P&S Mobile Genomics

Introduction & Project Proposals

Dr. Mohammed Alser

@mealser

ETH Zurich

Fall 2021

5 October 2021

SAFARI

ETH zürich

The Role of This Course

Projects & Seminars: Mobile Genomics

- We will cover the **basics** of **genome analysis** to understand the **speed-accuracy tradeoff** in using computationally-lightweight heuristics versus accurate computationally-expensive algorithms.

- Students will **experimentally** evaluate different heuristic **algorithms** and observe their effect on **the end results**.

- This evaluation will give the students the chance to carry out a **hands-on project** to implement one or more of these heuristic algorithms in **their smartphones** and **help the society by enabling on-site analysis of genomic data**.

Key Objectives

- Multiple components that are aimed at improving students'
  - Basic knowledge in genome analysis (dry lab)
  - Technical skills in genome analysis and computer architecture
  - Critical thinking and analysis
  - Familiarity with key research directions
  - Technical presentation of your project

Key Goal

(Learn how to)

efficiently implement

one of the key steps in genome

analysis on portable devices

Prerequisites of the Course

- No prior knowledge in bioinformatics or genome analysis is required.
- A good knowledge in C programming language and programming is required.
- Interest in making things efficient and solving problems

Course Info: Who Are We?

- **Onur Mutlu**
  - Full Professor @ ETH Zurich ITET (INFK), since September 2015
  - Strecker Professor @ Carnegie Mellon University ECE/CS, 2009-2016, 2016-…
  - PhD from UT-Austin, worked at Google, VMware, Microsoft Research, Intel, AMD
  - https://people.inf.ethz.ch/omutlu/
  - omutlu@gmail.com (Best way to reach me)
  - https://people.inf.ethz.ch/omutlu/projects.htm
- Research and Teaching in:
  - Computer architecture, computer systems, hardware security, bioinformatics
  - Memory and storage systems
  - Hardware security, safety, predictability
  - Fault tolerance
  - Hardware/software cooperation
  - Architectures for bioinformatics, health, medicine
  - …

Course Info: Who Are We?

Mohammed Alser

- Lecturer and Senior Researcher, SAFARI Research Group, ETH Zürich, since Sept. 2018.
- PhD from Bilkent University (Turkey) 2018, worked at UCLA, TU Dresden, and PETRONAS.
- Received the IEEE Turkey Doctoral Dissertation Award and a number of international prestigious awards.

- https://twitter.com/mealser

- My main research is in bioinformatics, computational genomics, metagenomics, and computer architecture.

- I am especially excited about **building** new data structures, algorithms, and architectures that **make intelligent genome analysis a reality.**

Course Info: Who Are We?

Juan Gómez Luna

Senior Researcher and Lecturer

Processing-In-Memory | Heterogeneous computing | Memory Systems | Bioinformatics | Medical imaging

Nour Almadhoun Alserr

Senior Researcher

Data privacy | Bioinformatics | Computational Genomics

Can Firtina

PhD Student

Genome Assembly | Sequence Analysis & Alignment | Biologically-Inspired Computing Paradigms | Brain-Computer Interfaces | Phase-change memory

- Get to know them and their research: https://safari.ethz.ch/safari-group/

Course Requirements and Expectations

- Attendance required for all meetings
- Study the learning materials
- Each student will carry out a hands-on project
  - Build, implement, code, and design with close engagement from the supervisors
- Participation
  - Ask questions, contribute thoughts/ideas
  - Read relevant papers
- Presentation & GitHub repository

We will help the projects with good progress to get published in good venues!

Course Website

- https://safari.ethz.ch/projects_and_seminars/fall2021/doku.php?id=genome_seq_mobile
- Useful information for the course
- Check your email and Moodle frequently for announcements
- We will also have Moodle for Q&A, announcements, ..

Next Meetings

- We will give you a chance to select a project,
- Then, we will have **1-1 meetings** to match your interests, skills, and background with a suitable project.
- It is important that you **study the learning materials** before our next meeting!
- We will start the projects **next week**.

WHAT IS GENOME ANALYSIS?

What is Genome Analysis?

Genomic analysis

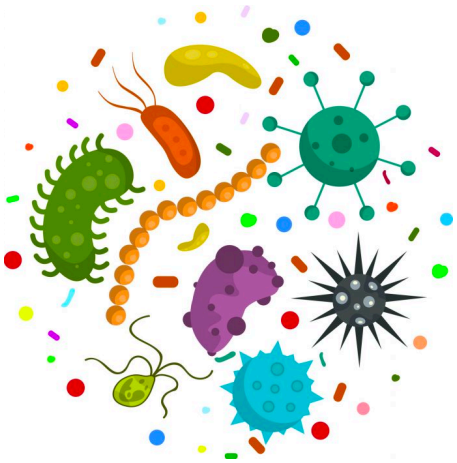
Atom RSS Feed

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

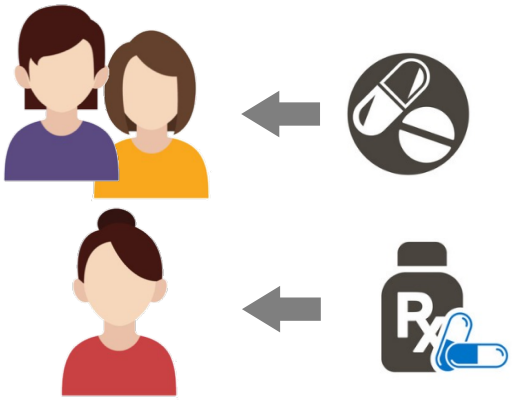
Applications of Genome Analysis

Understanding **genetic variations**



Predicting the presence and relative abundances of **microbes** in a sample

Rapid surveillance of **disease outbreaks**



Developing **personalized medicine**

And many other applications …

How to Analyze a Genome?

NO

machine gives the **complete sequence** of genome as output

>CCTCCTCAGTGCCACCCAGCCCACTGGCAGCTCCCAAACAGGCTCTTATTAAAACACCCTGTTCCCTGCCCCTTGGAGTGAGGTGTCAAG
GACCTAAACTAAAAAAAAAAAAAGAAAAAGAAAAGAAAAAGAATTTAAAATTTAAGTAATTCTTTGAAAAAAACTAATTTCTAAGCTTCTT
CATGTCAAGGACCTAATGTGCTAAACAGCACTTTTTTGACCATTATTTTGGATCTGAAAGAAATCAAGAATAAATGAAGGACTTGATACATTG
GAAGAGGAGAGTCAAGGACCTACAGAAAAAAAAAAAAAAGAAAAAGAAAAGAAAAAGA**A**TTTAAAATTTAAGTAATTCTTTGAAAAAA
ACTAATTTCTAAGCTTCTT**C**ATGTCAAGGACCTAATGTCTGTGTTGCAGGTCTTCTTGCATTTCCCTGTCAAAAGAAAAAGAATTTAAAATTT
AAGTAATTCTTTGAAAAAAACTAATTTCTAAGCTTCTTCATGTCAAGGACCTAATGTCAGGCCAAGAGTTGCAAAAAAAAAAAAAGAAAAA
GAAAAGAAAAAGAATTTAAAATTTA**AGTAATTCTTTGAAAAAAACTAATTTCTAAGCTTCTTCAT**GTCAAGGACCTAATGTAGCCAGAATGG
TTGTGGGATGGGAGCCTCTGTGGACCGACCAGGTAGCTCTCTTTTCCACACTGTAGTCTCAAAGCTTCTTCATGTGGTTTCTCTGAGTGAAA
AAAAAAAAAAGAAAAAGAAAAGAAAAAGAATTTAAAATTTAAGTAATTCTTTGAAAAAAACTAATTTCTAAGCTT**T**TTCATGTCAAGGACC
TAATGTAGCTATACTGAACGTTATCTAGGGGAAAGATTGAAGGGGAGCTCTAAGGTCAACACACCACCACTTCCCAGAAAGCTTCTTCA……

DNA Testing

Fall DNA special

Just 55 CHF ~~89 CHF~~

Order now

The promotion ends today in 12 more hours!

https://www.myheritage.ch/dna

DNA Testing

Fall DNA specia

Just 55 CHF ~~89 CH~~

now

ay in 12 more hours!

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/

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

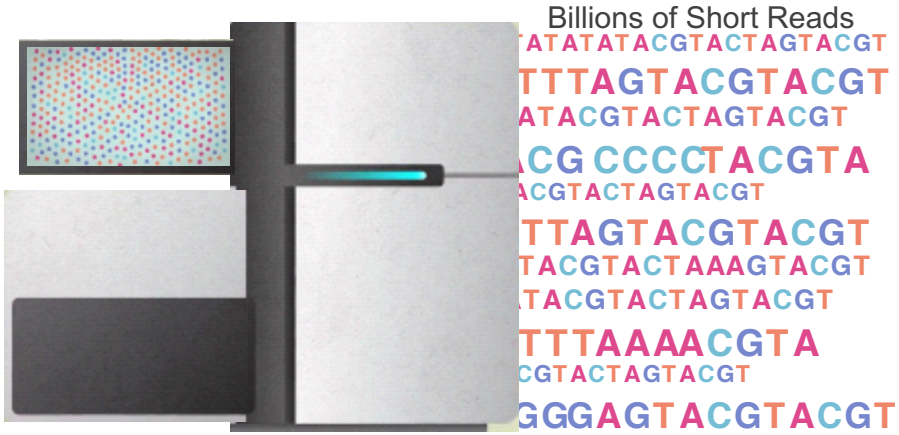
… and more! All produce data with different properties.

Genome Sequencer is a Chopper

Regardless the sequencing machine,

reads still lack information about their order and location

(which part of genome they are originated from)

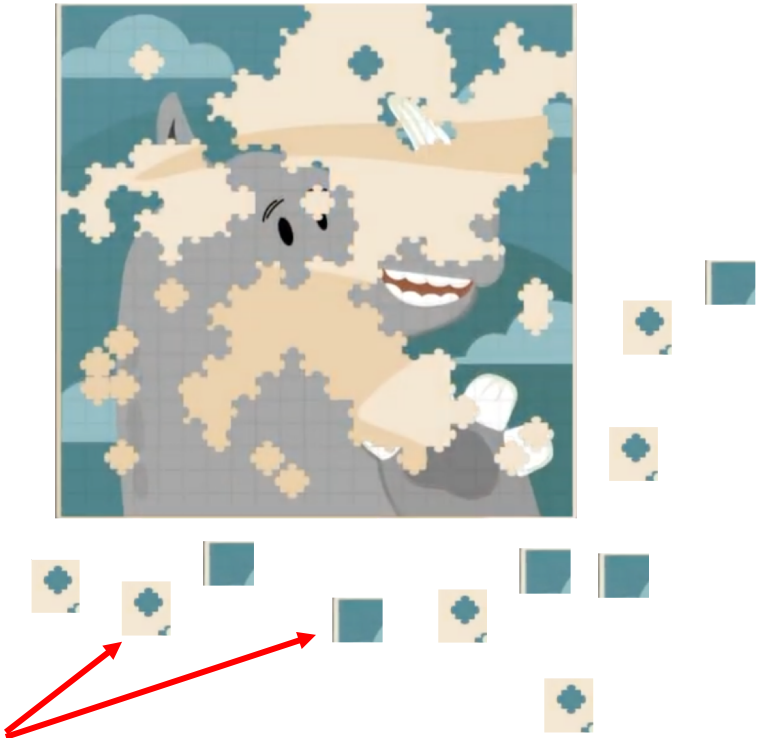


Solving the Puzzle

.FASTA file

Reference genome

.FASTQ file



Reads

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

Reference Genome

.FASTA file:

```
>NG_008679.1:5001-38170 Homo sapiens paired box 6 (PAX6)
ACCCTCTTTTCTTATCATTGACATTTAAACTCTGGGGCAGGTCCTCGCGTAGAACGCGGCTGTCAGATCT
GCCACTTCCCCTGCCGAGCGGCGGTGAGAAGTGTGGGAACCGGCGCTGCCAGGCTCACCTGCCTCCCCGC
CCTCCGCTCCCAGGTAACCGCCCGGGCTCCGGCCCCGGCCCGGCTCGGGGCCCGCGGGGCCTCTCCGCTG
CCAGCGACTGCTGTCCCCAAATCAAAGCCCGCCCCAAGTGGCCCCGGGGCTTGATTTTTGCTTTTAAAAG
GAGGCATACAAAGATGGAAGCGAGTTACTGAGGGAGGGATAGGAAGGGGGGTGGAGGAGGGACTTGTCTT
TGCCGAGTGTGCTCTTCTGCAAAAGTAGCAAAATGTTCCACTCCTAAGAGTGGACTTCCAGTCCGGCCCT
GAGCTGGGAGTAGGGGGCGGGAGTCTGCTGCTGCTGTCTGCTAAAGCCACTCGCGACCGCGAAAAATGCA
GGAGGTGGGGACGCACTTTGCATCCAGACCTCCTCTGCATCGCAGTTCACGACATCCACGCTTGGGAAAG
TCCGTACCCGCGCCTGGAGCGCTTAAAGACACCCTGCCGCGGGTCGGGCGAGGTGCAGCAGAAGTTTCCC
GCGGTTGCAAAGTGCAGATGGCTGGACCGCAACAAAGTCTAGAGATGGGGTTCGTTTCTCAGAAAGACGC
```

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
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
….
```

Genomic Reads

.FASTQ file:

Identifier — `@HWI-EAS209_0006_FC706VJ:5:58:5894:21141#ATCACG/1`

Sequence — `TTAATTGGTAAATAAATCTCCTAATAGCTTAGATNTTACCTTNNNNNNNNNNTAGTTTCTTGAGA`

'+' sign — `+`

Quality scores — `efcfffffcfeefffcffffffddf`feed]`]_Ba_^__[YBBBBBBBBBBRTT\]][]dddd``

Base T

phred Quality] = 29

Obtaining .FASTQ Files

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

NCBI Resources How To

SRA SRA Advanced

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

Full Send to:

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

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

Submitted by: The Wellcome Trust Sanger Institute (SC)

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

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

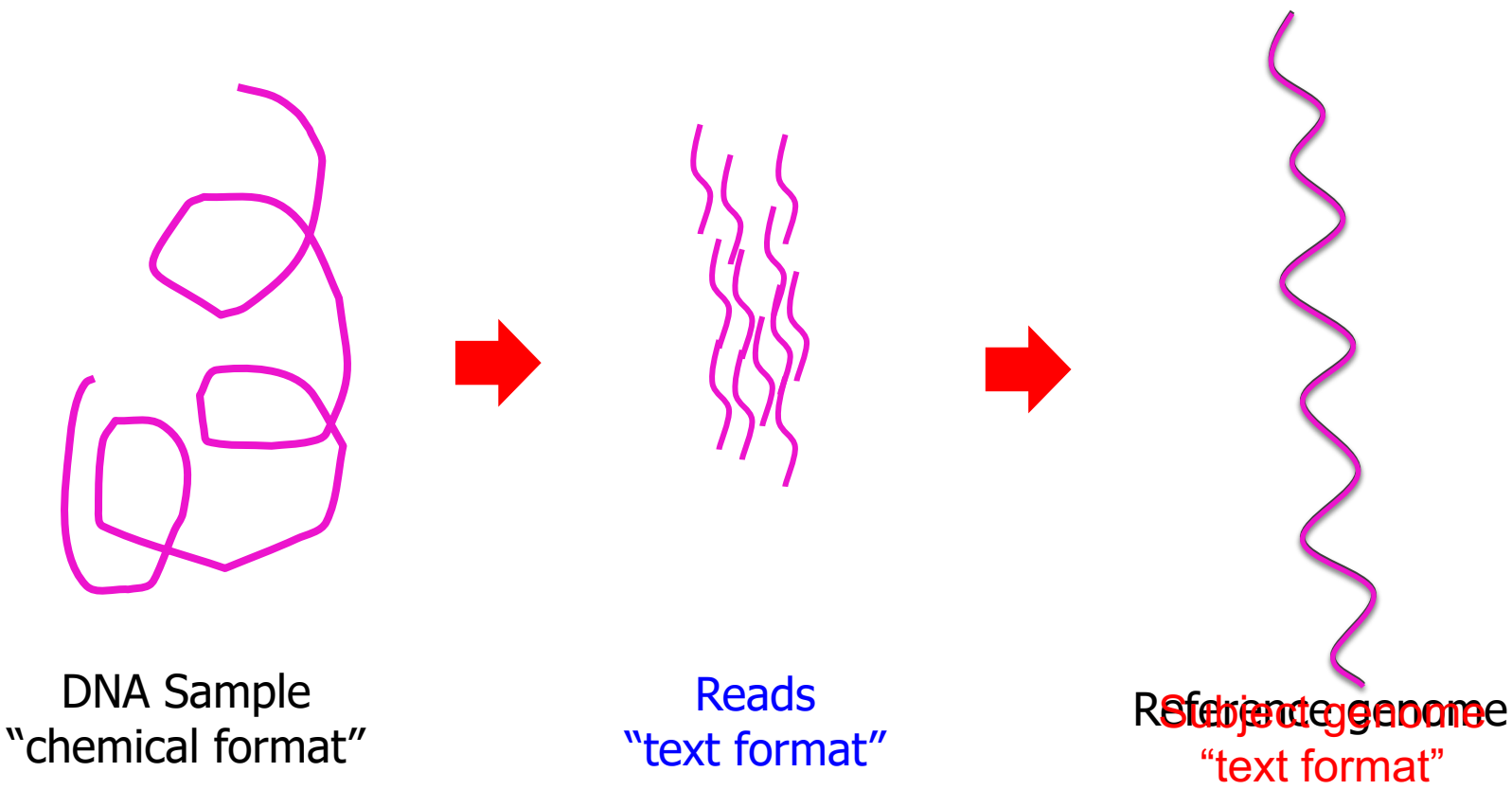
Library:
Name: 6511095
Instrument: Illumina HiSeq 2000
Strategy: WGS
Source: GENOMIC
Selection: RANDOM
Layout: PAIRED
Construction protocol: Standard

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

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

Read Mapping

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



Matching Each Read with Reference Genome

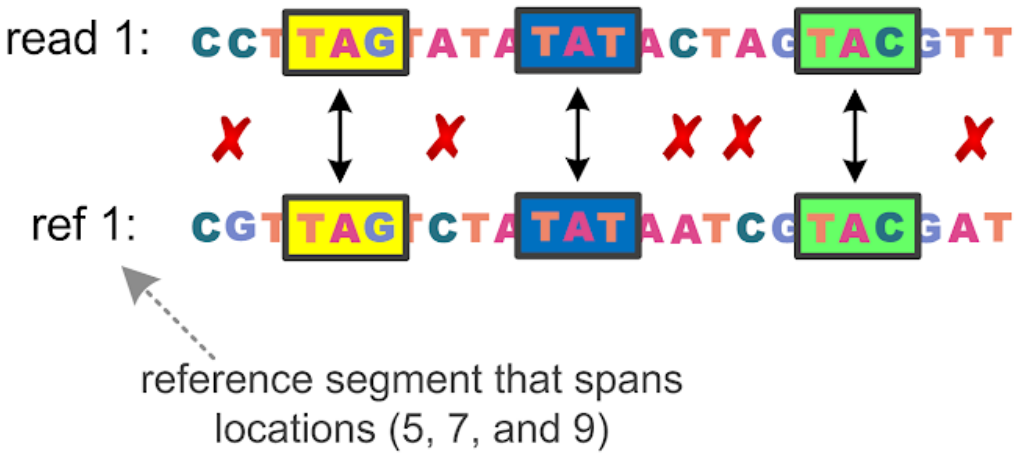
.FASTA file:

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

.FASTQ file:

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

Base-by-Base Comparison



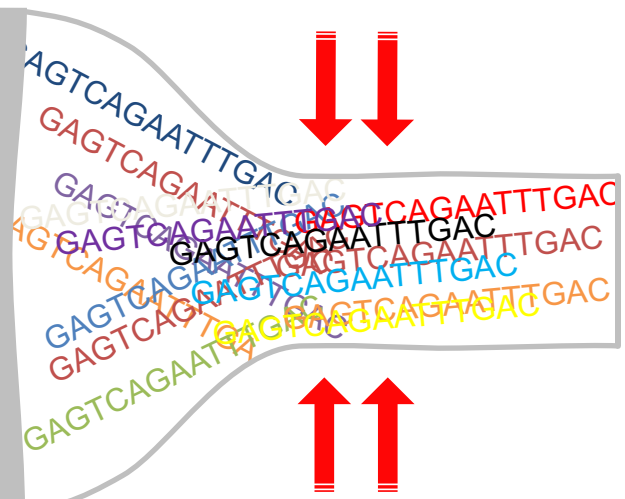
Analysis is Bottlenecked in Read Mapping!!

48 Human whole genomes

at 30× coverage

in about 2 days

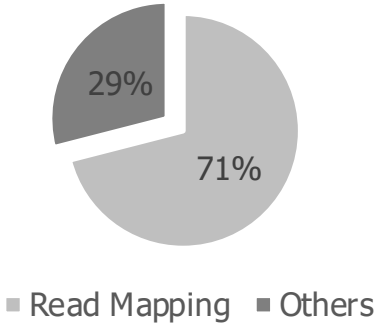
Illumina NovaSeq 6000



1 Human genome

32 CPU hours

on a 48-core processor



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

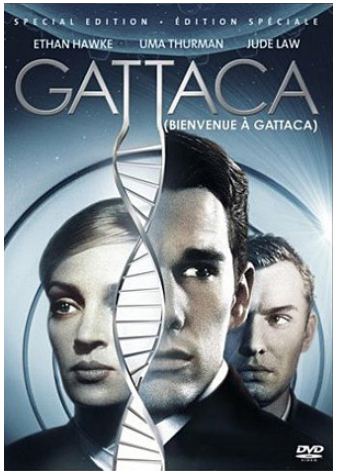
What is Intelligent Genome Analysis?

- Fast genome analysis — Bandwidth
  - *Real-time analysis*
- Using intelligent architectures — Energy-efficiency & Latency
  - *Specialized HW with less data movement*
- DNA is a valuable asset — Privacy
  - *Controlled-access analysis*
- Population-scale genome analysis — Scalability
  - *Sequence anywhere at large scale!*
- Avoiding erroneous analysis — Accuracy
  - *E.g., your father is not your father*

Fast Genome Analysis?

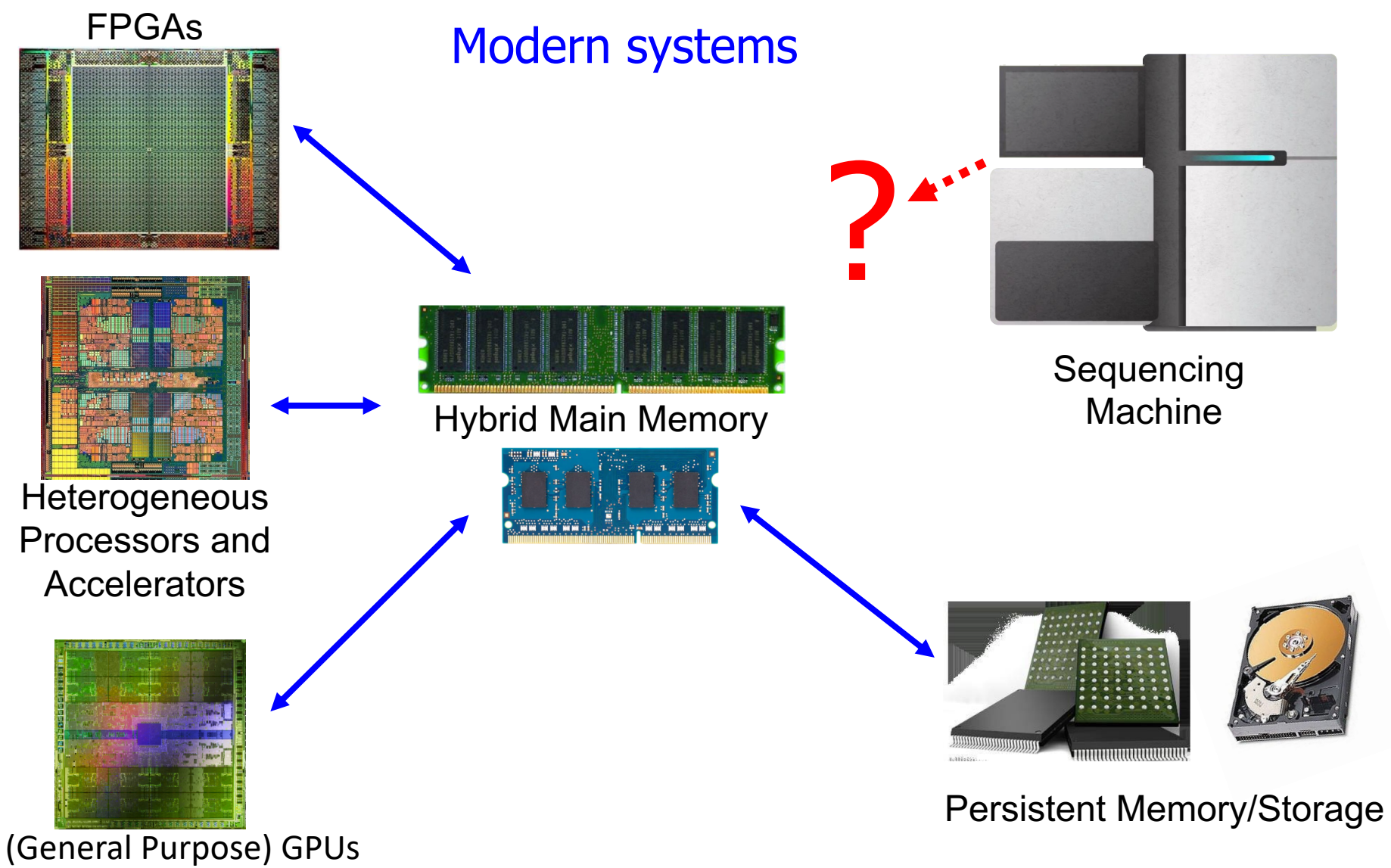
- **Fast** genome analysis in mere seconds using limited computational resources (i.e., personal computer or small hardware).

1997

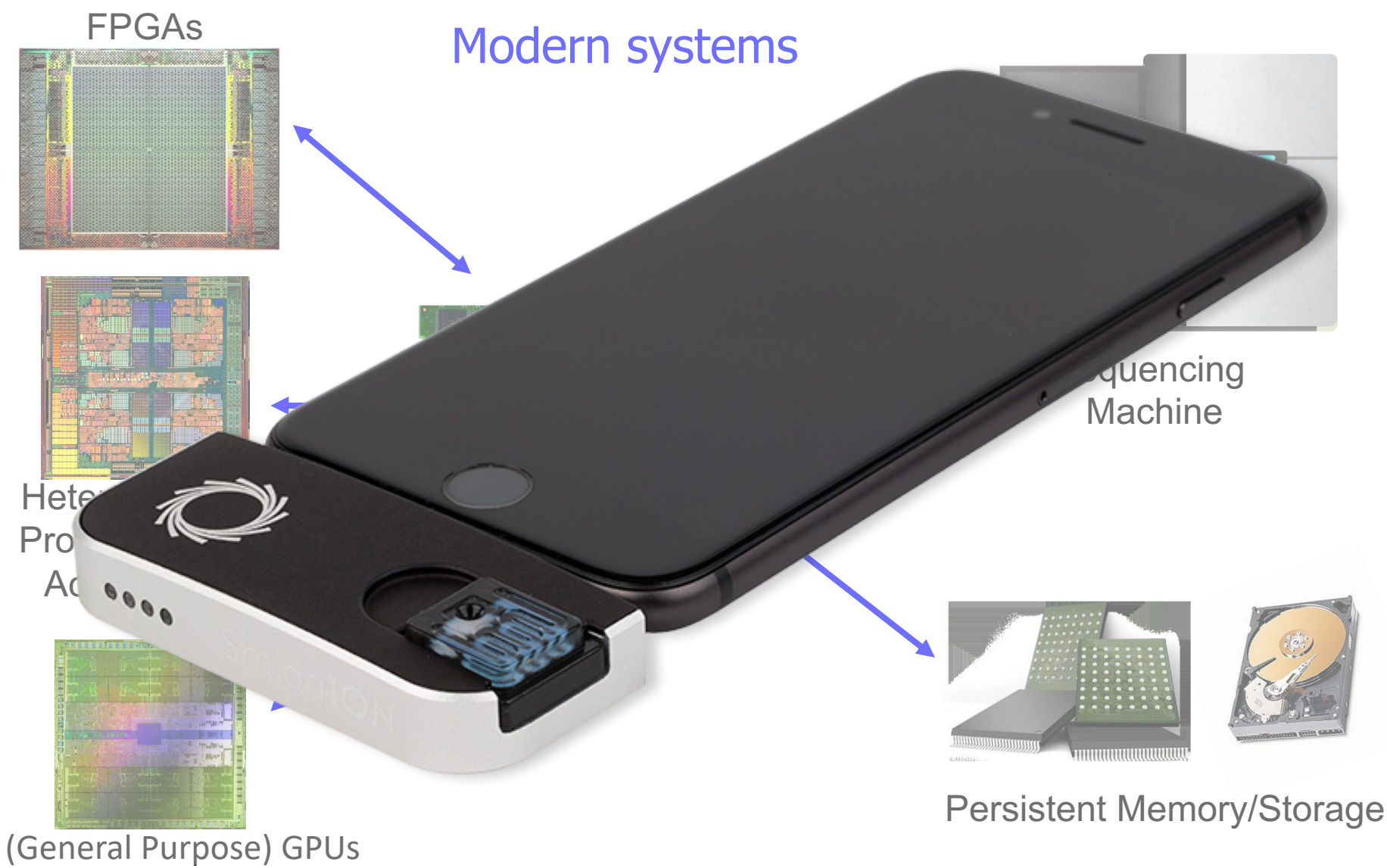


2015

Intelligent Architecture?



Intelligent Architecture?



https://nanoporetech.com/products/smidgion

Privacy-Preserving Genome Analysis?

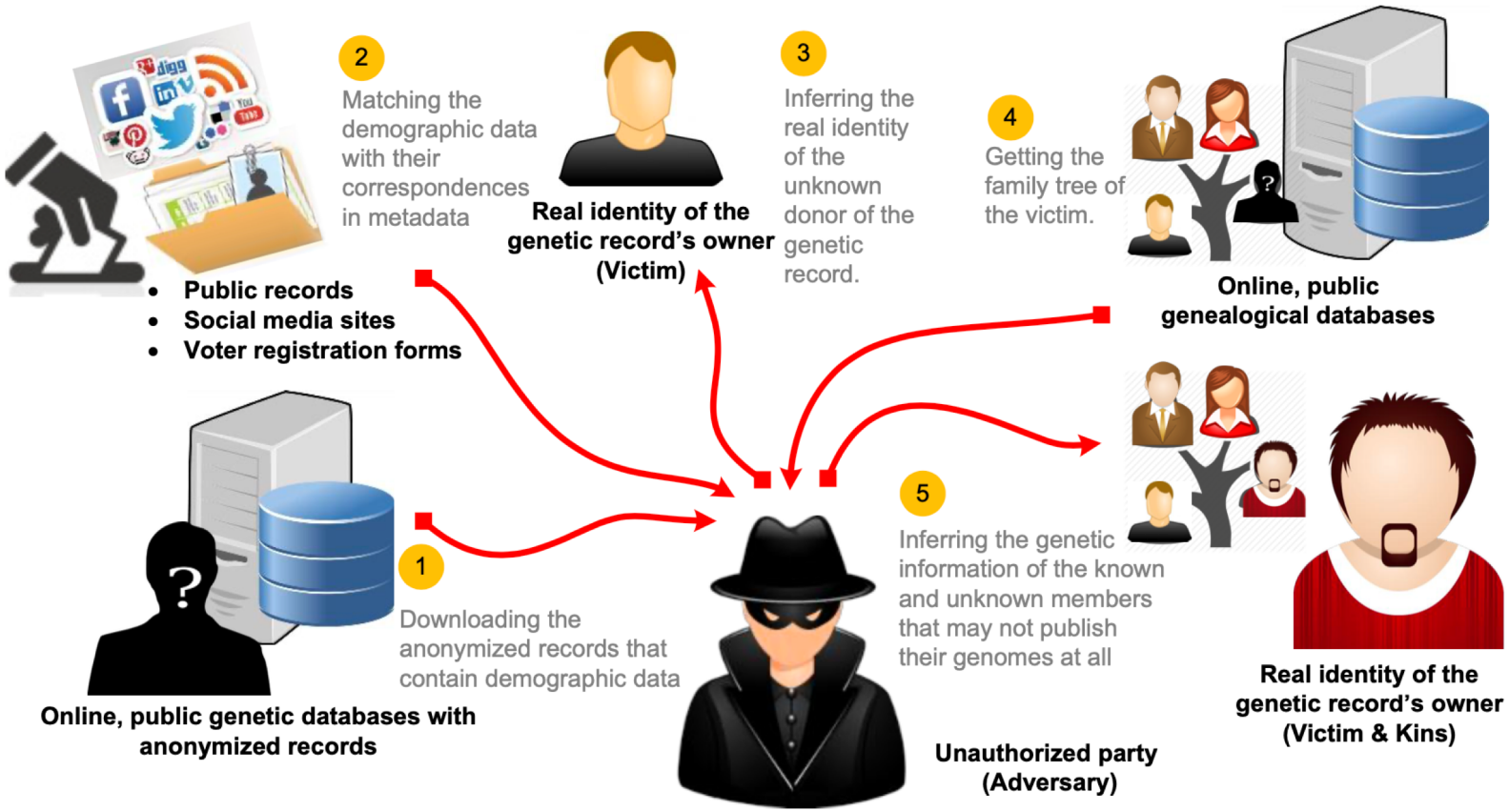


Fig. 5. A completion attack.

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.

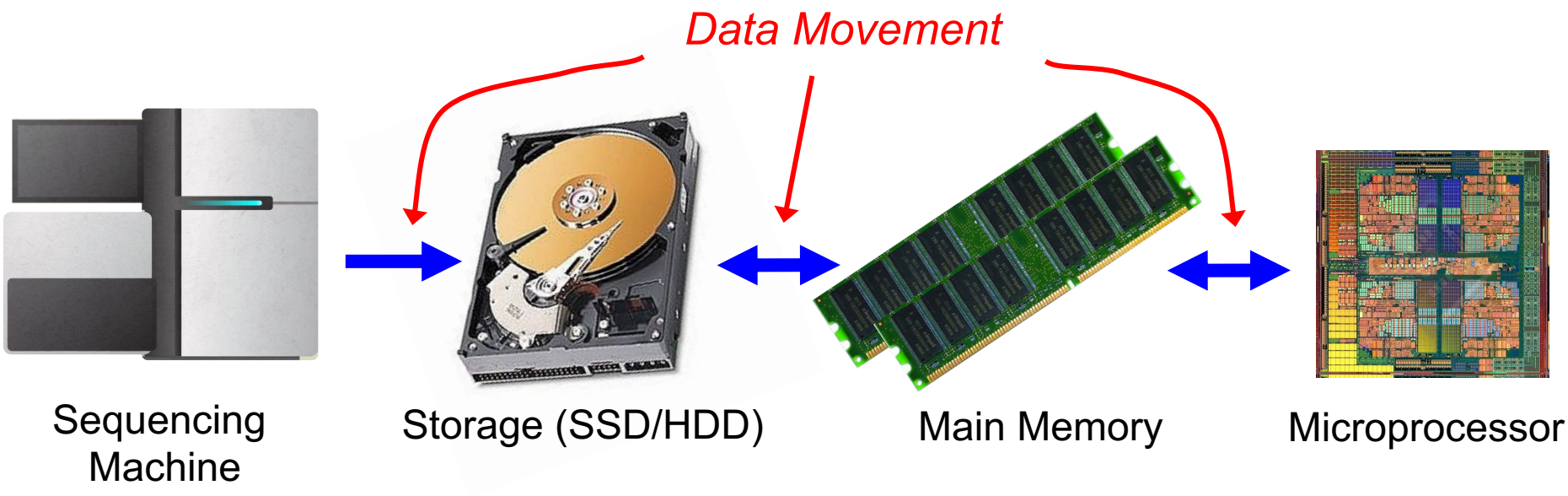
Keywords: Genomics, Privacy, Bioinformatics

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.

Pushing Towards New Architectures

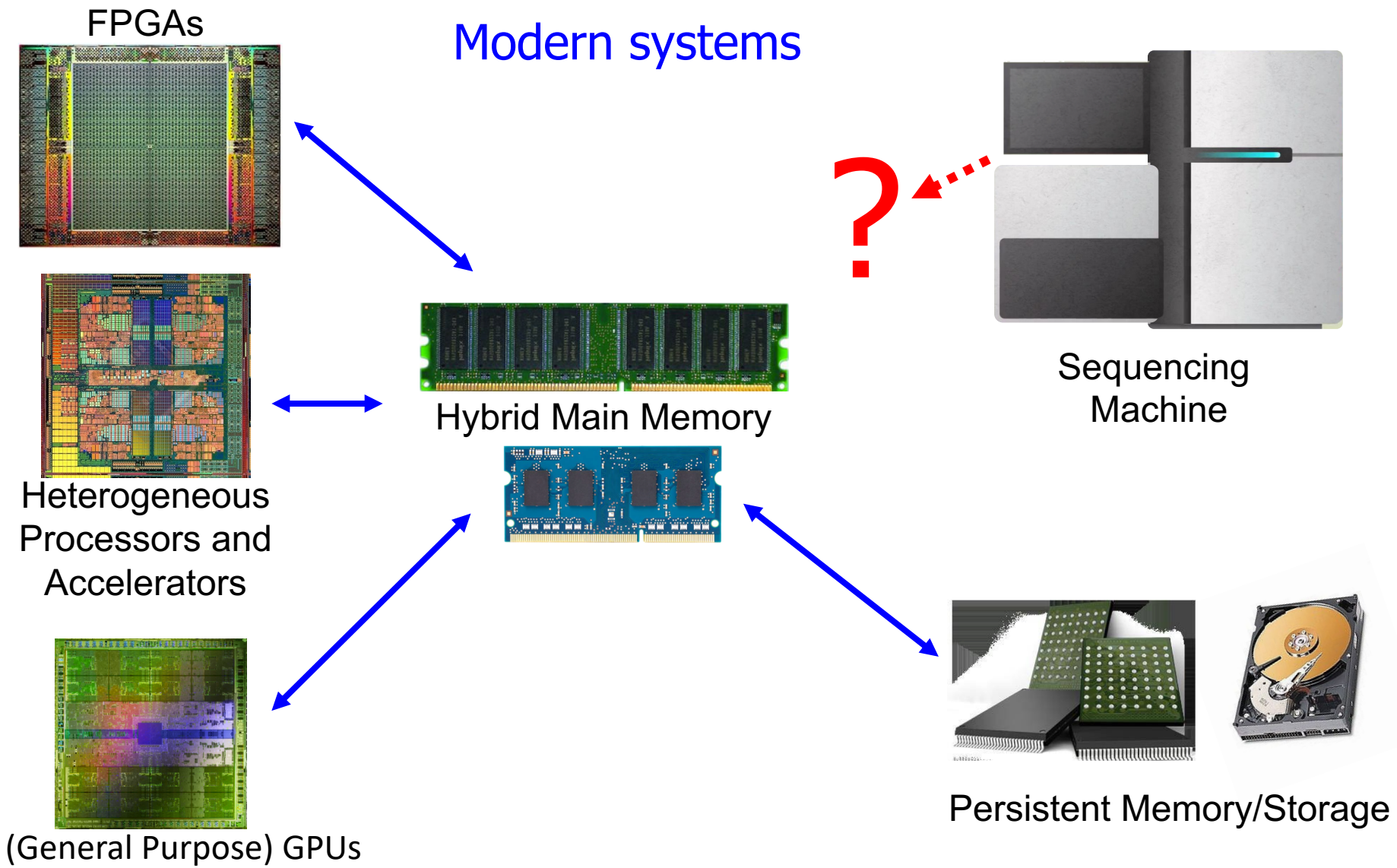
- **Data movement** dominates performance and is a **major** system **energy bottleneck** (accounting for 40%-62%)



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

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

Processing Genomic Data Where it Makes Sense



Achieving Intelligent Genome Analysis?

How and where to enable

fast, accurate, cheap,

privacy-preserving, and exabyte scale

analysis of genomic data?

Most speedup comes from parallelism enabled by novel architectures and algorithms

Read Mapping in 111 pages!

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

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

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

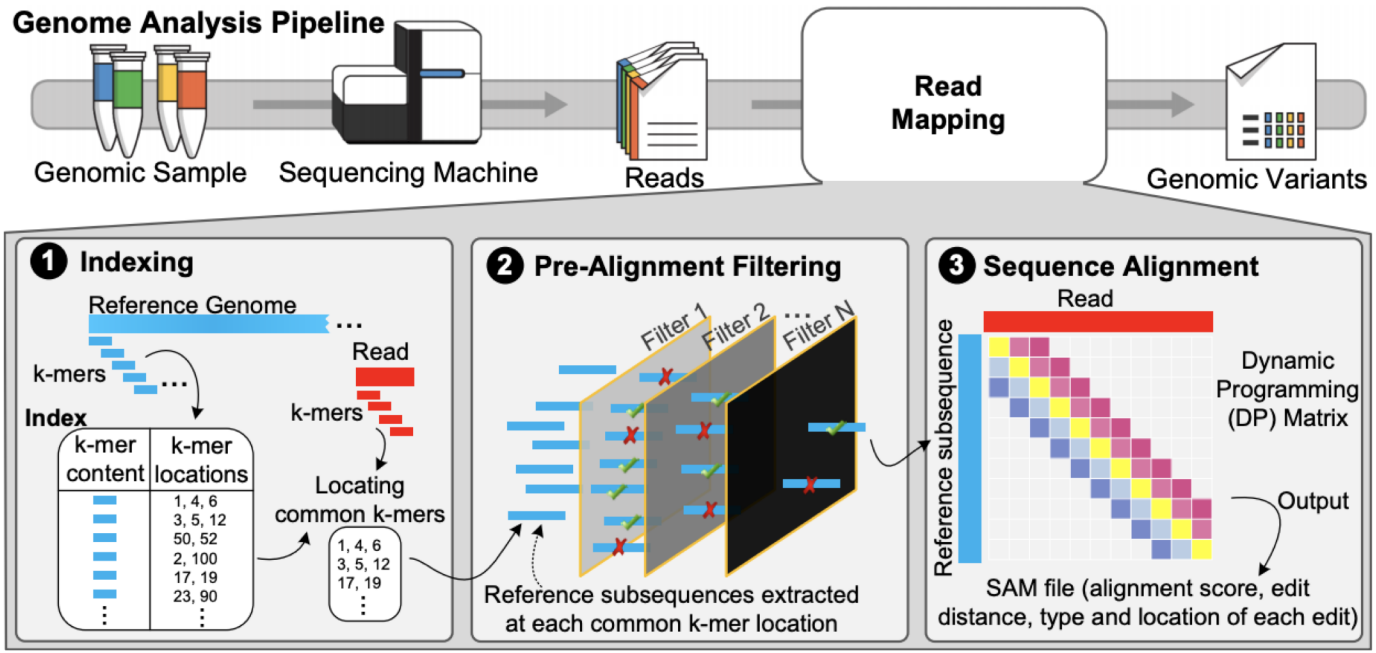
Genome Biology

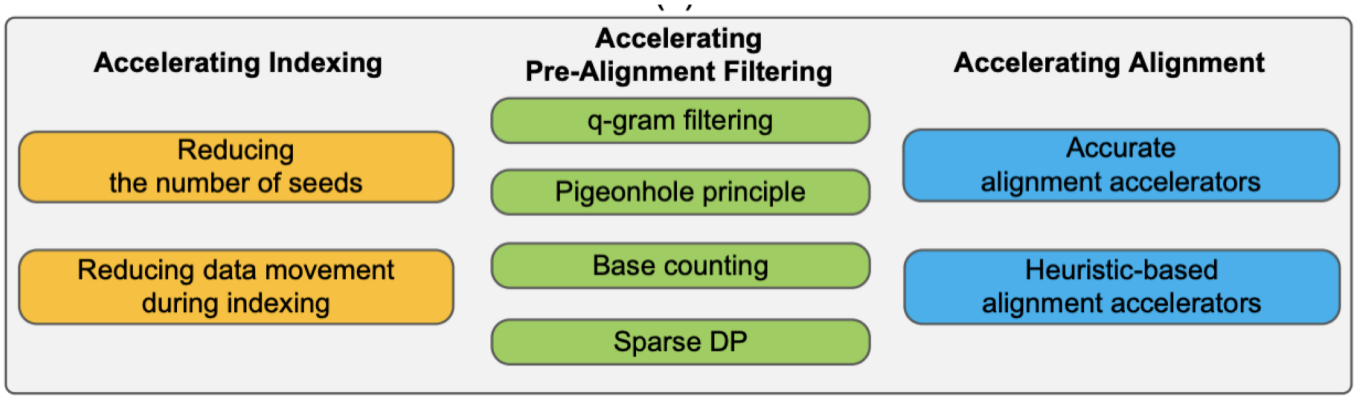
REVIEW Open Access

Technology dictates algorithms: recent developments in read alignment

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

Accelerating Read Mapping

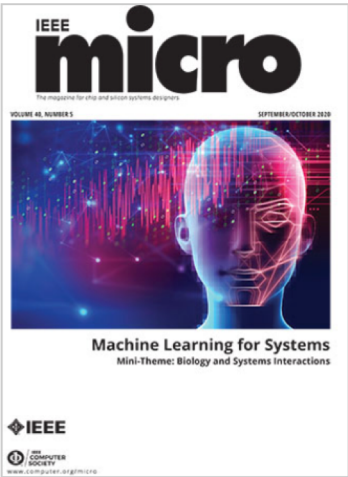




Alser+, "Accelerating Genome Analysis: A Primer on an Ongoing Journey", IEEE Micro, 2020.

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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Past Issues

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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

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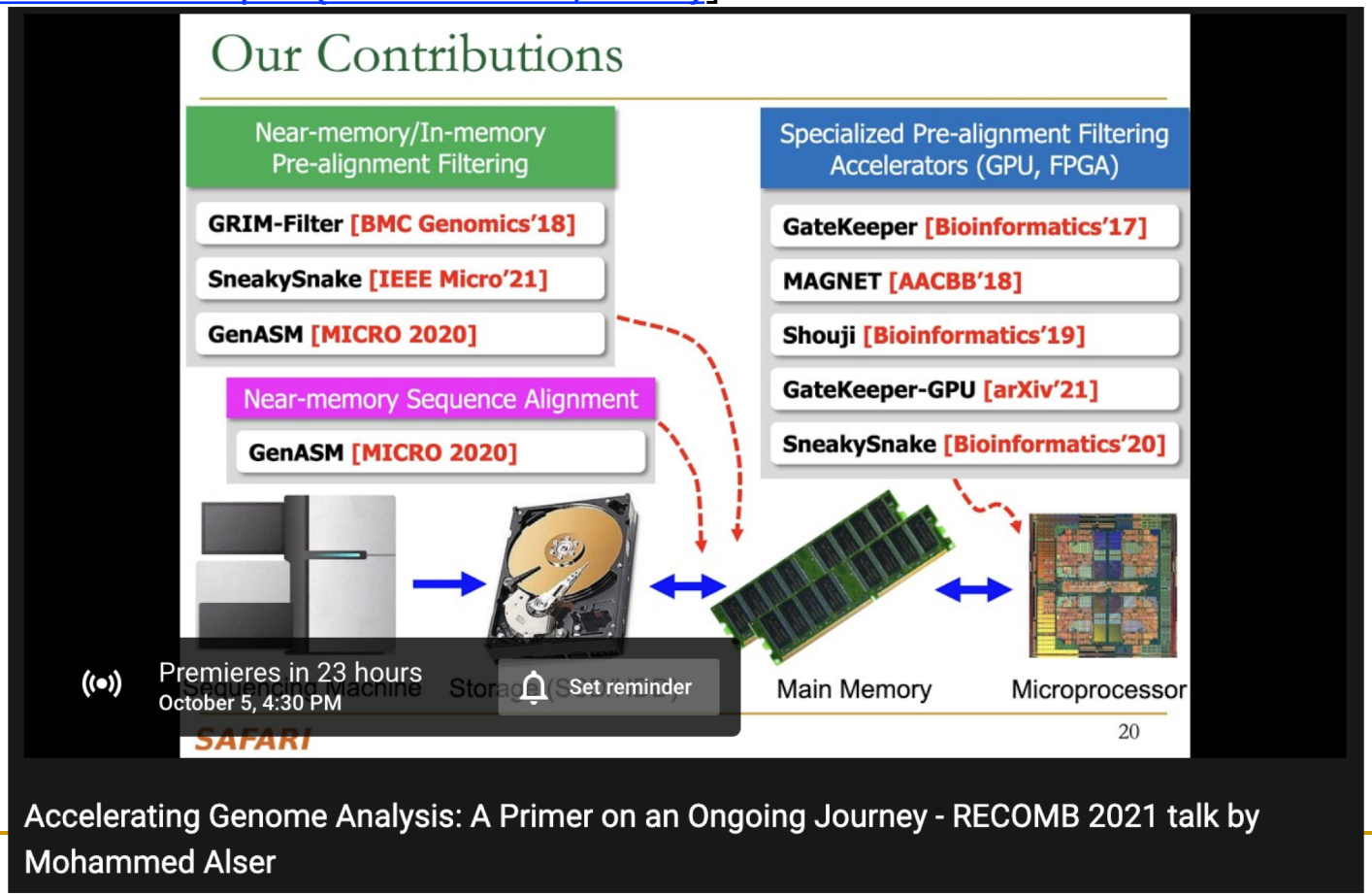
Jeremie Kim, ETH Zurich and Carnegie Mellon University
Saugata Ghose, University of Illinois at Urbana–Champaign and Carnegie Mellon University
Can Alkan, Bilkent University
Onur Mutlu, ETH Zurich, Carnegie Mellon University, and Bilkent University

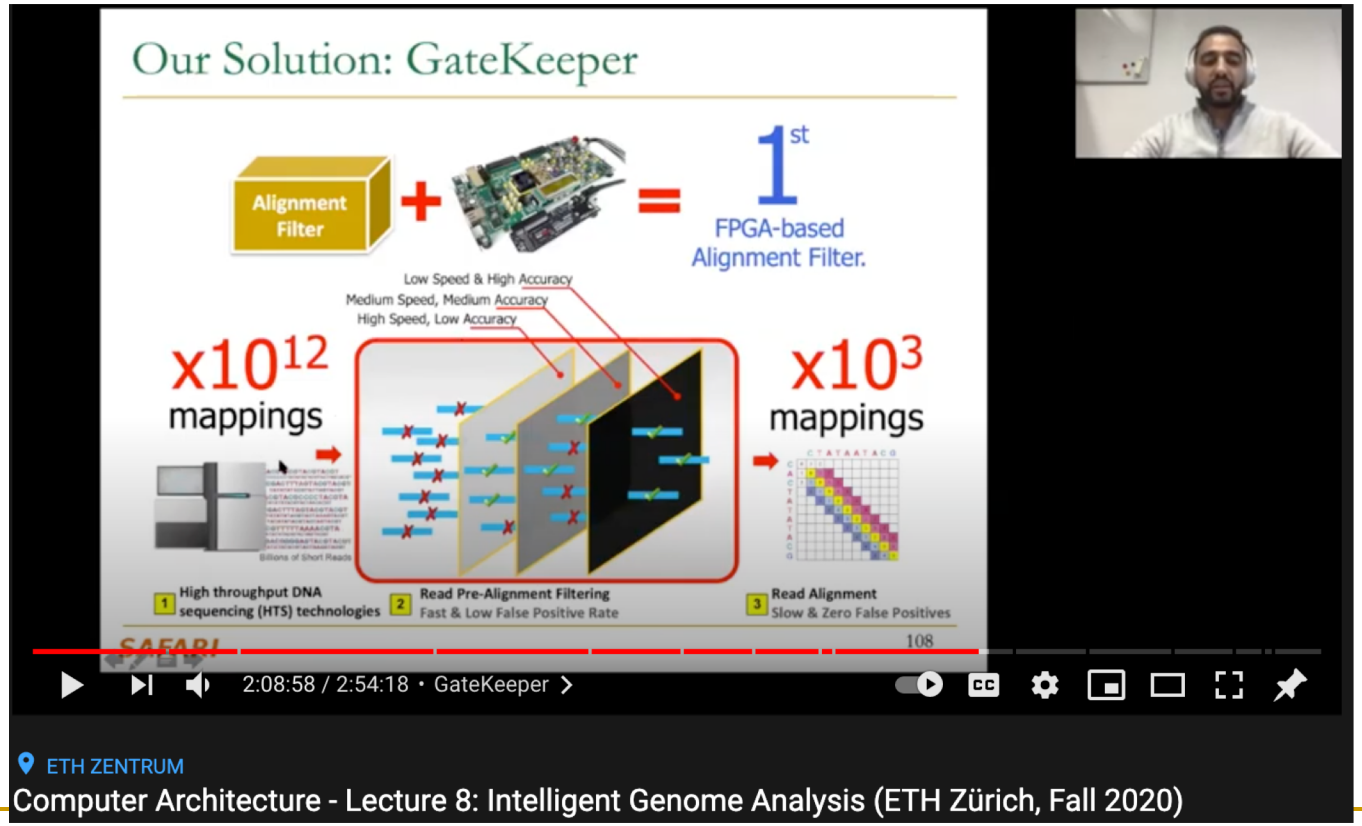
More on Accelerating Genome Analysis …

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



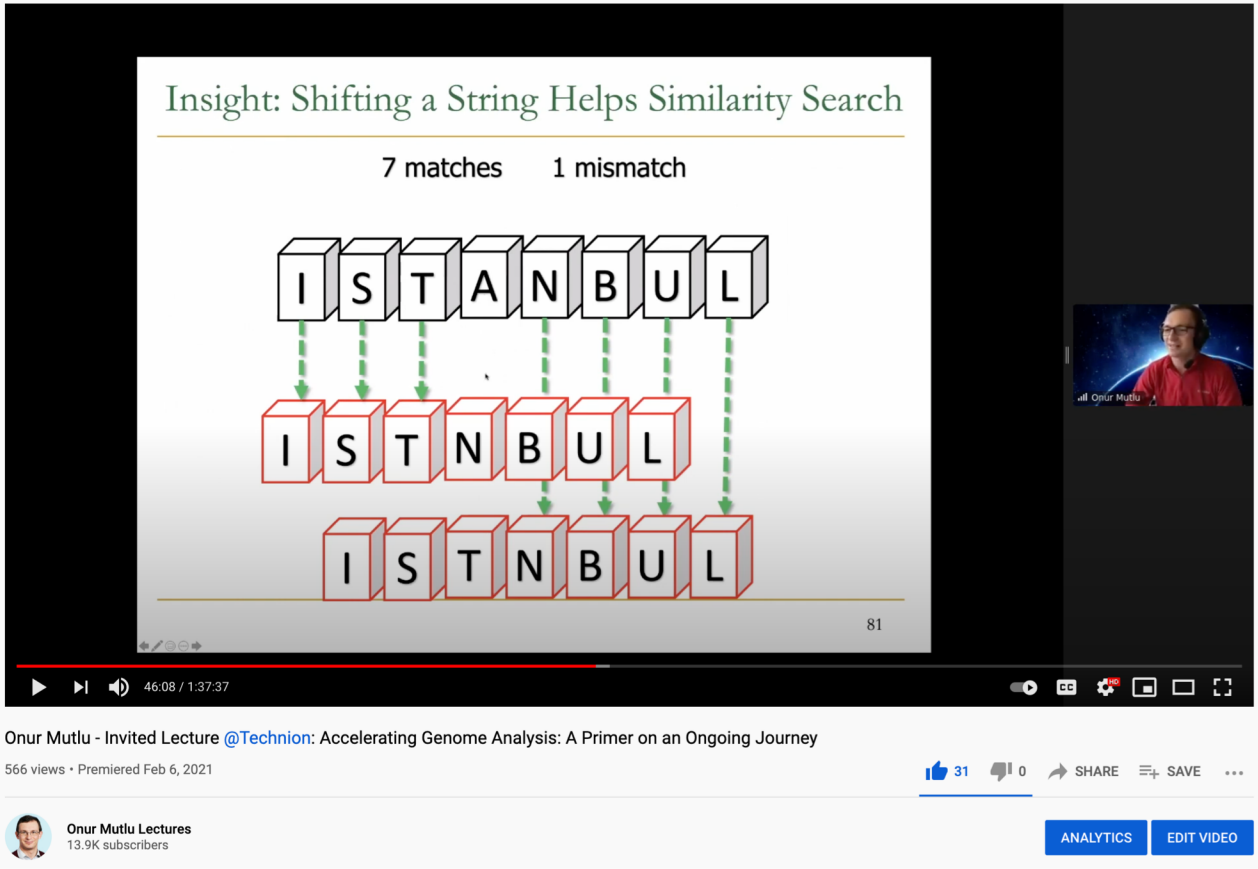
More on Intelligent Genome Analysis …

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



More on Fast Genome Analysis …

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



Detailed Lectures on Genome Analysis

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

Prior Research on Genome Analysis (1/2)

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

Prior Research on Genome Analysis (2/2)

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

P&S Mobile Genomics

Introduction & Project Proposals

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Fall 2021

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