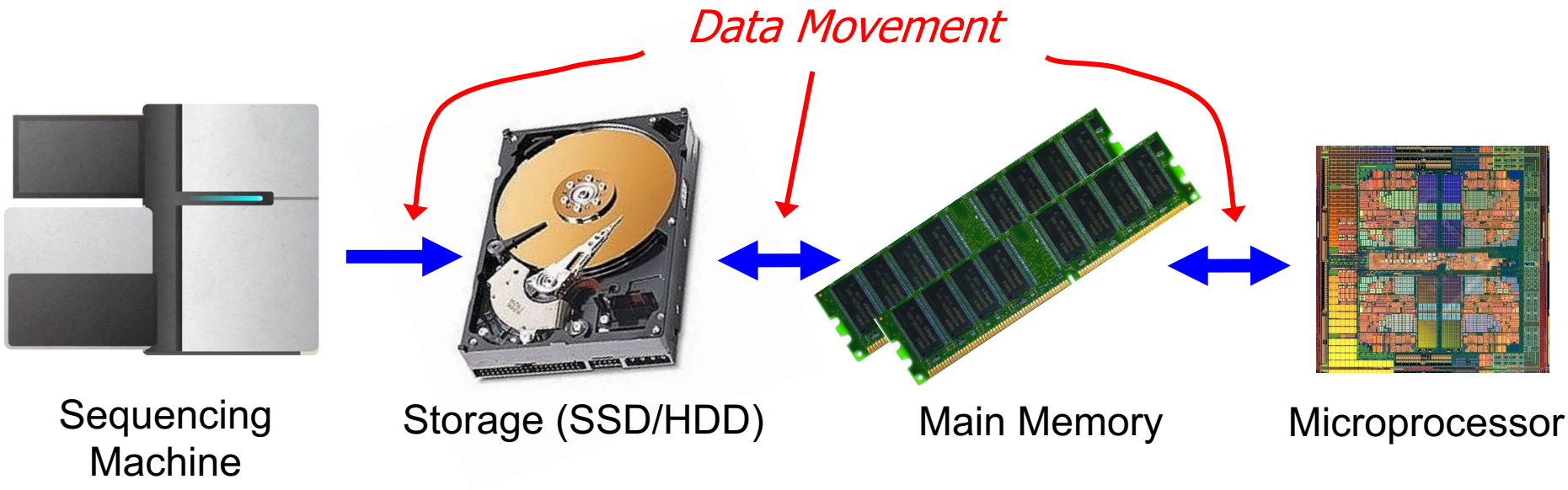
Data analysis

is performed

far away from the data

Data Movement Dominates Performance

- **Data movement** dominates performance and is a **major** system **energy bottleneck** (accounting for 40%-62%)



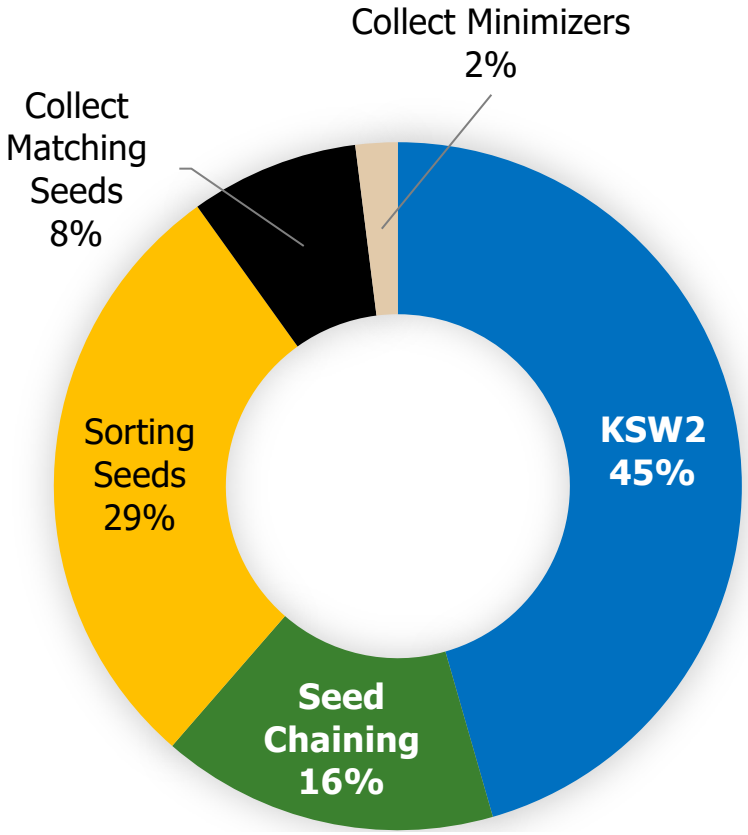
Single memory request consumes >160x-800x more energy compared to performing an addition operation

* Boroumand et al., "Google Workloads for Consumer Devices: Mitigating Data Movement Bottlenecks," ASPLOS 2018
⋆ Kestor et al., "Quantifying the Energy Cost of Data Movement in Scientific Applications," IISWC 2013
☆ Pandiyan and Wu, "Quantifying the energy cost of data movement for emerging smart phone workloads on mobile platforms," IISWC 2014

Read Mapping Execution Time

>60%

of the read mapper's execution time is spent in sequence alignment



minimap2

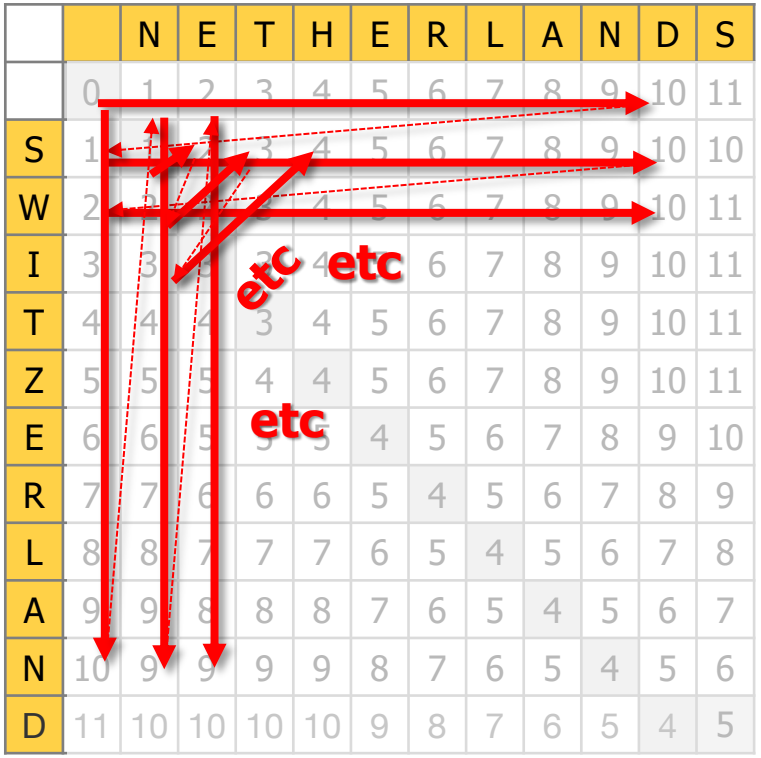
ONT FASTQ size: 103MB (151 reads), Mean length: 356,403 bp, std: 173,168 bp, longest length: 817,917 bp

Sequence Alignment in Unavoidable

- Quadratic-time dynamic-programming algorithm **WHY?!**

  Enumerating all possible prefixes

- NETHERLANDS x SWITZERLAND
- NETHERLANDS x S
  NETHERLANDS x SW
  NETHERLANDS x SWI
  NETHERLANDS x SWIT
  NETHERLANDS x SWITZ
  NETHERLANDS x SWITZE
  NETHERLANDS x SWITZER
  NETHERLANDS x SWITZERL
  NETHERLANDS x SWITZERLA
  NETHERLANDS x SWITZERLAN
  NETHERLANDS x SWITZERLAND



Sequence Alignment in Unavoidable

- **Quadratic-time** dynamic-programming algorithm
  - Enumerating all possible prefixes
- **Data dependencies** limit the computation parallelism
  - Processing row (or column) after another
- **Entire matrix** is computed even though strings can be dissimilar.
  - Number of differences is computed only at the backtraking step.

		N	E	T	H	E	R	L	A	N	D	S
	0	1	2	3	4	5	6	7	8	9	10	11
S	1	1	2	3	4	5	6	7	8	9	10	10
W	2	2	2	3	4	5	6	7	8	9	10	11
I	3	3	3	3	4	5	6	7	8	9	10	11
T	4	4	4	3	4	5	6	7	8	9	10	11
Z	5	5	5	4	4	5	6	7	8	9	10	11
E	6	6	5	5	5	4	5	6	7	8	9	10
R	7	7	6	6	6	5	4	5	6	7	8	9
L	8	8	7	7	7	6	5	4	5	6	7	8
A	9	9	8	8	8	7	6	5	4	5	6	7
N	10	9	9	9	9	8	7	6	5	4	5	6
D	11	10	10	10	10	9	8	7	6	5	4	5

Computational Cost is Mathematically Proven

Computer Science > Computational Complexity

[Submitted on 1 Dec 2014 (v1), last revised 15 Aug 2017 (this version, v4)]

Edit Distance Cannot Be Computed in Strongly Subquadratic Time (unless SETH is false)

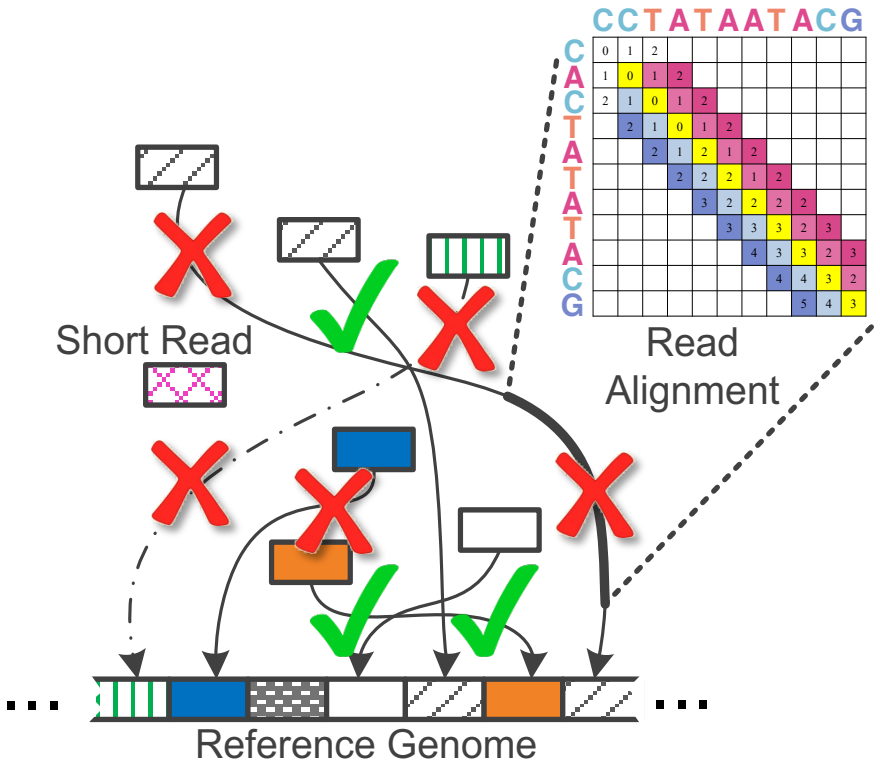
Arturs Backurs, Piotr Indyk

The edit distance (a.k.a. the Levenshtein distance) between two strings is defined as the minimum number of insertions, deletions or substitutions of symbols needed to transform one string into another. The problem of computing the edit distance between two strings is a classical computational task, with a well-known algorithm based on dynamic programming. Unfortunately, all known algorithms for this problem run in nearly quadratic time.

In this paper we provide evidence that the near-quadratic running time bounds known for the problem of computing edit distance might be tight. Specifically, we show that, if the edit distance can be computed in time $O(n^{2-\delta})$ for some constant $\delta > 0$, then the satisfiability of conjunctive normal form formulas with N variables and M clauses can be solved in time $M^{O(1)}2^{(1-\epsilon)N}$ for a constant $\epsilon > 0$. The latter result would violate the Strong Exponential Time Hypothesis, which postulates that such algorithms do not exist.

https://arxiv.org/abs/1412.0348

Large Search Space for Mapping Location



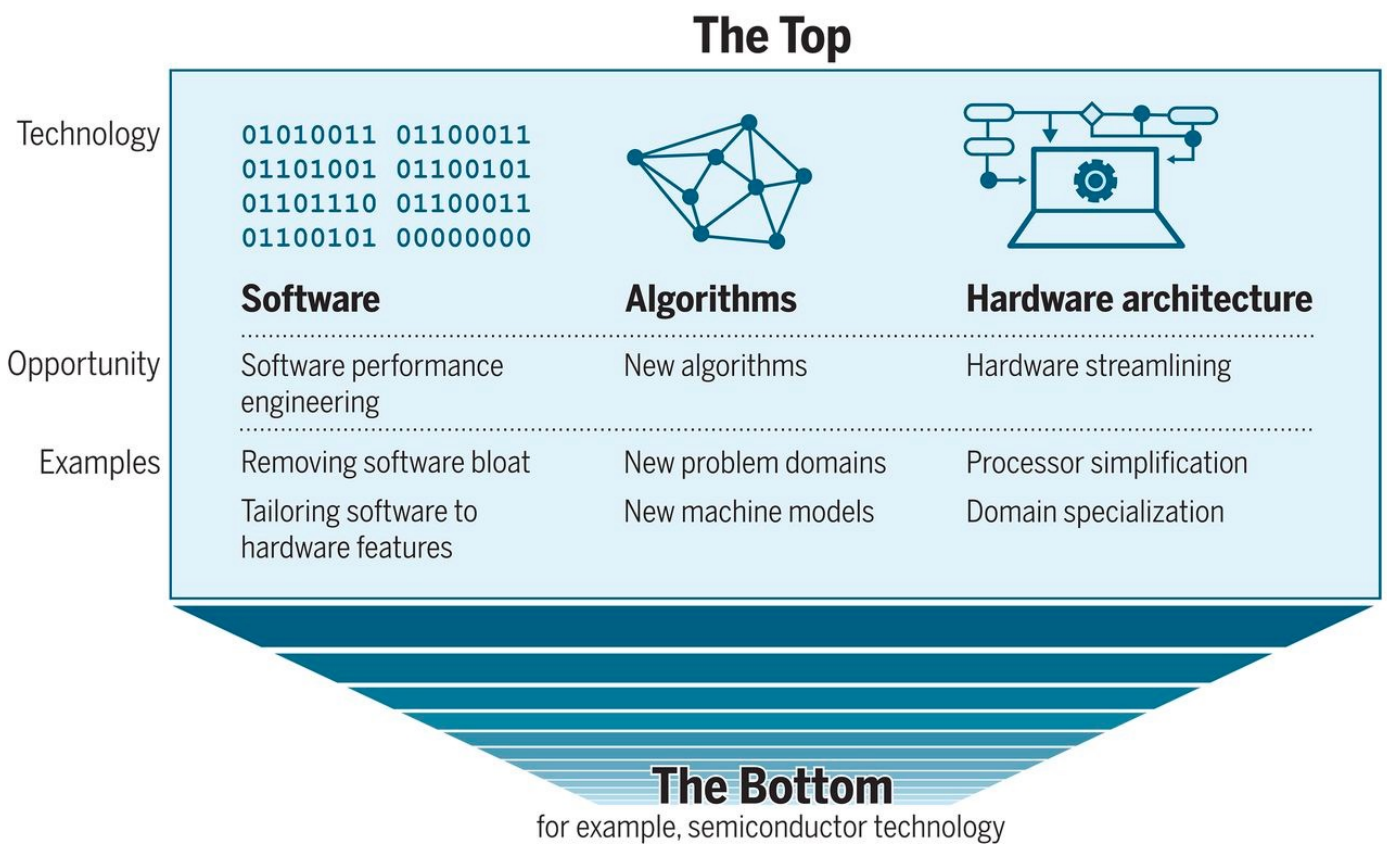
98%

of candidate locations have high dissimilarity with a given read

Cheng *et al*, *BMC bioinformatics* (2015)
Xin *et al*, *BMC genomics* (2013)

Computing System

Leiserson+, "[There's plenty of room at the Top: What will drive computer performance after Moore's law?](#)", Science, 2020



Data
Problem
Algorithm
Program/Language
Runtime System (VM, OS, MM)
ISA (Architecture)
Microarchitecture
Logic
Devices
Electrons

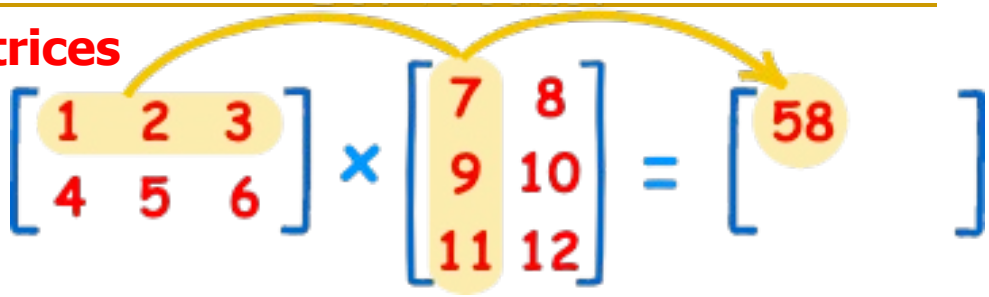
Richard Feynman, "[There's Plenty of Room at the Bottom: An Invitation to Enter a New Field of Physics](#)", a lecture given at Caltech, 1959.

Image source: https://science.sciencemag.org/content/368/6495/eaam9744

Software & Hardware Optimizations

Multiplying Two 4096-by-4096 Matrices

```
for i in xrange(4096):
  for j in xrange(4096):
    for k in xrange(4096):
      C[i][j] += A[i][k] *
B[k][j]
```



Implementation	Running time (s)	Absolute speedup
Python	25,552.48	1x
Java	2,372.68	11x
C	542.67	47x
Parallel loops	69.80	366x
Parallel divide and conquer	3.80	6,727x
plus vectorization	1.10	23,224x
plus AVX intrinsics	0.41	62,806x

Leiserson+, "There's plenty of room at the Top: What will drive computer performance after Moore's law?", Science, 2020

FASTQ Parsing

Program	Language	t_{gzip} (s)	t_{plain} (s)	Comments
fqcnt_rs2_needletail.rs	Rust	9.3	0.8	needletail; fasta/4-line fastq
fqcnt_c1_kseq.c	C	9.7	1.4	multi-line fasta/fastq
fqcnt_cr1_klib.cr	Crystal	9.7	1.5	kseq.h port
fqcnt_nim1_klib.nim	Nim	10.5	2.3	kseq.h port
fqcnt_jl1_klib.jl	Julia	11.2	2.9	kseq.h port
fqcnt_js1_k8.js	Javascript	17.5	9.4	kseq.h port
fqcnt_go1.go	Go	19.1	2.8	4-line only
fqcnt_lua1_klib.lua	LuaJIT	28.6	27.2	partial kseq.h port
fqcnt_py2_rfq.py	PyPy	28.9	14.6	partial kseq.h port
fqcnt_py2_rfq.py	Python	42.7	19.1	partial kseq.h port

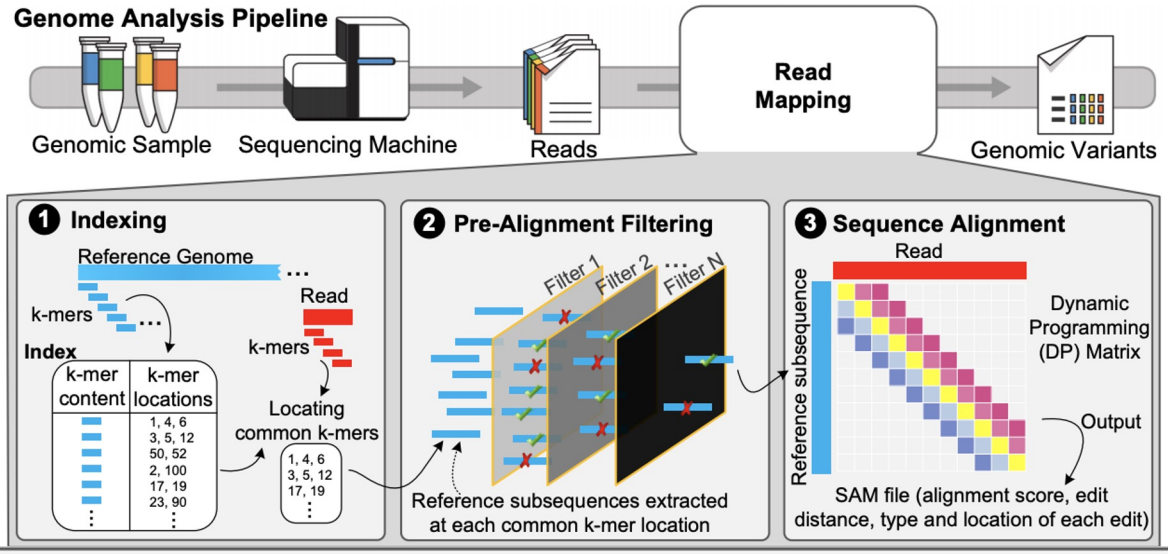
https://github.com/lh3/biofast

We need intelligent algorithms and intelligent architectures that handle data well

Agenda for Today

- What is Read Mapping?
- What Makes Read Mapper Slow?
- **Algorithmic & Hardware Acceleration**
  - Seed Filtering Technique
  - Pre-alignment Filtering Technique
  - Read Alignment Acceleration

Accelerating Read Mapping



Accelerating Indexing	Accelerating Pre-Alignment Filtering	Accelerating Alignment
Reducing the number of seeds	q-gram filtering	Accurate alignment accelerators
Reducing data movement during indexing	Pigeonhole principle	Heuristic-based alignment accelerators
	Base counting	
	Sparse DP	

Alser+, "Accelerating Genome Analysis: A Primer on an Ongoing Journey", IEEE Micro, 2020.

Ongoing Directions

- **Seed Filtering Technique:**
  - Goal: Reducing the number of seed (k-mer) locations.
    - Heuristic (limits the number of mapping locations for each seed).
    - Supports exact matches only.
- **Pre-alignment Filtering Technique:**
  - Goal: Reducing the number of *invalid mappings (>E)*.
    - Supports both exact and inexact matches.
    - Provides some falsely-accepted mappings.
- **Read Alignment Acceleration:**
  - Goal: Performing read alignment at scale.
    - Limits the numeric range of each cell in the DP table and hence supports limited scoring function.
    - May not support backtracking step due to random memory accesses.

Our Contributions

Near-memory/In-memory Pre-alignment Filtering

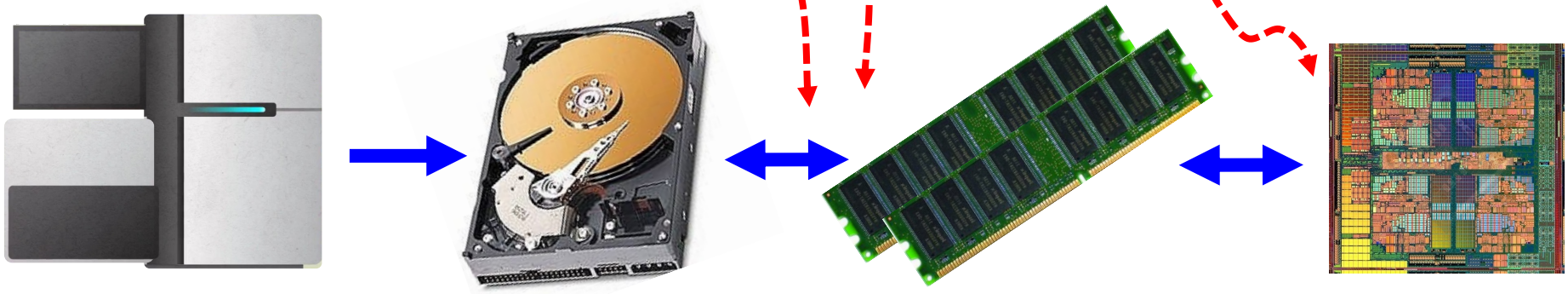
- **GRIM-Filter [BMC Genomics'18]**
- **GenASM [MICRO 2020]**
- **SneakySnake [IEEE Micro'21]**

Near-memory Sequence Alignment

- **GenASM [MICRO 2020]**

Specialized Pre-alignment Filtering Accelerators (GPU, FPGA)

- **GateKeeper [Bioinformatics'17]**
- **MAGNET [AACBB'18]**
- **Shouji [Bioinformatics'19]**
- **GateKeeper-GPU [arXiv'21]**
- **SneakySnake [Bioinformatics'20]**



Sequencing Machine | Storage (SSD/HDD) | Main Memory | Microprocessor

Read Mapping in 111 pages!

In-depth analysis of 107 read mappers (1988-2020)

Mohammed Alser, Jeremy Rotman, Dhrithi Deshpande, Kodi Taraszka, Huwenbo Shi, Pelin Icer Baykal, Harry Taegyun Yang, Victor Xue, Sergey Knyazev, Benjamin D. Singer, Brunilda Balliu, David Koslicki, Pavel Skums, Alex Zelikovsky, Can Alkan, Onur Mutlu, Serghei Mangul
"Technology dictates algorithms: Recent developments in read alignment"
Genome Biology, 2021
[Source code]

Alser *et al. Genome Biology* (2021) 22:249
https://doi.org/10.1186/s13059-021-02443-7

Genome Biology

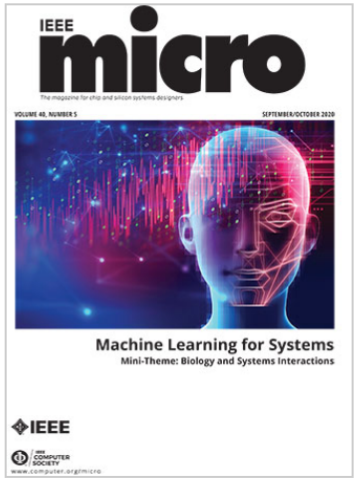
REVIEW Open Access

Technology dictates algorithms: recent developments in read alignment

Mohammed Alser[1,2,3†], Jeremy Rotman[4†], Dhrithi Deshpande[5], Kodi Taraszka[4], Huwenbo Shi[6,7], Pelin Icer Baykal[8], Harry Taegyun Yang[4,9], Victor Xue[4], Sergey Knyazev[8], Benjamin D. Singer[10,11,12], Brunilda Balliu[13], David Koslicki[14,15,16], Pavel Skums[8], Alex Zelikovsky[8,17], Can Alkan[2,18], Onur Mutlu[1,2,3†] and Serghei Mangul[5*†]

Detailed Analysis of Tackling the Bottleneck

Mohammed Alser, Zülal Bingöl, Damla Senol Cali, Jeremie Kim, Saugata Ghose, Can Alkan, Onur Mutlu
"Accelerating Genome Analysis: A Primer on an Ongoing Journey"
IEEE Micro, August 2020.



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IEEE Micro

Accelerating Genome Analysis: A Primer on an Ongoing Journey

Sept.-Oct. 2020, pp. 65-75, vol. 40
DOI Bookmark: 10.1109/MM.2020.3013728

Authors

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Saugata Ghose, University of Illinois at Urbana–Champaign and Carnegie Mellon University
Can Alkan, Bilkent University
Onur Mutlu, ETH Zurich, Carnegie Mellon University, and Bilkent University

Near-memory Pre-alignment Filtering

Gagandeep Singh, Mohammed Alser, Damla Senol Cali, Dionysios Diamantopoulos, Juan Gomez-Luna, Henk Corporaal, Onur Mutlu,
"FPGA-Based Near-Memory Acceleration of Modern Data-Intensive Applications"
IEEE Micro, 2021.
[Source Code]

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IEEE Micro

FPGA-Based Near-Memory Acceleration of Modern Data-Intensive Applications

July-Aug. 2021, pp. 39-48, vol. 41
DOI Bookmark: 10.1109/MM.2021.3088396

Authors

Gagandeep Singh, ETH Zürich, Zürich, Switzerland
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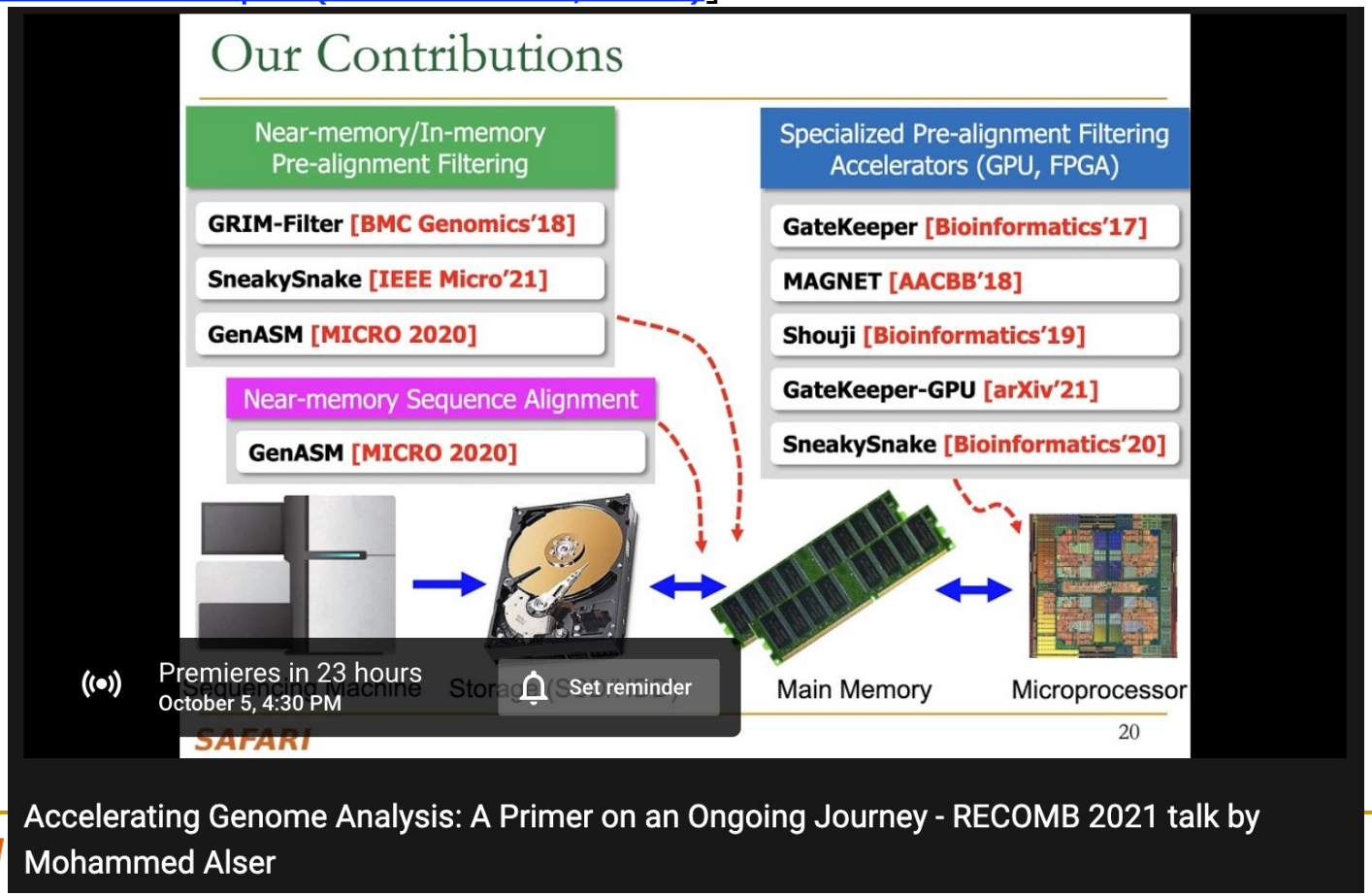
Juan Gomez-Luna, ETH Zürich, Zürich, Switzerland
Henk Corporaal, Eindhoven University of Technology, Eindhoven, The Netherlands
Onur Mutlu, ETH Zürich, Zürich, Switzerland

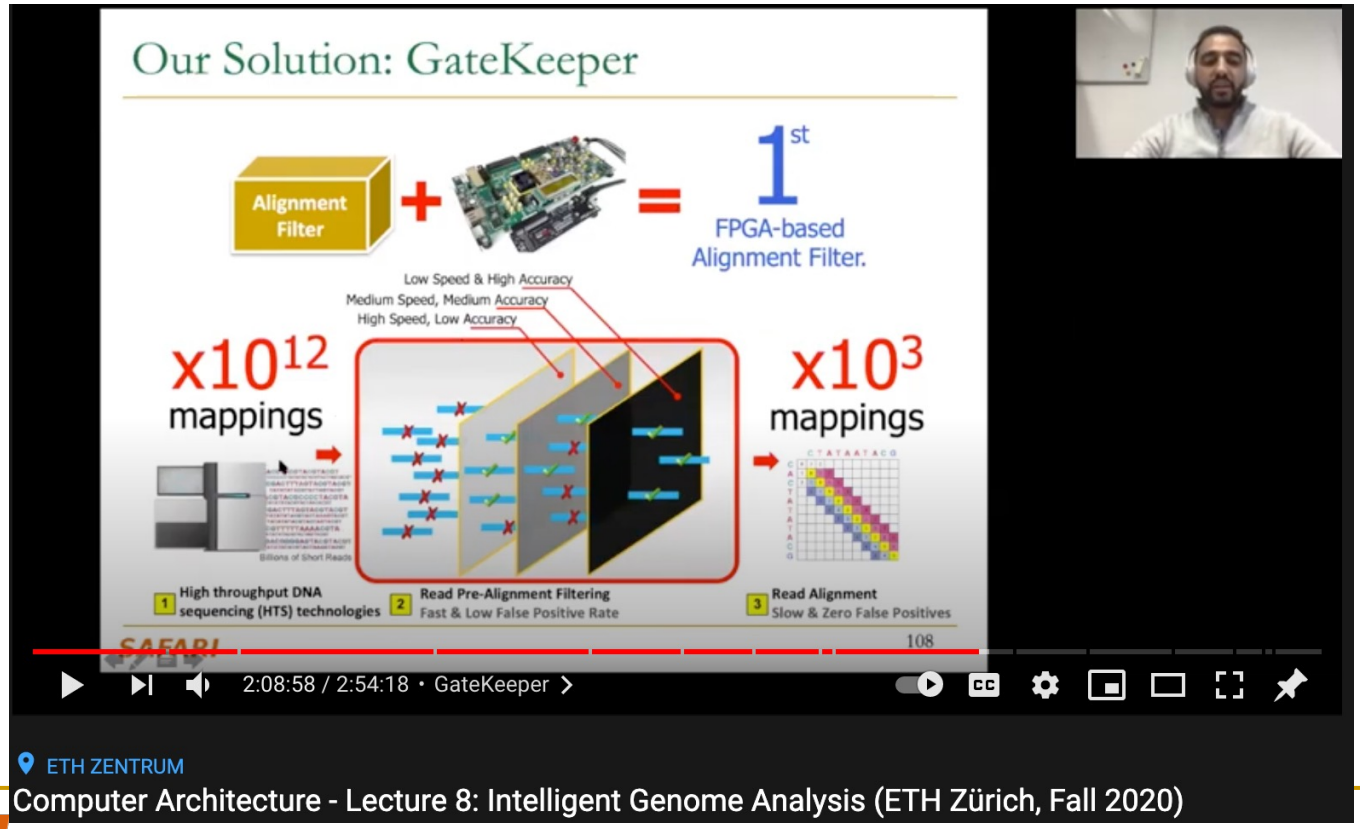
More on Accelerating Genome Analysis ...

- Mohammed Alser,
  "Accelerating Genome Analysis: A Primer on an Ongoing Journey"
  Talk at RECOMB 2021, Virtual, August 30, 2021.
  [Slides (pptx) (pdf)]
  [Talk Video (27 minutes)]
  [Related Invited Paper (at IEEE Micro, 2020)]



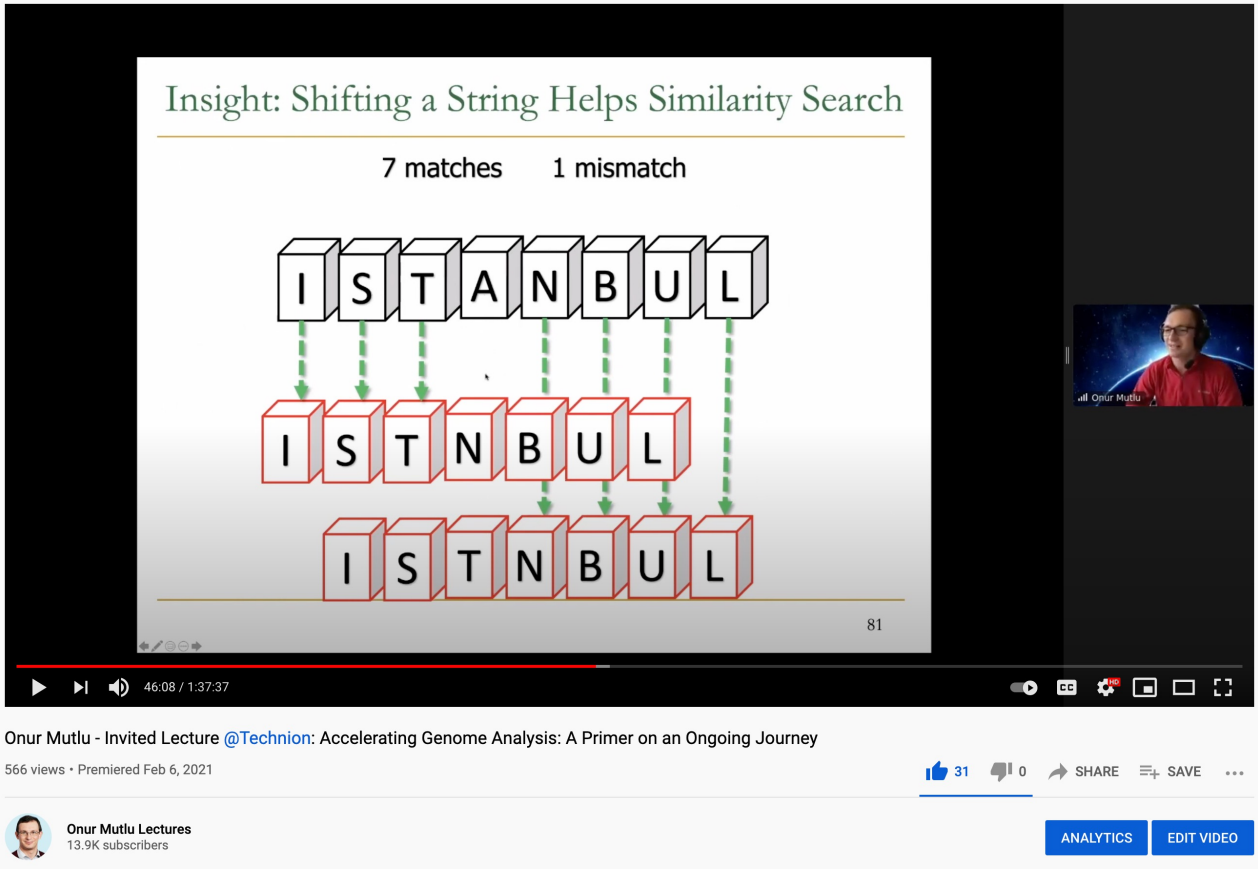
More on Intelligent Genome Analysis …

- Mohammed Alser,
  "Computer Architecture - Lecture 8: Intelligent Genome Analysis"
  ETH Zurich, Computer Architecture Course, Lecture 8, Virtual, 15 October 2021.
  [Slides (pptx) (pdf)]
  [Talk Video (2 hour 54 minutes, including Q&A)]
  [Related Invited Paper (at IEEE Micro, 2020)]



More on Fast Genome Analysis …

- Onur Mutlu,
  "Accelerating Genome Analysis: A Primer on an Ongoing Journey"
  Invited Lecture at Technion, Virtual, 26 January 2021.
  [Slides (pptx) (pdf)]
  [Talk Video (1 hour 37 minutes, including Q&A)]
  [Related Invited Paper (at IEEE Micro, 2020)]



Detailed Lectures on Genome Analysis

- Computer Architecture, Fall 2020, Lecture 3a
  - **Introduction to Genome Sequence Analysis** (ETH Zürich, Fall 2020)
  - https://www.youtube.com/watch?v=CrRb32v7SJc&list=PL5Q2soXY2Zi9xidyIgBxUz7xRPS-wisBN&index=5
- Computer Architecture, Fall 2020, Lecture 8
  - **Intelligent Genome Analysis** (ETH Zürich, Fall 2020)
  - https://www.youtube.com/watch?v=ygmQpdDTL7o&list=PL5Q2soXY2Zi9xidyIgBxUz7xRPS-wisBN&index=14
- Computer Architecture, Fall 2020, Lecture 9a
  - **GenASM: Approx. String Matching Accelerator** (ETH Zürich, Fall 2020)
  - https://www.youtube.com/watch?v=XoLpzmN-Pas&list=PL5Q2soXY2Zi9xidyIgBxUz7xRPS-wisBN&index=15
- Accelerating Genomics Project Course, Fall 2020, Lecture 1
  - **Accelerating Genomics** (ETH Zürich, Fall 2020)
  - https://www.youtube.com/watch?v=rgjl8ZyLsAg&list=PL5Q2soXY2Zi9E2bBVAgCqLgwiDRQDTyId

Prior Research on Genome Analysis (1/2)

- Alser+, "Technology dictates algorithms: Recent developments in read alignment", *Genome Biology*, 2021.
- Alser + "SneakySnake: A Fast and Accurate Universal Genome Pre-Alignment Filter for CPUs, GPUs, and FPGAs.", *Bioinformatics,* 2020.
- Senol Cali+, "GenASM: A High-Performance, Low-Power Approximate String Matching Acceleration Framework for Genome Sequence Analysis", *MICRO* 2020.
- Kim+, "AirLift: A Fast and Comprehensive Technique for Translating Alignments between Reference Genomes", *arXiv*, 2020
- Alser+, "Accelerating Genome Analysis: A Primer on an Ongoing Journey", *IEEE Micro*, 2020.

Prior Research on Genome Analysis (2/2)

- Firtina+, "Apollo: a sequencing-technology-independent, scalable and accurate assembly polishing algorithm", *Bioinformatics*, 2019.
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P&S Genomics

Lecture 4: Read Mapping

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