P&S Accelerating Genomics

Lecture 6: MAGNET & Shouji

Dr. Mohammed Alser


@mealser

ETH Zurich

Fall 2022

24 November 2022

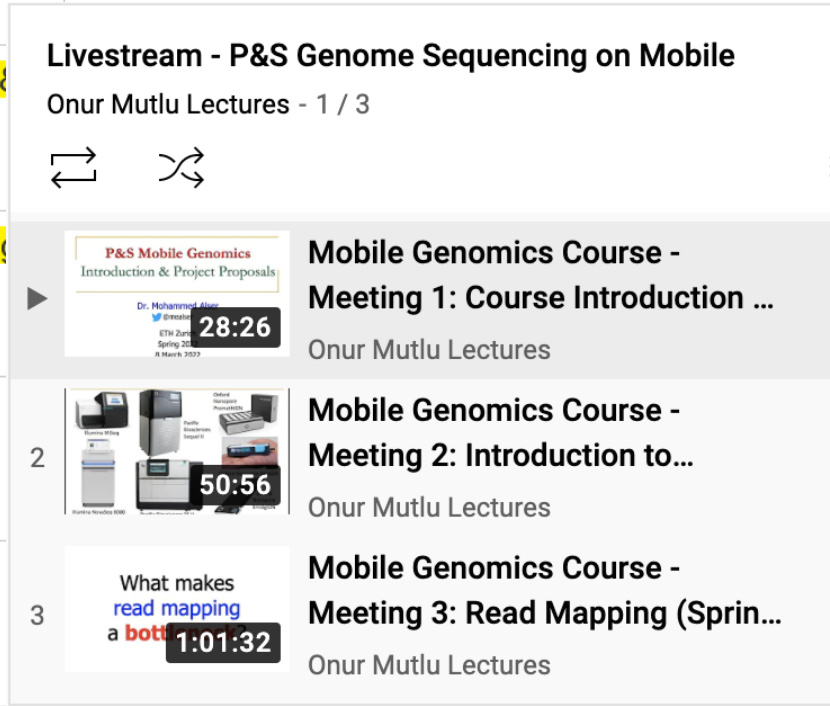
SAFARI

ETH zürich

Previous Lectures

Fall 2022 Meetings/Schedule

Week	Date	Livestream	Meeting
W1	13.10 Thu.	YouTube Live	L1: Intelligent Genomic Analyses (PDF) (PPT) YouTube Video
W2	27.10 Thu.	YouTube Live	L2: P&S Course Introduction & Logistics (PDF) (PPT)
W3	3.11 Thu.	YouTube Premiere	L3: Introduction to Sequencing (PDF) (PPT)
W4	10.11 Thu.	YouTube Premiere	L4: Read Mapping (PDF) (PPT)
W5	17.11 Thu.	YouTube Premiere	L5: GateKeeper (PDF) (PPT)



https://safari.ethz.ch/projects_and_seminars/fall2022/doku.php?id=bioinformatics

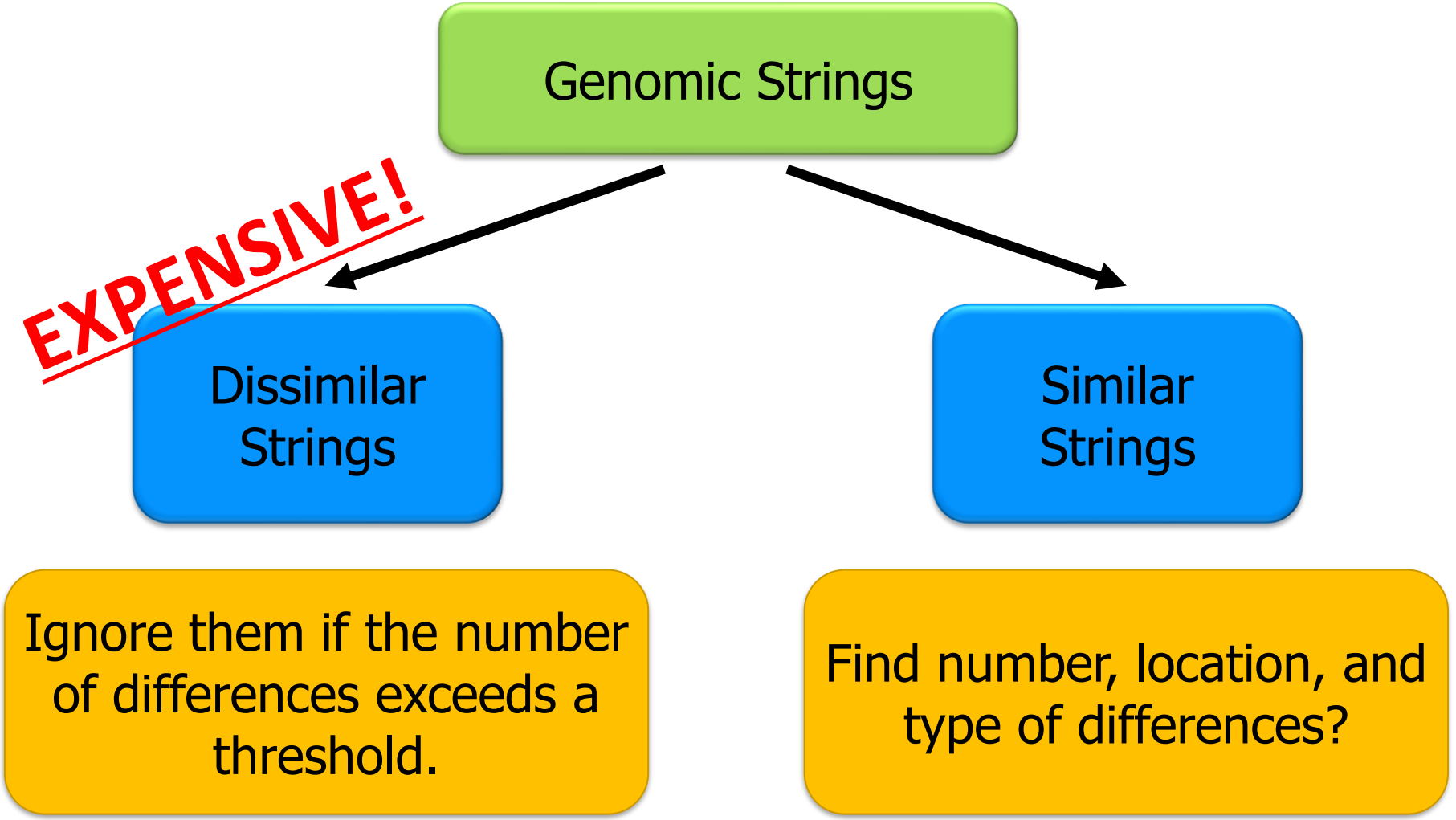
We need intelligent algorithms and intelligent architectures that handle data well

Goal: Minimizing Alignment Time

Sequence Alignment is expensive

Our goal is to accelerate read mapping by reducing the need for dynamic programming algorithms

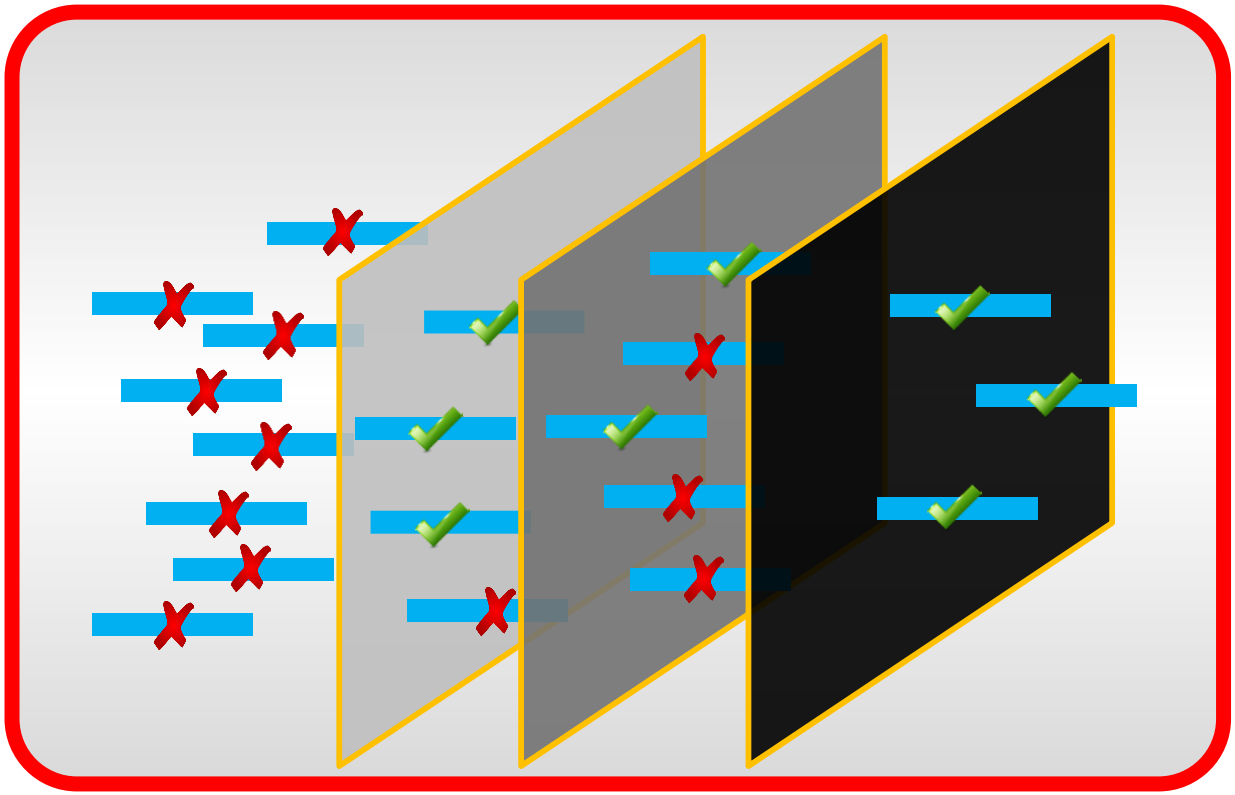
Key Idea


Genomic Strings
EXPENSIVE!
Dissimilar Strings
Similar Strings
Ignore them if the number of differences exceeds a threshold.
Find number, location, and type of differences?

Ideal Filtering Algorithm

Step 2

Query the Index



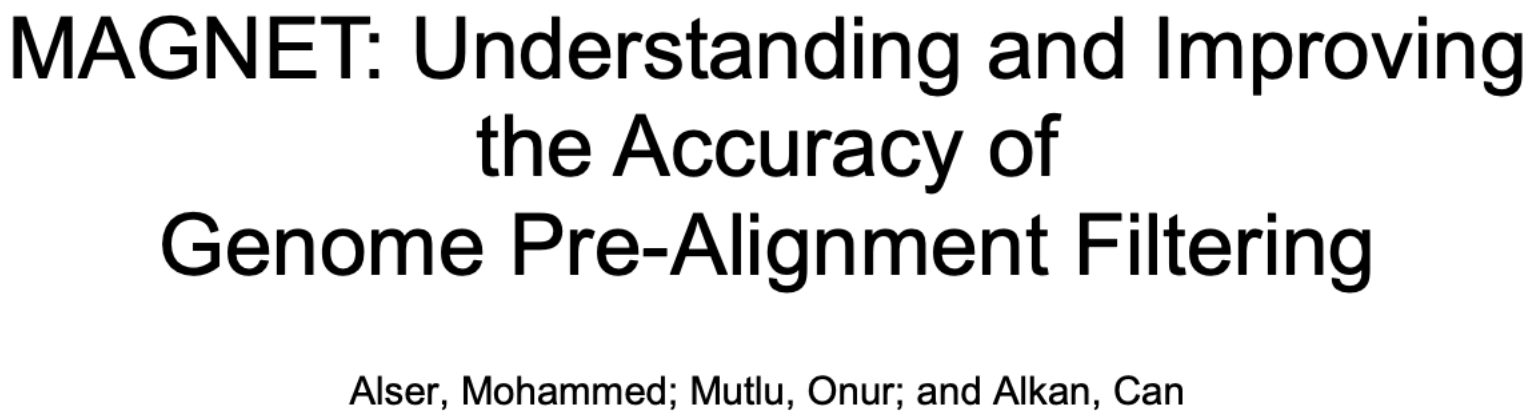
Step 3

Read Alignment

1. Filter out most of dissimilar sequences.
2. Preserve all similar sequences.
3. Do it quickly.

MAGNET

Alser, Mohammed, Onur Mutlu, and Can Alkan.
"MAGNET: understanding and improving the accuracy of genome pre-alignment filtering"
IPSI Transaction (2017).
[Source code]



On the False Positives of GateKeeper

We investigate four major sources of false positives:

- Leading and trailing zeros
- Random zeros
- Conservative counting
- Lack of backtracking

Leading and Trailing Zeros

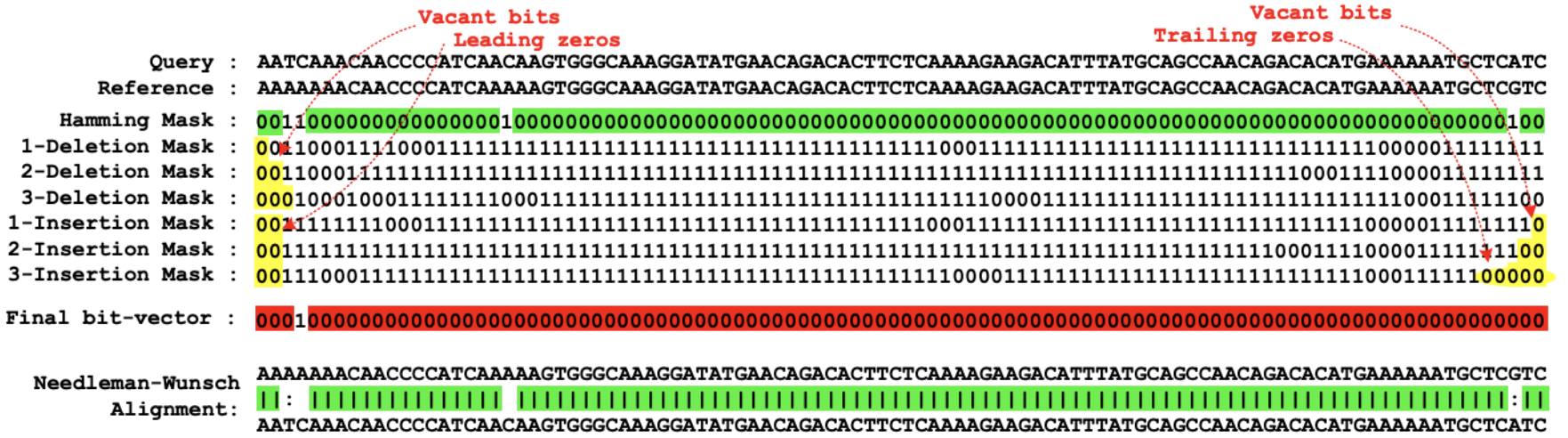


Fig. 3: Examples of an invalid mapping that passes the SHD filter due to the leading and trailing zeros (first source of false positives). We use an edit distance threshold of 3 and an SRS threshold of 2. While the regions that are highlighted in green are part of the correct alignment, the wrong alignment provided by SHD is highlighted in red. The yellow highlighted bits indicate a source of false positive.

Random Zeros

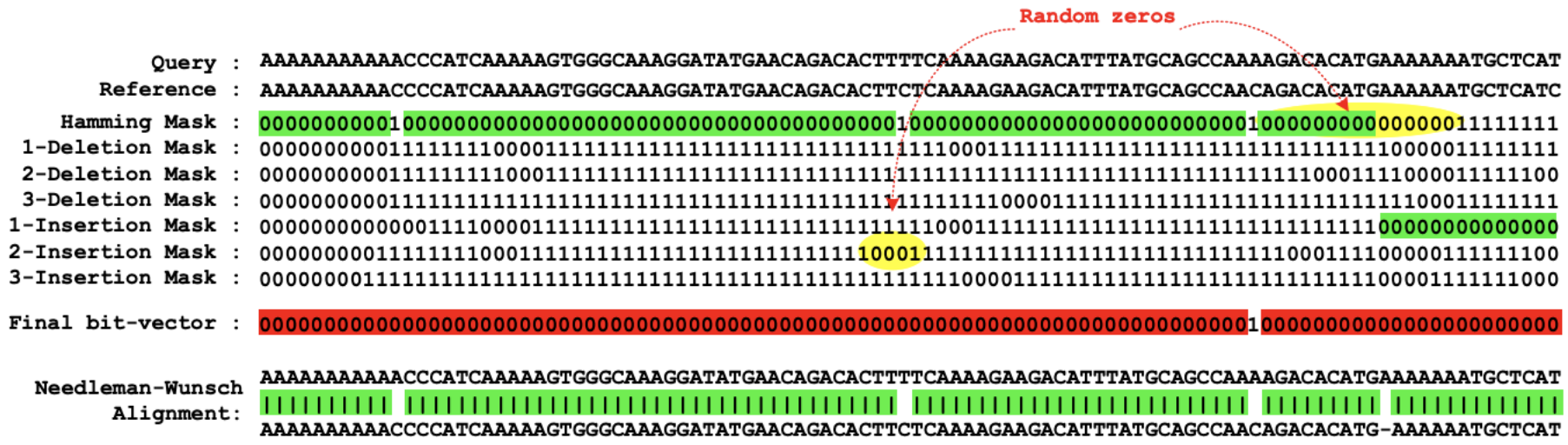


Fig 4: Examples of an incorrect mapping that passes the SHD filter due to random zeros (second source false positives). While the edit distance threshold is 3, a mapping of 4 edits (as examined at the end of the figure by Needleman-Wunsch algorithm) passes as a false positive.

Conservative Counting

Fig 5: An example of an incorrect mapping that passes the SHD filter due to conservative counting of the short streak of '1's in the final bit-vector.

Lack of Backtracking

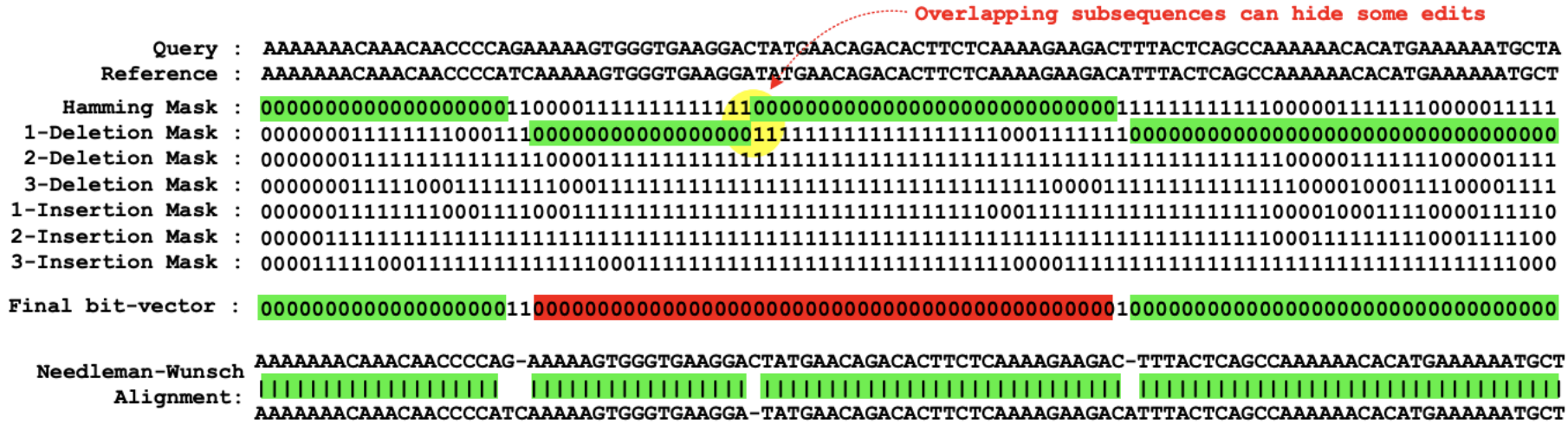


Fig 6: An example of an incorrect mapping that passes the SHD filter due to the lack of backtracking (overlapping identical subsequences).

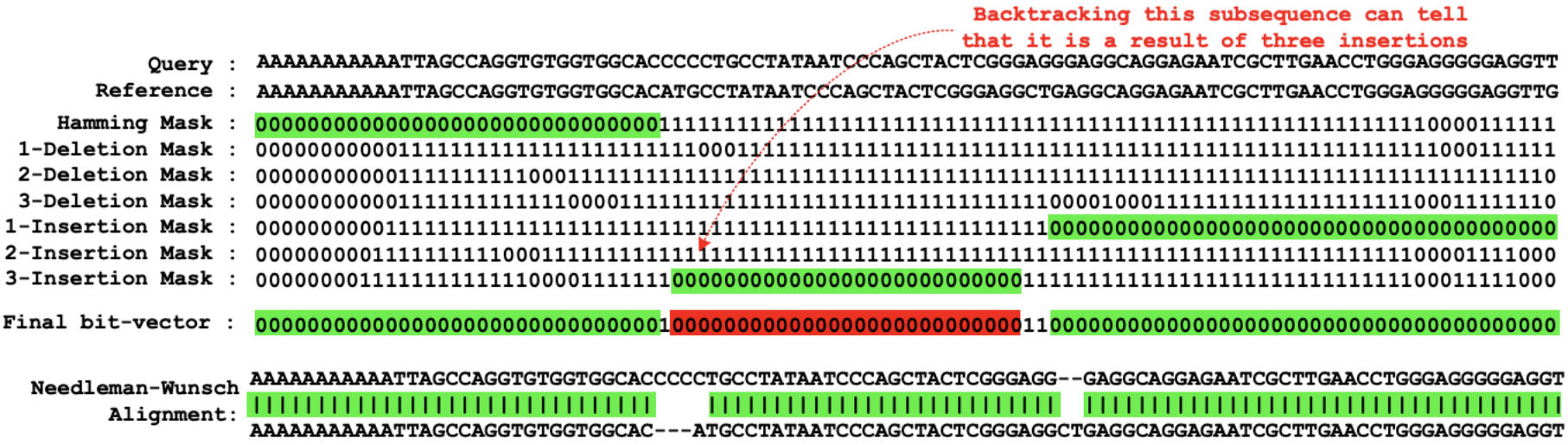


Fig. 7: An example of an invalid mapping that passes the SHD filter due to the lack of backtracking.

Can we improve the accuracy?

MAGNET (AACBB 2018, TIR 2017)

- Key observation:
  - Correct alignment always includes non-overlapping long identical subsequences.
- Key idea:
  - Count the **consecutive zeros** in each mask and select the longest in a divide-and-conquer approach.

MAGNET Walkthrough

Build Neighborhood Map → Track the Diagonally Consecutive Matches → ACCEPT iff number of '1' ≤ Threshold

Find the longest segment of consecutive zeros

Exclude the errors from the search space

Divide the problem into two subproblems and repeat

Total number of edits = number of 1's in MAGNET bit-vector

Number of Iterations in MAGNET

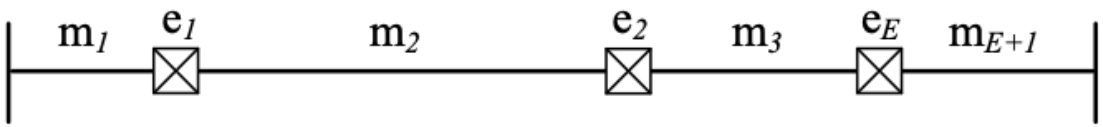


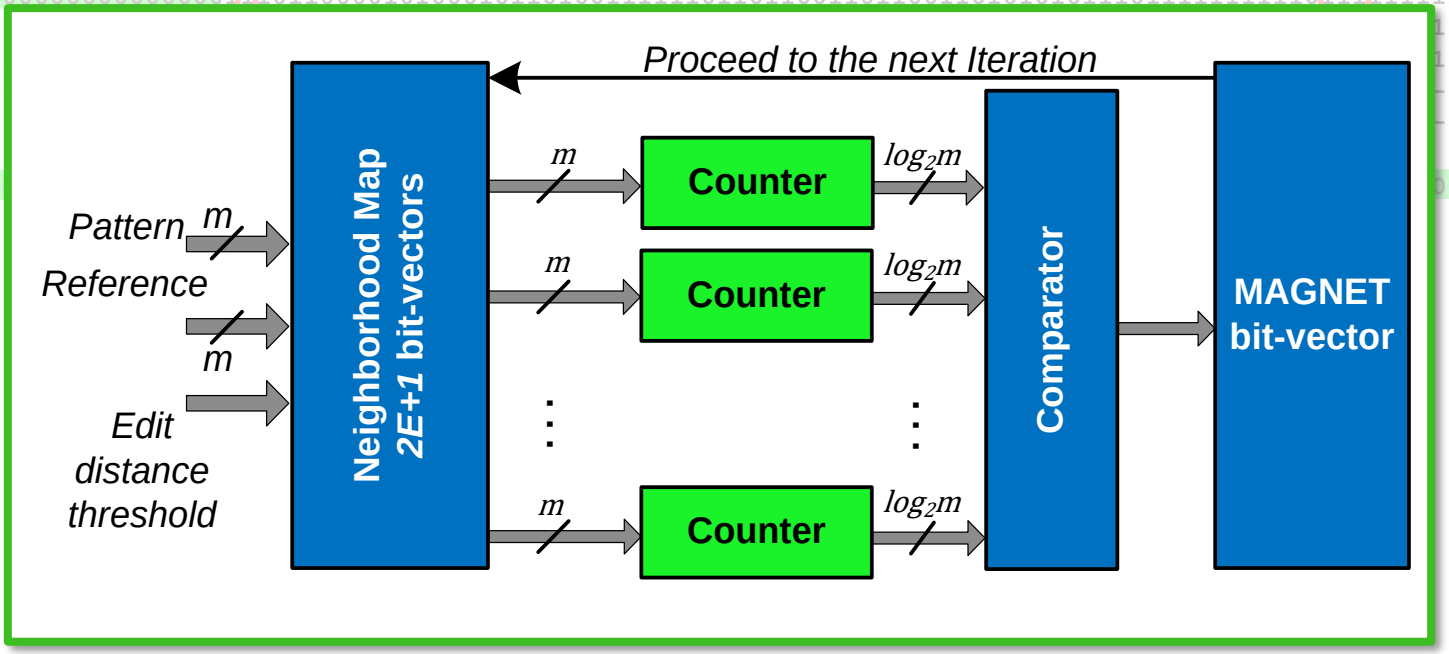
Fig. 1: Random edit distribution in a read sequence. The edits (e_1, e_2, …, e_E) act as dividers resulting in several identical subsequences (m_1, m_2, …, m_{E+1}) between the read and the reference.

MAGNET Walkthrough

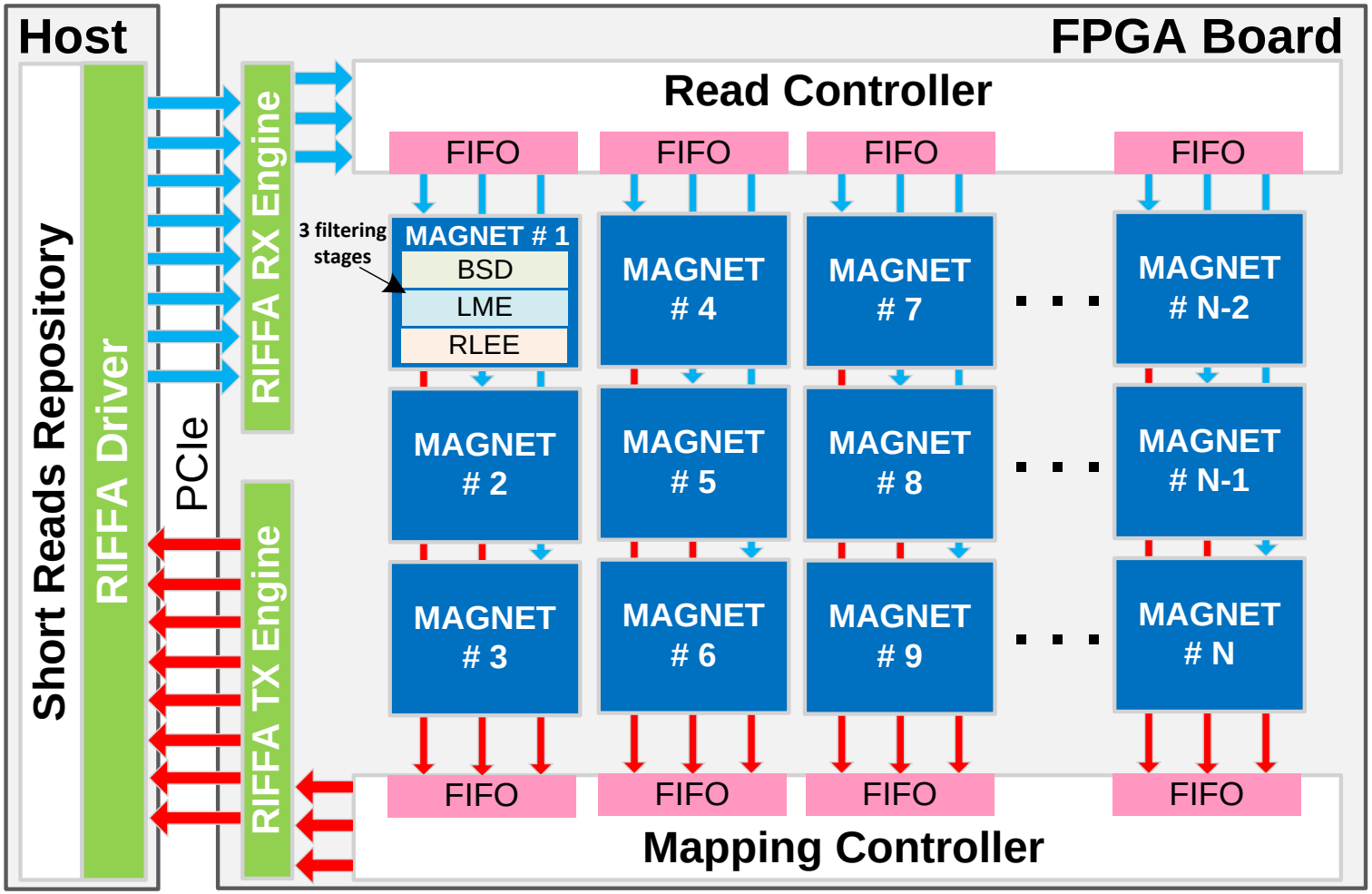
Build Neighborhood Map | Identifying *E*+1 non-overlapping subsequences | ACCEPT iff number of '1' ≤ Threshold

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

- log_2ReadLength-bit counter.



MAGNET Accelerator



MAGNET (AACBB 2018, TIR 2017)

- Key observation:
  - Correct alignment always includes non-overlapping long identical subsequences.
- Key idea:
  - Count the **consecutive zeros** in each mask and select the longest in a divide-and-conquer approach.
- Key result:
  - MAGNET is 74x - 460x **faster** than its CPU implementation.
  - Contains up to **2 or 8 filtering units**, each of which has **10 folds the footprint** of that of GateKeeper on the FPGA.
  - MAGNET is 3.5x to 25552x (as GateKeeper stop filtering after E=4%[250bp] or 8%[100bp]) **more accurate** than GateKeeper and SHD.
- Weaknesses: Challenging to be implemented on FPGA due to random search.

More on MAGNET

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

Alser, Mohammed, Onur Mutlu, and Can Alkan. "MAGNET: understanding and improving the accuracy of genome pre-alignment filtering." *IPSI Transaction* (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.

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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 (as in GateKeeper) is ineffective for hardware design.

Dot Plot [Lipman and Pearson, 1985]

	T	G	T	G	C	A	G	G	G
T	*		*						
G		*		*			*	*	*
G		*		*			*	*	*
C					*				
A						*			
G		*		*			*	*	*
G		*		*			*	*	*

"dot plot" or "dot matrix" is a visual representation of the similarities between two closely similar genomic sequences that is used in FASTA/FASTP (Lipman and Pearson, 1985).

Shouji

- **Key observation:**
  - Correct alignment always includes long identical subsequences.
  - Processing the entire mapping at once (as in GateKeeper) is ineffective for hardware design.
- **Key idea:**
  - Use **overlapping** sliding window approach to quickly and accurately find all long segments of consecutive zeros.

Building the Neighborhood Map

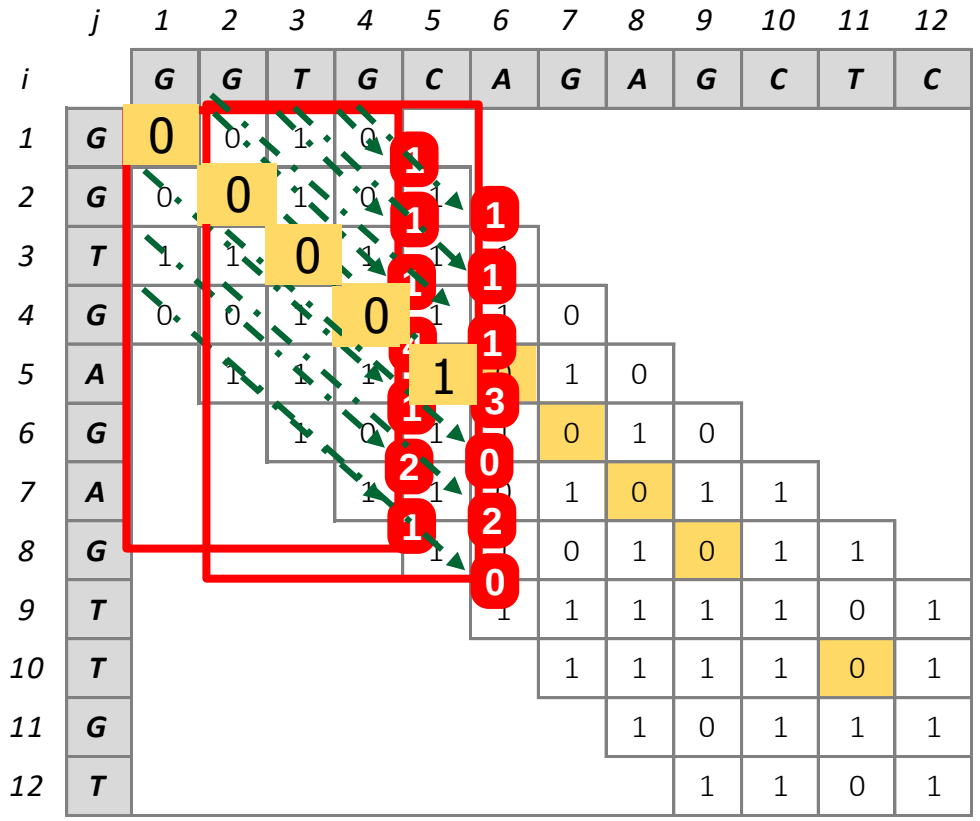
- Given a text sequence T[1…m], a pattern sequence P[1…m], and an edit distance threshold E, the neighborhood map represents the comparison result of the i^{th} character of P with the j^{th} character of T, where i and j satisfy $1 \leq i \leq m$ and $i-E \leq j \leq i+E$. The entry N[i, j] of the neighborhood map can be calculated as follows:

$$N[i,j] = \begin{cases} 0, & \text{if } P[i] = T[j] \\ 1, & \text{if } P[i] \neq T[j] \end{cases} \qquad (1)$$

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 Neighborhood Map

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

	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 @ Shouji Bit-vector

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

ACCEPT iff number of '1' ≤ Threshold

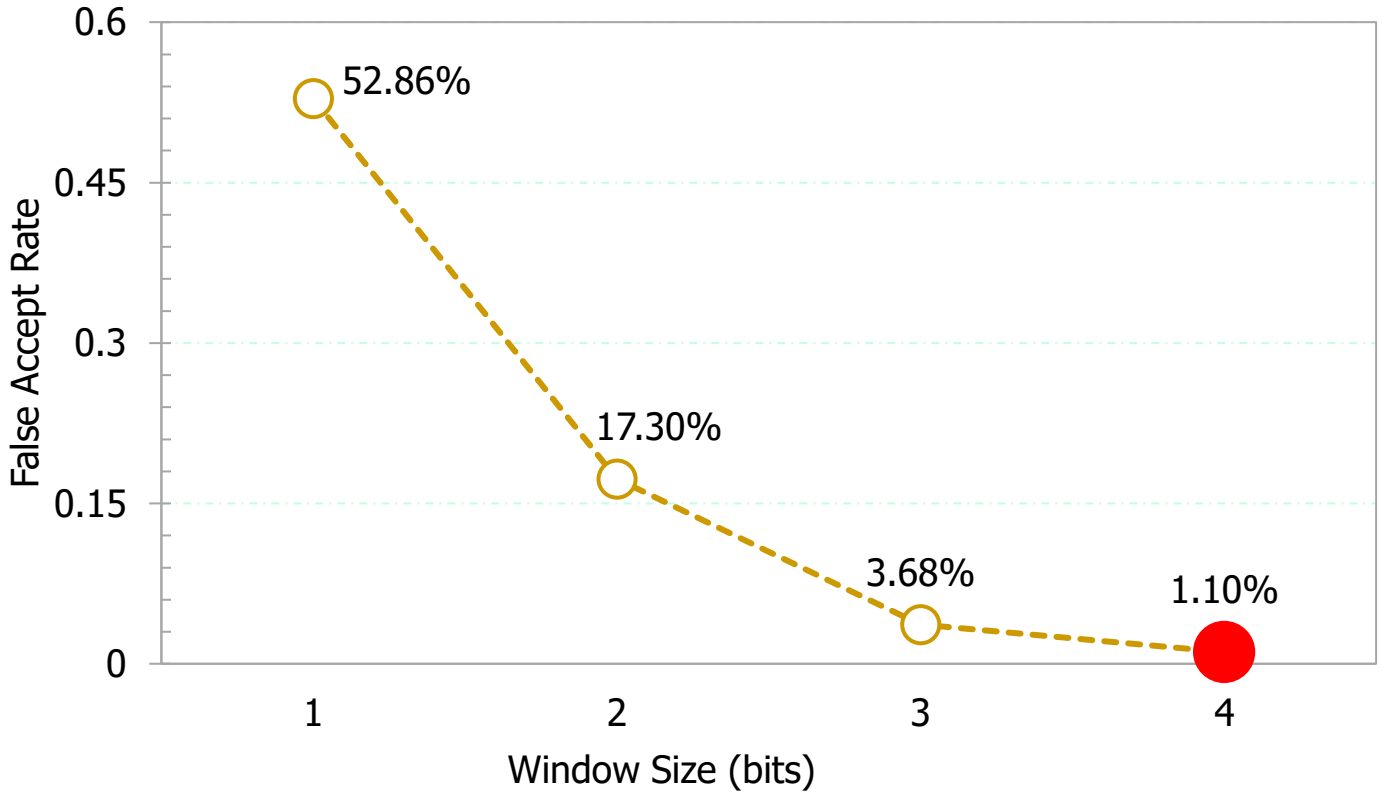
Shouji: a fast and efficient pre-alignment filter for sequence alignment, *Bioinformatics* 2019, https://doi.org/10.1093/bioinformatics/btz234

What Does Shouji Mean?

Named after a traditional Japanese door that is designed to slide open http://www.aisf.or.jp/~jaanus/deta/s/shouji.htm.

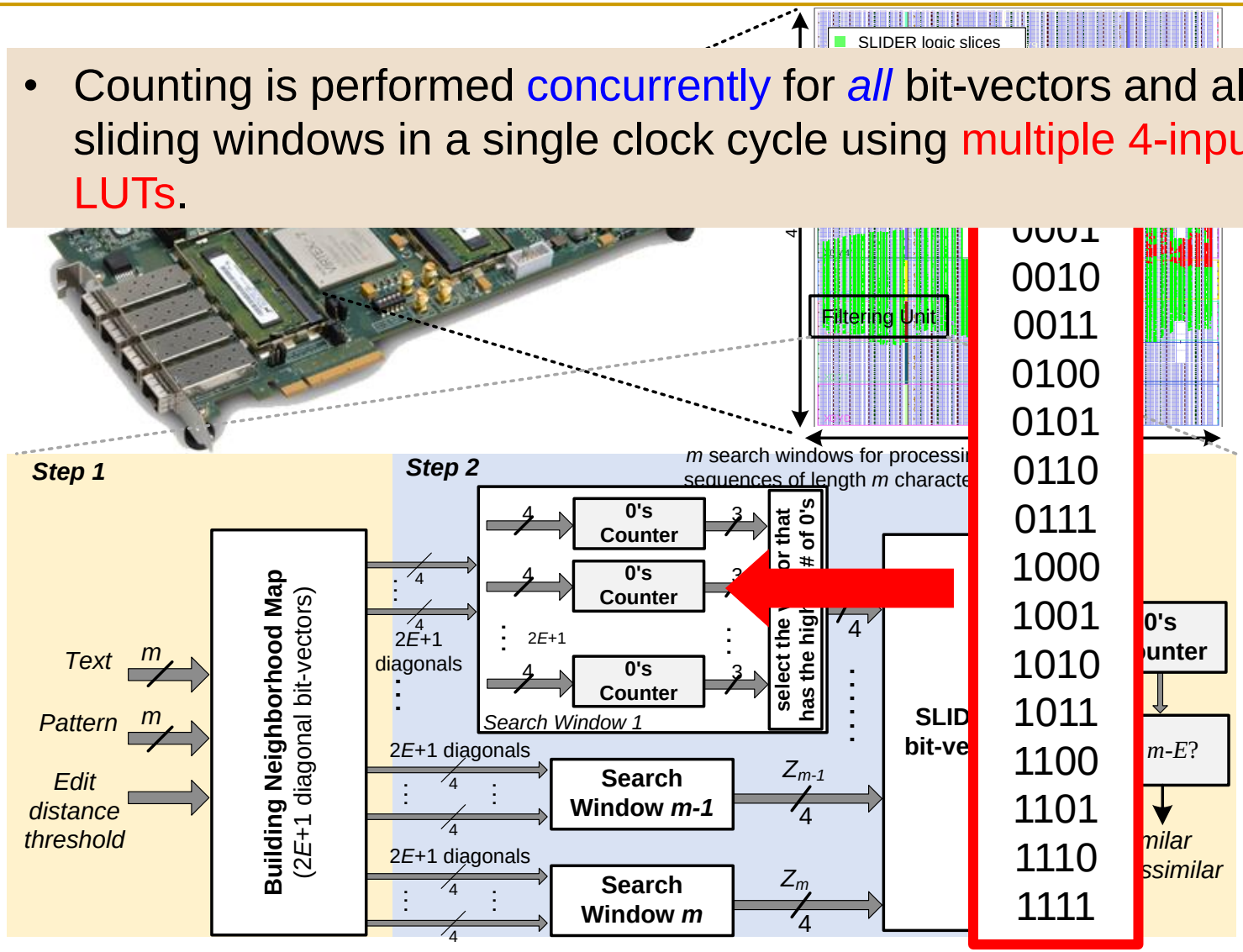
Sliding Window Size

- 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.



Shouji

- **Key observation:**
  - Correct alignment always includes long identical subsequences.
  - Processing the entire mapping at once (as in GateKeeper) 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).

More on Shouji

Download and test for yourself

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

Bioinformatics, 2019, 1–9
doi: 10.1093/bioinformatics/btz234
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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

Assignment #2

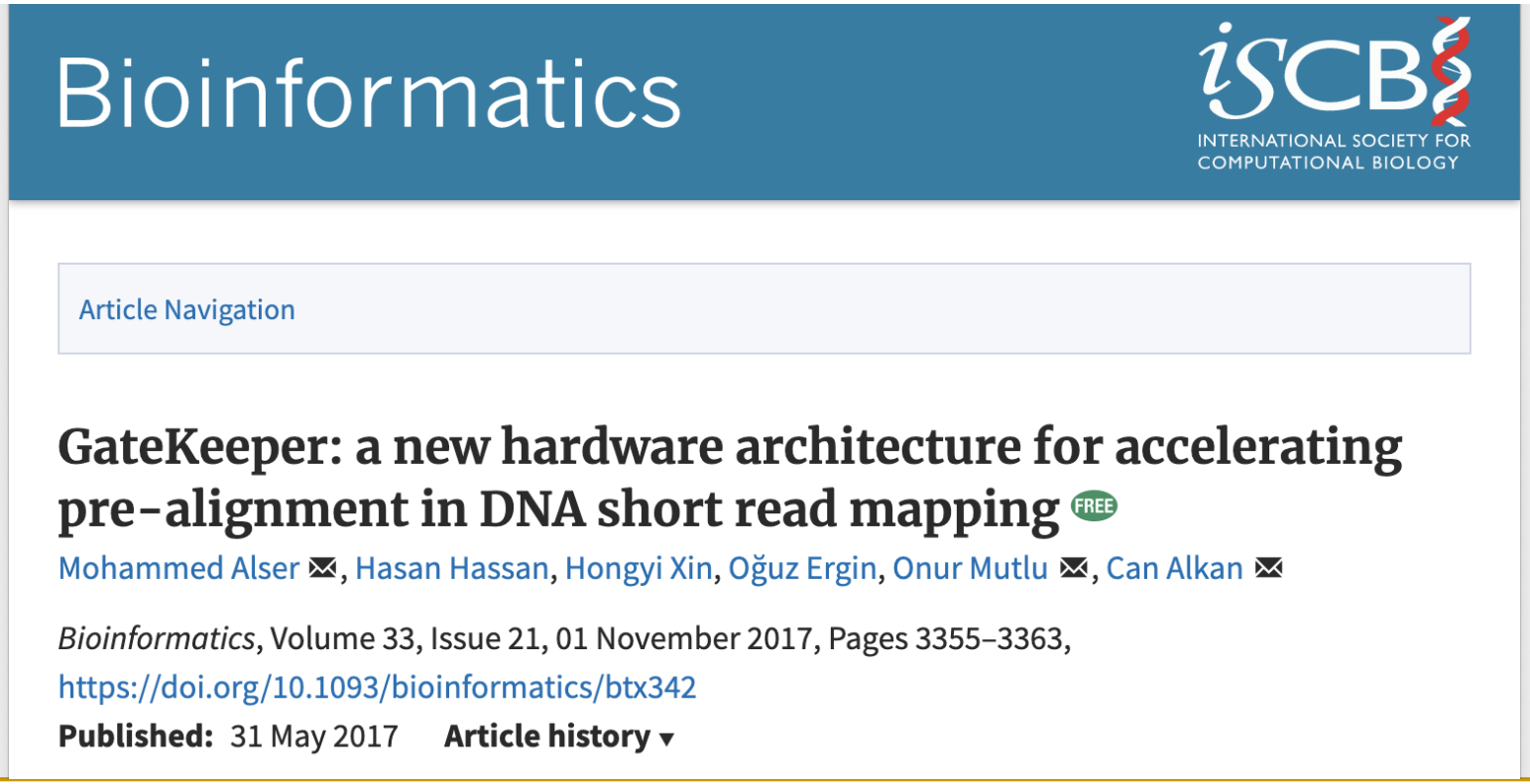
- Which one out of the three pre-alignment filters, GateKeeper, MAGNET, and Shouji is more efficient? why?
  - Hint:

	GateKeeper	MAGNET	Shouji	Justification
Time complexity				
Space complexity				
FPGA resource				
Accuracy				
Speed				

Most speedup comes from parallelism enabled by novel architectures and algorithms

More on GateKeeper [Alser+, Bioinformatics 2017]

Mohammed Alser, Hasan Hassan, Hongyi Xin, Oguz Ergin, Onur Mutlu, and Can Alkan
"GateKeeper: A New Hardware Architecture for Accelerating Pre-Alignment in DNA Short Read Mapping"
Bioinformatics, [published online, May 31], 2017.
[Source Code]
[Online link at Bioinformatics Journal]



Bioinformatics

ISCB INTERNATIONAL SOCIETY FOR COMPUTATIONAL BIOLOGY

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** ▾

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

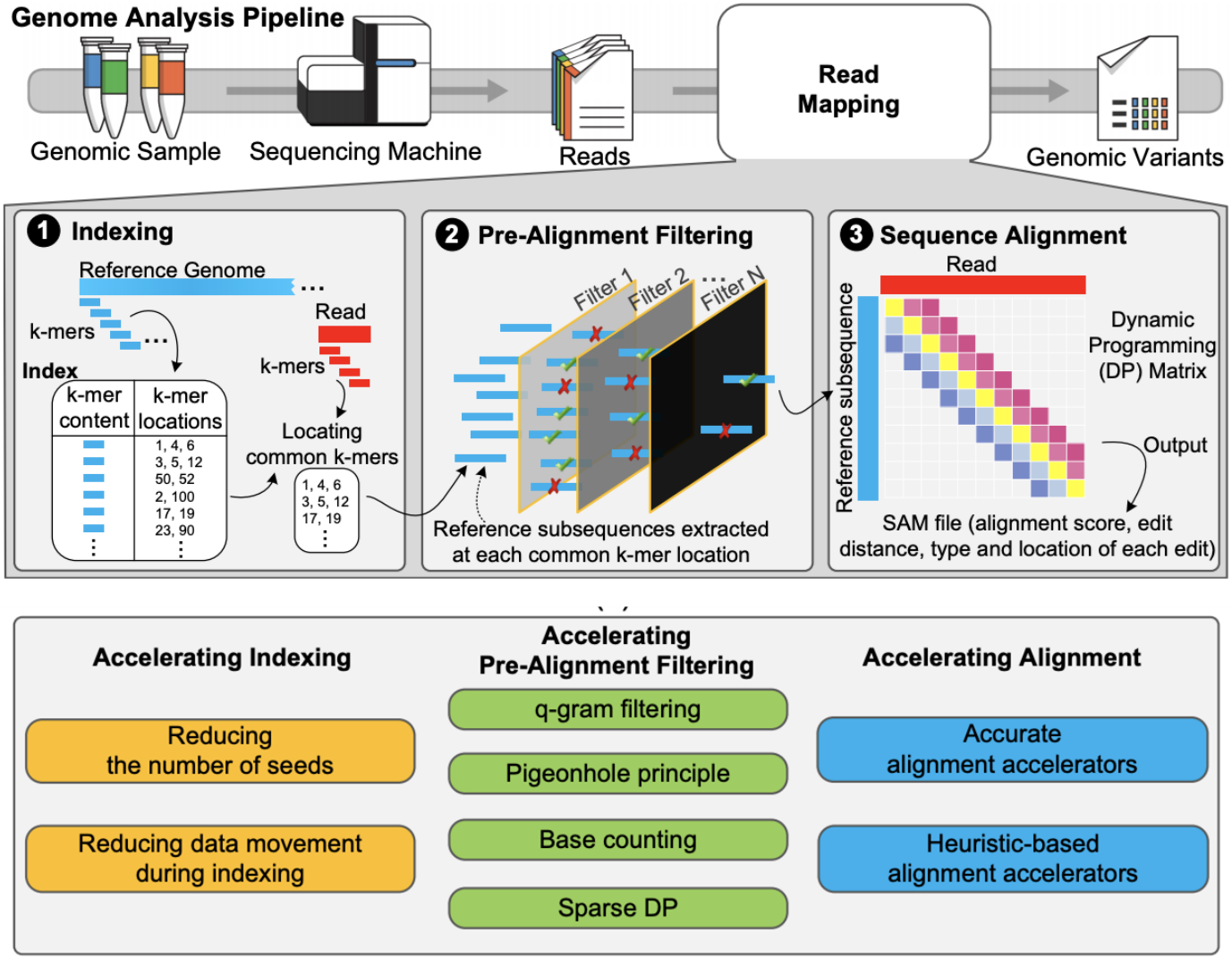
Genome Biology

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*†]

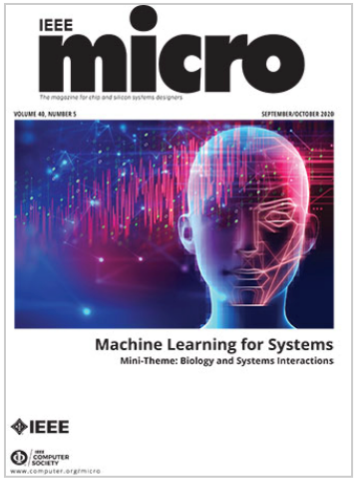
Accelerating Read Mapping



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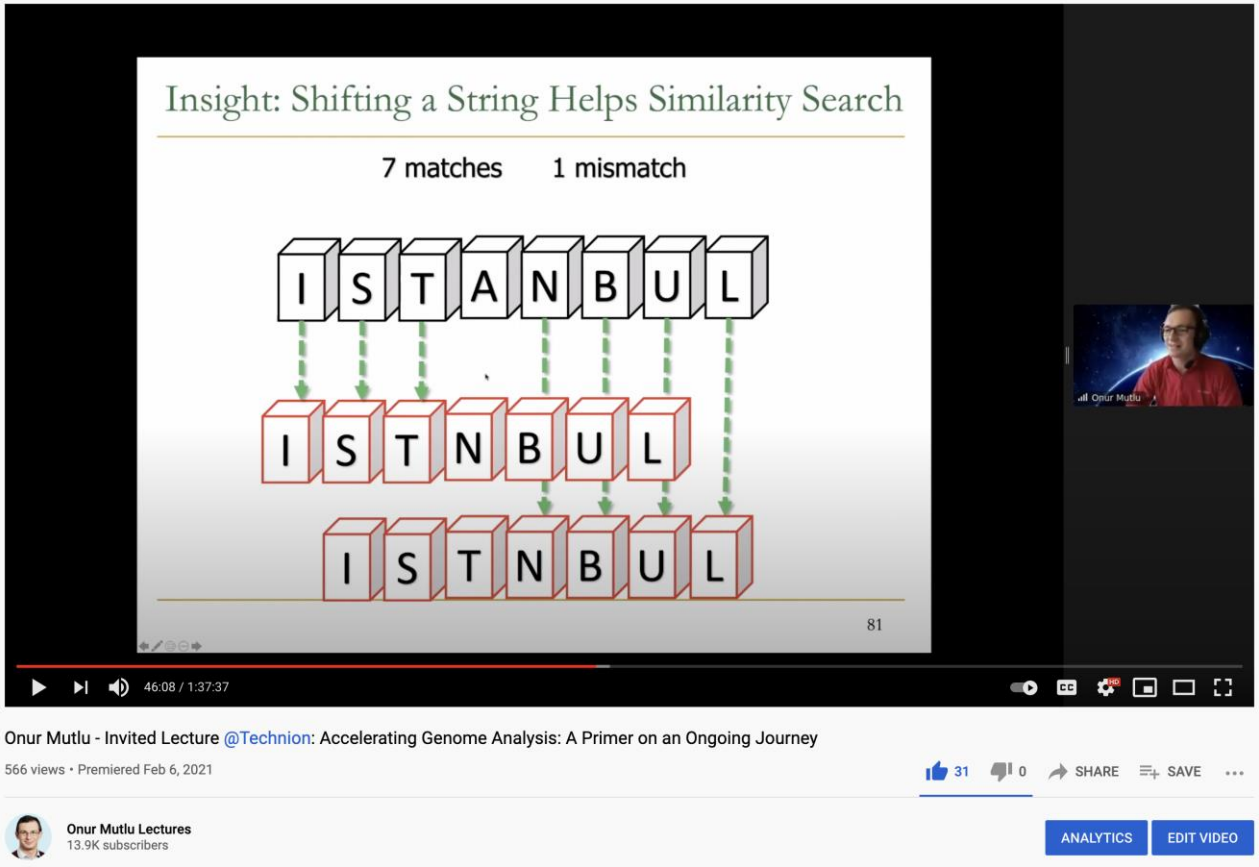
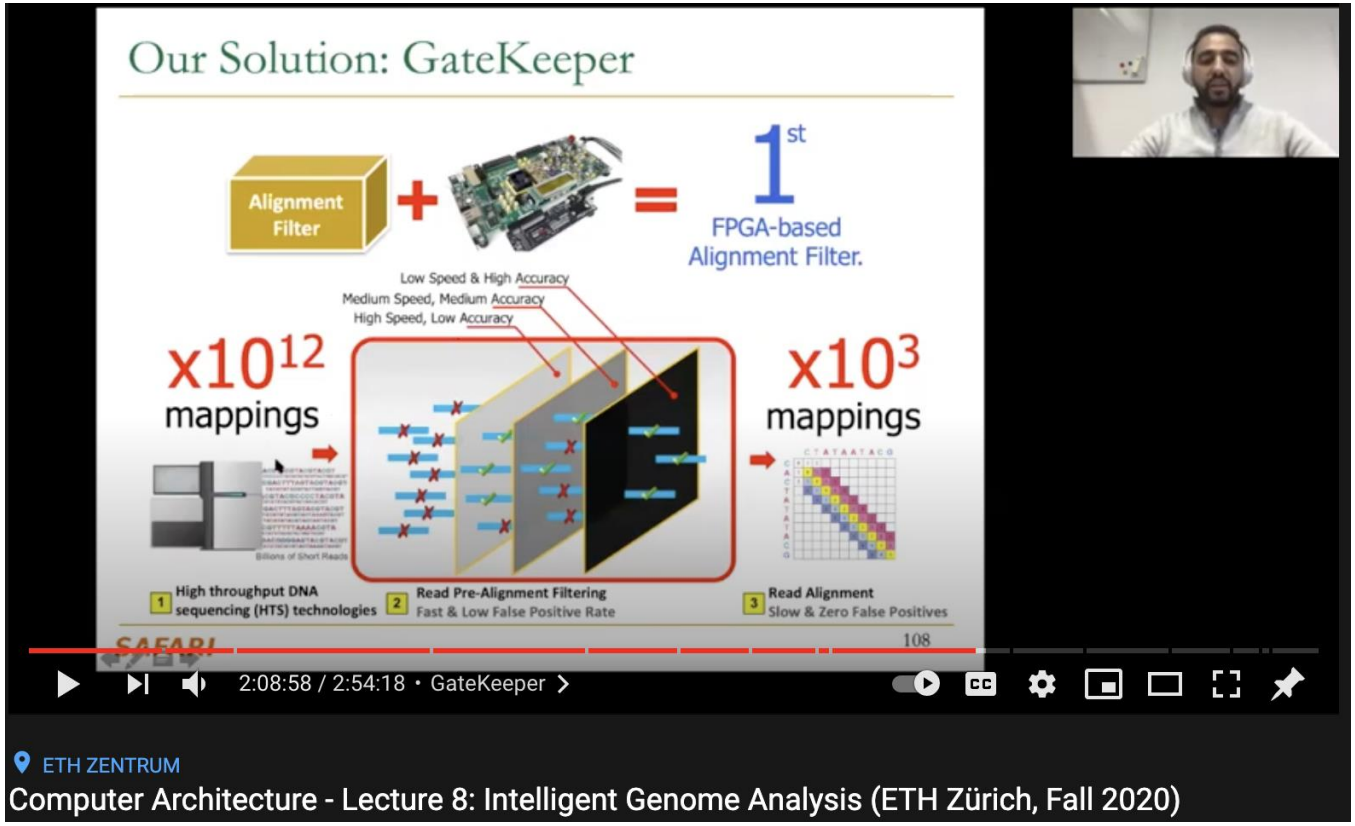
Saugata Ghose, University of Illinois at Urbana–Champaign and Carnegie Mellon University
Can Alkan, Bilkent University
Onur Mutlu, ETH Zurich, Carnegie Mellon University, and Bilkent University

More on 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)]



More on Intelligent Genome Analysis …



https://www.youtube.com/watch?v=ygmQpdDTL7o

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 + "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.
- Alser+, "Technology dictates algorithms: Recent developments in read alignment", *arXiv*, 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 Accelerating Genomics

Lecture 6: MAGNET & Shouji

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ETH Zurich

Fall 2022

24 November 2022

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