Computer Architecture

Lecture 10:
Intelligent Genome Analysis

Dr. Mohammed Alser

@mealser

ETH Zurich

Fall 2021

29 October 2021

SAFARI

ETH zürich

Agenda for Today

- What is Genome Analysis?
- What is Intelligent Genome Analysis?

- How we Analyze Genome?
- What is Read Mapping?
- What Makes Read Mapper Slow?

- Algorithmic & Hardware Acceleration
  - Seed Filtering Technique
  - Pre-alignment Filtering Technique
  - Read Alignment Acceleration

- Where is Read Mapping Going Next?

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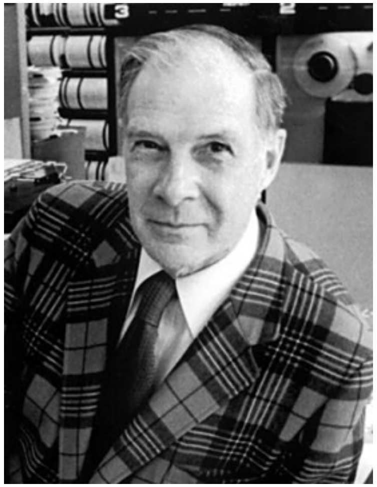
What is Data Analysis?

"The purpose of computing is [to gain] insight, not numbers"

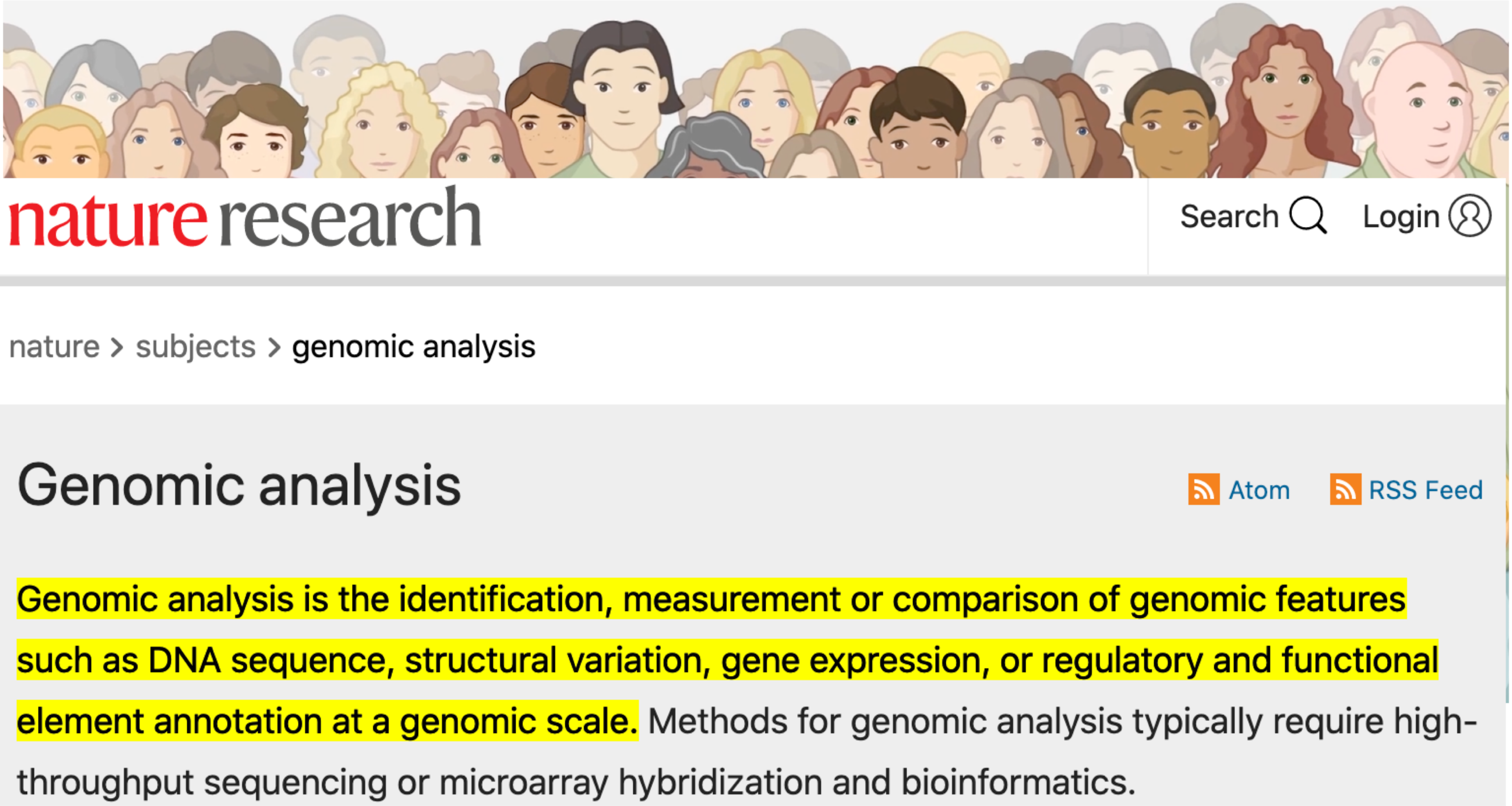
Richard Hamming



What is Genome Analysis?

https://onlinelearning.hms.harvard.edu/hmx/courses/genetic-testing/
https://www.nature.com/subjects/genomic-analysis

What is Genome Analysis?



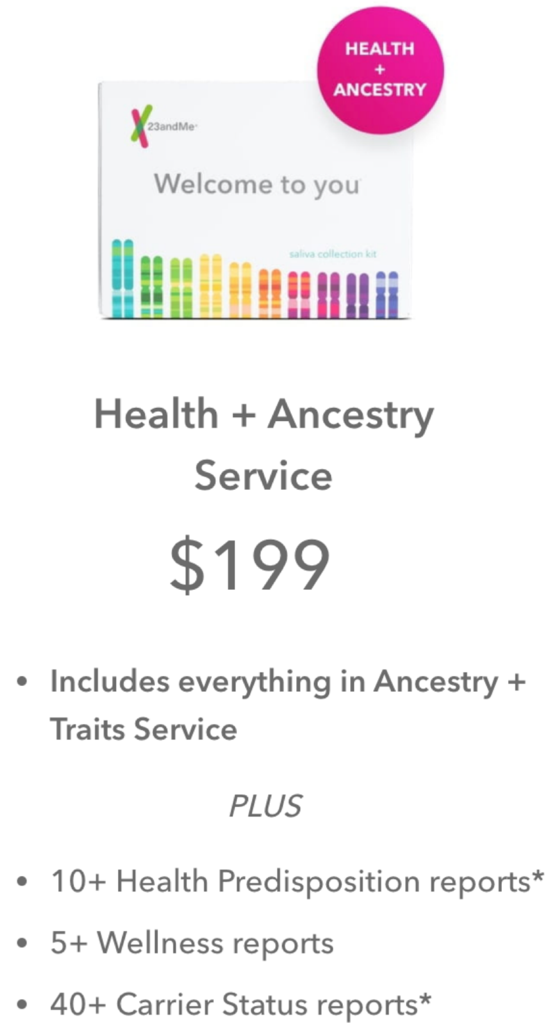
nature > subjects > genomic analysis

Genomic analysis

Genomic analysis is the identification, measurement or comparison of genomic features such as DNA sequence, structural variation, gene expression, or regulatory and functional element annotation at a genomic scale. Methods for genomic analysis typically require high-throughput sequencing or microarray hybridization and bioinformatics.

https://onlinelearning.hms.harvard.edu/hmx/courses/genetic-testing/
https://www.nature.com/subjects/genomic-analysis

DNA Testing



Health + Ancestry Service

$199

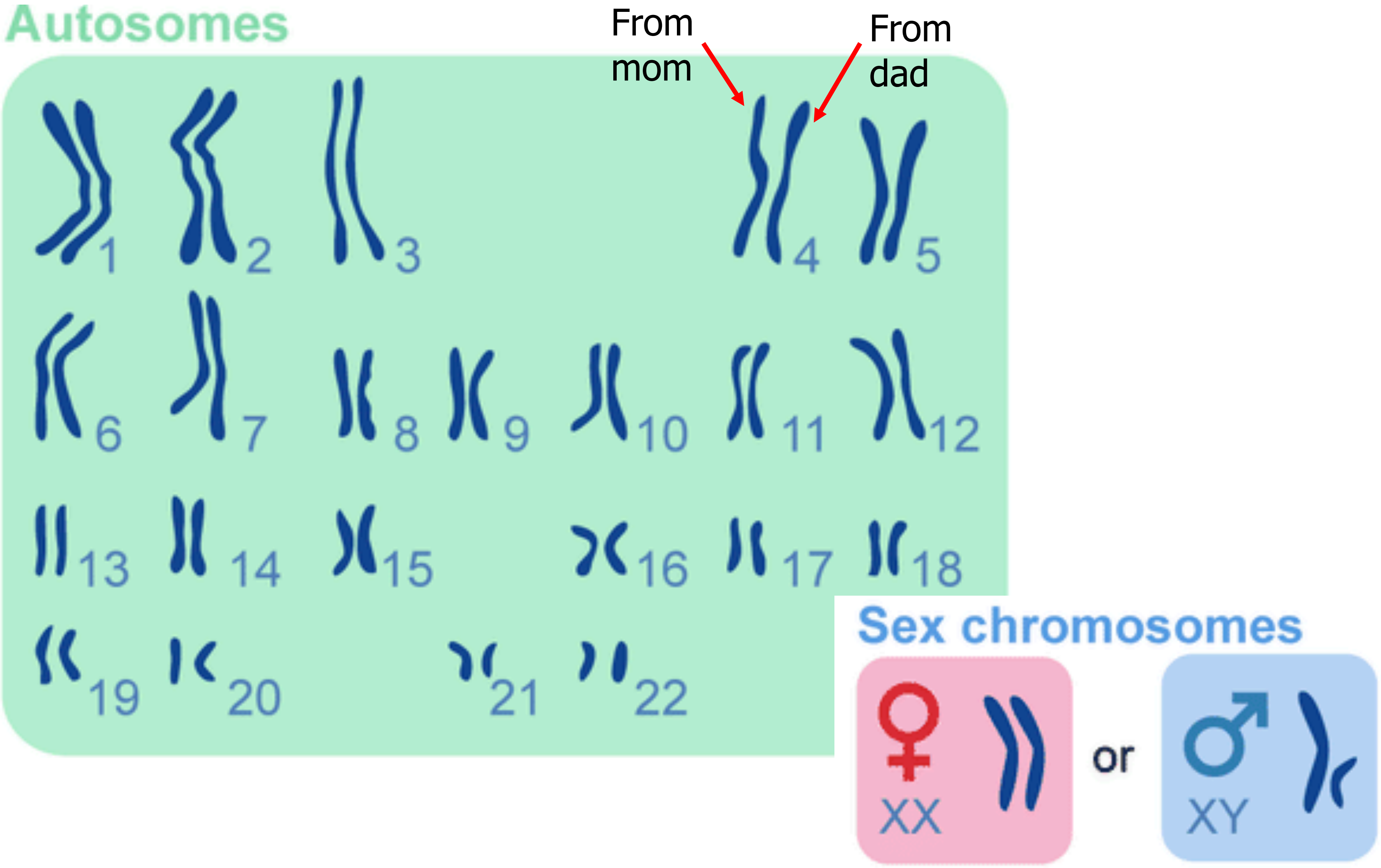
- Includes everything in Ancestry + Traits Service

PLUS

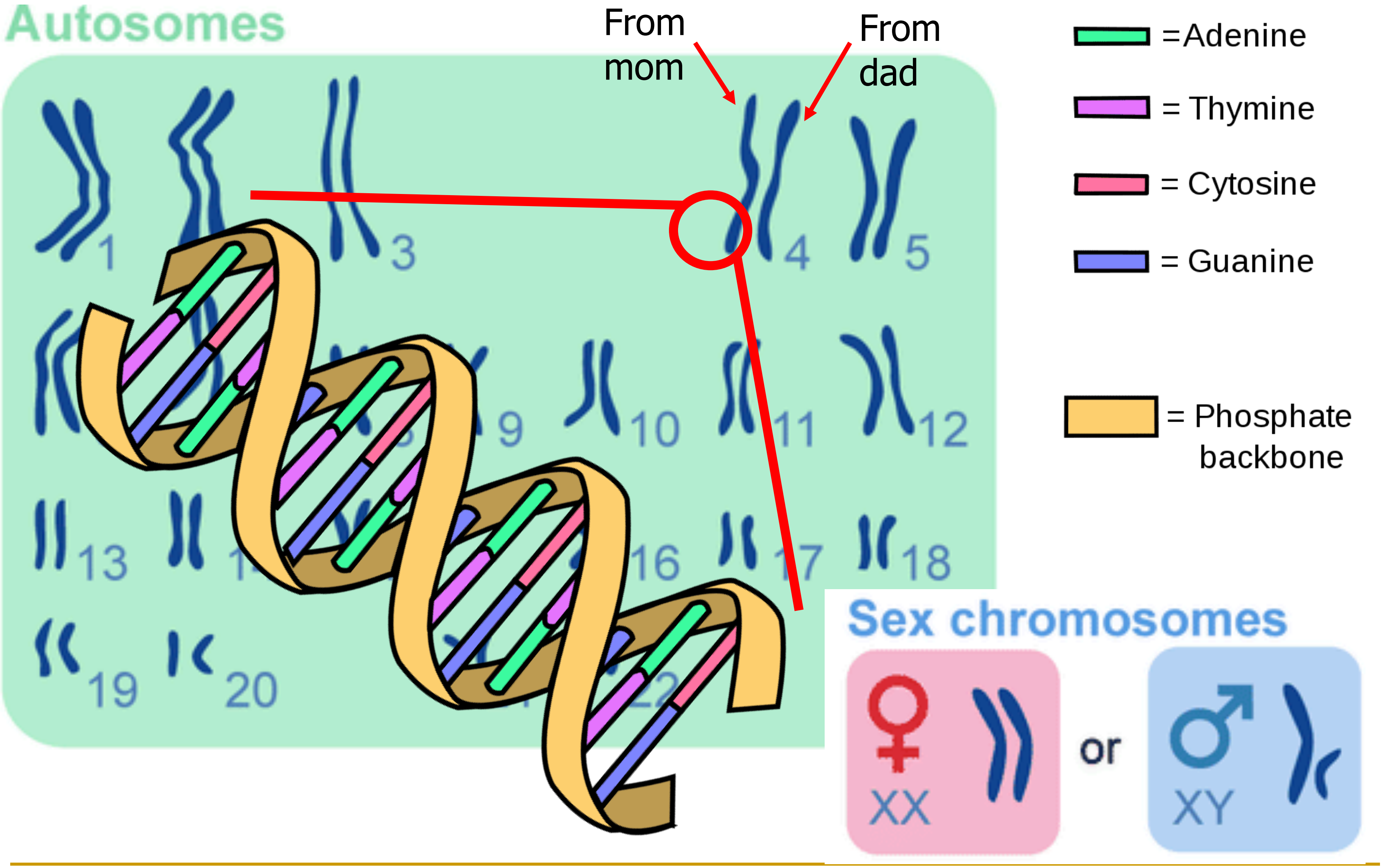
- 10+ Health Predisposition reports*
- 5+ Wellness reports
- 40+ Carrier Status reports*

https://www.myheritage.ch/dna https://www.23andme.com/

Human Chromosomes (23 Pairs)



Human Chromosomes (23 Pairs)



From mom

From dad

🟩 =Adenine

🟪 = Thymine

🟥 = Cytosine

🟦 = Guanine

🟨 = Phosphate backbone

Finding SNPs Associated with Complex Trait

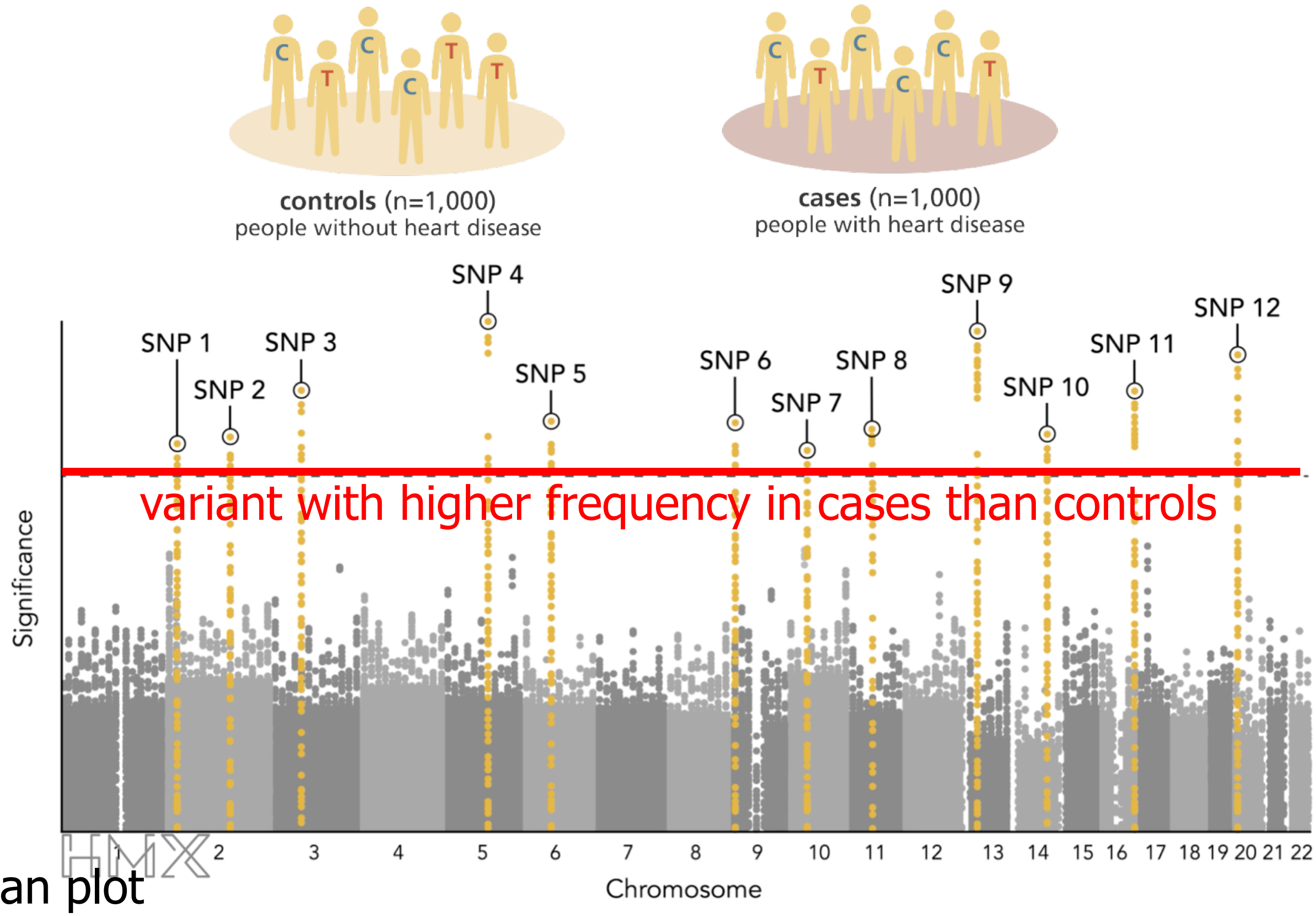
	SNP1 SNP2	Blood Pressure
Individual #1	...ACATGCCGACATTTCATAGGCC...	180
Individual #2	...ACATGCCGACATTTCATAAGCC...	175
Individual #3	...ACATGCCGACATTTCATAGGCC...	170
Individual #4	...ACATGCCGACATTTCATAAGCC...	165
Individual #5	...ACATGCCGACATTTCATAGGCC...	160
Individual #6	...ACATGCCGACATTTCATAGGCC...	145
Individual #7	...ACATGCCGACATTTCATAAGCC...	140
Individual #8	...ACATGCCGACATTTCATAAGCC...	130
Individual #9	...ACATGTCGACATTTCATAGGCC...	120
Individual #10	...ACATGTCGACATTTCATAAGCC...	120
Individual #11	...ACATGTCGACATTTCATAGGCC...	115
Individual #12	...ACATGTCGACATTTCATAAGCC...	110
Individual #13	...ACATGTCGACATTTCATAGGCC...	110
Individual #14	...ACATGTCGACATTTCATAAGCC...	110
Individual #15	...ACATGTCGACATTTCATAGGCC...	105
Individual #16	...ACATGTCGACATTTCATAAGCC...	100

SNP: single nucleotide polymorphism

SAFARI Eleazar Eskin: Discovering the Causal Variants Involved in GWAS Studies, CGSI 2018, UCLA

Genome-Wide Association Study (GWAS)

- Detecting genetic variants associated with phenotypes using two groups of people.

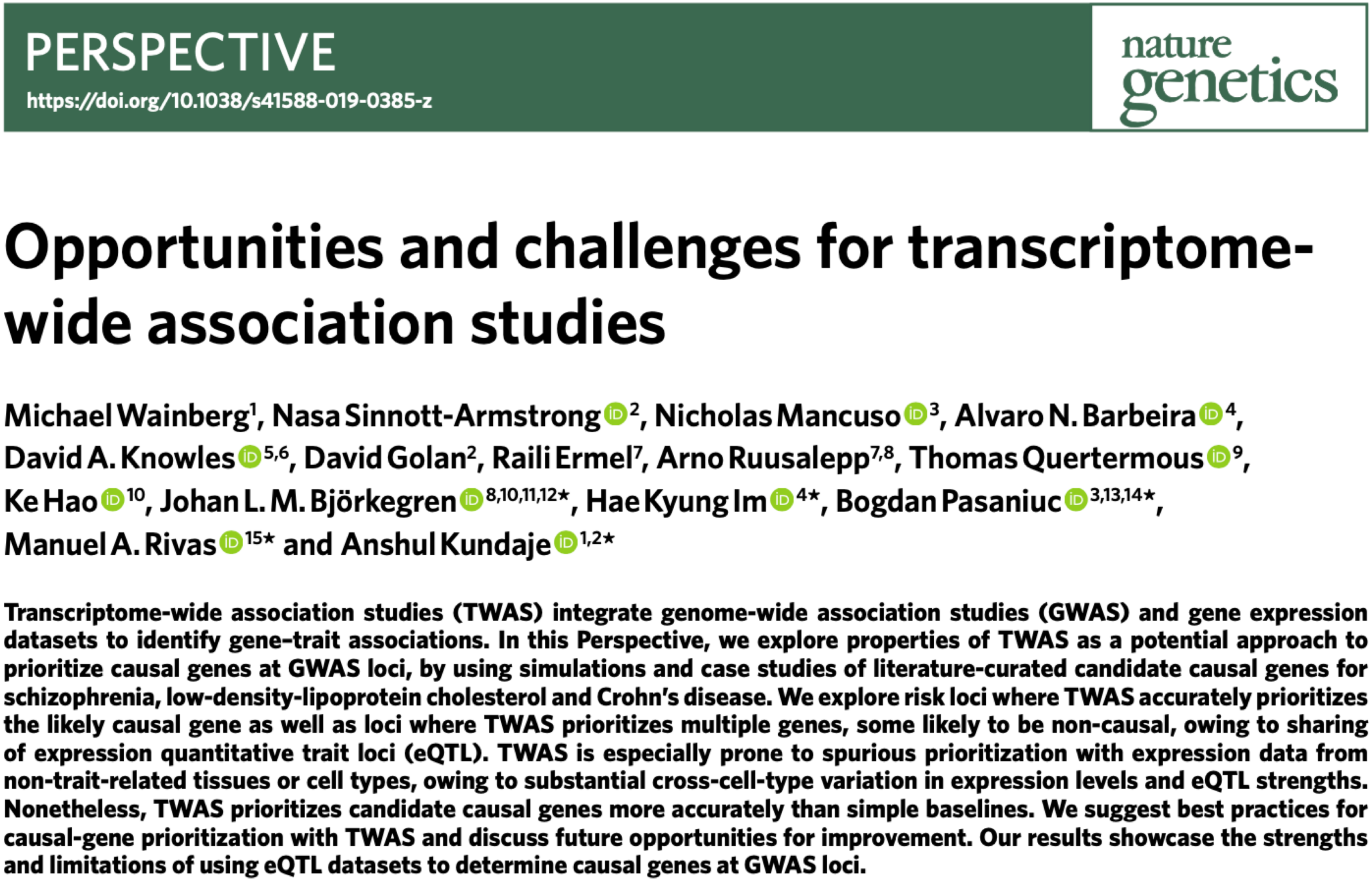


variant with higher frequency in cases than controls

Manhattan plot

https://onlinelearning.hms.harvard.edu/hmx/courses/genetic-testing/

Similar Association Studies



PERSPECTIVE
https://doi.org/10.1038/s41588-019-0385-z

nature genetics

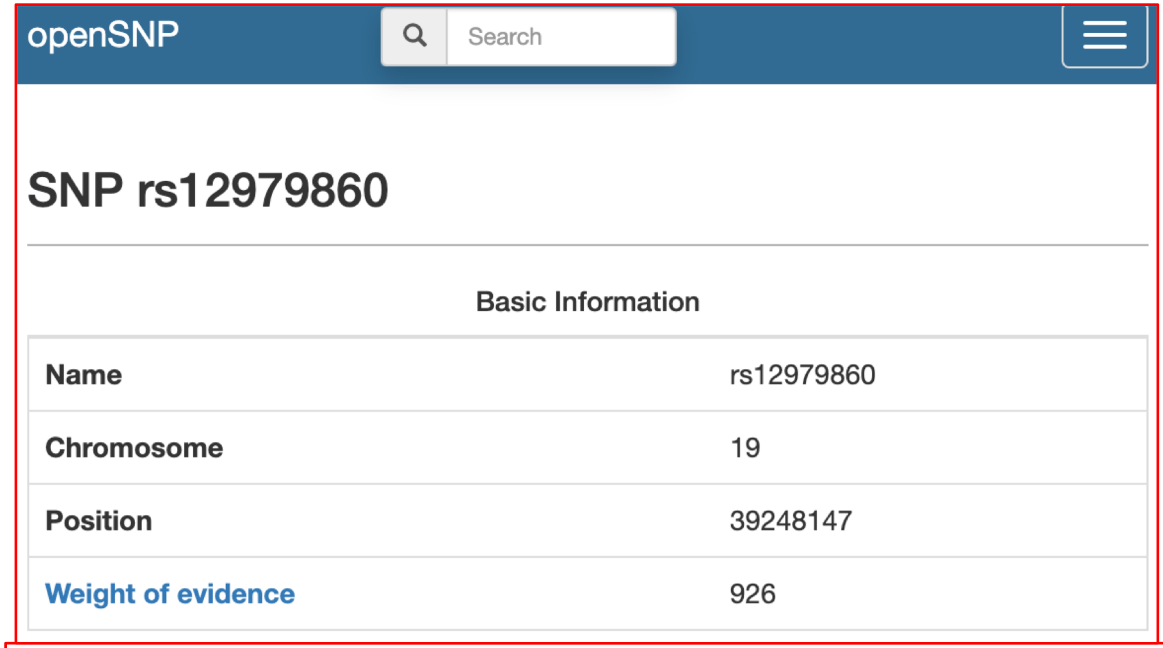
Opportunities and challenges for transcriptome-wide association studies

Michael Wainberg[1], Nasa Sinnott-Armstrong[2], Nicholas Mancuso[3], Alvaro N. Barbeira[4], David A. Knowles[5,6], David Golan[2], Raili Ermel[7], Arno Ruusalepp[7,8], Thomas Quertermous[9], Ke Hao[10], Johan L. M. Björkegren[8,10,11,12*], Hae Kyung Im[4*], Bogdan Pasaniuc[3,13,14*], Manuel A. Rivas[15*] and Anshul Kundaje[1,2*]

Transcriptome-wide association studies (TWAS) integrate genome-wide association studies (GWAS) and gene expression datasets to identify gene-trait associations. In this Perspective, we explore properties of TWAS as a potential approach to prioritize causal genes at GWAS loci, by using simulations and case studies of literature-curated candidate causal genes for schizophrenia, low-density-lipoprotein cholesterol and Crohn's disease. We explore risk loci where TWAS accurately prioritizes the likely causal gene as well as loci where TWAS prioritizes multiple genes, some likely to be non-causal, owing to sharing of expression quantitative trait loci (eQTL). TWAS is especially prone to spurious prioritization with expression data from non-trait-related tissues or cell types, owing to substantial cross-cell-type variation in expression levels and eQTL strengths. Nonetheless, TWAS prioritizes candidate causal genes more accurately than simple baselines. We suggest best practices for causal-gene prioritization with TWAS and discuss future opportunities for improvement. Our results showcase the strengths and limitations of using eQTL datasets to determine causal genes at GWAS loci.

Wainberg+, "Opportunities and challenges for transcriptome-wide association studies", *Nature genetics,* 2019.

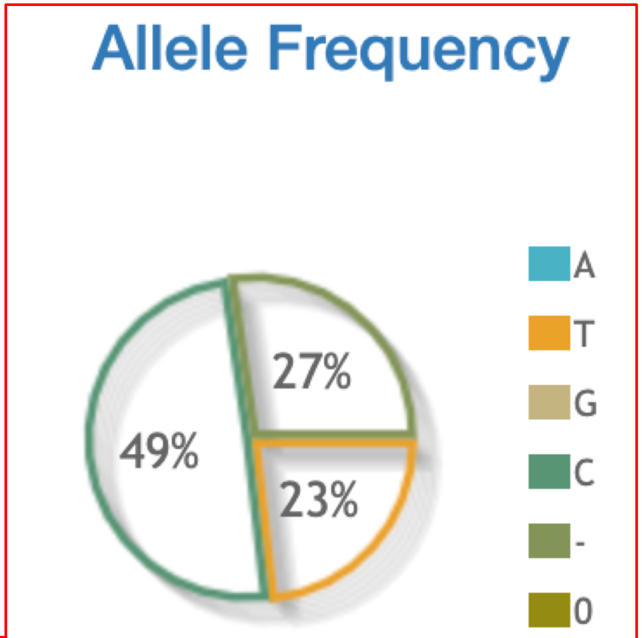
SNPs and Personalized Medicine



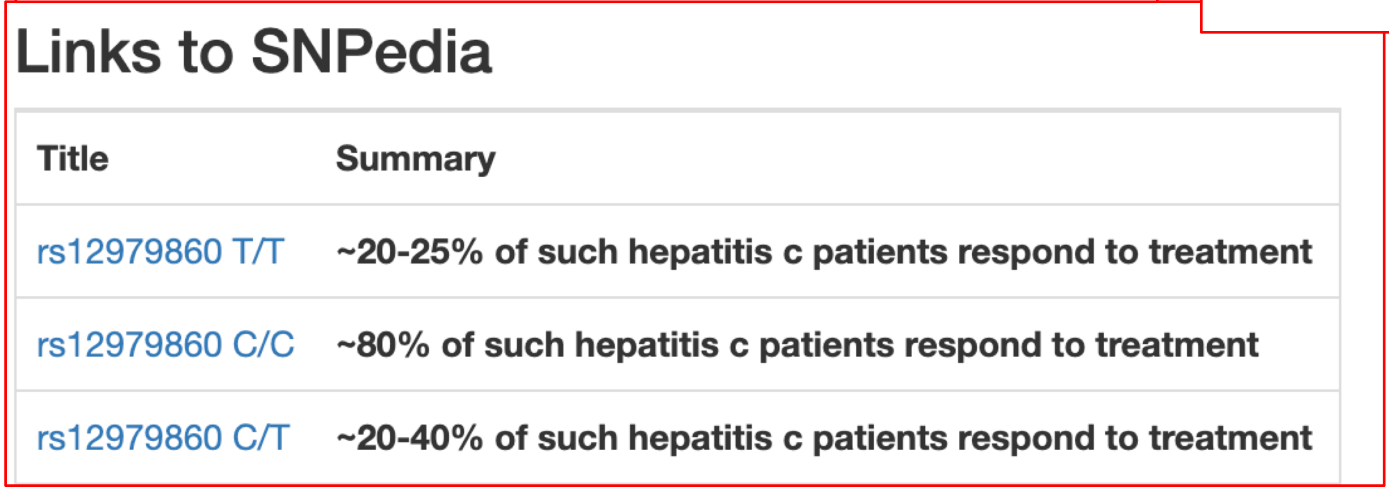
SNP rs12979860

Basic Information

Name	rs12979860
Chromosome	19
Position	39248147
Weight of evidence	926



Allele Frequency



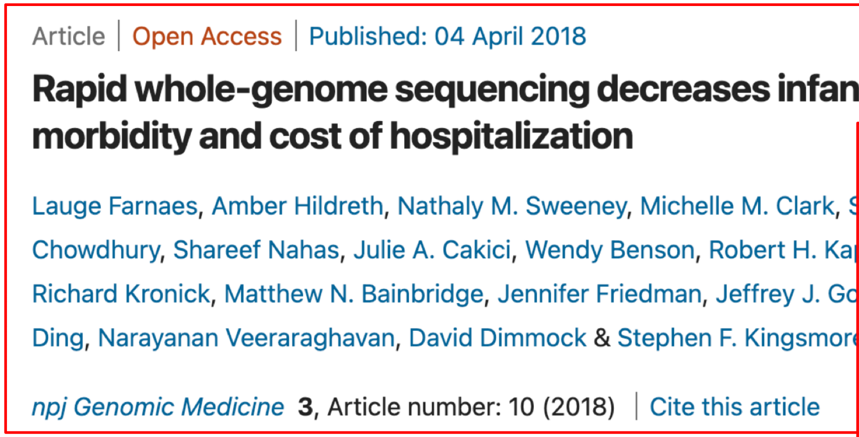
Links to SNPedia

Title	Summary
rs12979860 T/T	~20-25% of such hepatitis c patients respond to treatment
rs12979860 C/C	~80% of such hepatitis c patients respond to treatment
rs12979860 C/T	~20-40% of such hepatitis c patients respond to treatment

https://opensnp.org/snps/rs12979860

Personalized Medicine for Critically Ill Infants

- rWGS can be performed in 2-day (costly) or 5-day time to interpretation.
- Diagnostic rWGS for infants
  - Avoids morbidity
  - Reduces hospital stay length by 6%-69%
  - Reduces inpatient cost by $800,000-$2,000,000.

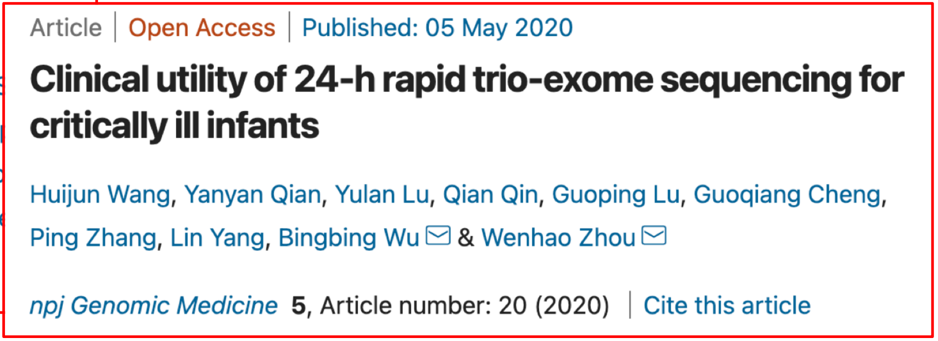


Article | Open Access | Published: 04 April 2018

Rapid whole-genome sequencing decreases infant morbidity and cost of hospitalization

Lauge Farnaes, Amber Hildreth, Nathaly M. Sweeney, Michelle M. Clark, S
Chowdhury, Shareef Nahas, Julie A. Cakici, Wendy Benson, Robert H. Ka
Richard Kronick, Matthew N. Bainbridge, Jennifer Friedman, Jeffrey J. Go
Ding, Narayanan Veeraraghavan, David Dimmock & Stephen F. Kingsmore

npj Genomic Medicine **3**, Article number: 10 (2018) | Cite this article



Article | Open Access | Published: 05 May 2020

Clinical utility of 24-h rapid trio-exome sequencing for critically ill infants

Huijun Wang, Yanyan Qian, Yulan Lu, Qian Qin, Guoping Lu, Guoqiang Cheng, Ping Zhang, Lin Yang, Bingbing Wu ✉ & Wenhao Zhou ✉

npj Genomic Medicine **5**, Article number: 20 (2020) | Cite this article

Farnaes+, "Rapid whole-genome sequencing decreases infant morbidity and cost of hospitalization", NPJ Genomic Medicine, 2018

Personalized Medicine in UK

"From 2019, all seriously ill children in UK will be offered whole genome sequencing as part of their care"

NHS
National Institute for Health Research

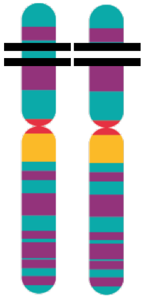
Much Larger Structural Variations!

AUTISM
Weiss, *N Eng J Med* 2008
Deletion of 593 kb

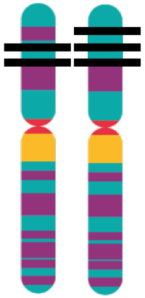
SCHIZOPHRENIA
McCarthy, *Nat Genet* 2009
Duplication of 593 kb

OBESITY
Walters, *Nature* 2010
Deletion of 593 kb

UNDERWEIGHT
Jacquemont, *Nature* 2011
Duplication of 593 kb



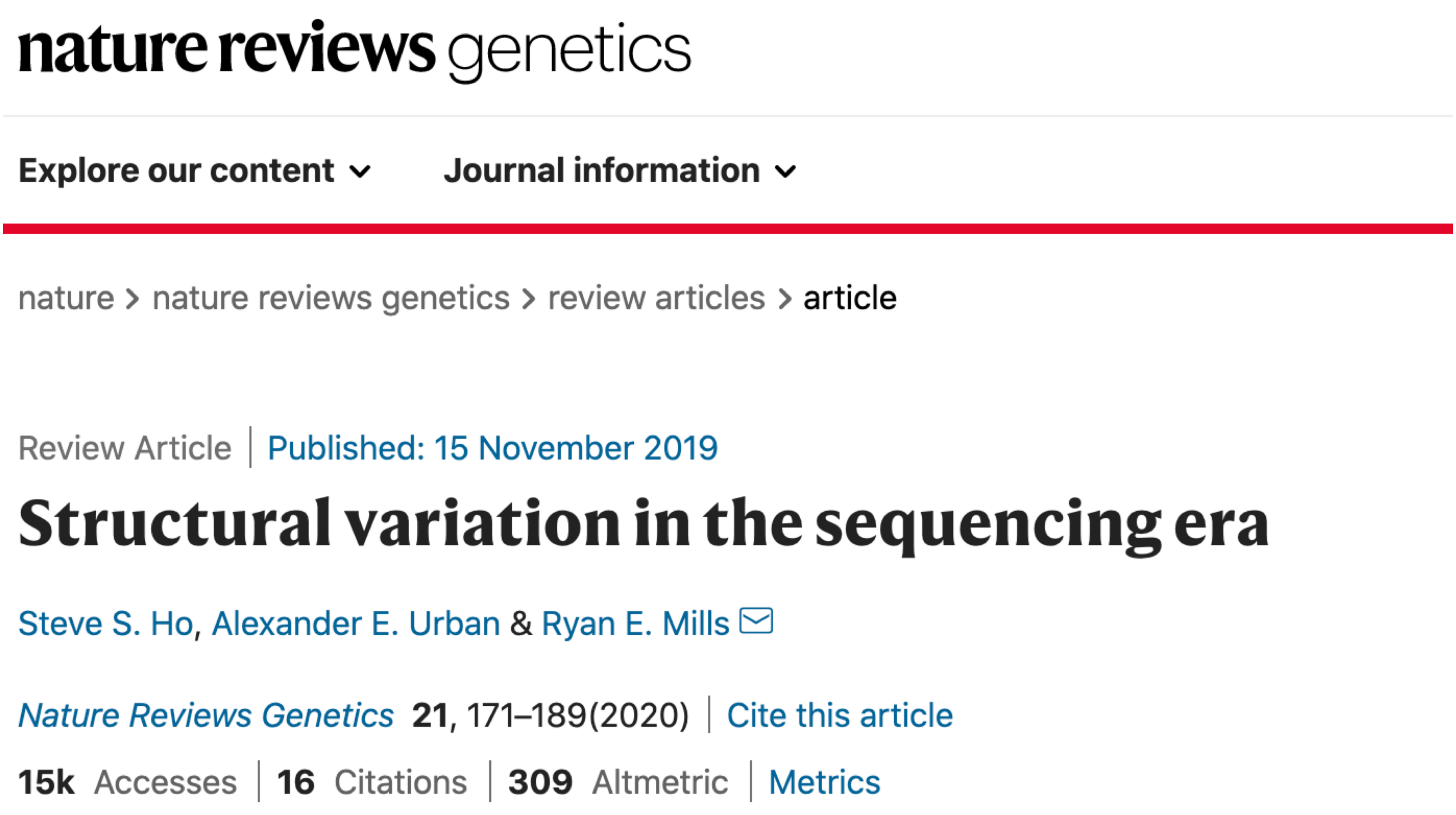
Deletion in the short arm
of chromosome 16 (16p11.2)



Duplication in the short arm
of chromosome 16 (16p11.2)

CNV: copy number variation

Recommended Reading



nature reviews genetics

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Review Article | Published: 15 November 2019

Structural variation in the sequencing era

Steve S. Ho, Alexander E. Urban & Ryan E. Mills ✉

Nature Reviews Genetics **21**, 171–189(2020) | Cite this article

15k Accesses | **16** Citations | **309** Altmetric | Metrics

Ho+, "Structural variation in the sequencing era", Nature Reviews Genetics, 2020

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- Where is Read Mapping Going Next?

What is Intelligent Genome Analysis?

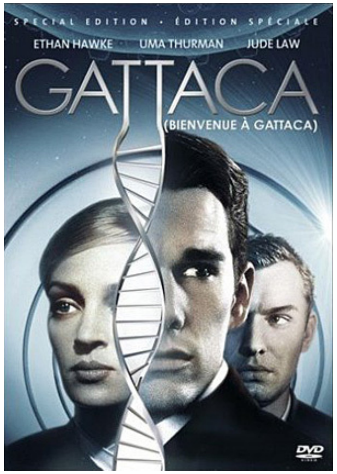
- Fast genome analysis — Bandwidth
  - *Real-time analysis?*
- Population-scale genome analysis — Scalability
  - *Number of analyses per day!*
- Using intelligent architectures — Energy-efficiency & Portability
  - *Small specialized HW with less data movement*
- DNA is a valuable asset — Privacy
  - *Controlled-access analysis*
- Avoiding erroneous analysis — Accuracy
  - *E.g., your father is not your father*

Does intelligent genome analysis really matter?

Fast Genome Analysis?

- **Fast** genome analysis in mere seconds using limited computational resources (i.e., personal computer or small hardware).

1997

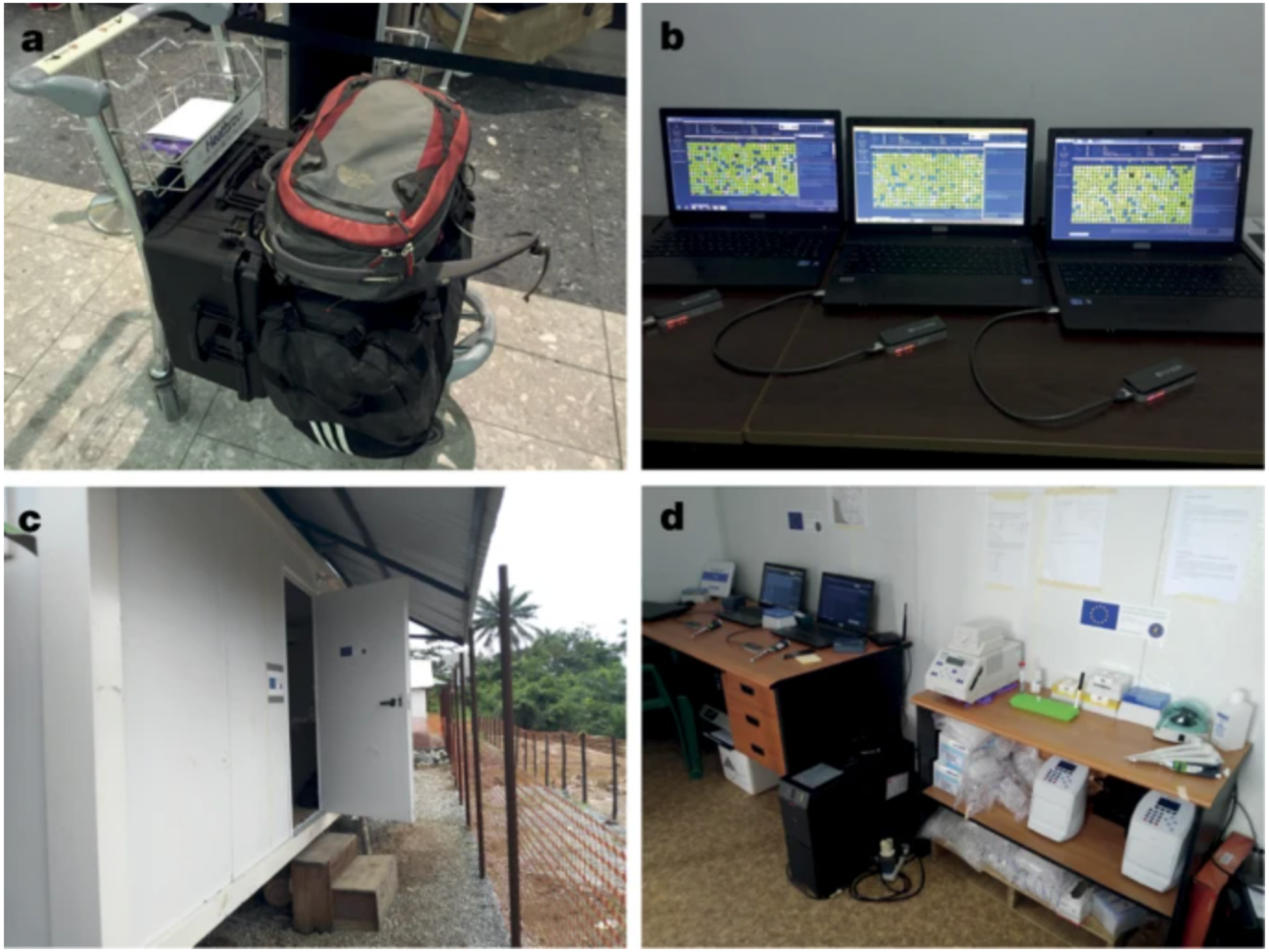


2015

FROM THE DIRECTOR OF THE INCREDIBLES & MISSION: IMPOSSIBLE - GHOST PROTOCOL
GEORGE CLOONEY
TOMORROWLAND
REMEMBER TOMORROW MAY 22
EXPERIENCE IT IN IMAX

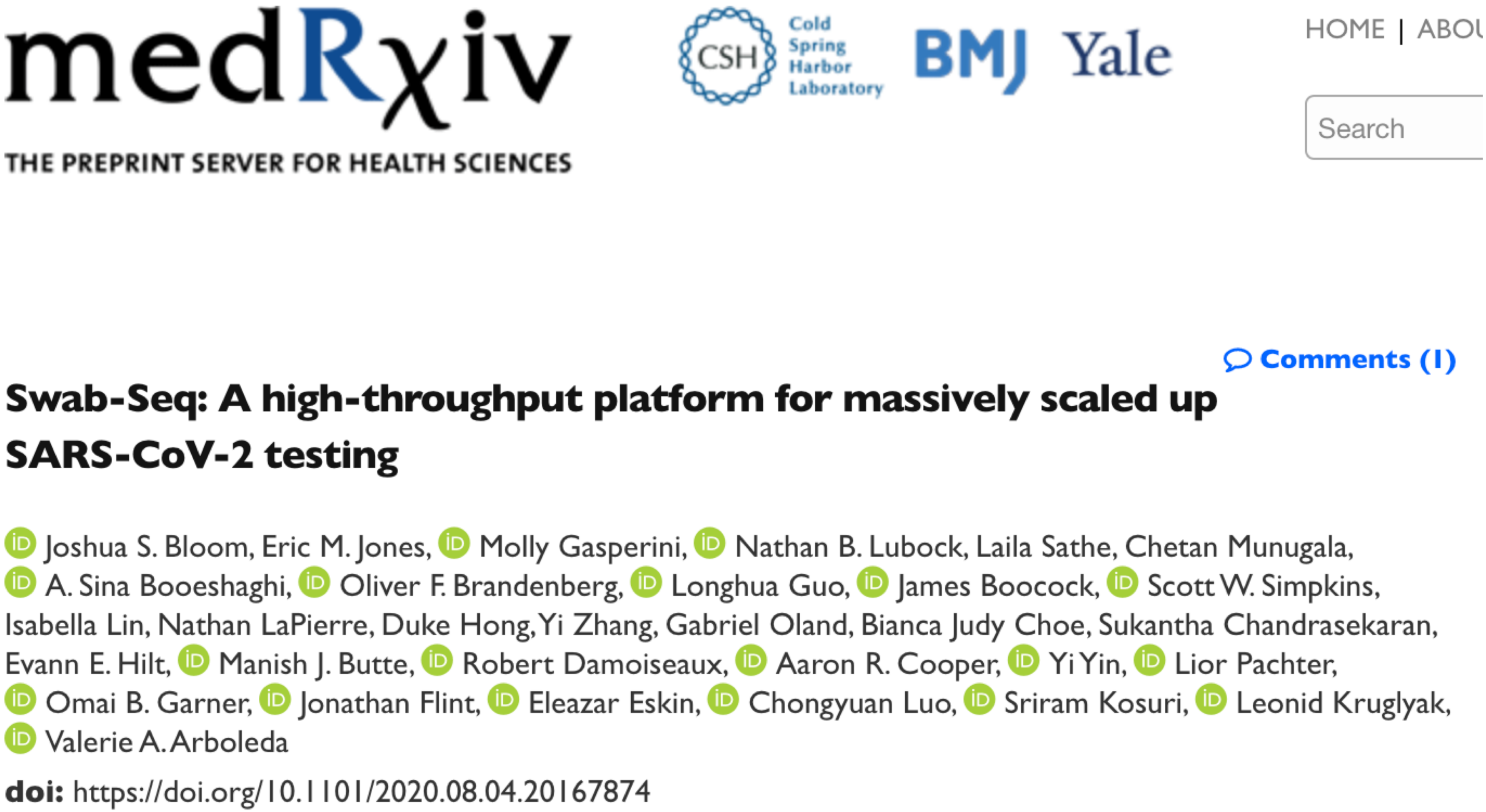
Rapid Surveillance of Disease Outbreaks?

Figure 1: Deployment of the portable genome surveillance system in Guinea.



Quick+, "Real-time, portable genome sequencing for Ebola surveillance", *Nature*, 2016

Scalable SARS-CoV-2 Testing


medRxiv
THE PREPRINT SERVER FOR HEALTH SCIENCES
CSH Cold Spring Harbor Laboratory
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Yale
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Comments (1)

Swab-Seq: A high-throughput platform for massively scaled up SARS-CoV-2 testing

Joshua S. Bloom, Eric M. Jones, Molly Gasperini, Nathan B. Lubock, Laila Sathe, Chetan Munugala, A. Sina Booeshaghi, Oliver F. Brandenberg, Longhua Guo, James Boocock, Scott W. Simpkins, Isabella Lin, Nathan LaPierre, Duke Hong, Yi Zhang, Gabriel Oland, Bianca Judy Choe, Sukantha Chandrasekaran, Evann E. Hilt, Manish J. Butte, Robert Damoiseaux, Aaron R. Cooper, Yi Yin, Lior Pachter, Omai B. Garner, Jonathan Flint, Eleazar Eskin, Chongyuan Luo, Sriram Kosuri, Leonid Kruglyak, Valerie A. Arboleda

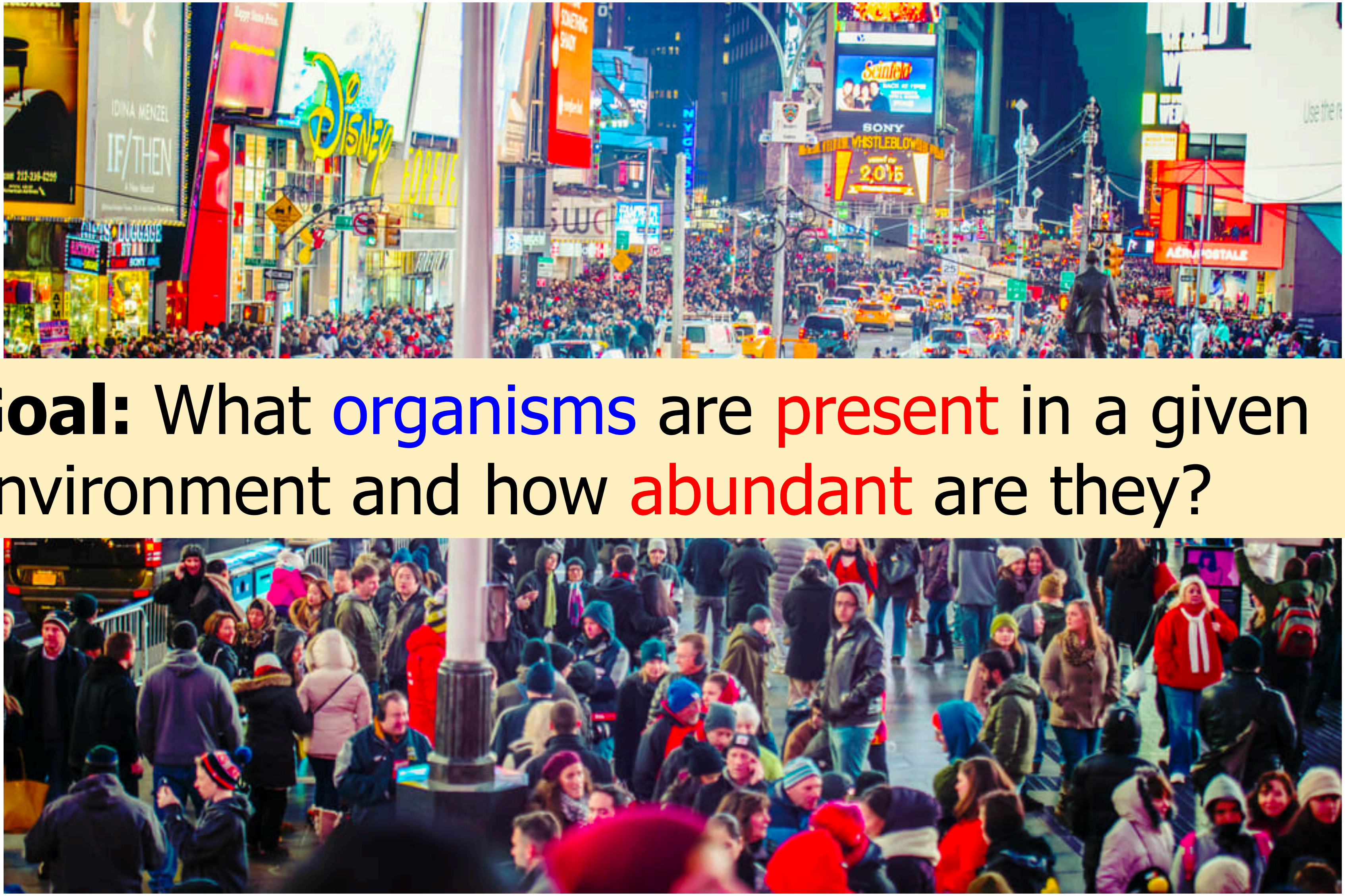
doi: https://doi.org/10.1101/2020.08.04.20167874

Bloom+, "Swab-Seq: A high-throughput platform for massively scaled up SARS-CoV-2 testing", *medRxiv*, 2020

Population-Scale Microbiome Profiling

https://blog.wego.com/7-crowded-places-and-events-that-you-will-love/

Population-Scale Microbiome Profiling



Goal: What organisms are present in a given environment and how abundant are they?

SAFARI https://blog.wego.com/7-crowded-places-and-events-that-you-will-love/

City-Scale Microbiome Profiling

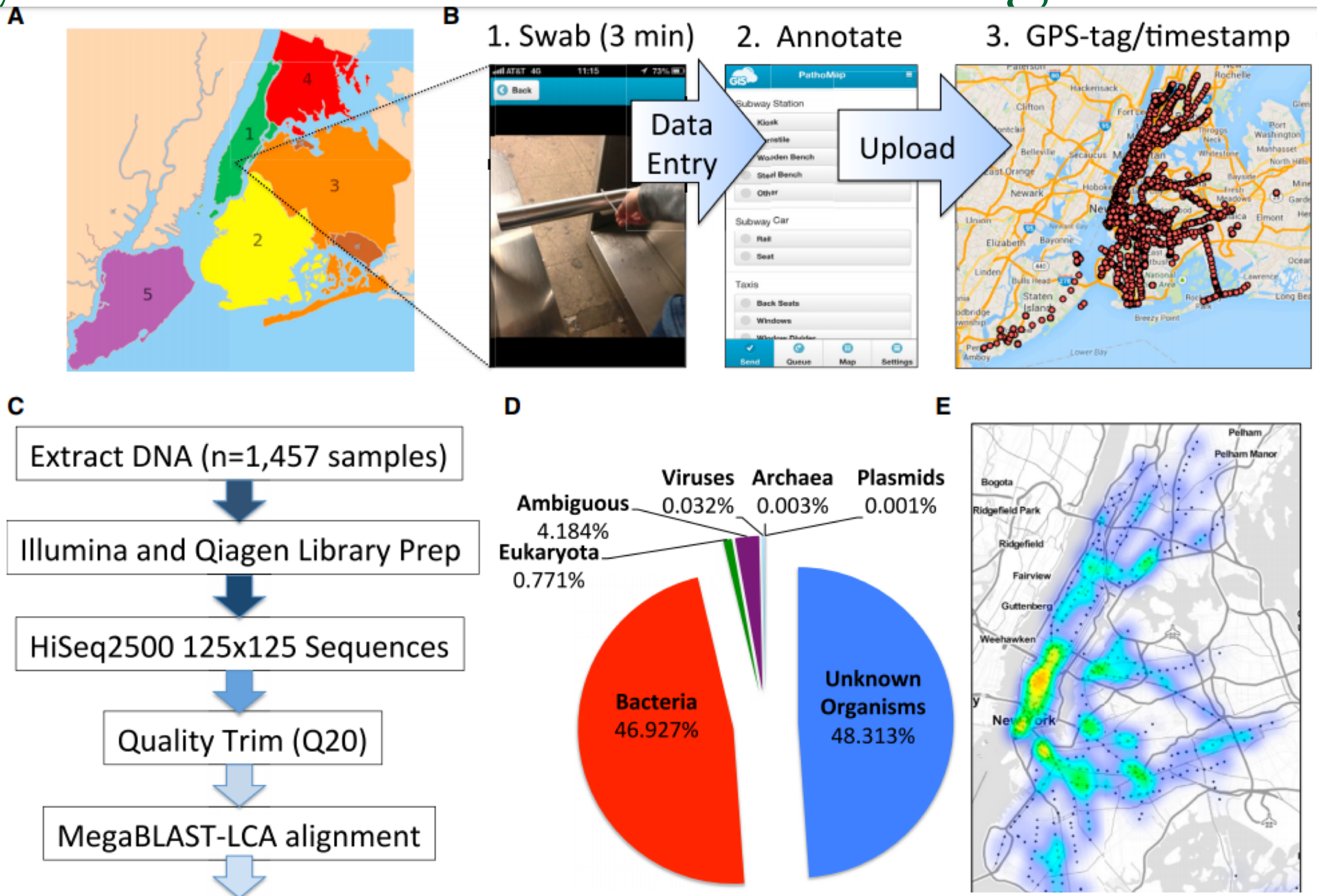


Figure 1. The Metagenome of New York City

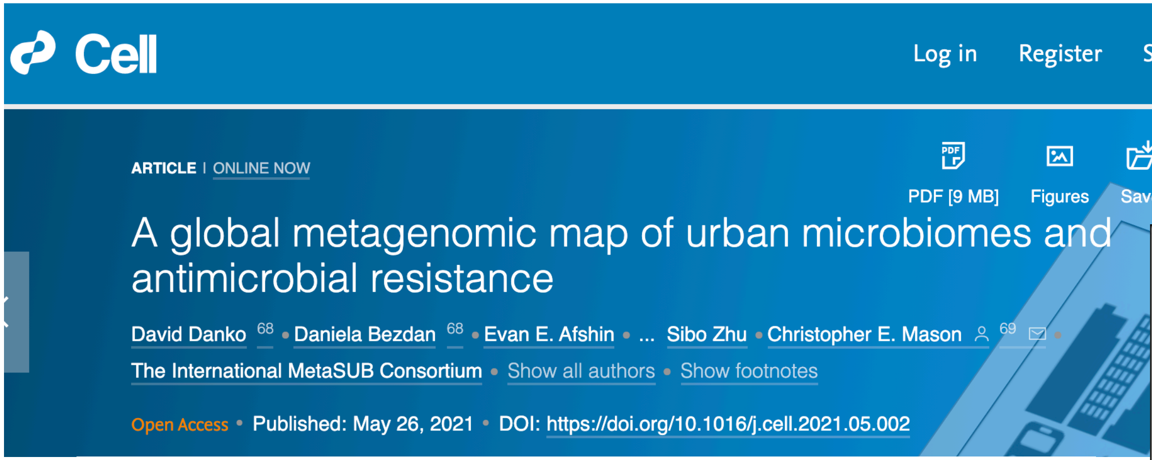
(A) The five boroughs of NYC include (1) Manhattan (green)

(B) The collection from the 466 subway stations of NYC across the 24 subway lines involved three main steps: (1) collection with Copan Elution swabs, (2) data entry into the database, and (3) uploading of the data. An image is shown of the current collection database, taken from http://pathomap.giscloud.com.

(C) Workflow for sample DNA extraction, library preparation, sequencing, quality trimming of the FASTQ files, and alignment with MegaBLAST and MetaPhlAn to discern taxa present

Afshinnekoo+, "Geospatial Resolution of Human and Bacterial Diversity with City-Scale Metagenomics", Cell Systems, 2015

Population-Scale Microbiome Profiling



Cell | Log in | Register | Su

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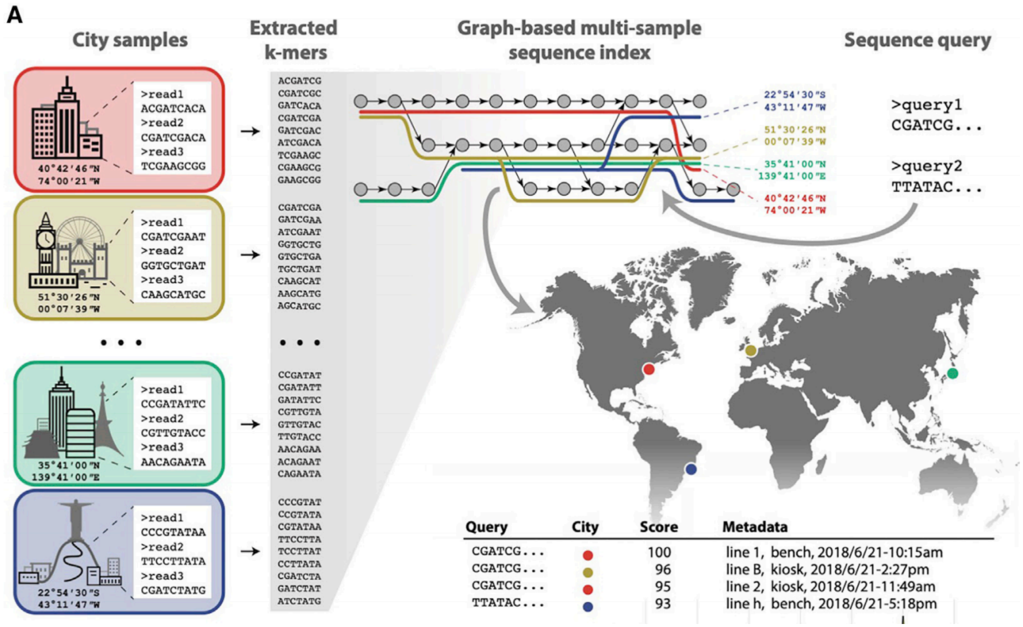
PDF [9 MB] | Figures | Save

A global metagenomic map of urban microbiomes and antimicrobial resistance

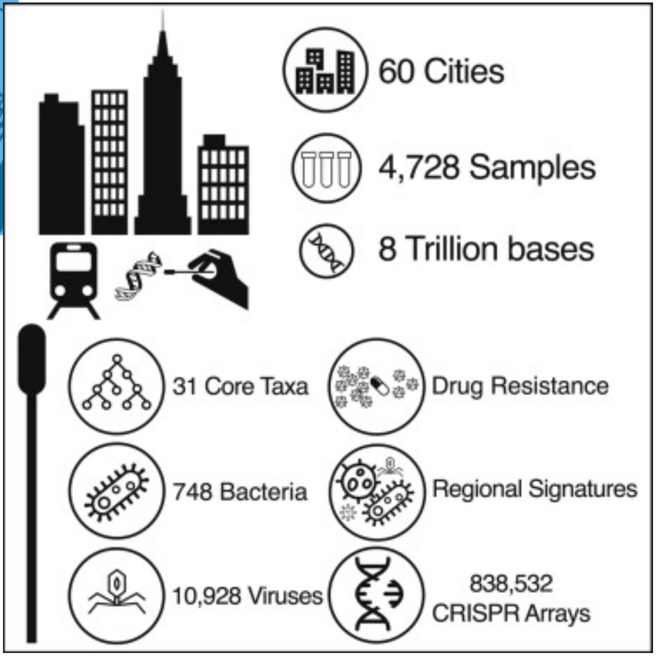
David Danko [68] • Daniela Bezdan [68] • Evan E. Afshin • ... Sibo Zhu • Christopher E. Mason [69] •
The International MetaSUB Consortium • Show all authors • Show footnotes

Open Access • Published: May 26, 2021 • DOI: https://doi.org/10.1016/j.cell.2021.05.002



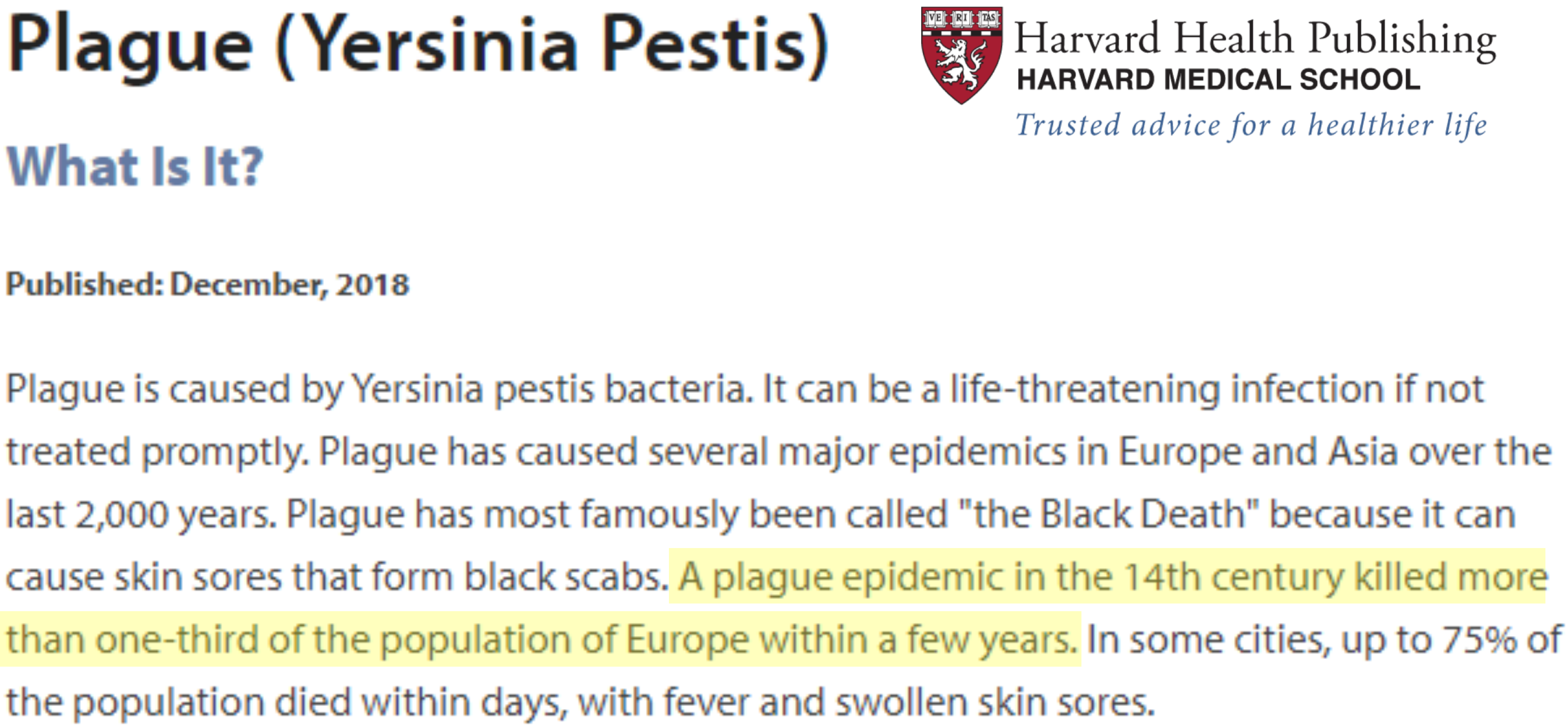
A
City samples
Extracted k-mers
Graph-based multi-sample sequence index
Sequence query
>read1 ACGATCACA >read2 CGATCGACA >read3 TCGAAGCGG
40°42'46"N 74°00'21"W
>read1 CGATCGAAT >read2 GGTGCTGAT >read3 CAAGCATGC
51°30'26"N 00°07'39"W
>read1 CCGATATTC >read2 CGTTGTACC >read3 AACAGAATA
35°41'00"N 139°41'00"E
>read1 CCCGTATAA >read2 TTCCTTATA >read3 CGATCTATG
22°54'30"S 43°11'47"W
ACGATCG CGATCGC GATCACA CGATCGA GATCGAC ATCGACA TCGAAGC CGAAGCG GAAGCGG
CGATCGA GATCGAA ATCGAAT GGTGCTG GTGCTGA TGCTGAT CAAGCAT AAGCATG AGCATGC
CCGATAT CGATATT GATATTC CGTTGTA GTTGTAC TTGTACC AACAGAA ACAGAAT CAGAATA
CCCGTAT CCGTATA CGTATAA TTCCTTA TCCTTAT CCTTATA CGATCTA GATCTAT ATCTATG
>query1 CGATCG...
>query2 TTATAC...

Query	City	Score	Metadata
CGATCG...	🟥	100	line 1, bench, 2018/6/21-10:15am
CGATCG...	🟨	96	line B, kiosk, 2018/6/21-2:27pm
CGATCG...	🟥	95	line 2, kiosk, 2018/6/21-11:49am
TTATAC...	🟦	93	line h, bench, 2018/6/21-5:18pm



Danko+, "A global metagenomic map of urban microbiomes and antimicrobial resistance", Cell, 2021

Plague in New York Subway System?



Plague (Yersinia Pestis)

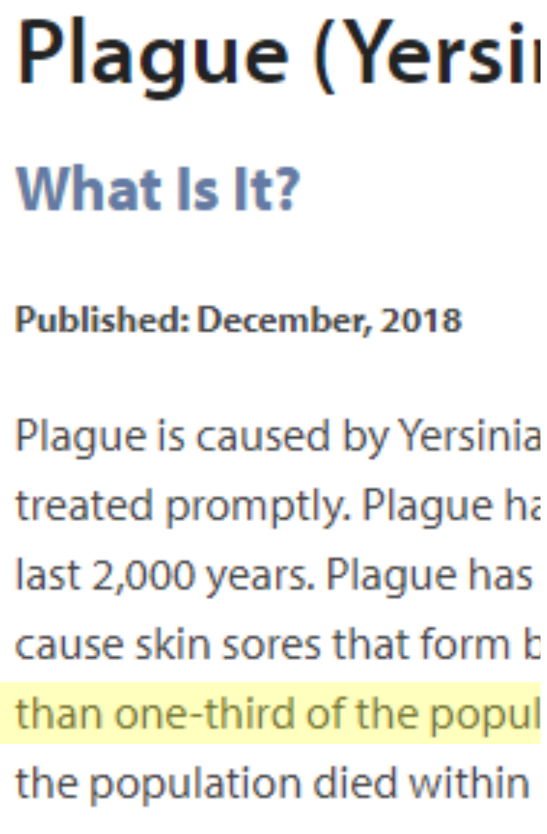
Harvard Health Publishing
HARVARD MEDICAL SCHOOL
Trusted advice for a healthier life

What Is It?

Published: December, 2018

Plague is caused by Yersinia pestis bacteria. It can be a life-threatening infection if not treated promptly. Plague has caused several major epidemics in Europe and Asia over the last 2,000 years. Plague has most famously been called "the Black Death" because it can cause skin sores that form black scabs. A plague epidemic in the 14th century killed more than one-third of the population of Europe within a few years. In some cities, up to 75% of the population died within days, with fever and swollen skin sores.

Plague in New York Subway System?

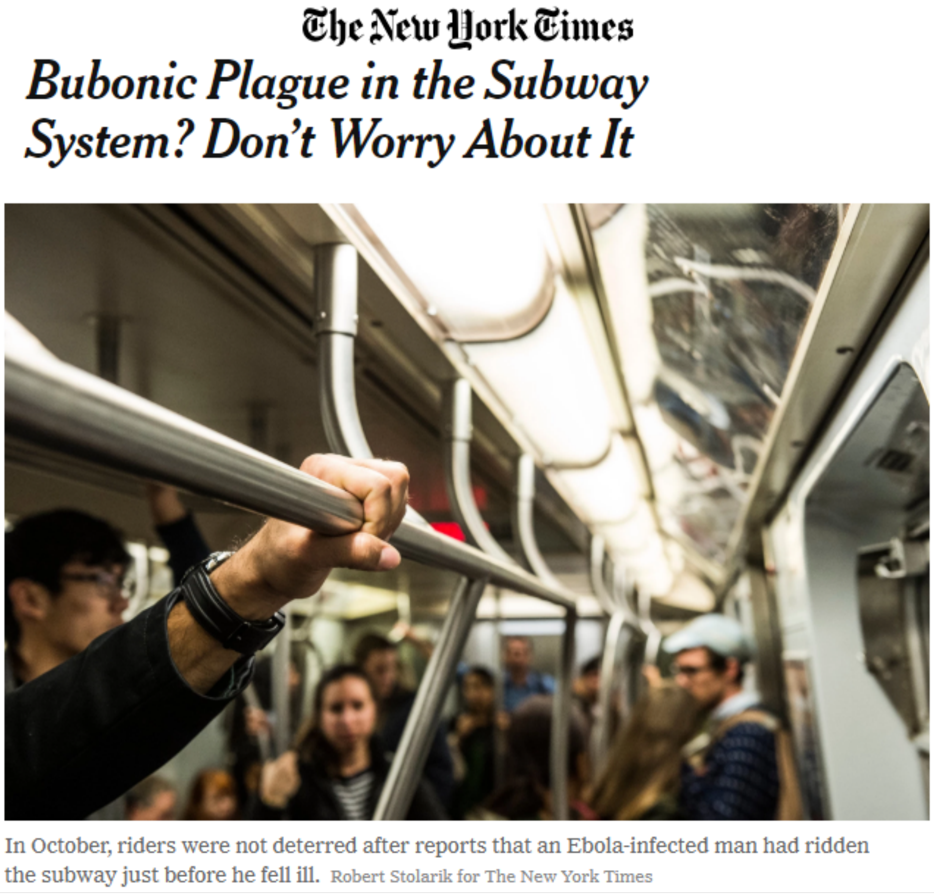


Plague (Yersi

What Is It?

Published: December, 2018

Plague is caused by Yersinia
treated promptly. Plague ha he
last 2,000 years. Plague has n
cause skin sores that form b re
than one-third of the popul of
the population died within



The New York Times

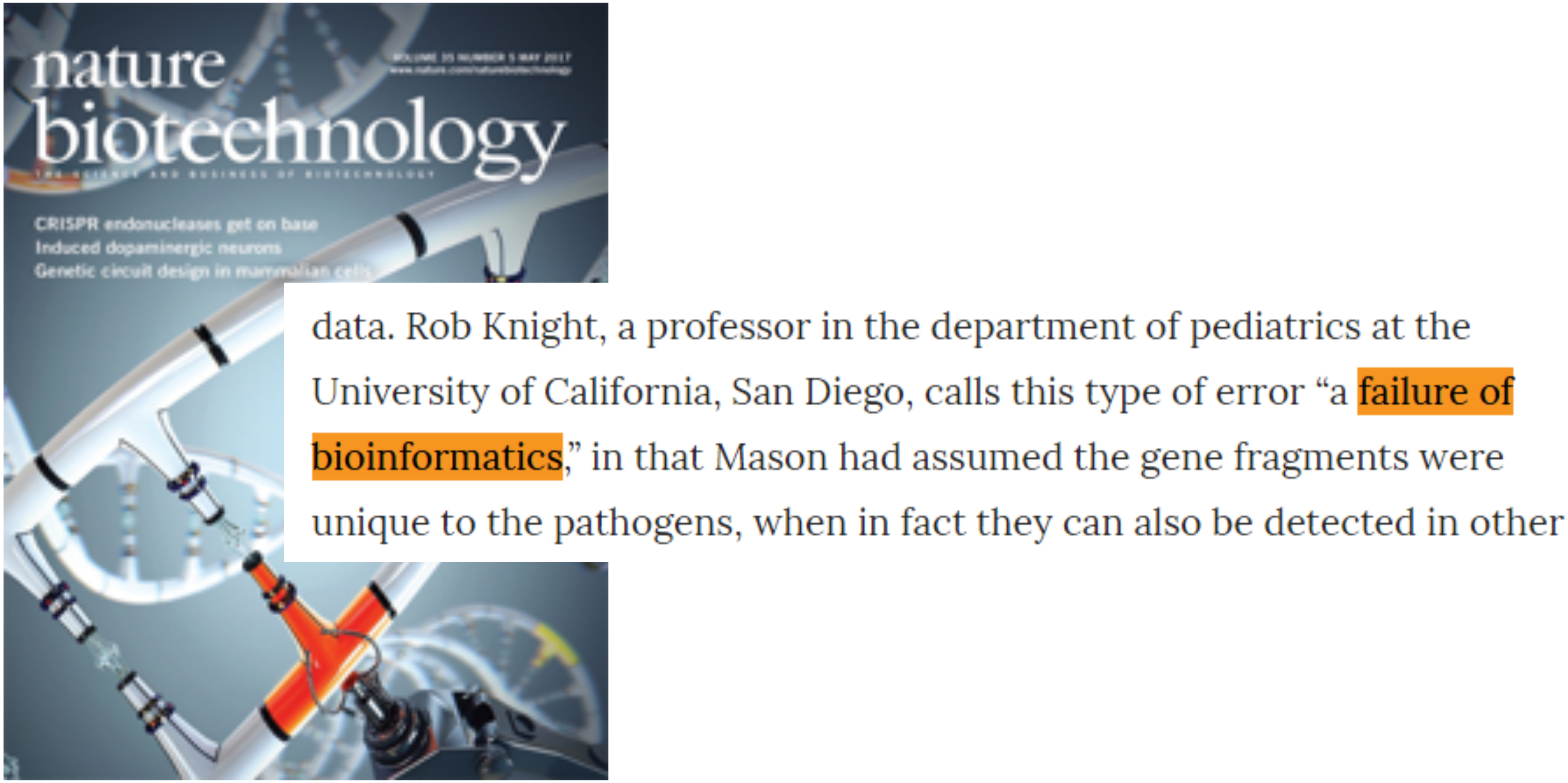
Bubonic Plague in the Subway System? Don't Worry About It

In October, riders were not deterred after reports that an Ebola-infected man had ridden the subway just before he fell ill. Robert Stolarik for The New York Times

https://www.nytimes.com/2015/02/07/nyregion/bubonic-plague-in-the-subway-system-dont-worry-about-it.html

The findings of Yersinia Pestis in the subway received wide coverage in the lay press, causing some alarm among New York residents

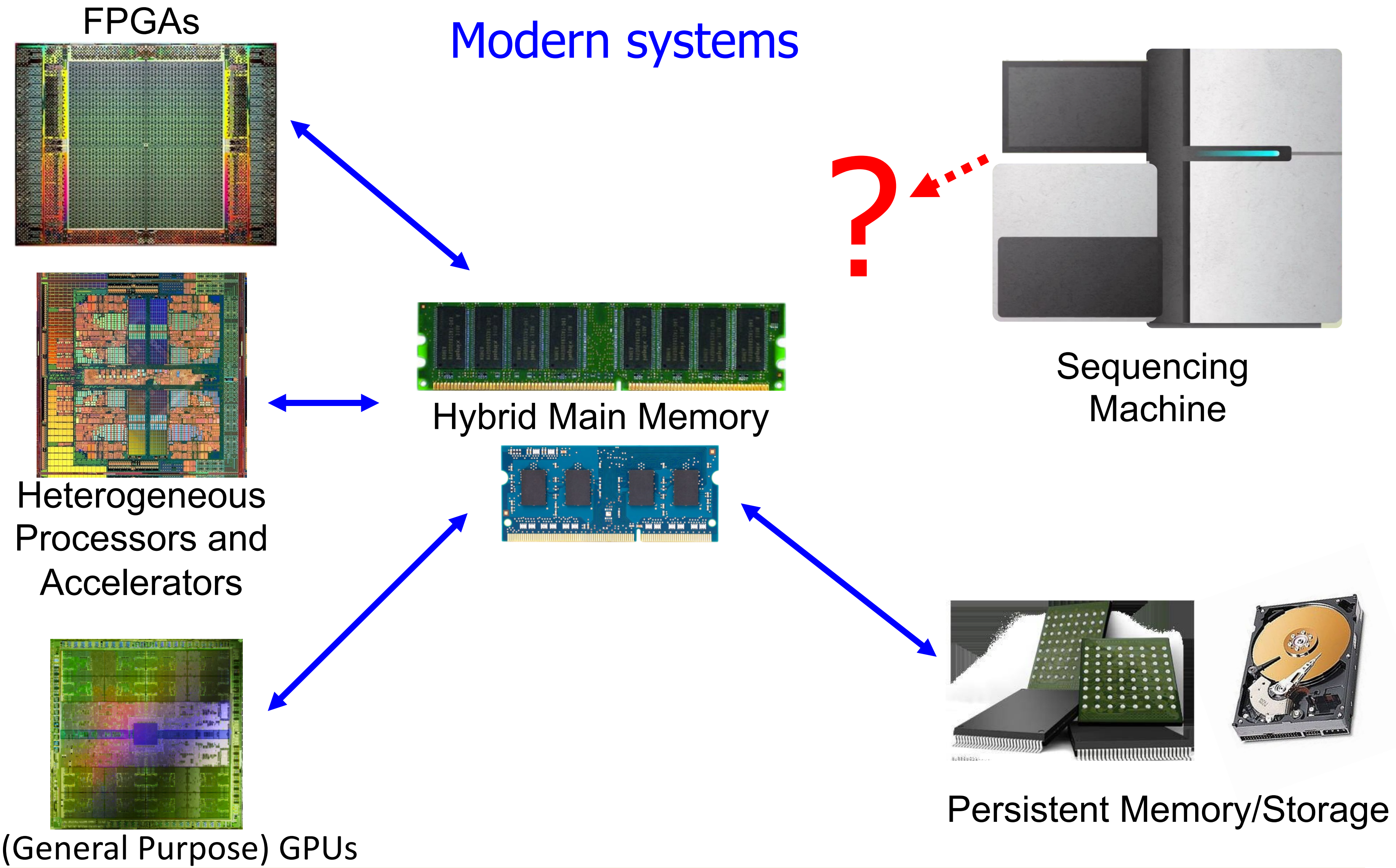
Failure of Bioinformatics


nature
biotechnology
VOLUME 35 NUMBER 5 MAY 2017
www.nature.com/naturebiotechnology
THE SCIENCE AND BUSINESS OF BIOTECHNOLOGY
CRISPR endonucleases get on base
Induced dopaminergic neurons
Genetic circuit design in mammalian cells

data. Rob Knight, a professor in the department of pediatrics at the University of California, San Diego, calls this type of error "a failure of bioinformatics," in that Mason had assumed the gene fragments were unique to the pathogens, when in fact they can also be detected in other

Living in a microbial world
Charles Schmidt
Nature Biotechnology, **volume 35**, pages401–403 (2017)
https://www.nature.com/articles/nbt.3868

Intelligent Architecture?



FPGAs

Modern systems

Sequencing Machine

Hybrid Main Memory

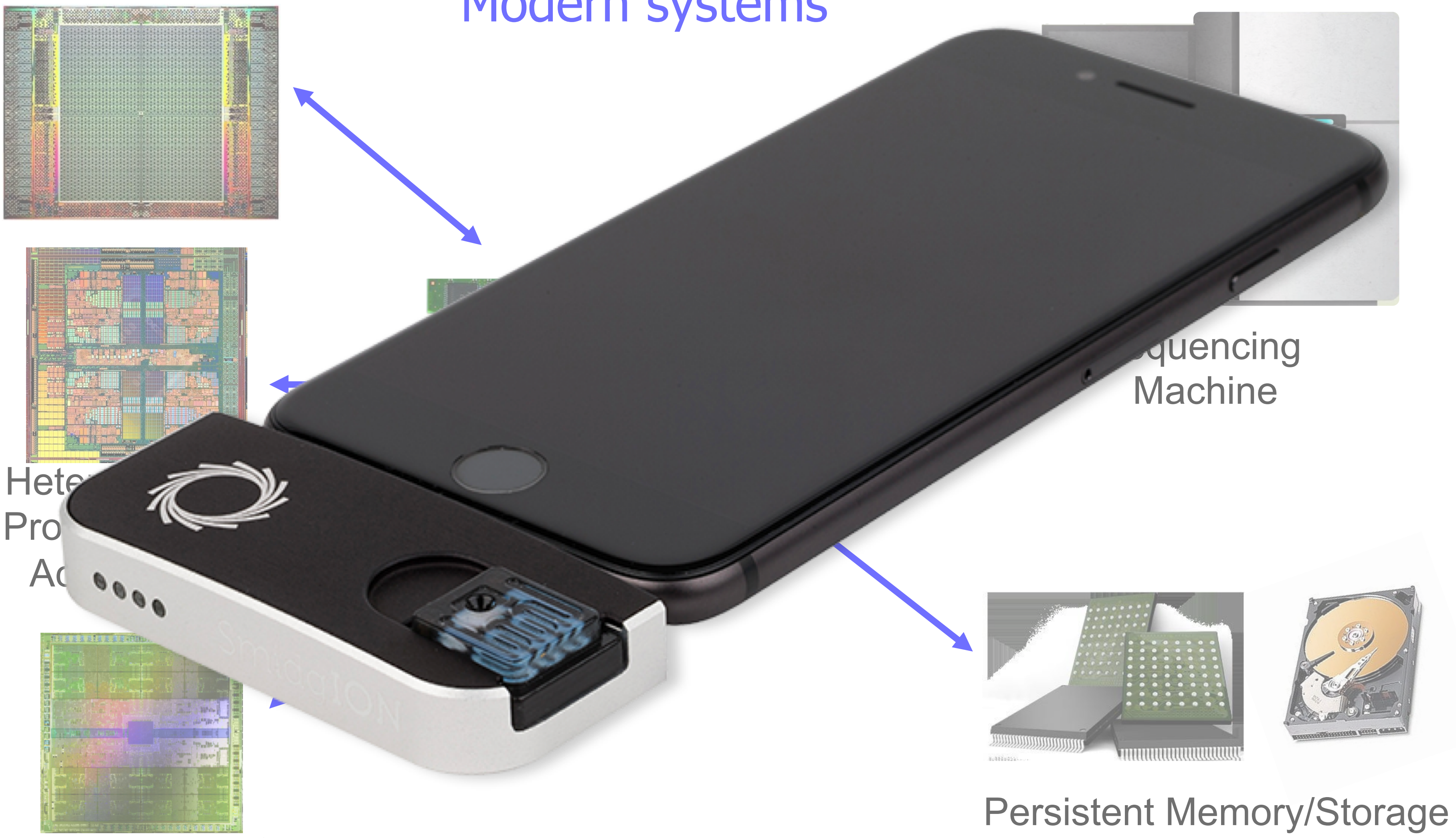
Heterogeneous Processors and Accelerators

Persistent Memory/Storage

(General Purpose) GPUs

Intelligent Architecture?

Modern systems



(General Purpose) GPUs

https://nanoporetech.com/products/smidgion

Privacy-Preserving Genome Analysis?

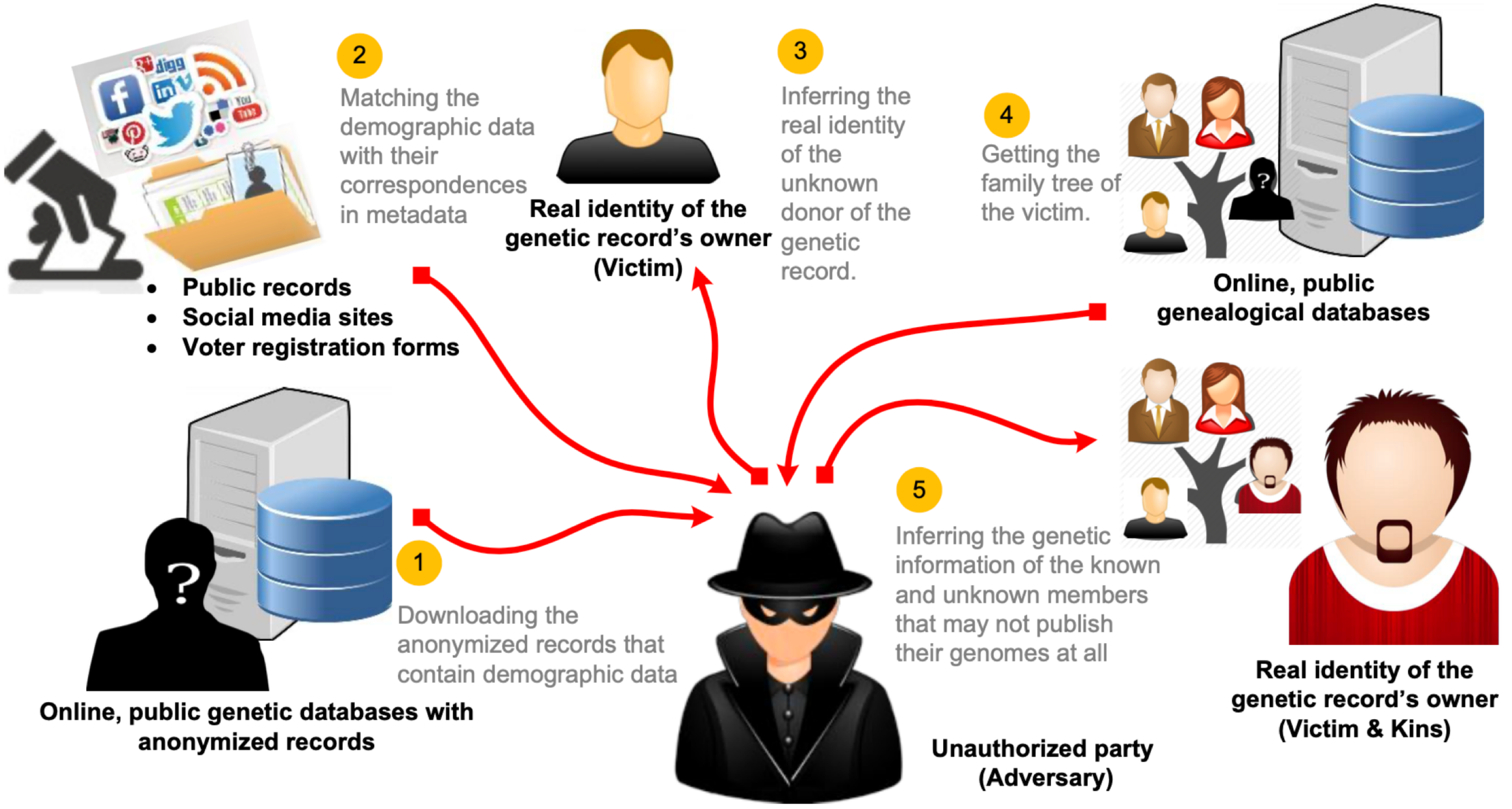
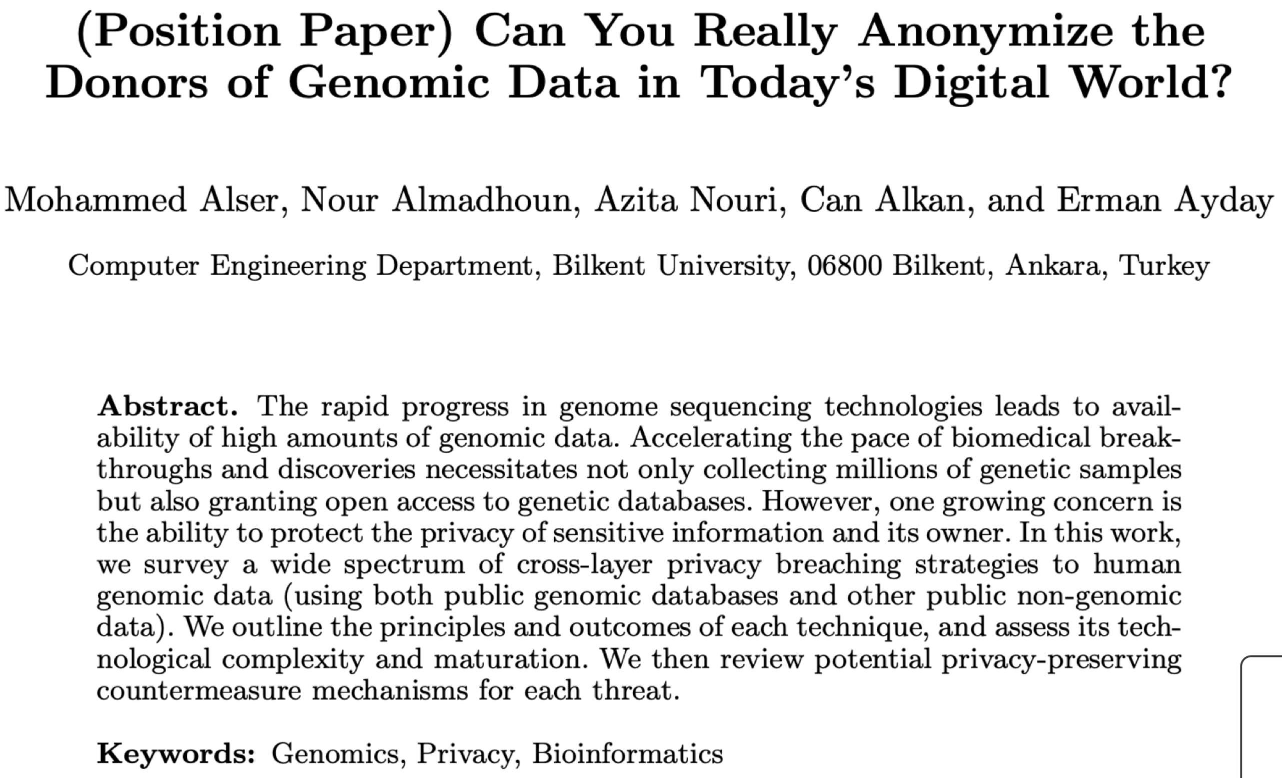

2
Matching the demographic data with their correspondences in metadata
Real identity of the genetic record's owner (Victim)
3
Inferring the real identity of the unknown donor of the genetic record.
4
Getting the family tree of the victim.
Online, public genealogical databases
- Public records
- Social media sites
- Voter registration forms
1
Downloading the anonymized records that contain demographic data
Online, public genetic databases with anonymized records
5
Inferring the genetic information of the known and unknown members that may not publish their genomes at all
Real identity of the genetic record's owner (Victim & Kins)
Unauthorized party (Adversary)

Fig. 5. A completion attack.

Alser+, "**Can you really anonymize the donors of genomic data in today's digital world?**" *10th International Workshop on Data Privacy Management (DPM)*, 2015.

Can you Really Anonymize the Donors?



(Position Paper) Can You Really Anonymize the Donors of Genomic Data in Today's Digital World?

Mohammed Alser, Nour Almadhoun, Azita Nouri, Can Alkan, and Erman Ayday

Computer Engineering Department, Bilkent University, 06800 Bilkent, Ankara, Turkey

Abstract. The rapid progress in genome sequencing technologies leads to availability of high amounts of genomic data. Accelerating the pace of biomedical breakthroughs and discoveries necessitates not only collecting millions of genetic samples but also granting open access to genetic databases. However, one growing concern is the ability to protect the privacy of sensitive information and its owner. In this work, we survey a wide spectrum of cross-layer privacy breaching strategies to human genomic data (using both public genomic databases and other public non-genomic data). We outline the principles and outcomes of each technique, and assess its technological complexity and maturation. We then review potential privacy-preserving countermeasure mechanisms for each threat.

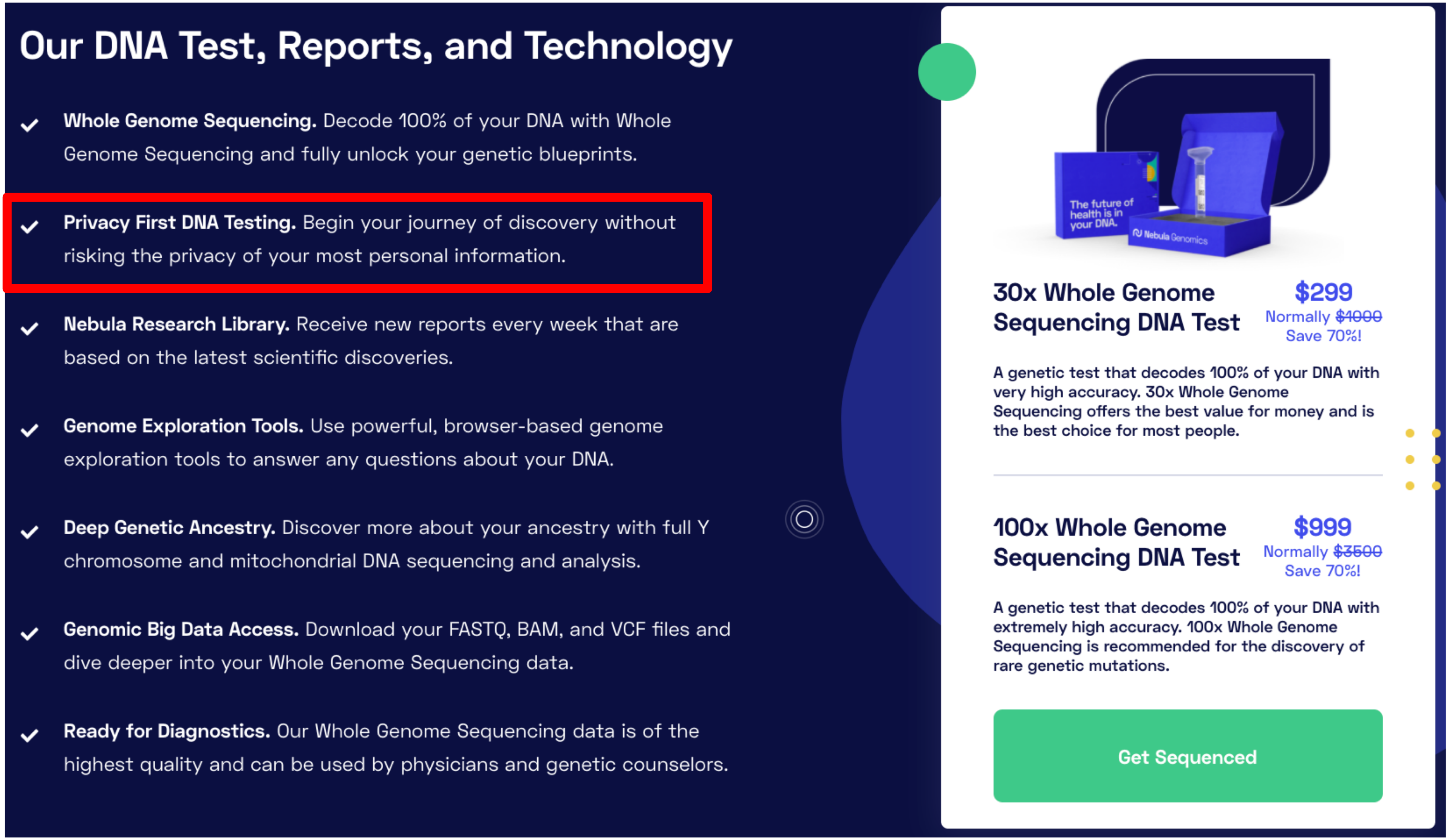
Keywords: Genomics, Privacy, Bioinformatics

DPM 2015

Vienna, Austria
September 21-22, 2015

Alser+, "Can you really anonymize the donors of genomic data in today's digital world?" *10th International Workshop on Data Privacy Management (DPM)*, 2015.

Privacy-Preserving DNA Test



Our DNA Test, Reports, and Technology

- ✓ **Whole Genome Sequencing.** Decode 100% of your DNA with Whole Genome Sequencing and fully unlock your genetic blueprints.
- ✓ **Privacy First DNA Testing.** Begin your journey of discovery without risking the privacy of your most personal information.
- ✓ **Nebula Research Library.** Receive new reports every week that are based on the latest scientific discoveries.
- ✓ **Genome Exploration Tools.** Use powerful, browser-based genome exploration tools to answer any questions about your DNA.
- ✓ **Deep Genetic Ancestry.** Discover more about your ancestry with full Y chromosome and mitochondrial DNA sequencing and analysis.
- ✓ **Genomic Big Data Access.** Download your FASTQ, BAM, and VCF files and dive deeper into your Whole Genome Sequencing data.
- ✓ **Ready for Diagnostics.** Our Whole Genome Sequencing data is of the highest quality and can be used by physicians and genetic counselors.

30x Whole Genome Sequencing DNA Test — **$299**
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Save 70%!

A genetic test that decodes 100% of your DNA with very high accuracy. 30x Whole Genome Sequencing offers the best value for money and is the best choice for most people.

100x Whole Genome Sequencing DNA Test — **$999**
Normally ~~$3500~~
Save 70%!

A genetic test that decodes 100% of your DNA with extremely high accuracy. 100x Whole Genome Sequencing is recommended for the discovery of rare genetic mutations.

https://nebula.org/whole-genome-sequencing/

Achieving Intelligent Genome Analysis?

How and where to enable

fast, accurate, cheap,

privacy-preserving, and exabyte scale

analysis of genomic data?

Agenda for Today

- What is Genome Analysis?
- What is Intelligent Genome Analysis?

- **How we Analyze Genome?**
- What is Read Mapping?
- What Makes Read Mapper Slow?

- Algorithmic & Hardware Acceleration
  - Seed Filtering Technique
  - Pre-alignment Filtering Technique
  - Read Alignment Acceleration

- Where is Read Mapping Going Next?

Genome Analysis

NO machine can read the ***entire*** content of a genome

>CCTCCTCAGTGCCACCCAGCCCACTGGCAGCTCCCAAACAGGCTCTTATTAAAACACCCTGTTCCCTGCCCCTTGGAGTGAGGTGTCAAG
GACCTAAACTAAAAAAAAAAAAAAGAAAAAGAAAAGAAAAAGAATTTAAAATTTAAGTAATTCTTTGAAAAAAACTAATTTCTAAGCTTCTT
CATGTCAAGGACCTAATGTGCTAAACAGCACTTTTTTGACCATTATTTTGGATCTGAAAGAAATCAAGAATAAATGAAGGACTTGATACATTG
GAAGAGGAGAGTCAAGGACCTACAGAAAAAAAAAAAAAAAGAAAAAGAAAAGAAAAAGAATTTAAAATTTAAGTAATTCTTTGAAAAAA
ACTAATTTCTAAGCTTCTTCATGTCAAGGACCTAATGTCTGTGTTGCAGGTCTTCTTGCATTTCCCTGTCAAAAGAAAAAGAATTTAAAATTT
AAGTAATTCTTTGAAAAAAACTAATTTCTAAGCTTCTTCATGTCAAGGACCTAATGTCAGGCCAAGAGTTGCAAAAAAAAAAAAAAGAAAAA
GAAAAGAAAAAGAATTTAAAATTTAAGTAATTCTTTGAAAAAAACTAATTTCTAAGCTTCTTCATGTCAAGGACCTAATGTAGCCAGAATGG
TTGTGGGATGGGAGCCTCTGTGGACCGACCAGGTAGCTCTCTTTTCCACACTGTAGTCTCAAAGCTTCTTCATGTGGTTTCTCTGAGTGAAA
AAAAAAAAAAGAAAAAGAAAAGAAAAAGAATTTAAAATTTAAGTAATTCTTTGAAAAAAACTAATTTCTAAGCTTTTTCATGTCAAGGACC
TAATGTAGCTATACTGAACGTTATCTAGGGGAAAGATTGAAGGGGAGCTCTAAGGTCAACACACCACCACTTCCCAGAAAGCTTCTTCA……

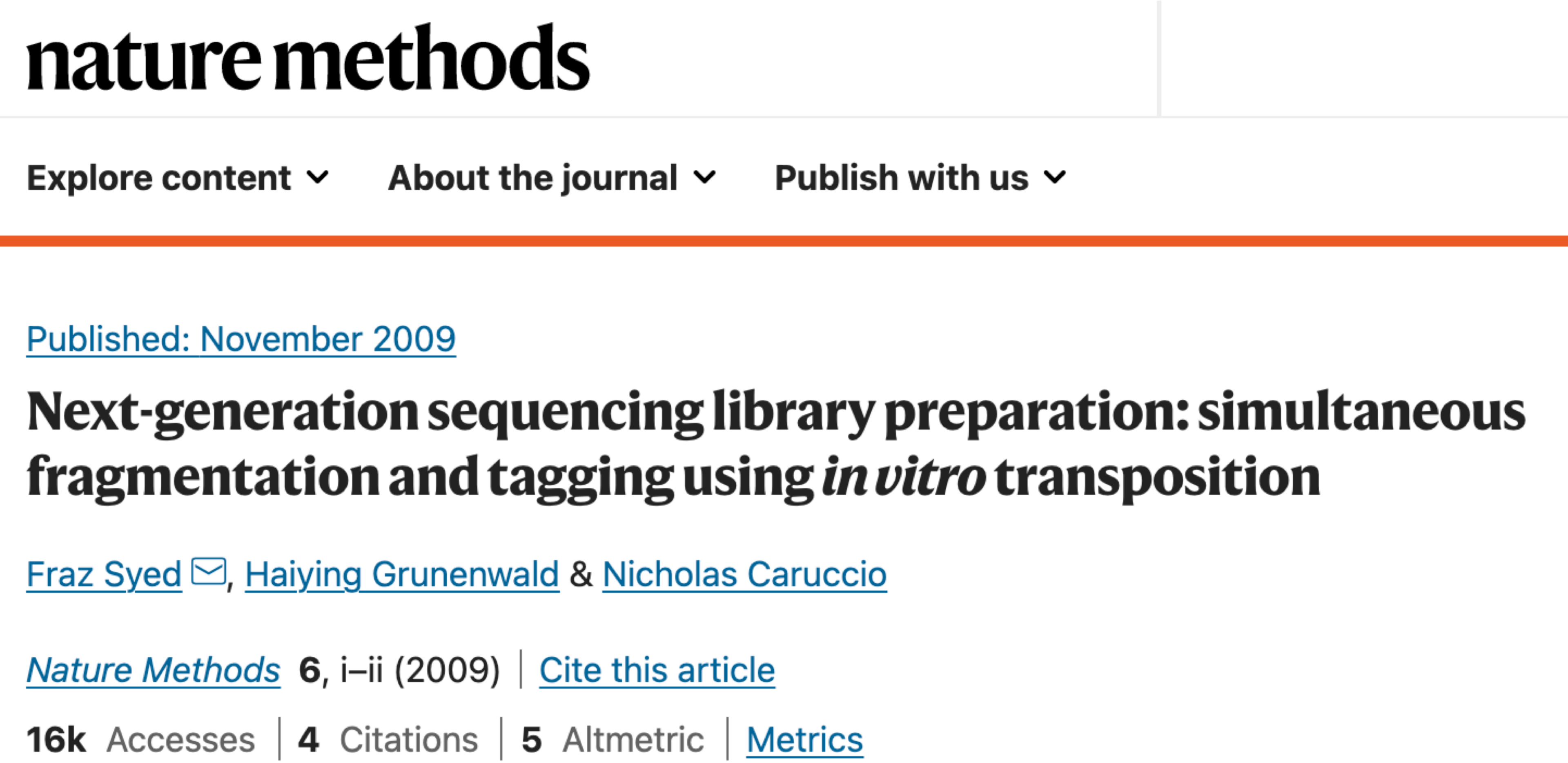
Genome Analysis

NO machine can read the ***entire*** content of a genome

Why?!

>CCT CAAG
GACC TCTT
CATGT CATTG
GAAG AAAA
ACTA ATTT
AAGT AAAA
GAAA ATGG
TTGTC GAAA
AAAAAAAAAAGAAAAAGAAAAGAAAAAGAATTTAAAATTTAAGTAATTCTTTGAAAAAAACTAATTTCTAAGCTTTTTCATGTCAAGGACC
TAATGTAGCTATACTGAACGTTATCTAGGGGAAAGATTGAAGGGGAGCTCTAAGGTCAACACACCACCACTTCCCAGAAAGCTTCTTCA......

Suggested Readings



Published: November 2009

Next-generation sequencing library preparation: simultaneous fragmentation and tagging using *in vitro* transposition

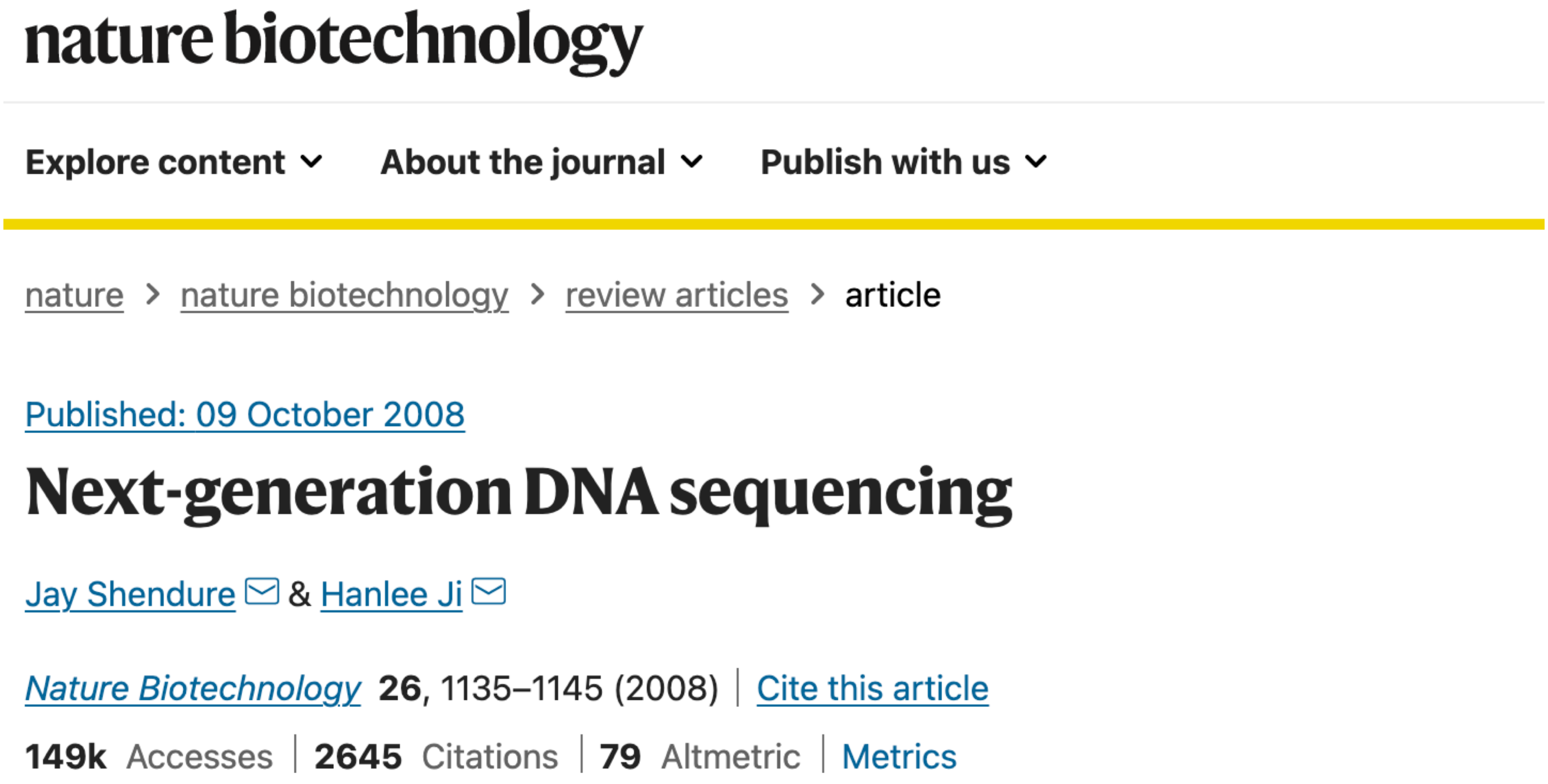
Fraz Syed, Haiying Grunenwald & Nicholas Caruccio

Nature Methods **6**, i–ii (2009) | Cite this article

16k Accesses | **4** Citations | **5** Altmetric | Metrics

https://www.nature.com/articles/nmeth.f.272

Suggested Readings



Published: 09 October 2008

Next-generation DNA sequencing

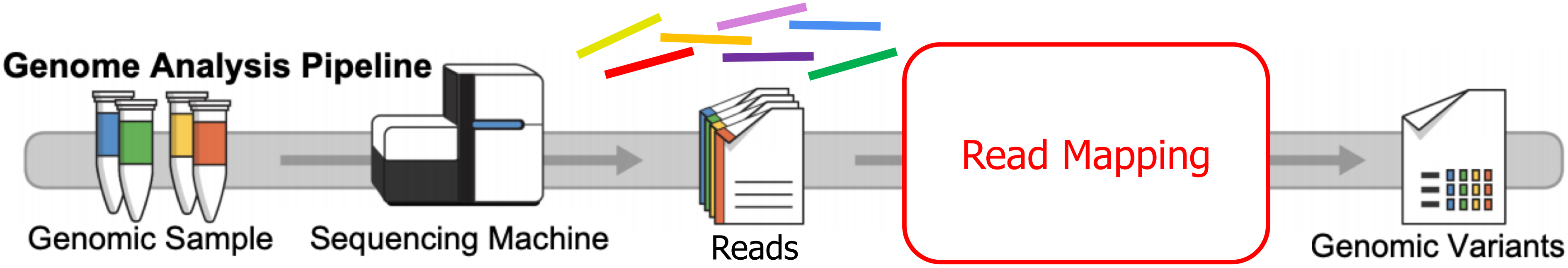
Jay Shendure & Hanlee Ji

Nature Biotechnology **26**, 1135–1145 (2008) | Cite this article

149k Accesses | **2645** Citations | **79** Altmetric | Metrics

https://www.nature.com/articles/nbt1486

Genome Sequencer is a Chopper



CCCCCCTATATATACGTACTAGTACGT
ACGACTTTAGTACGTACGT
TATATATACGTACTAGTACGT
ACGTACG CCCCTACGTA
TATATATACGTACTAGTACGT
ACGACTTTAGTACGTACGT
TATATATACGTACTAAAGTACGT
TATATATACGTACTAGTACGT
ACG TTTTTAAAACGTA
TATATATACGTACTAGTACGT
ACGAC GGGGAGTACGTACGT

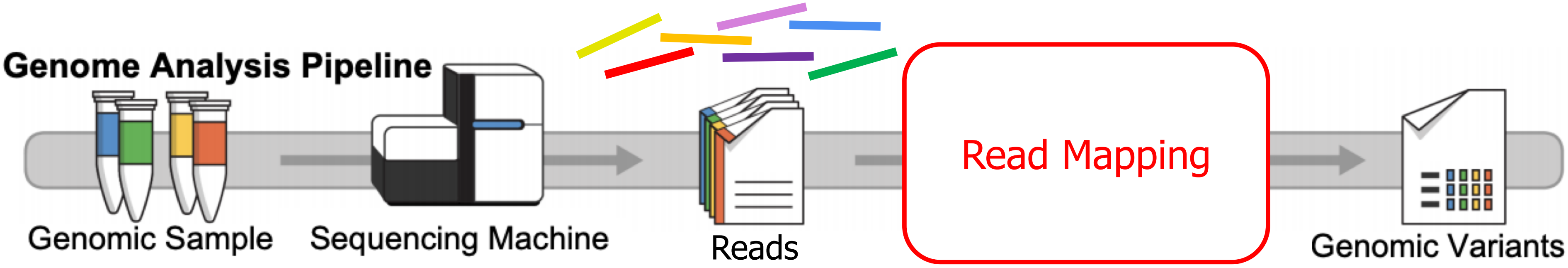
$1\text{x}10^{12}$ bases*

44 hours*

<1000 $

* NovaSeq 6000

Genome Sequencer is a Chopper



Current sequencing machine provides **small randomized fragments** of the original DNA sequence

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

High-Throughput Sequencers

Illumina MiSeq

Pacific Biosciences Sequel II

Oxford Nanopore PromethION

Oxford Nanopore MinION

Illumina NovaSeq 6000

Pacific Biosciences RS II

Oxford Nanopore SmidgION

… and more! All produce data with different properties.

Oxford Nanopore Sequencers

MinION Mk1B

MinION Mk1C

GridION Mk1

PromethION 24/48

	MinION Mk1B	MinION Mk1C	GridION Mk1	PromethION 24	PromethION 48
Read length	> 2Mb	> 2Mb	> 2Mb	> 2Mb	> 2Mb
Yield per flow cell	50 Gb	50 Gb	50 Gb	220 Gb	220 Gb
Number of flow cells per device	1	1	5	24	48
Yield per device	<50 Gb	<50 Gb	<250 Gb	<5.2 Tb	<10.5 Tb
Starting price	$1,000	$4,990	$49,995	$195,455	$327,455

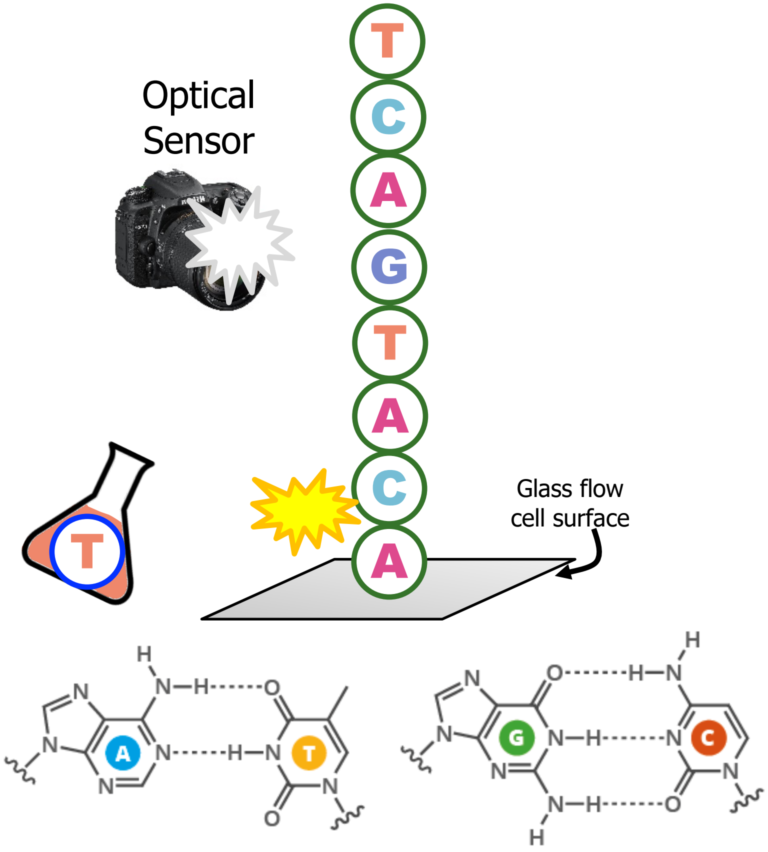
https://nanoporetech.com/products/comparison

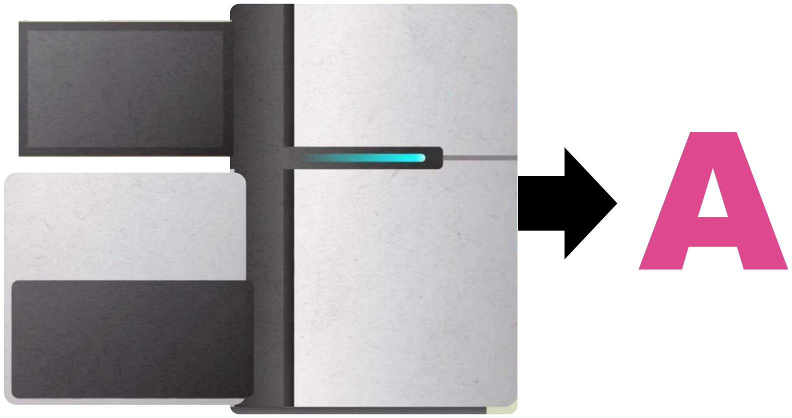
Illumina Sequencers

Run time	9.5–19 hrs	4–24 hrs	4–55 hrs	12–30 hrs	24-48 hrs	13-44 hrs
Max. reads per run	4 million	25 million	25 million	400 million	1 billion	20 billion
Max. read length	2 × 150 bp	2 × 150 bp	2 × 300 bp	2 × 150 bp	2 × 150 bp	2 x 250
Max. output	1.2 Gb	7.5 Gb	15 Gb	120 Gb	300 Gb	6000 Gb
Estimated price	$19,900	$49,500	$128,000	$275,000	$335,000	$985,000

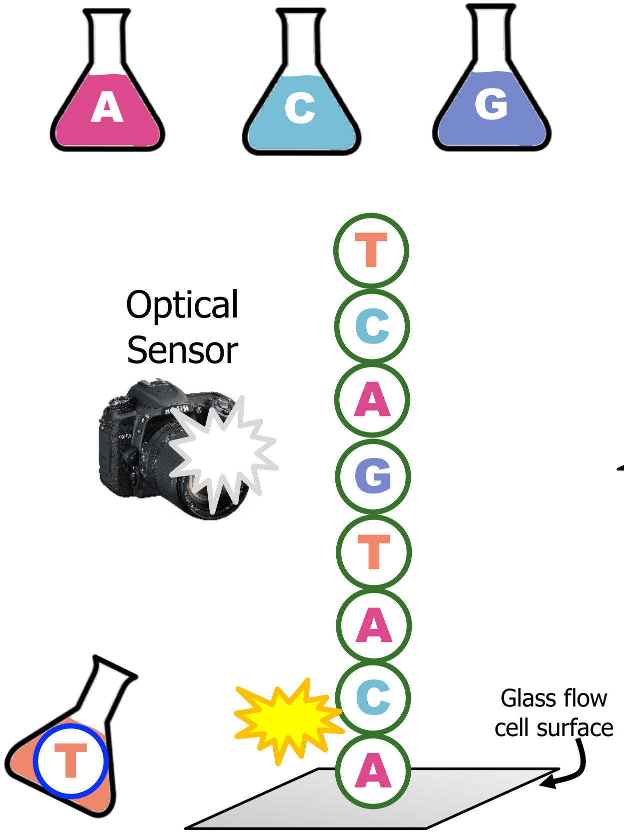
https://www.illumina.com/systems/sequencing-platforms.html

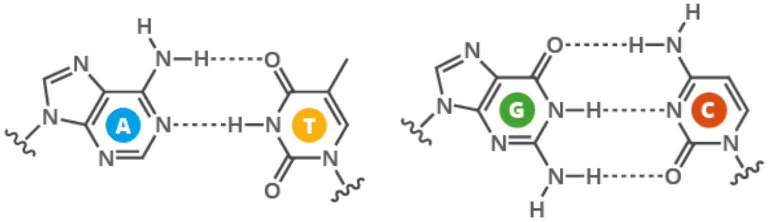
How Does Illumina Machine Work?

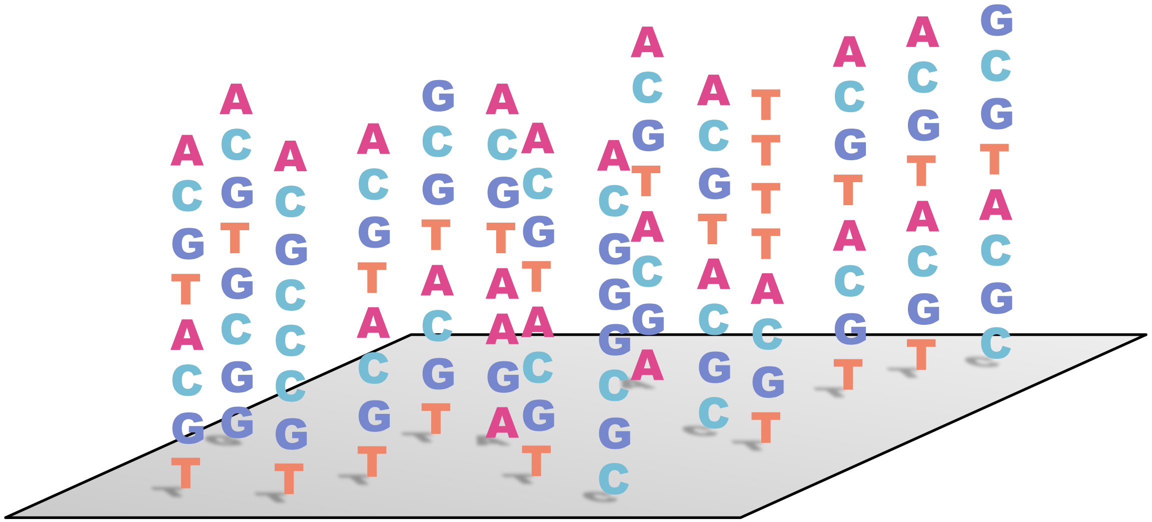


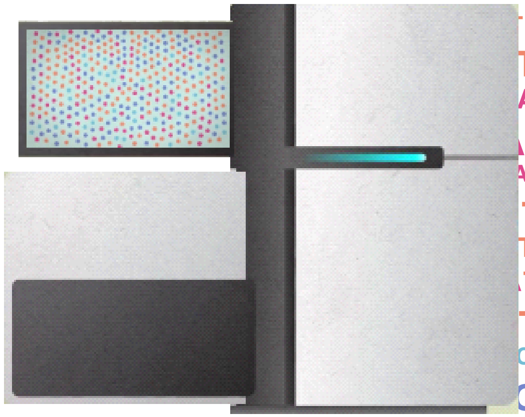


How Does Illumina Machine Work?







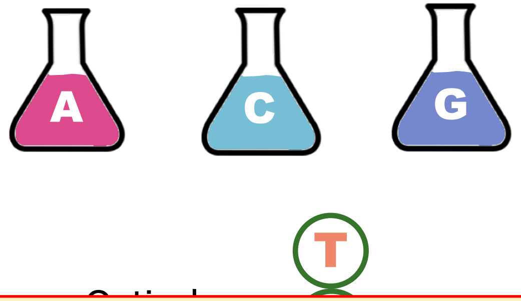


Billions of Short Reads

ATATATACGTACTAGTACGT
TTTAGTACGTACGT
ATACGTACTAGTACGT
CG CCCCTACGTA
ACGTACTAGTACGT
TTAGTACGTACGT
TACGTACTAAAGTACGT
TACGTACTAGTACGT
TTTAAAACGTA
CGTACTAGTACGT
GGGAGTACGTACGT

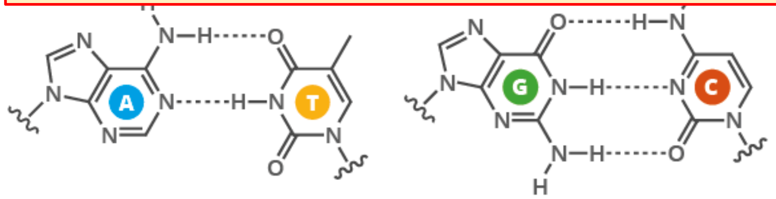
DNA fragment = Read

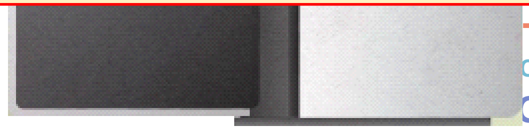
How Does Illumina Machine Work?



Check Illumina virtual tour:

https://emea.illumina.com/systems/sequencing-platforms/iseq/tour.html





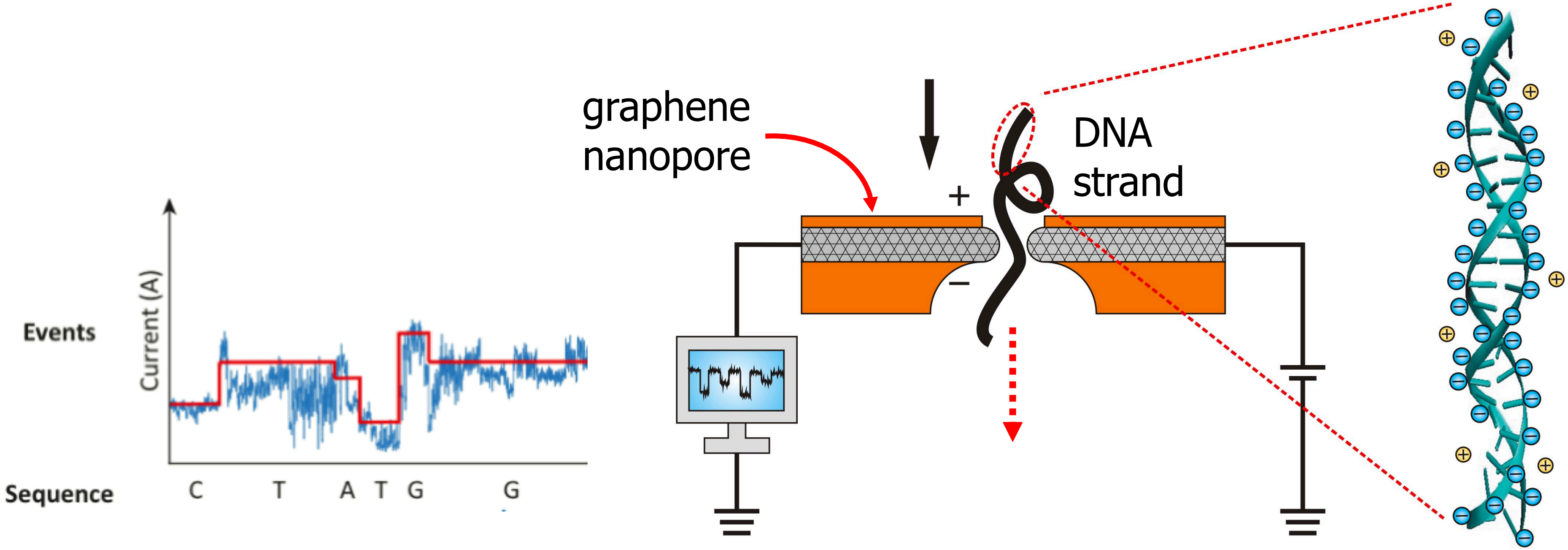
TTTAAAACGTA

CGTACTAGTACGT

GGGAGTACGTACGT

DNA fragment = Read

How Does Nanopore Machine Work?

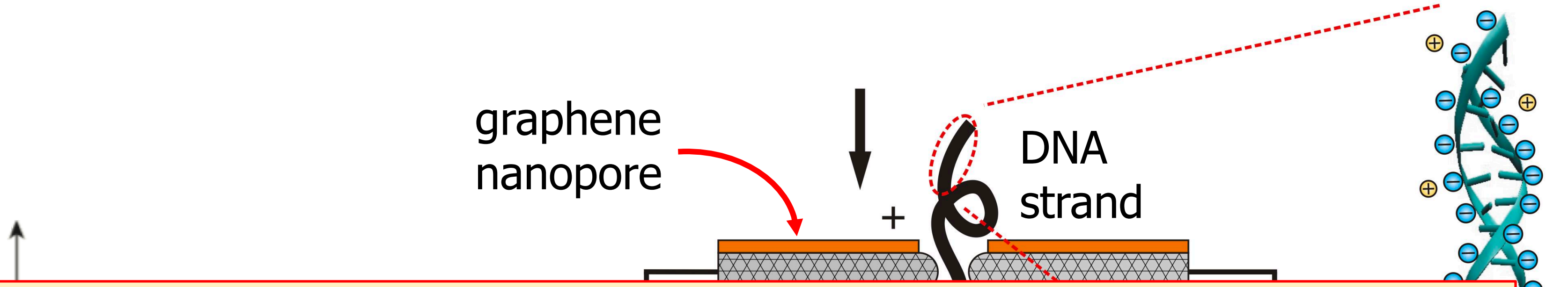


- **Nanopore** is a nano-scale hole (<20nm).
- In nanopore sequencers, an **ionic current** passes through the nanopores
- When the DNA strand passes through the nanopore, the sequencer measures the the **change in current**
- This change is used to identify the bases in the strand with the help of **different electrochemical structures** of the different bases

SAFARI

Figure is adapted from: https://phys.org/news/2013-12-gene-sequencing-future.html

How Does Nanopore Machine Work?



Check Nanopore virtual tour:

https://nanoporetech.com/resource-centre/minion-video

measures the the **change in current**

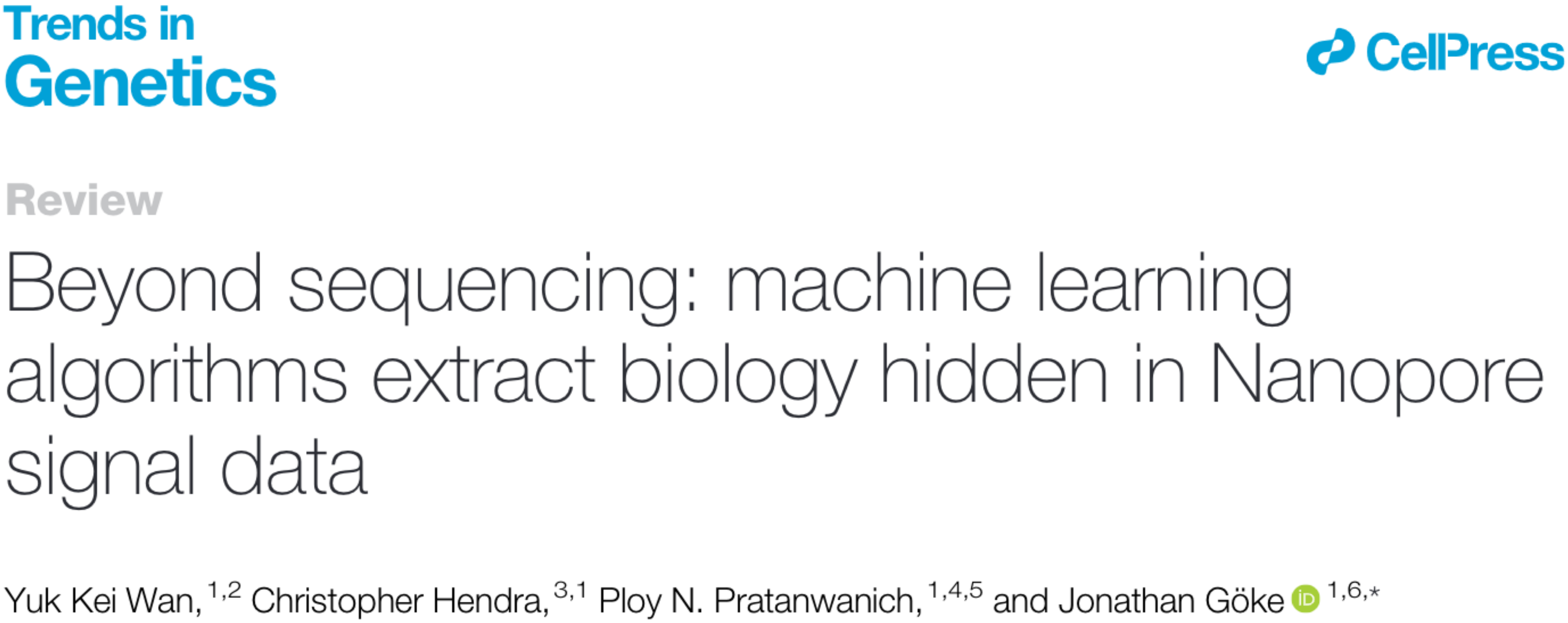
- This change is used to identify the bases in the strand with the help of **different electrochemical structures** of the different bases

SAFARI

Figure is adapted from: https://phys.org/news/2013-12-gene-sequencing-future.html

Machine Learning for Nanopore Machine

Wan+
"Beyond sequencing: machine learning algorithms extract biology hidden in Nanopore signal data"
Trends in Genetics, October 25, 2021



Trends in Genetics

CellPress

Review

Beyond sequencing: machine learning algorithms extract biology hidden in Nanopore signal data

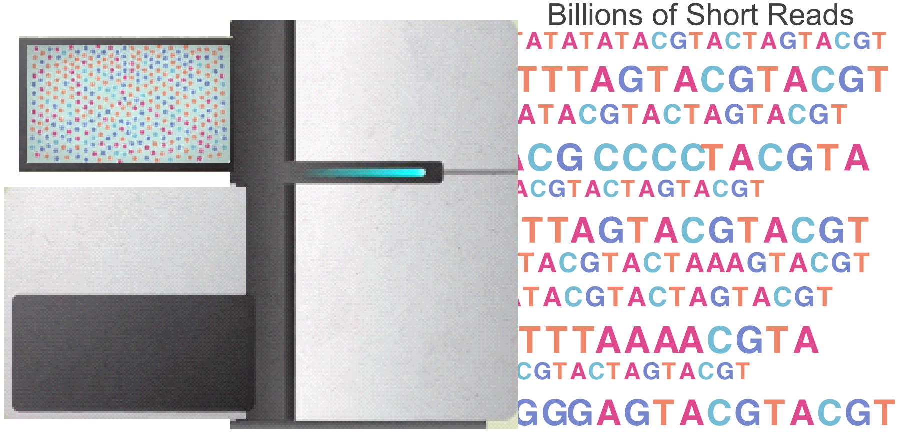
Yuk Kei Wan,[1,2] Christopher Hendra,[3,1] Ploy N. Pratanwanich,[1,4,5] and Jonathan Göke[1,6,*]

Common Disadvantages!

Regardless the sequencing machine,

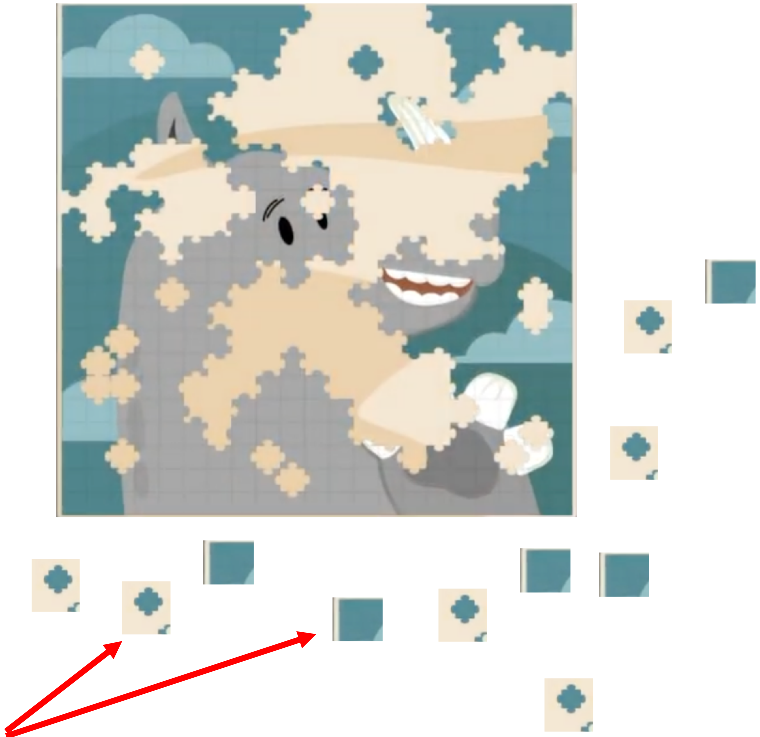
reads still lack information about their order and location

(which part of genome they are originated from)



Solving the Puzzle

Reference genome



Reads

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

HTS Sequencing Output

Small pieces of a puzzle
short reads (Illumina)

Large pieces of a puzzle
long reads (ONT & PacBio)

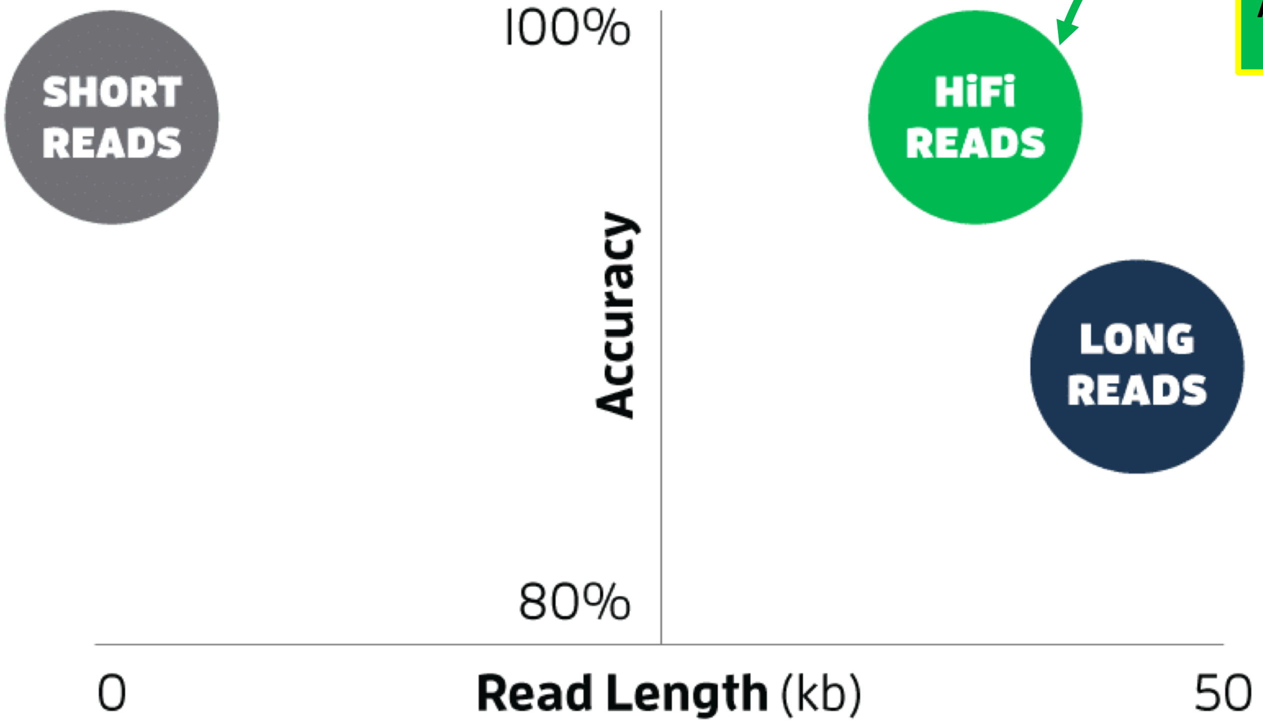
Which sequencing technology is the best?

- ☐ 100-300 bp
- ☐ low error rate (~0.1%)

- ☐ 500-2M bp
- ☐ high error rate (~15%)

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

HiFi Reads (PacBio)



Long: 10-20 kb
Accurate: 99.8%

But still very expensive!

Wenger+, "Accurate circular consensus long-read sequencing improves variant detection and assembly of a human genome", *Nature Biotechnology*, 2019

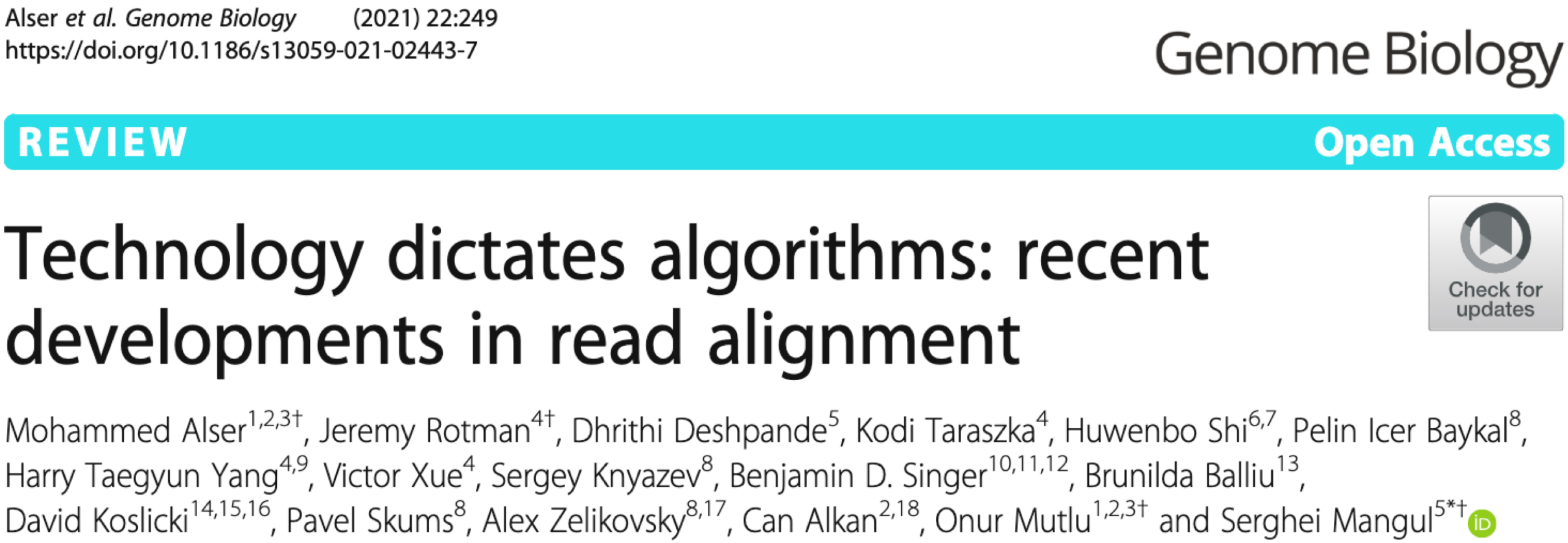
https://labs.wsu.edu/genomicscore/illumina-sequencing/
https://pacbio.gs.washington.edu/

Changes in sequencing technologies can render some read mapping algorithms irrelevant

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

Check for updates

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*†]

Looking forward,

Will we be able to read

the entire genome sequence?

Agenda for Today

- What is Genome Analysis?
- What is Intelligent Genome Analysis?

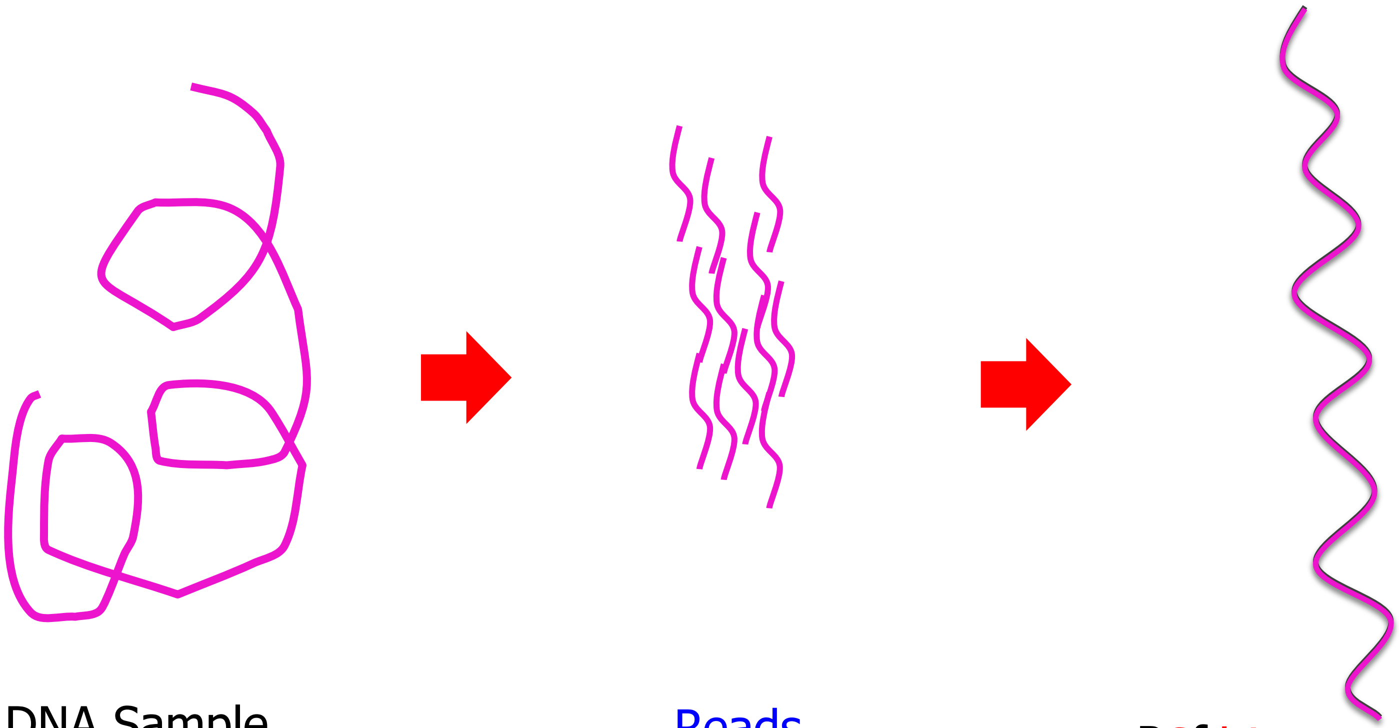
- How we Analyze Genome?
- **What is Read Mapping?**
- What Makes Read Mapper Slow?

- Algorithmic & Hardware Acceleration
  - Seed Filtering Technique
  - Pre-alignment Filtering Technique
  - Read Alignment Acceleration

- Where is Read Mapping Going Next?

Read Mapping

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



DNA Sample
"chemical format"

Reads
"text format"

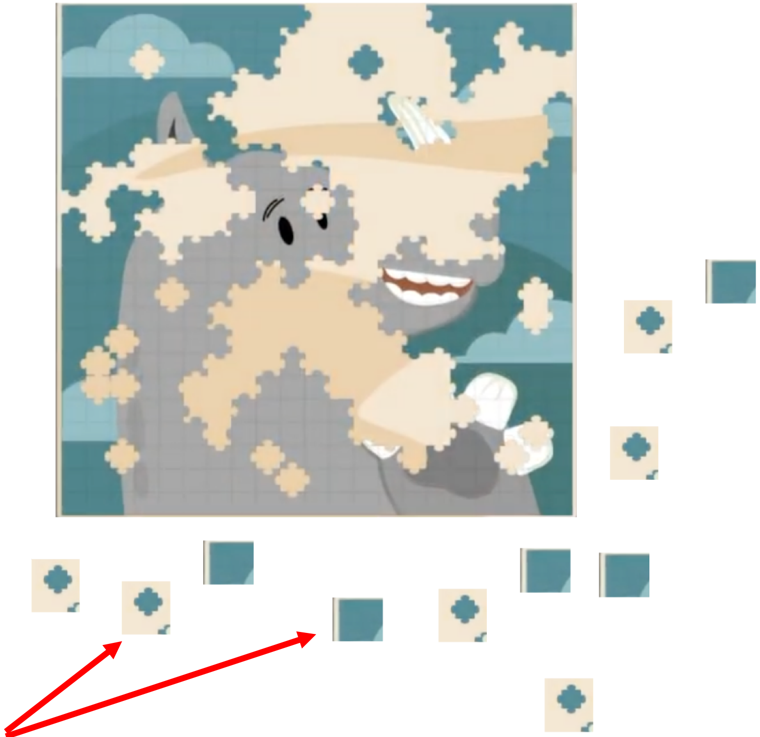
Reference genome
Subject genome
"text format"

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.

ws
Print"

The New York Times

National Edition
Arizona and New Mexico: M
cloudy in New Mexico, thunderst
in the mountains. Partly sunny
where. Highs 80 mountains, ove
deserts. Weather map is on Page

No. 51,432 Copyright © 2000 The New York Times TUESDAY, JUNE 27, 2000 Printed in Arizona ONE DOLL

tic Code of Human Life Is Cracked by Scientist

The Book of Life

The 3 billion **base pairs** ...

... of the intertwining double helix of **DNA** ...

... that make up the set of **chromosomes** in our cells, have been sequenced.

BASE PAIRS
Rungs between the strands of the double helix

BASES
A adenine
C cytosine
G guanine
T thymine

By ordering the base units, scientists hope to locate the genes and determine their functions.

The New York Times

A SHARED SUCCE

2 Rivals' Announcem
Marks New Medica
Era, Risks and All

By NICHOLAS WADE
WASHINGTON, June 26 — I
achievement that represents a
nacle of human self-knowledge
rival groups of scientists said t
that they had deciphered the he
tary script, the set of instruc
that defines the human organis

15 February 2001
nature
www.nature.com
the human genome
Nuclear fission
Five-dimensional energy landscapes
Seafloor spreading
The view from under the Arctic ice
Career prospects
Sequence creates new opportunities
naturejobs
genomics special
16 February 2001
Science
Vol 291 No. 5507
Pages 1145-1434 $9
THE HUMAN GENOME
AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE
TIME
EXCLUSIVE Q&A
DR. LAURA ON THE OFFENSIVE
J. Craig Venter
Francis Collins
Cracking The Code!
The inside story of how these bitter rivals mapped our DNA, the historic feat that changes medicine forever
CELERA

A C
G T

3.2×10^9 bases

13 years

$>3 \times 10^9$ $

SAFARI

Three Decades & Yet to be Complete!

The complete sequence of a human genome

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

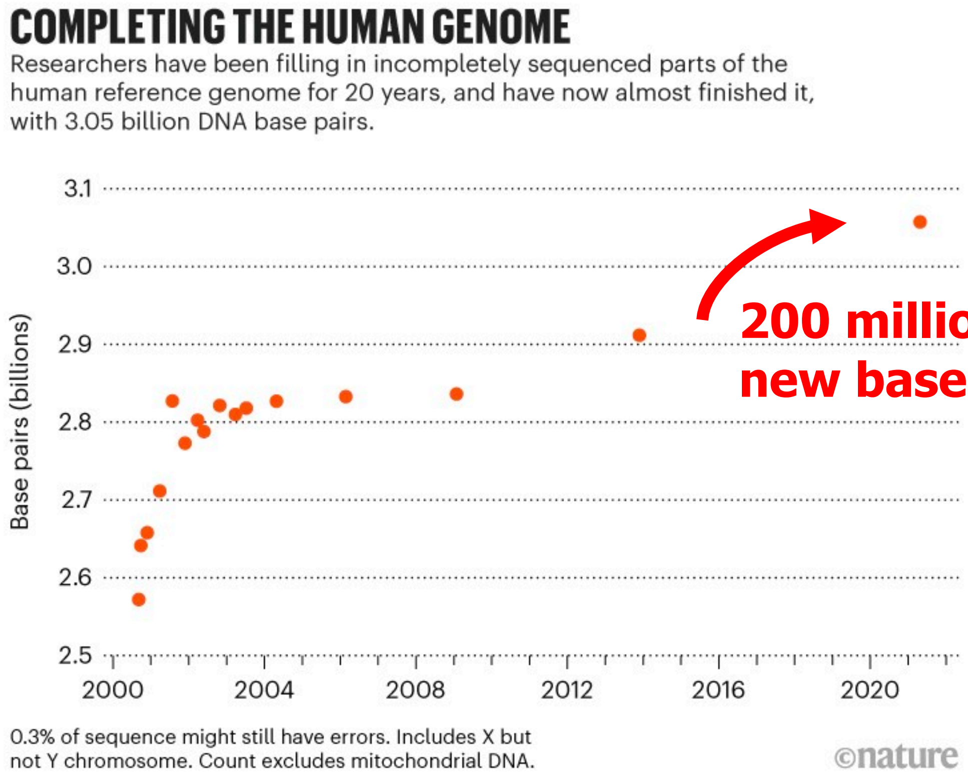
Samantha Zarate, Urvashi Surti, Rajiv C. McCoy, Me

Rachel J. O'Neill, Winston Timp, Justin M. Zook, Mic

Adam M. Phillippy

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

27 May 2021



COMPLETING THE HUMAN GENOME

Researchers have been filling in incompletely sequenced parts of the human reference genome for 20 years, and have now almost finished it, with 3.05 billion DNA base pairs.

0.3% of sequence might still have errors. Includes X but not Y chromosome. Count excludes mitochondrial DNA.

©nature

200 million new bases

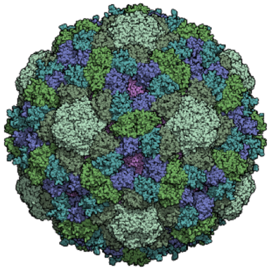
https://www.biorxiv.org/content/10.1101/2021.05.26.445798v1

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
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
….
```

How Long is DNA?



Phi X174 virus
5.386 Killo bp

E. coli O157:H7
5.44 Million bp

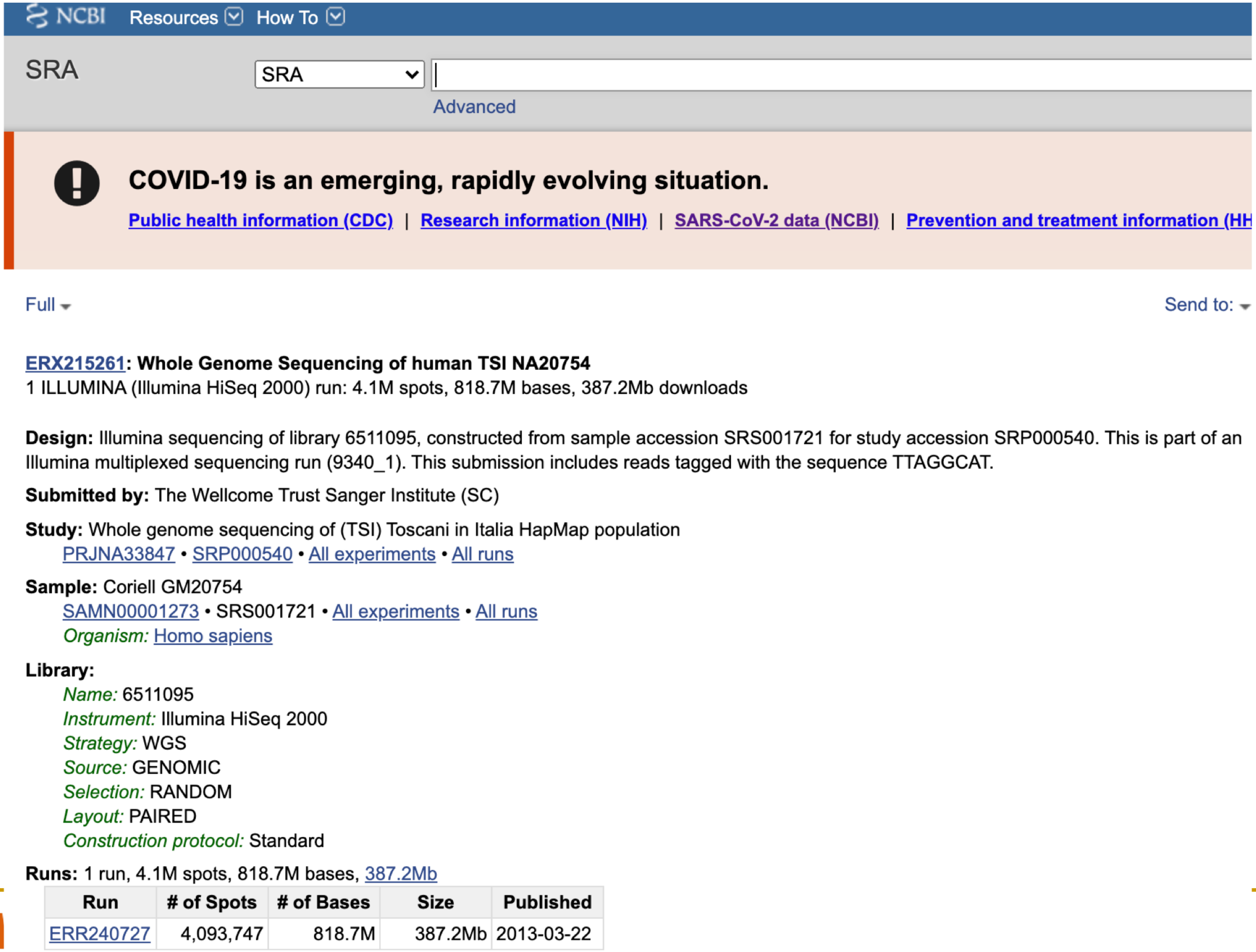
Homo Sapiens
3.2 Billion bp

Onion, Allium Cepa
16 Billion bp

Paris Japonica
149 Billion bp

Obtaining .FASTQ Files

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



COVID-19 is an emerging, rapidly evolving situation.

Public health information (CDC) | Research information (NIH) | SARS-CoV-2 data (NCBI) | Prevention and treatment information (HH

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

SAFA

Let's learn
how to map a read

Read Mapping: A Brute Force Algorithm

Reference
Read

Very expensive!

$O(m^2kn)$

m: read length

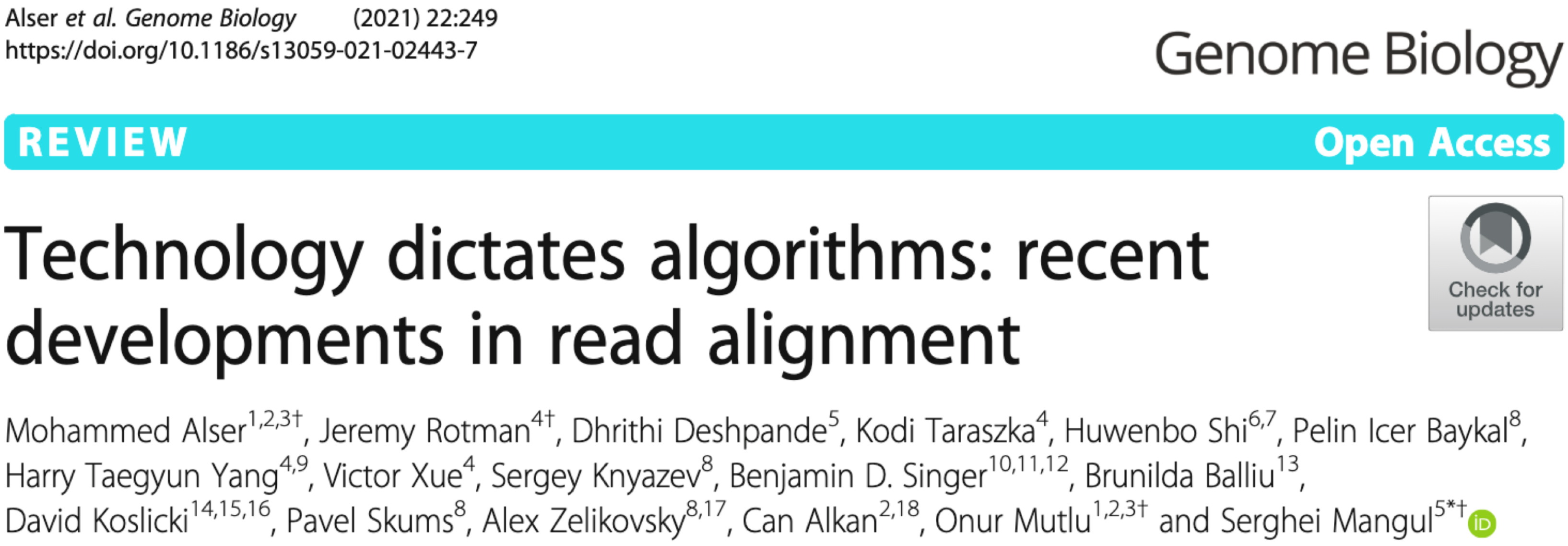
k: no. of reads

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

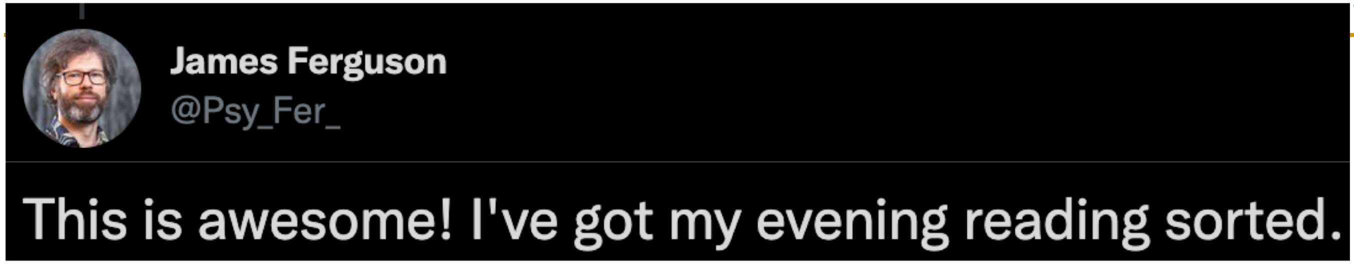
REVIEW Open Access

Technology dictates algorithms: recent developments in read alignment

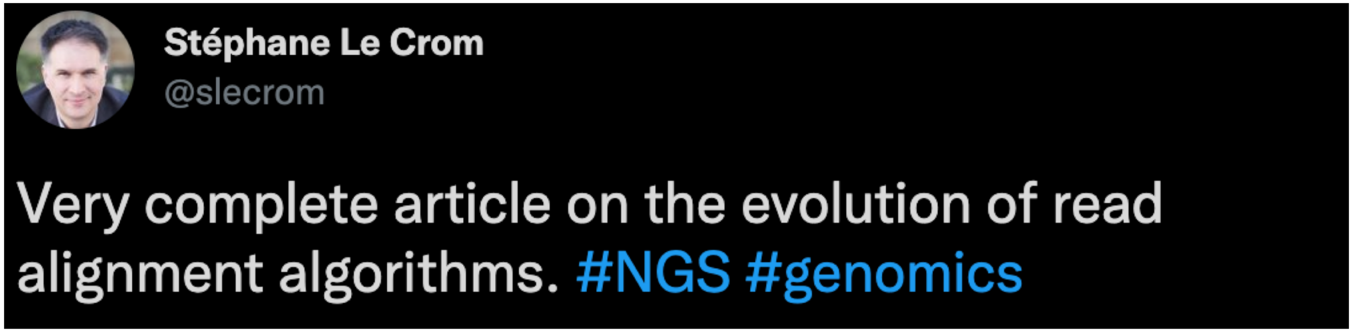
Check for updates

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*†]

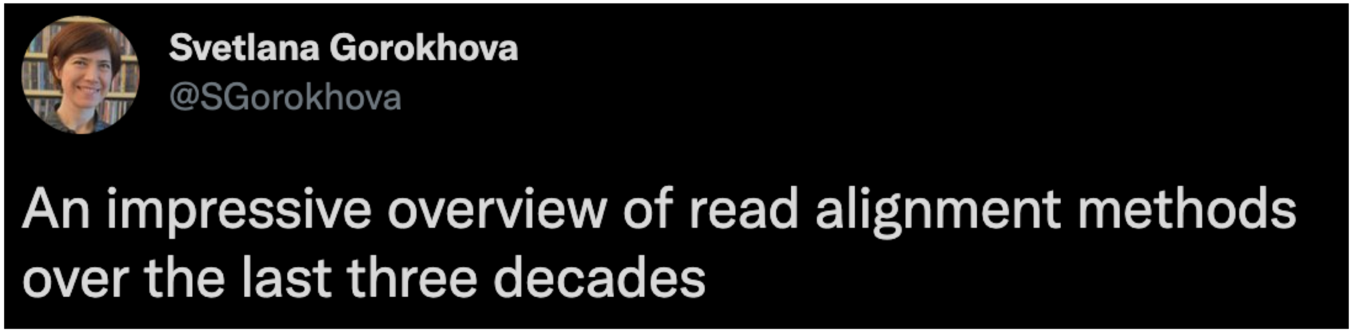
Feedback From Our Community!


James Ferguson
@Psy_Fer_

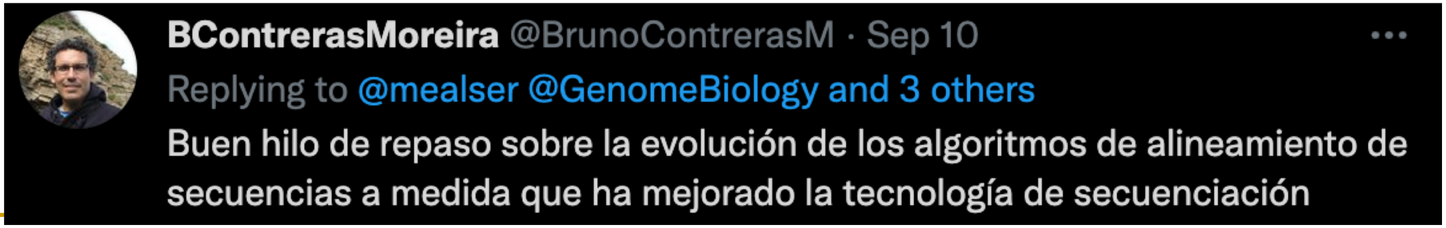
This is awesome! I've got my evening reading sorted.


Stéphane Le Crom
@slecrom

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


Svetlana Gorokhova
@SGorokhova

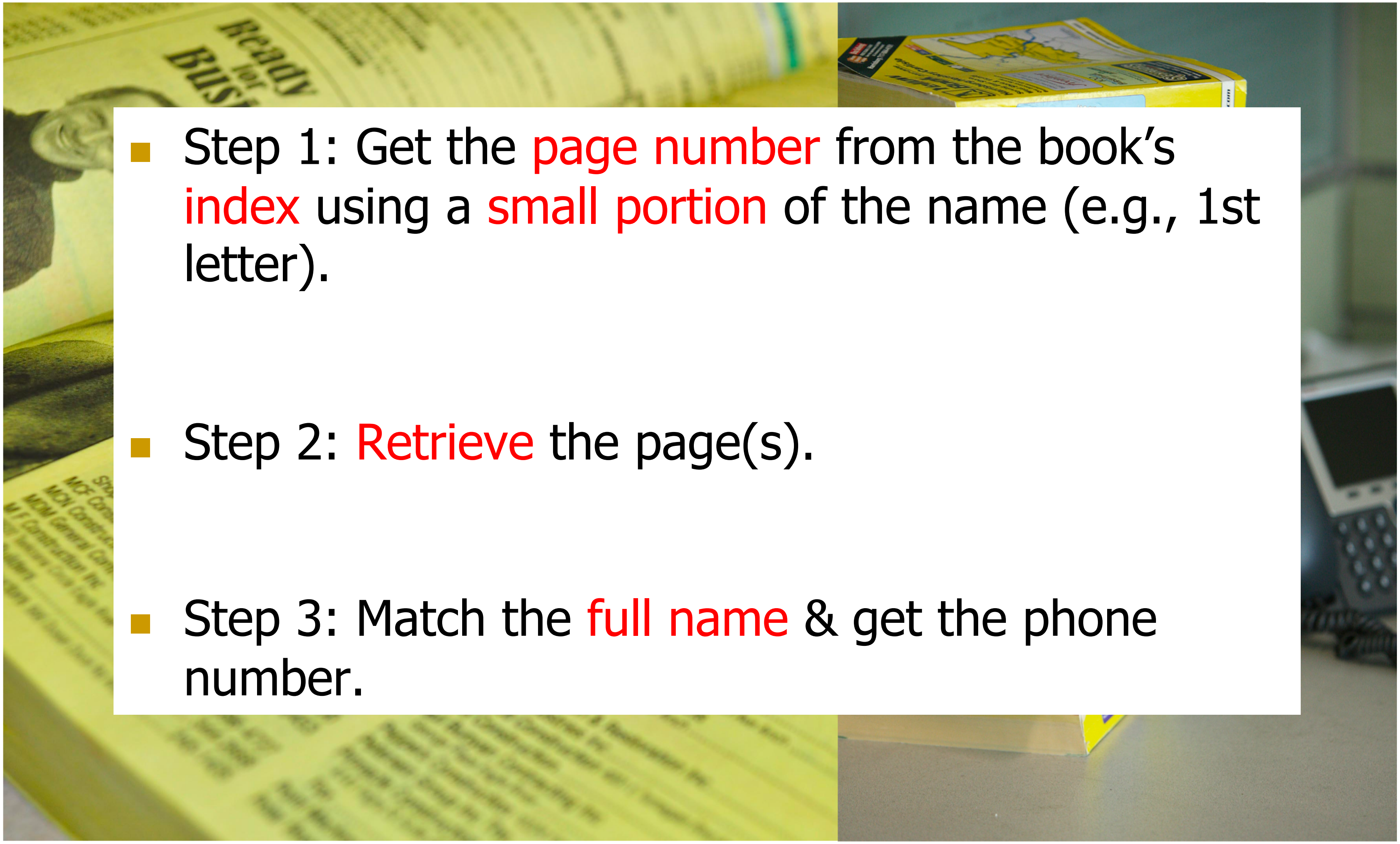
An impressive overview of read alignment methods over the last three decades


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

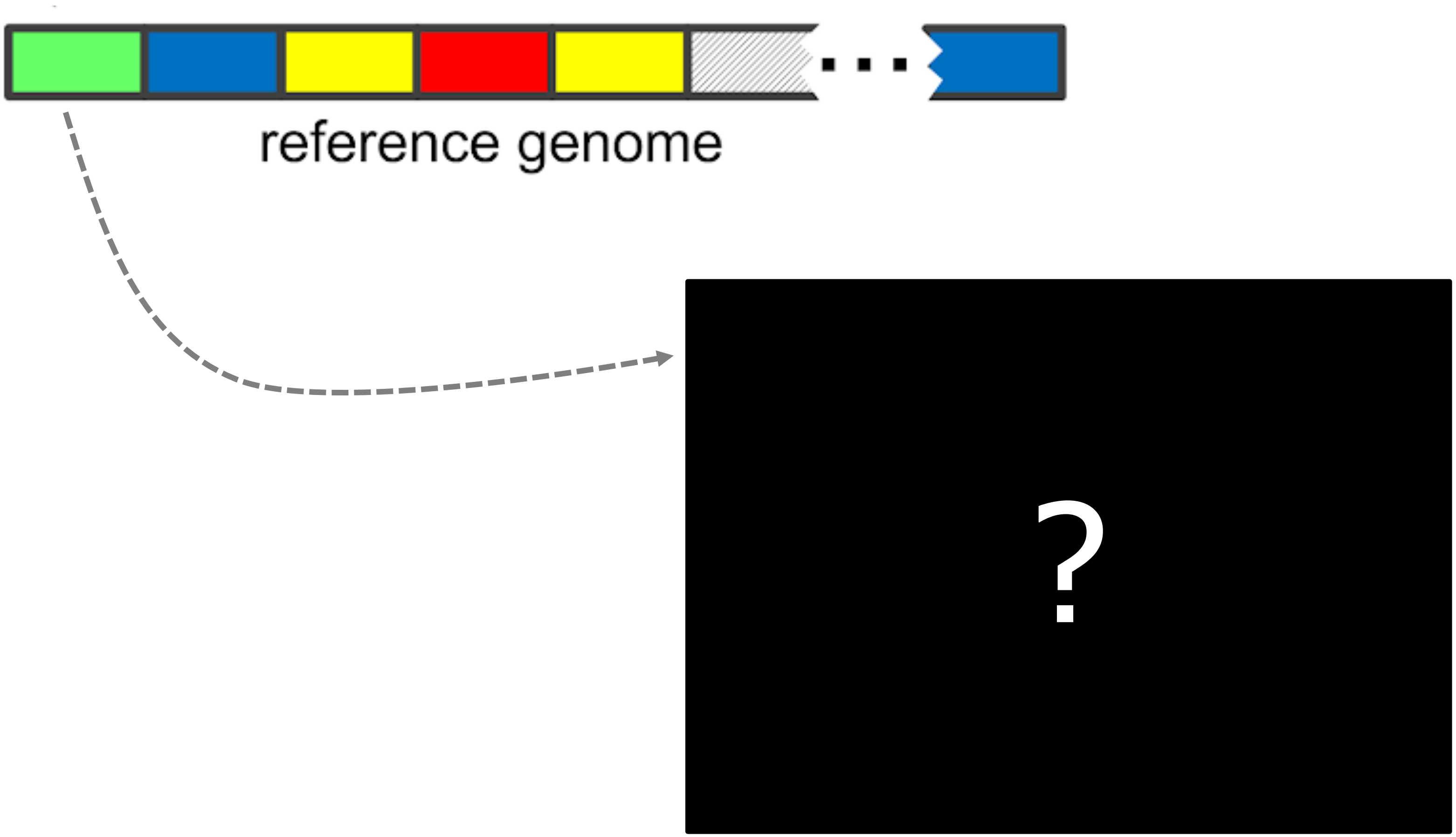
.FASTA file:

```
>NG_008679.1:5001-38170 Homo sapiens paired box 6 (PAX6)
ACCCT🟩TCATTGACATTTAAACTCTGGGCAGGT🟦GAACGCGGCTGTCAGATCT
GCCACTTCCCCTGCCGAGCGGCGGTGAGAAGTGTGGGAACCGGCGCTGCCAGGCTCACCTGCCTCCCCGC
CCTCCGCTCCCAGGTAACCGCCC🟨CCCCGGCCCGGCTCGGGGCCCGCGGGGCCTCTCCGCTG
CCAGCGACTGCTGTCCCCAAATCAAAGCCCGCCCCAAGTGGCCCCGGGGCTTGATTTTGCTTTTAAAAG
GAGGCATACAAAGATGGAAGCGAGTTACTGAGGGAGGGATAGGAAGGGGGGTGGAGGAGGGACTTGTCTT
TGCCGAGTGT🟦CAAAAGTAGCA🟩CTCCTAA🟥TCCAGTCCGGCCCT
GAGCTGGGAGTAGGGGGCGGGAGTCTGCTGCTGCTGTCTGCTAAAGCCACTCGCGACCGCGAAAAATGCA
GGAGGTGGGGACGCACTTTGCATCCAGACCTCCTCTGCATCGCAGTTC🟨ACGCTTGGGAAAG
TCCGTACCCGCGCCT🟥AAAGACACCCTGCCGCGGGTCGGGCGAGGTGCAGCAGAAGTTTCCC
GCGGTTGCAAAGTGCAGATGGCTGGACCGCAACAAAGTCTAGAGATGGGGTTCGTTTCTCAGAAAGACGC
```

.FASTQ file:

```
@HWI-EAS209_0006_FC706VJ:5:58:5894:21141#ATCACG/1
T🟦AATAAATCT🟩TTAGATN🟥NNNNNNNNTAG
+HWI-EAS209_0006_FC706VJ:5:58:5894:21141#ATCACG/1
efcfffffcfeefffcffffffddf`feed]`]_Ba_^__[YBBBBBBBBBBRTT
```

Step 1: Indexing the Reference Genome

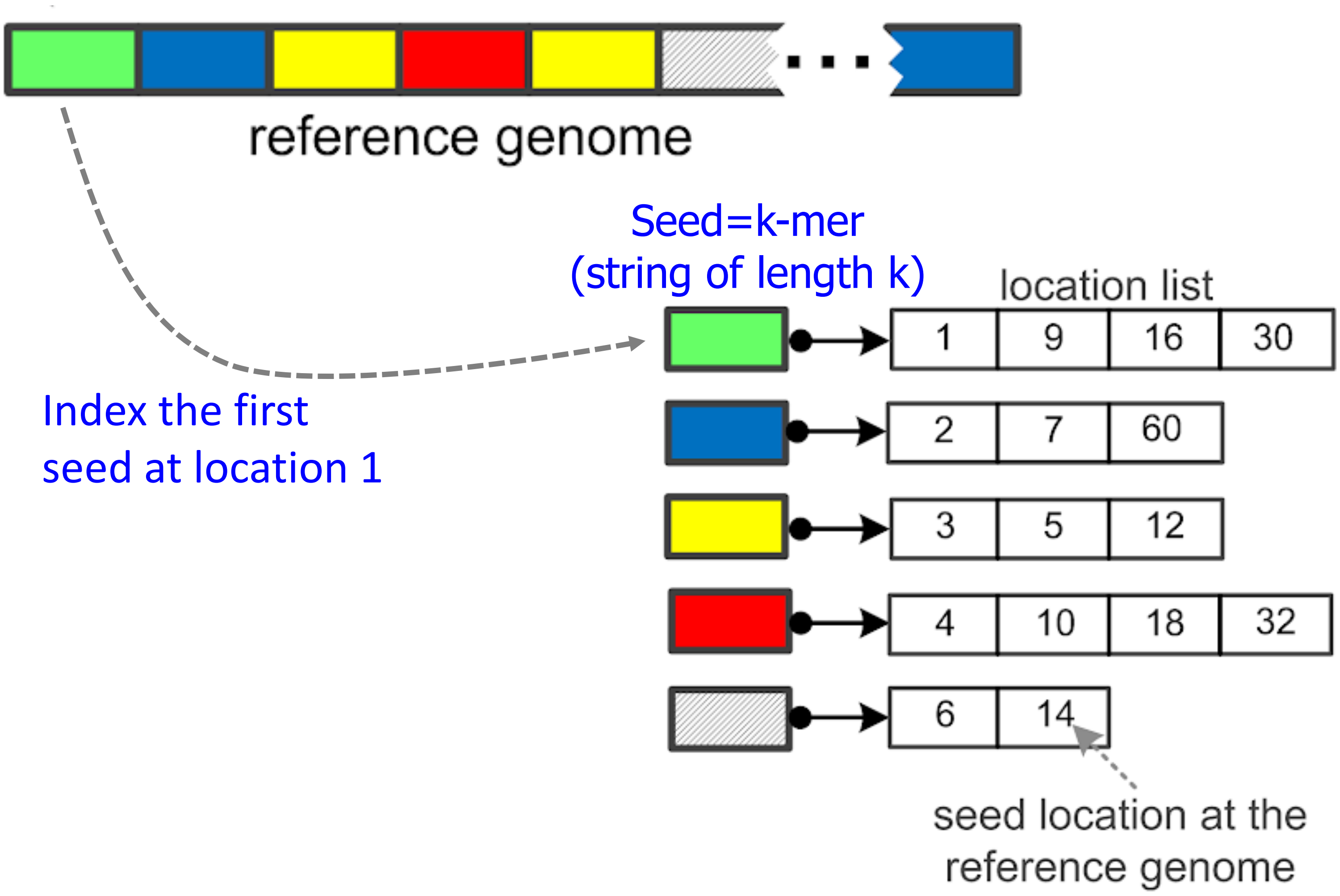


Popular Indexing Technique

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



Seed=k-mer
(string of length k)

Index the first
seed at location 1

🟩	1	9	16	30
🟦	2	7	60	
🟨	3	5	12	
🟥	4	10	18	32
▨	6	14		

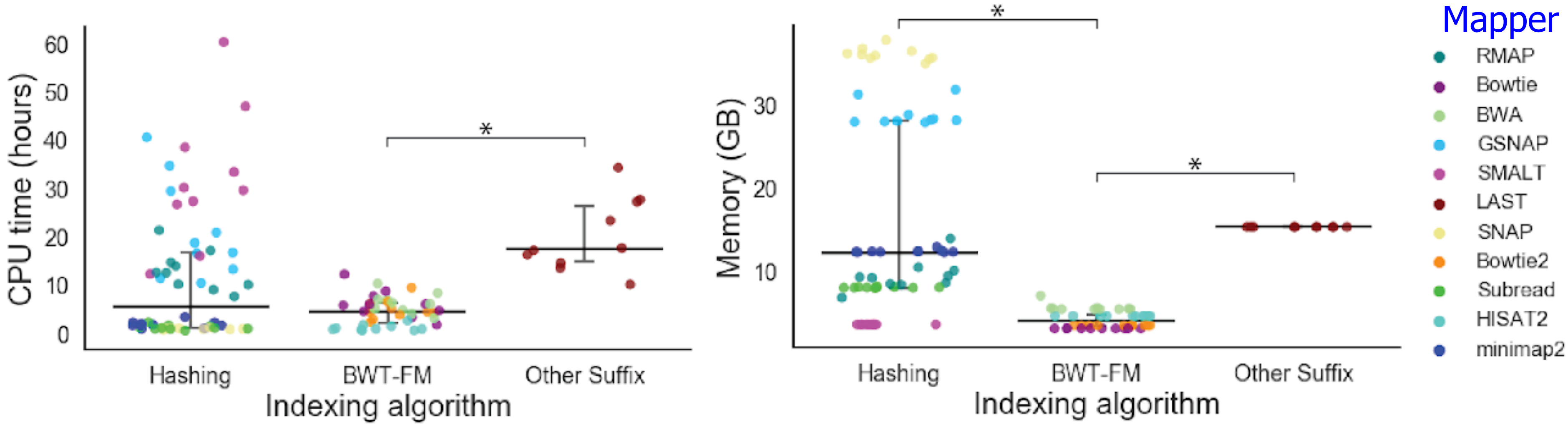
Genome Index Properties

- 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

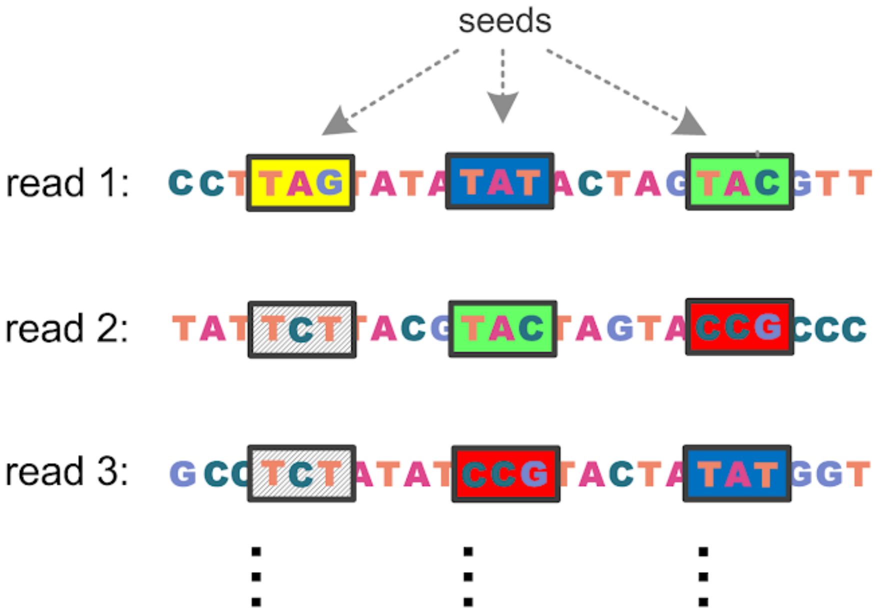
*Human genome = 3.2 GB

Performance of Human Genome Indexing

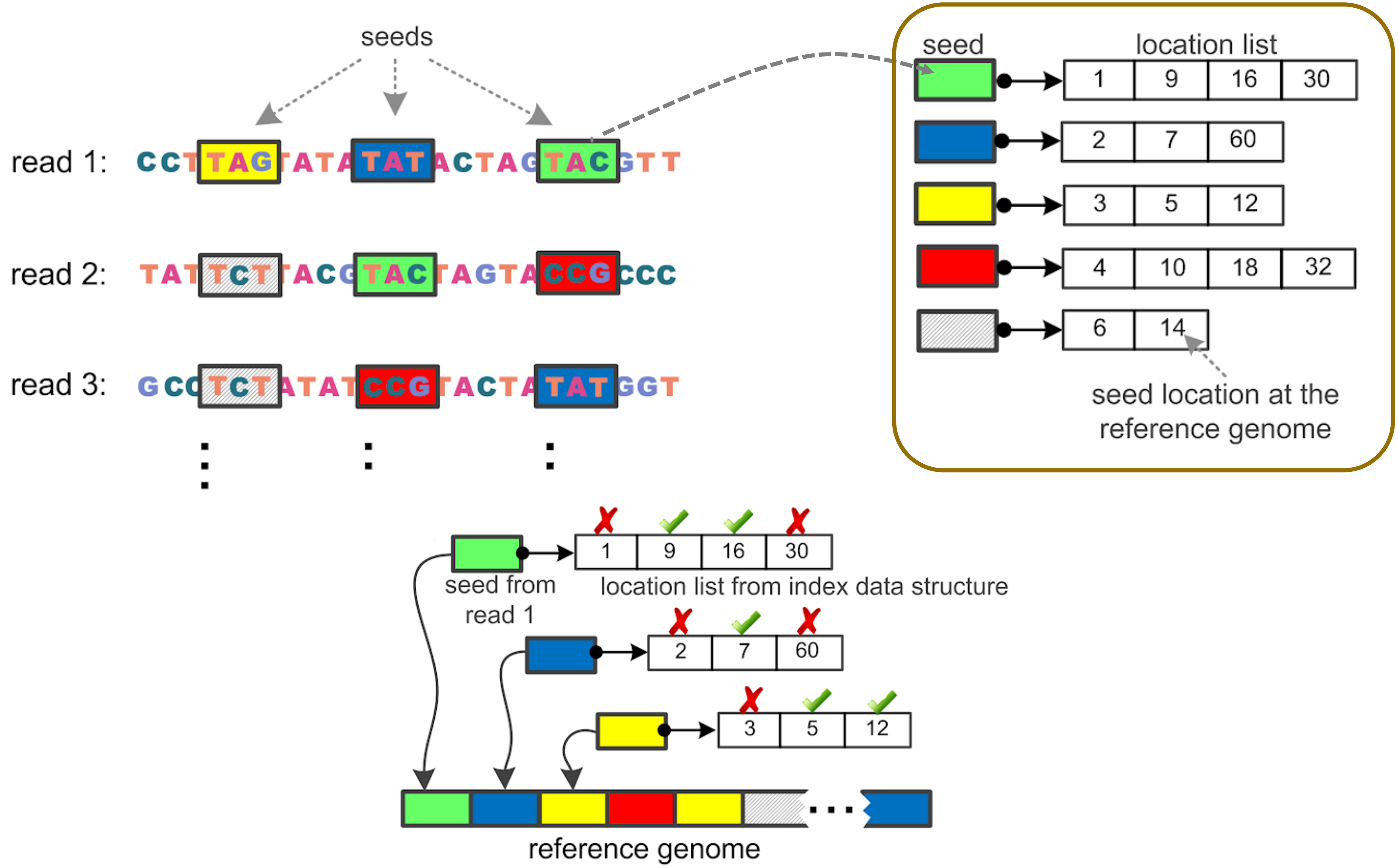


Alser+, "Technology dictates algorithms: Recent developments in read alignment", Genome Biology, 2021

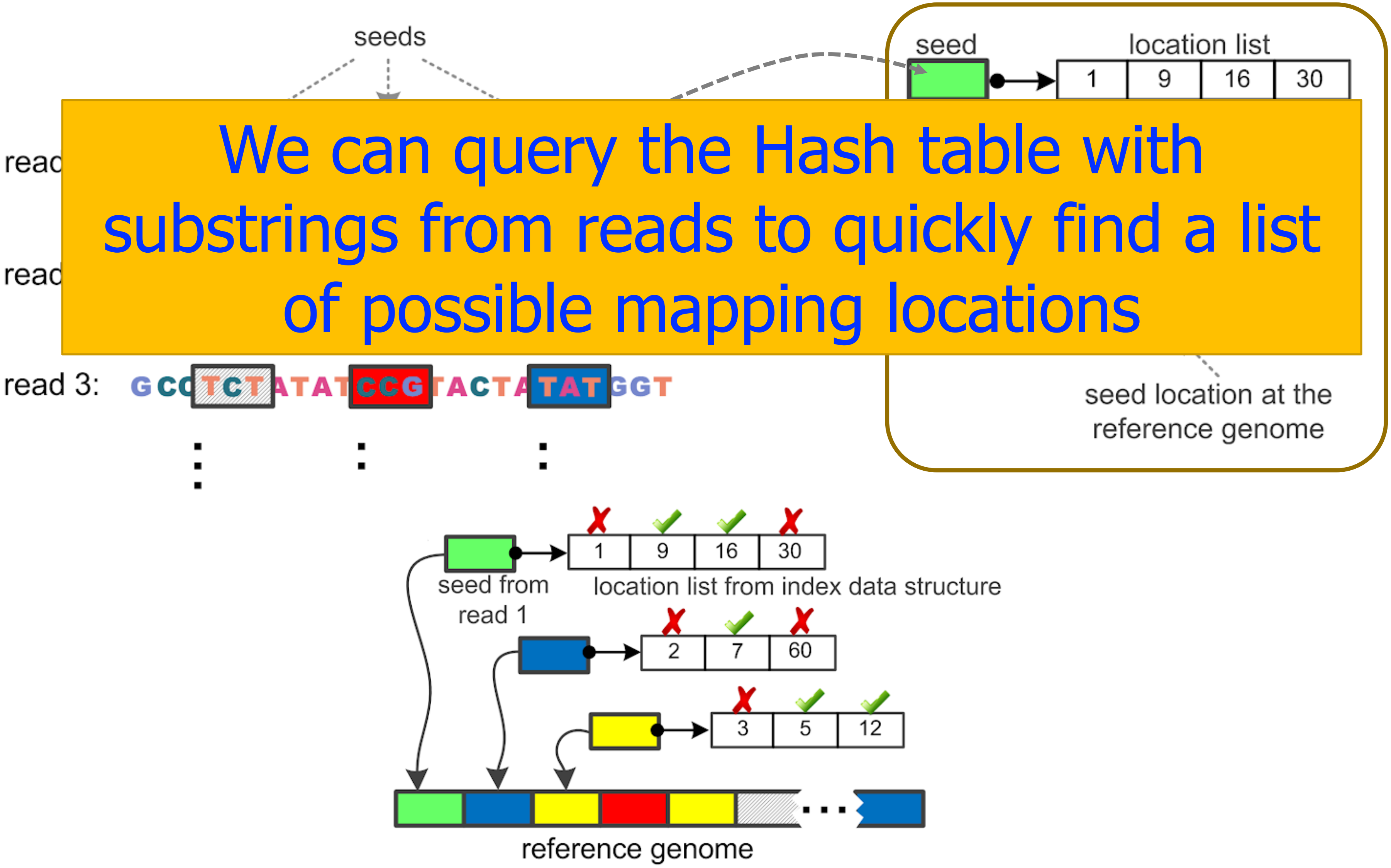
Step 2: Query the Index Using Read Seeds


seeds
read 1: CCTTAGTATATATACTAGTACGTT
read 2: TATTCTTACGTACTAGTACCGCCC
read 3: GCCTCTATATCCGTACTATATGGT
⋮
⋮
⋮

Step 2: Query the Index Using Read Seeds


seeds
read 1: CCTTAGTATATATACTAGTACGTT
read 2: TATTCTTACGTACTAGTACCGCCC
read 3: GCCTCTATATCCGTACTATATGGT
seed
location list
1 9 16 30
2 7 60
3 5 12
4 10 18 32
6 14
seed location at the reference genome
seed from read 1
location list from index data structure
1 9 16 30
2 7 60
3 5 12
reference genome

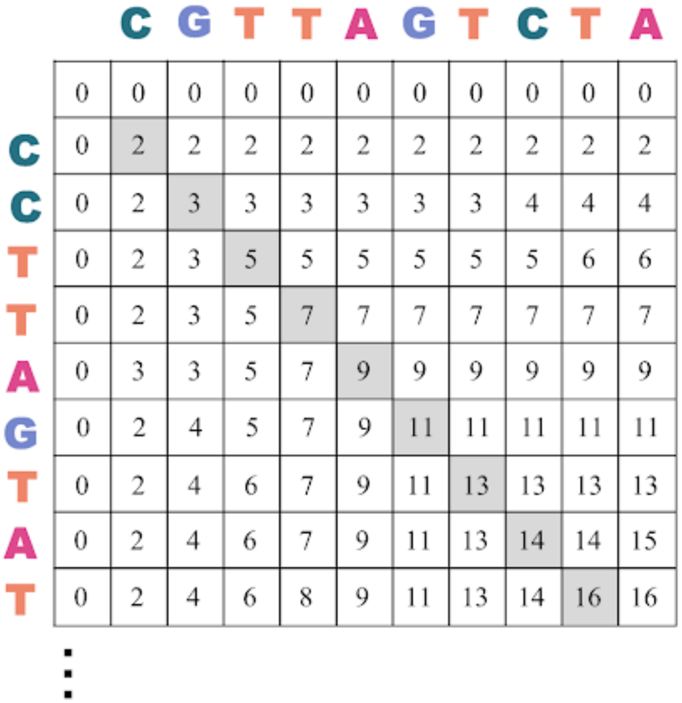
Step 2: Query the Index Using Read Seeds



We can query the Hash table with substrings from reads to quickly find a list of possible mapping locations

SAFARI

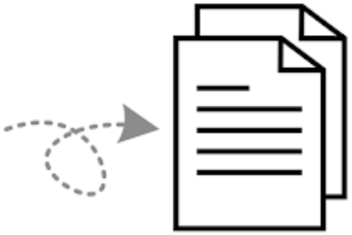
Step 3: Sequence Alignment (Verification)



		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

…

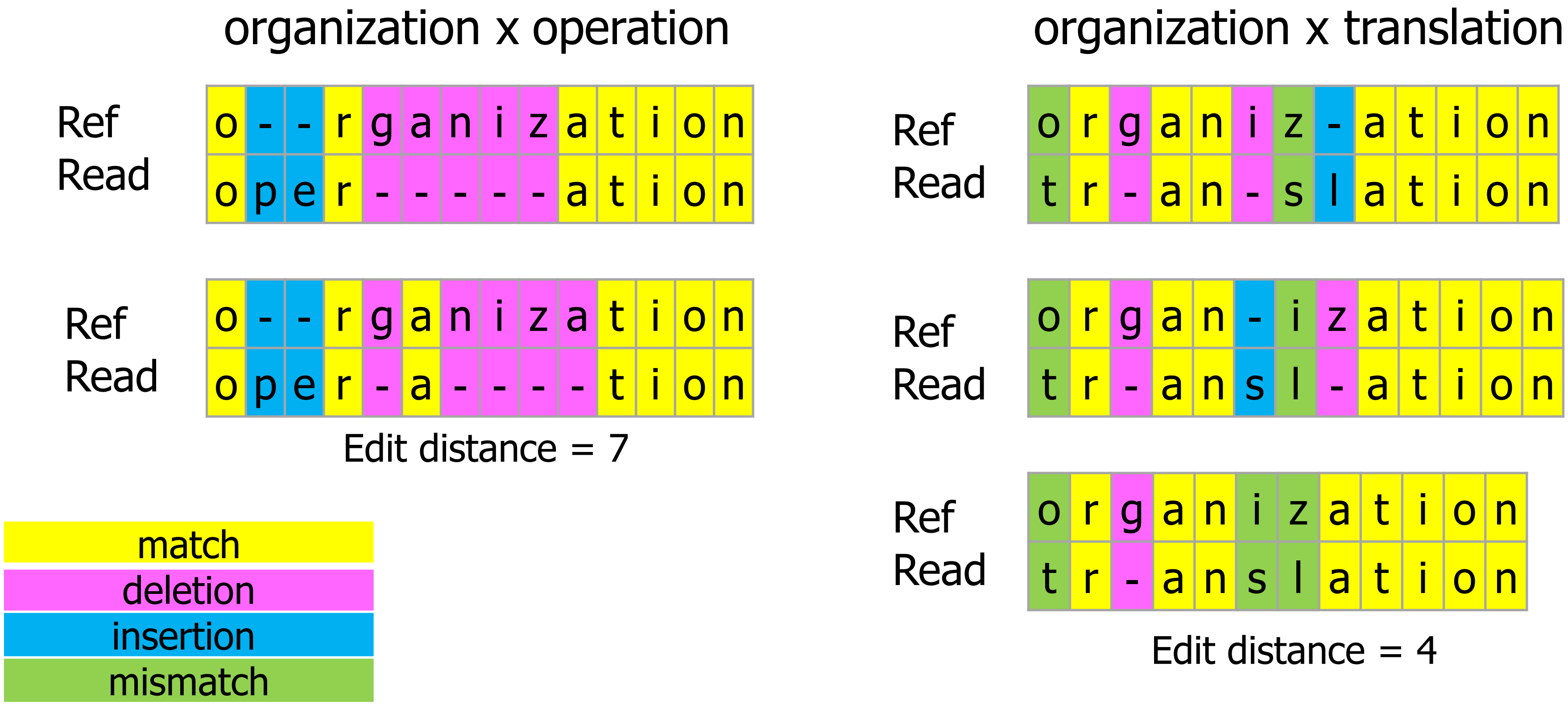
⋮



.bam/.sam file contains necessary alignment information (e.g., type, location, and number of each edit)

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

Ref	o	-	-	r	g	a	n	i	z	a	t	i	o	n
Read	o	p	e	r	-	-	-	-	-	a	t	i	o	n

Ref	o	-	-	r	g	a	n	i	z	a	t	i	o	n
Read	o	p	e	r	-	a	-	-	-	-	t	i	o	n

Edit distance = 7

organization x translation

Ref	o	r	g	a	n	i	z	-	a	t	i	o	n
Read	t	r	-	a	n	-	s	l	a	t	i	o	n

Ref	o	r	g	a	n	-	i	z	a	t	i	o	n
Read	t	r	-	a	n	s	l	-	a	t	i	o	n

Ref	o	r	g	a	n	i	z	a	t	i	o	n
Read	t	r	-	a	n	s	l	a	t	i	o	n

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

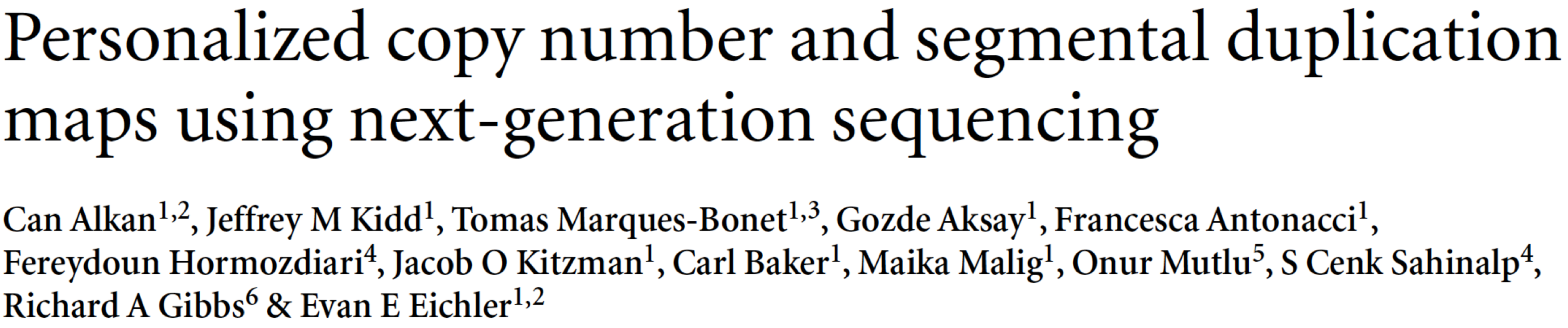
Alser+, "Technology dictates algorithms: Recent developments in read alignment", Genome Biology, 2021

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

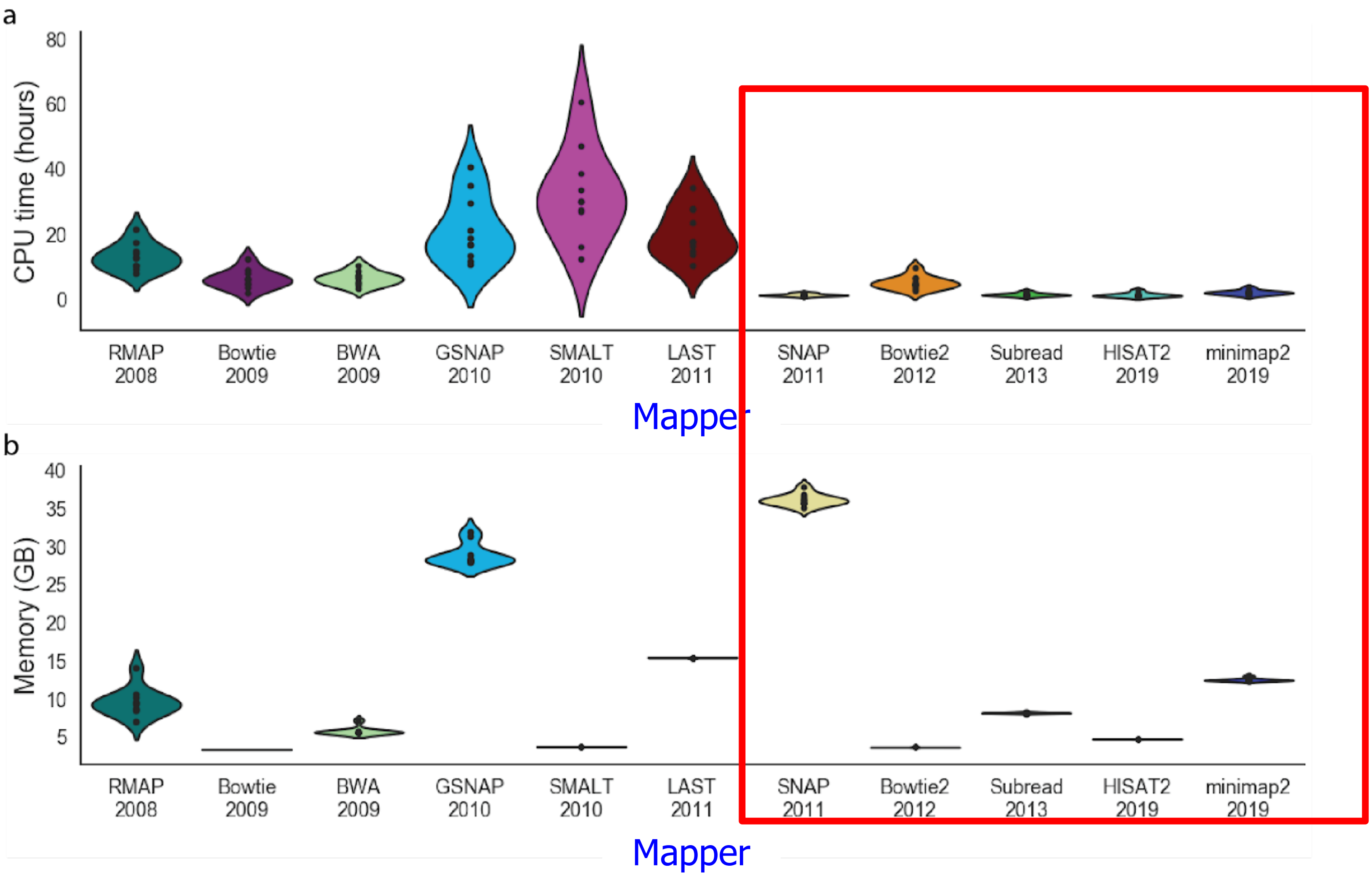


Personalized copy number and segmental duplication maps using next-generation sequencing

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]

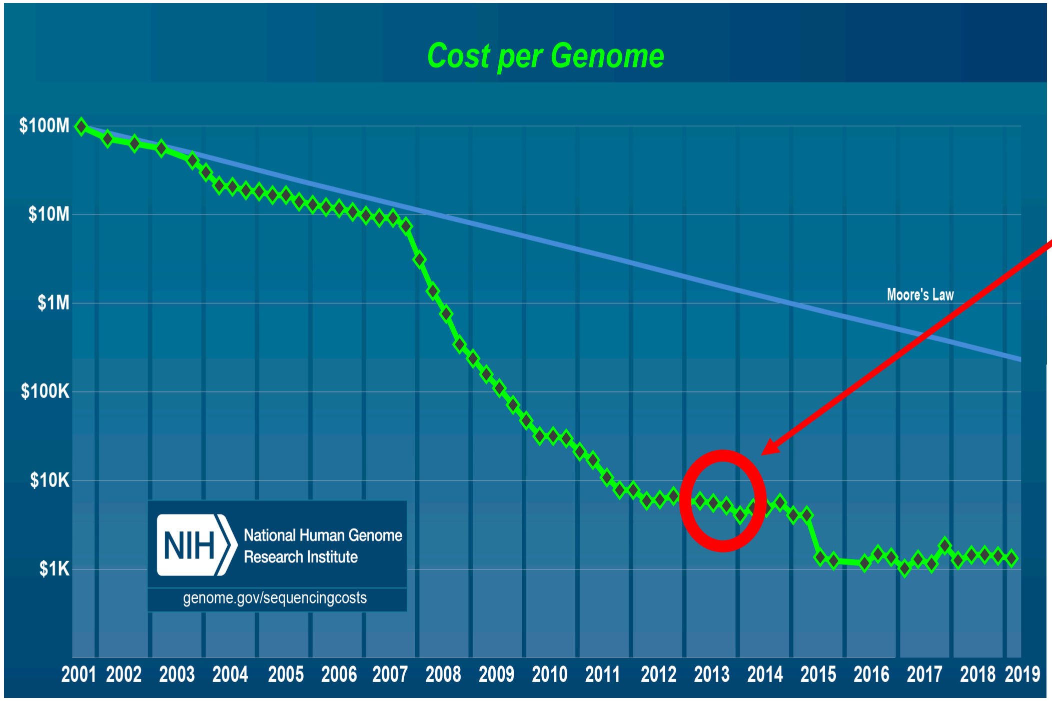
Alkan+, "Personalized copy number and segmental duplication maps using next-generation sequencing", Nature Genetics 2009.

Performance of Read Mapping

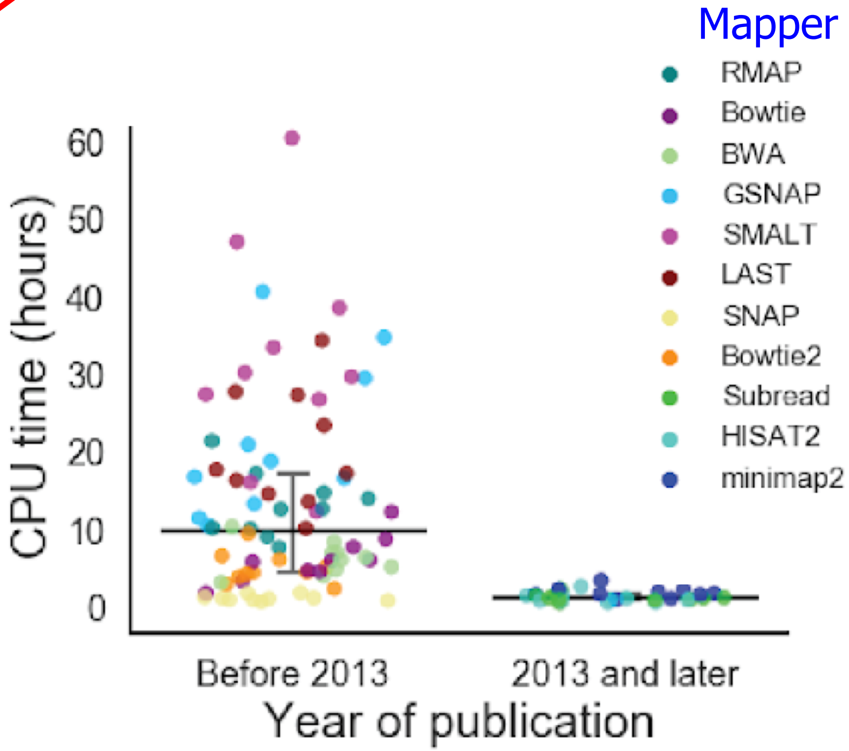


Alser+, "Technology dictates algorithms: Recent developments in read alignment", Genome Biology, 2021

The Need for Speed



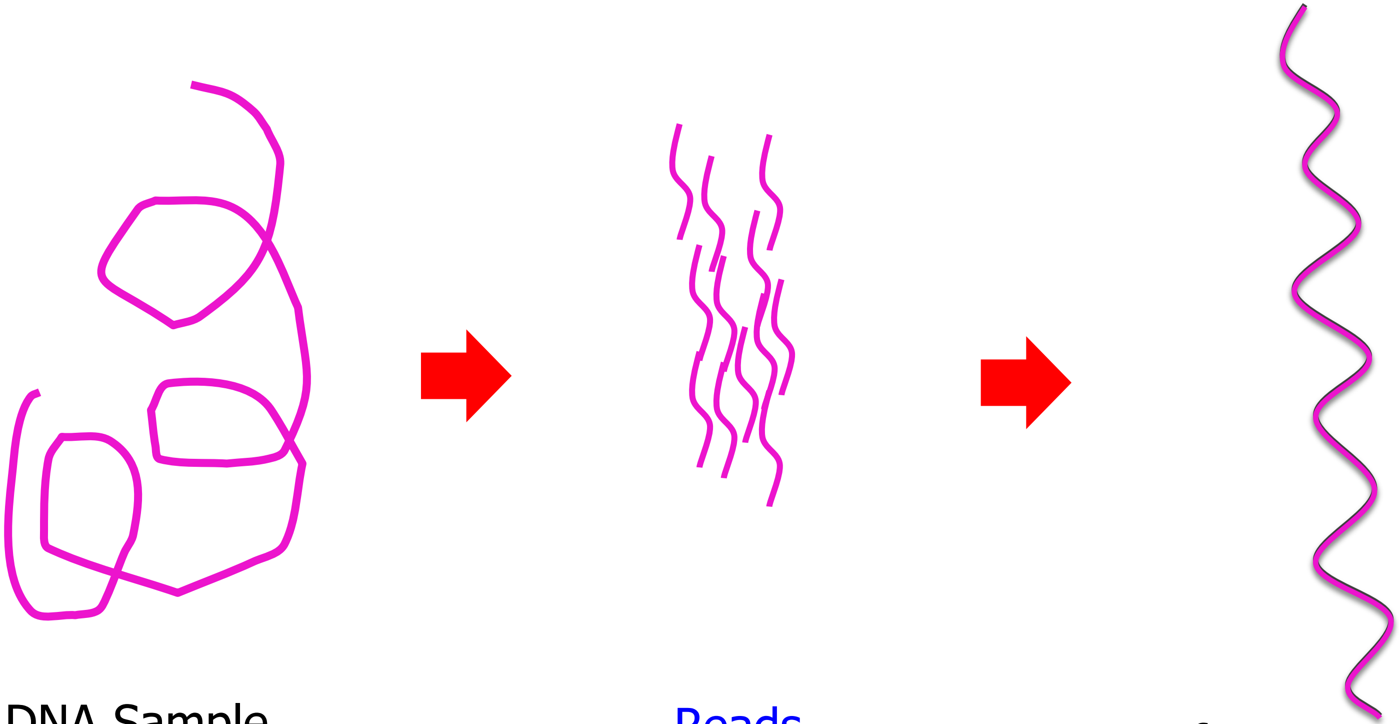
Did we realize the **need** for **faster** genome analysis?



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



DNA Sample
"chemical format"

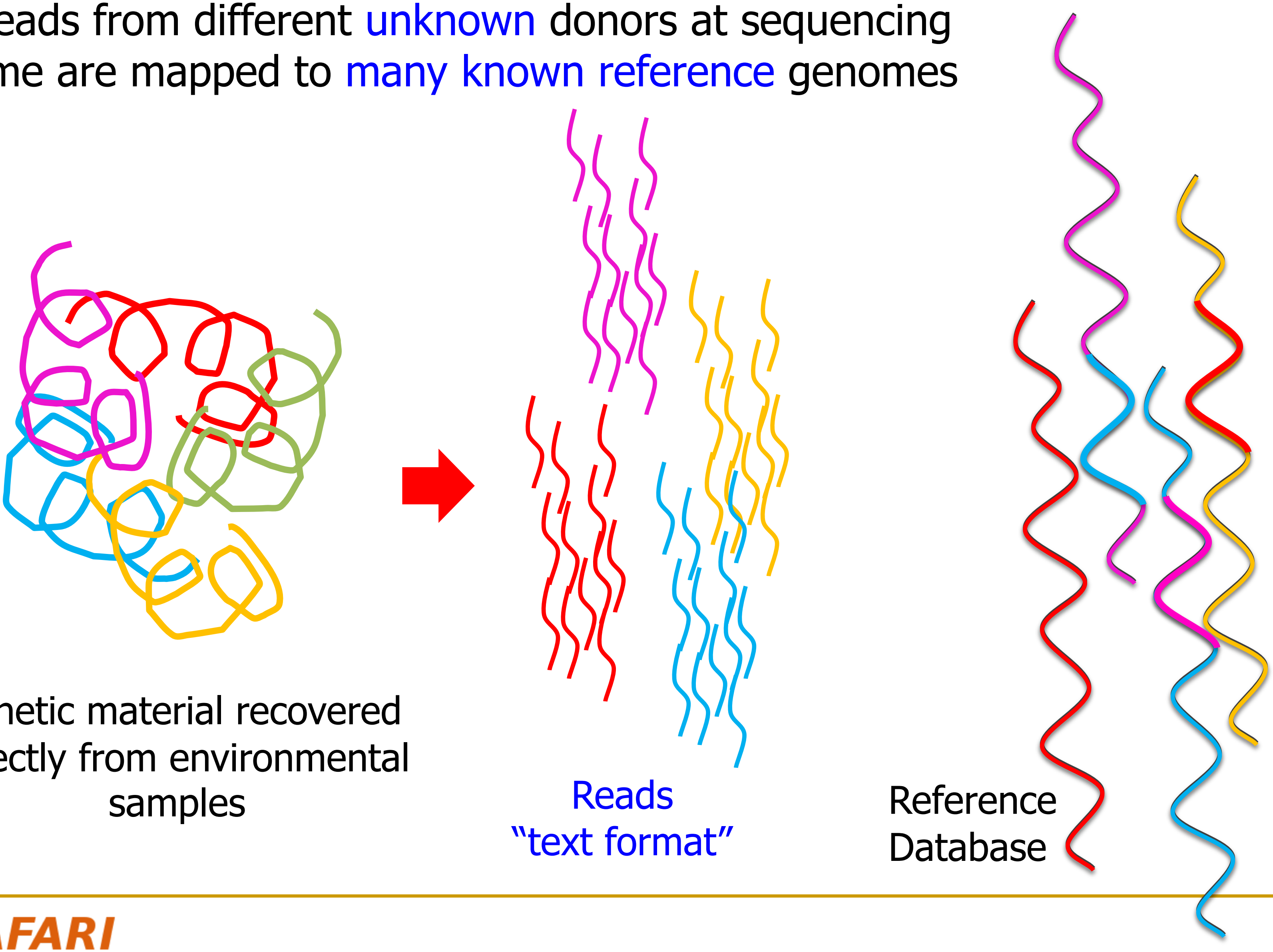
Reads
"text format"

Reference genome

Subject genome
"text format"

Metagenomics Analysis

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

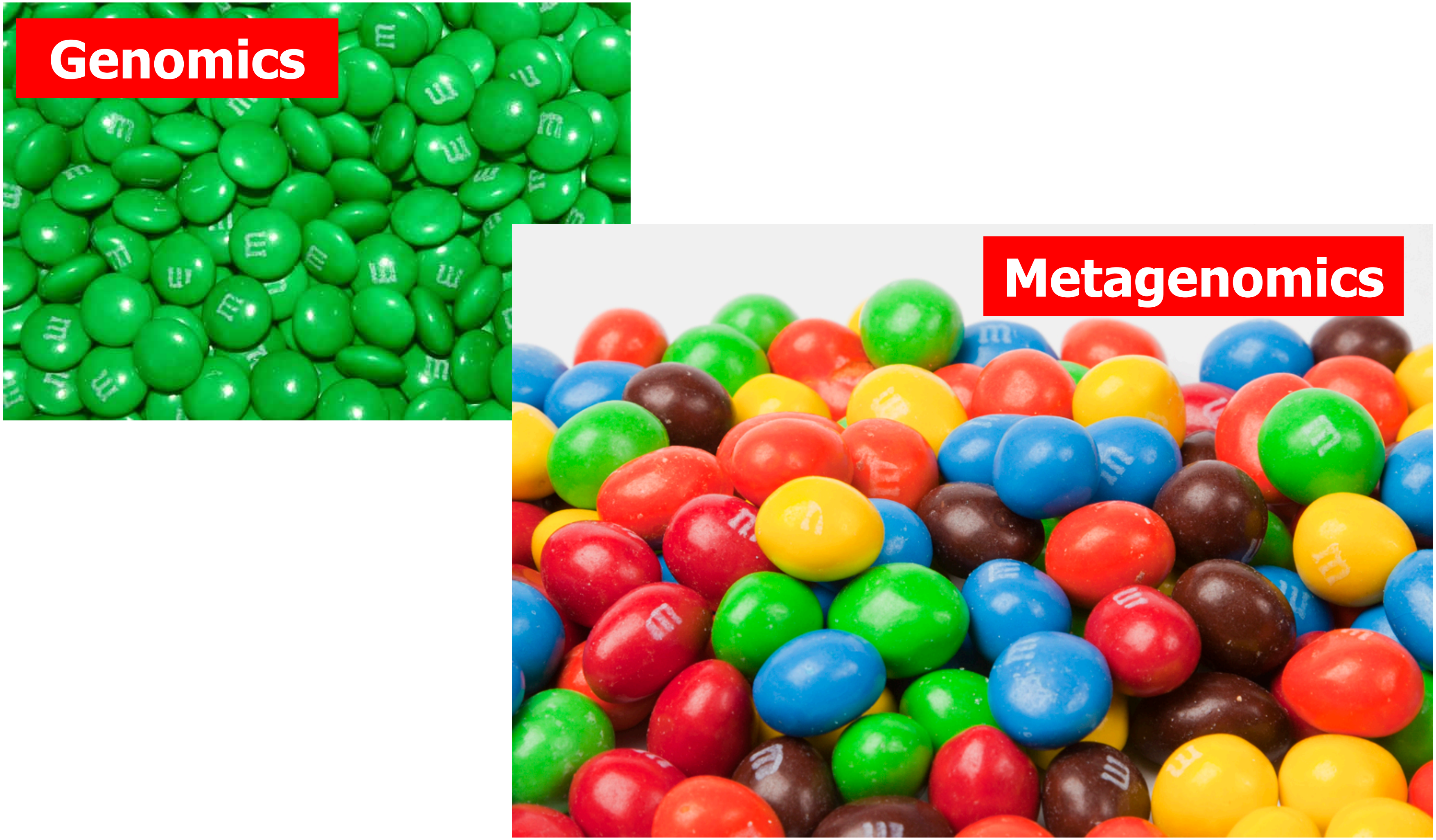


genetic material recovered directly from environmental samples

Reads
"text format"

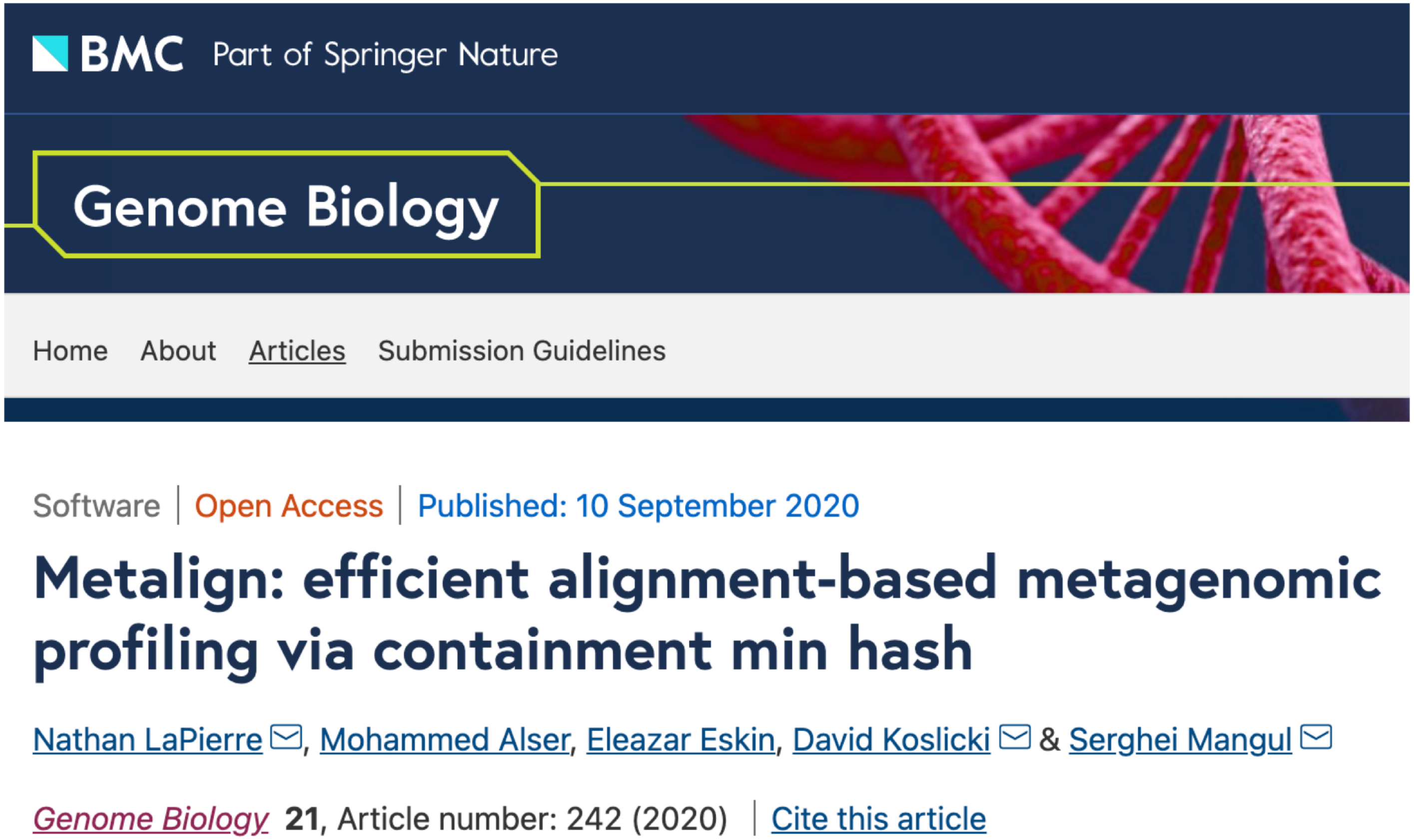
Reference Database

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

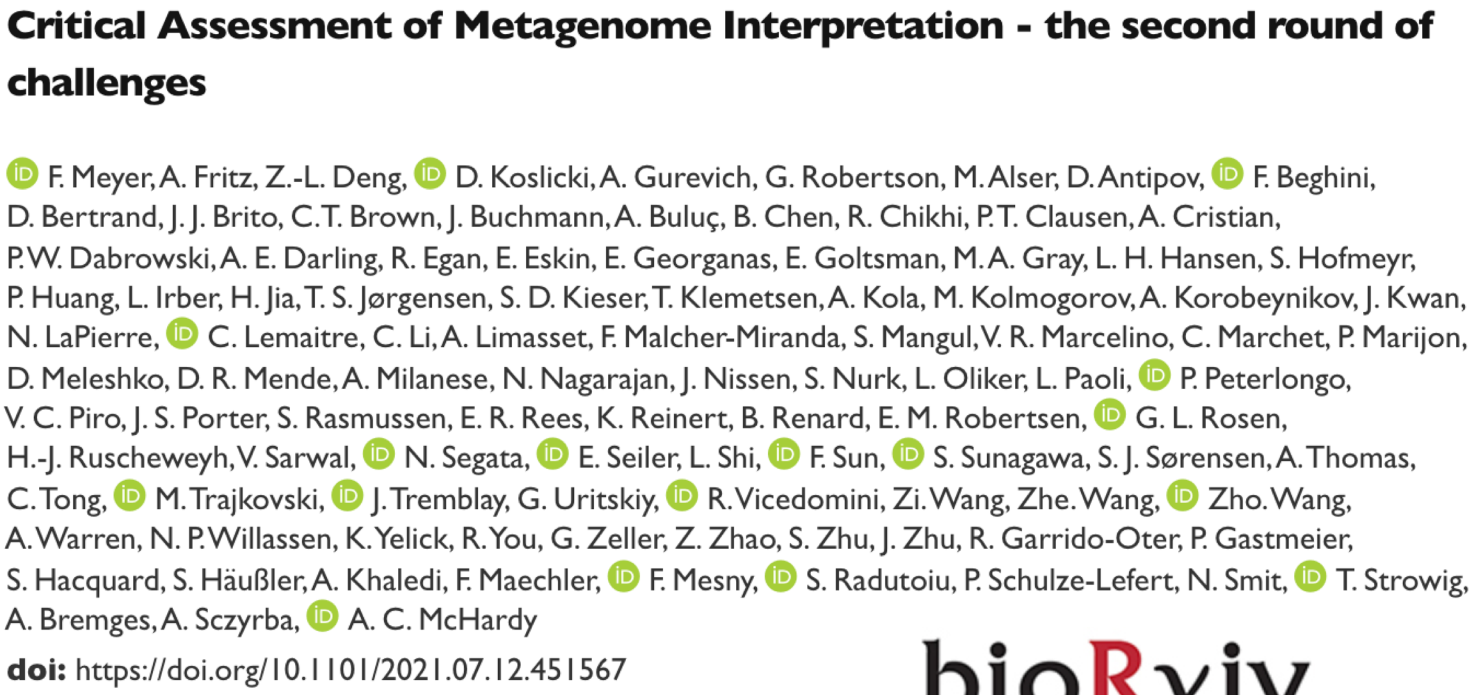
Check Also CAMI II Paper

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

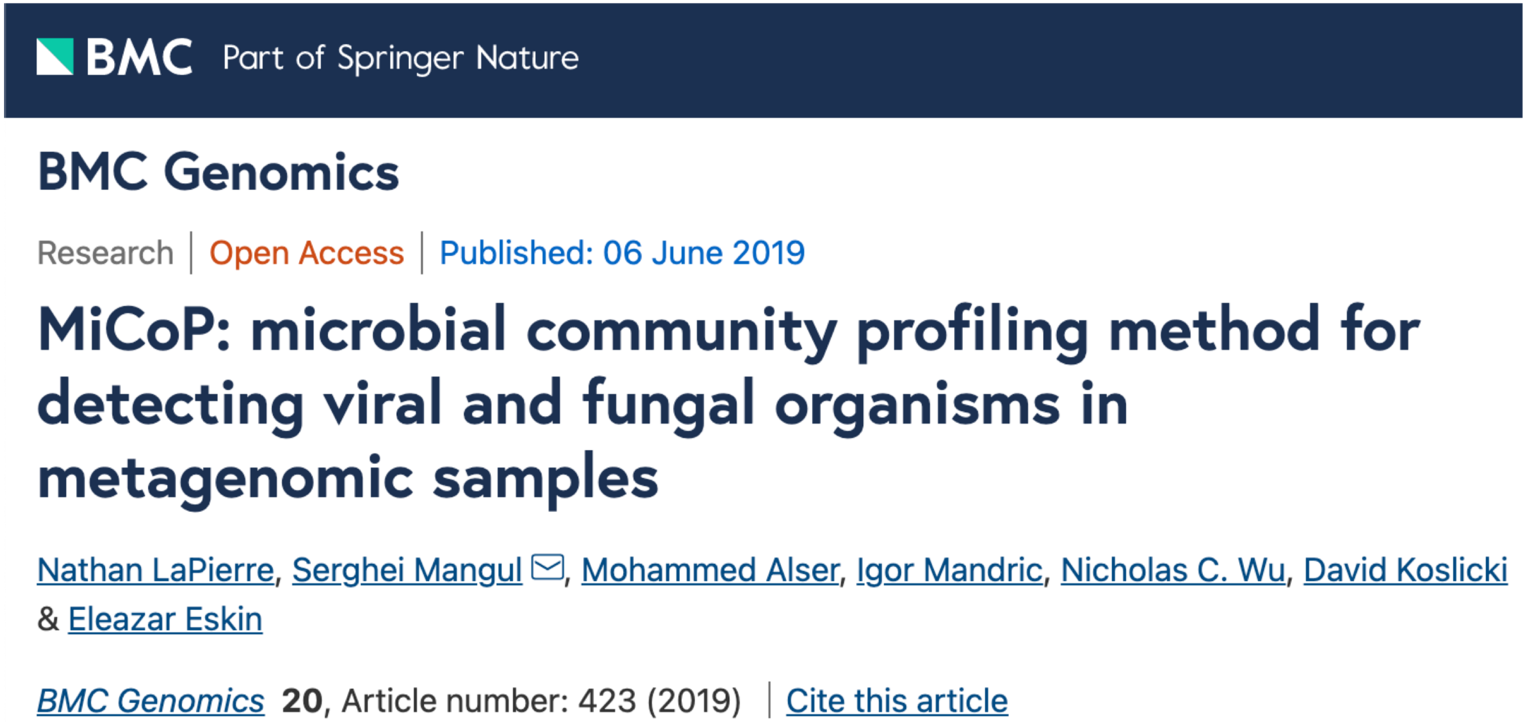
F. Meyer, A. Fritz, Z.-L. Deng, D. Koslicki, A. Gurevich, G. Robertson, M. Alser, D. Antipov, F. Beghini, D. Bertrand, J. J. Brito, C.T. Brown, J. Buchmann, A. Buluç, B. Chen, R. Chikhi, P.T. Clausen, A. Cristian, P.W. Dabrowski, A. E. Darling, R. Egan, E. Eskin, E. Georganas, E. Goltsman, M.A. Gray, 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

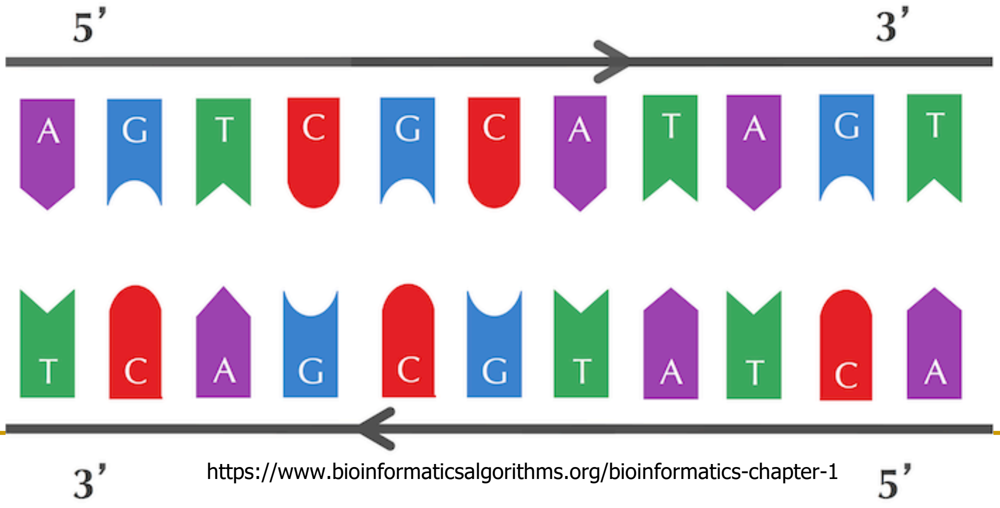
MiCoP: microbial community profiling method for detecting viral and fungal organisms in metagenomic samples

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

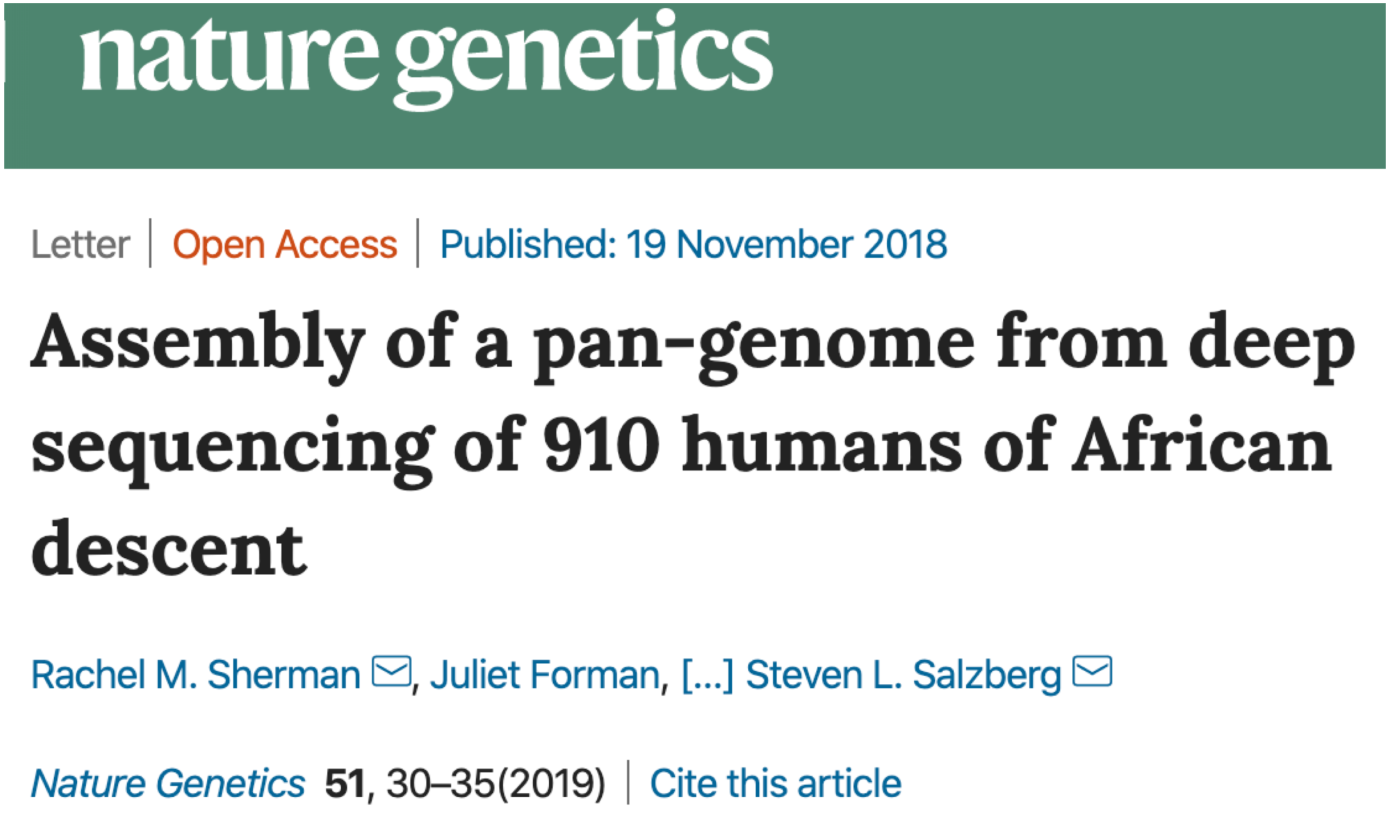


https://www.bioinformaticsalgorithms.org/bioinformatics-chapter-1

Revisiting the Puzzle

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

Reference Genome Bias



nature genetics

Letter | Open Access | Published: 19 November 2018

Assembly of a pan-genome from deep sequencing of 910 humans of African descent

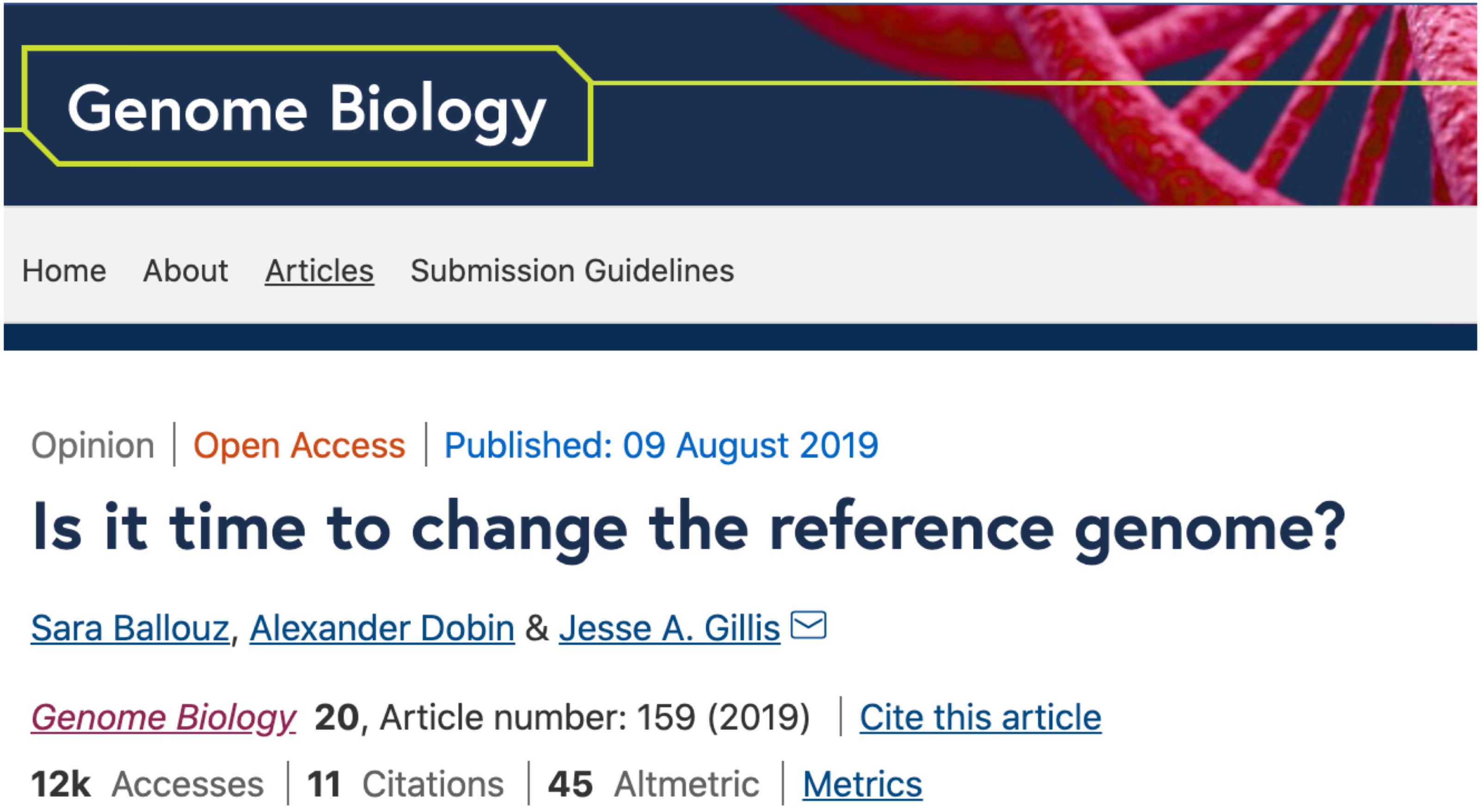
Rachel M. Sherman ✉, Juliet Forman, [...] Steven L. Salzberg ✉

Nature Genetics **51**, 30–35(2019) | Cite this article

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

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

Time to Change the Reference Genome



Genome Biology

Opinion | Open Access | Published: 09 August 2019

Is it time to change the reference genome?

Sara Ballouz, Alexander Dobin & Jesse A. Gillis

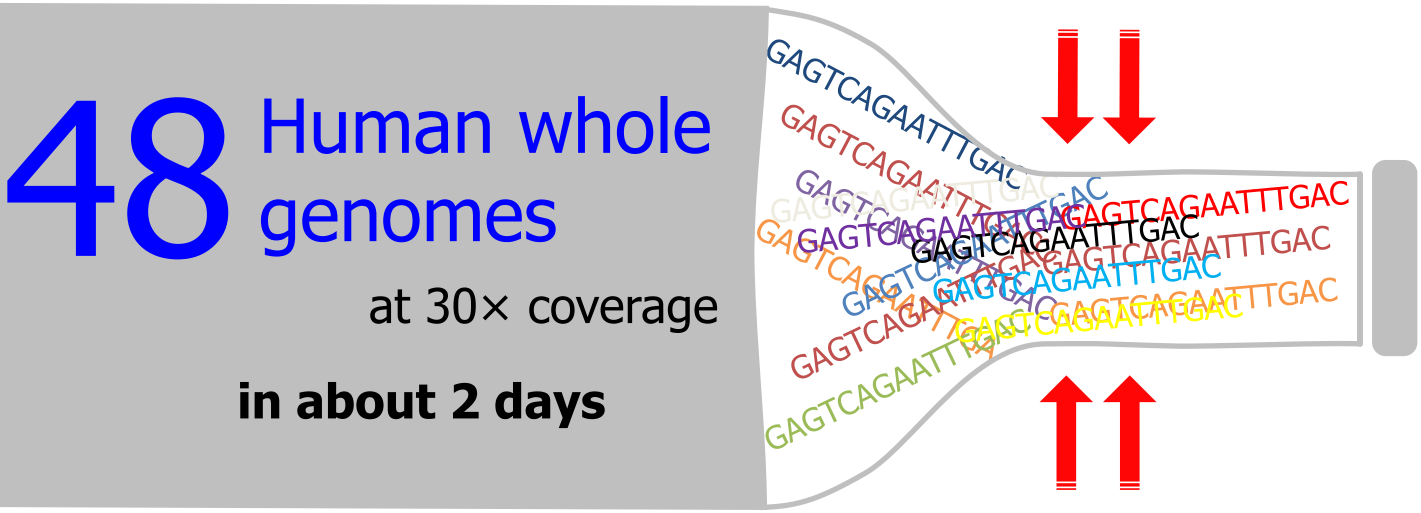
Genome Biology **20**, Article number: 159 (2019) | Cite this article

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"

SAFARI Ballouz+, "Is it time to change the reference genome?", Genome Biology, 2019

Analysis is Bottlenecked in Read Mapping!!



48 Human whole genomes

at 30× coverage

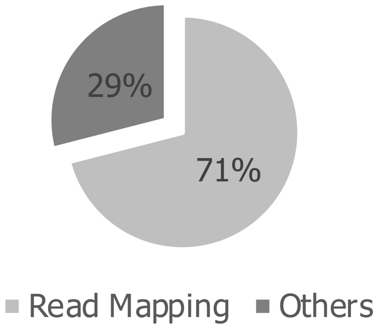
in about 2 days

Illumina NovaSeq 6000

1 Human genome

32 CPU hours

on a 48-core processor



SAFARI 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 Genome Analysis?
- What is Intelligent Genome Analysis?

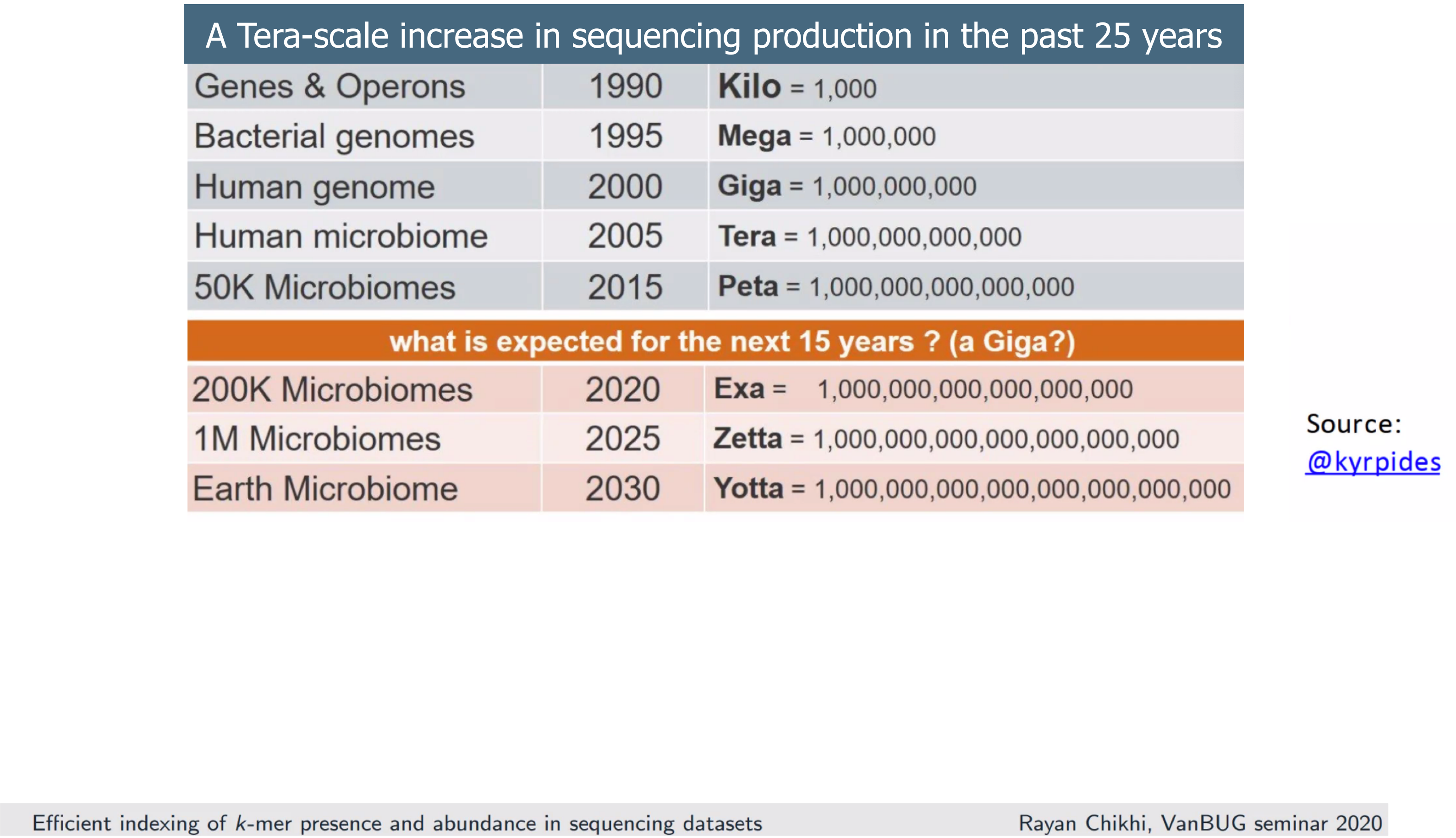
- How we Analyze Genome?
- What is Read Mapping?
- **What Makes Read Mapper Slow?**

- Algorithmic & Hardware Acceleration
  - Seed Filtering Technique
  - Pre-alignment Filtering Technique
  - Read Alignment Acceleration

- Where is Read Mapping Going Next?

What makes
read mapping
a **bottleneck**?

A Tsunami of Sequencing Data



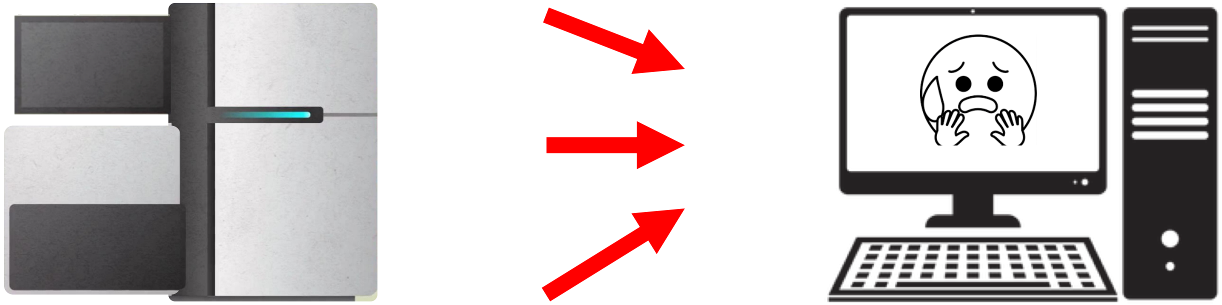
A Tera-scale increase in sequencing production in the past 25 years

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

Efficient indexing of *k*-mer presence and abundance in sequencing datasets   Rayan Chikhi, VanBUG seminar 2020

Lack of Specialized Compute Capability



Specialized Machine
for Sequencing

General-Purpose Machine
for Analysis

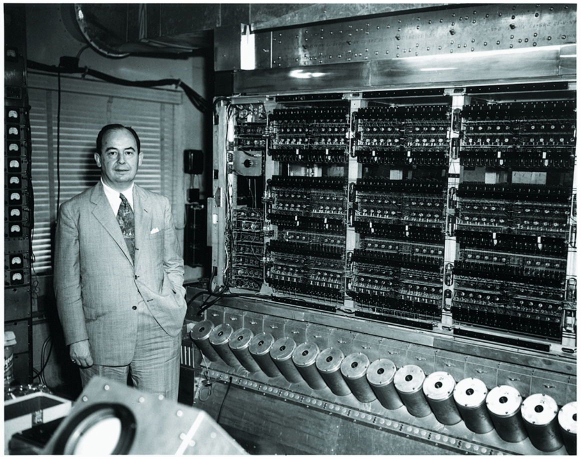
FAST

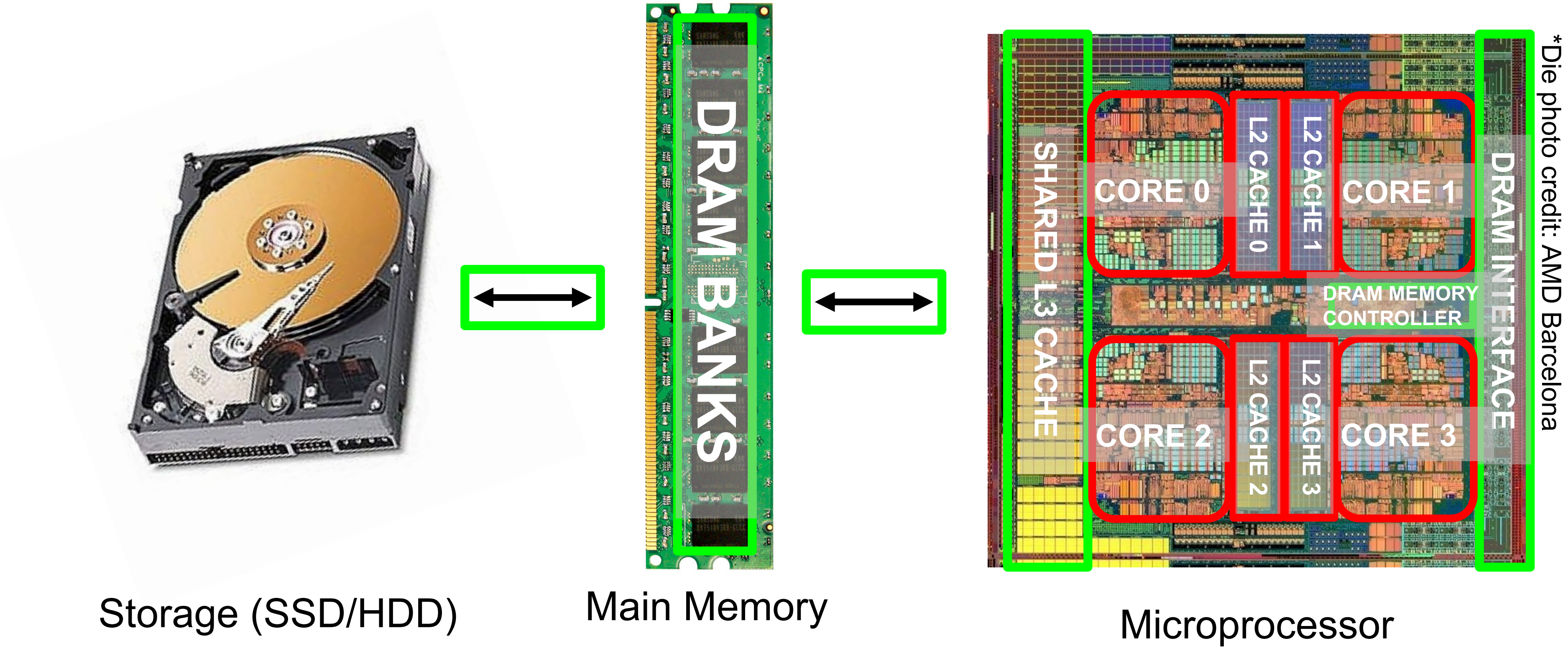
SLOW

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**





*Die photo credit: AMD Barcelona

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

The Problem

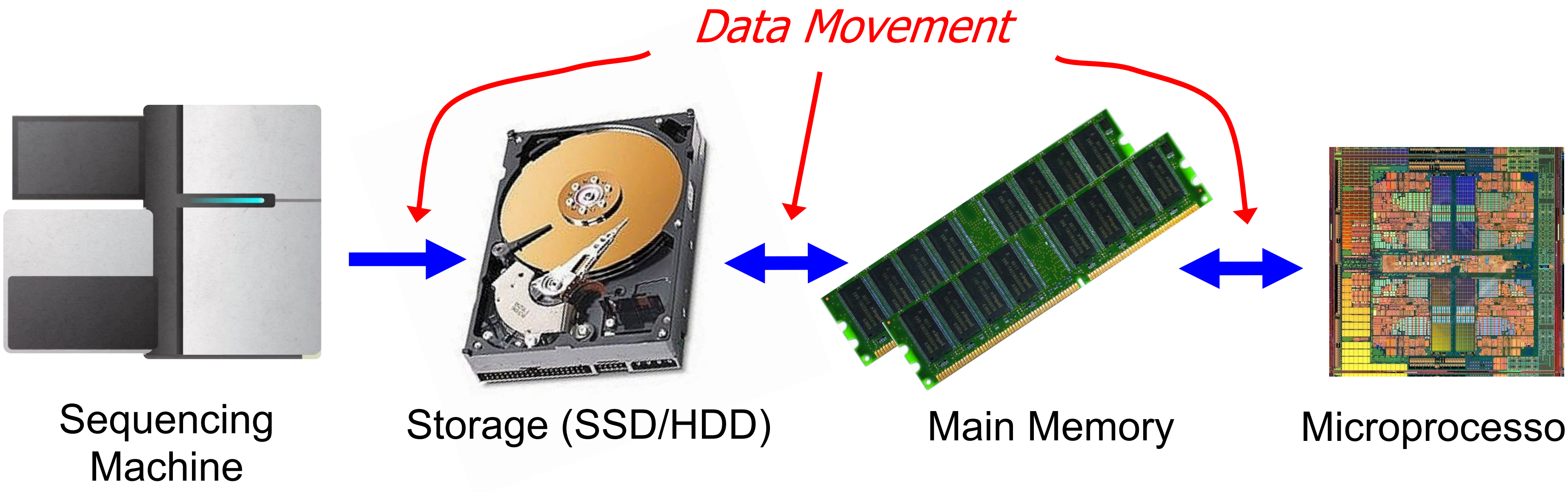
Data analysis

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%)



Data Movement

Sequencing Machine

Storage (SSD/HDD)

Main Memory

Microprocessor

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

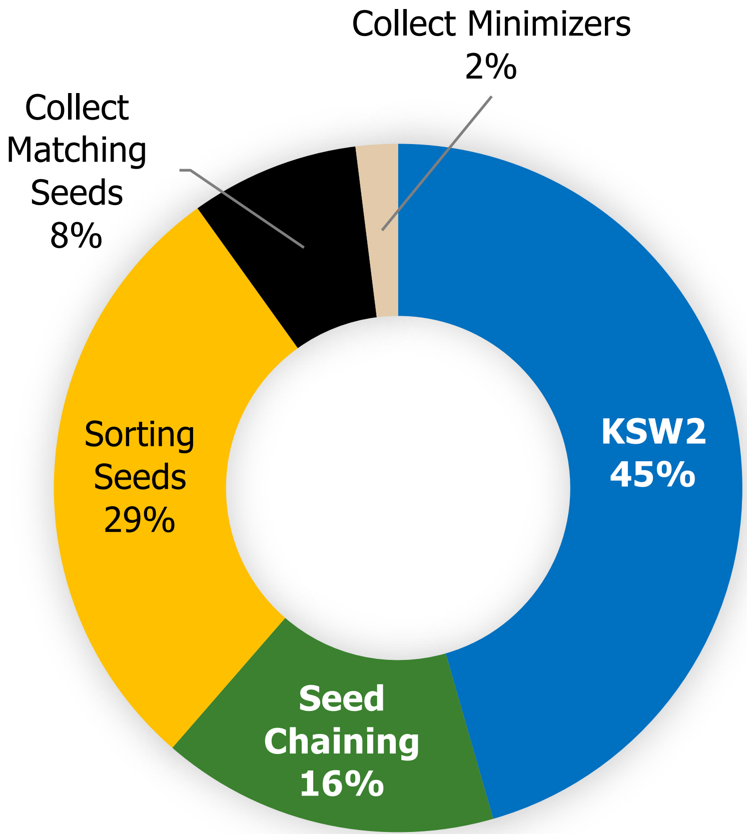
★ Kestor et al., "Quantifying the Energy Cost of Data Movement in Scientific Applications," IISWC 2013

☆ 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

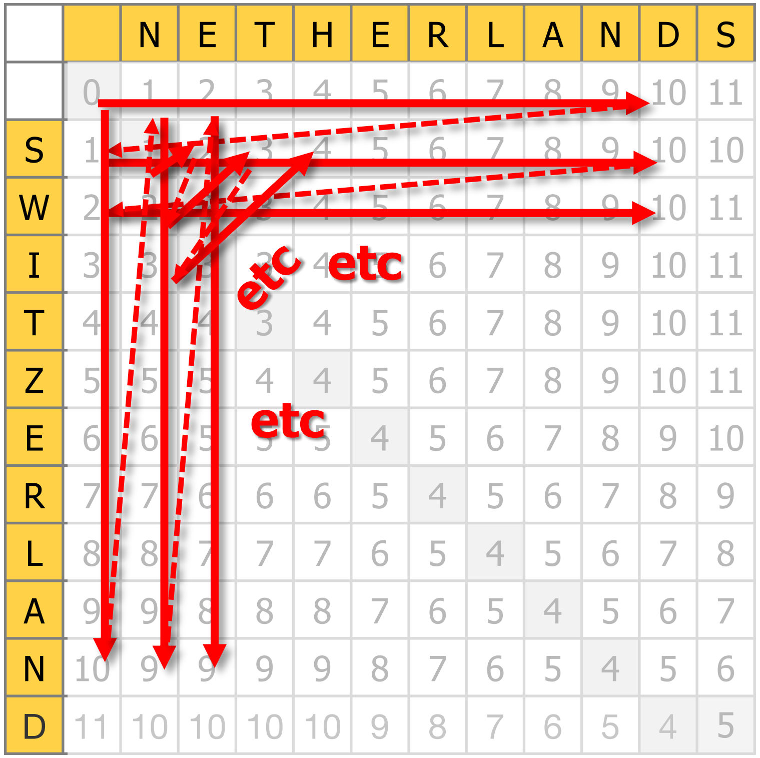
ONT FASTQ size: 103MB (151 reads), Mean length: 356,403 bp, std: 173,168 bp, longest length: 817,917 bp

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



		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

Sequence Alignment in Unavoidable

- Quadratic-time dynamic-programming algorithm

  Enumerating all possible prefixes

- Data dependencies limit the computation parallelism

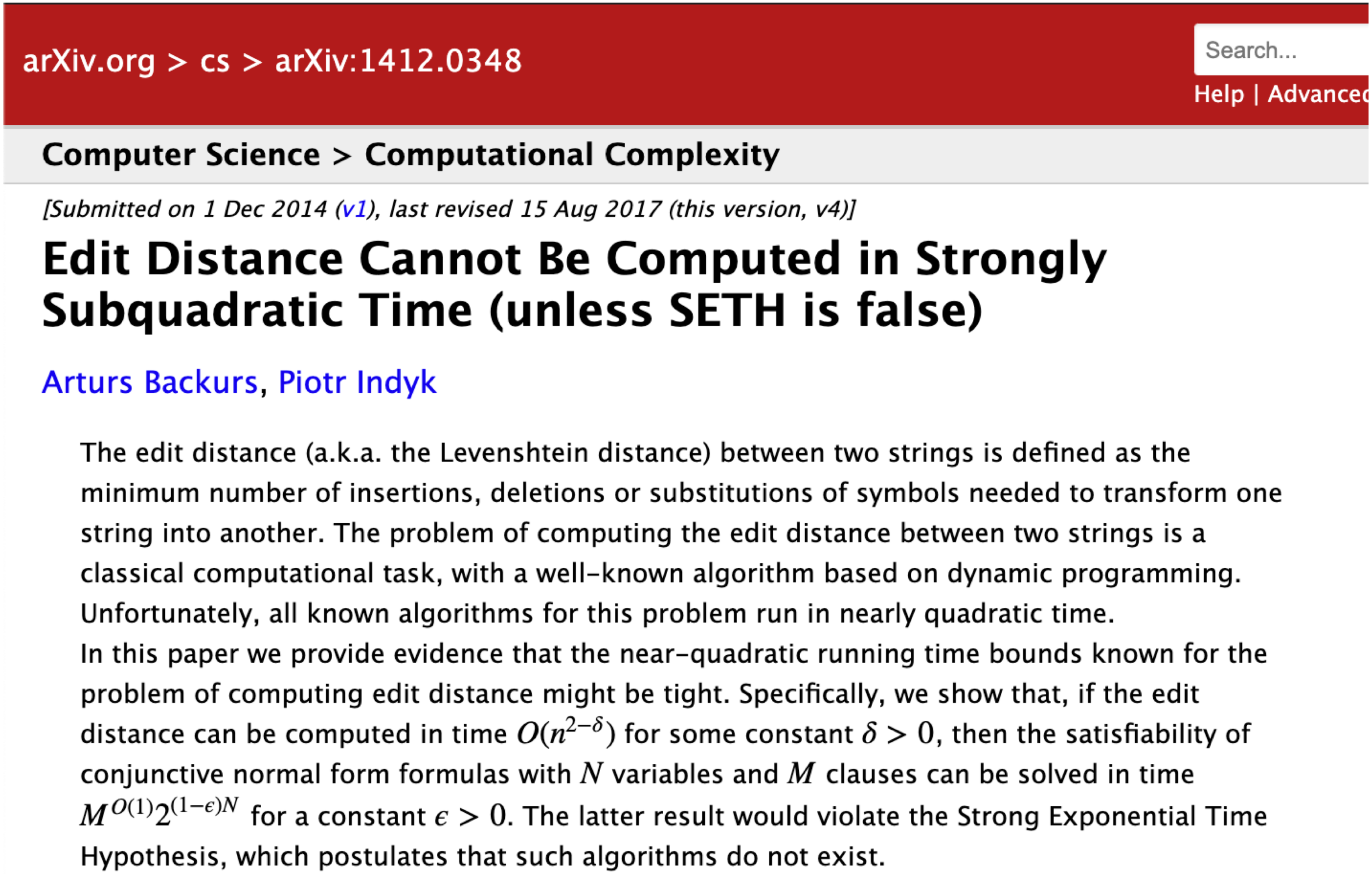
  Processing row (or column) after another

- 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



arXiv.org > cs > arXiv:1412.0348

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)

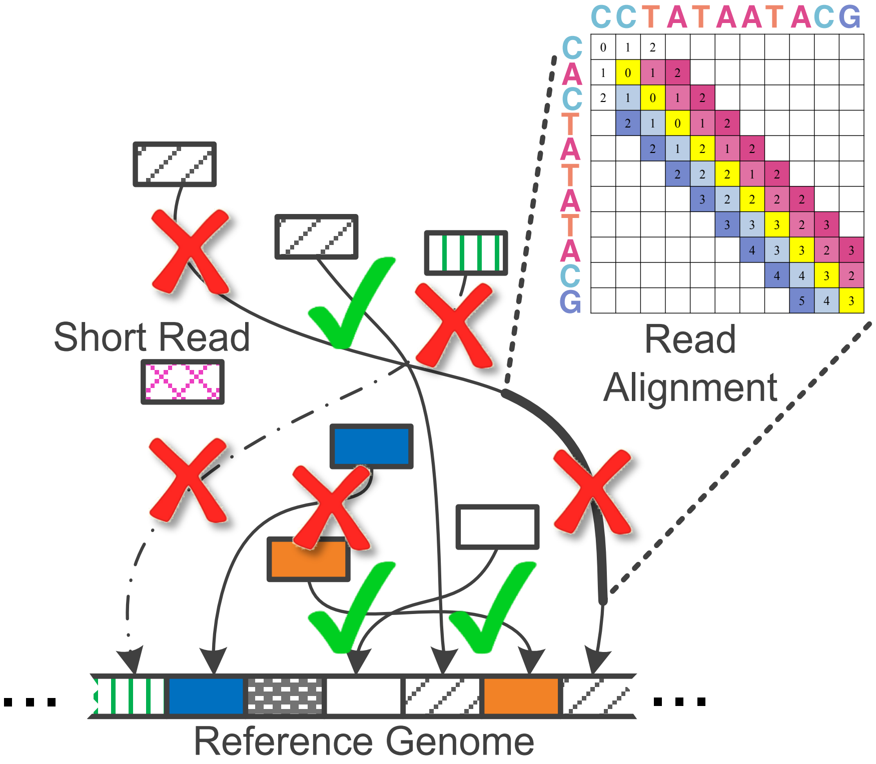
Arturs Backurs, Piotr Indyk

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



	C	C	T	A	T	A	A	T	A	C	G
C	0	1	2								
A	1	0	1	2							
C	2	1	0	1	2						
T		2	1	0	1	2					
A			2	1	2	1	2				
T				2	2	2	1	2			
A					3	2	2	2	2		
T						3	3	3	2	3	
A							4	3	3	2	3
C								4	4	3	2
G									5	4	3

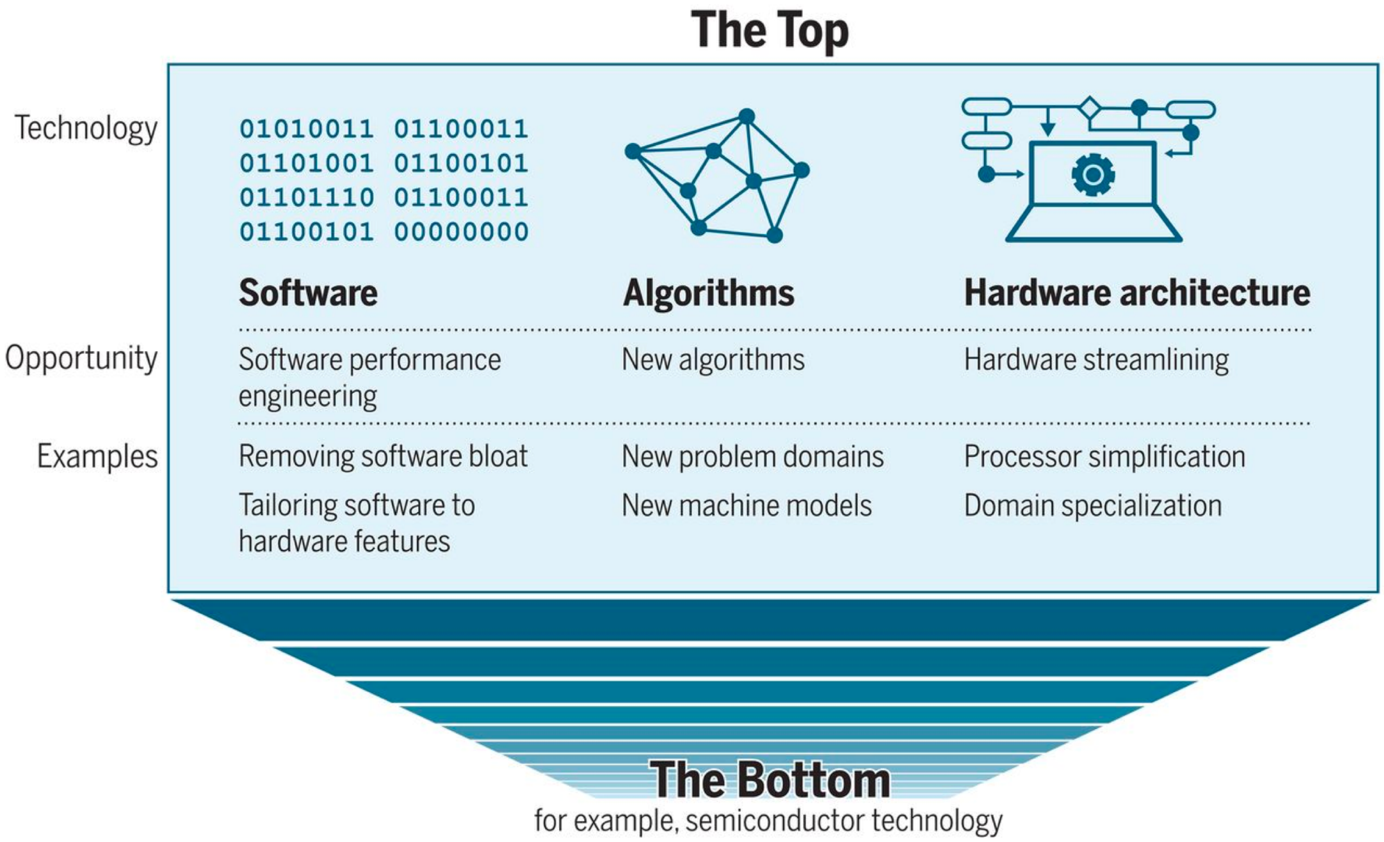
98%

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

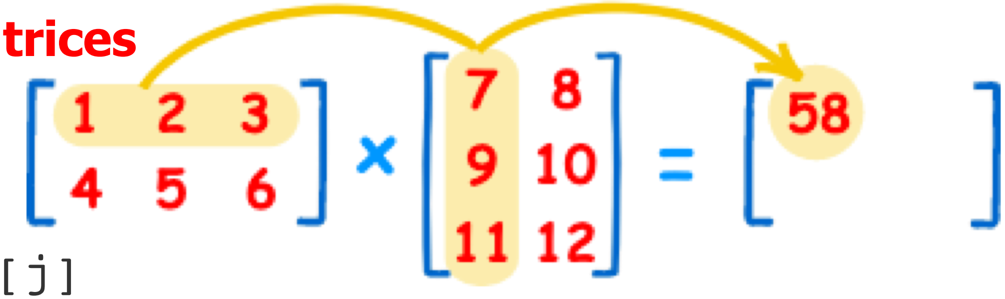
Richard Feynman, "There's Plenty of Room at the Bottom: An Invitation to Enter a New Field of Physics", a lecture given at Caltech, 1959.

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

Software & Hardware Optimizations

Multiplying Two 4096-by-4096 Matrices

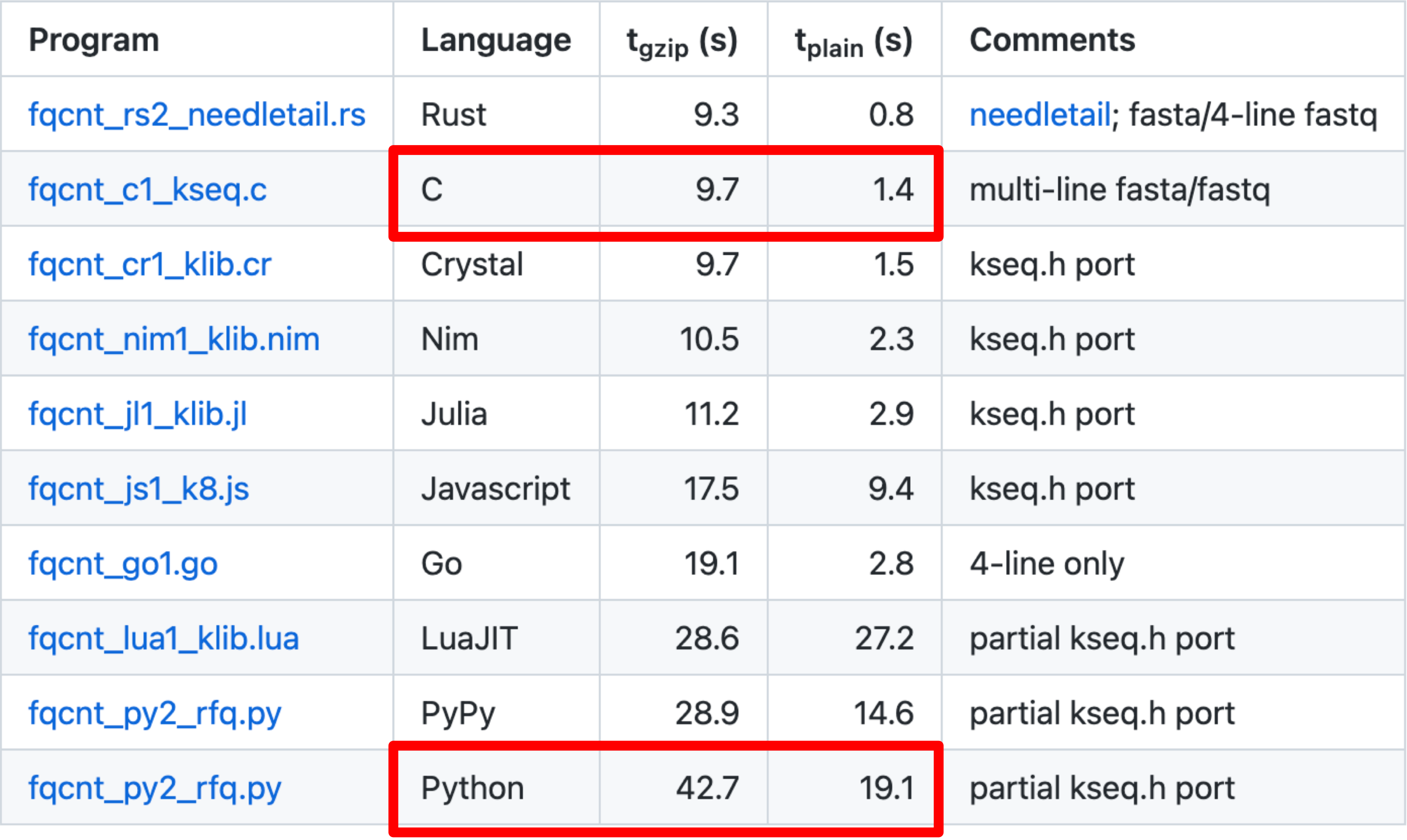
```
for i in xrange(4096):
 for j in xrange(4096):
  for k in xrange(4096):
   C[i][j] += A[i][k] * B[k][j]
```



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

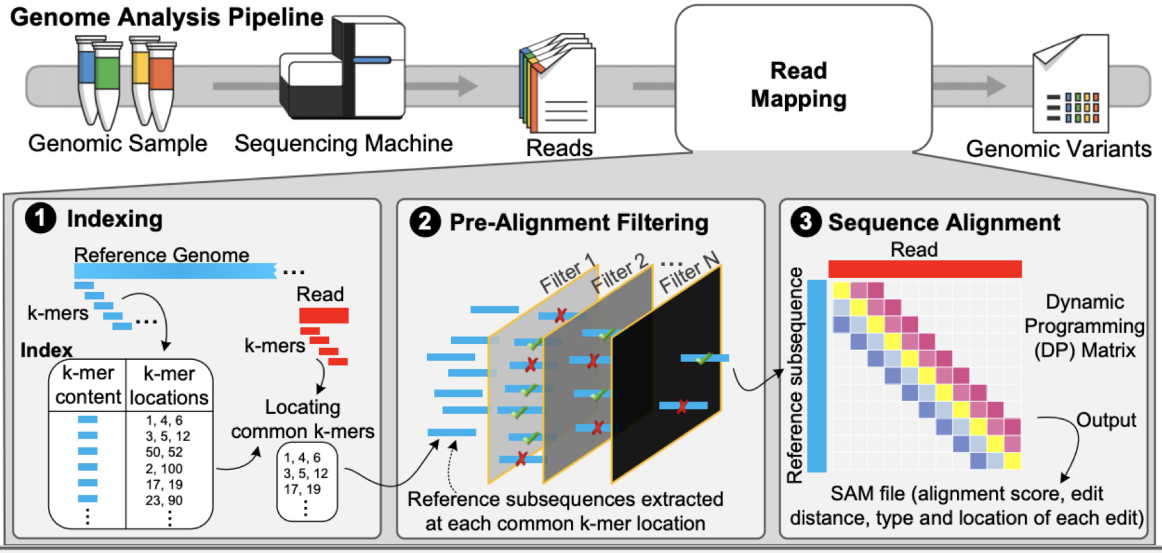
- What is Genome Analysis?
- What is Intelligent Genome Analysis?

- How we Analyze Genome?
- What is Read Mapping?
- What Makes Read Mapper Slow?

- **Algorithmic & Hardware Acceleration**
  - Seed Filtering Technique
  - Pre-alignment Filtering Technique
  - Read Alignment Acceleration

- Where is Read Mapping Going Next?

Accelerating Read Mapping



Accelerating Indexing

- Reducing the number of seeds
- Reducing data movement during indexing

Accelerating Pre-Alignment Filtering

- q-gram filtering
- Pigeonhole principle
- Base counting
- Sparse DP

Accelerating Alignment

- Accurate alignment accelerators
- Heuristic-based alignment accelerators

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

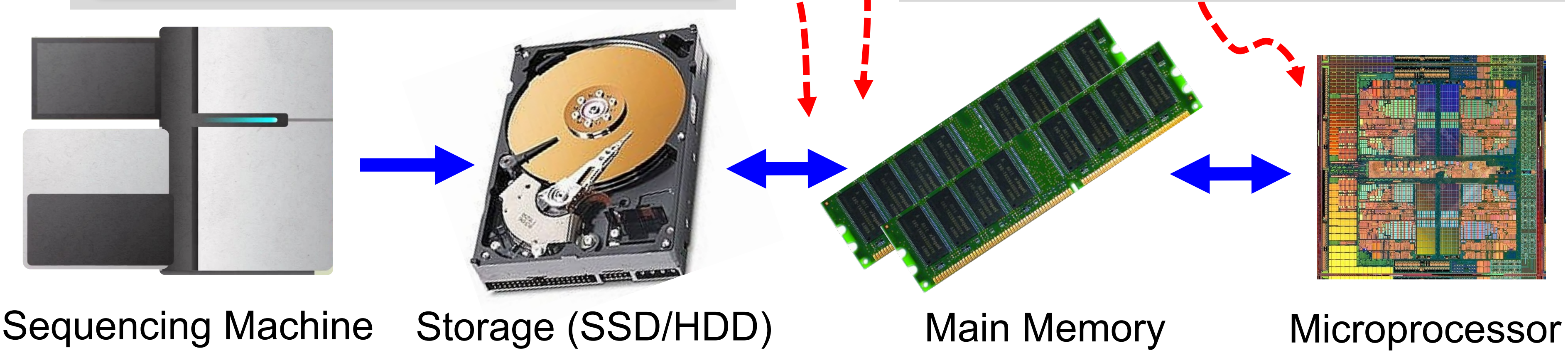
- **GRIM-Filter [BMC Genomics'18]**
- **GenASM [MICRO 2020]**
- **SneakySnake [IEEE Micro'21]**

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]**



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FastHASH

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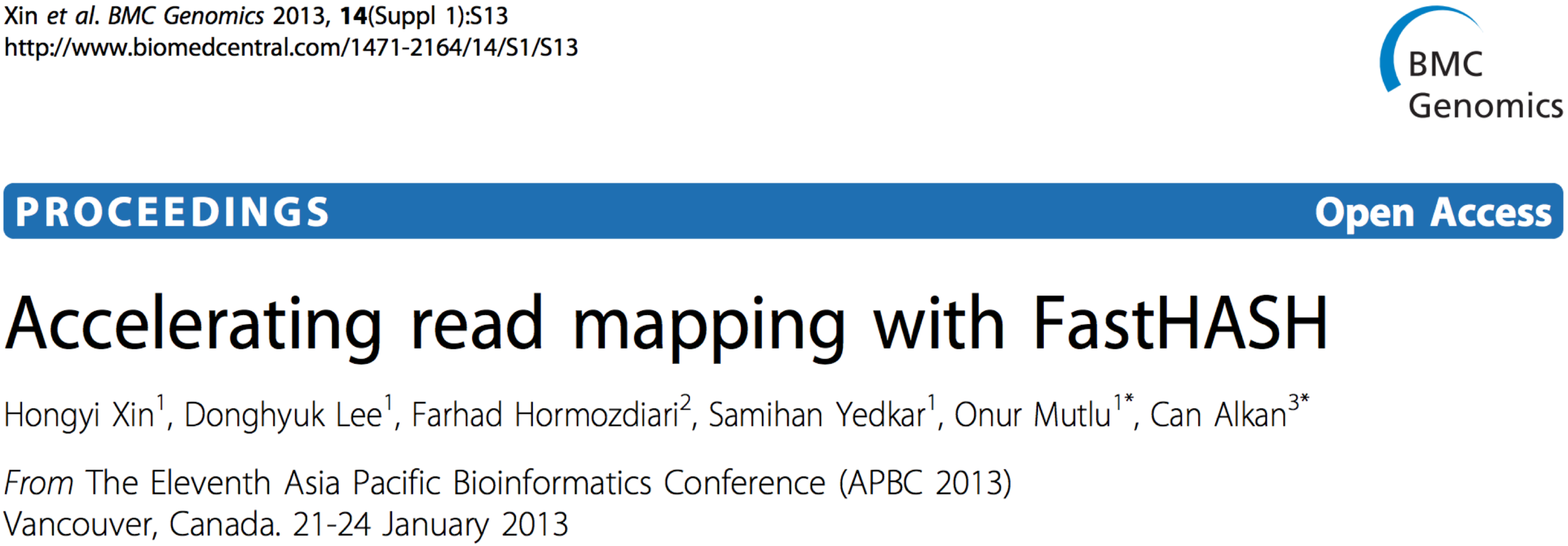


Xin *et al. BMC Genomics* 2013, **14**(Suppl 1):S13
http://www.biomedcentral.com/1471-2164/14/S1/S13

BMC Genomics

PROCEEDINGS Open Access

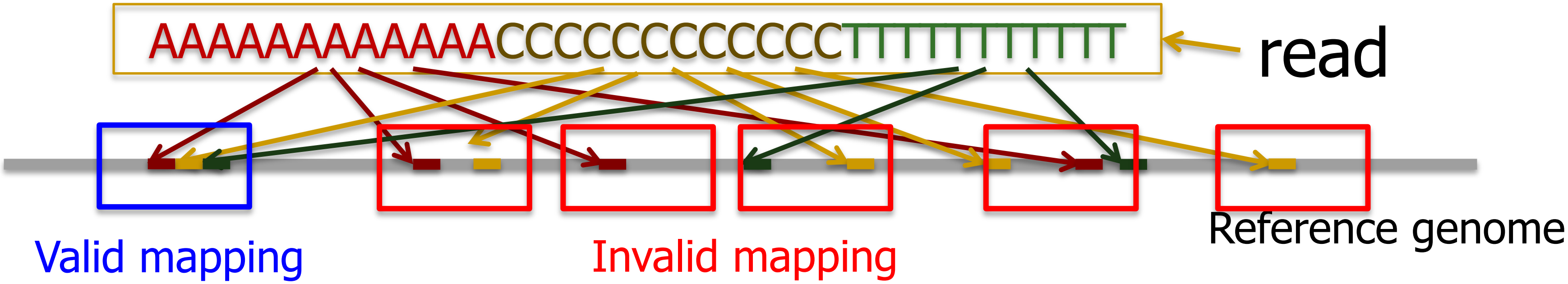
Accelerating read mapping with FastHASH

Hongyi Xin[1], Donghyuk Lee[1], Farhad Hormozdiari[2], Samihan Yedkar[1], Onur Mutlu[1*], Can Alkan[3*]

From The Eleventh Asia Pacific Bioinformatics Conference (APBC 2013)
Vancouver, Canada. 21-24 January 2013

Key Observations

- **Observation 1 (Adjacent k-mers)**
  - **Key insight:** Adjacent k-mers in the read should also be adjacent in the reference genome
  - **Key idea:** 1) sort the location list based on their number of locations and 2) search for adjacent locations in the k-mers' location lists



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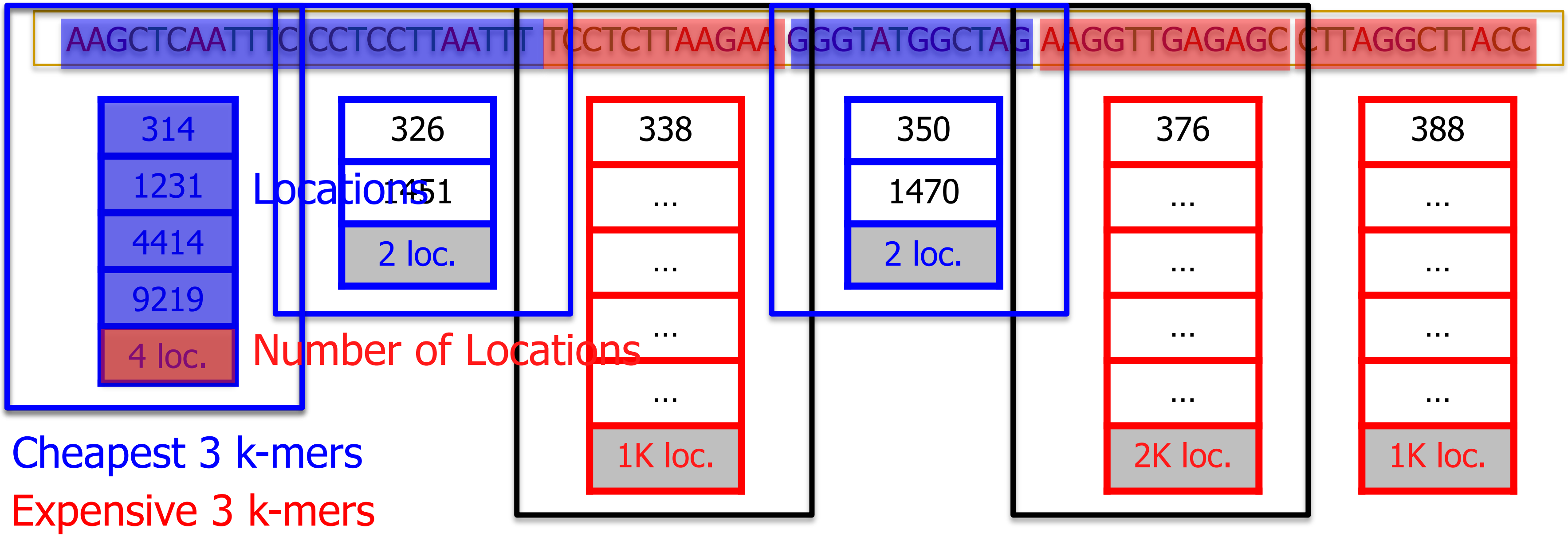
  - **Key insight:** Adjacent k-mers in the read should also be adjacent in the reference genome
  - **Key idea:** 1) sort the location list based on their number of locations and 2) search for adjacent locations in the k-mers' location lists

- **Observation 2 (Cheap k-mers)**
  - **Key insight:** Some k-mers are cheaper to verify than others because they have shorter location lists (they occur less frequently in the reference genome)
  - **Key Idea:** Read mapper can choose the cheapest k-mers and verify their locations

Cheap K-mer Selection

- occurrence threshold = 500



Previous work needs to verify:

3004 locations

FastHASH verifies only:

8 locations

FastHASH Conclusion

- Problem: Existing read mappers perform poorly in mapping billions of short reads to the reference genome, in the presence of errors

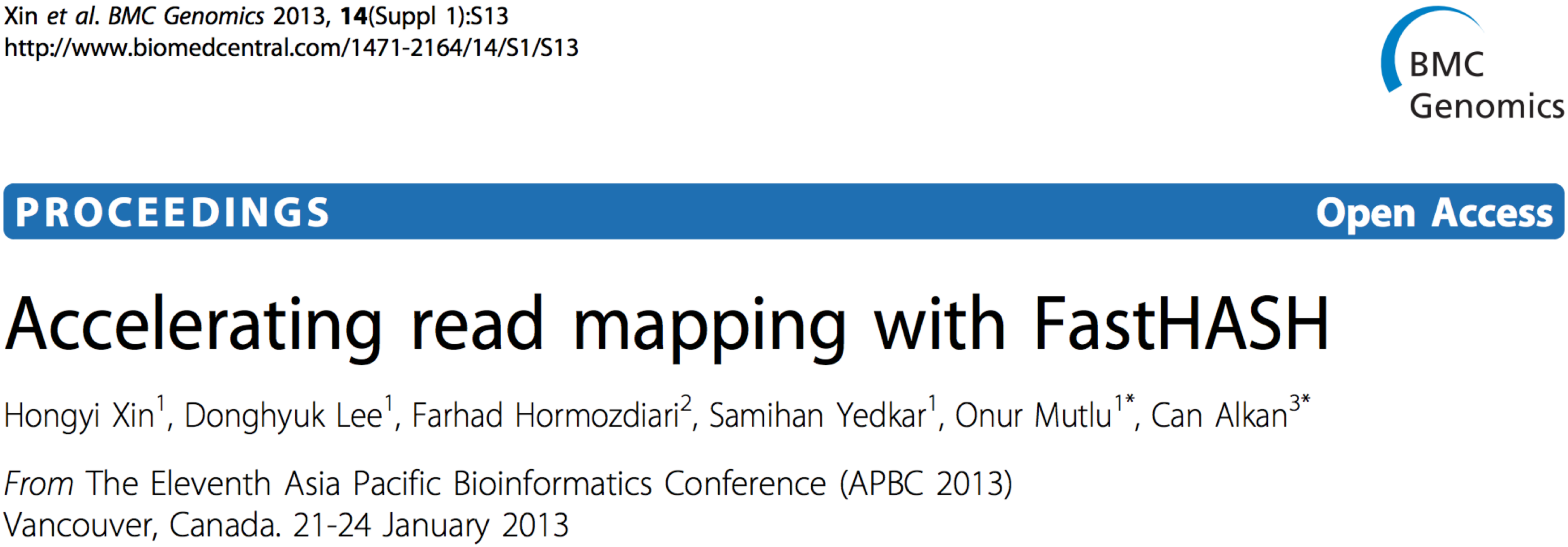
- Observation: Most of the verification calculations are unnecessary → filter them out

- Key Idea: To reduce the cost of unnecessary verification
  - Select Cheap and Adjacent k-mers.

- Key Result: FastHASH obtains up to 19x speedup over the state-of-the-art mapper without losing valid mappings

More on FastHASH

- Download source code and try for yourself
  - Download link to FastHASH



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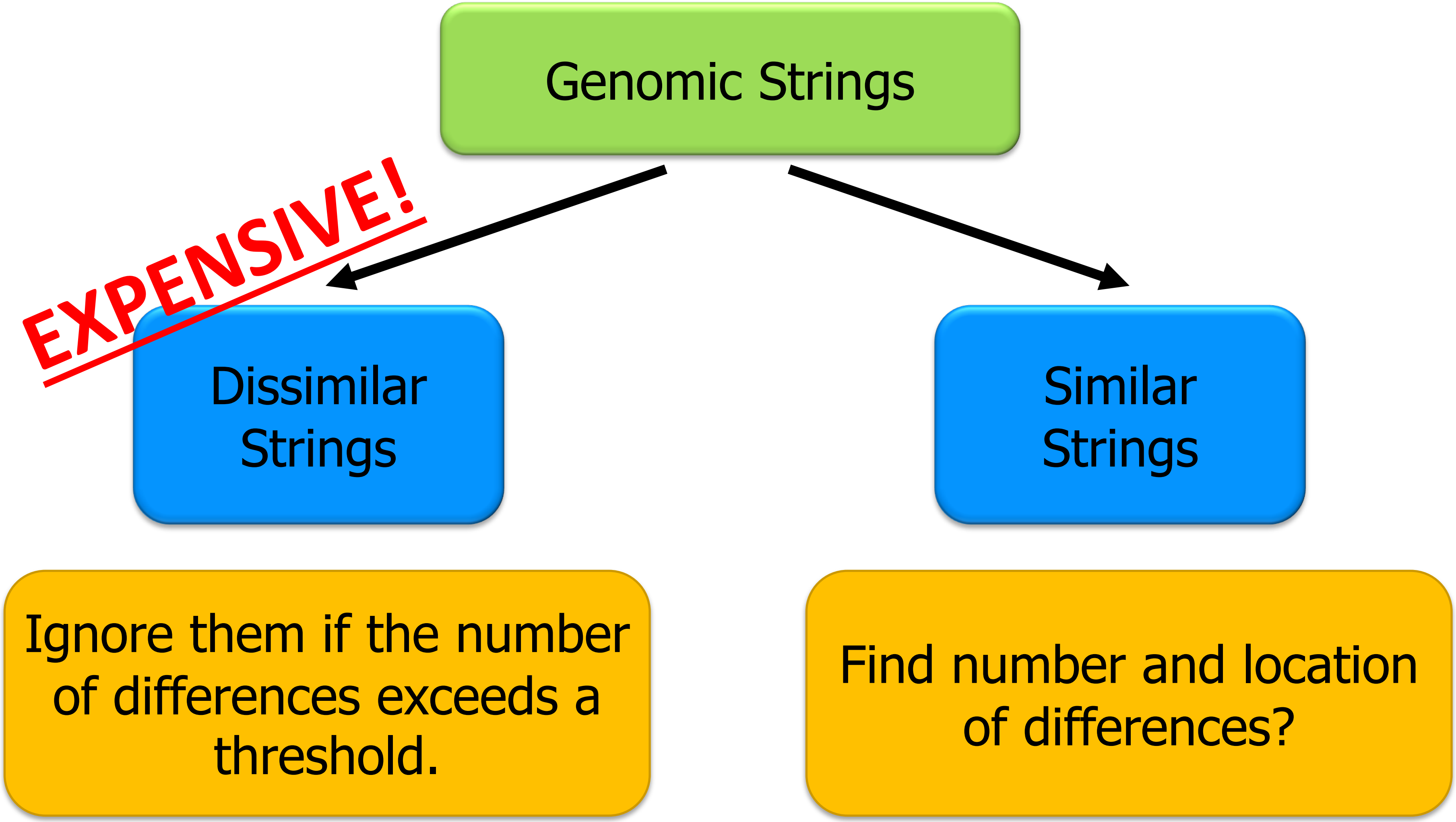
Pre-alignment Filtering Technique

Sequence Alignment is expensive

Our goal is to reduce the need for dynamic programming algorithms

Key Idea



Genomic Strings

EXPENSIVE!

Dissimilar Strings

Similar Strings

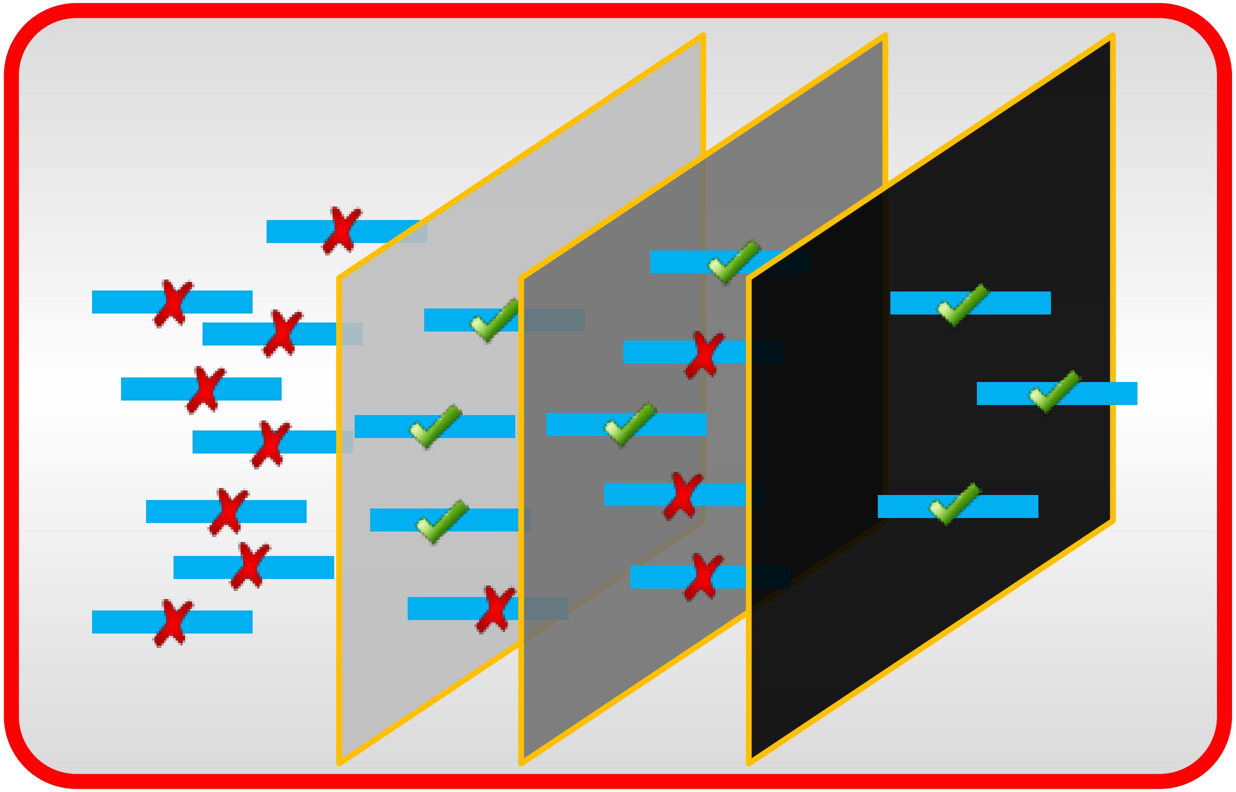
Ignore them if the number of differences exceeds a threshold.

Find number and location of differences?

Ideal Filtering Algorithm

Step 2

Query the Index

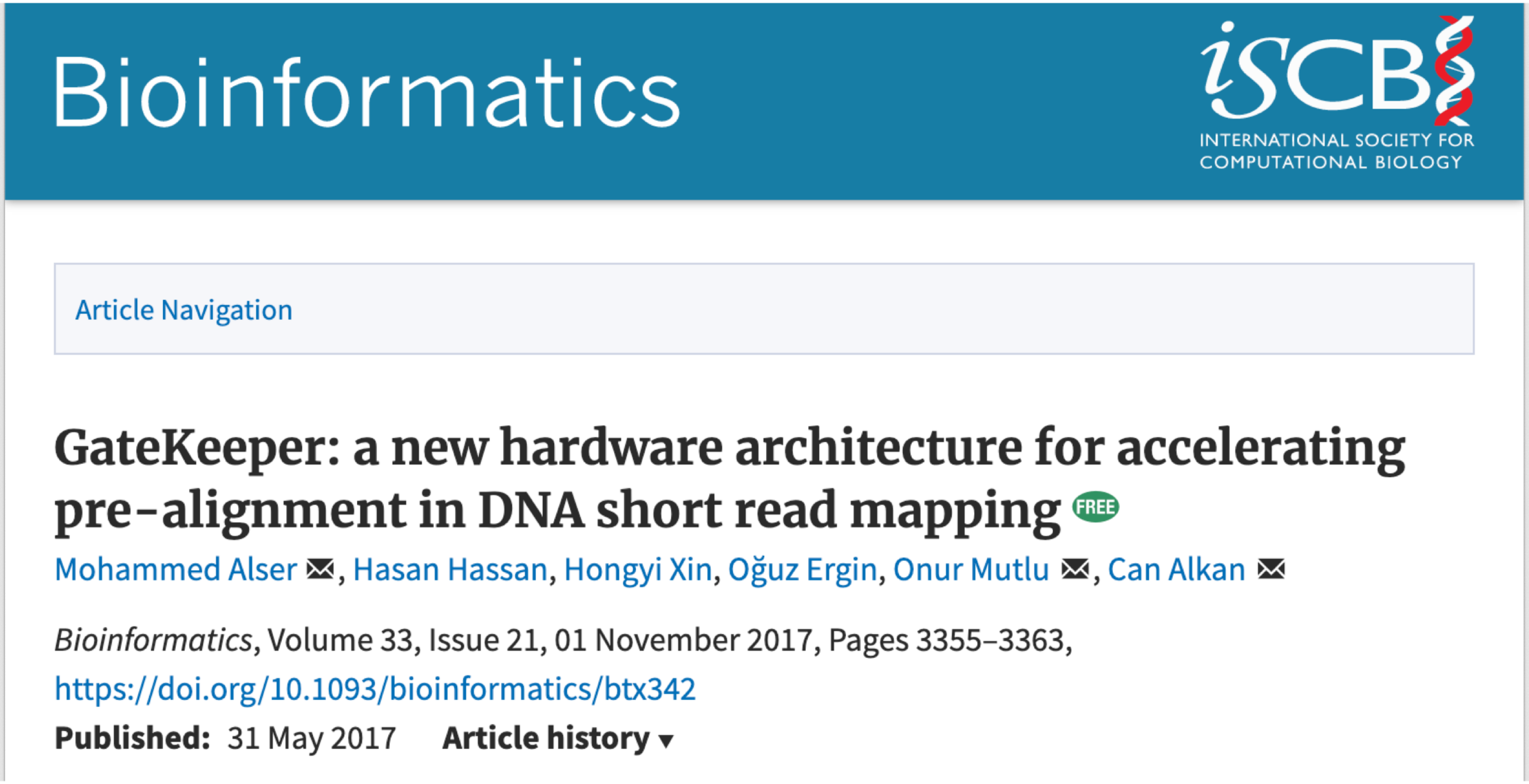


Step 3

Read Alignment

1. Filter out most of incorrect mappings.
2. Preserve all correct mappings.
3. Do it quickly.

GateKeeper



Bioinformatics

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Article Navigation

GateKeeper: a new hardware architecture for accelerating pre-alignment in DNA short read mapping FREE

Mohammed Alser ✉, Hasan Hassan, Hongyi Xin, Oğuz Ergin, Onur Mutlu ✉, Can Alkan ✉

Bioinformatics, Volume 33, Issue 21, 01 November 2017, Pages 3355–3363,
https://doi.org/10.1093/bioinformatics/btx342

Published: 31 May 2017 **Article history** ▾

Alser+, "GateKeeper: A New Hardware Architecture for Accelerating Pre-Alignment in DNA Short Read Mapping", Bioinformatics, 2017.

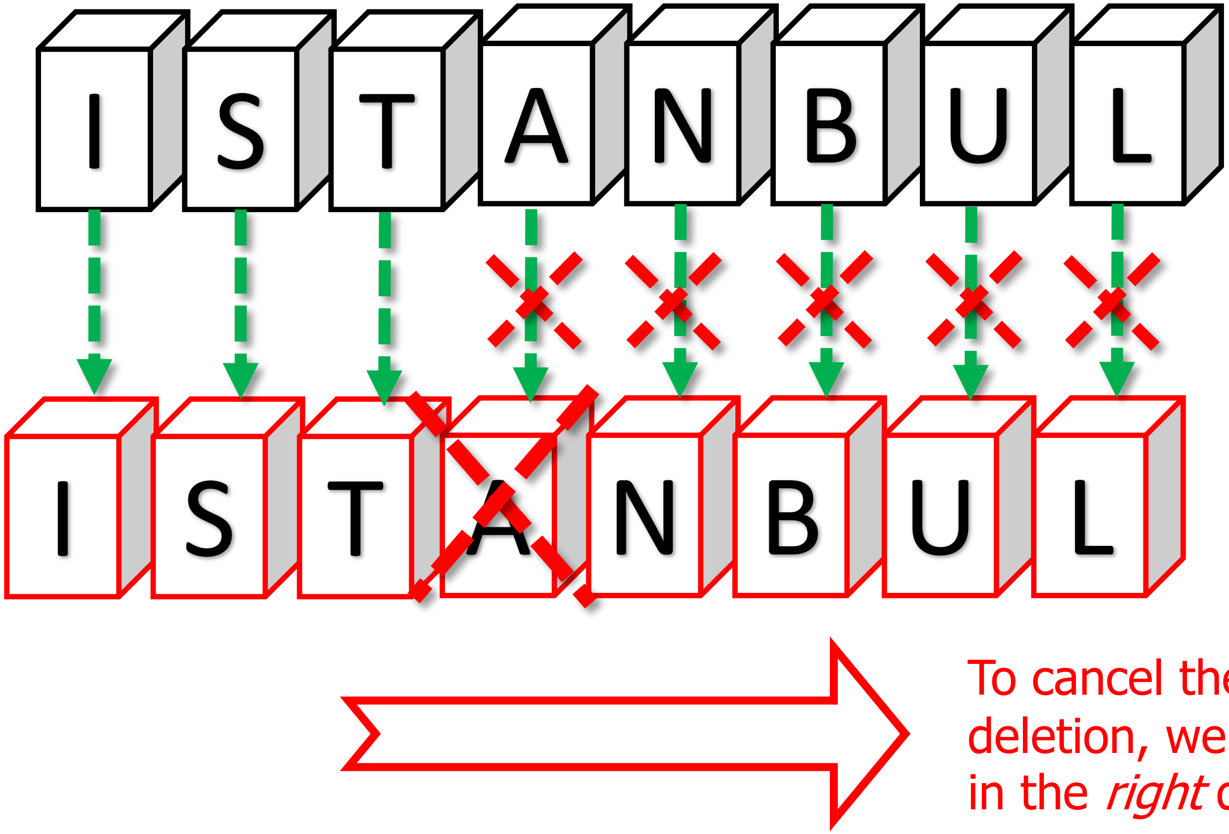
GateKeeper

- **Key observation:**
  - If two strings differ by *E* edits, then every bp match can be aligned in at most 2*E* shifts.
- **Key idea:**
  - Compute "Shifted Hamming Distance": AND of 2*E*+1 Hamming vectors of two strings, to identify invalid mappings
    - Uses *bit-parallel operations* that nicely map to FPGA architectures
- **Key result:**
  - GateKeeper is 90x-130x faster than SHD (Xin et al., 2015) and the Adjacency Filter (Xin et al., 2013), with only a 7% false positive rate
  - The addition of GateKeeper to the mrFAST mapper (Alkan et al., 2009) results in 10x end-to-end speedup in read mapping

Hamming Distance (∑⊕)

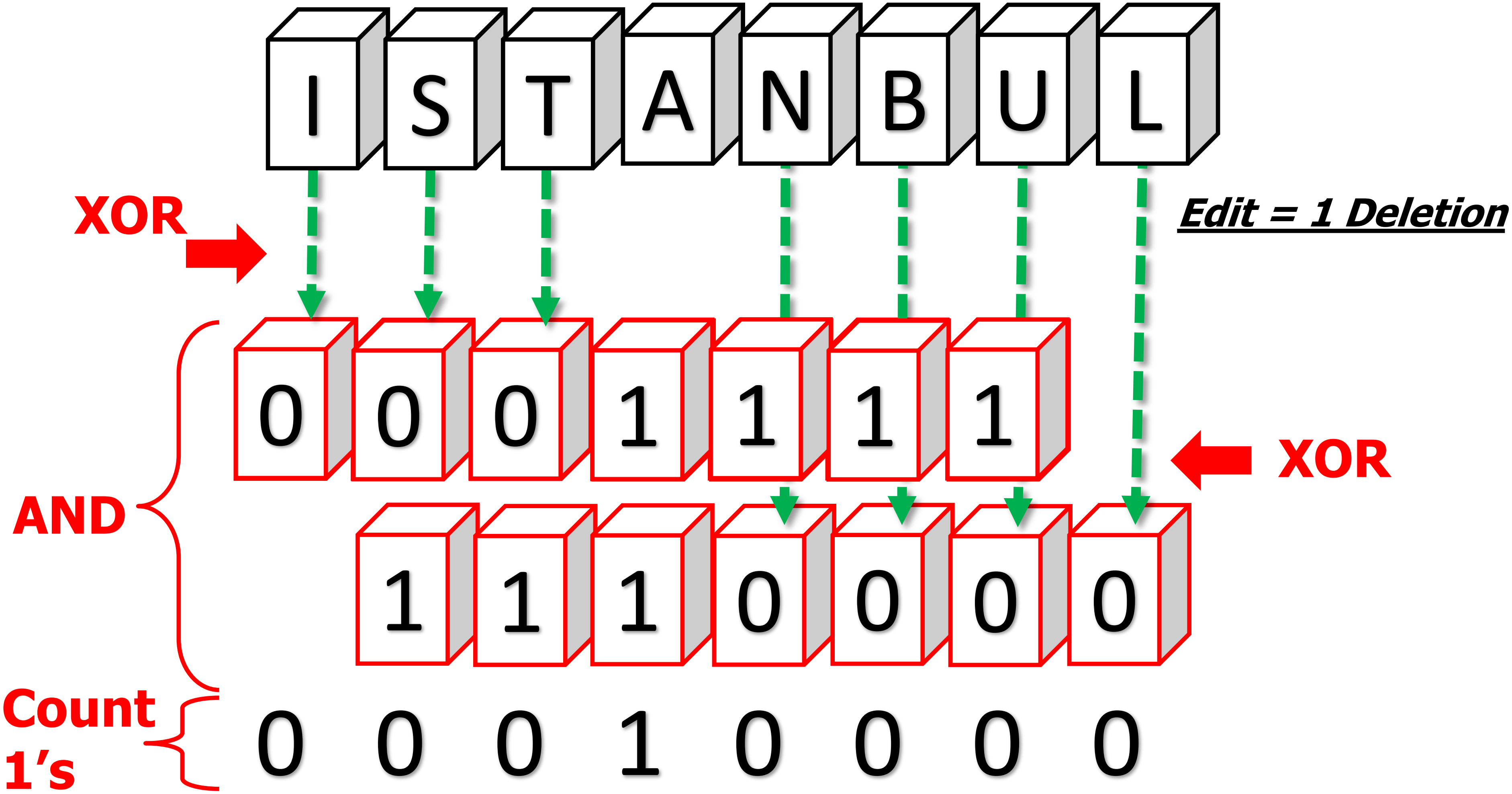
3 matches 5 mismatches

Edit = 1 Deletion



To cancel the effect of a deletion, we need to shift in the *right* direction

Shifted Hamming Distance (Xin+ 2015)



I S T A N B U L

XOR

Edit = 1 Deletion

0 0 0 1 1 1 1

XOR

AND

1 1 1 0 0 0 0

Count 1's

0 0 0 1 0 0 0 0

7 matches 1 mismatches

GateKeeper Walkthrough

Generate 2E+1 masks

Amend random zeros: 101 → 111 & 1001 → 1111

AND all masks, ACCEPT iff number of '1' ≤ Threshold

```
            Query :GAGAGAGATATTTAGTGTTGCAGCACTACAACACAAAAGAGGACCAACTTACGTGTCTAAAAGGGGAACATTGTTGGGCCGGA
        Reference :GAGAGAGATAGTTAGTGTTGCAGCCACTACAACACAAAAGAGGACCAACTTACGTGTCTAAAAGGGGAGACATTGTTGGGCCGG

     Hamming Mask :00000000001000000000000011111110111100011101101011011111111110001000001111011010010101
  1-Deletion Mask :11111111111001111101111100000000000000000000000000000000000000000000011000000000000000
  2-Deletion Mask :00000000101101110011111111111110111100011101101011011111111110001000100111011010010101
  3-Deletion Mask :11111111111011101100110111011101100010010011111111111111100101100110101101110111011111
 1-Insertion Mask :11111111111011111011111101110110001001001111111111111100101100110000101110111011111 0
 2-Insertion Mask :00000010011111001111111110010001101010100110101111111111111111011100111111100011110110 0
 3-Insertion Mask :11111110111011001100011111111101011011111100110010111011111111011101110101011100100 0

         AND Mask :000000000010000000000000100000000000000000000000000000000000000000000000000000000000000
```

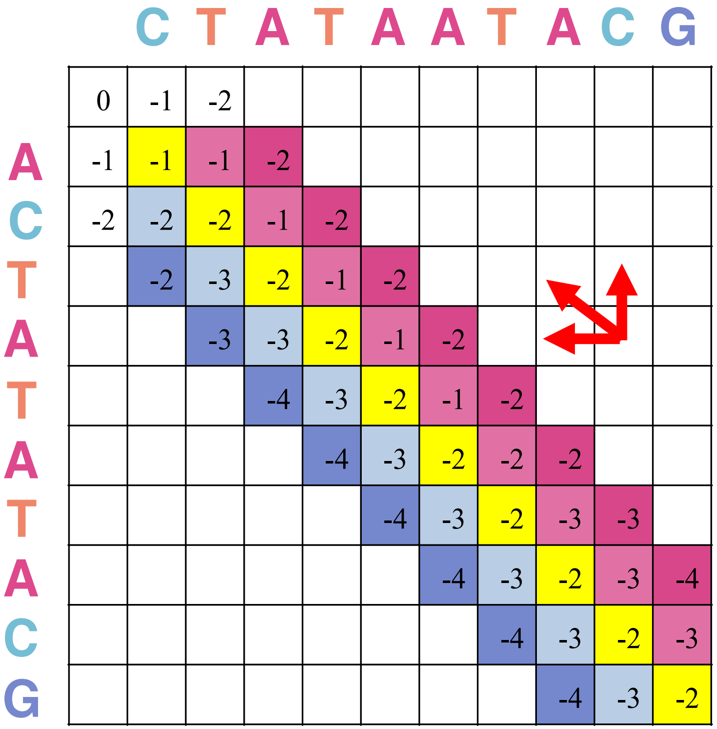
```
1-D                                                                                    .111
2-D                                                                                    0000
3-D                                                                                    .110
1-Ir                                                                                   .111
2-Ir                                                                                   .110
3-Ir                                                                                   .100
                                                                                       .000
                                                                                       0000
```

Our goal to track the diagonally consecutive matches in the neighborhood map.

```
Needleman-Wunsch  GAGAGAGATATTTAGTGTTGCAG-CACTACAACACAAAAGAGGACCAACTTACGTGTCTAAAAGGGGAACATTGTTGGGCCGG
       Alignment :|||||||||| ||||||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||::|||||||||||||||
                  GAGAGAGATAGTTAGTGTTGCAGCCACTACAACACAAAAGAGGACCAACTTACGTGTCTAAAAGGGGAGACATTGTTGGGCCGG
```

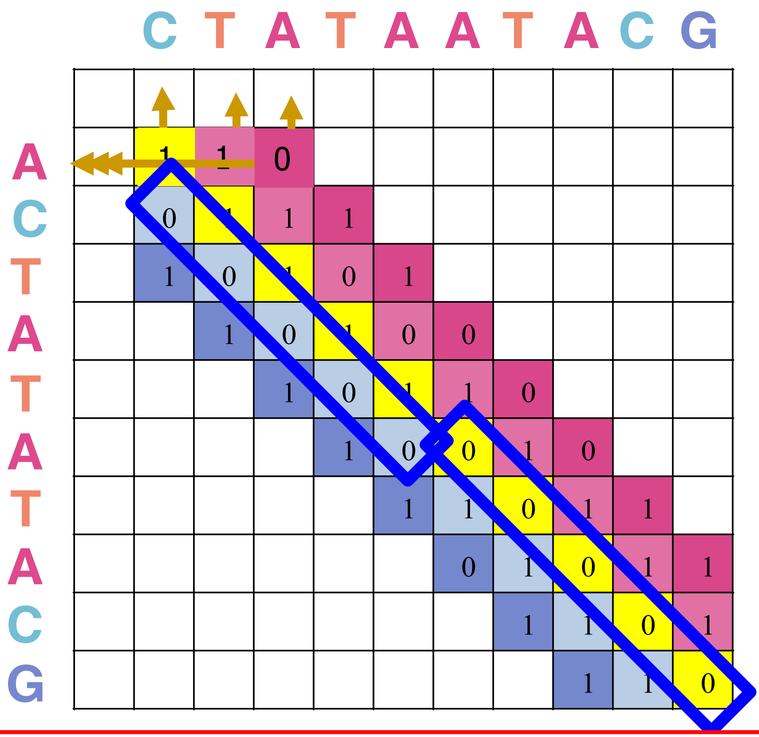
Alignment Matrix vs. Neighborhood Map

Needleman-Wunsch



		C	T	A	T	A	A	T	A	C	G
	0	-1	-2								
A	-1	-1	-1	-2							
C	-2	-2	-2	-1	-2						
T		-2	-3	-2	-1	-2					
A			-3	-3	-2	-1	-2				
T				-4	-3	-2	-1	-2			
A					-4	-3	-2	-2	-2		
T						-4	-3	-2	-3	-3	
A							-4	-3	-2	-3	-4
C								-4	-3	-2	-3
G									-4	-3	-2

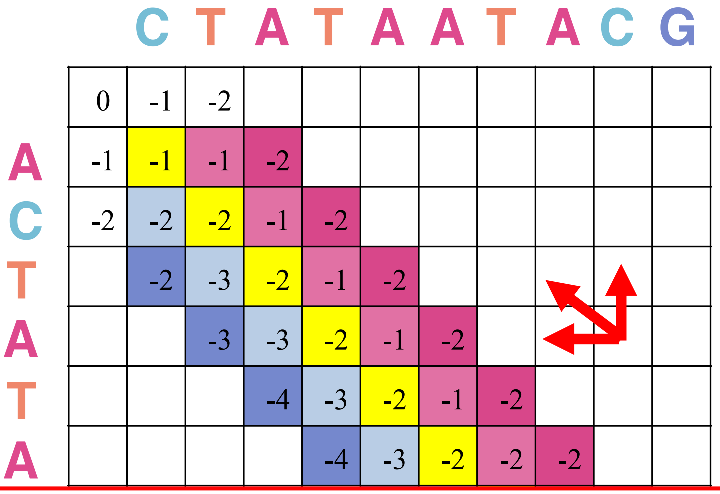
Neighborhood Map



		C	T	A	T	A	A	T	A	C	G
A		1	1	0							
C		0	1	1	1						
T		1	0	1	0	1					
A			1	0	1	0	0				
T				1	0	1	1	0			
A					1	0	0	1	0		
T						1	1	0	1	1	
A							0	1	0	1	1
C								1	1	0	1
G									1	1	0

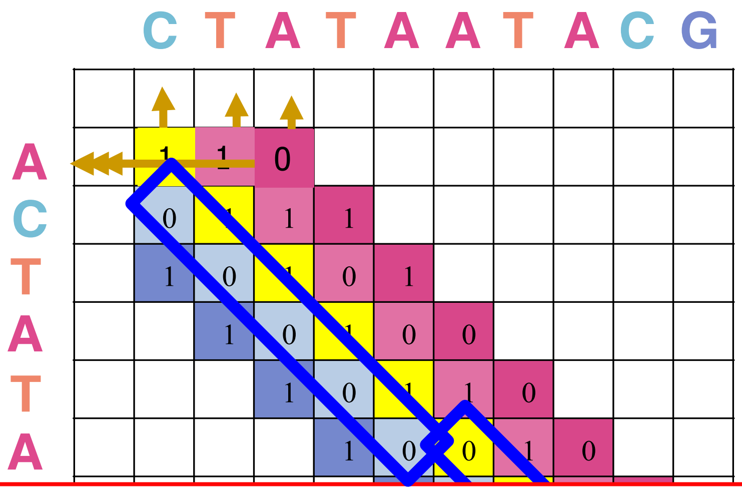
Our goal to track the diagonally consecutive matches in the neighborhood map.

Alignment Matrix vs. Neighborhood Map



Needleman-Wunsch

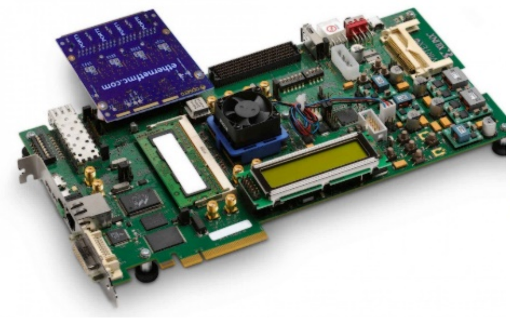
		C	T	A	T	A	A	T	A	C	G
	0	-1	-2								
A	-1	-1	-1	-2							
C	-2	-2	-2	-1	-2						
T		-2	-3	-2	-1	-2					
A			-3	-3	-2	-1	-2				
T				-4	-3	-2	-1	-2			
A					-4	-3	-2	-2	-2		

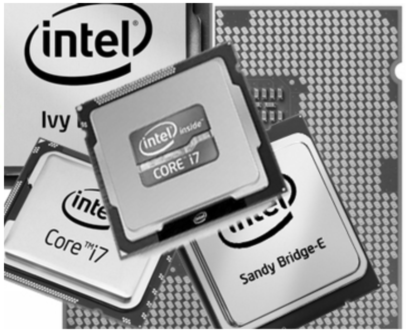


Neighborhood Map

		C	T	A	T	A	A	T	A	C	G
A		1	1	0							
C		0	1	1	1						
T		1	0	1	0	1					
A			1	0	1	0	0				
T				1	0	1	1	0			
A					1	0	0	1	0		

Independent vectors can be processed in parallel using hardware technologies





Our Solution: GateKeeper

Alignment Filter

+

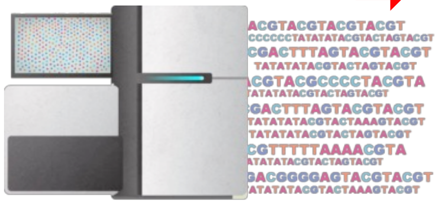
=

1^{st}

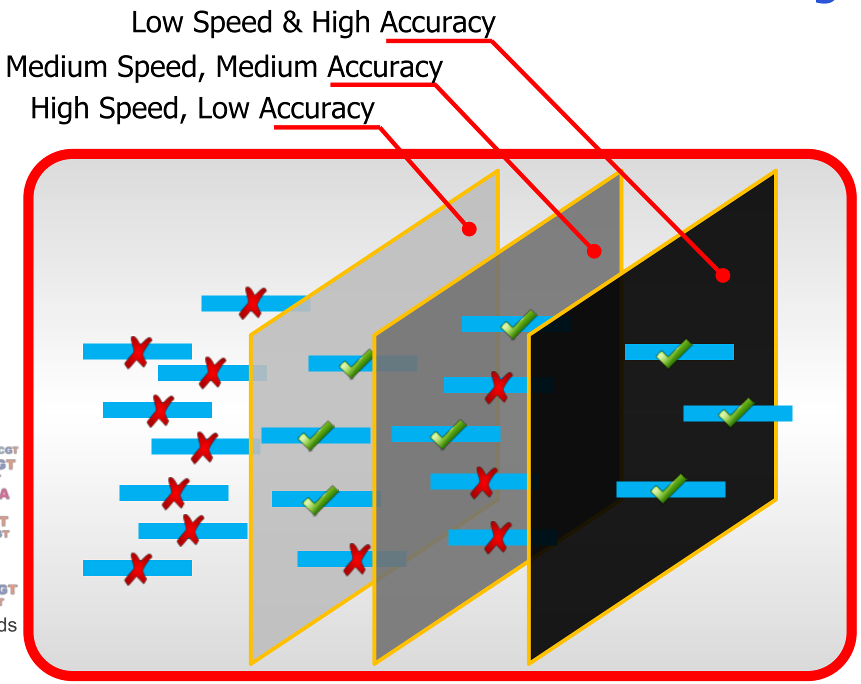
FPGA-based Alignment Filter.

$x10^{12}$

mappings



Billions of Short Reads



Low Speed & High Accuracy

Medium Speed, Medium Accuracy

High Speed, Low Accuracy

$x10^{3}$

mappings

		C	T	A	T	A	A	T	A	C	G
C	0	1	2								
A	1	0	1	2							
C	2	1	0	1	2						
T		2	1	0	1	2					
A			2	1	2	1	2				
T				2	2	2	1	2			
A					3	2	2	2	2		
T						3	3	3	2	3	
A							4	3	3	2	3
C								4	4	3	2
G									5	4	3

1 **High throughput DNA sequencing (HTS) technologies**

2 **Read Pre-Alignment Filtering**
Fast & Low False Positive Rate

3 **Read Alignment**
Slow & Zero False Positives

GateKeeper Walkthrough (cont'd)

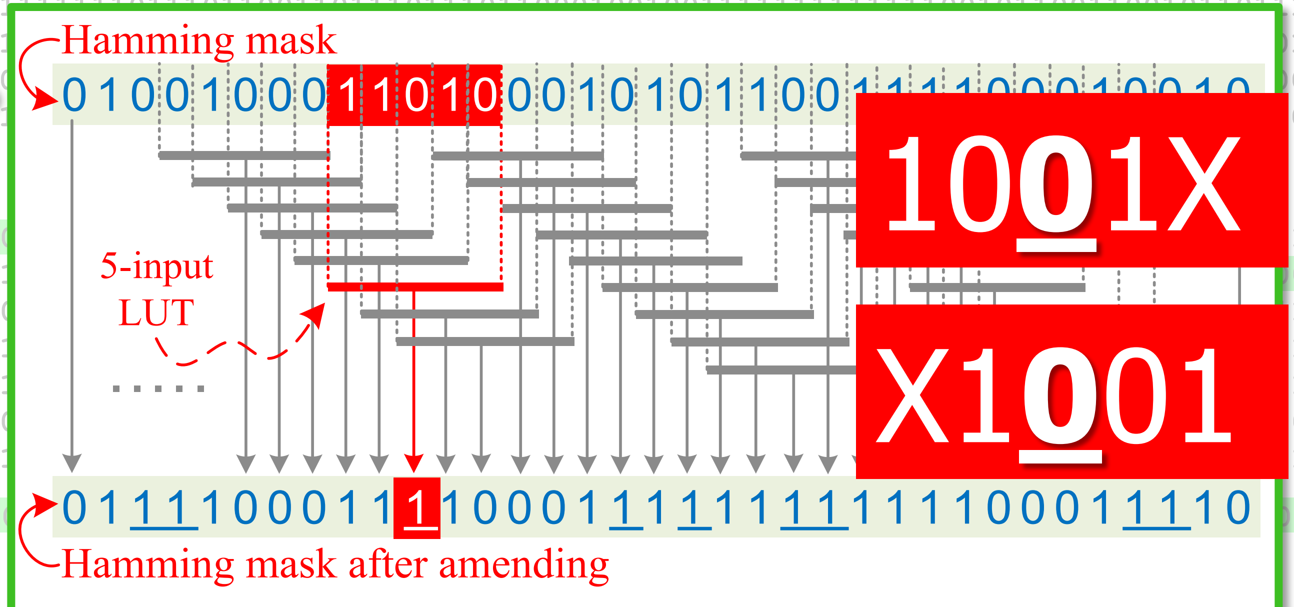
Generate 2E+1 masks

Amend random zeros: 101 → 111 & 1001 → 1111

AND all masks, ACCEPT iff number of '1' ≤ Threshold

- E right-shift registers (length=ReadLength)
- E left-shift registers (length=ReadLength)
- (2E+1) * (ReadLength) 2-XOR operations.

- (2E)*(ReadLength) 2-AND operations.
- (ReadLength/4) 5-input LUT.
- log_2ReadLength-bit counter.



- (2E+1)*(ReadLength) 5-input LUT.

Virtex-7 FPGA Layout

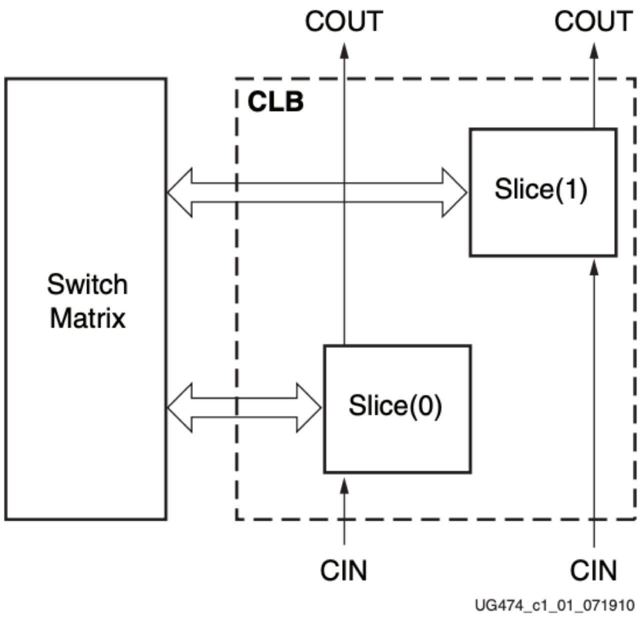
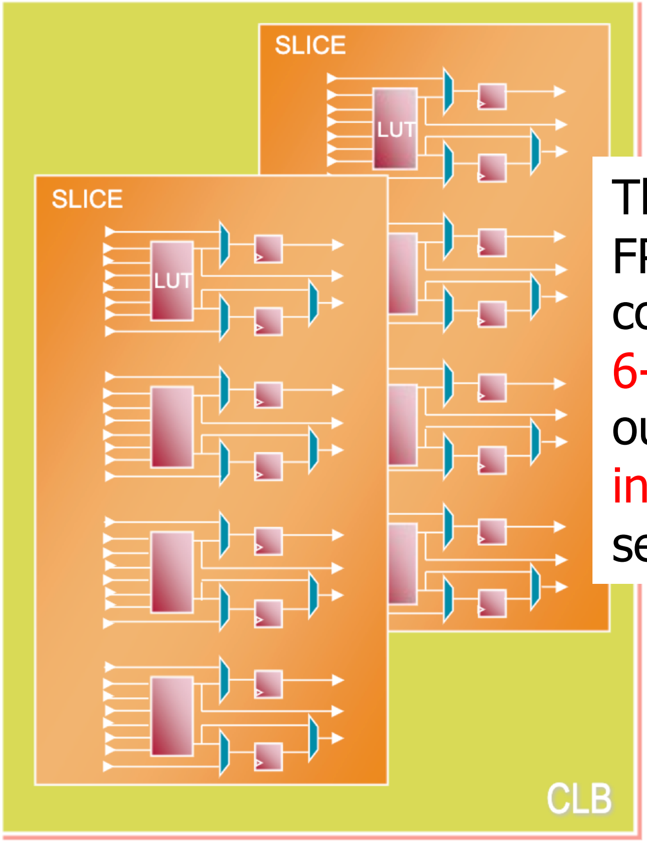


Figure 1-1: **Arrangement of Slices within the CLB**



The LUTs in 7 series FPGAs can be configured as either a 6-input LUT with one output, or as two 5-input LUTs with separate outputs

Table 2-1: **Logic Resources in One CLB**

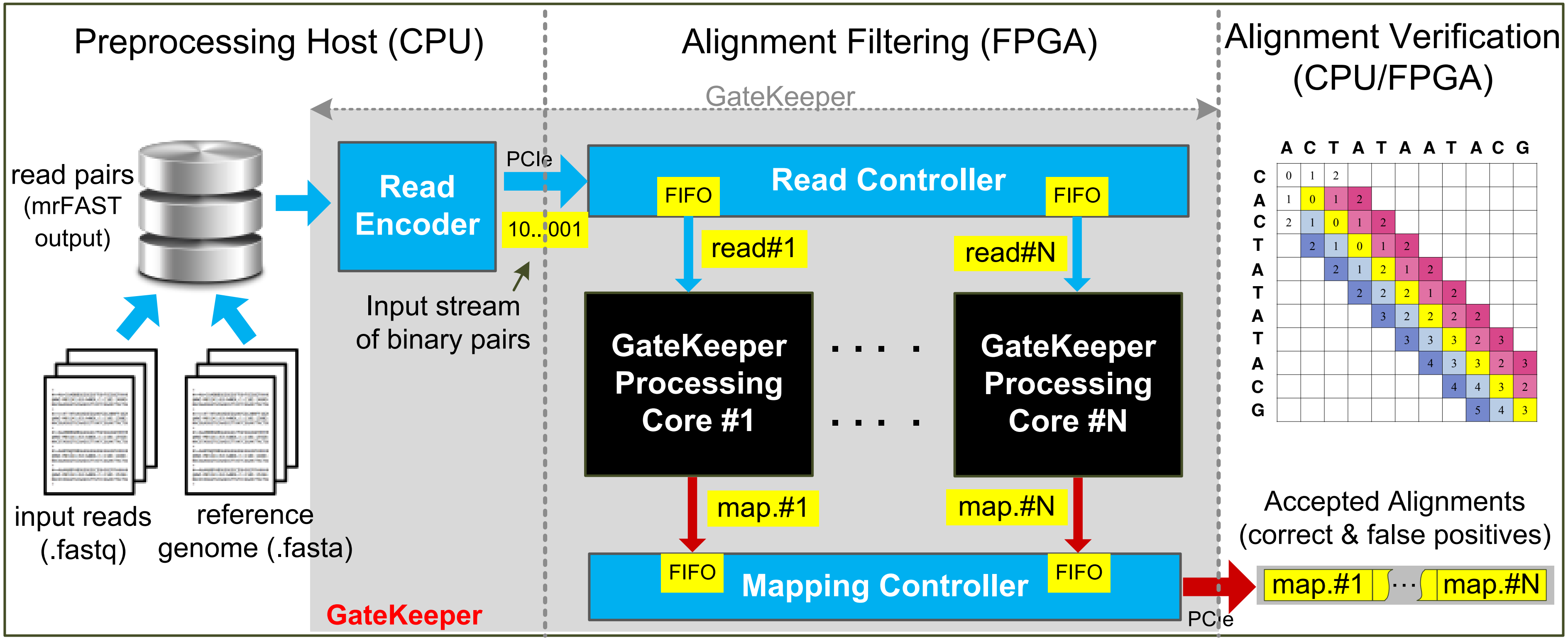
Slices	LUTs	Flip-Flops	Arithmetic and Carry Chains	Distributed RAM[1]	Shift Registers[1]
2	8	16	2	256 bits	128 bits

SAFARI

"7 Series FPGAs Configurable Logic Block", User Guide, Xilinx 2016

GateKeeper Accelerator Architecture

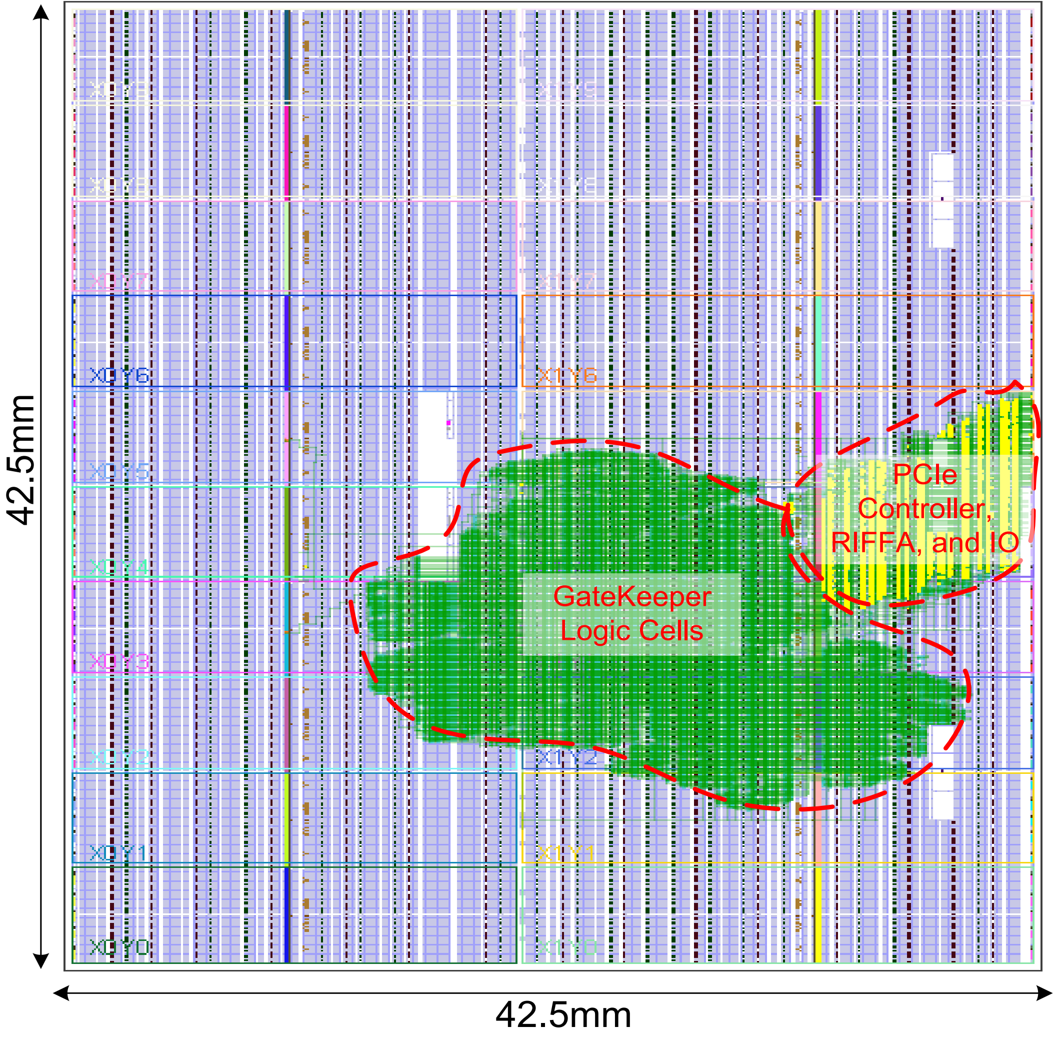
- **Maximum data throughput** =~13.3 billion bases/sec
- Can examine **8 (300 bp) or 16 (100 bp) mappings concurrently** at 250 MHz
- **Occupies 50%** (100 bp) to **91%** (300 bp) of the FPGA slice LUTs and registers


Preprocessing Host (CPU)
Alignment Filtering (FPGA)
Alignment Verification (CPU/FPGA)
GateKeeper
read pairs (mrFAST output)
input reads (.fastq)
reference genome (.fasta)
Read Encoder
PCIe
10...001
Input stream of binary pairs
Read Controller
FIFO
FIFO
read#1
read#N
GateKeeper Processing Core #1
. . . .
GateKeeper Processing Core #N
map.#1
map.#N
FIFO
FIFO
Mapping Controller
PCIe
GateKeeper
Accepted Alignments (correct & false positives)
map.#1
map.#N

	A	C	T	A	T	A	A	T	A	C	G
C	0	1	2								
A	1	0	1	2							
C	2	1	0	1	2						
T		2	1	0	1	2					
A			2	1	2	1	2				
T				2	2	2	1	2			
A					3	2	2	2	2		
T						3	3	3	2	3	
A							4	3	3	2	3
C								4	4	3	2
G									5	4	3

FPGA Chip Layout

GateKeeper: 17.6%, PCIe Controller, RIFFA, and IO: 5%



300 bp

E=15

GateKeeper: Speed & Accuracy Results

90x-130x faster filter

than SHD (Xin et al., 2015) and the Adjacency Filter (Xin et al., 2013)

4x lower false accept rate

than the Adjacency Filter (Xin et al., 2013)

10x speedup in read mapping

with the addition of GateKeeper to the mrFAST mapper (Alkan et al., 2009)

Freely available online

github.com/BilkentCompGen/GateKeeper

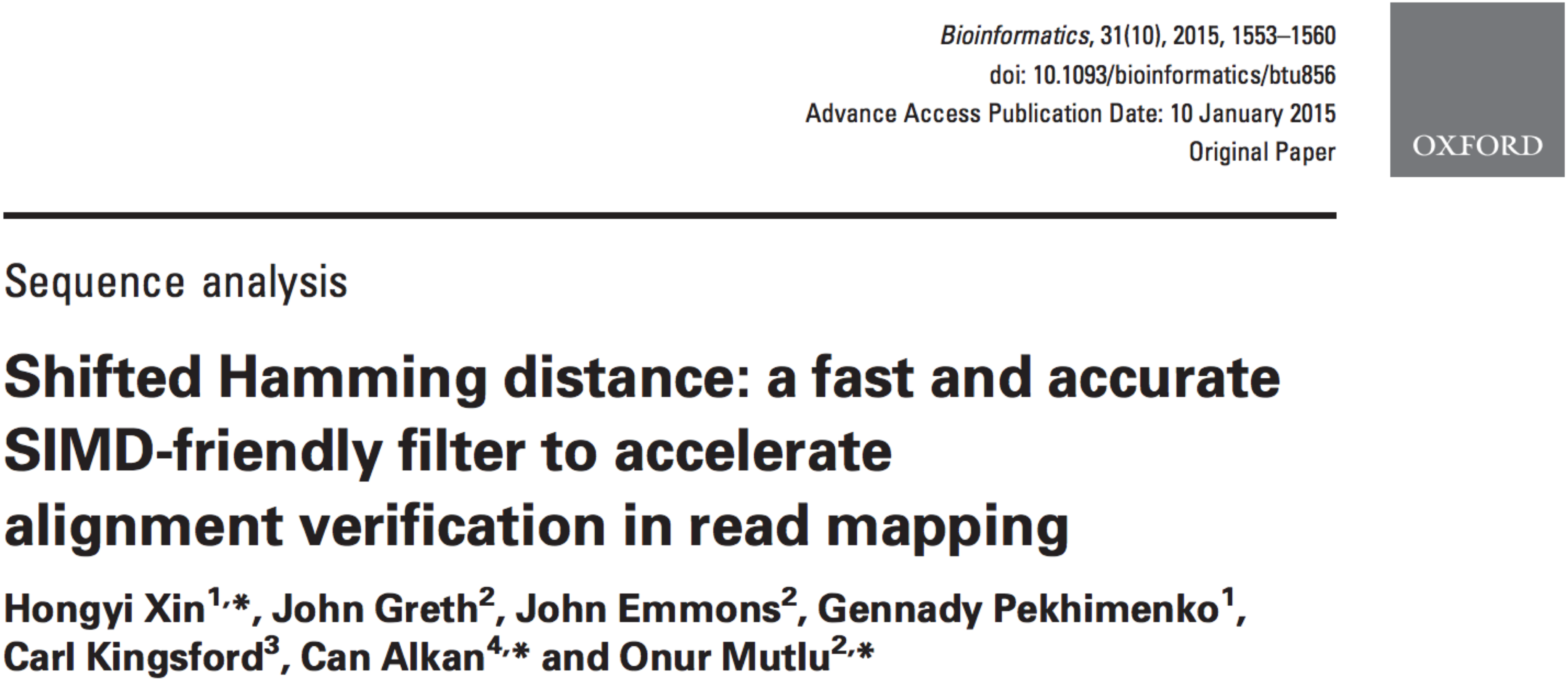
GateKeeper Conclusions

- FPGA-based pre-alignment greatly speeds up read mapping
  - 10x speedup of a state-of-the-art mapper (mrFAST)

- FPGA-based pre-alignment can be integrated with the sequencer
  - It can help to hide the complexity and details of the FPGA
  - Enables real-time filtering while sequencing

More on SHD (SIMD Implementation)

- Download and test for yourself
- https://github.com/CMU-SAFARI/Shifted-Hamming-Distance



Bioinformatics, 31(10), 2015, 1553–1560
doi: 10.1093/bioinformatics/btu856
Advance Access Publication Date: 10 January 2015
Original Paper

OXFORD

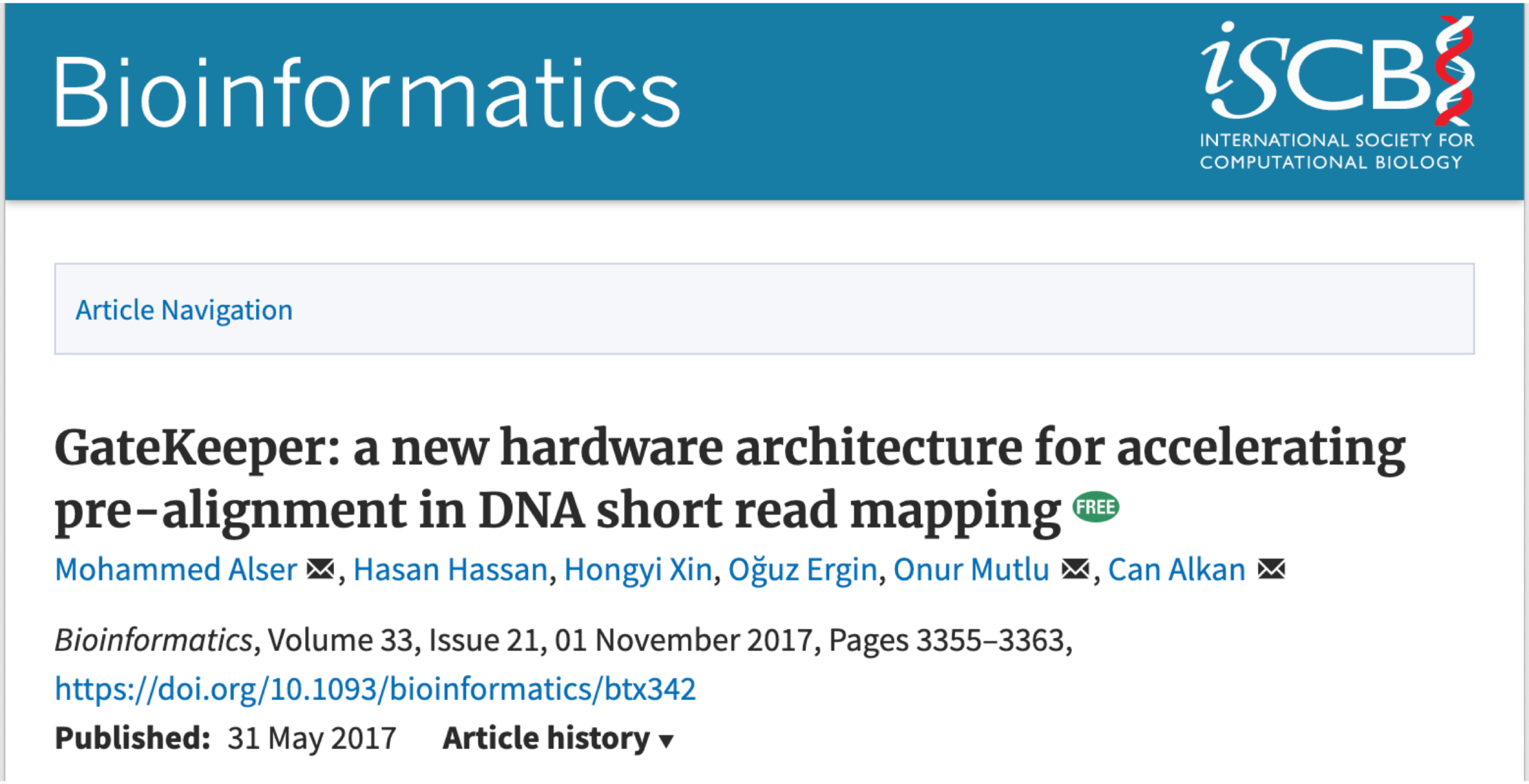
Sequence analysis

Shifted Hamming distance: a fast and accurate SIMD-friendly filter to accelerate alignment verification in read mapping

Hongyi Xin[1,*], John Greth[2], John Emmons[2], Gennady Pekhimenko[1], Carl Kingsford[3], Can Alkan[4,*] and Onur Mutlu[2,*]

More on GateKeeper

- Download and test for yourself https://github.com/BilkentCompGen/GateKeeper



Bioinformatics

GateKeeper: a new hardware architecture for accelerating pre-alignment in DNA short read mapping FREE

Mohammed Alser ✉, Hasan Hassan, Hongyi Xin, Oğuz Ergin, Onur Mutlu ✉, Can Alkan ✉

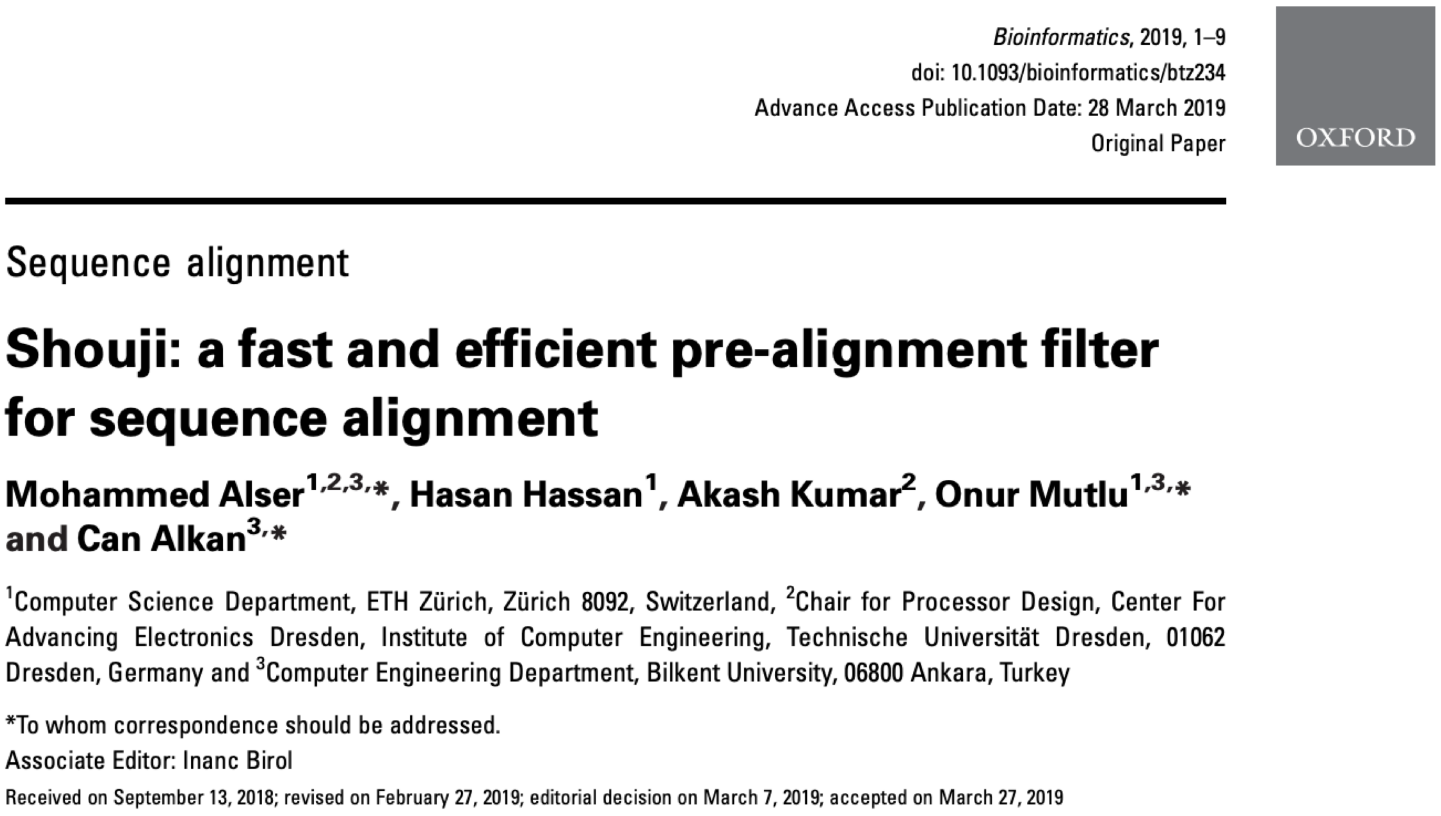
Bioinformatics, Volume 33, Issue 21, 01 November 2017, Pages 3355–3363, https://doi.org/10.1093/bioinformatics/btx342

Published: 31 May 2017 **Article history ▾**

Alser+, "GateKeeper: A New Hardware Architecture for Accelerating Pre-Alignment in DNA Short Read Mapping", Bioinformatics, 2017.

Can we do better? Scalability?

Shouji (障子)



Bioinformatics, 2019, 1–9
doi: 10.1093/bioinformatics/btz234
Advance Access Publication Date: 28 March 2019
Original Paper

Sequence alignment

Shouji: a fast and efficient pre-alignment filter for sequence alignment

Mohammed Alser[1,2,3,*], Hasan Hassan[1], Akash Kumar[2], Onur Mutlu[1,3,*] and Can Alkan[3,*]

[1]Computer Science Department, ETH Zürich, Zürich 8092, Switzerland, [2]Chair for Processor Design, Center For Advancing Electronics Dresden, Institute of Computer Engineering, Technische Universität Dresden, 01062 Dresden, Germany and [3]Computer Engineering Department, Bilkent University, 06800 Ankara, Turkey

*To whom correspondence should be addressed.

Associate Editor: Inanc Birol

Received on September 13, 2018; revised on February 27, 2019; editorial decision on March 7, 2019; accepted on March 27, 2019

Alser+, "Shouji: a fast and efficient pre-alignment filter for sequence alignment", *Bioinformatics* 2019, https://doi.org/10.1093/bioinformatics/btz234

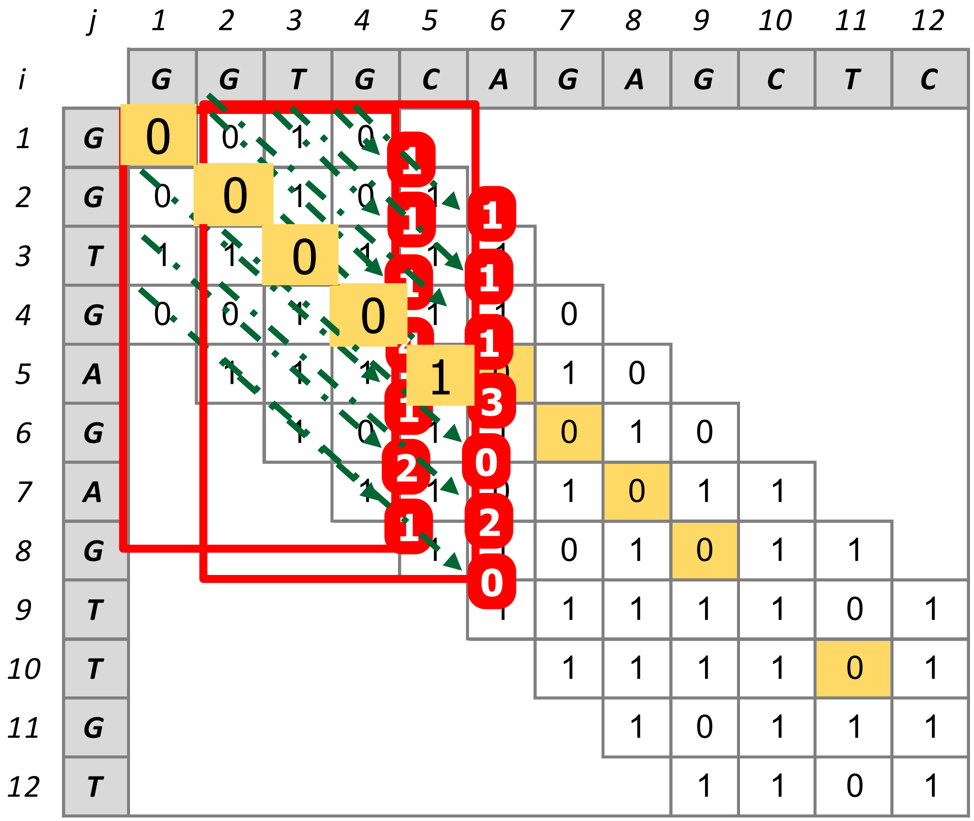
Shouji

- **Key observation:**
  - Correct alignment always includes long identical subsequences.
  - Processing the entire mapping at once is ineffective for hardware design.
- **Key idea:**
  - Use **overlapping** sliding window approach to quickly and accurately find all long segments of consecutive zeros.
- **Key result:**
  - Shouji on FPGA is up to three orders of magnitude faster than its CPU implementation.
  - Shouji accelerates **best-performing CPU read aligner** Edlib (Bioinformatics 2017) by up to 18.8x using 16 filtering units that work in parallel.
  - Shouji is 2.4x to 467x more accurate than GateKeeper (Bioinformatics 2017) and SHD (Bioinformatics 2015).

Shouji Walkthrough

Building the Neighborhood Map

Finding all common subsequences (diagonal segments of consecutive zeros) shared between two given sequences.



Storing it @ Shouji Bit-vector

0	0	0	0	**1**	0	0	0	0	**1**	0	**1**

ACCEPT iff number of '1' ≤ Threshold

Shouji: a fast and efficient pre-alignment filter for sequence alignment, *Bioinformatics* 2019, https://doi.org/10.1093/bioinformatics/btz234

Shouji Walkthrough

Building the Nei[illegible]

	j	1	2	3	4	5	6	7	8	9	10	11	12
i		G	G	T	G	C	A	G	A	G	C	T	C
1	G	0	0	1	0								
2	G	0	0	1	0	1							
3	T	1	1	0	1	1	1						
4	G	0	0	1	0	1	1	0					
5	A		1	1	1	1	0	1	0				
6	G			1	0	1	1	0	1	0			
7	A				1	1	0	1	0	1	1		
8	G					1	1	0	1	0	1	1	
9	T						1	1	1	1	1	0	1
10	T							1	1	1	1	0	1
11	G								1	0	1	1	1
12	T									1	1	0	1

Storing it @ [illegible] vector

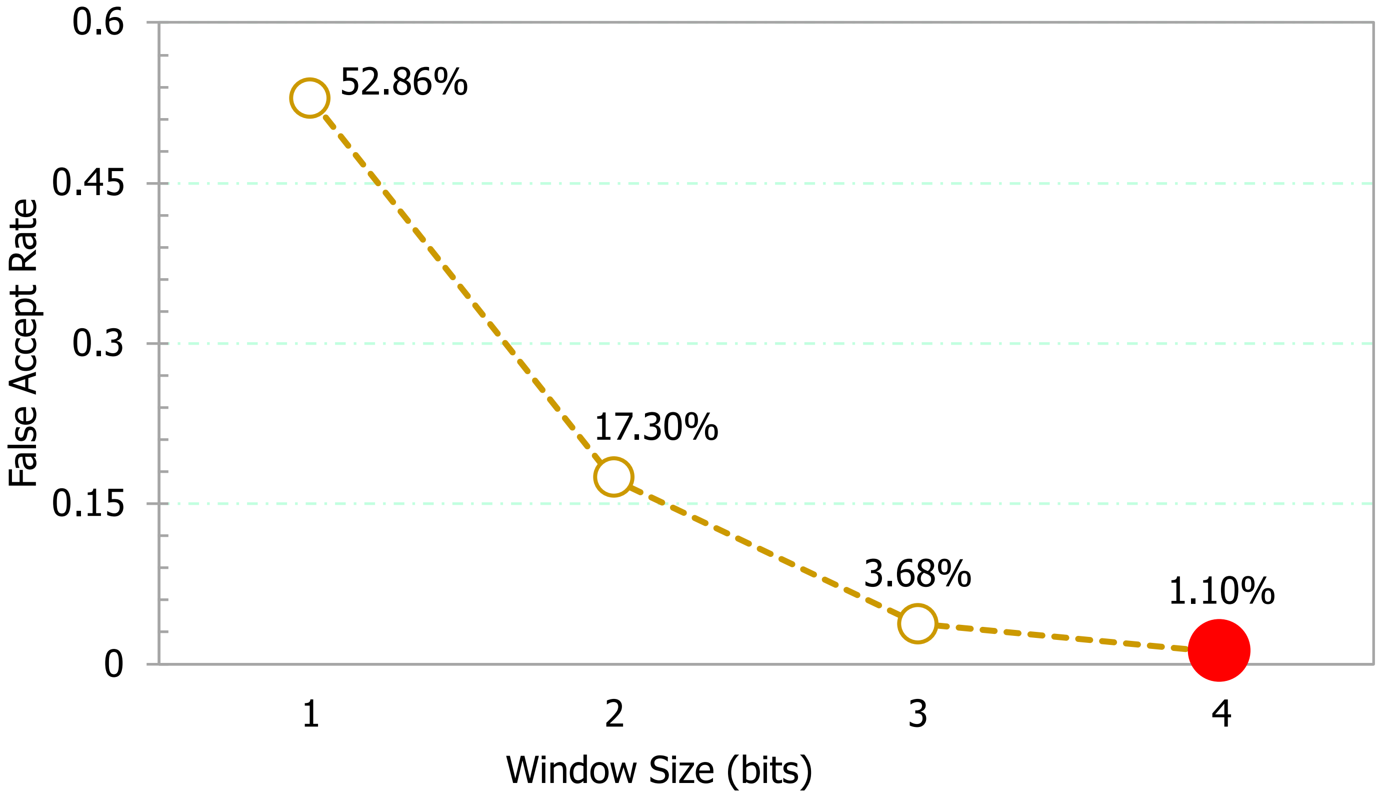
0	0	0	0	**1**	0	0	0	0	**1**	0	**1**

ACCEPT iff number of '1' ≤ Threshold

Shouji: a fast and efficient pre-alignment filter for sequence alignment, *Bioinformatics* 2019, https://doi.org/10.1093/bioinformatics/btz234

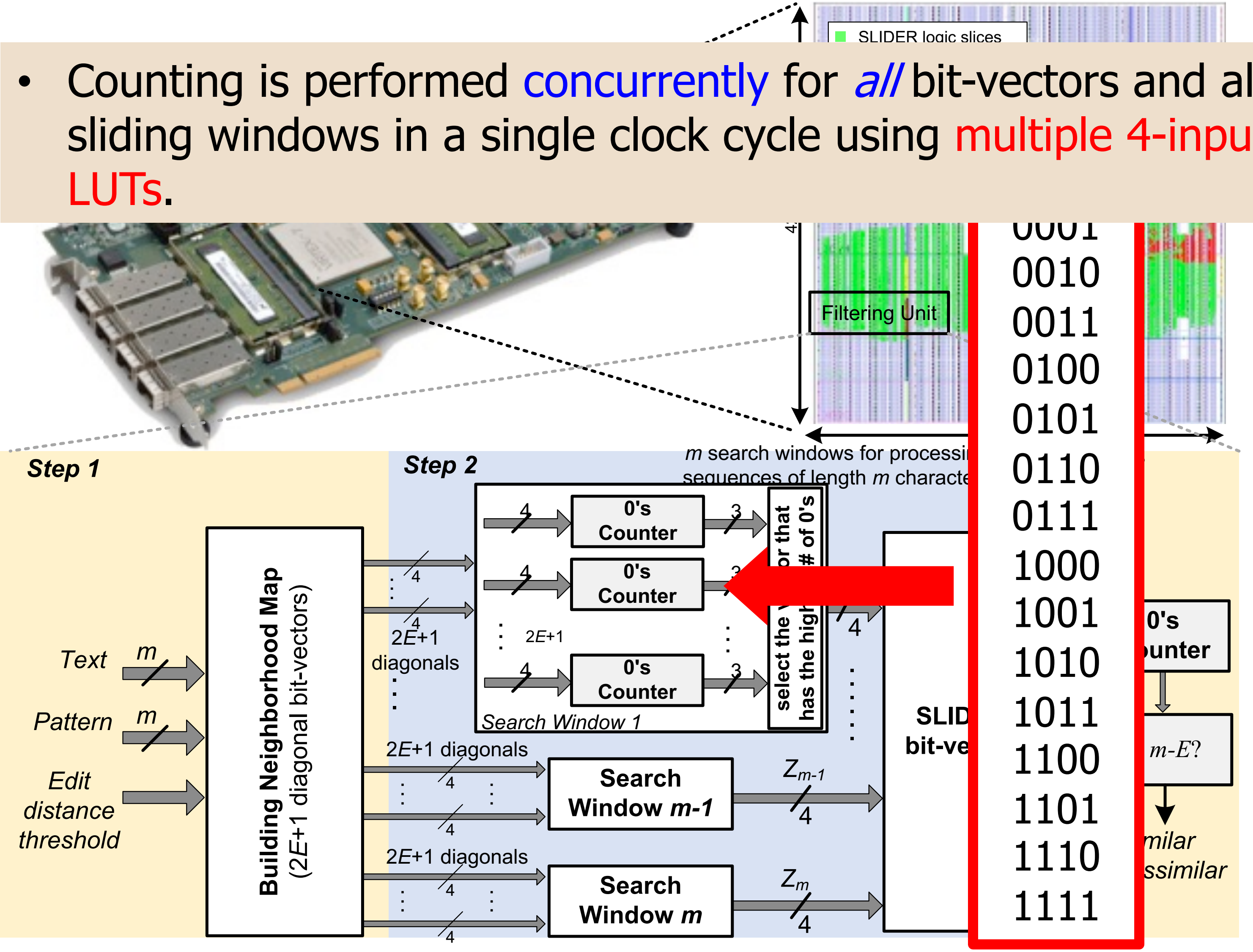
Sliding Window Size

- The reason behind the selection of the window size is due to the minimal possible length of the identical subsequence that is a single match (e.g., such as `101').



Hardware Implementation

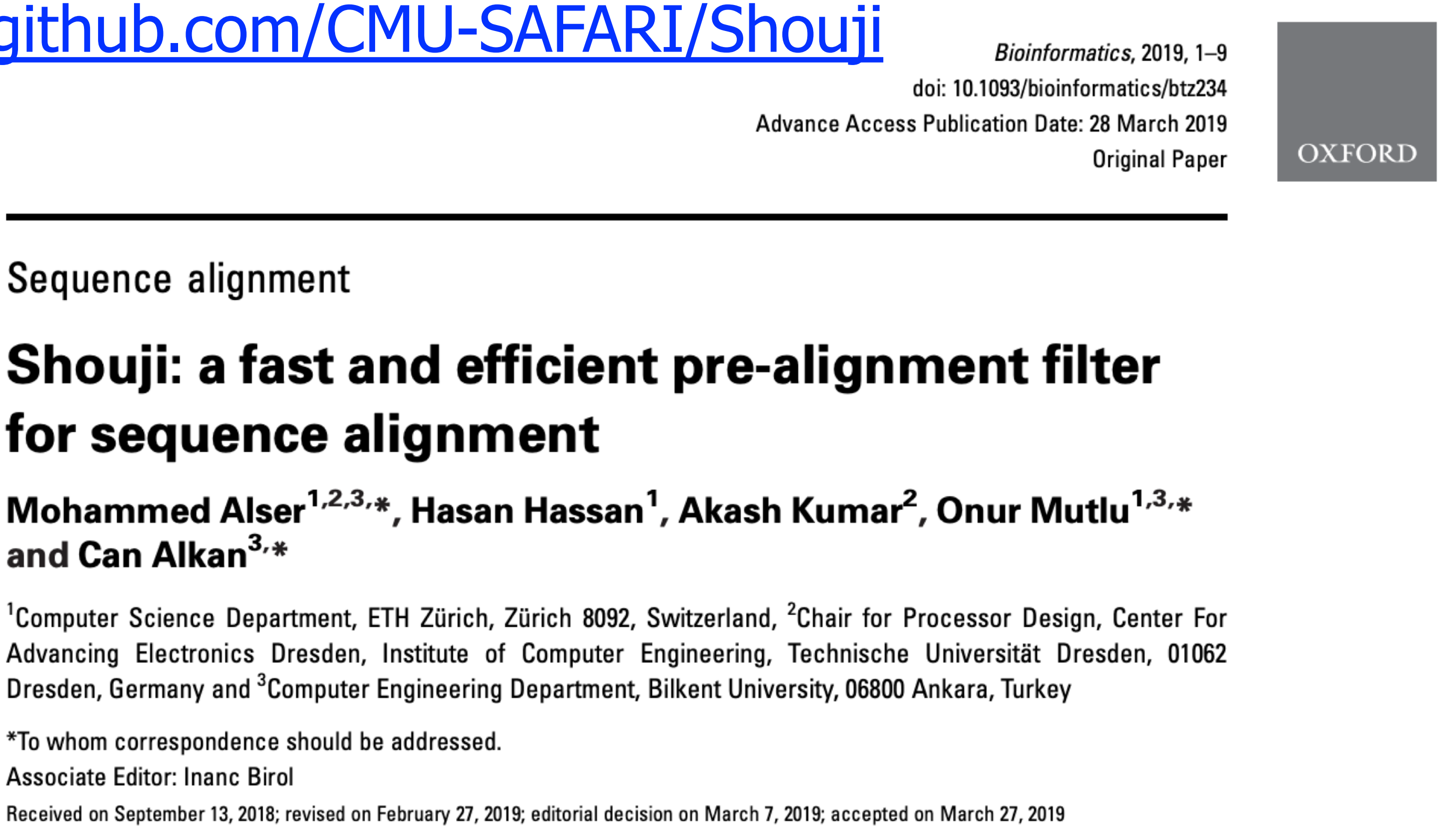
- Counting is performed concurrently for *all* bit-vectors and all sliding windows in a single clock cycle using multiple 4-input LUTs.



More on Shouji

Download and test for yourself

https://github.com/CMU-SAFARI/Shouji



Bioinformatics, 2019, 1–9
doi: 10.1093/bioinformatics/btz234
Advance Access Publication Date: 28 March 2019
Original Paper

Sequence alignment

Shouji: a fast and efficient pre-alignment filter for sequence alignment

Mohammed Alser[1,2,3,*], Hasan Hassan[1], Akash Kumar[2], Onur Mutlu[1,3,*] and Can Alkan[3,*]

[1]Computer Science Department, ETH Zürich, Zürich 8092, Switzerland, [2]Chair for Processor Design, Center For Advancing Electronics Dresden, Institute of Computer Engineering, Technische Universität Dresden, 01062 Dresden, Germany and [3]Computer Engineering Department, Bilkent University, 06800 Ankara, Turkey

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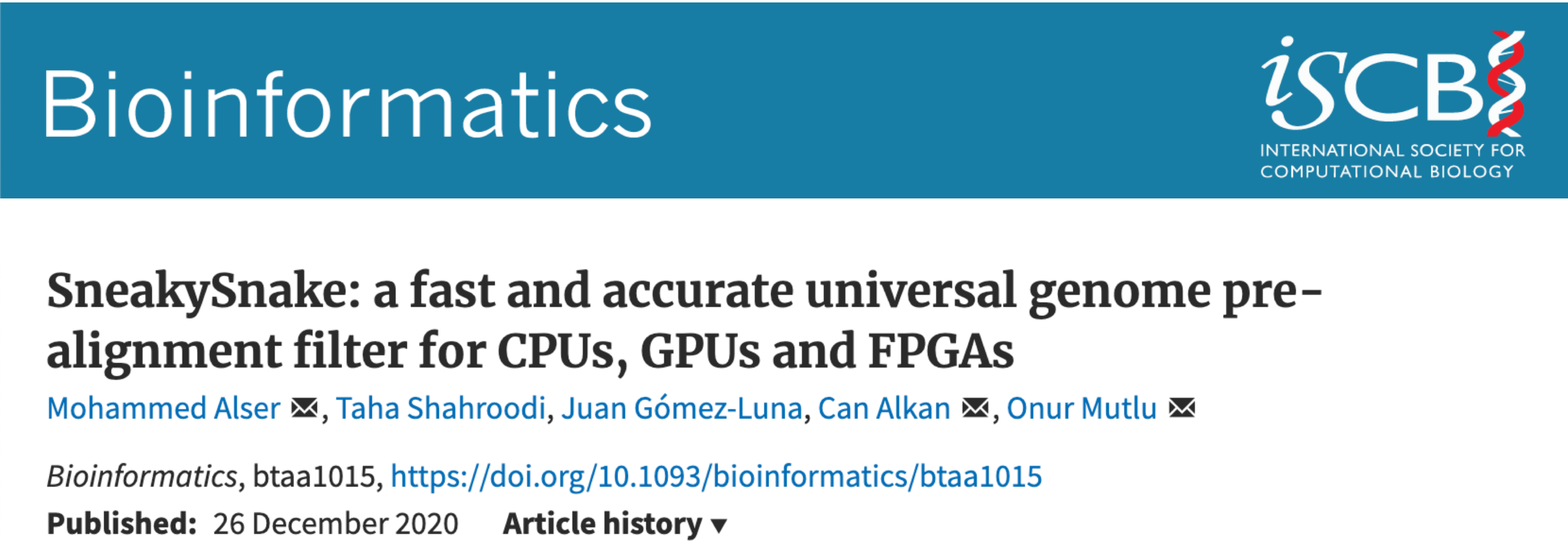
Alser+, "Shouji: a fast and efficient pre-alignment filter for sequence alignment", *Bioinformatics* 2019,
https://doi.org/10.1093/bioinformatics/btz234

Specialized Hardware for Pre-alignment Filtering

Mohammed Alser, Taha Shahroodi, Juan-Gomez Luna, Can Alkan, and Onur Mutlu,
"SneakySnake: A Fast and Accurate Universal Genome Pre-Alignment Filter for CPUs, GPUs, and FPGAs"
Bioinformatics, 2020.
[Source Code]
[Online link at Bioinformatics Journal]



Bioinformatics

iSCB INTERNATIONAL SOCIETY FOR COMPUTATIONAL BIOLOGY

SneakySnake: a fast and accurate universal genome pre-alignment filter for CPUs, GPUs and FPGAs

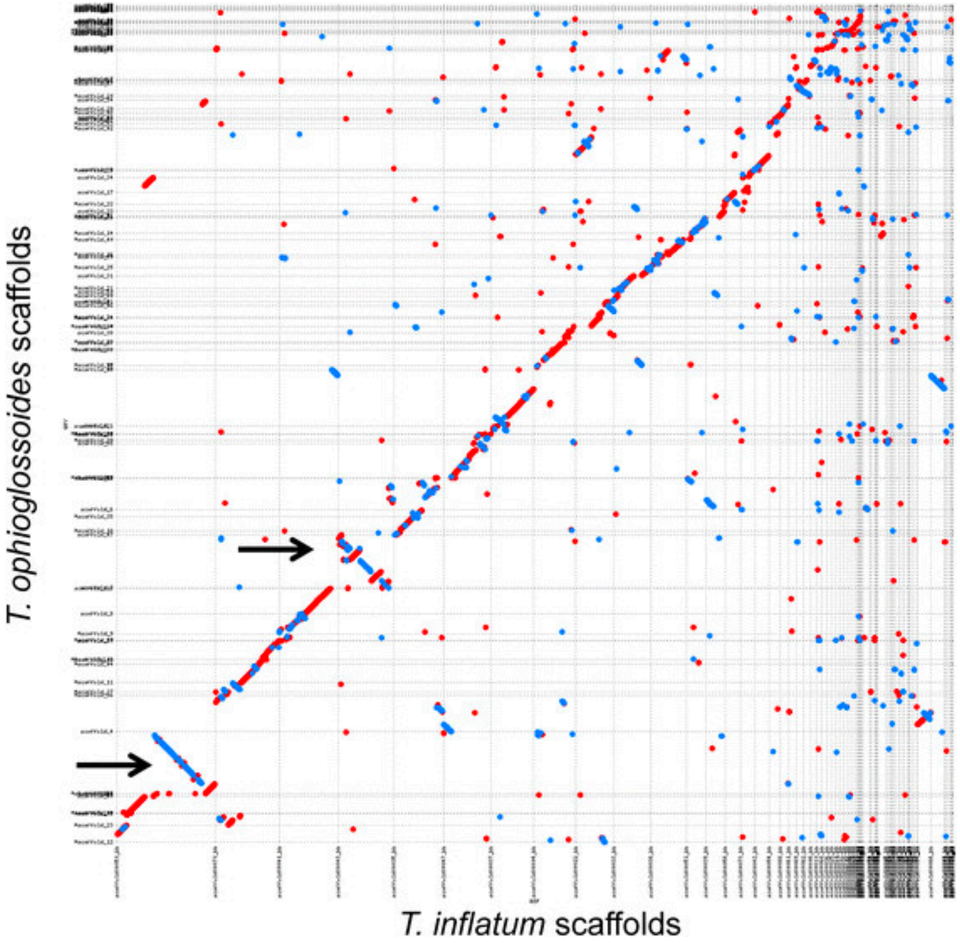
Mohammed Alser ✉, Taha Shahroodi, Juan Gómez-Luna, Can Alkan ✉, Onur Mutlu ✉

Bioinformatics, btaa1015, https://doi.org/10.1093/bioinformatics/btaa1015

Published: 26 December 2020 **Article history** ▾

SneakySnake

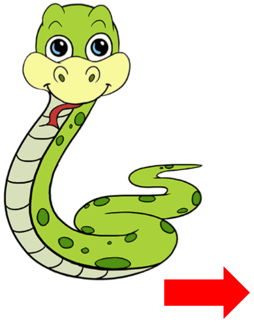
- **Key observation:**
  - Correct alignment is a sequence of non-overlapping long matches.



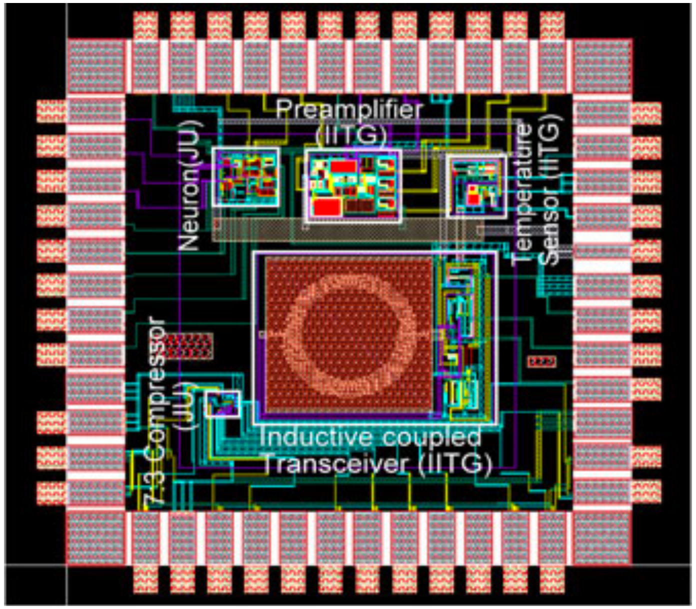
Dot plot, dot matrix
(Lipman and Pearson, 1985)

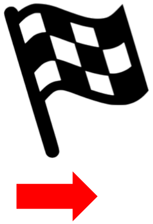
SneakySnake

- **Key observation:**
  - Correct alignment is a sequence of non-overlapping long matches
- **Key idea:**
  - Approximate edit distance calculation is similar to Single Net Routing problem in VLSI chip



VLSI chip layout


Preamplifier (IITG)
Neuron(JU)
Temperature Sensor (IITG)
7:3 Compressor (JU)
Inductive coupled Transceiver (IITG)



SneakySnake Walkthrough

Building Neighborhood Map → Finding the Optimal Routing Path → Examining the Snake Survival

$E = 3$

Given two genomic sequences, a reference sequence $R[1 \ldots m]$ and a query sequence $Q[1 \ldots m]$, and an edit distance threshold E, we calculate the entry $Z[i, j]$ of the chip maze, where $1 \leq i \leq (2E + 1)$ and $1 \leq j \leq m$, as follows:

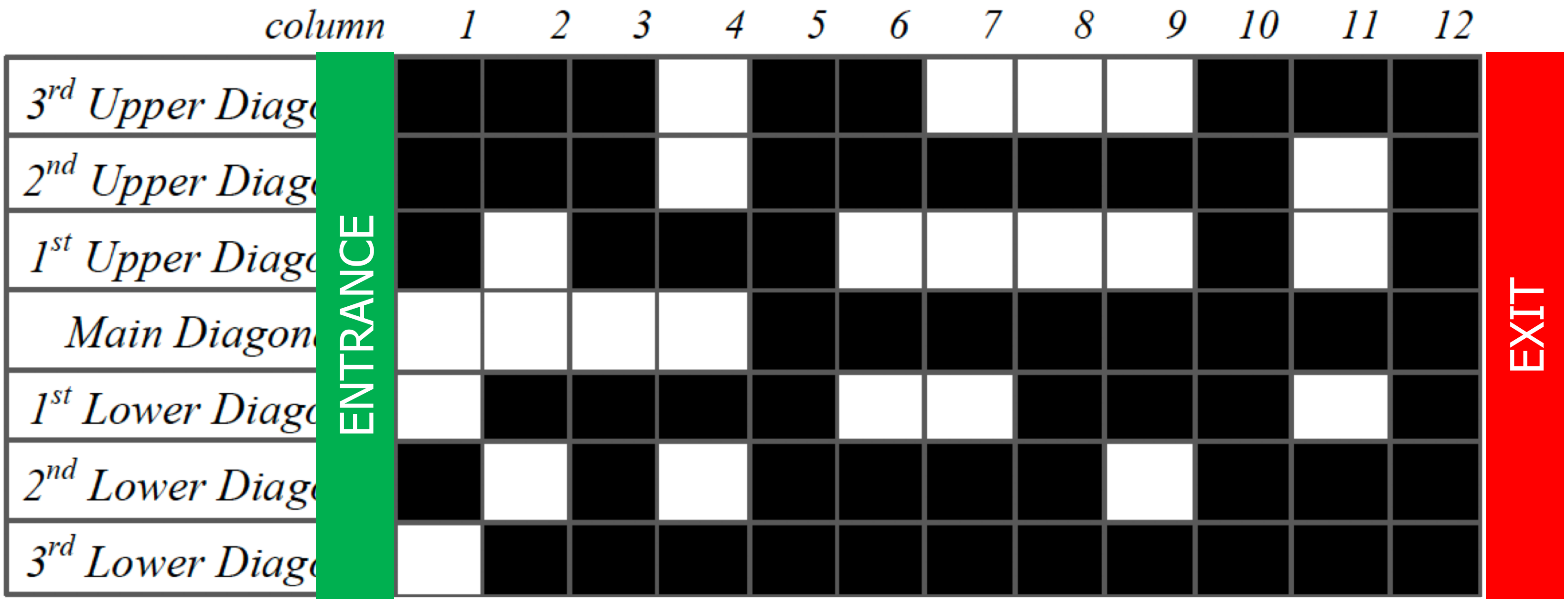
$$Z[i,j] = \begin{cases} 0, & if \;\; i = E + 1,\; Q[j] = R[j], \\ 0, & if \;\; 1 \leq i \leq E,\; Q[j - i] = R[j], \\ 0, & if \;\; i > E + 1,\; Q[j + i - E - 1] = R[j], \\ 1, & otherwise \end{cases} \tag{1}$$

column	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*
3rd Upper Diagonal	1	1	1	0	1	1	0	0	0	1	1	1
2nd Upper Diagonal	1	1	1	0	1	1	1	1	1	1	0	1
1st Upper Diagonal	1	0	1	1	1	0	0	0	0	1	0	1
Main Diagonal	0	0	0	0	1	1	1	1	1	1	1	1
1st Lower Diagonal	0	1	1	1	1	0	0	1	1	1	0	1
2nd Lower Diagonal	1	0	1	0	1	1	1	1	0	1	1	1
3rd Lower Diagonal	0	1	1	1	1	1	1	1	1	1	1	1

SneakySnake Walkthrough

Building Neighborhood Map → Finding the Optimal Routing Path → Examining the Snake Survival

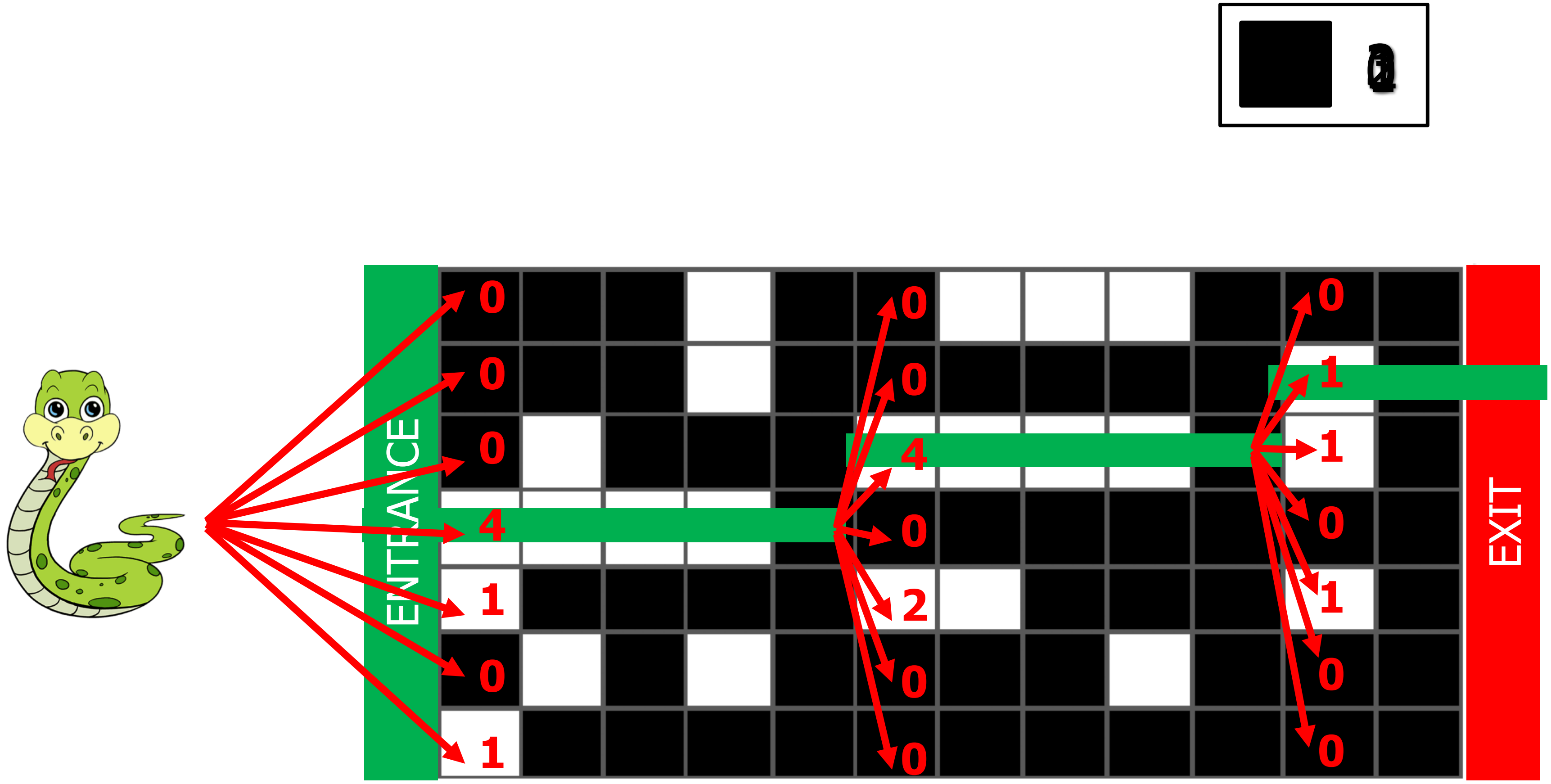
E = 3



column	1	2	3	4	5	6	7	8	9	10	11	12
3rd Upper Diag	■	■	■	□	■	■	□	□	□	■	■	■
2nd Upper Diag	■	■	■	□	■	■	■	■	■	■	□	■
1st Upper Diag	■	□	■	■	■	□	□	□	□	■	□	■
Main Diagon	□	□	□	□	■	■	■	■	■	■	■	■
1st Lower Diag	□	■	■	■	■	□	□	■	■	■	□	■
2nd Lower Diag	■	□	■	□	■	■	■	■	□	■	■	■
3rd Lower Diag	□	■	■	■	■	■	■	■	■	■	■	■

SneakySnake Walkthrough

Building Neighborhood Map → Finding the Optimal Routing Path → Examining the Snake Survival

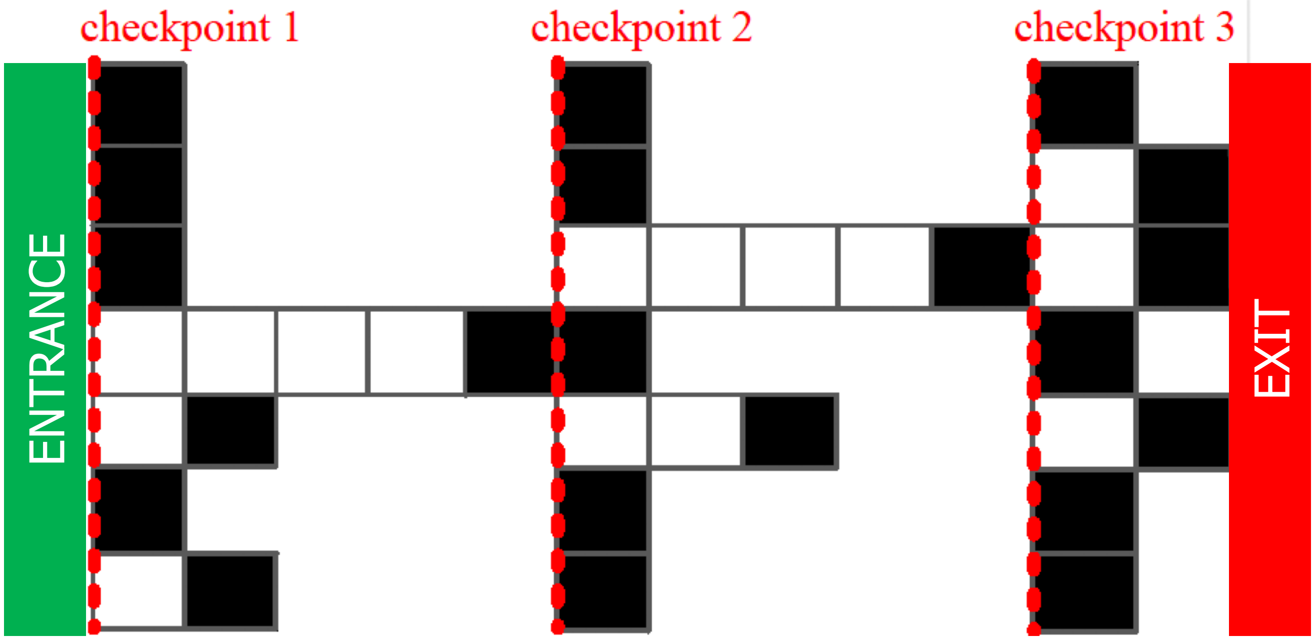


SneakySnake Walkthrough

Building Neighborhood Map → Finding the Routing Travel Path → Examining the Snake Survival

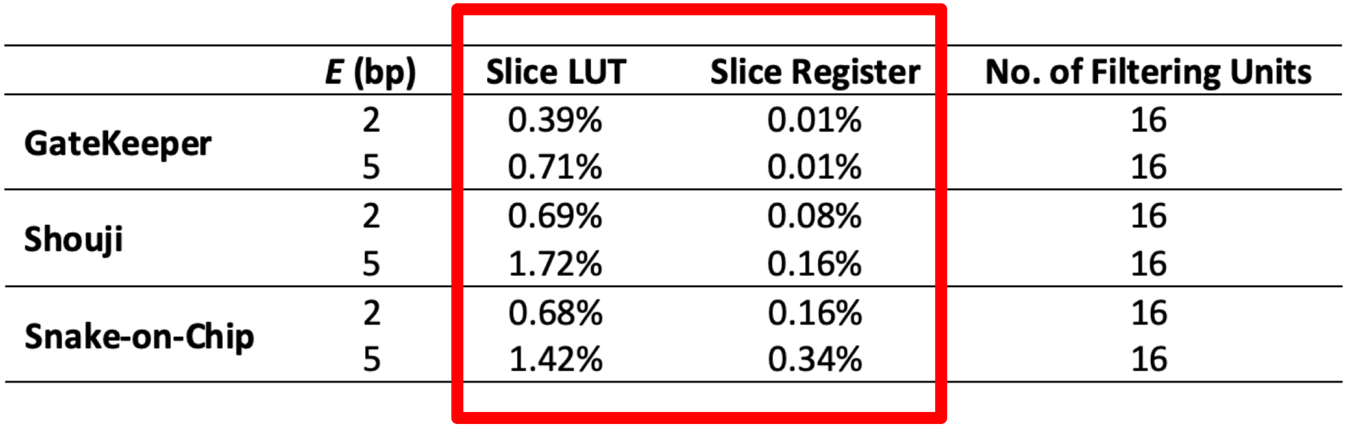
This is what you actually need to build and it can be done on-the-fly!

■ 3



FPGA Resource Analysis

- FPGA resource usage for a single filtering unit of GateKeeper, Shouji, and Snake-on-Chip for a sequence length of 100 and under different edit distance thresholds (E).



	E (bp)	Slice LUT	Slice Register	No. of Filtering Units
GateKeeper	2	0.39%	0.01%	16
	5	0.71%	0.01%	16
Shouji	2	0.69%	0.08%	16
	5	1.72%	0.16%	16
Snake-on-Chip	2	0.68%	0.16%	16
	5	1.42%	0.34%	16

Key Results of SneakySnake

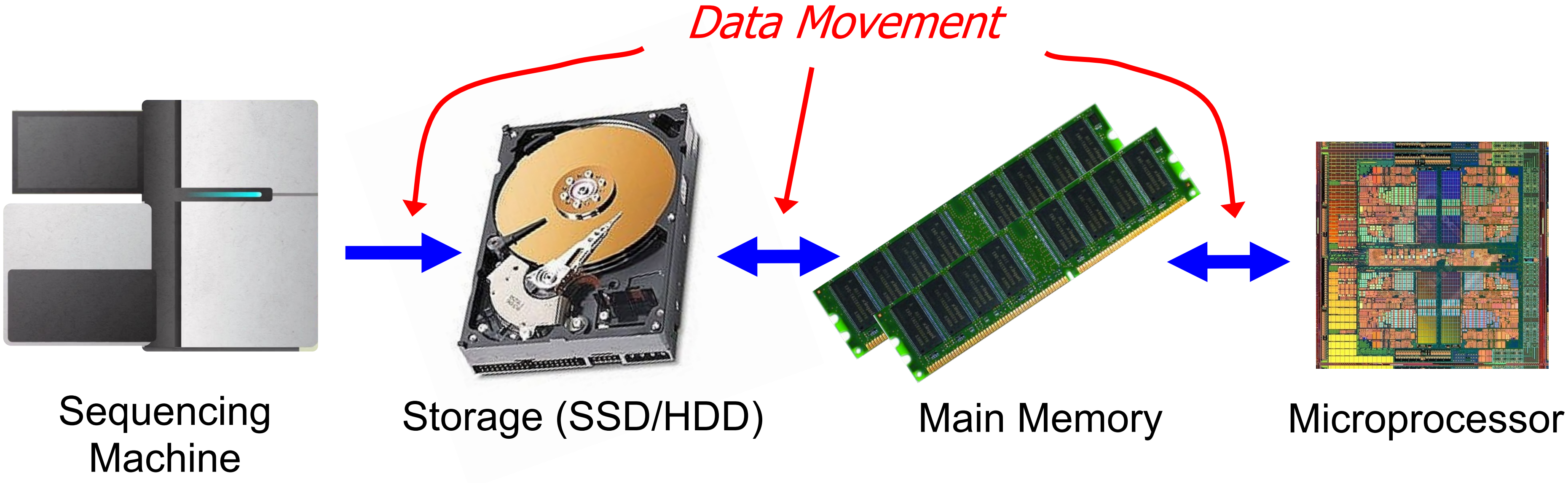
- SneakySnake is up to four orders of magnitude more accurate than Shouji (Bioinformatics'19) and GateKeeper (Bioinformatics'17)

- Using short reads, SneakySnake accelerates Edlib (Bioinformatics'17) and Parasail (BMC Bioinformatics'16) by
  - up to 37.7× and 43.9× (>12× on average), on CPUs
  - up to 413× and 689× (>400× on average) with *FPGA/GPU acceleration*

- Using long reads, SneakySnake accelerates Parasail and KSW2 by 140.1× and 17.1× on average, respectively, on CPUs

Data Movement Dominates Performance

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



Data Movement

Sequencing Machine

Storage (SSD/HDD)

Main Memory

Microprocessor

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

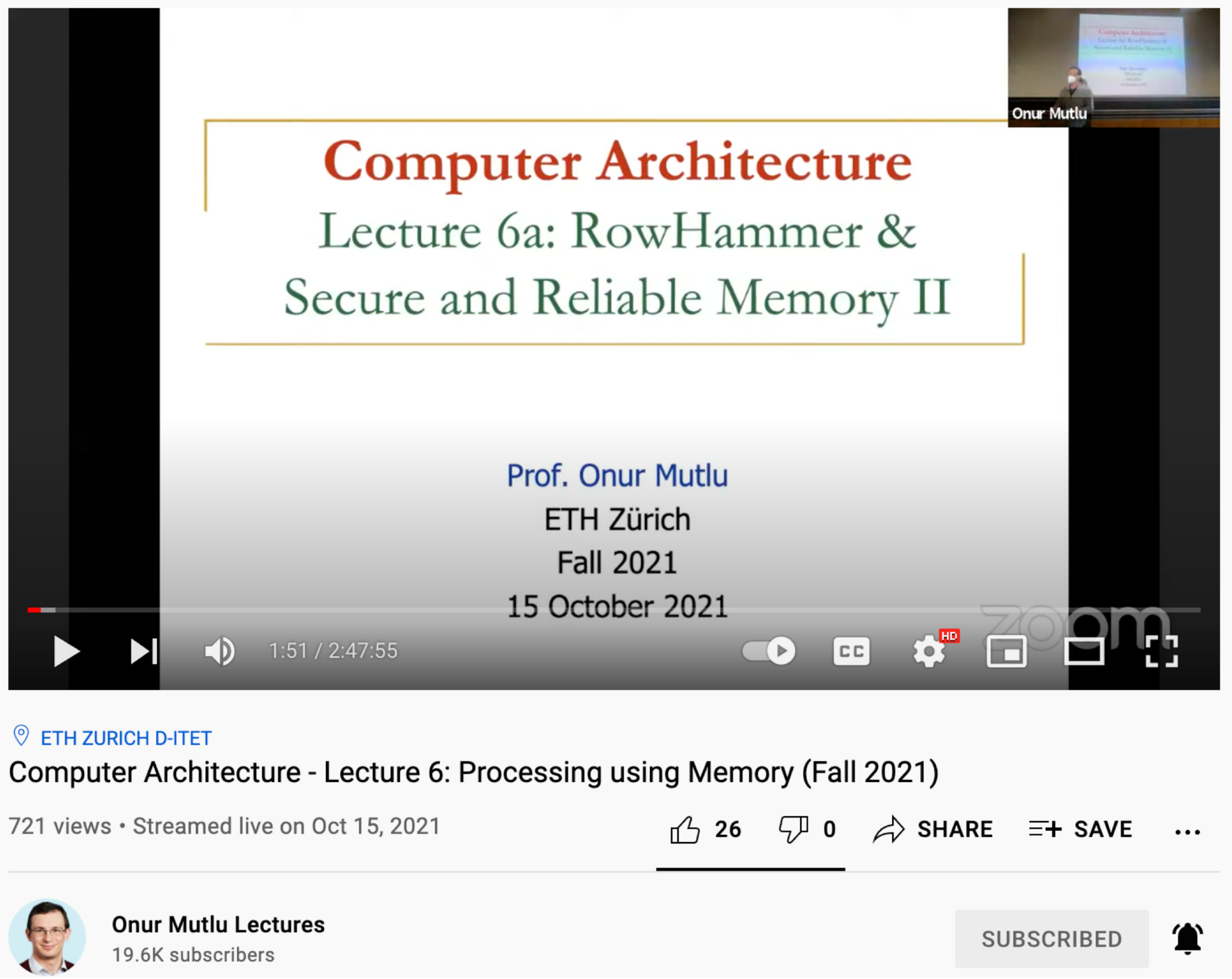
Read Mapping & Filtering in Memory

We need to design

mapping & filtering algorithms

that fit processing-in-memory

Processing Using Memory



Computer Architecture

Lecture 6a: RowHammer &

Secure and Reliable Memory II

Prof. Onur Mutlu

ETH Zürich

Fall 2021

15 October 2021

ETH ZURICH D-ITET

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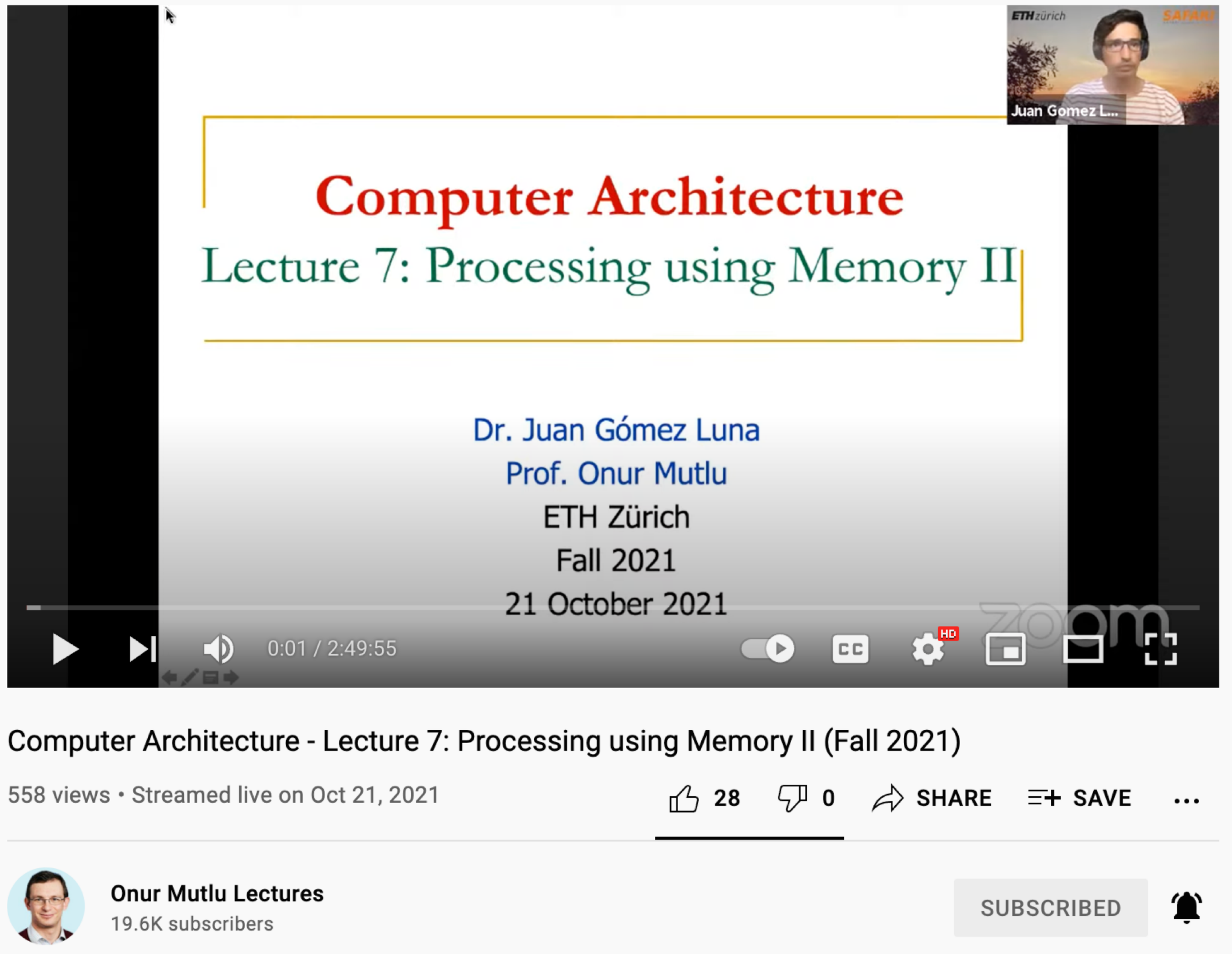
Processing Using Memory II



Computer Architecture

Lecture 7: Processing using Memory II

Dr. Juan Gómez Luna

Prof. Onur Mutlu

ETH Zürich

Fall 2021

21 October 2021

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558 views • Streamed live on Oct 21, 2021

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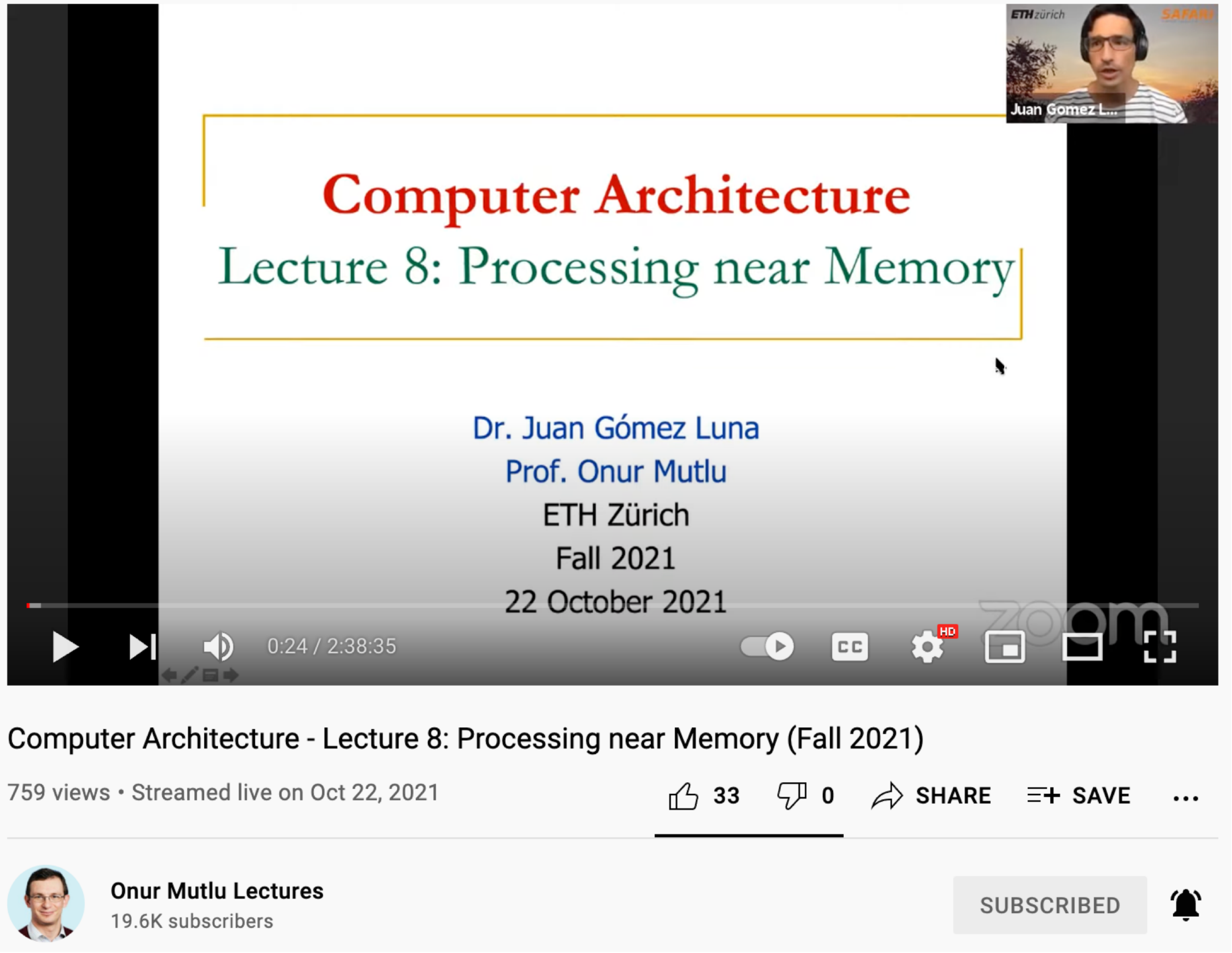
Processing Near Memory



Computer Architecture

Lecture 8: Processing near Memory

Dr. Juan Gómez Luna

Prof. Onur Mutlu

ETH Zürich

Fall 2021

22 October 2021

Computer Architecture - Lecture 8: Processing near Memory (Fall 2021)

759 views • Streamed live on Oct 22, 2021

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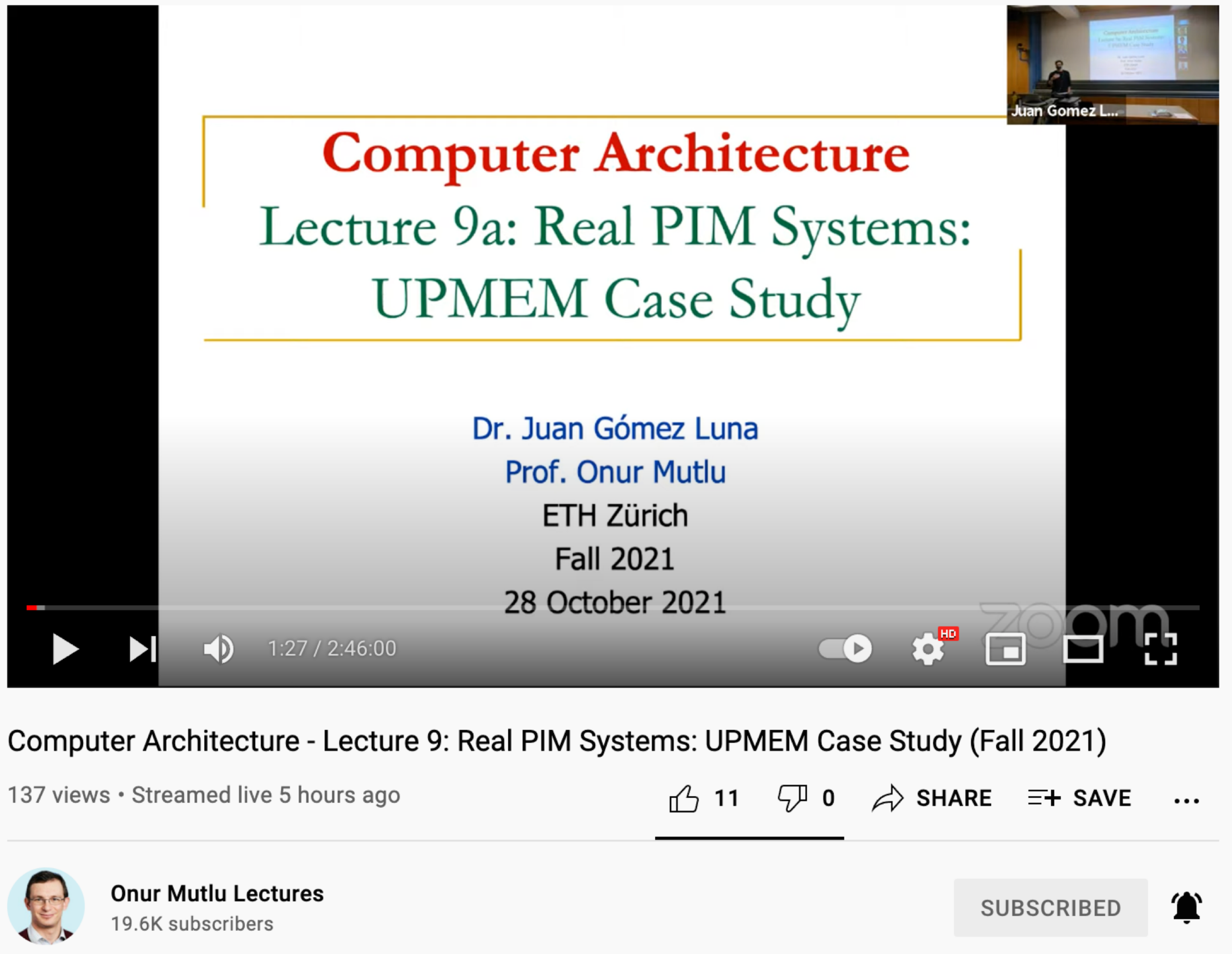
https://www.youtube.com/watch?v=kpgLmX9sdcI

Using Real PIM System



Computer Architecture

Lecture 9a: Real PIM Systems: UPMEM Case Study

Dr. Juan Gómez Luna

Prof. Onur Mutlu

ETH Zürich

Fall 2021

28 October 2021

Computer Architecture - Lecture 9: Real PIM Systems: UPMEM Case Study (Fall 2021)

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Onur Mutlu Lectures

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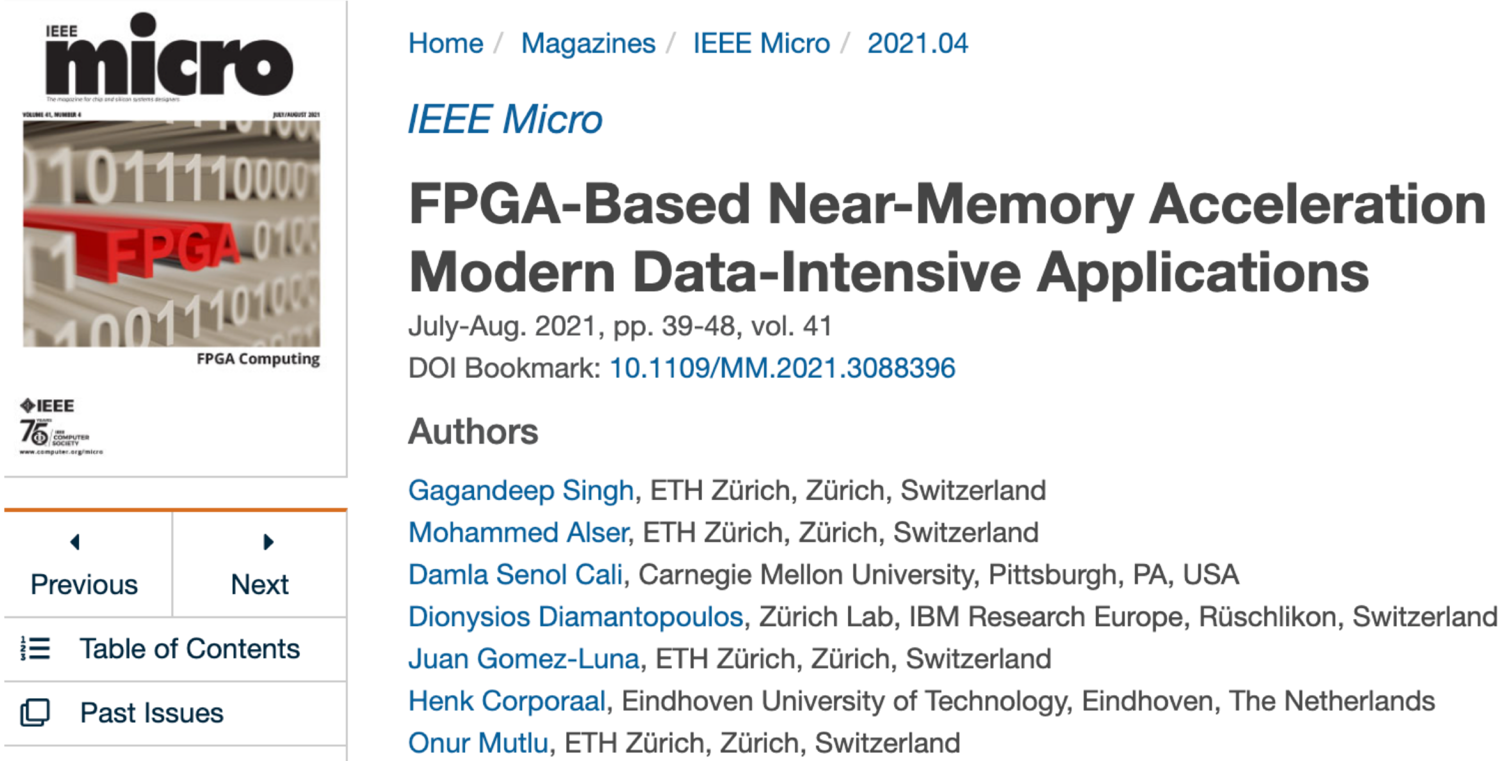
https://www.youtube.com/watch?v=TuVw_SKaTCo

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
Mohammed Alser, ETH Zürich, Zürich, Switzerland
Damla Senol Cali, Carnegie Mellon University, Pittsburgh, PA, USA
Dionysios Diamantopoulos, Zürich Lab, IBM Research Europe, Rüschlikon, Switzerland
Juan Gomez-Luna, ETH Zürich, Zürich, Switzerland
Henk Corporaal, Eindhoven University of Technology, Eindhoven, The Netherlands
Onur Mutlu, ETH Zürich, Zürich, Switzerland

Near-memory SneakySnake

- Problem: Read Mapping is heavily bottlenecked by data movement from main memory

- Solution: Perform read mapping near where data resides (i.e., near-memory)

- We carefully redesigned the accelerator logic of SneakySnake to exploit near-memory computation capability on modern FPGA boards with high-bandwidth memory

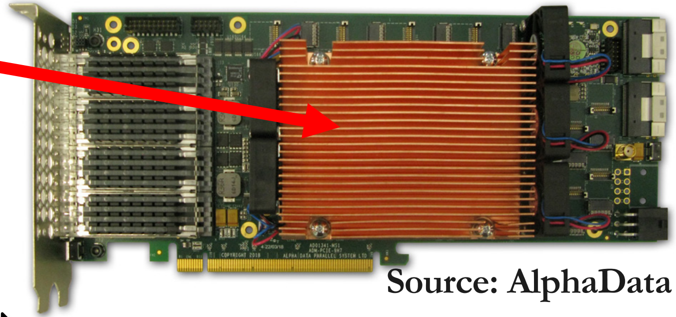
Heterogeneous System: CPU+FPGA

We evaluate two POWER9+FPGA systems:

1. **HBM-based AD9H7 board:** Xilinx Virtex Ultrascale+™ XCVU37P-2
2. **DDR4-based AD9V3 board:** Xilinx Virtex Ultrascale+™ XCVU3P-2

FPGA + HBM on the same package substrate

HBM-based AD9H7 board

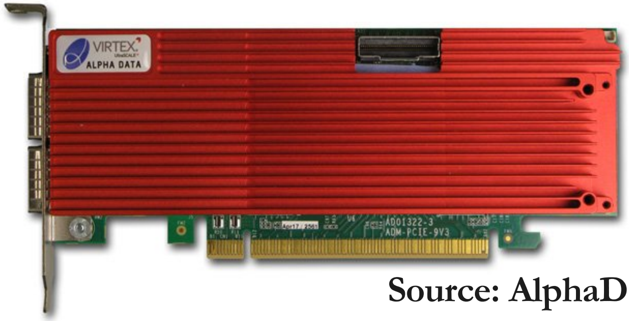


Source: AlphaData

Source: IBM

POWER9 AC922

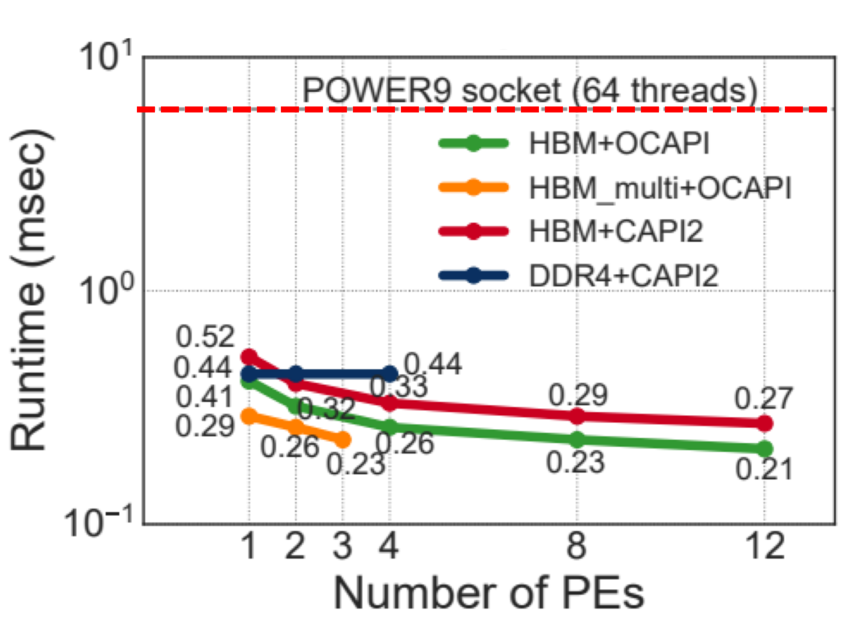
CAPI2

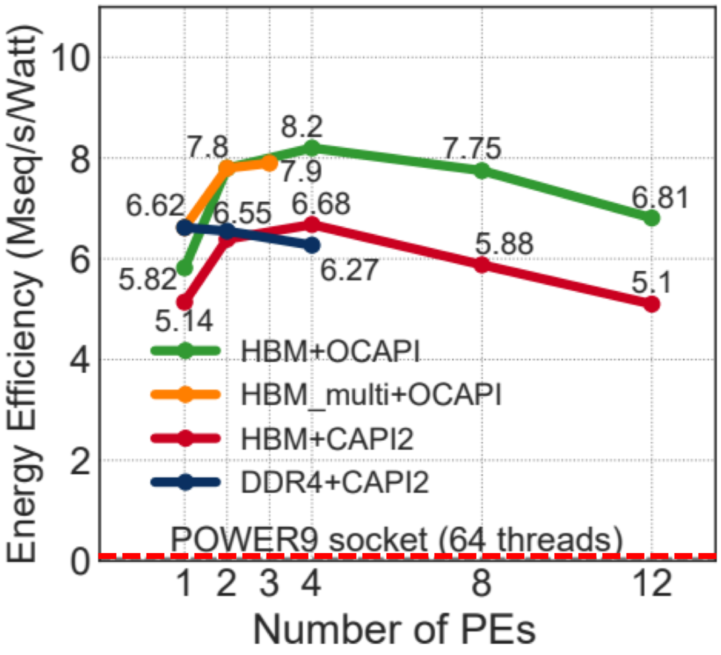


Source: AlphaData

DDR4-based AD9V3 board

Key Results of Near-memory SneakySnake

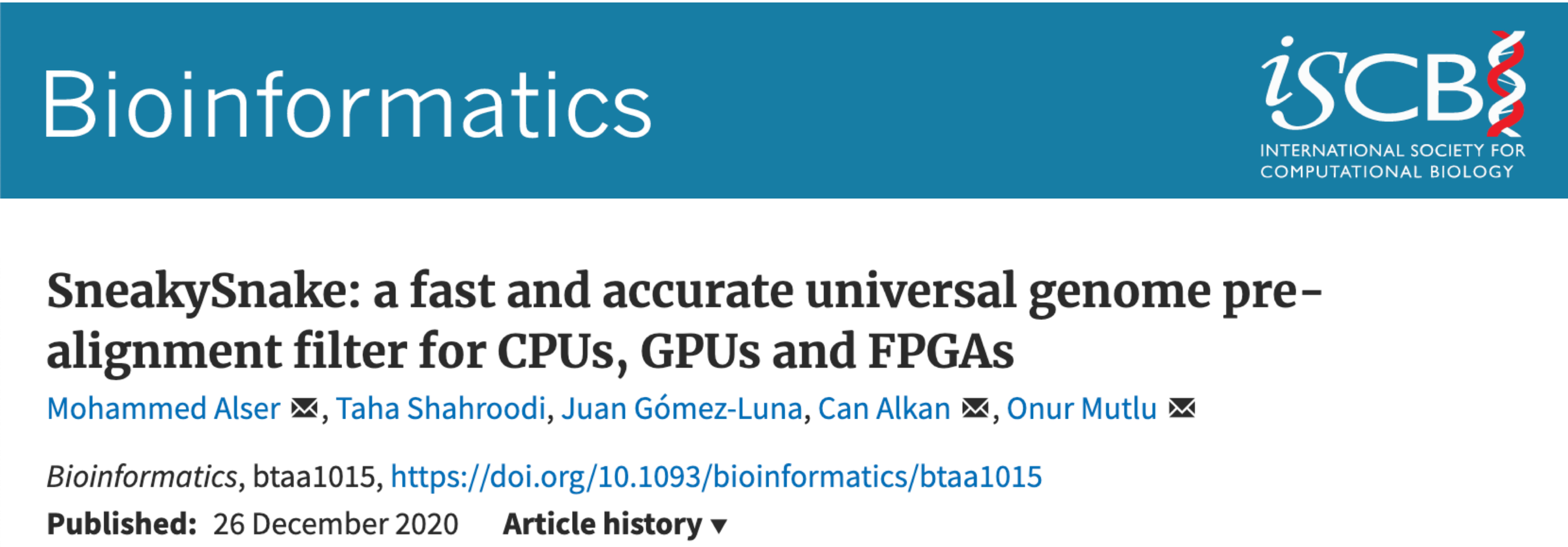




Near-memory pre-alignment filtering improves **performance** and **energy efficiency** by 27.4× and 133×, respectively, over a 16-core (64 hardware threads) IBM POWER9 CPU

More on SneakySnake [Bioinformatics 2020]

Mohammed Alser, Taha Shahroodi, Juan-Gomez Luna, Can Alkan, and Onur Mutlu,
"SneakySnake: A Fast and Accurate Universal Genome Pre-Alignment Filter for CPUs, GPUs, and FPGAs"
Bioinformatics, 2020.
[Source Code]
[Online link at Bioinformatics Journal]



SneakySnake: a fast and accurate universal genome pre-alignment filter for CPUs, GPUs and FPGAs

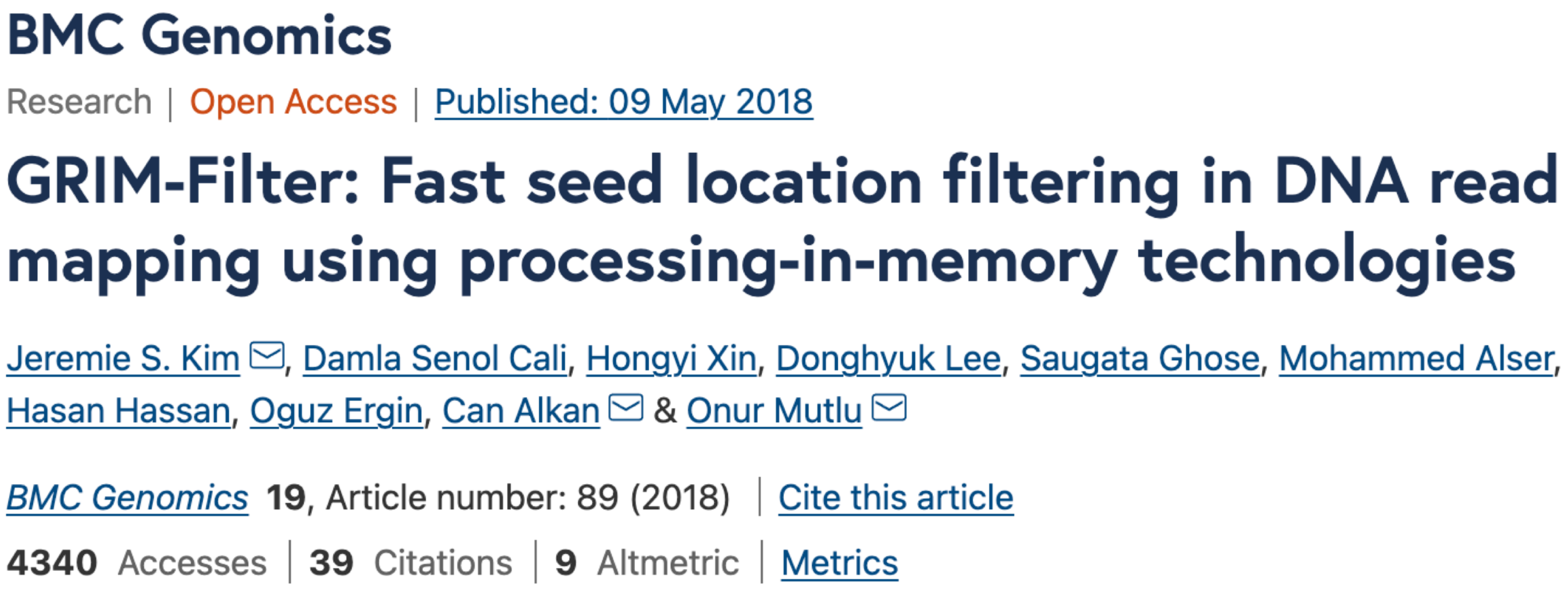
Mohammed Alser ✉, Taha Shahroodi, Juan Gómez-Luna, Can Alkan ✉, Onur Mutlu ✉

Bioinformatics, btaa1015, https://doi.org/10.1093/bioinformatics/btaa1015

Published: 26 December 2020 **Article history ▾**

GRIM-Filter

- Jeremie S. Kim, Damla Senol Cali, Hongyi Xin, Donghyuk Lee, Saugata Ghose, Mohammed Alser, Hasan Hassan, Oguz Ergin, Can Alkan, and Onur Mutlu, **"GRIM-Filter: Fast Seed Location Filtering in DNA Read Mapping Using Processing-in-Memory Technologies"**
  to appear in ***BMC Genomics***, 2018.
  Proceedings of the 16th Asia Pacific Bioinformatics Conference (***APBC***),
  Yokohama, Japan, January 2018.
  arxiv.org Version (pdf)



BMC Genomics

Research | Open Access | Published: 09 May 2018

GRIM-Filter: Fast seed location filtering in DNA read mapping using processing-in-memory technologies

Jeremie S. Kim ✉, Damla Senol Cali, Hongyi Xin, Donghyuk Lee, Saugata Ghose, Mohammed Alser, Hasan Hassan, Oguz Ergin, Can Alkan ✉ & Onur Mutlu ✉

BMC Genomics **19**, Article number: 89 (2018) | Cite this article

4340 Accesses | **39** Citations | **9** Altmetric | Metrics

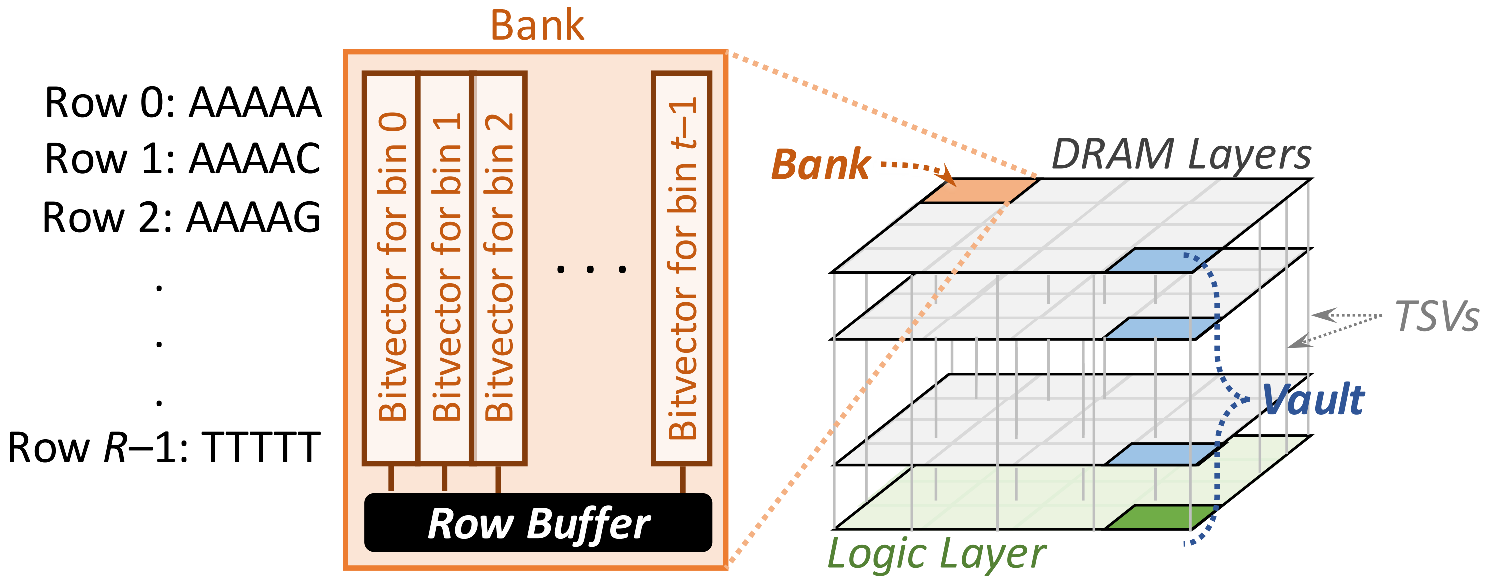
GRIM-Filter

- **Key observation:** FPGA and GPU accelerators are Heavily bottlenecked by Data Movement.

- **Key idea:** exploiting the high memory bandwidth and the logic layer of 3D-stacked memory to perform highly-parallel filtering in the DRAM chip itself.

- **Key results:**
  - We propose an algorithm called **GRIM-Filter**
  - GRIM-Filter with processing-in-memory is 1.8x-3.7x (2.1x on average) faster than FastHASH filter (BMC Genomics'13) across real data sets.
  - GRIM-Filter has 5.6x-6.4x (6.0x on average) lower falsely accepted pairs than FastHASH filter (BMC Genomics'13) across real data sets.

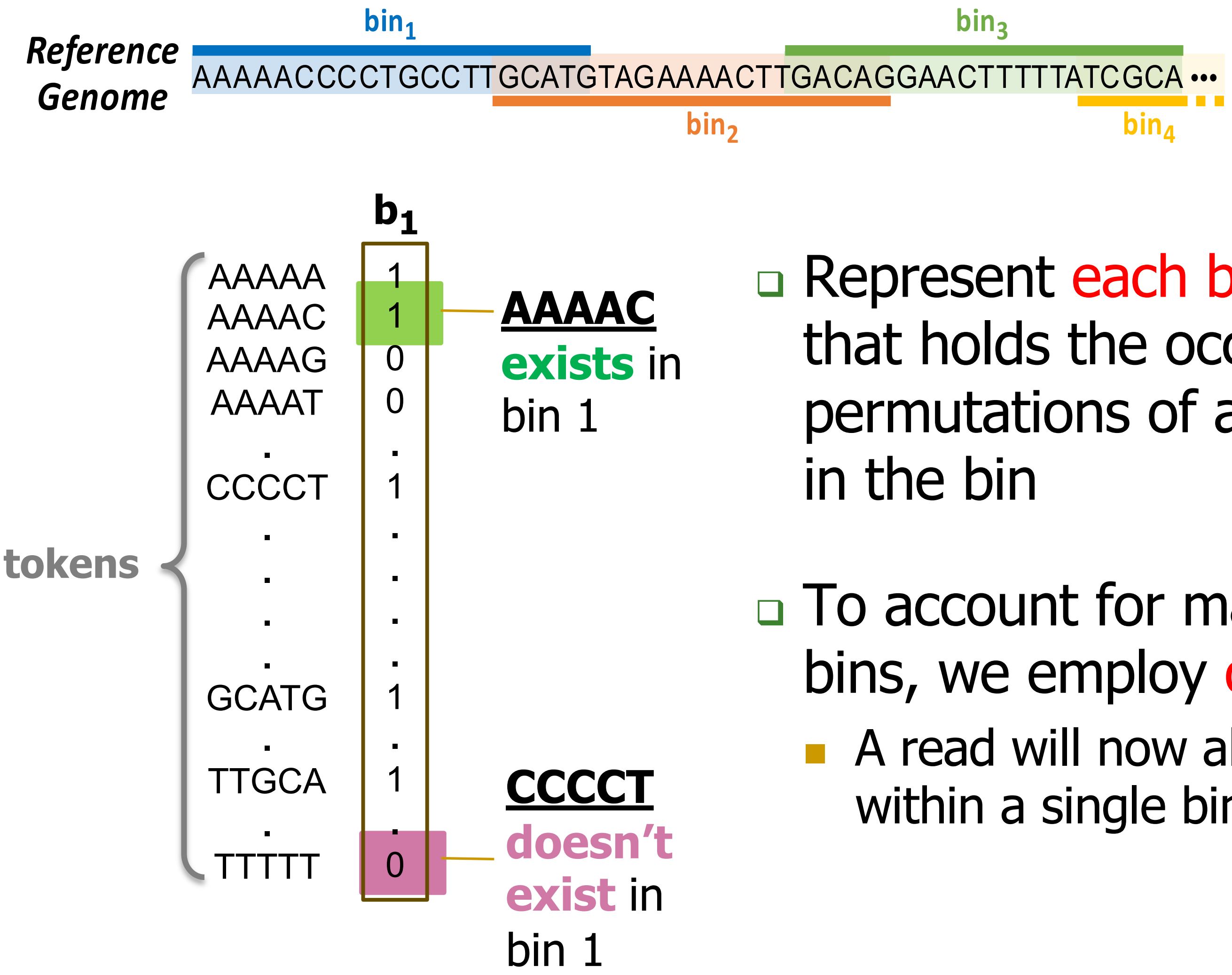
GRIM-Filter in 3D-Stacked DRAM



- Each DRAM layer is organized as an array of **banks**
  - A **bank** is an array of cells with a row buffer to transfer data

- The layout of bitvectors in a bank enables filtering many bins in parallel

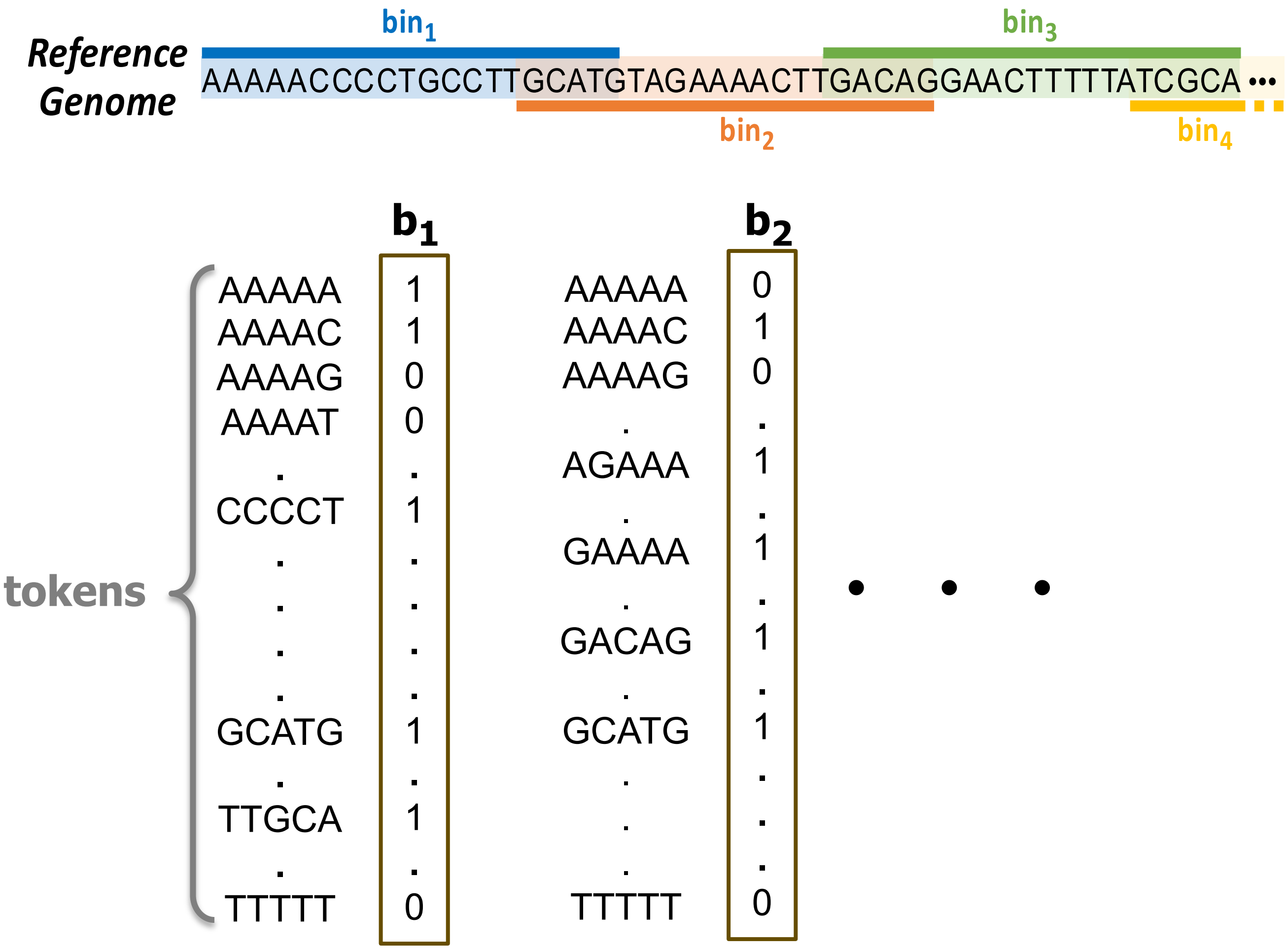
GRIM-Filter: Bitvectors



- Represent each bin with a **bitvector** that holds the occurrence of all permutations of a small string (**token**) in the bin

- To account for matches that straddle bins, we employ overlapping bins
  - A read will now always completely fall within a single bin

GRIM-Filter: Bitvectors

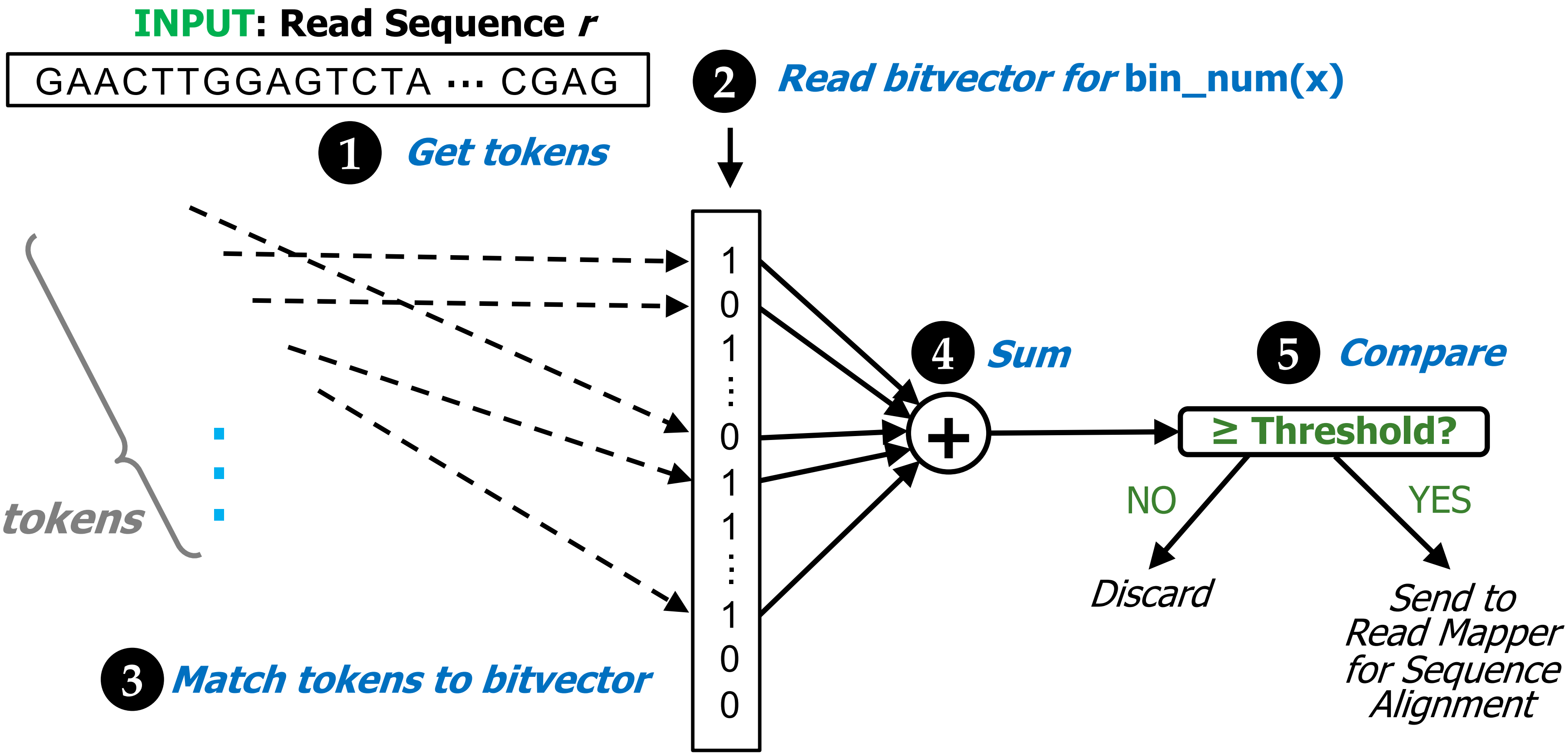


Storing all bitvectors requires $\underline{4^n * t}$ bits in memory,
where
t = number of bins
&
n = token length.

For **bin size** ~200, and **n** = 5, **memory footprint** ~3.8 GB

GRIM-Filter: Checking a Bin

How GRIM-Filter determines whether to **discard** potential match locations in a given bin **prior** to alignment



More on GRIM-Filter

- Jeremie S. Kim, Damla Senol Cali, Hongyi Xin, Donghyuk Lee, Saugata Ghose, Mohammed Alser, Hasan Hassan, Oguz Ergin, Can Alkan, and Onur Mutlu, **"GRIM-Filter: Fast Seed Location Filtering in DNA Read Mapping Using Processing-in-Memory Technologies"**
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  *Proceedings of the 16th Asia Pacific Bioinformatics Conference (**APBC**)*, Yokohama, Japan, January 2018.
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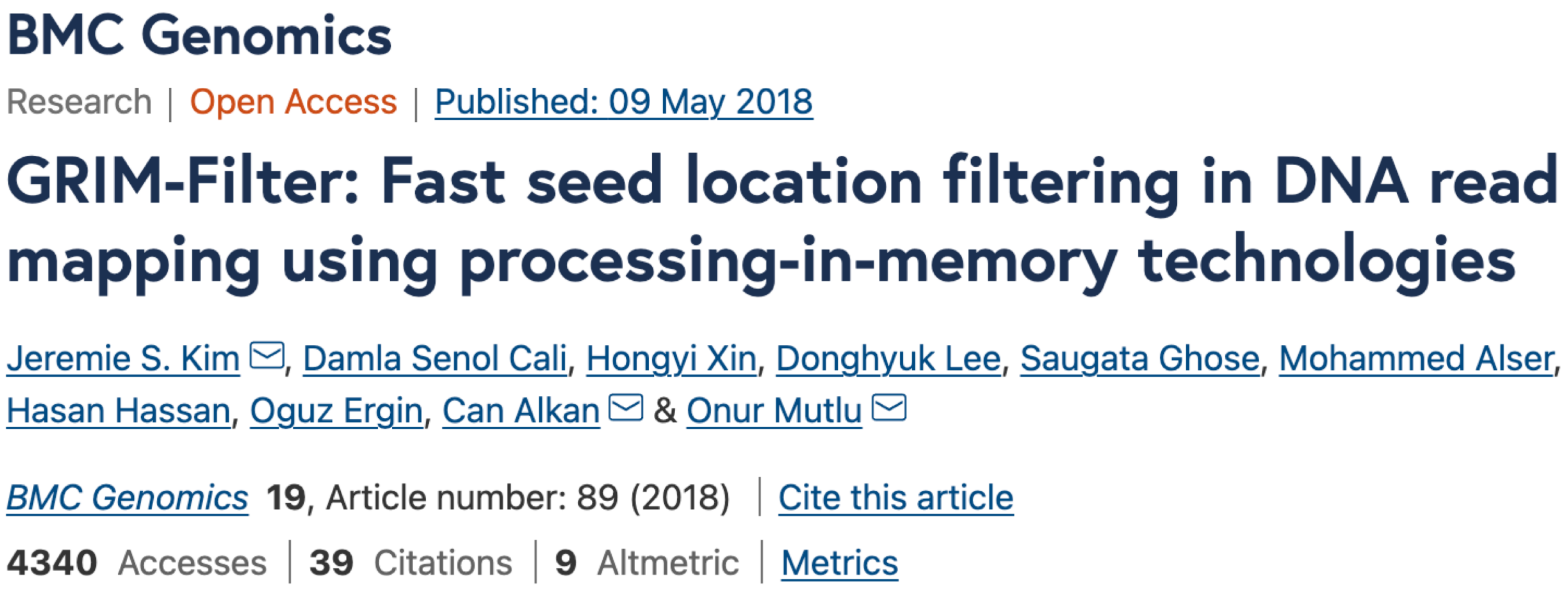

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GRIM-Filter: Fast seed location filtering in DNA read mapping using processing-in-memory technologies

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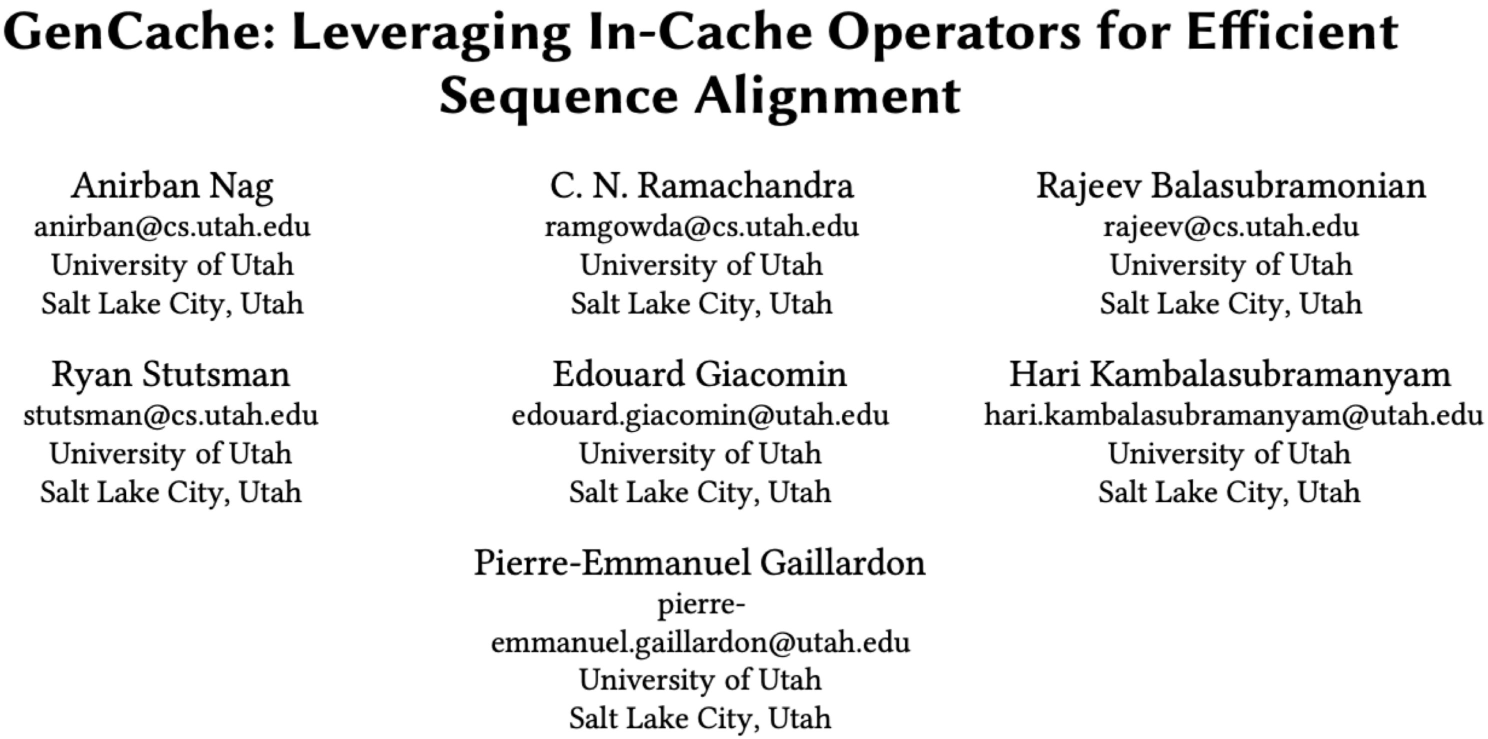
GenCache



GenCache: Leveraging In-Cache Operators for Efficient Sequence Alignment

Anirban Nag
anirban@cs.utah.edu
University of Utah
Salt Lake City, Utah

C. N. Ramachandra
ramgowda@cs.utah.edu
University of Utah
Salt Lake City, Utah

Rajeev Balasubramonian
rajeev@cs.utah.edu
University of Utah
Salt Lake City, Utah

Ryan Stutsman
stutsman@cs.utah.edu
University of Utah
Salt Lake City, Utah

Edouard Giacomin
edouard.giacomin@utah.edu
University of Utah
Salt Lake City, Utah

Hari Kambalasubramanyam
hari.kambalasubramanyam@utah.edu
University of Utah
Salt Lake City, Utah

Pierre-Emmanuel Gaillardon
pierre-emmanuel.gaillardon@utah.edu
University of Utah
Salt Lake City, Utah

Nag, Anirban, et al. "GenCache: Leveraging In-Cache Operators for Efficient Sequence Alignment." *Proceedings of the 52nd Annual IEEE/ACM International Symposium on Microarchitecture (**MICRO 52**)* , ACM, 2019.

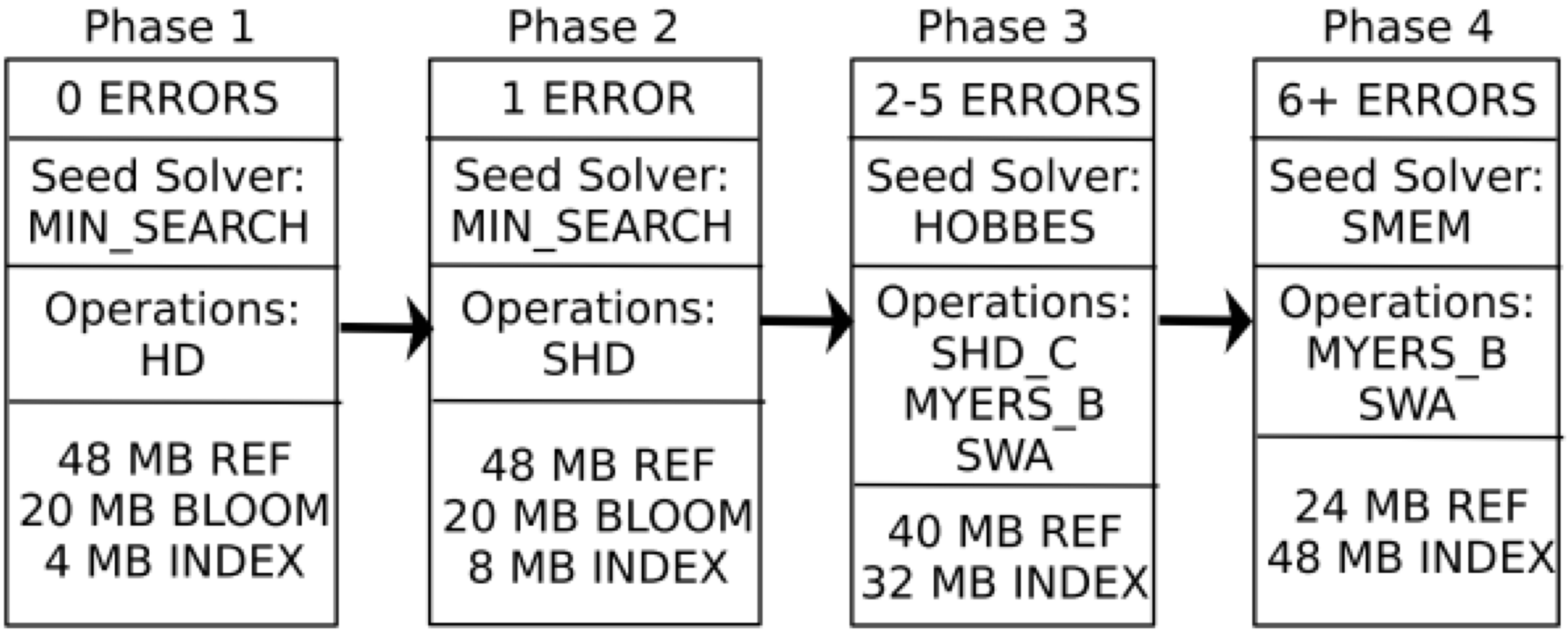
GenCache

- **Key observation:** State-of-the-art alignment accelerators are still bottlenecked by memory.

- **Key ideas:**
  - Performing in-cache alignment + pre-alignment filtering by enabling processing-in-cache using previous proposal, ComputeCache (HPCA'17).
  - Using different Pre-alignment filters depending on the selected edit distance threshold.

- Results:
  - GenCache on CPU is 1.36x faster than GenAx (ISCA 2018). GenCache in cache is 5.26x faster than GenAx.
  - GenCache chip has 16.4% higher area, 34.7% higher peak power, and 15% higher average power than GenAx.

GenCache's Four Phases



Phase 1

0 ERRORS

Seed Solver: MIN_SEARCH

Operations: HD

48 MB REF
20 MB BLOOM
4 MB INDEX

Phase 2

1 ERROR

Seed Solver: MIN_SEARCH

Operations: SHD

48 MB REF
20 MB BLOOM
8 MB INDEX

Phase 3

2-5 ERRORS

Seed Solver: HOBBES

Operations:
SHD_C
MYERS_B
SWA

40 MB REF
32 MB INDEX

Phase 4

6+ ERRORS

Seed Solver: SMEM

Operations:
MYERS_B
SWA

24 MB REF
48 MB INDEX

Figure 7: Four phases in the new alignment algorithm that exploits in-cache operators.

Throughput Results

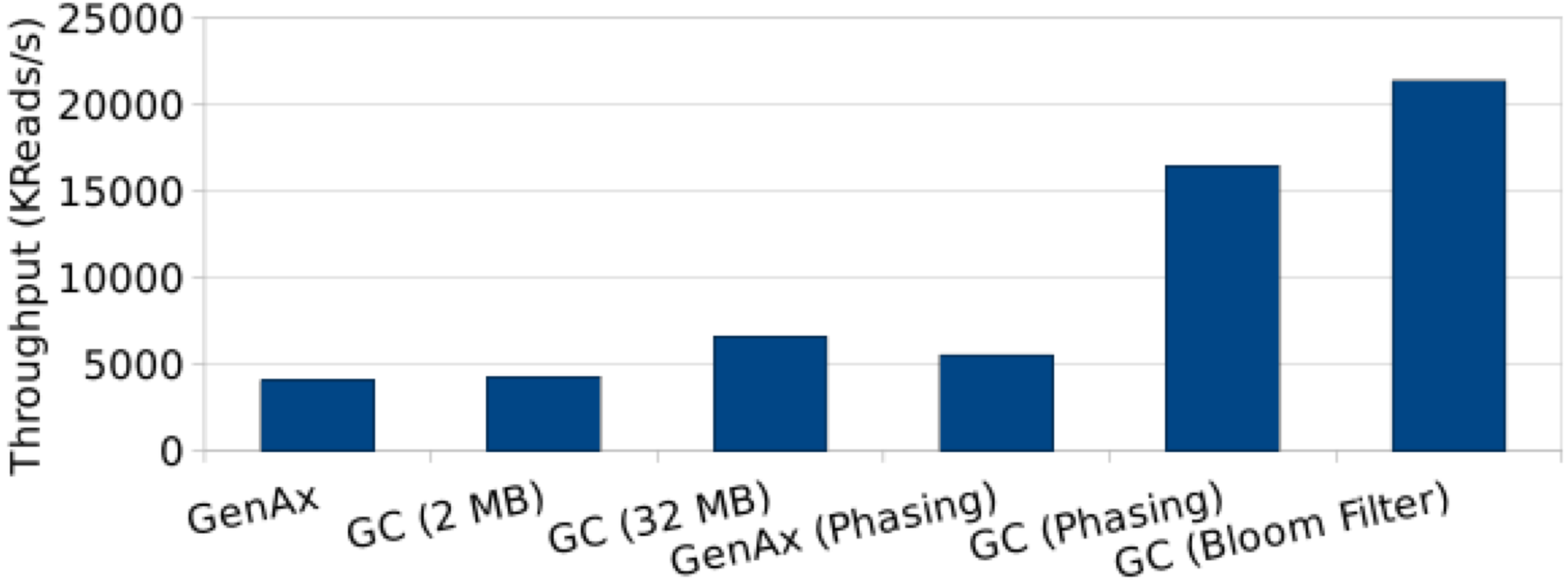


Figure 9: Throughput improvement of GenCache (Hardware & Software).

Ongoing Directions

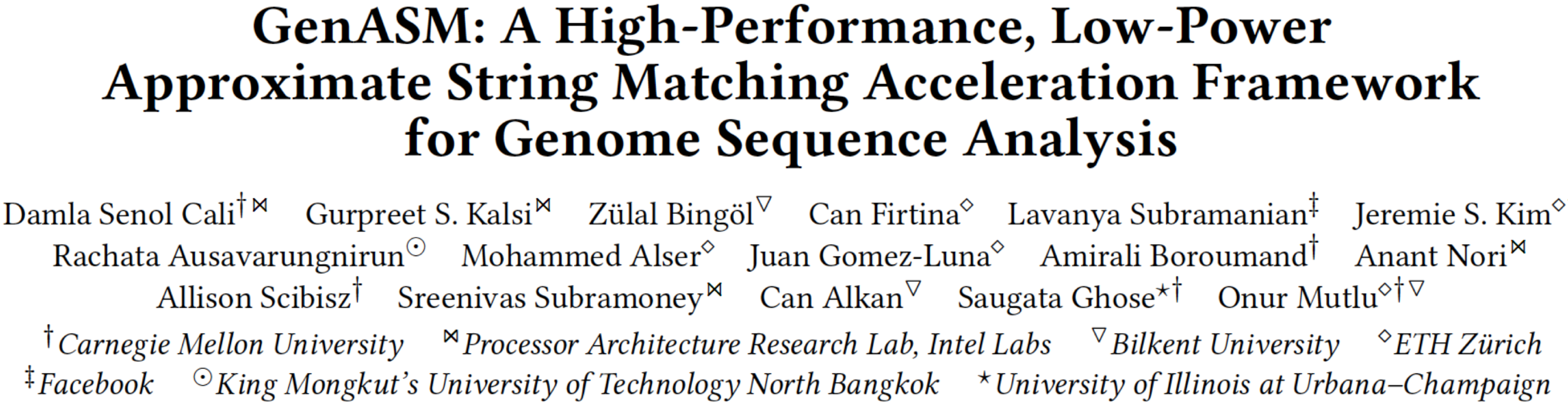
- **Seed Filtering Technique:**
  - Goal: Reducing the number of seed (k-mer) locations.
    - Heuristic (limits the number of mapping locations for each seed).
    - Supports exact matches only.

- **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.

GenASM Framework **[MICRO 2020]**

- Damla Senol Cali, Gurpreet S. Kalsi, Zulal Bingol, Can Firtina, Lavanya Subramanian, Jeremie S. Kim, Rachata Ausavarungnirun, Mohammed Alser, Juan Gomez-Luna, Amirali Boroumand, Anant Nori, Allison Scibisz, Sreenivas Subramoney, Can Alkan, Saugata Ghose, and Onur Mutlu,
"GenASM: A High-Performance, Low-Power Approximate String Matching Acceleration Framework for Genome Sequence Analysis"
Proceedings of the 53rd International Symposium on Microarchitecture (***MICRO***), Virtual, October 2020.
[Lightning Talk Video (1.5 minutes)]
[Lightning Talk Slides (pptx) (pdf)]
[Talk Video (18 minutes)]
[Slides (pptx) (pdf)]



GenASM: A High-Performance, Low-Power Approximate String Matching Acceleration Framework for Genome Sequence Analysis

Damla Senol Cali[†⋈] Gurpreet S. Kalsi[⋈] Zülal Bingöl[▽] Can Firtina[◇] Lavanya Subramanian[‡] Jeremie S. Kim[◇†]
Rachata Ausavarungnirun[⊙] Mohammed Alser[◇] Juan Gomez-Luna[◇] Amirali Boroumand[†] Anant Nori[⋈]
Allison Scibisz[†] Sreenivas Subramoney[⋈] Can Alkan[▽] Saugata Ghose[⋆†] Onur Mutlu[◇†▽]

[†] *Carnegie Mellon University* [⋈] *Processor Architecture Research Lab, Intel Labs* [▽] *Bilkent University* [◇] *ETH Zürich*
[‡] *Facebook* [⊙] *King Mongkut's University of Technology North Bangkok* [⋆] *University of Illinois at Urbana–Champaign*

Near-memory GenASM Framework

- **Our goal:** Accelerate approximate string matching (ASM) by designing a fast and flexible framework, which can accelerate multiple steps of genome sequence analysis.

- **Key ideas:** Exploit the high memory bandwidth and the logic layer of 3D-stacked memory to perform highly-parallel ASM in the DRAM chip itself.
- Modify and extend Bitap[1,2], ASM algorithm with fast and simple bitwise operations, such that it now:
  - Supports long reads
  - Supports traceback
  - Is highly parallelizable
- Co-design of our modified scalable and memory-efficient algorithms with low-power and area-efficient hardware accelerators

[1] R. A. Baeza-Yates and G. H. Gonnet. "A New Approach to Text Searching." *CACM,* 1992.
[2] S. Wu and U. Manber. "Fast Text Searching: Allowing Errors." *CACM,* 1992.

Key Results of the GenASM Framework

(1) Read Alignment

- **116×** speedup, **37×** less power than **Minimap2** (state-of-the-art **SW**)
- **111×** speedup, **33×** less power than **BWA-MEM** (state-of-the-art **SW**)
- **3.9×** better throughput, **2.7×** less power than **Darwin** (state-of-the-art **HW**)
- **1.9×** better throughput, **82%** less logic power than **GenAx** (state-of-the-art **HW**)

(2) Pre-Alignment Filtering

- **3.7×** speedup, **1.7×** less power than **Shouji** (state-of-the-art **HW**)

(3) Edit Distance Calculation

- **22–12501×** speedup, **548–582×** less power than **Edlib** (state-of-the-art **SW**)
- **9.3–400×** speedup, **67×** less power than **ASAP** (state-of-the-art **HW**)

Conclusion on Our Contributions

Near-memory/In-memory Pre-alignment Filtering

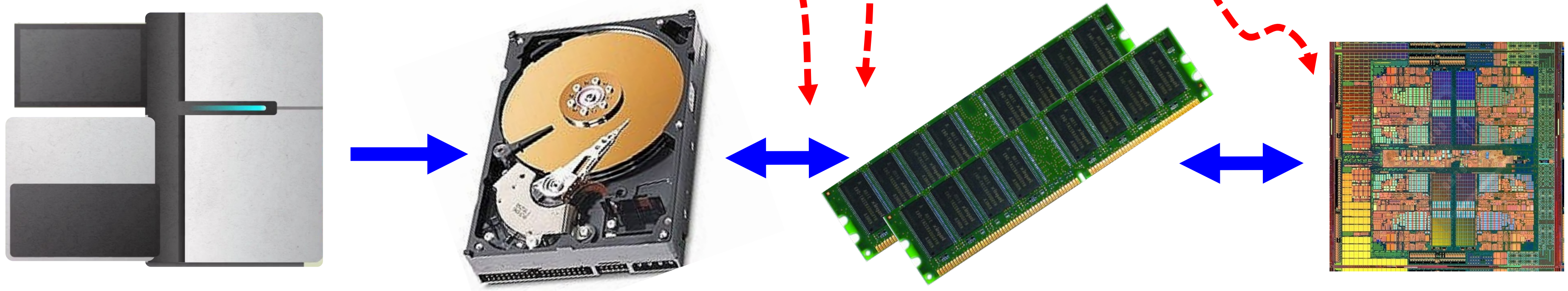
- **GRIM-Filter** **[BMC Genomics’18]**
- **GenASM** **[MICRO 2020]**
- **SneakySnake** **[IEEE Micro’21]**

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

Conclusion on Ongoing Directions

- Read alignment can be substantially accelerated using computationally inexpensive and accurate pre-alignment filtering algorithms designed for specialized hardware.

- All the three directions are used by mappers today, but filtering has replaced alignment as the bottleneck.

- Pre-alignment filtering does *not* sacrifice any of the aligner capabilities, as it does *not* modify or replace the alignment step.

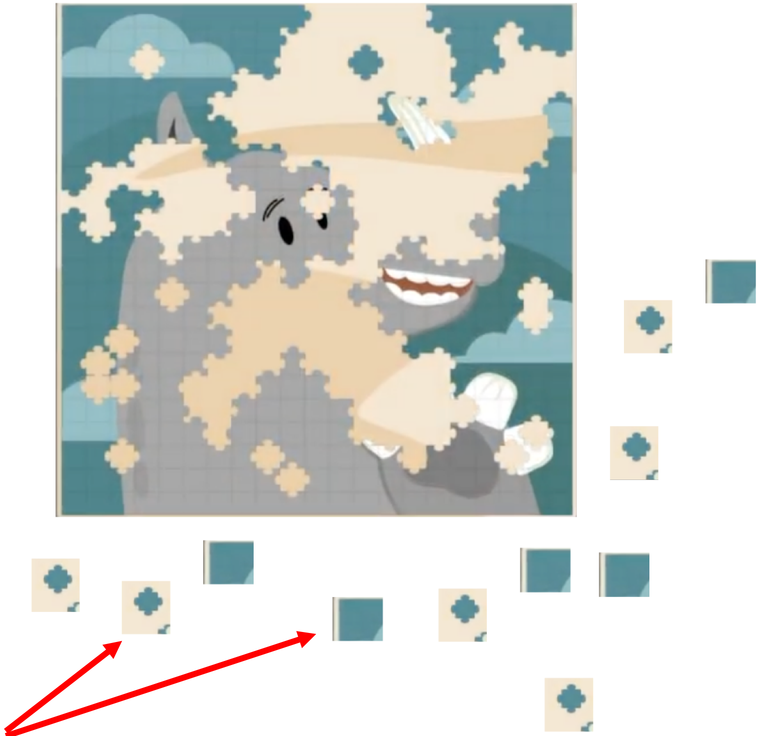
What else can be done?

What if we got a new version of the reference genome?

.FASTA file

Reference genome

.FASTQ file

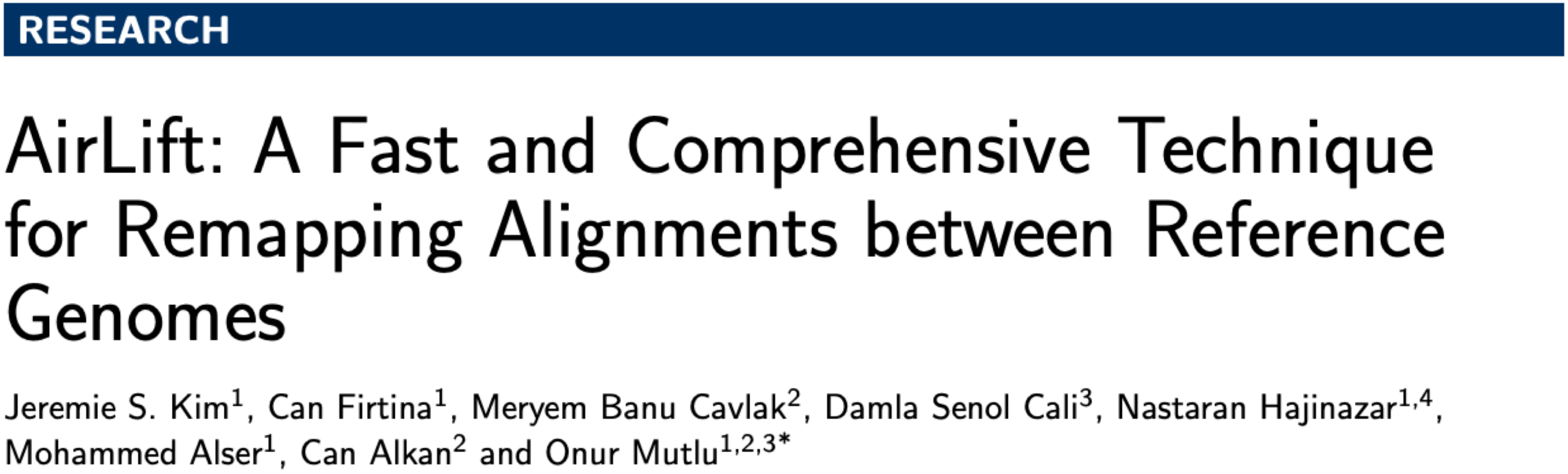


Reads

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

AirLift [Kim+, arXiv 2021]

Jeremie S. Kim, Can Firtina, Meryem Banu Cavlak, Damla Senol Cali, Mohammed Alser, Nastaran Hajinazar, Can Alkan, Onur Mutlu
"AirLift: A Fast and Comprehensive Technique for Translating Alignments between Reference Genomes", arXiv, 2021
[Source Code]
[Online link at arXiv]



RESEARCH

AirLift: A Fast and Comprehensive Technique for Remapping Alignments between Reference Genomes

Jeremie S. Kim[1], Can Firtina[1], Meryem Banu Cavlak[2], Damla Senol Cali[3], Nastaran Hajinazar[1,4], Mohammed Alser[1], Can Alkan[2] and Onur Mutlu[1,2,3]*

AirLift

- **Key observation:** Reference genomes are updated frequently. Repeating *read mapping is a computationally expensive workload.*

- **Key idea:** Update the mapping results of only affected reads depending on how a region in the old reference relates to another region in the new reference.

- **Key results:**
  - reduces number of reads that needs to be re-mapped to new reference by up to 99%
  - reduces overall runtime to re-map reads by 6.94x, 208x, and 16.4x for large (human), medium (C. elegans), and small (yeast) reference genomes

Clustering the Reference Genome Regions

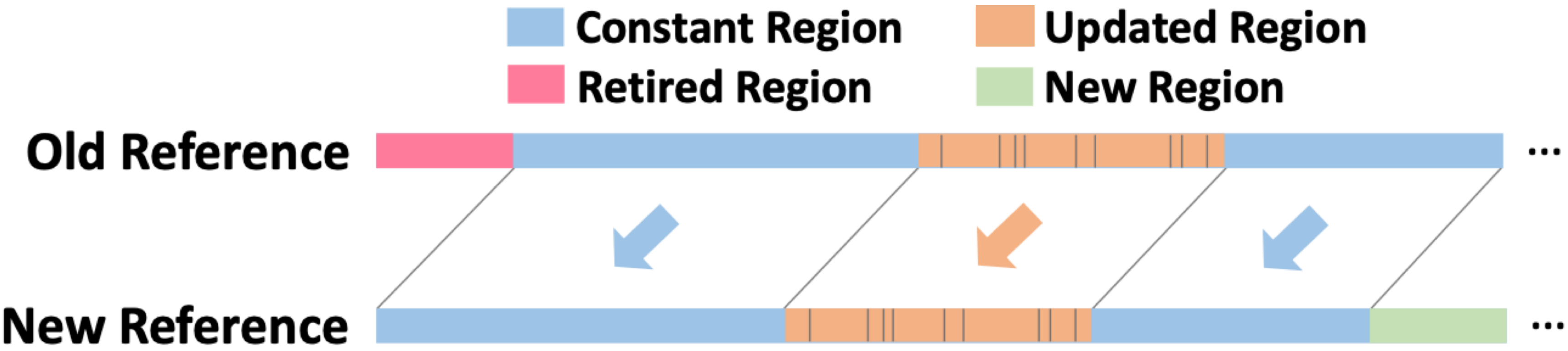
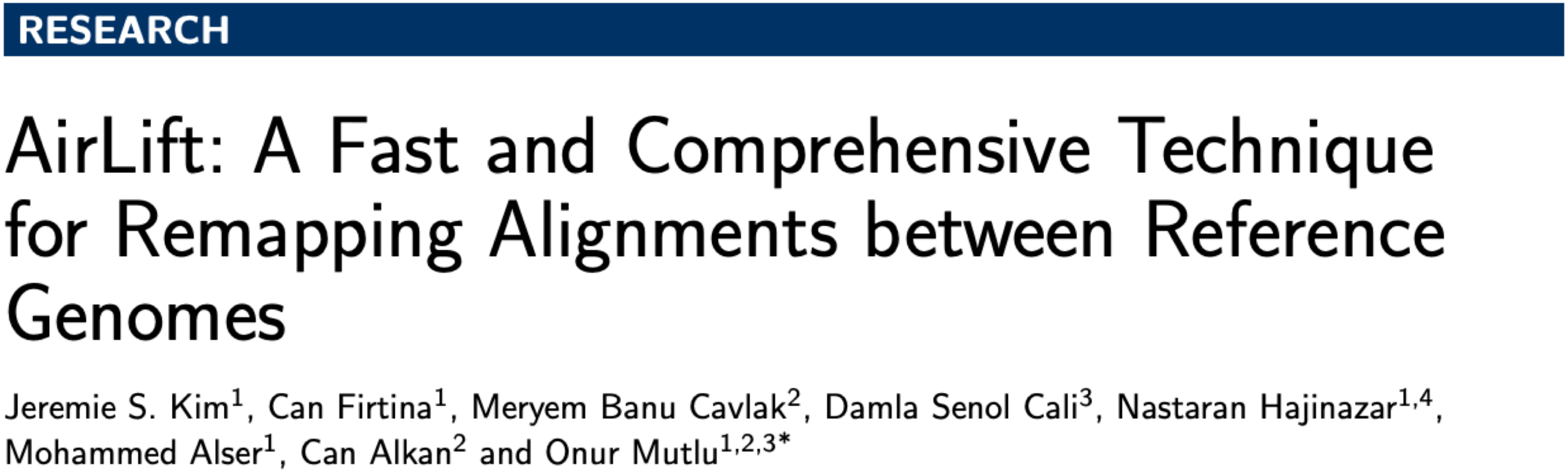


Fig. 2. Reference Genome Regions.

More Details on AirLift

Jeremie S. Kim, Can Firtina, Meryem Banu Cavlak, Damla Senol Cali, Mohammed Alser, Nastaran Hajinazar, Can Alkan, Onur Mutlu
"AirLift: A Fast and Comprehensive Technique for Translating Alignments between Reference Genomes", arXiv, 2021
[Source Code]
[Online link at arXiv]



RESEARCH

AirLift: A Fast and Comprehensive Technique for Remapping Alignments between Reference Genomes

Jeremie S. Kim[1], Can Firtina[1], Meryem Banu Cavlak[2], Damla Senol Cali[3], Nastaran Hajinazar[1,4], Mohammed Alser[1], Can Alkan[2] and Onur Mutlu[1,2,3*]

Agenda for Today

- What is Genome Analysis?
- What is Intelligent Genome Analysis?

- How we Analyze Genome?
- What is Read Mapping?
- What Makes Read Mapper Slow?

- Algorithmic & Hardware Acceleration
  - Seed Filtering Technique
  - Pre-alignment Filtering Technique
  - Read Alignment Acceleration

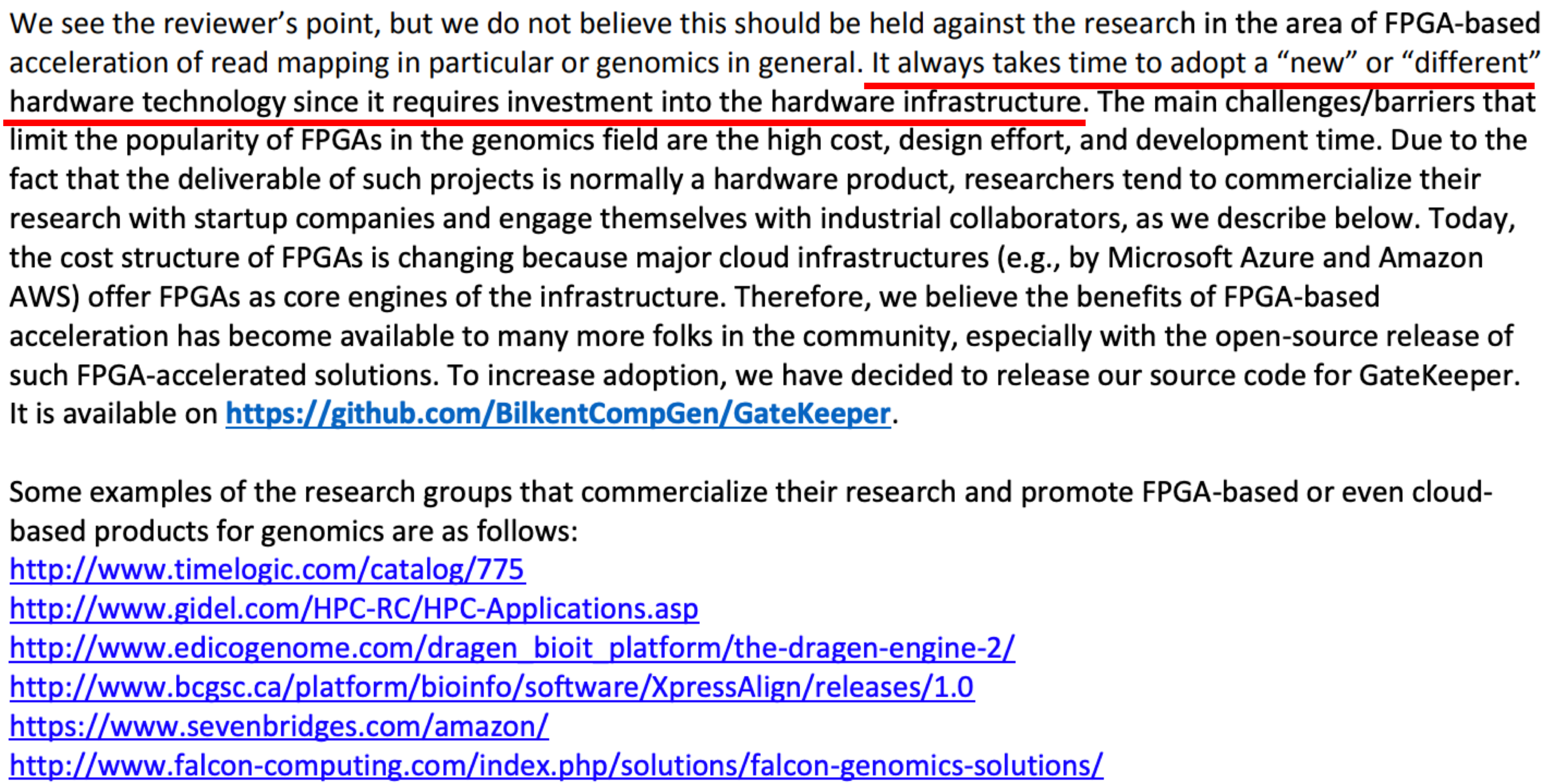
- **Where is Read Mapping Going Next?**

Adoption of hardware accelerators in genome analysis

Bioinformatics: **Reviewer #6** (Dec. 2016)

I have a major concern with the work that is actually not a problem with the manuscript at all. Specifically, I have the concern that there has been little to no adoption of previous specialized hardware solutions related to improving the speed of alignment. While there has been considerable work in this area (which the authors do an admirable job of citing), it does not seem that these hardware-based solutions have gained any type of real traction in the community, as the vast majority of alignment is still performed on "regular" CPUs, where the extent of hardware acceleration is the adoption of specific SIMD or vectorized instructions. While I don't think that this practical concern should preclude publication of the current work, it is something worth considering (what, if any, of the proposed improvements to the SHD filter could be "back-ported" to a software-only solution).

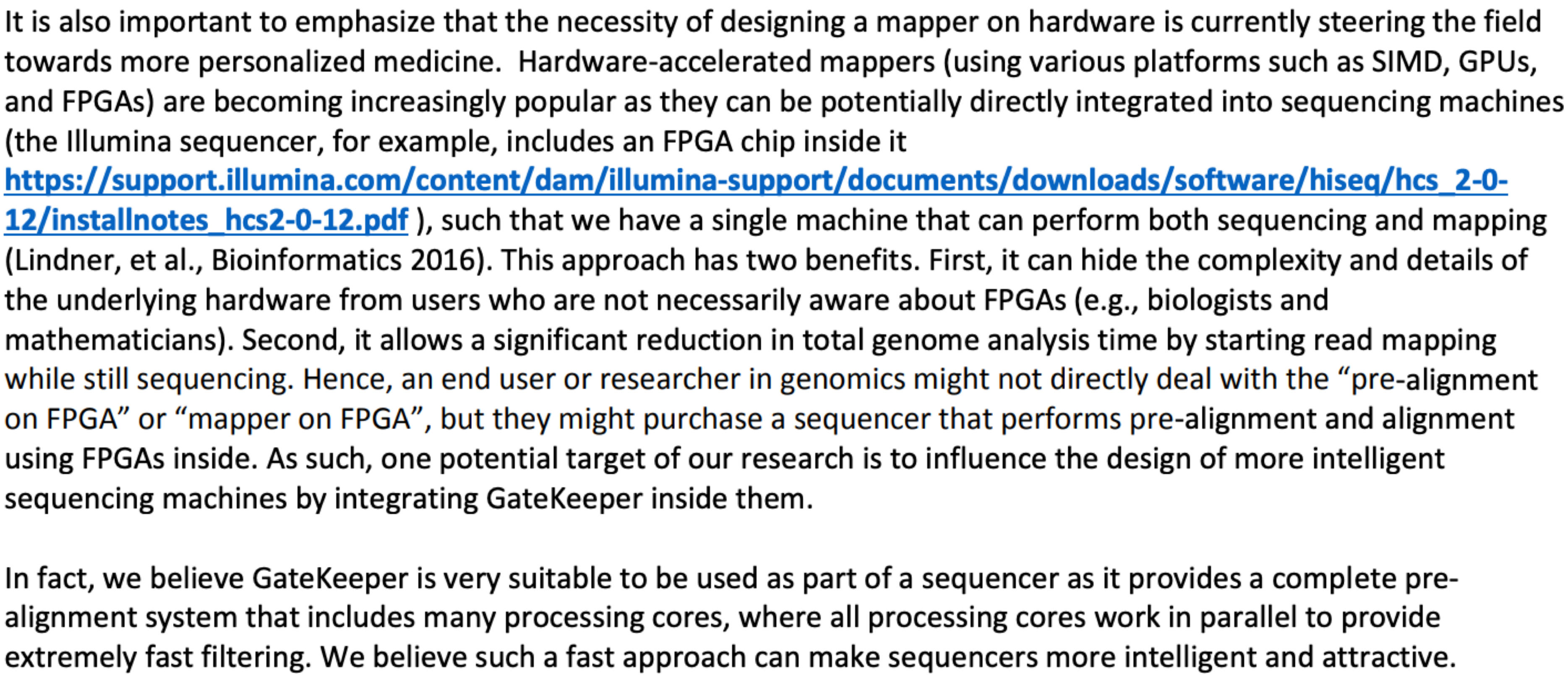
Our Response



We see the reviewer's point, but we do not believe this should be held against the research in the area of FPGA-based acceleration of read mapping in particular or genomics in general. It always takes time to adopt a "new" or "different" hardware technology since it requires investment into the hardware infrastructure. The main challenges/barriers that limit the popularity of FPGAs in the genomics field are the high cost, design effort, and development time. Due to the fact that the deliverable of such projects is normally a hardware product, researchers tend to commercialize their research with startup companies and engage themselves with industrial collaborators, as we describe below. Today, the cost structure of FPGAs is changing because major cloud infrastructures (e.g., by Microsoft Azure and Amazon AWS) offer FPGAs as core engines of the infrastructure. Therefore, we believe the benefits of FPGA-based acceleration has become available to many more folks in the community, especially with the open-source release of such FPGA-accelerated solutions. To increase adoption, we have decided to release our source code for GateKeeper. It is available on **https://github.com/BilkentCompGen/GateKeeper**.

Some examples of the research groups that commercialize their research and promote FPGA-based or even cloud-based products for genomics are as follows:
http://www.timelogic.com/catalog/775
http://www.gidel.com/HPC-RC/HPC-Applications.asp
http://www.edicogenome.com/dragen_bioit_platform/the-dragen-engine-2/
http://www.bcgsc.ca/platform/bioinfo/software/XpressAlign/releases/1.0
https://www.sevenbridges.com/amazon/
http://www.falcon-computing.com/index.php/solutions/falcon-genomics-solutions/

Our Response (cont'd)



It is also important to emphasize that the necessity of designing a mapper on hardware is currently steering the field towards more personalized medicine. Hardware-accelerated mappers (using various platforms such as SIMD, GPUs, and FPGAs) are becoming increasingly popular as they can be potentially directly integrated into sequencing machines (the Illumina sequencer, for example, includes an FPGA chip inside it https://support.illumina.com/content/dam/illumina-support/documents/downloads/software/hiseq/hcs_2-0-12/installnotes_hcs2-0-12.pdf), such that we have a single machine that can perform both sequencing and mapping (Lindner, et al., Bioinformatics 2016). This approach has two benefits. First, it can hide the complexity and details of the underlying hardware from users who are not necessarily aware about FPGAs (e.g., biologists and mathematicians). Second, it allows a significant reduction in total genome analysis time by starting read mapping while still sequencing. Hence, an end user or researcher in genomics might not directly deal with the "pre-alignment on FPGA" or "mapper on FPGA", but they might purchase a sequencer that performs pre-alignment and alignment using FPGAs inside. As such, one potential target of our research is to influence the design of more intelligent sequencing machines by integrating GateKeeper inside them.

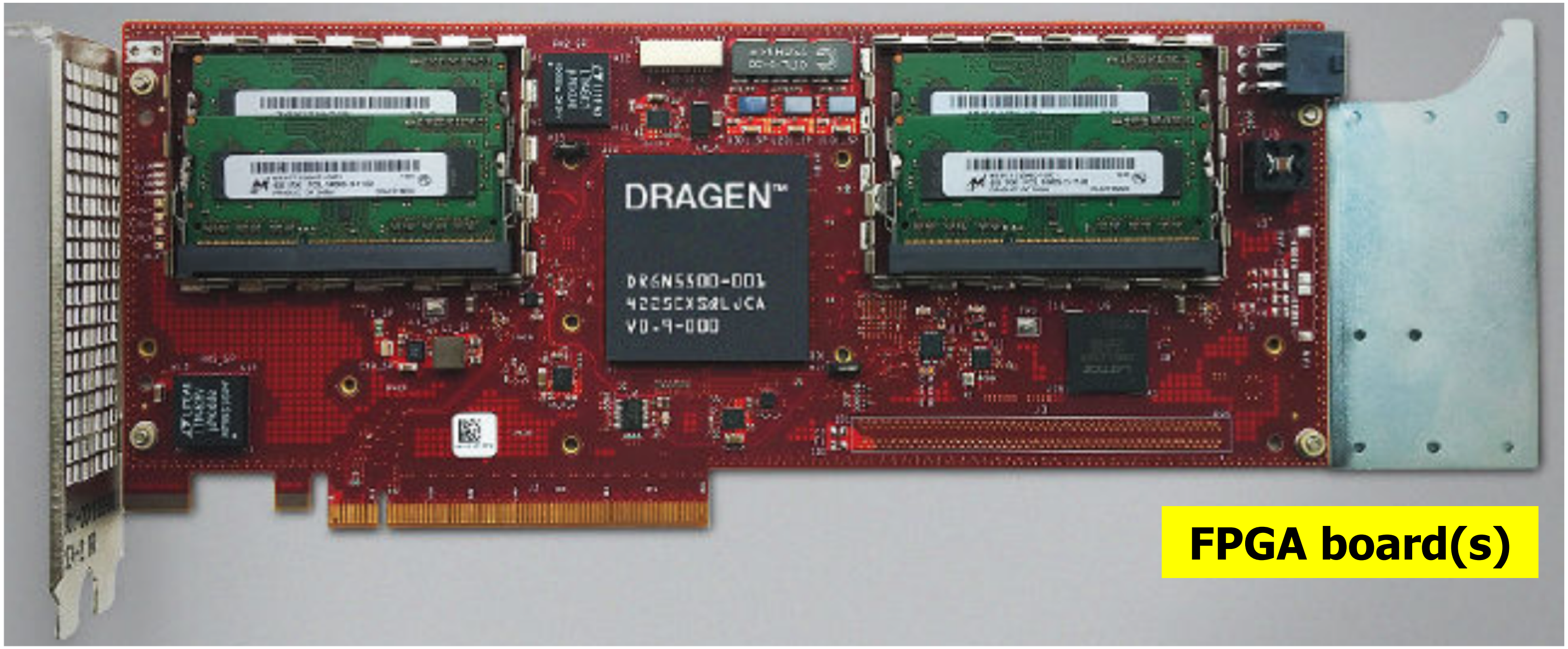
In fact, we believe GateKeeper is very suitable to be used as part of a sequencer as it provides a complete pre-alignment system that includes many processing cores, where all processing cores work in parallel to provide extremely fast filtering. We believe such a fast approach can make sequencers more intelligent and attractive.

Dream
and, they will come

Computing landscape is very different from 10-20 years ago

Illumina DRAGEN Bio-IT Platform (2018)

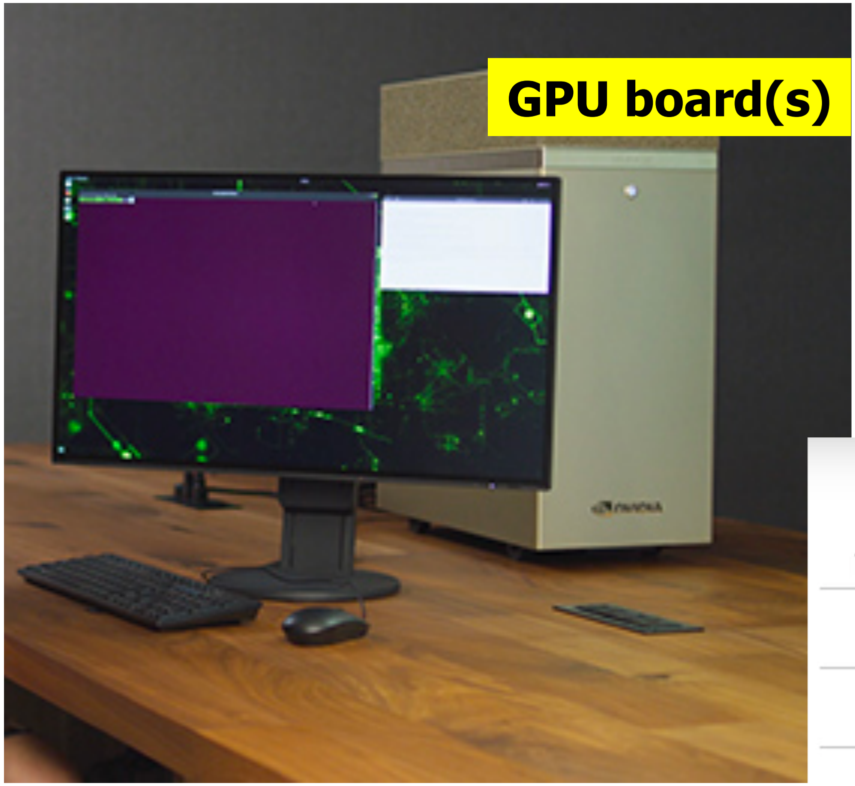
- Processes whole genome at 30x coverage in ~25 minutes with hardware support for data compression



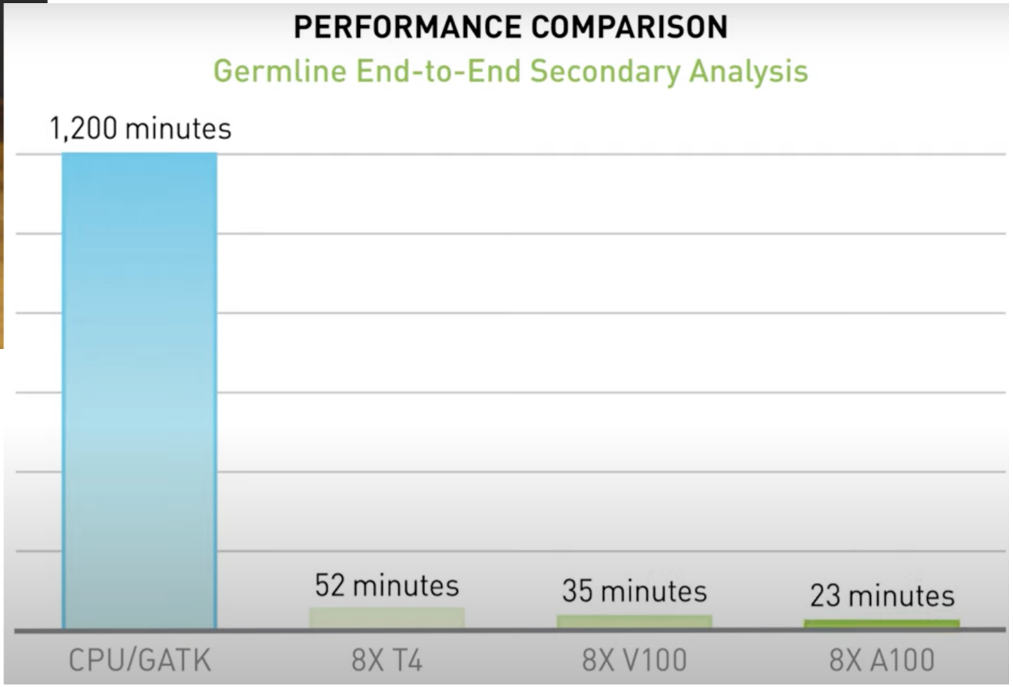
FPGA board(s)

emea.illumina.com/products/by-type/informatics-products/dragen-bio-it-platform.html
emea.illumina.com/company/news-center/press-releases/2018/2349147.html

NVIDIA Clara Parabricks (2020)



A University of Michigan's startup in 2018 and joined NVIDIA in 2020



https://developer.nvidia.com/clara-parabricks

Computing

is Still Bottlenecked by Data Movement

Adoption Challenges of Hardware Accelerators

- Accelerate the entire read mapping process rather than its individual steps (Amdahl's law)

- Reduce the high amount of data movement
  - Working directly on compressed data
  - Filter out unlikely-reused data at the very first component of the compute system

- Develop flexible hardware architectures that do NOT conservatively **limit the range** of supported parameter values at design time

- Adapt existing genomic data formats for hardware accelerators or develop more efficient file formats

Adoption Challenges of Hardware Accelerators

- Maintaining the same (or better) accuracy/sensitivity of the output results of the software version
  - Using heuristic algorithms to gain speedup!

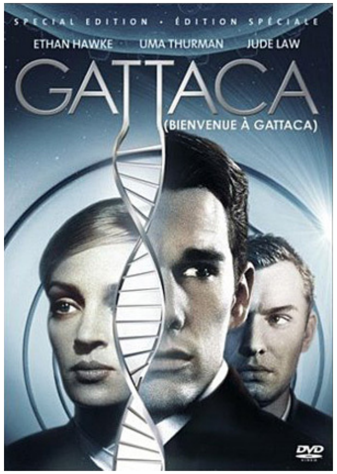
- High hardware cost

- Long development life-cycle for FPGA platforms

Did we Achieve Our Goal?

- **Fast** genome analysis in mere seconds using limited computational resources (i.e., personal computer or small hardware).

1997



2015

FROM THE DIRECTOR OF THE INCREDIBLES & MISSION: IMPOSSIBLE - GHOST PROTOCOL
GEORGE CLOONEY
TOMORROWLAND
REMEMBER TOMORROW MAY 22
EXPERIENCE IT IN IMAX

Open Questions

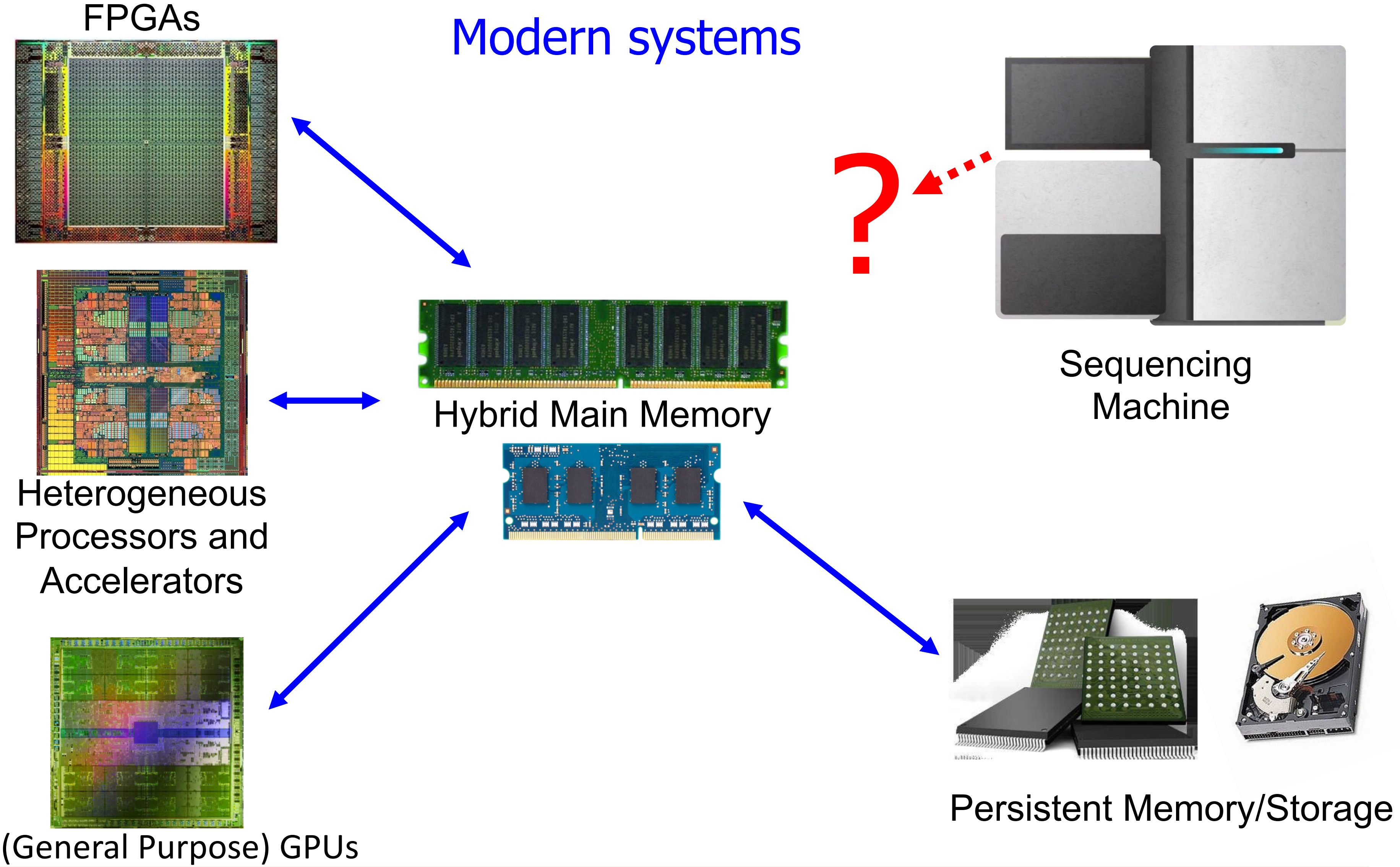
How and where to enable

fast, accurate, cheap,

privacy-preserving, and exabyte scale

analysis of genomic data?

Pushing Towards New Architectures



FPGAs

Modern systems

?

Sequencing Machine

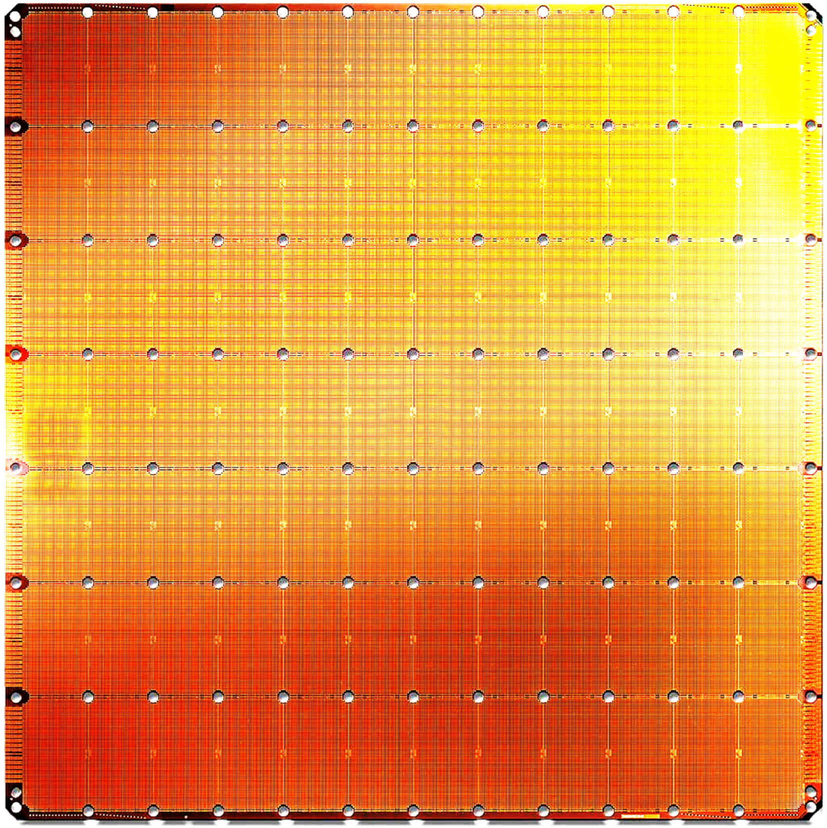
Hybrid Main Memory

Heterogeneous Processors and Accelerators

Persistent Memory/Storage

(General Purpose) GPUs

Cerebras's Wafer Scale Engine (2019)



- The largest ML accelerator chip
- 400,000 cores

NVIDIA TITAN V

Cerebras WSE
1.2 Trillion transistors
46,225 mm^2

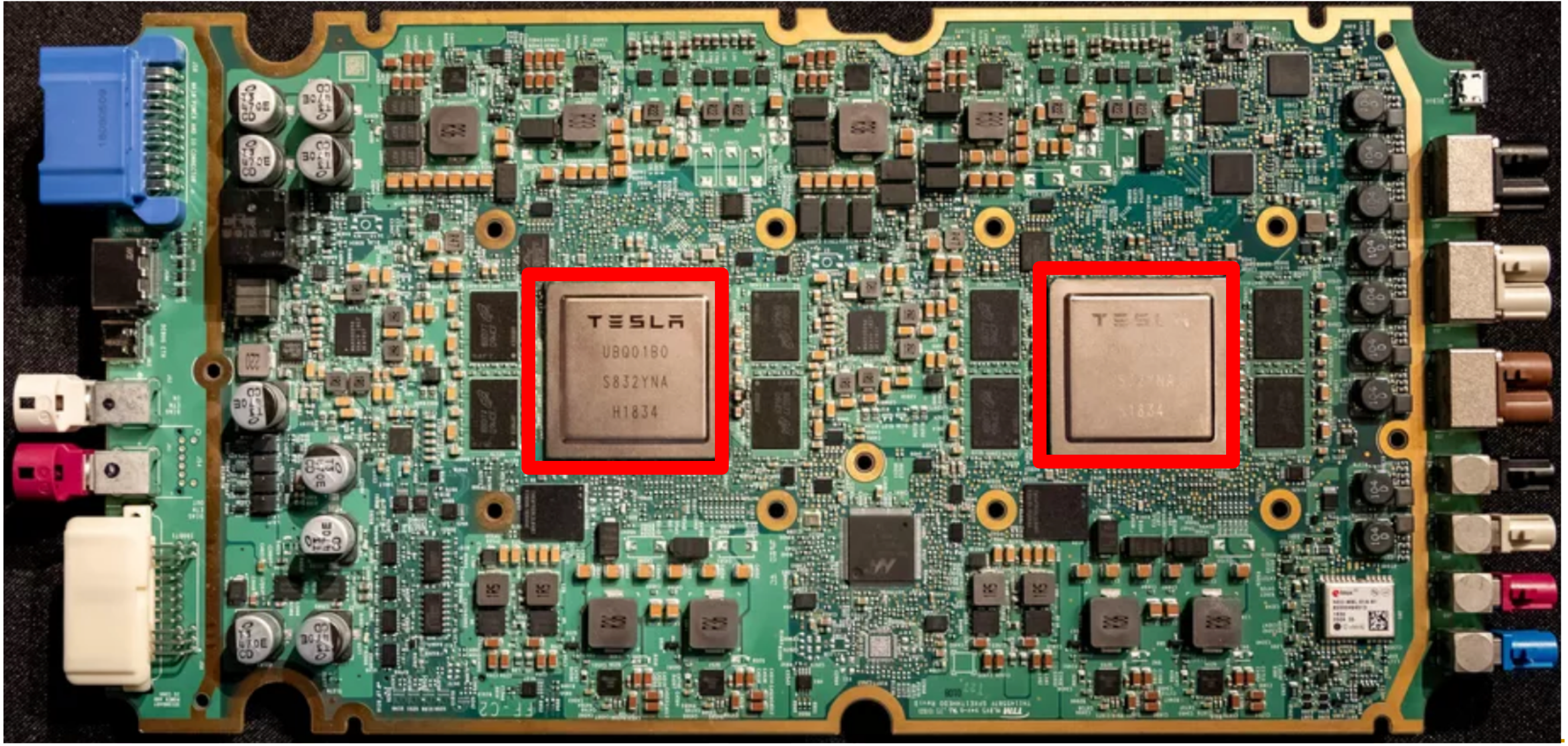
Largest GPU
21.1 Billion transistors
815 mm^2

https://www.cerebras.net/cerebras-wafer-scale-engine-why-we-need-big-chips-for-deep-learning/

TESLA Full Self-Driving Computer (2019)

- ML accelerator: 260 mm^2, 6 billion transistors, 600 GFLOPS GPU, 12 ARM 2.2 GHz CPUs.
- Two redundant chips for better safety.

https://youtu.be/Ucp0TTmvqOE?t=4236



Where is Read Mapping Going Next?

Will 100% accurate genome-long reads alleviate/eliminate the need for read mapping?

Think about metagenomics, pan-genomics, ...

Lecture Conclusion

- System design for bioinformatics is a critical problem
  - It has large scientific, medical, societal, personal implications

- This lecture is about accelerating a key step in bioinformatics: genome sequence analysis
  - In particular, read mapping

- Many bottlenecks exist in accessing and manipulating huge amounts of genomic data during analysis

- We cover various recent ideas to accelerate read mapping
  - A journey since September 2006

Key Takeaways

- Population-scale analyses are not an easy task

- You need to consider **many** things in designing a new system + have good intuition/insight into ideas/tradeoffs

- But, it is fun and can be **very rewarding/impactful**

- And, enables a great future
  - It has large scientific, medical, societal, personal implications

- **Very hot topic for graduate studies and research!**

Key Conclusion

Most speedup comes from

parallelism enabled by

novel architectures and algorithms

Acknowledgments

Onur Mutlu, ETH Zurich

Can Alkan, Bilkent University

Serghei Mangul, USC

- Many colleagues and collaborators
  - Damla Senol Cali, Jeremie Kim, Hasan Hassan, Can Firtina, Juan Gómez Luna, Hongyi Xin, …
- Funders:
  - NIH and Industrial Partners (Alibaba, AMD, Google, Facebook, HP Labs, Huawei, IBM, Intel, Microsoft, Nvidia, Oracle, Qualcomm, Rambus, Samsung, Seagate, VMware)
- All papers, source code, and more are at:
  - https://people.inf.ethz.ch/omutlu/projects.htm

Work With Us

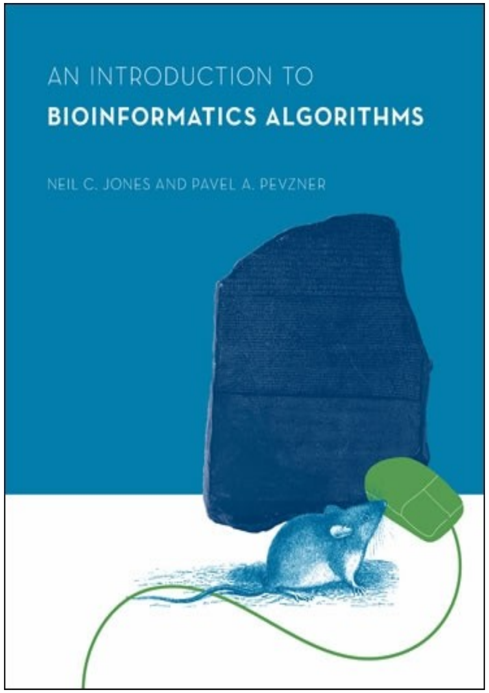
- If you are already a student at ETH and are interested in doing research with SAFARI research group on similar topics, Talk to me:
    - ALSERM@ethz.ch

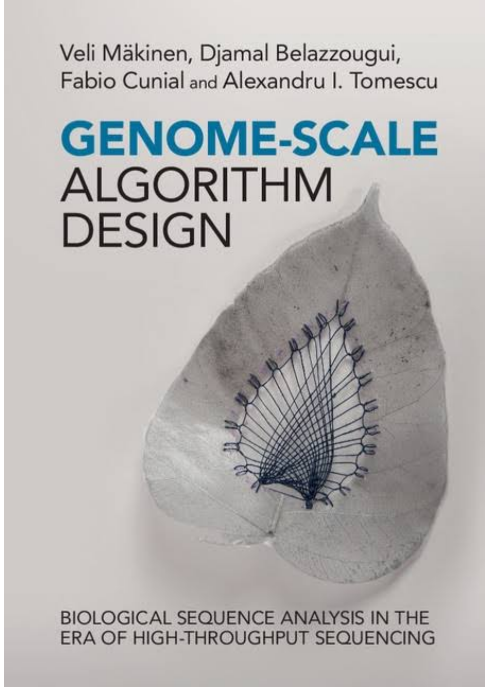
Openings @ SAFARI

- We are **hiring** enthusiastic and motivated students and researchers at all levels.
- Join us now: safari.ethz.ch/apply

Recommended Readings

- Jones, Neil C. and Pavel Pevzner. "An introduction to bioinformatics algorithms," MIT press, 2004.
- Mäkinen, Veli, Djamal Belazzougui, Fabio Cunial, and Alexandru I. Tomescu. "Genome-scale algorithm design," Cambridge University Press, 2015.

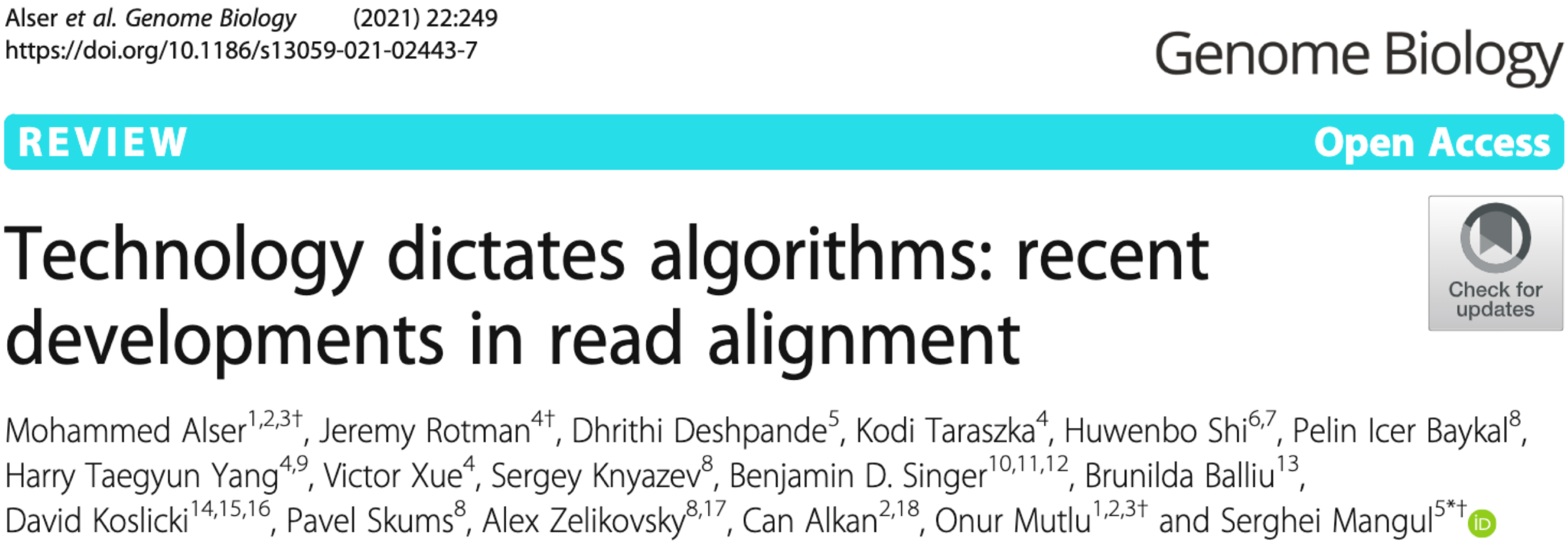



Veli Mäkinen, Djamal Belazzougui,
Fabio Cunial and Alexandru I. Tomescu
GENOME-SCALE
ALGORITHM
DESIGN
BIOLOGICAL SEQUENCE ANALYSIS IN THE
ERA OF HIGH-THROUGHPUT SEQUENCING

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

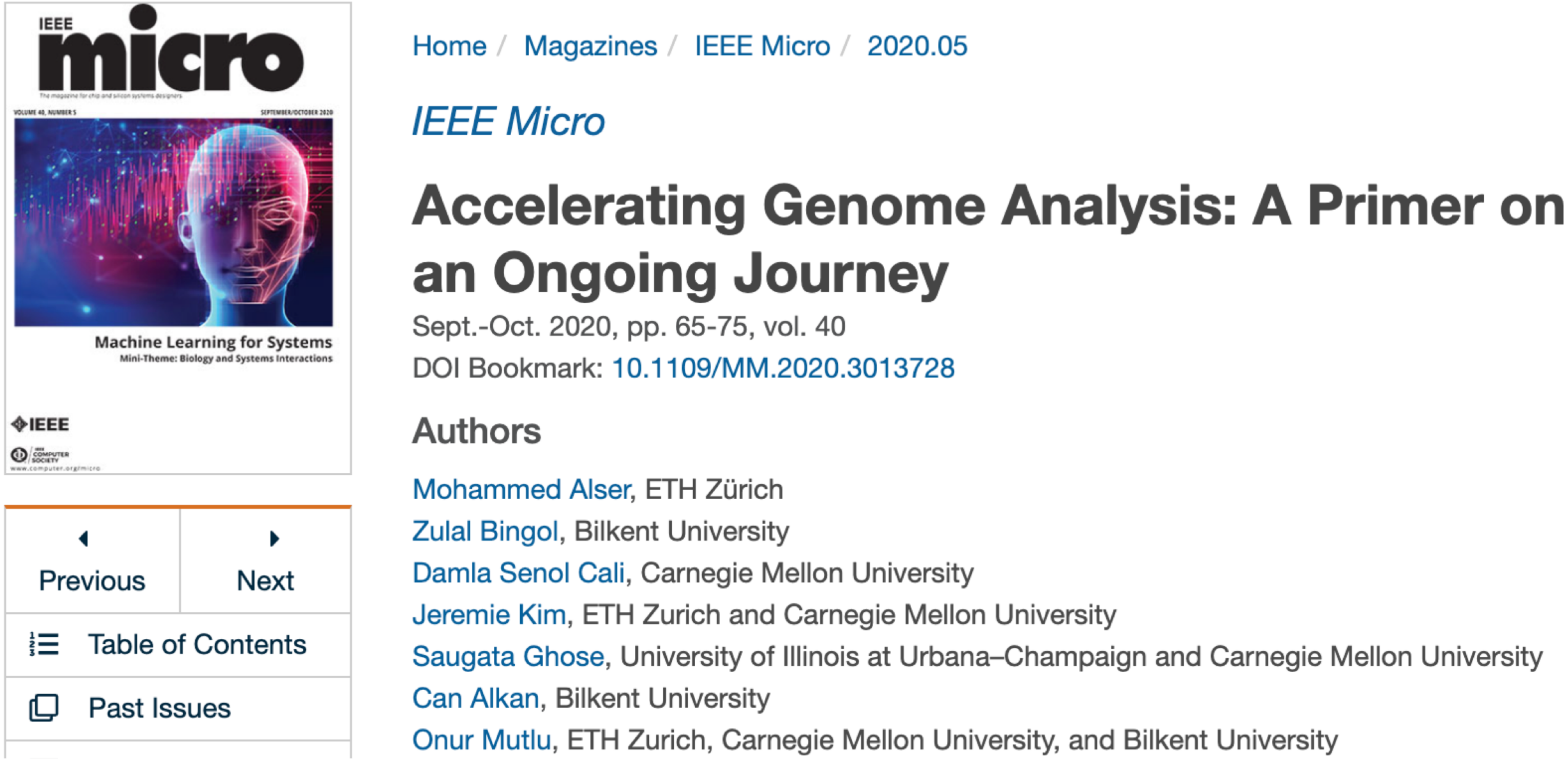
Technology dictates algorithms: recent developments in read alignment

Check for updates

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

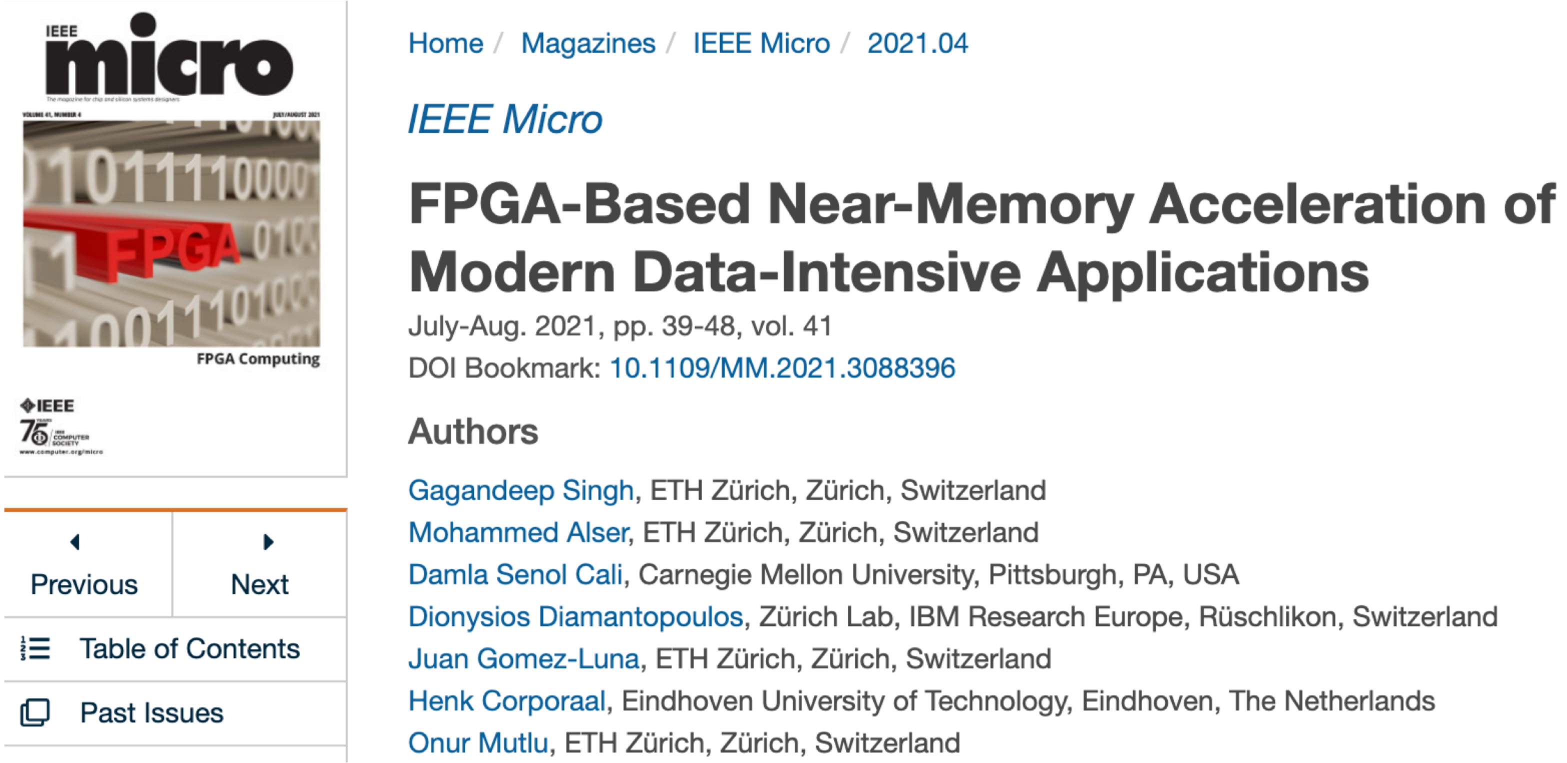
DOI Bookmark: 10.1109/MM.2020.3013728

Authors

Mohammed Alser, ETH Zürich
Zulal Bingol, Bilkent University
Damla Senol Cali, Carnegie Mellon University
Jeremie Kim, ETH Zurich and Carnegie Mellon University
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]



Home / Magazines / IEEE Micro / 2021.04

IEEE Micro

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

July-Aug. 2021, pp. 39-48, vol. 41

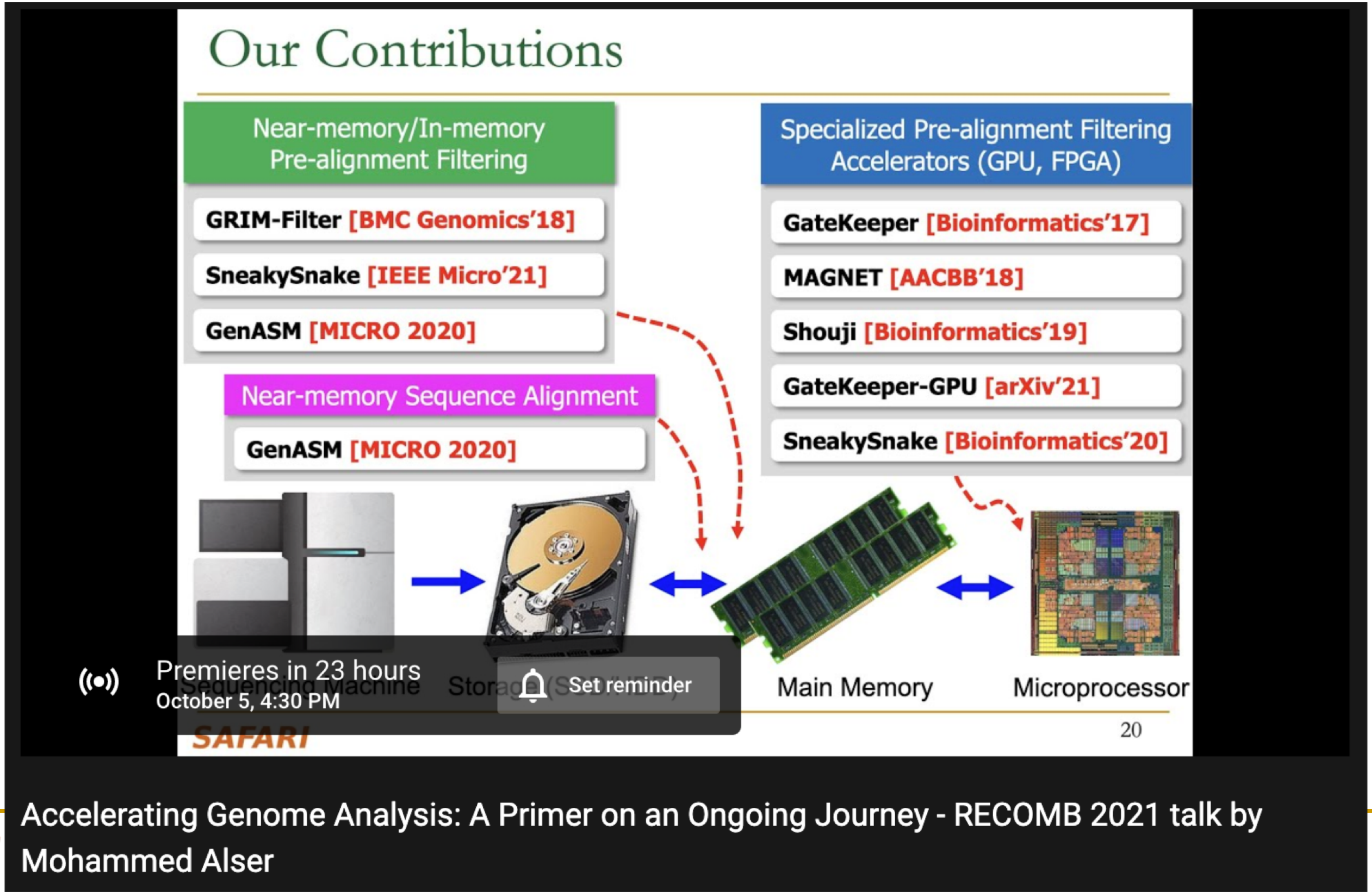
DOI Bookmark: 10.1109/MM.2021.3088396

Authors

Gagandeep Singh, ETH Zürich, Zürich, Switzerland
Mohammed Alser, ETH Zürich, Zürich, Switzerland
Damla Senol Cali, Carnegie Mellon University, Pittsburgh, PA, USA
Dionysios Diamantopoulos, Zürich Lab, IBM Research Europe, Rüschlikon, Switzerland
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)]



Our Contributions

Near-memory/In-memory Pre-alignment Filtering

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

Near-memory Sequence Alignment

- GenASM [MICRO 2020]

Specialized Pre-alignment Filtering Accelerators (GPU, FPGA)

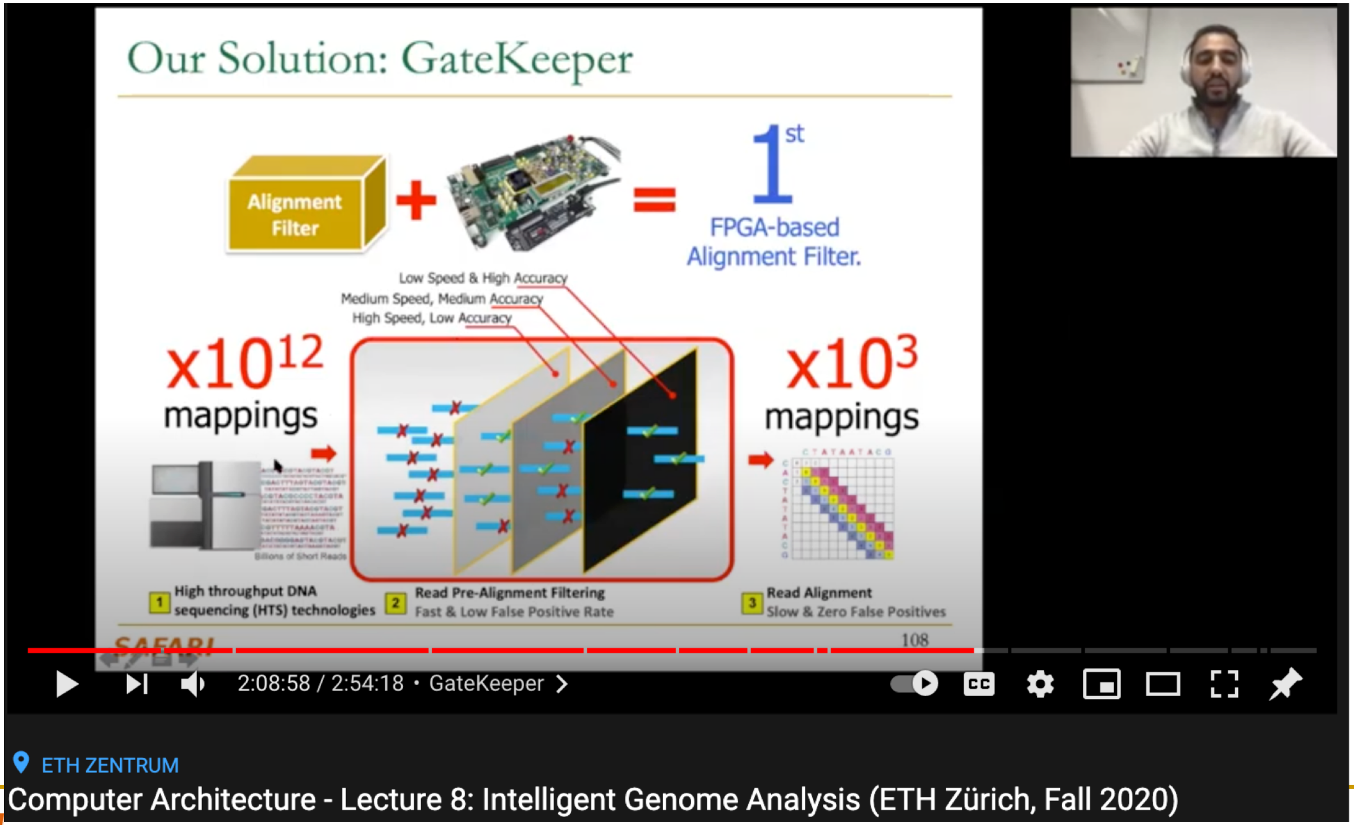
- GateKeeper [Bioinformatics'17]
- MAGNET [AACBB'18]
- Shouji [Bioinformatics'19]
- GateKeeper-GPU [arXiv'21]
- SneakySnake [Bioinformatics'20]

Premieres in 23 hours
October 5, 4:30 PM

Accelerating Genome Analysis: A Primer on an Ongoing Journey - RECOMB 2021 talk by Mohammed Alser

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)]



Our Solution: GateKeeper

Alignment Filter + = 1st FPGA-based Alignment Filter.

Low Speed & High Accuracy
Medium Speed, Medium Accuracy
High Speed, Low Accuracy

x10^12 mappings

x10^3 mappings

1 High throughput DNA sequencing (HTS) technologies

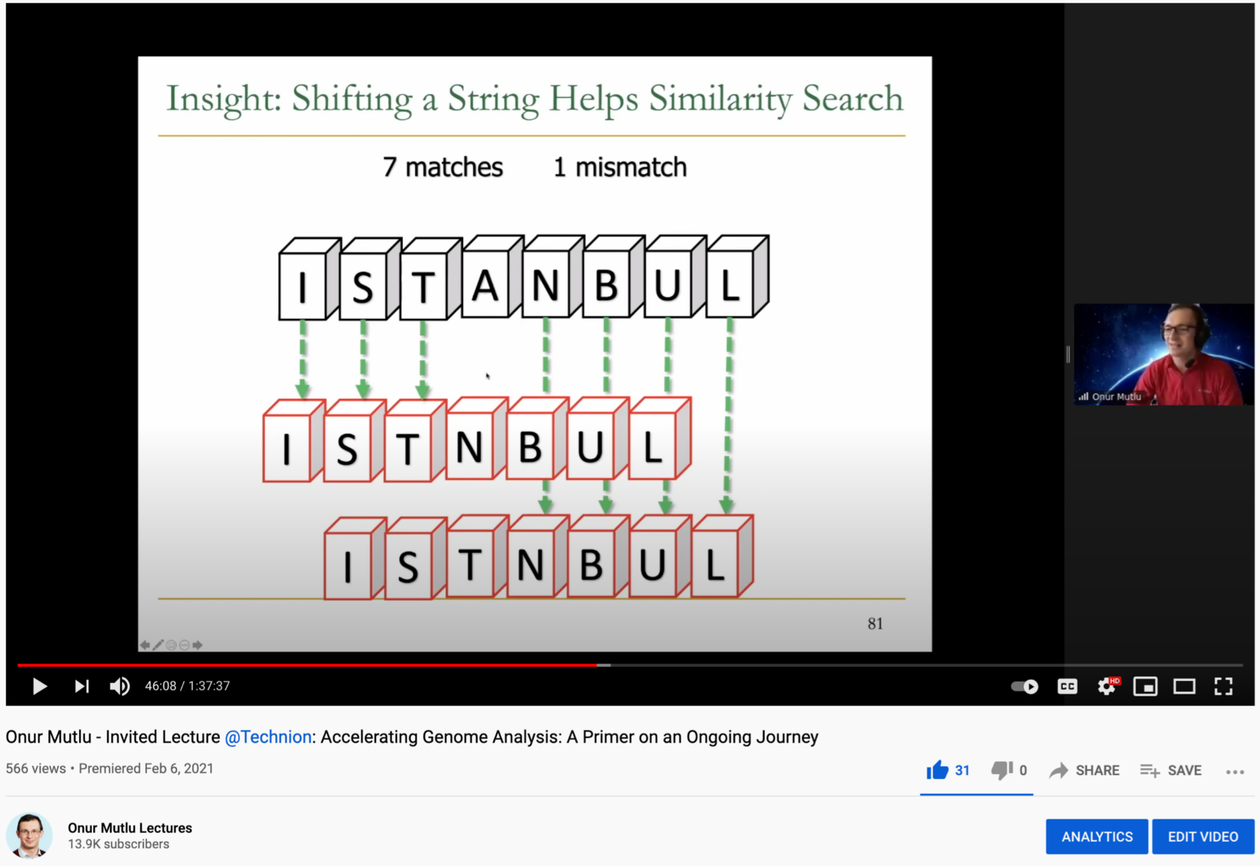
2 Read Pre-Alignment Filtering Fast & Low False Positive Rate

3 Read Alignment Slow & Zero False Positives

Computer Architecture - Lecture 8: Intelligent Genome Analysis (ETH Zürich, Fall 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)]



Insight: Shifting a String Helps Similarity Search

7 matches 1 mismatch

Onur Mutlu - Invited Lecture @Technion: Accelerating Genome Analysis: A Primer on an Ongoing Journey

566 views • Premiered Feb 6, 2021

Onur Mutlu Lectures
13.9K subscribers

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

https://www.youtube.com/onurmutlulectures

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.

- Alser+, “Shouji: a fast and efficient pre-alignment filter for sequence alignment”, *Bioinformatics* 2019.

- Kim+, "GRIM-Filter: Fast Seed Location Filtering in DNA Read Mapping Using Processing-in-Memory Technologies”, *BMC Genomics*, 2018.

- Alser+, "GateKeeper: A New Hardware Architecture for Accelerating Pre-Alignment in DNA Short Read Mapping”, *Bioinformatics*, 2017.

- Alser+, "MAGNET: understanding and improving the accuracy of genome pre-alignment filtering”, *IPSI Transaction*, 2017.

Computer Architecture

Lecture 10:
Intelligent Genome Analysis

Dr. Mohammed Alser

@mealser

ETH Zurich

Fall 2021

29 October 2021

SAFARI

ETH zürich