Accelerating Genome Analysis

A Primer on an Ongoing Journey

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ETH HAML Seminar

SAFARI

ETH zürich

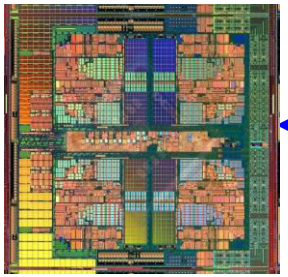
Who Am I?

- Onur Mutlu
  - Professor @ ETH Zurich CS, since September 2015 (officially May 2016)
  - 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)
  - Office hours: By appointment (email me)
- Research and Teaching in:
  - Computer architecture, computer systems, bioinformatics
  - Memory and storage systems
  - Hardware security
  - Fault tolerance
  - Hardware/software cooperation
  - …

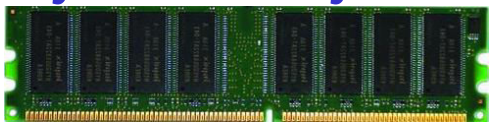
Current Research Focus Areas

***Research Focus:* Computer architecture, HW/SW, bioinformatics**

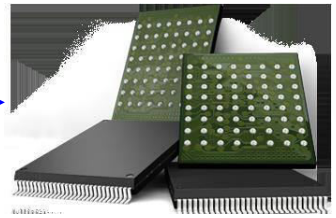
- *Memory and storage (DRAM, flash, emerging), interconnects*
- *Heterogeneous & parallel systems, GPUs, systems for data analytics*
- *System/architecture interaction, new execution models, new interfaces*
- *Hardware security, energy efficiency, fault tolerance, performance*
- *Genome sequence analysis & assembly algorithms and architectures*
- *Biologically inspired systems & system design for bio/medicine*



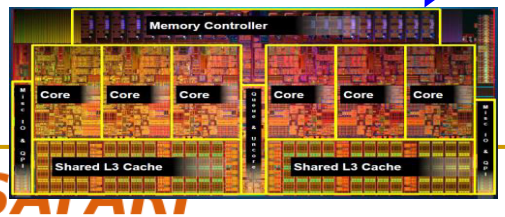
Heterogeneous Processors and Accelerators

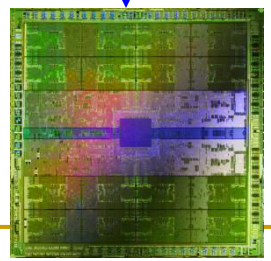


Hybrid Main Memory



Persistent Memory/Storage





Graphics and Vision Processing

Broad research spanning apps, systems, logic with architecture at the center

Four Key Current Directions

- Fundamentally Secure/Reliable/Safe Architectures
- Fundamentally Energy-Efficient Architectures
  - Memory-centric (Data-centric) Architectures
- Fundamentally Low-Latency Architectures
- Architectures for Genomics, Medicine, Health

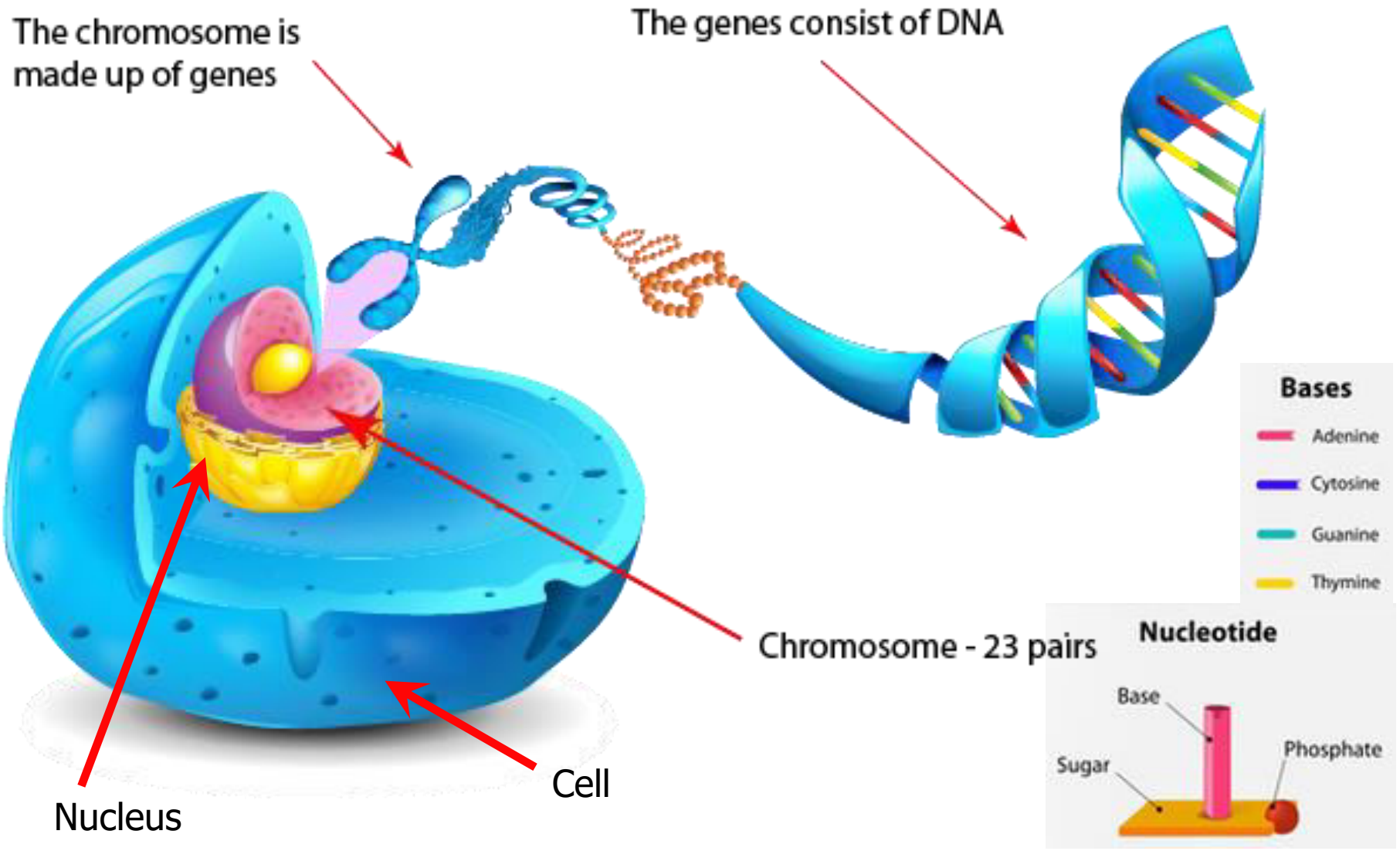
Overview

- System design for bioinformatics is a critical problem
  - It has large scientific, medical, societal, personal implications
- This talk 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 will cover various recent ideas to accelerate read mapping
  - My personal journey since September 2006

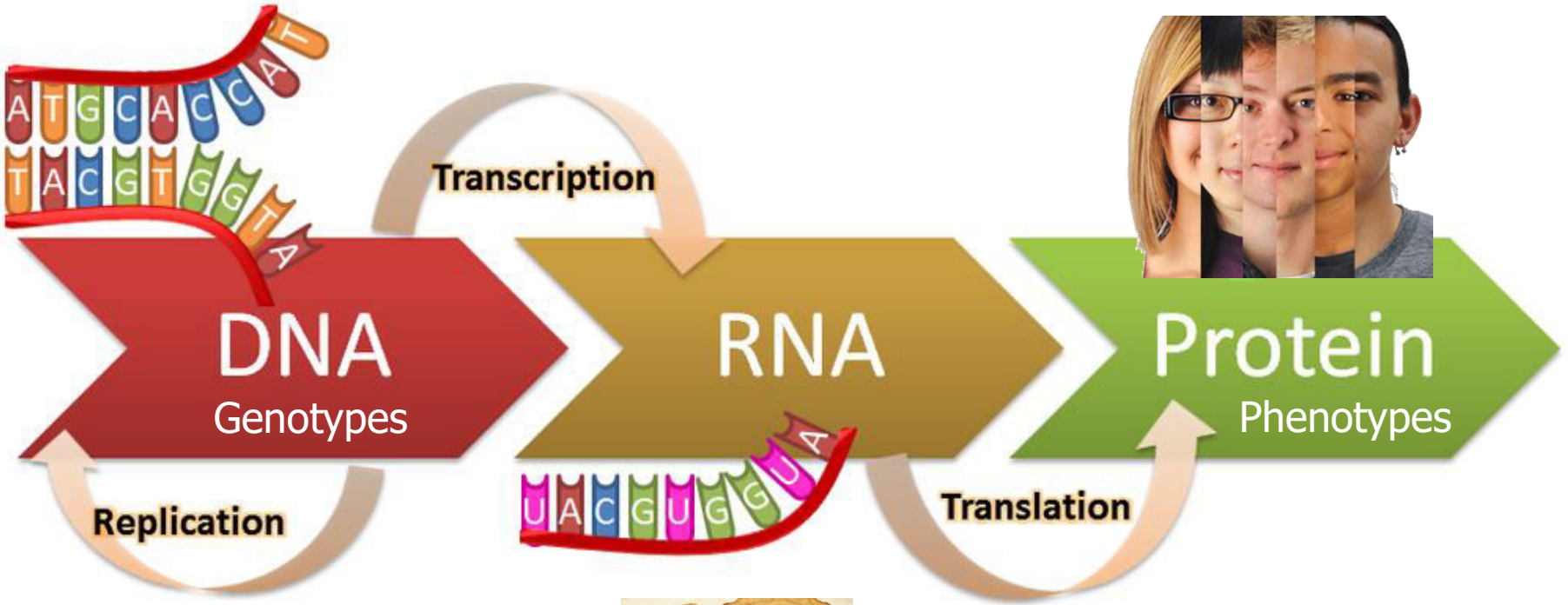
Agenda

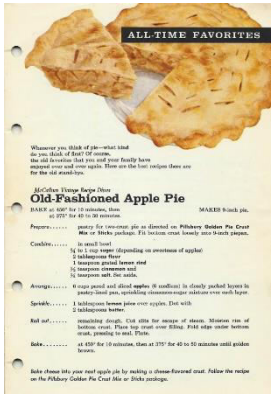
- The Problem: DNA Read Mapping
  - State-of-the-art Read Mapper Design
- Algorithmic Acceleration
  - Exploiting Structure of the Genome
  - Exploiting SIMD Instructions
- Hardware Acceleration
  - Specialized Architectures
  - Processing in Memory
- Future Opportunities: New Sequencing Technologies

What Is a Genome Made Of?

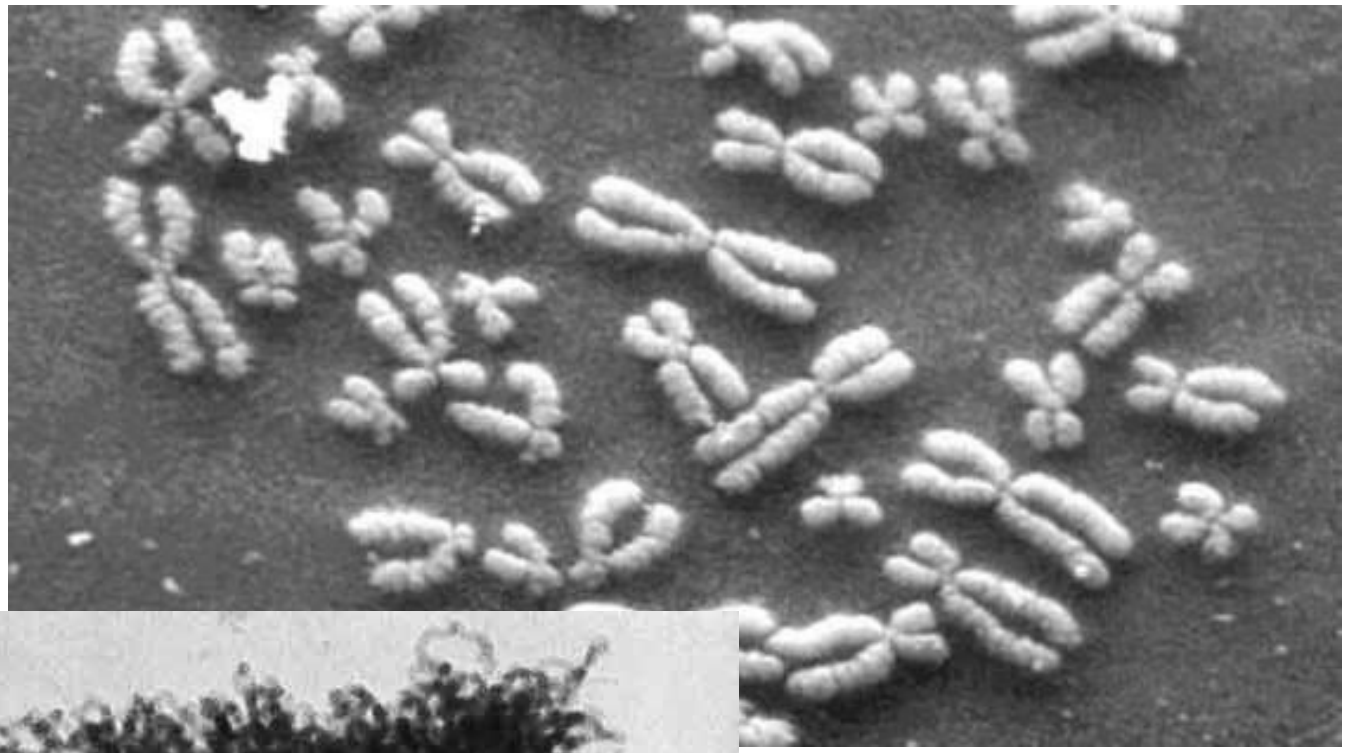


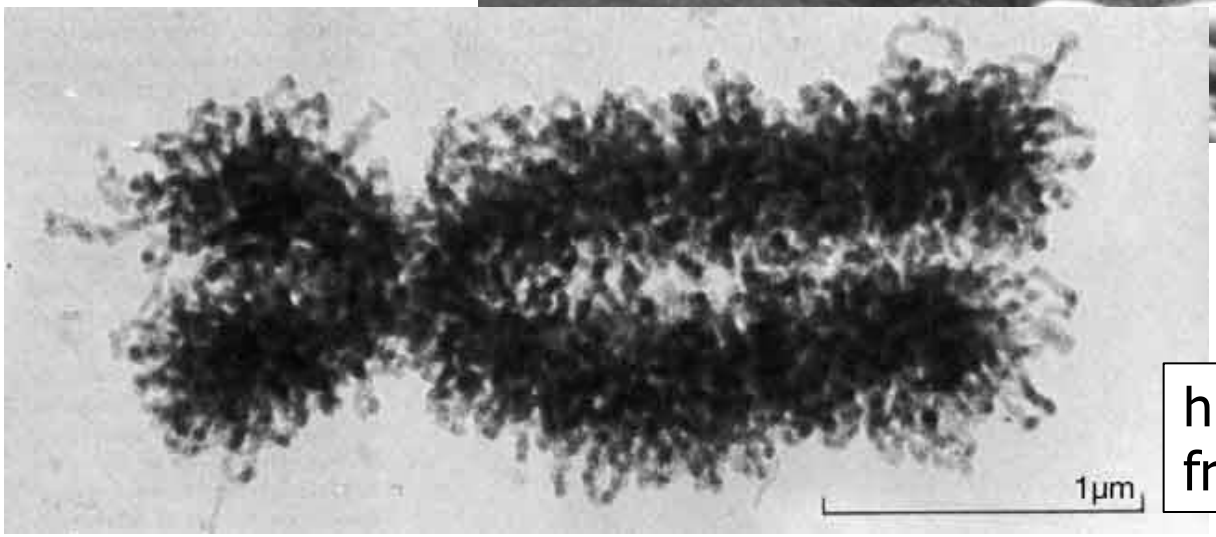
The Central Dogma of Molecular Biology





DNA Under Electron Microscope





human chromosome #12
from HeLa's cell

DNA Sequencing

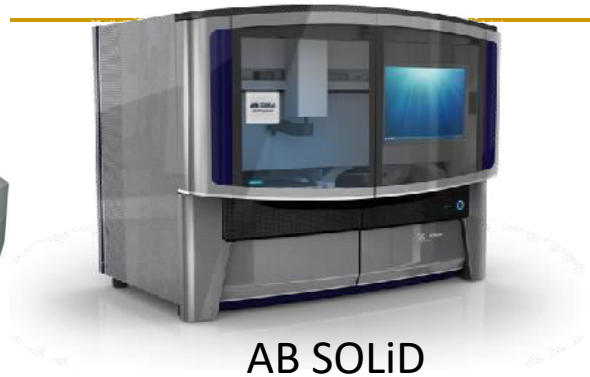
- Goal:
  - Find the complete sequence of A, C, G, T's in DNA.

- Challenge:
  - There is no machine that takes long DNA as an input, and gives the complete sequence as output
  - All sequencing machines chop DNA into pieces and identify relatively small pieces (but not how they fit together)

Untangling Yarn Balls & DNA Sequencing

Genome Sequencers

Roche/454



AB SOLiD

Illumina MiSeq

Complete Genomics

Oxford Nanopore MinION

Illumina HiSeq2000

Pacific Biosciences RS

Oxford Nanopore GridION

Illumina NovaSeq 6000

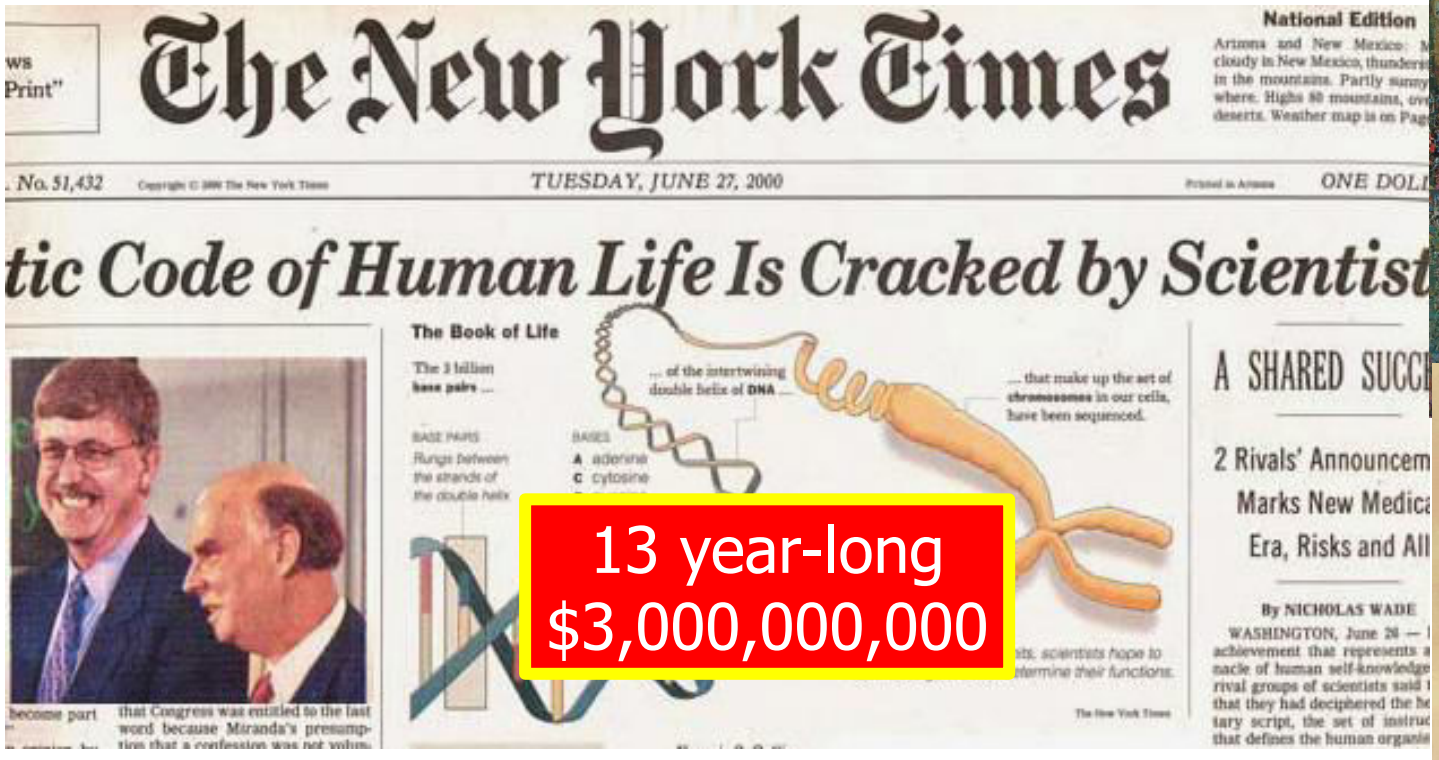
Ion Torrent PGM

Ion Torrent Proton

… and more! All produce data with different properties.

The Genomic Era

- 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.


The New York Times

National Edition

TUESDAY, JUNE 27, 2000

tic Code of Human Life Is Cracked by Scientist

The Book of Life

A SHARED SUCC

2 Rivals' Announcem

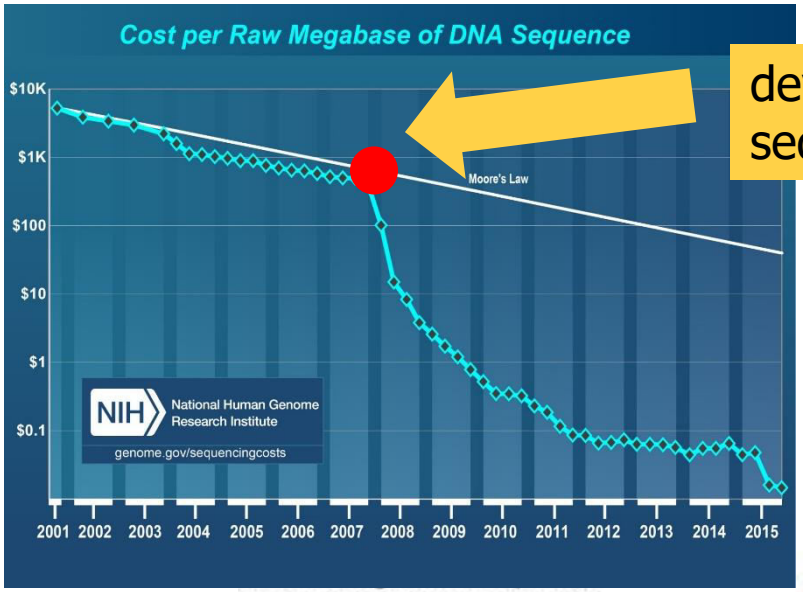
Marks New Medica

Era, Risks and All

By NICHOLAS WADE

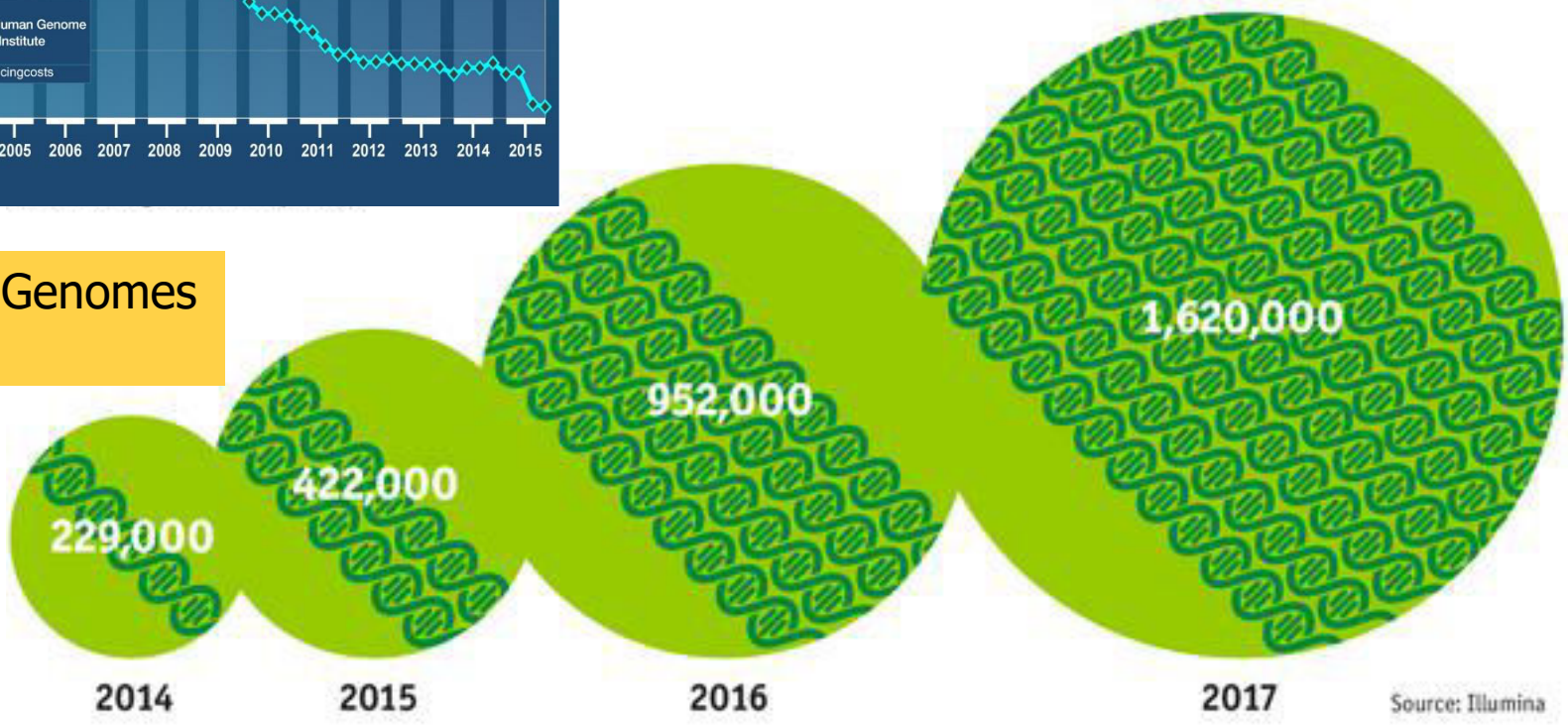
13 year-long
$3,000,000,000

The Genomic Era (continued)



development of high-throughput sequencing (HTS) technologies

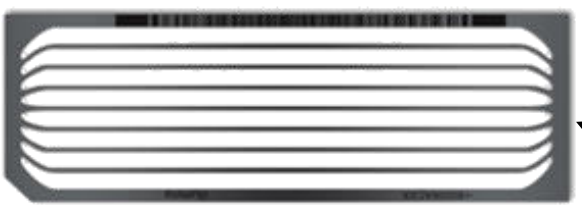
Number of Genomes Sequenced



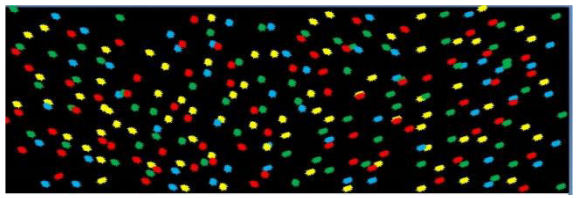
The Economist

http://www.economist.com/news/21631808-so-much-genetic-data-so-many-uses-genes-unzipped

High-Throughput Sequencing (HTS)



flow cell



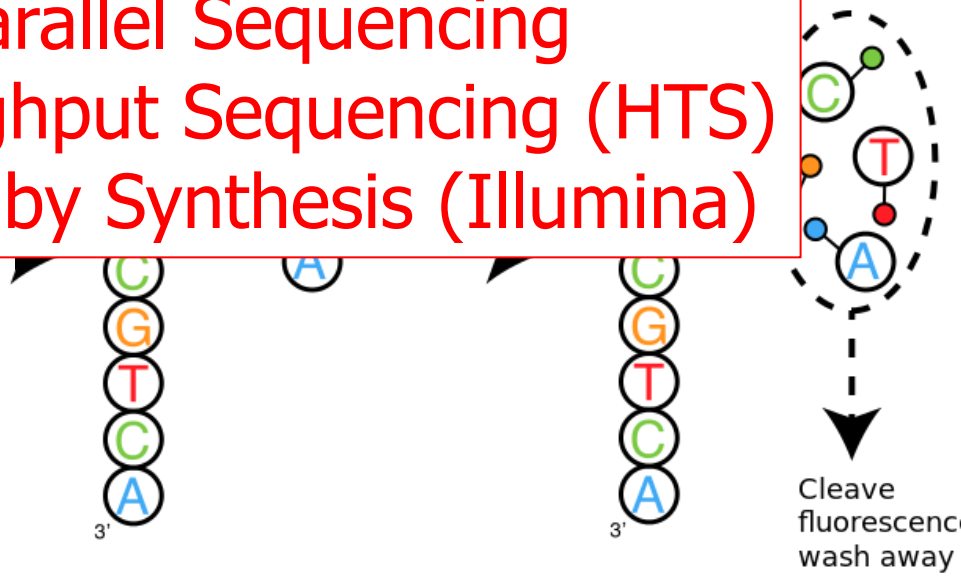
computer

orange = G

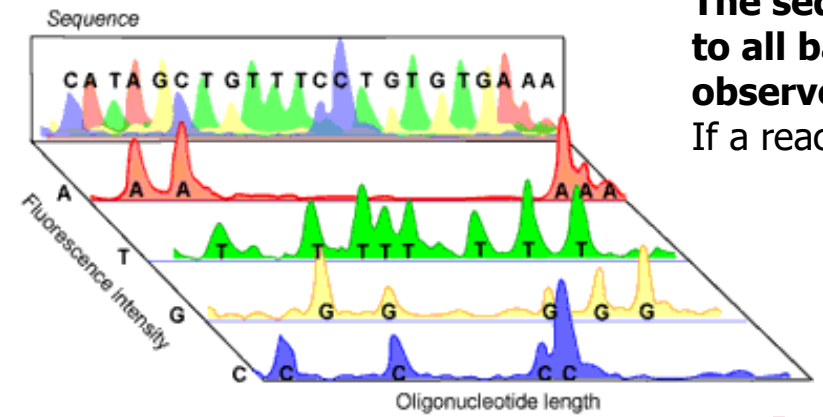
readout

AGTG

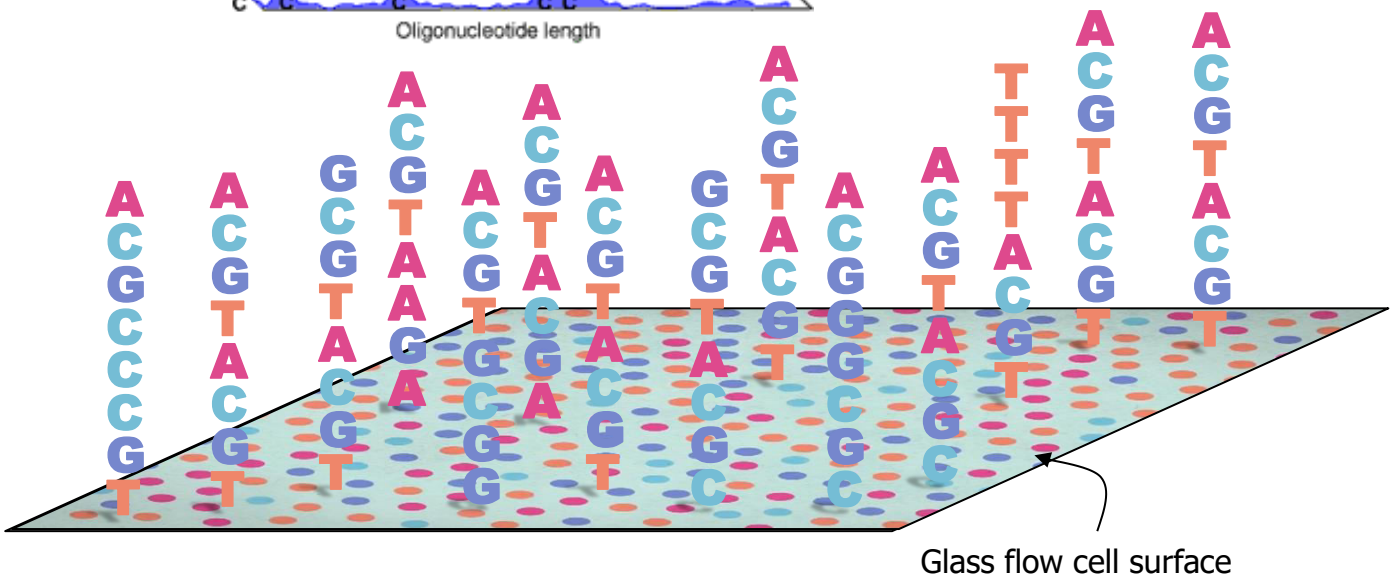
= Second Generation
= Next Generation
= Massively Parallel Sequencing
= High Throughput Sequencing (HTS)
= Sequencing by Synthesis (Illumina)

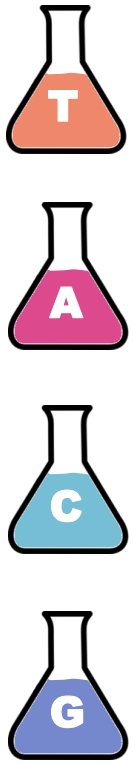


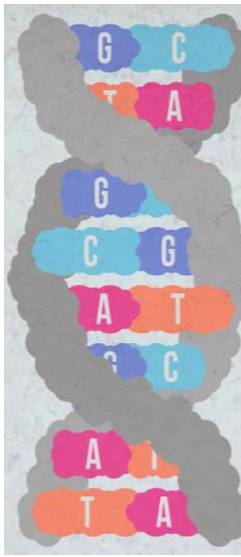
High-Throughput Sequencing (HTS)



The sequencer adds the molecule "T" to all bases near the flow cell surface and observes the chemical reaction via a CMOS sensor.
If a reaction happens then the base is "A"







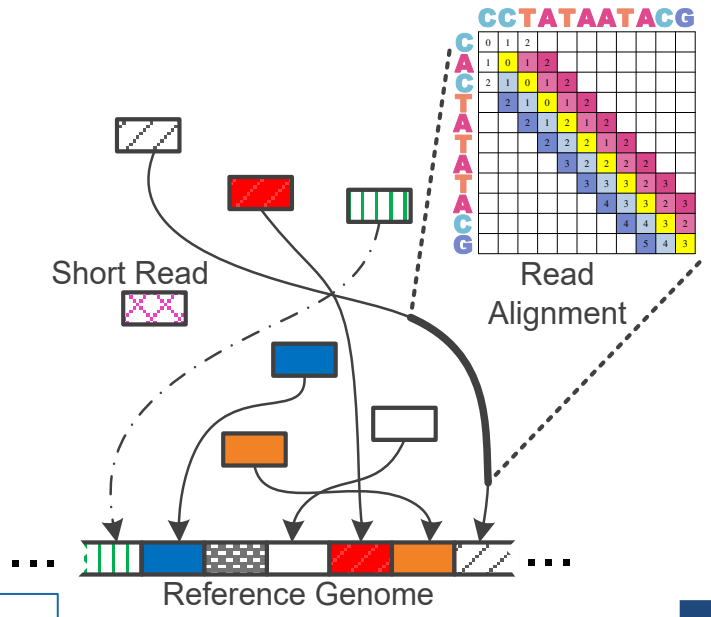
As a workaround, HTS technologies sequence random short DNA fragments (75-300 basepairs long) of copies of the original molecule.

High-Throughput Sequencing

- Massively parallel sequencing technology
  - Illumina, Roche 454, Ion Torrent, SOLID…
- Small DNA fragments are first amplified and then sequenced in parallel, leading to
  - High throughput
  - High speed
  - Low cost
  - Short reads
    - Amplification step limits the read length since too short or too long fragments are not amplified well.
- Sequencing is done by either reading optical signals as each base is added, or by detecting hydrogen ions instead of light, leading to:
  - Low error rates (relatively)
  - Reads lack information about their order and which part of genome they are originated from

Genome Analysis

1 Sequencing



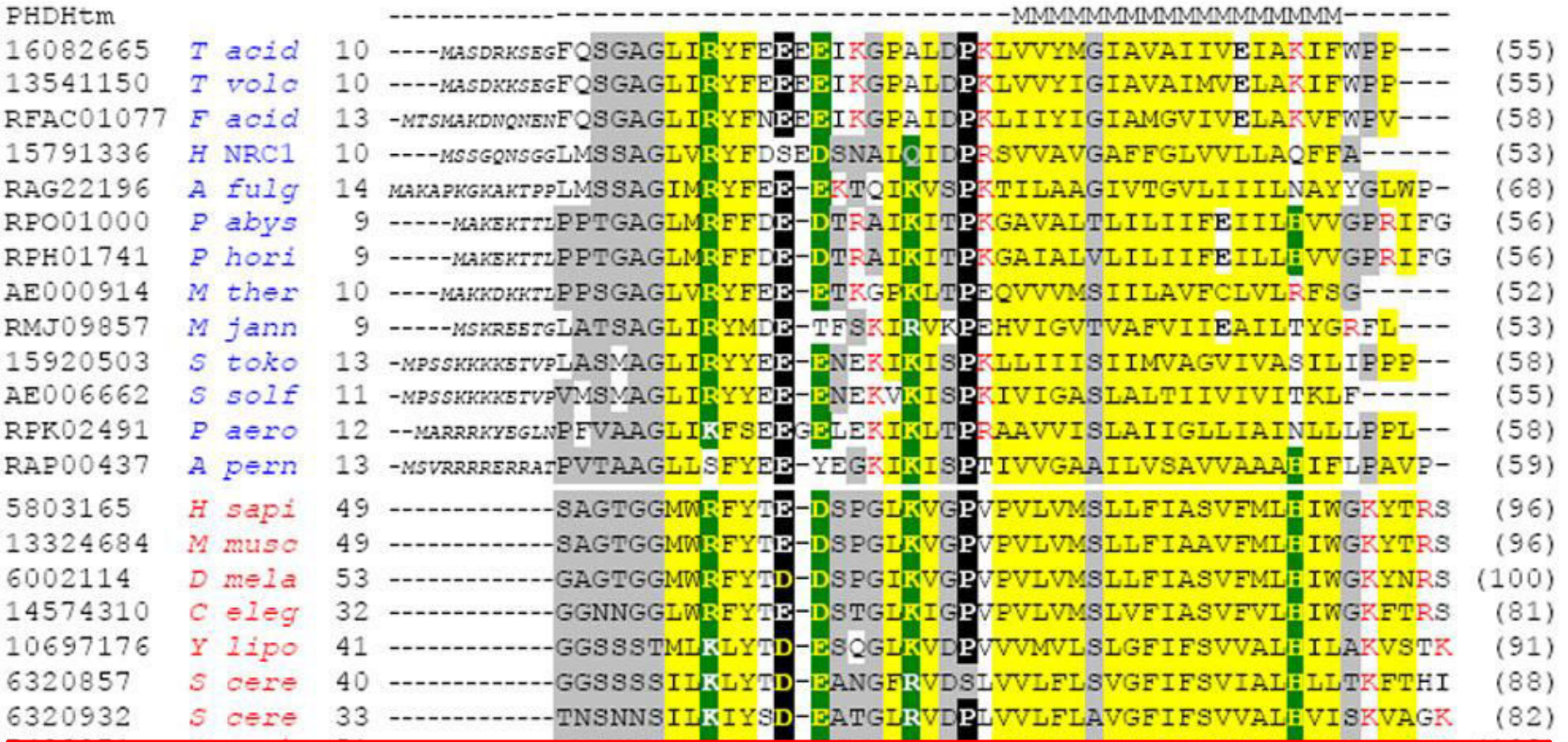
Read Mapping 2

```
reference: TTTATCGCTTCCATGACGCAG
read1:       ATCGCATCC
read2:      TATCGCATC
read3:           CATCCATGA
read4:         CGCTTCCAT
read5:               CCATGACGC
read6:             TTCCATGAC
```

3 Variant Calling

Scientific Discovery 4

Multiple sequence alignment



Example Question: If I give you a bunch of sequences, tell me where they are the same and where they are different.

The Genetic Similarity Between Species

Human ~ Human

99.9%

Human ~ Chimpanzee

96%

Human ~ Cat

90%

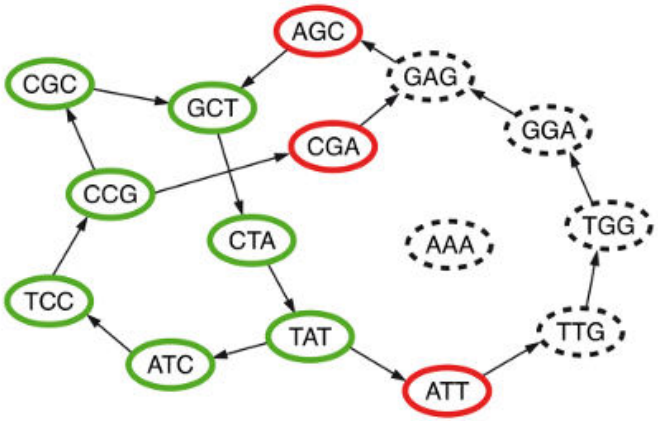
Human ~ Cow

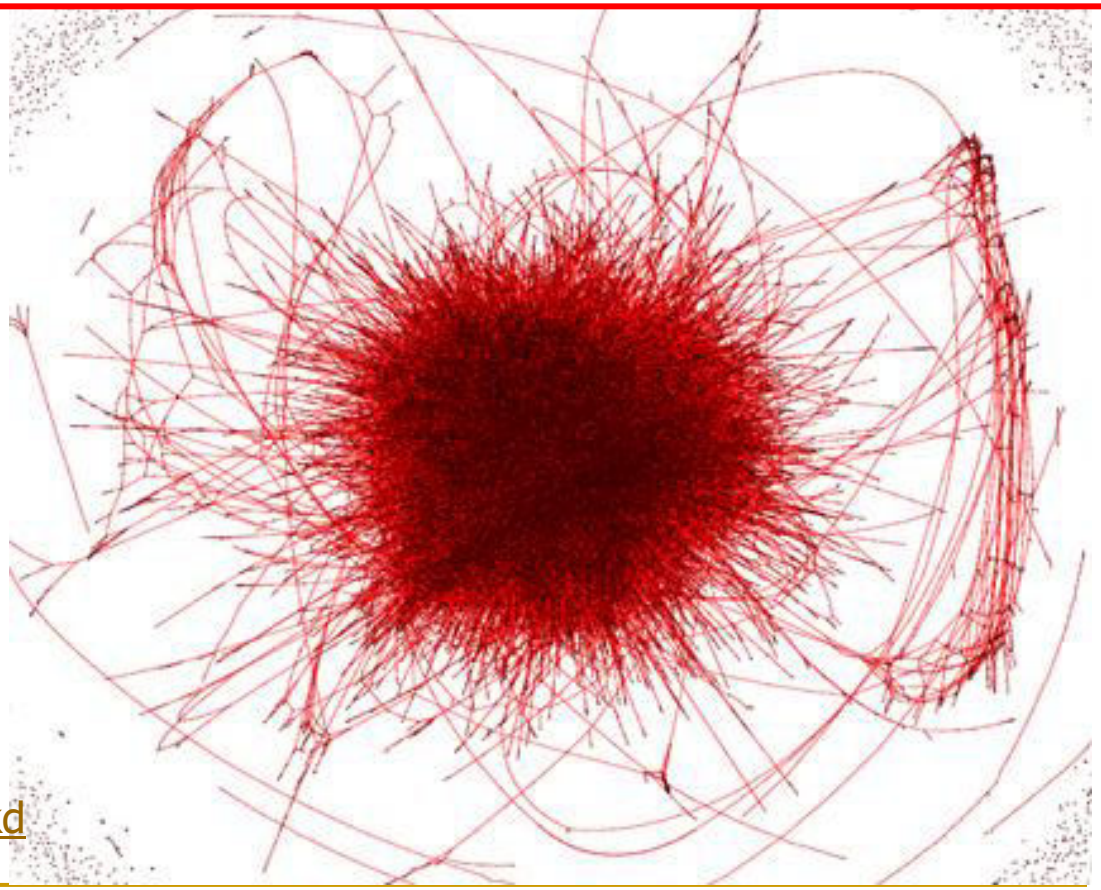
80%

Human ~ Banana

50-60%

Question 2: Given a bunch of short sequences, Can you identify the approximate species cluster for genomically unknown organisms (bacteria)?

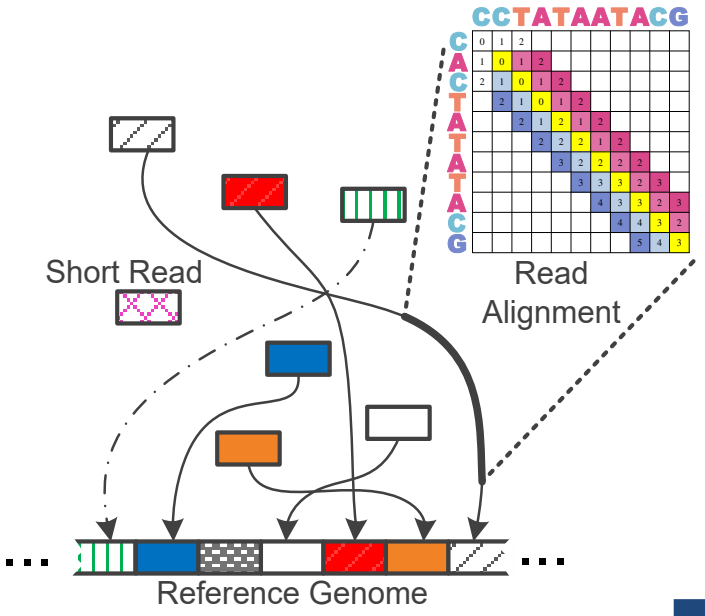




uncleaned de Bruijn graph

http://math.oregonstate.edu/~koslickd

1 Sequencing



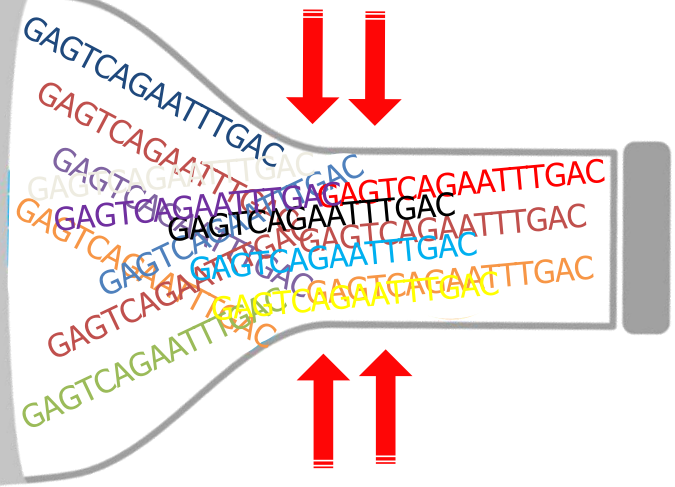
Read Mapping 2

Bottlenecked in Mapping!!

Illumina HiSeq4000

300 M

bases/min



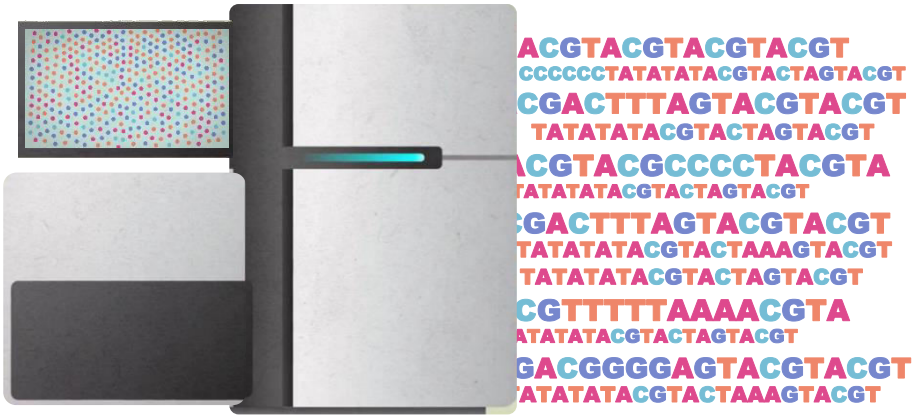
on average

2 M

bases/min

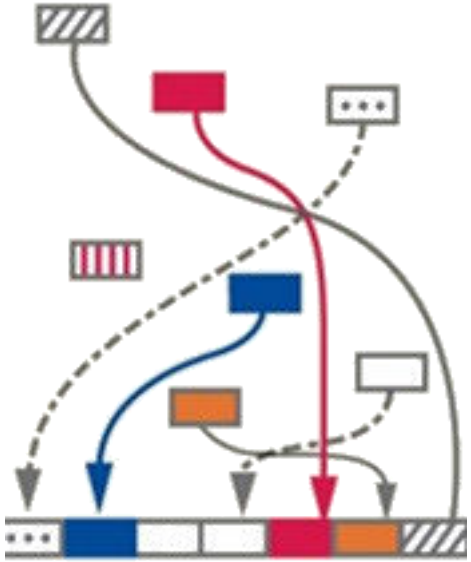
(0.6%)

The Read Mapping Bottleneck



Illumina HiSeq4000

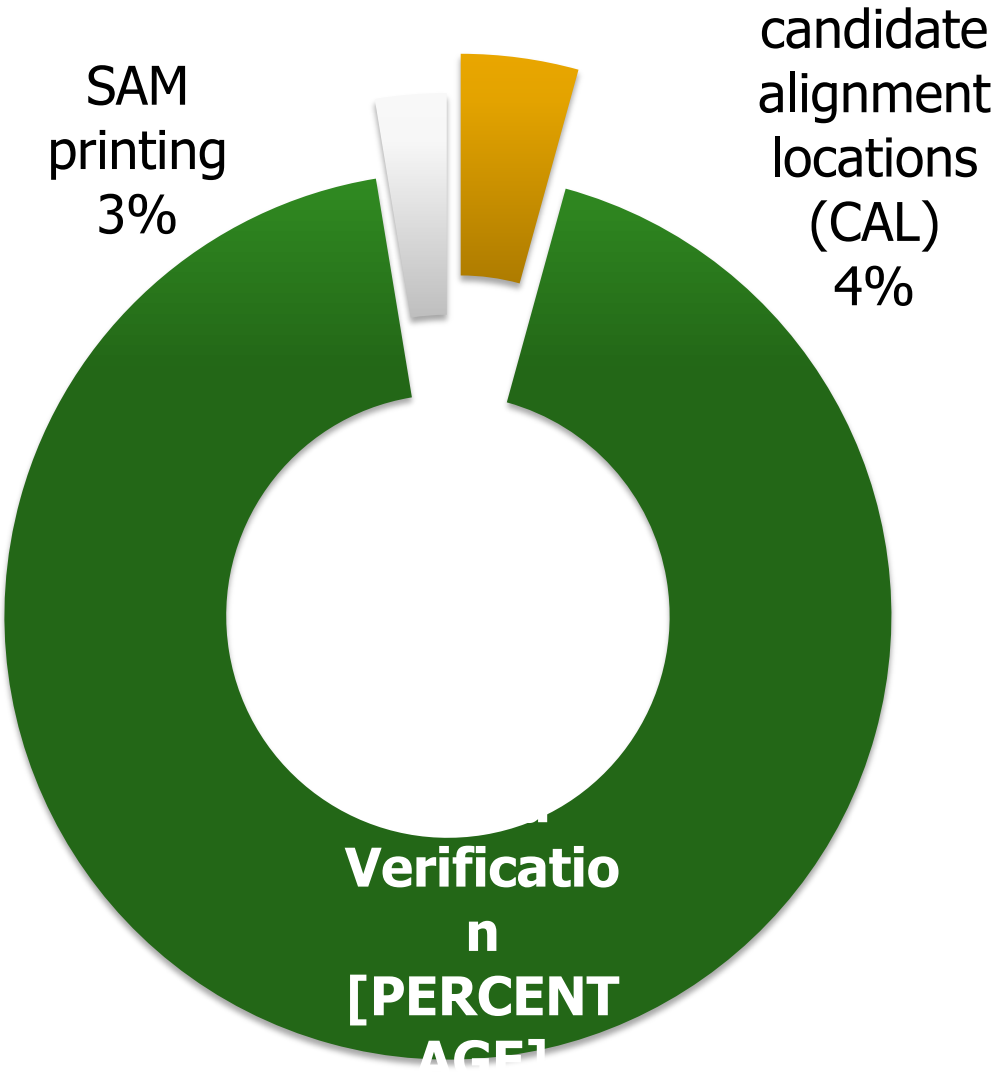
300 Million bases/minute



2 Million bases/minute

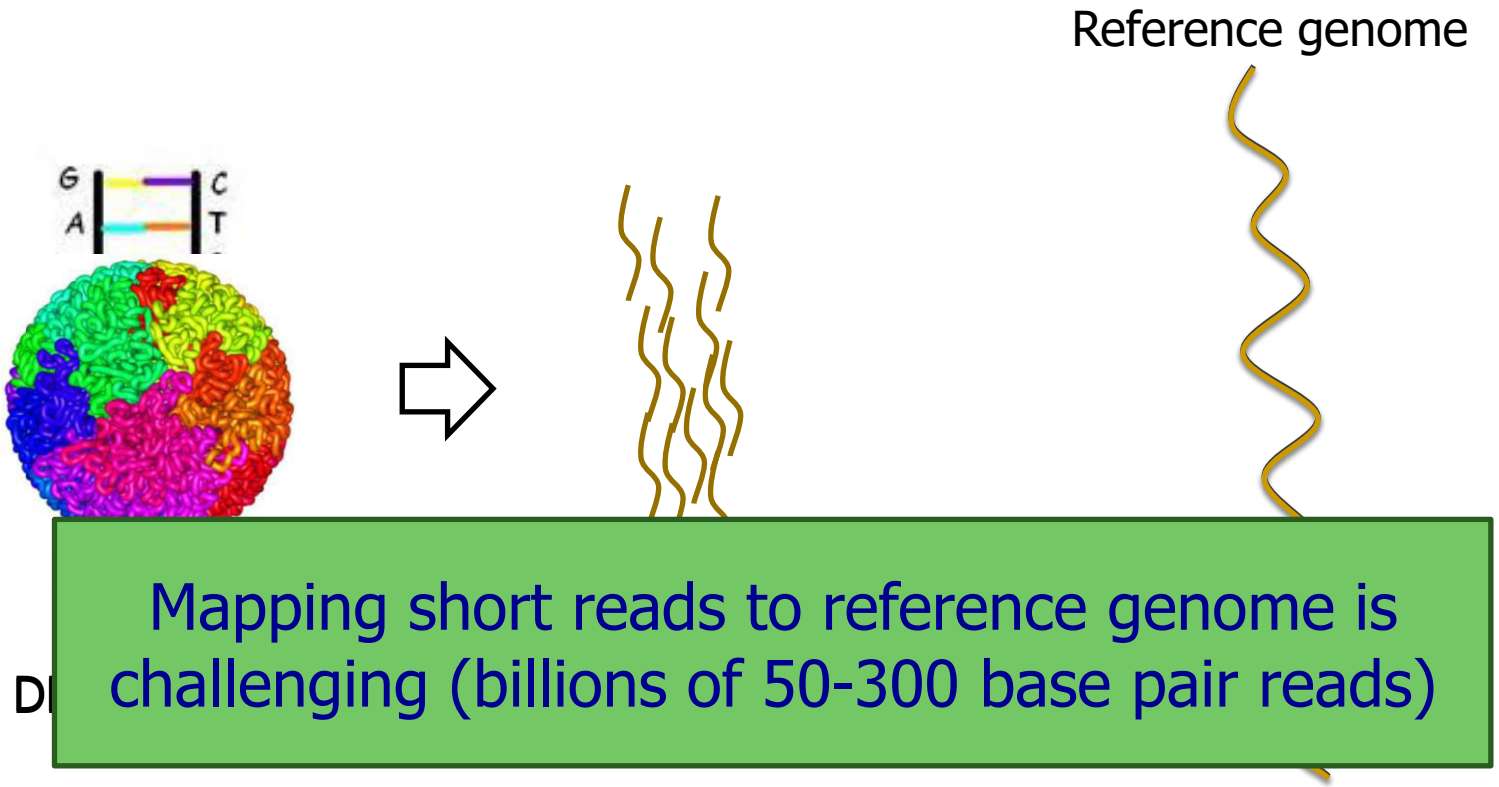
150X slower

Read Mapping Execution Time Breakdown



Read Mapping

- Map many short DNA fragments (reads) to a known reference genome with some minor differences allowed



Challenges in Read Mapping

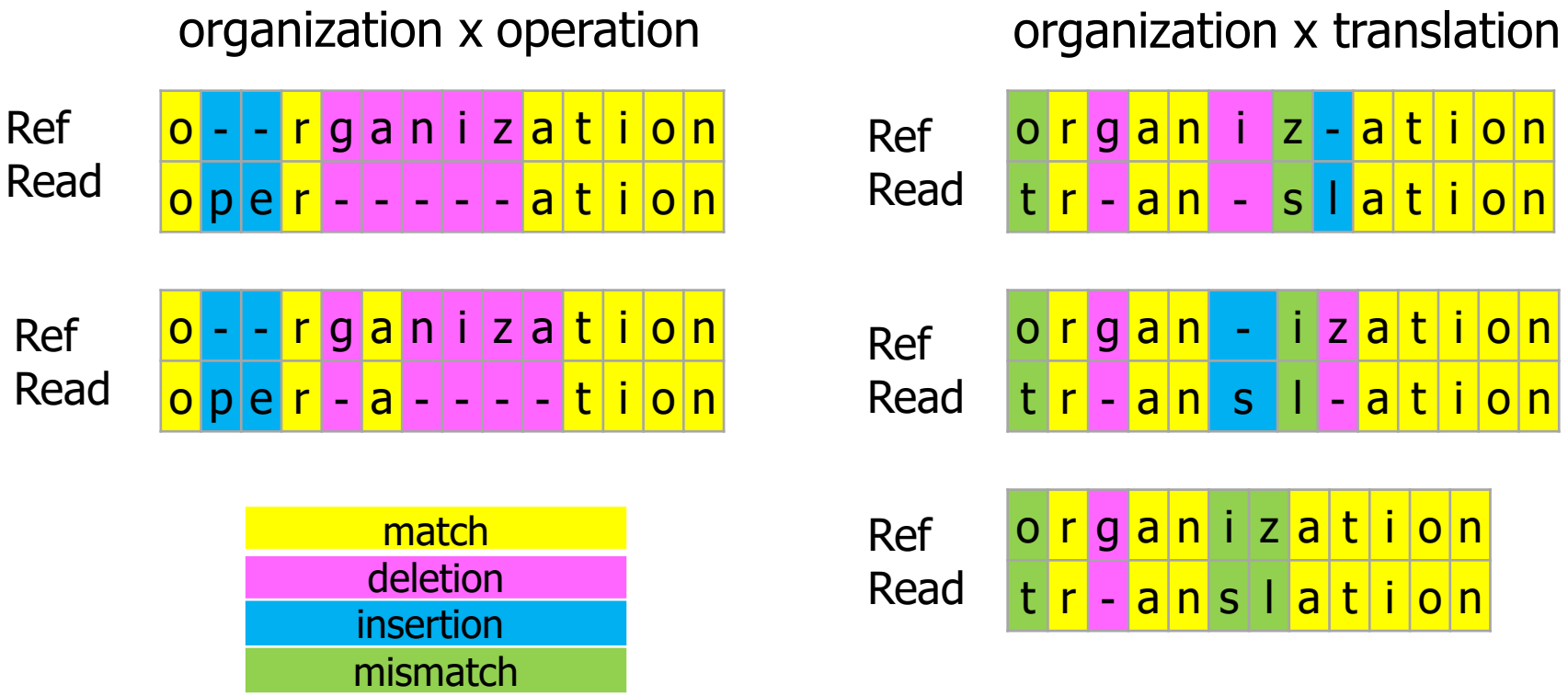
- Need to find many mappings of each read
  - A short read may map to many locations, especially with High-Throughput DNA Sequencing technologies
  - How can we find all mappings efficiently?

- Need to tolerate small variances/errors in each read
  - Each individual is different: Subject's DNA may slightly differ from the reference (Mismatches, insertions, deletions)
  - How can we efficiently map each read with up to *e* errors present?

- Need to map each read very fast (i.e., performance is important)
  - Human DNA is 3.2 billion base pairs long → Millions to billions of reads (State-of-the-art mappers take weeks to map a human's DNA)
  - How can we design a much higher performance read mapper?

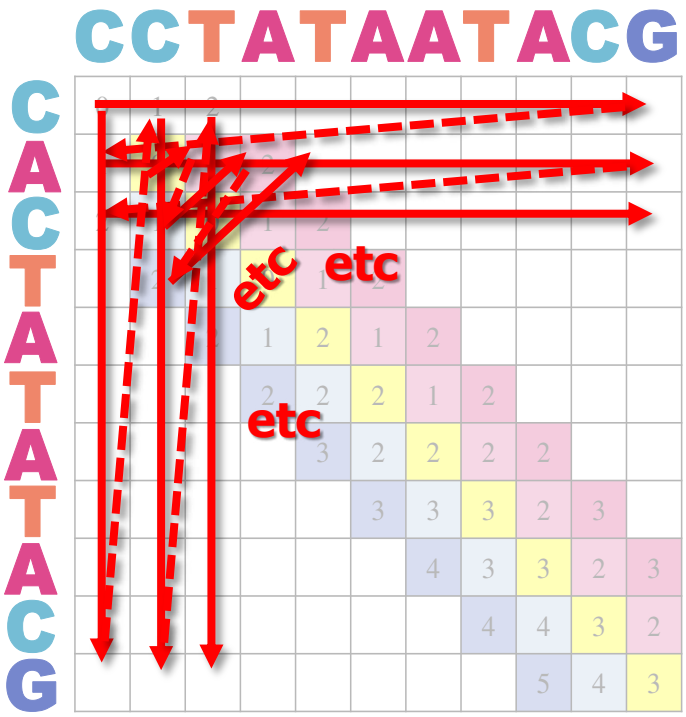
Read Alignment/Verification

- **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.



Why Is Read Alignment Slow?

- Quadratic-time dynamic-programming algorithm(s)
- Data dependencies limit the computation parallelism
- Entire matrix computed even though strings may be dissimilar.



Read Alignment

Agenda

- The Problem: DNA Read Mapping
  - State-of-the-art Read Mapper Design
- Algorithmic Acceleration
  - Exploiting Structure of the Genome
  - Exploiting SIMD Instructions
- Hardware Acceleration
  - Specialized Architectures
  - Processing in Memory
- Future Opportunities: New Sequencing Technologies

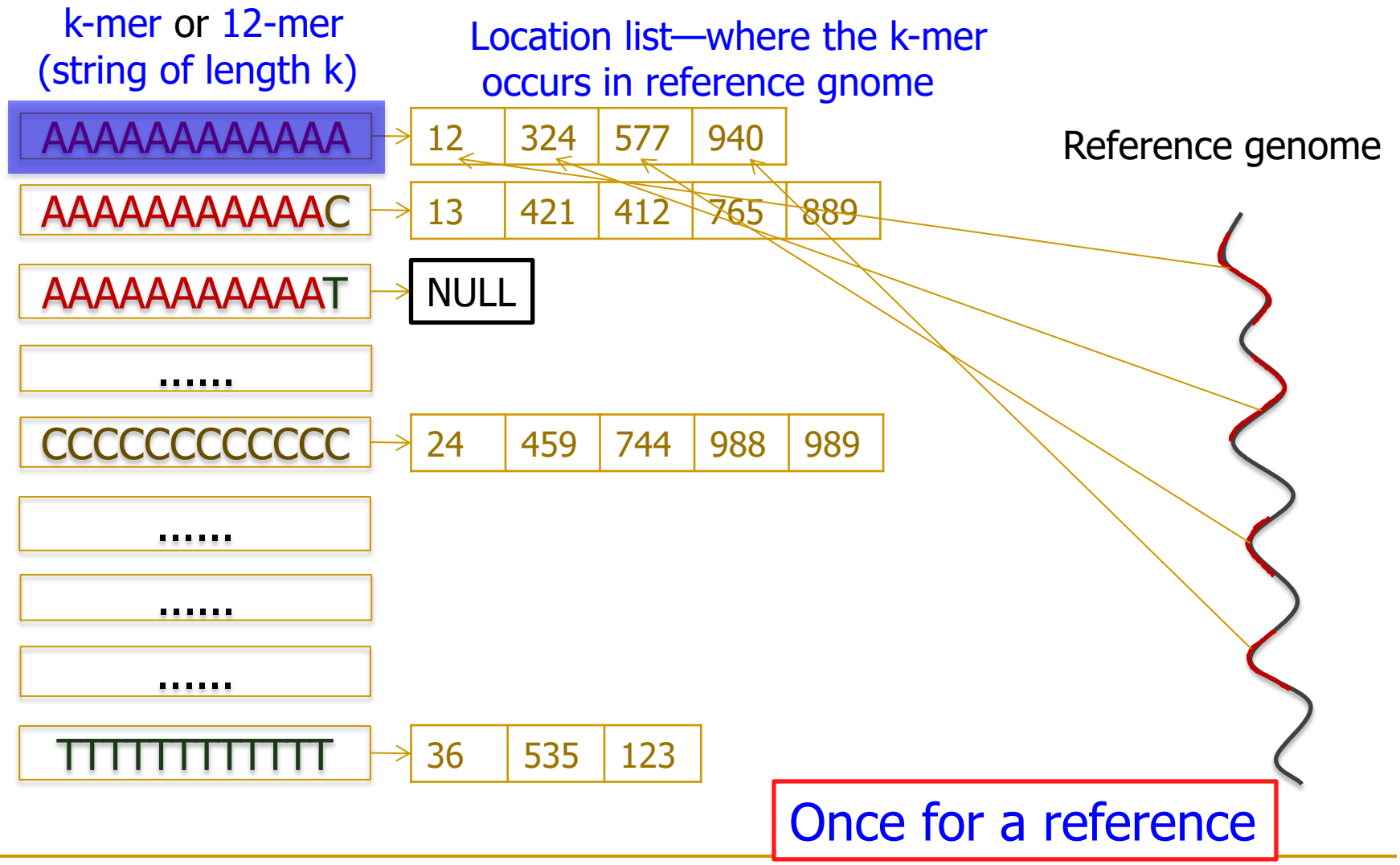
Read Mapping Algorithms: Two Styles

- Hash based seed-and-extend (hash table, suffix array, suffix tree)
  - Index the "k-mers" in the genome into a hash table (pre-processing)
  - When searching a read, find the location of a k-mer in the read; then extend through alignment
  - More sensitive, but slow
  - Requires large memory; this can be reduced with cost to run time
- Burrows-Wheeler Transform & Ferragina-Manzini Index based aligners
  - BWT is a compression method used to compress the genome index
  - Perfect matches can be found very quickly, memory lookup costs increase for imperfect matches
  - Reduced sensitivity

Hash Table Based Read Mappers

- Key Idea
  - Preprocess the reference into a *Hash Table*
  - Use *Hash Table* to map reads

Hash Table-Based Mappers [Alkan+ Nature Gen'09]



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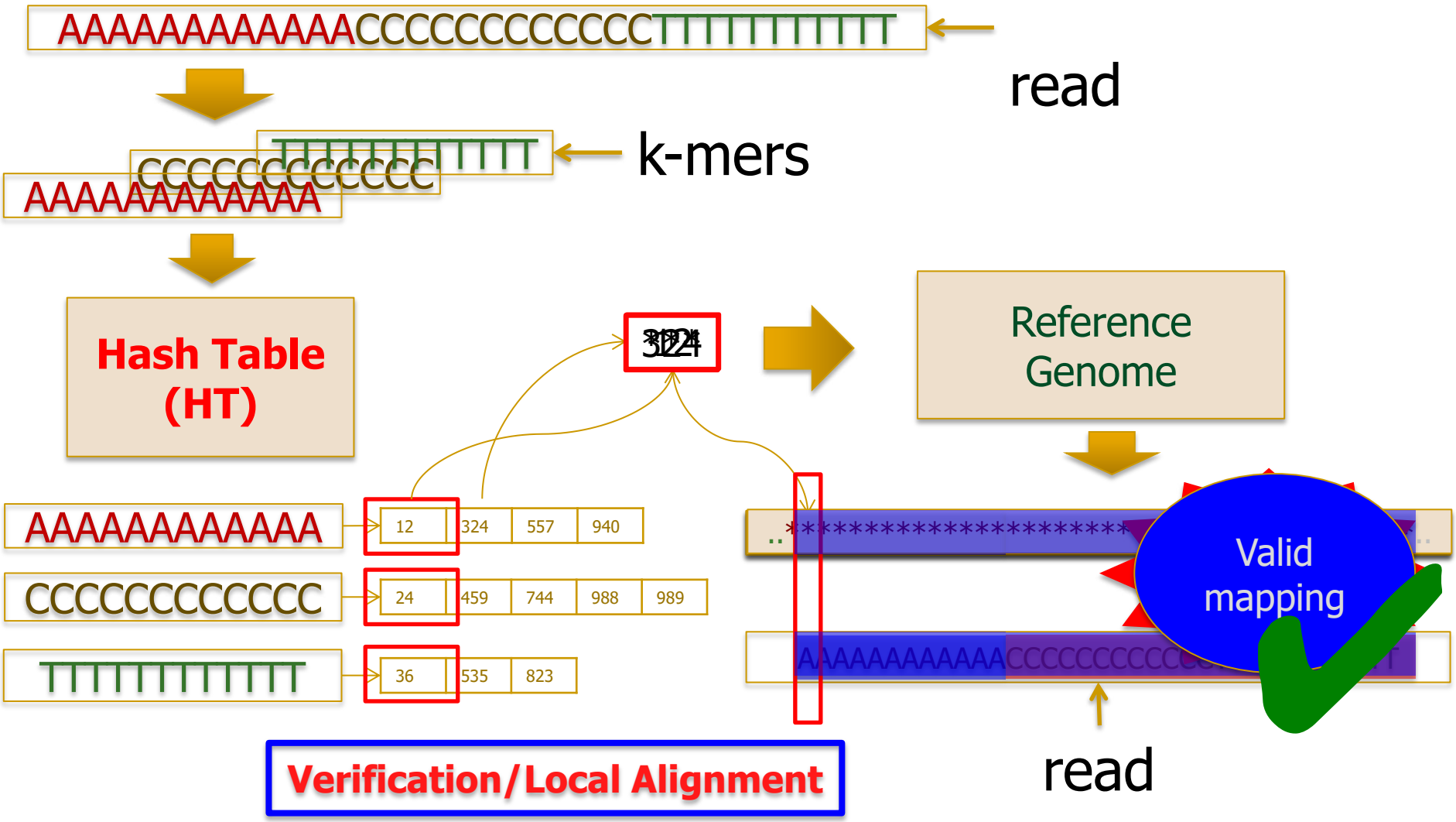


Advantages of Hash Table Based Mappers

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

nature genetics

http://mrfast.sourceforge.net/

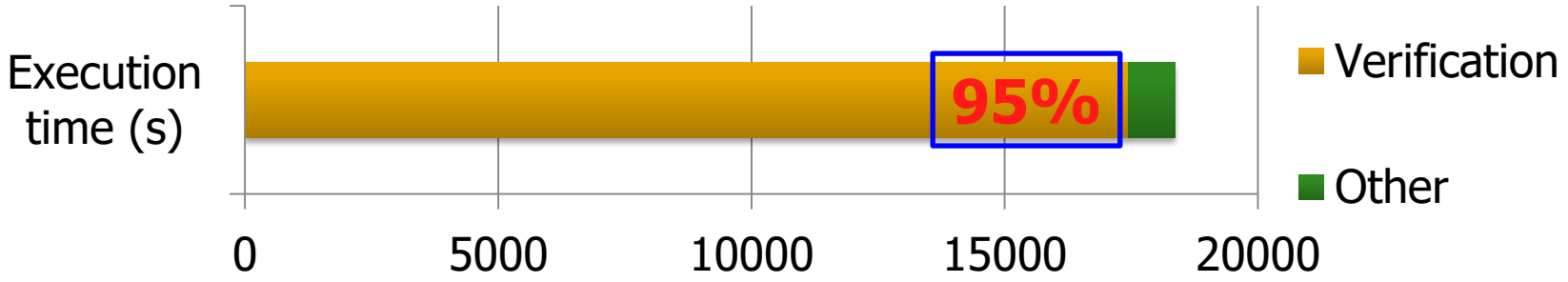
Personalized copy number and segmental duplication maps using next-generation sequencing

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.

Problem and Goal

- Poor performance of existing read mappers: Very slow
  - Verification/alignment takes too long to execute
  - Verification requires a memory access for reference genome + many base-pair-wise comparisons between the reference and the read (edit distance computation)



- Goal: Speed up the mapper by reducing the cost of verification

Agenda

- The Problem: DNA Read Mapping
  - State-of-the-art Read Mapper Design
- Algorithmic Acceleration
  - Exploiting Structure of the Genome
  - Exploiting SIMD Instructions
- Hardware Acceleration
  - Specialized Architectures
  - Processing in Memory
- Future Opportunities: New Sequencing Technologies

Reducing the Cost of Verification

- We observe that most verification (edit distance computation) calculations are unnecessary
  - 1 out of 1000 potential locations passes the verification process

- We observe that we can get rid of unnecessary verification calculations by
  - *Detecting and rejecting* *early* invalid mappings (filtering)
  - *Reducing* the *number* of potential mappings

Key Observations [Xin+, BMC Genomics 2013]

- Observation 1
  - Adjacent k-mers in the read should also be adjacent in the reference genome
  - Read mapper can quickly reject mappings that do **not** satisfy this property

- Observation 2
  - Some k-mers are cheaper to verify than others because they have shorter location lists (they occur less frequently in the reference genome)
    - Mapper needs to examine only *e+1* k-mers' locations to tolerate *e* errors
  - Read mapper can choose the cheapest *e+1* k-mers and verify their locations

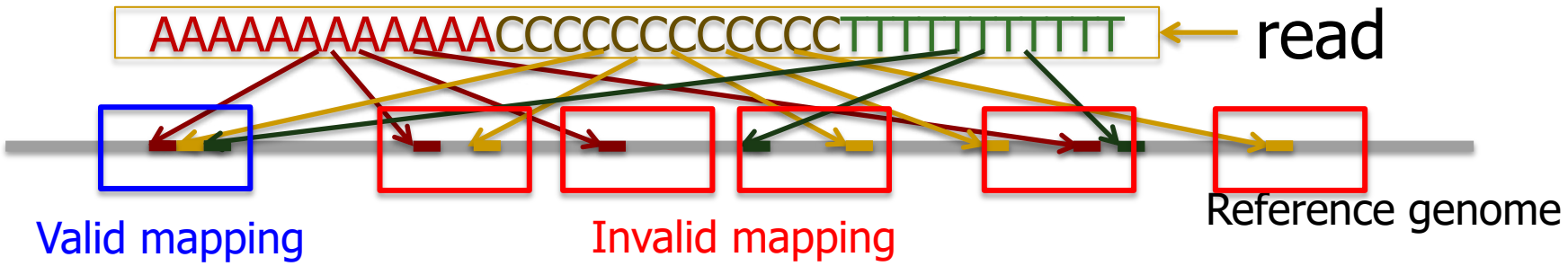
FastHASH Mechanisms [Xin+, BMC Genomics 2013]

- **Adjacency Filtering (AF)**: Rejects obviously invalid mapping locations at early stage to avoid unnecessary verifications

- **Cheap K-mer Selection (CKS):** Reduces the absolute number of potential mapping locations

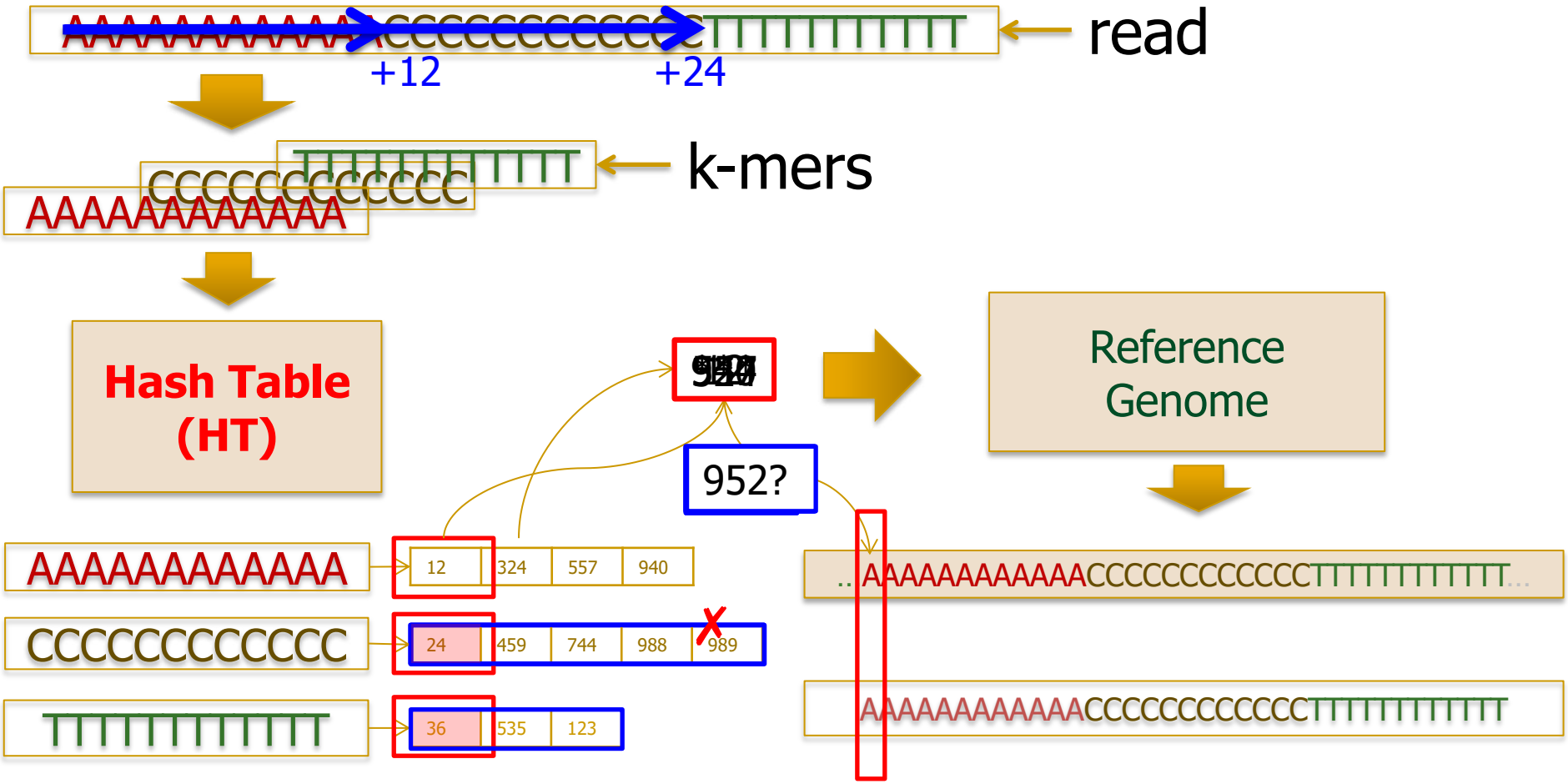
Adjacency Filtering (AF)

- **Goal:** detect and filter out invalid mappings at early stage
- **Key Insight:** For a valid mapping, adjacent k-mers in the read are also adjacent in the reference genome



- **Key Idea:** search for adjacent locations in the k-mers' location lists
  - If more than *e* k-mers fail → there must be more than e errors → invalid mapping

Adjacency Filtering (AF)



FastHASH Mechanisms [Xin+, BMC Genomics 2013]

- **Adjacency Filtering (AF)**: Rejects obviously invalid mapping locations at early stage to avoid unnecessary verifications

- **Cheap K-mer Selection (CKS):** Reduces the absolute number of potential mapping locations

Cheap K-mer Selection (CKS)

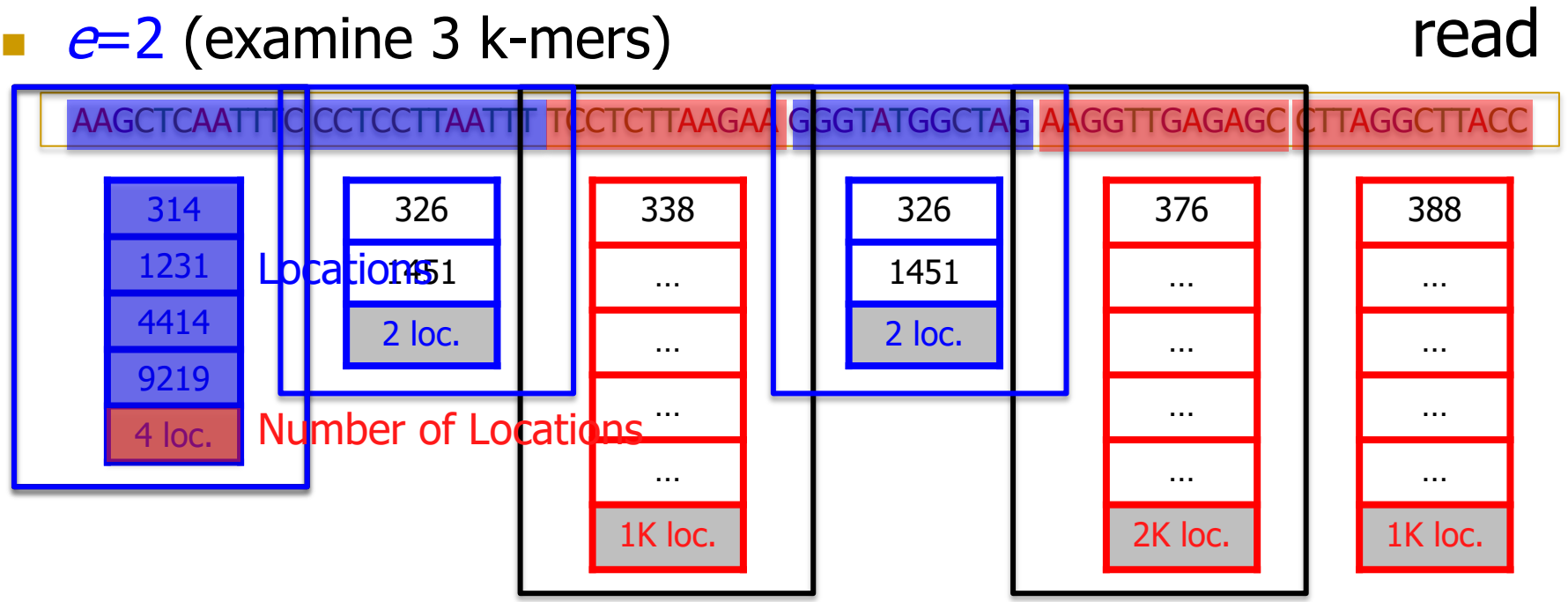
- **Goal:** Reduce the number of potential mappings

- **Key insight:**
  - K-mers have different cost to examine: Some k-mers are *cheaper* as they have fewer locations than others (occur less frequently in reference genome)

- **Key idea:**
  - Sort the k-mers based on their number of locations
  - Select the k-mers with fewest locations to verify

Cheap K-mer Selection

- *e*=2 (examine 3 k-mers)



Expensive 3 k-mers

Previous work needs to verify:

3004 locations

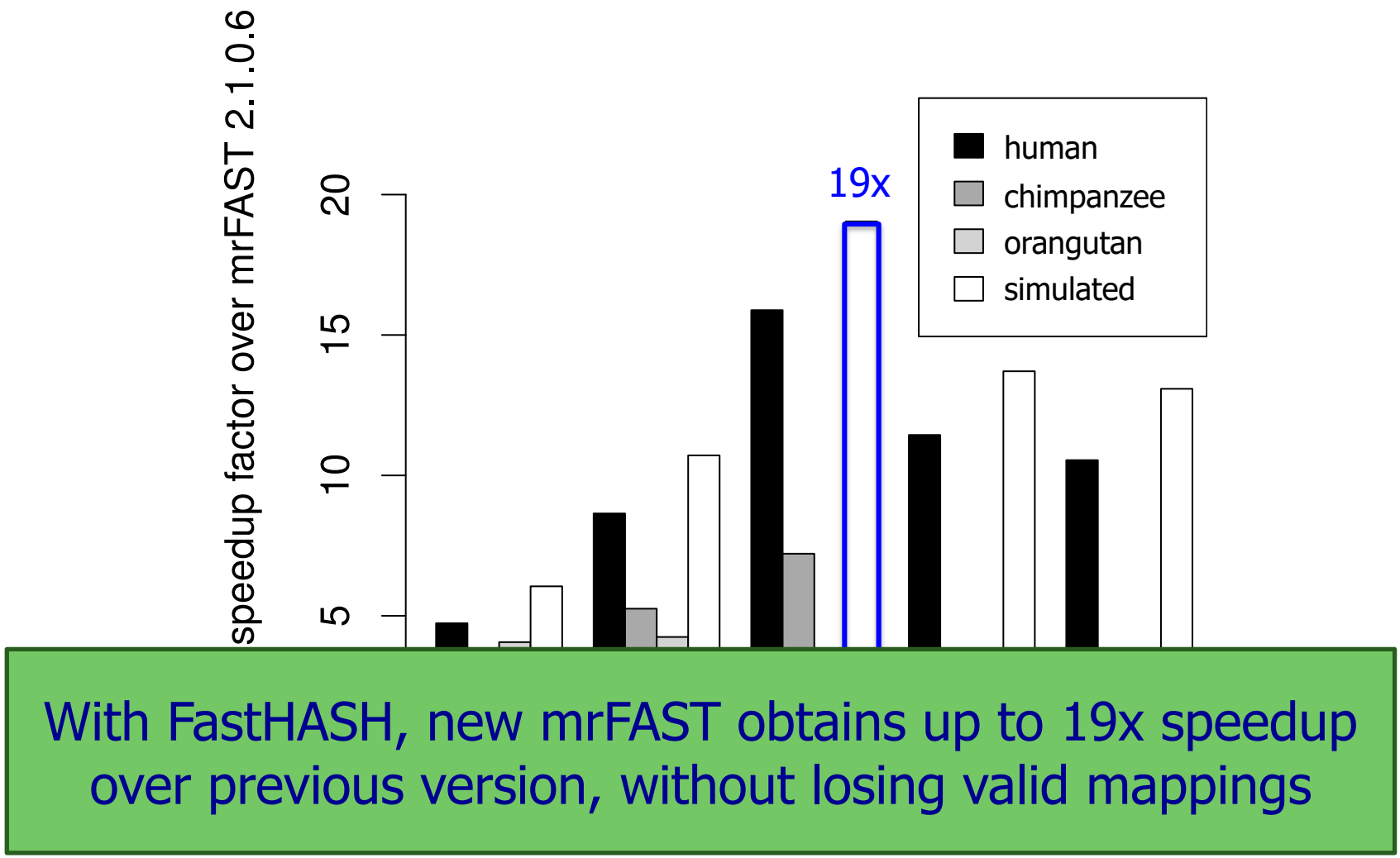
FastHASH verifies only:

8 locations

Methodology

- Implemented FastHASH on top of state-of-the-art mapper: mrFAST
  - New version mrFAST-2.5.0.0 over mrFAST-2.1.0.6
- Tested with real read sets generated from Illumina platform
  - 1M reads of a human (160 base pairs)
  - 500K reads of a chimpanzee (101 base pairs)
  - 500K reads of a orangutan (70 base pairs)
- Tested with simulated reads generated from reference genome
  - 1M simulated reads of human (180 base pairs)
- Evaluation system
  - Intel Core i7 Sandy Bridge machine
  - 16 GB of main memory

FastHASH Speedup

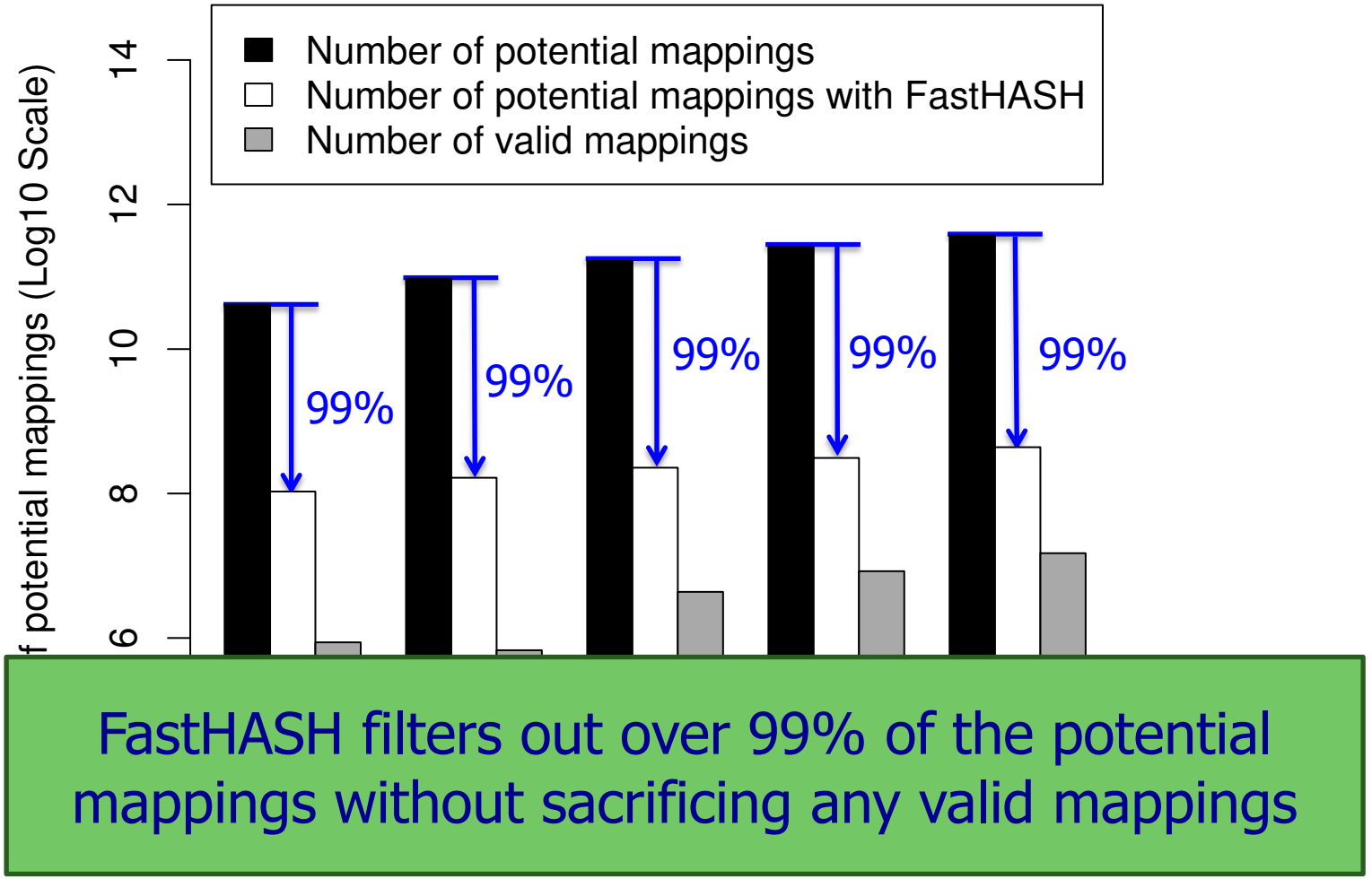


With FastHASH, new mrFAST obtains up to 19x speedup over previous version, without losing valid mappings

e: edit distance

Analysis

- Reduction of potential mappings with FastHASH



Reduction of potential mappings with FastHASH

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
  - Reject invalid mappings early (Adjacency Filtering)
  - Reduce the number of possible mappings to examine (Cheap K-mer Selection)
- 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

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

Agenda

- The Problem: DNA Read Mapping
  - State-of-the-art Read Mapper Design
- Algorithmic Acceleration
  - Exploiting Structure of the Genome
  - Exploiting SIMD Instructions
- Hardware Acceleration
  - Specialized Architectures
  - Processing in Memory
- Future Opportunities: New Sequencing Technologies

An Example: Shifted Hamming Distance

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

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,*]

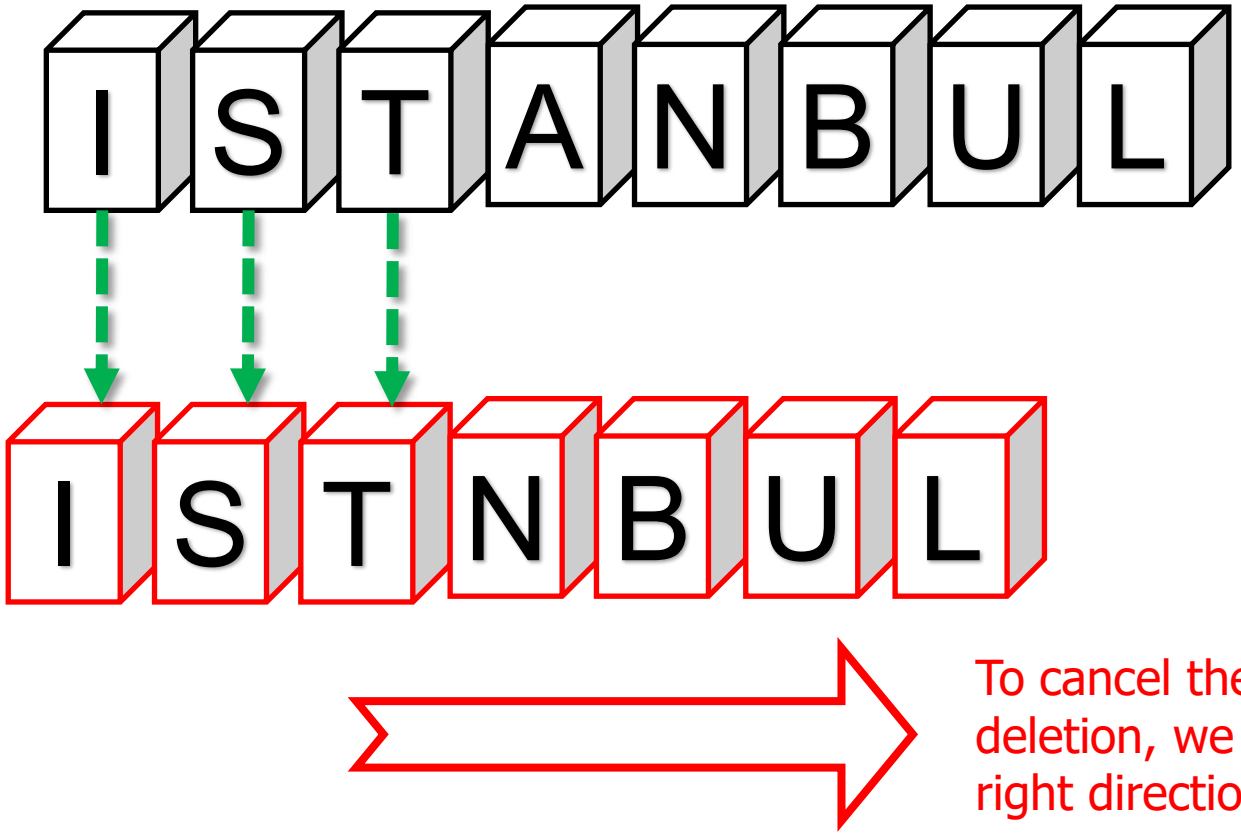
Xin+, **"Shifted Hamming Distance: A Fast and Accurate SIMD-friendly Filter to Accelerate Alignment Verification in Read Mapping", Bioinformatics 2015.**

Shifted Hamming Distance

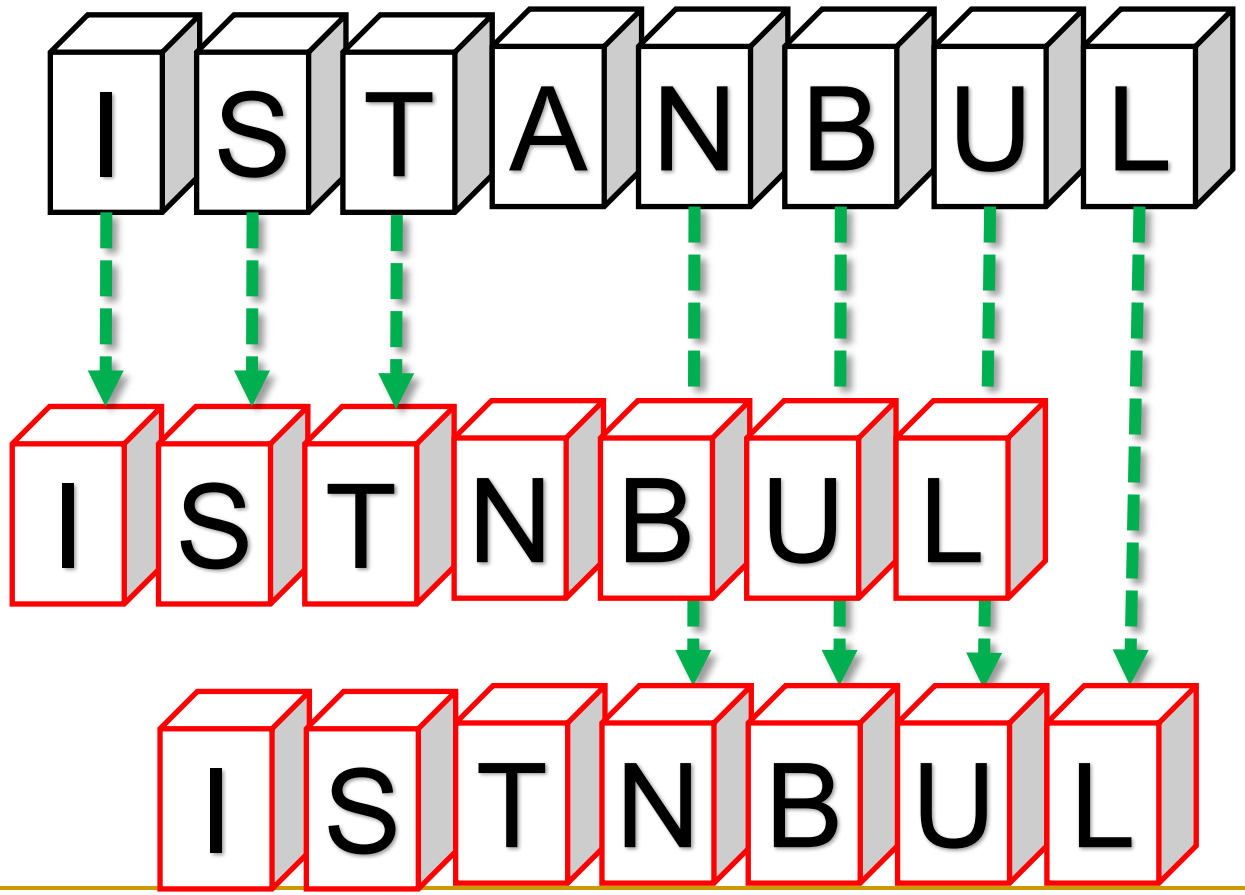
- Key observation:
  - If two strings differ by *E* edits, then every bp match can be aligned in at most *2E* shifts.
- Key idea:
  - Compute "Shifted Hamming Distance": AND of 2E Hamming Distances of two strings, to identify invalid mappings
    - Uses bit-parallel operations that nicely map to SIMD instructions
- Key result:
  - SHD is 3x faster than SeqAn (the best implementation of Gene Myers' bit-vector algorithm), with only a 7% false positive rate
  - The fastest CPU-based filtering (pre-alignment) mechanism

Insight: Shifting a String Helps Similarity Search

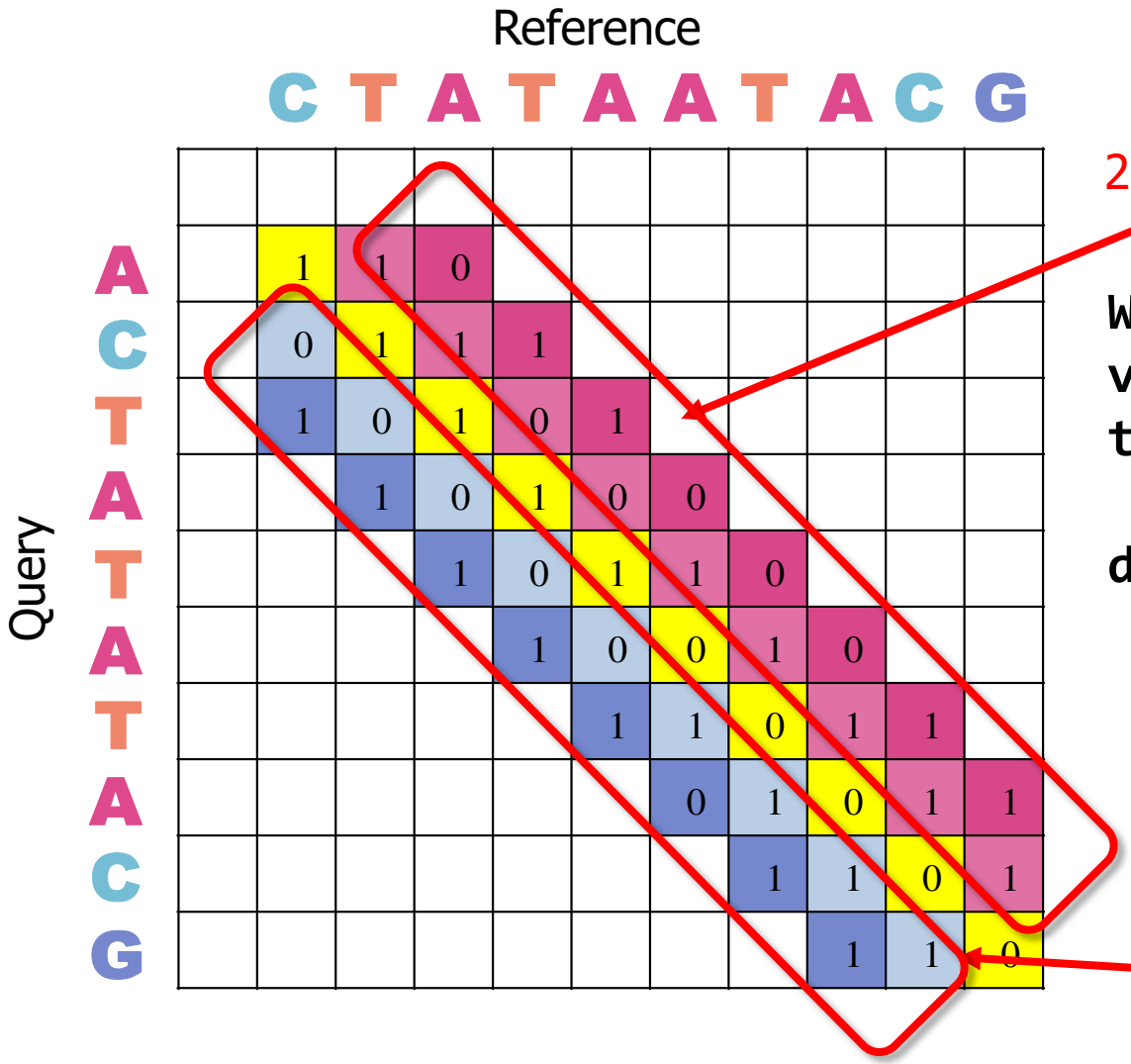
3 matches 5 mismatches



Insight: Shifting a String Helps Similarity Search



Highly Parallel Matrix Computation



We need to compute 2E+1 vectors, E=edit distance threshold

dp[i][j]= 0 if X[i]=Y[j]
1 if X[i]≠Y[j]

No data dependencies!

Key Idea of SHD Filtering

Generate 2E+1 masks → Amend random zeros: 101 → 111 & 1001 → 1111 → AND all masks, ACCEPT iff number of '1' ≤ Threshold

```
                Query :GAGAGAGATATTTAGTGTTGCAGCACTACAACACAAAAGAGGACCAACTTACGTGTCTAAAAGGGGGAACATTGTTGGGCCGGA
            Reference :GAGAGAGATAGTTAGTGTTGCAGCCACTACAACACAAAAGAGGACCAACTTACGTGTCTAAAAGGGGAGACATTGTTGGGCCGG

          Hamming Mask :00000000001000000000000111111101111000111011010110111111111000100000111101101001010
    1-Deletion Mask :11111111111001111101111100000000000000000000000000000000000000000011000000000000000
    2-Deletion Mask :00000000101101110011111111111111011110001110110101101111111110001000100111011010010
    3-Deletion Mask :11111111111011101100110111011101100010010011111111111111100101100110010110111011101111
  1-Insertion Mask :11111111111011111011111101110110001001001111111111111100101100110001010111011101111110
  2-Insertion Mask :00000010011111001111111110010001101010100110101111111111111011100111111100011110110 0
  3-Insertion Mask :11111111011101100110001111111110101101111110011001011101111111101110111010111001000

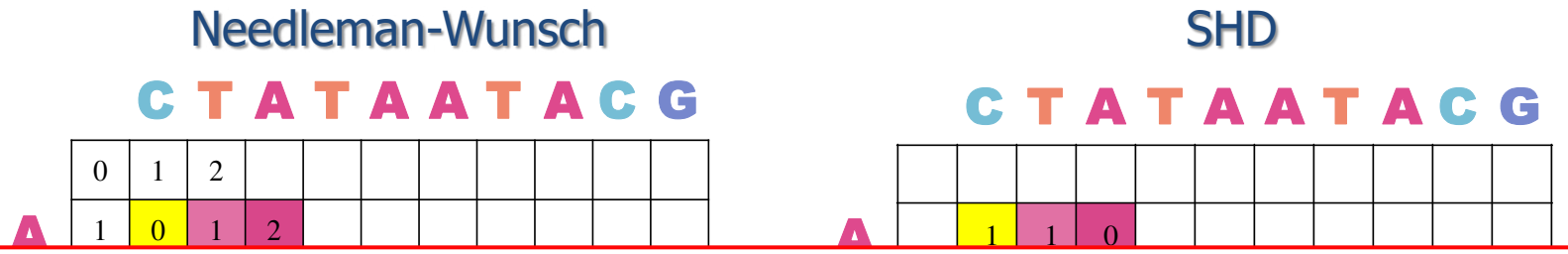
                                                --- Masks after amendment ---

          Hamming Mask :00000000001000000000000111111111111000111111101111111111111000100000111111111111111
    1-Deletion Mask :11111111111111111111111100000000000000000000000000000000000000000011000000000000000
    2-Deletion Mask :00000000111111111111111111111111111111000111111111111111111111000100011111111111111110
    3-Deletion Mask :11111111111111111111111111111111111000111111111111111111111111111111111111111111111111
  1-Insertion Mask :11111111111111111111111111111111000111111111111111111111111111000111111111111111110
  2-Insertion Mask :00000011111111111111111111111000111111111111111111111111111111111111111000111111100
  3-Insertion Mask :11111111111111111111000111111111111111111111111111111111111111111111111111111111000

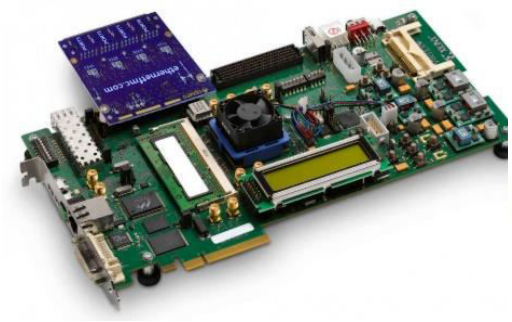
           AND Mask :00000000001000000000000100000000000000000000000000000000000000000001000000000000000

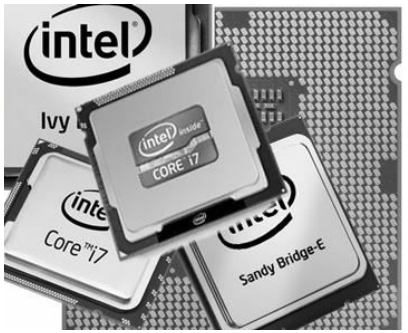

                     GAGAGAGATATTTAGTGTTGCAG-CACTACAACACAAAAGAGGACCAACTTACGTGTCTAAAAGGGGGAACATTGTTGGGCCGG
Needleman-Wunsch     ||||||||||  ||||||||||||  ||||||||||||||||||||||||||||||||||||||||||::||||||||||||||||
       Alignment :   GAGAGAGATAGTTAGTGTTGCAGCCACTACAACACAAAAGAGGACCAACTTACGTGTCTAAAAGGGGAGACATTGTTGGGCCGG
```

Alignment vs. Pre-alignment (Filtering)



- Independent vectors can be processed in parallel using hardware technologies






```
                |dp[i][j-1]   // Inser.
dp[i][j]=1+max  |dp[i-1][j]   // Del.
                |dp[i-1][j-1] // Subs.
```

Each cell depends on three pre-computed cells!

```
dp[i][j]=|0 if X[i]=Y[j]
         |1 if X[i]≠Y[j]
```

No data dependencies!

New Bottleneck: Filtering (Pre-Alignment)

Sequencing generates many reads, each of which potentially mapping to many locations

→

Filtering (Pre-alignment) eliminates the need to verify/align read to invalid mapping locations

→

Alignment/verification (costly edit distance computation) is performed **only** on reads that pass the filter)

- New bottleneck in read mapping becomes the "filtering (pre-alignment)" step

Agenda

- The Problem: DNA Read Mapping
  - State-of-the-art Read Mapper Design
- Algorithmic Acceleration
  - Exploiting Structure of the Genome
  - Exploiting SIMD Instructions
- Hardware Acceleration
  - Specialized Architectures
  - Processing in Memory
- Future Opportunities: New Sequencing Technologies

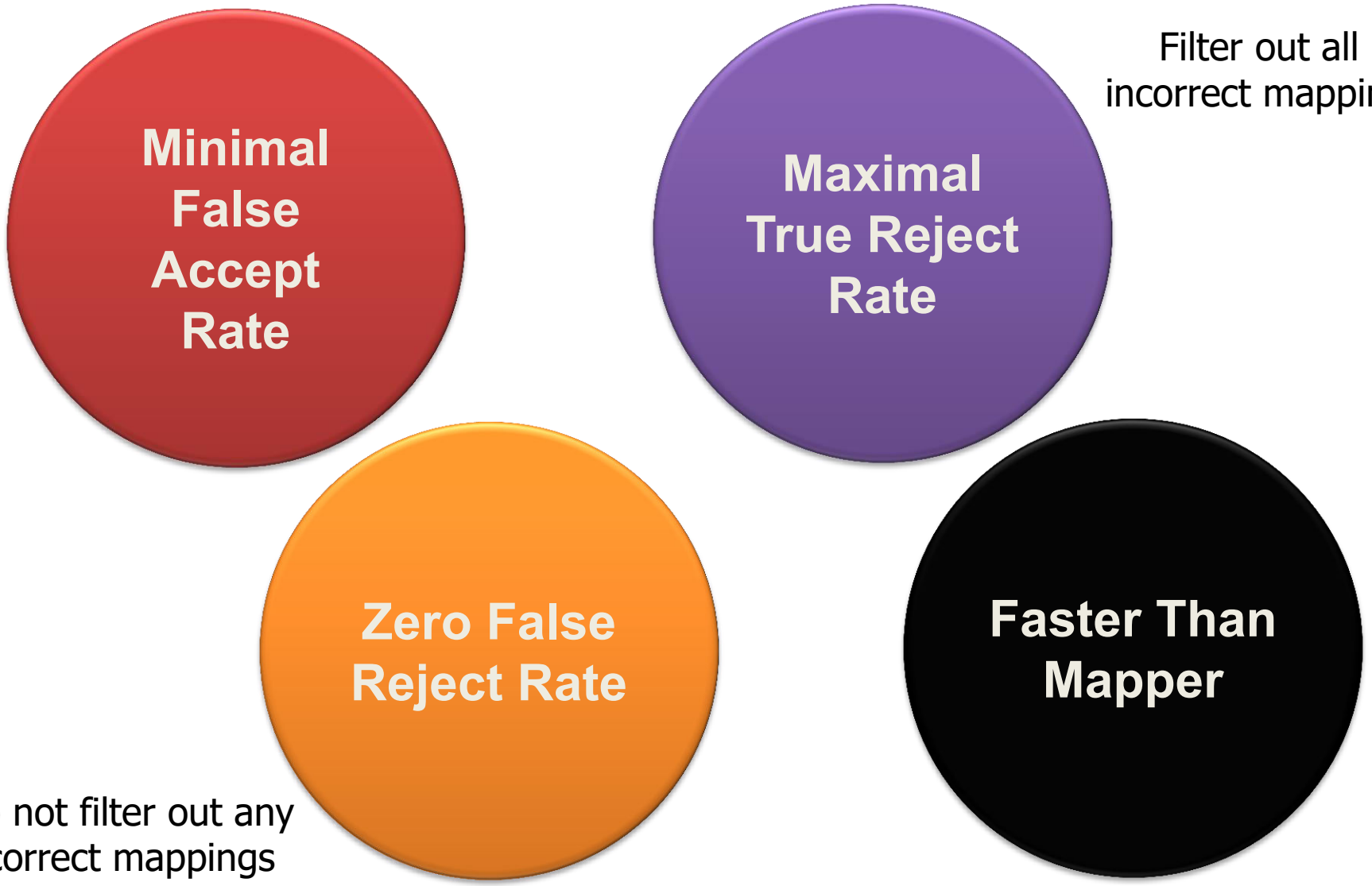
Location Filtering

- **Alignment** is expensive
  - We need to align millions to billions of reads
- M
  - f
  - out mismatches quickly

Our goal is to accelerate read mapping by improving the filtering step

- Both methods are used by mappers today, but filtering has replaced alignment as the bottleneck [Xin+, BMC Genomics 2013]

Ideal Filtering Algorithm



Alignment vs. Pre-alignment (Filtering)

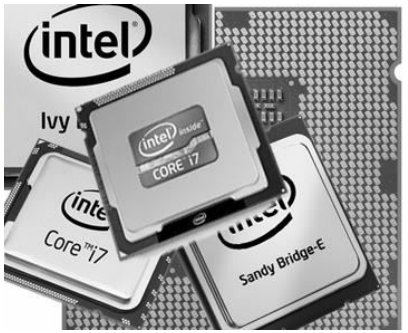
Needleman-Wunsch

		C	T	A	T	A	A	T	A	C	G
	0	1	2								
A	1	0	1	2							

GateKeeper

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

- Independent vectors can be processed in parallel using hardware technologies

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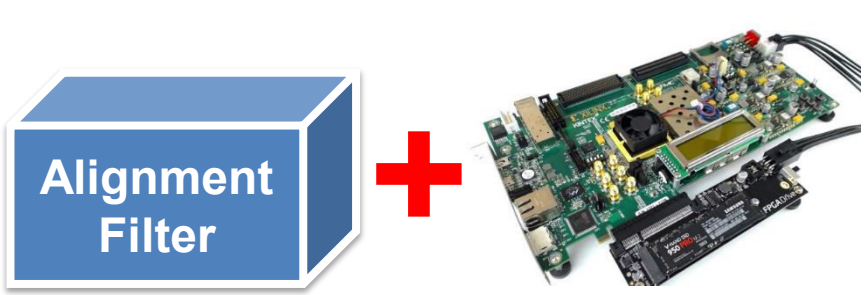
```

Each cell depends on three pre-computed cells!

```
dp[i][j]=|0 if X[i]=Y[j]
         |1 if X[i]≠Y[j]
```

No data dependencies!

Our Solution: GateKeeper

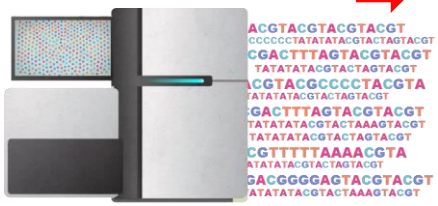


1st

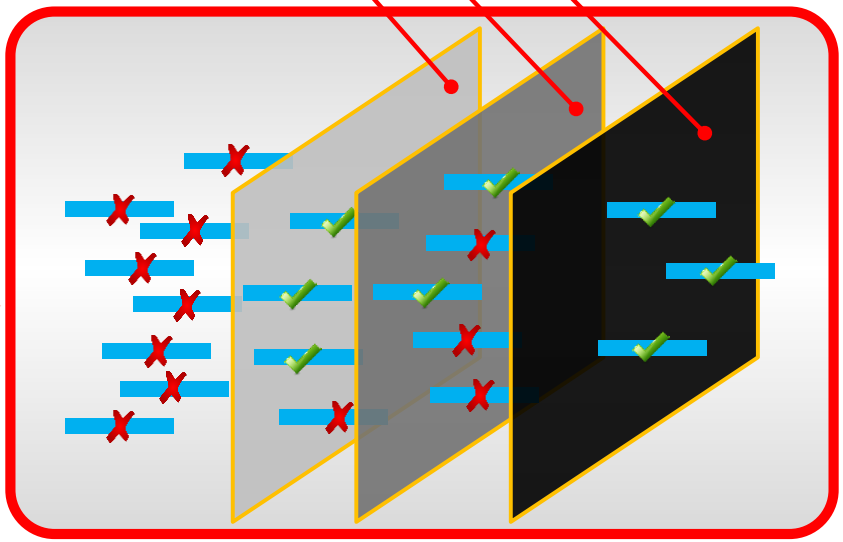
FPGA-based Alignment Filter.

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

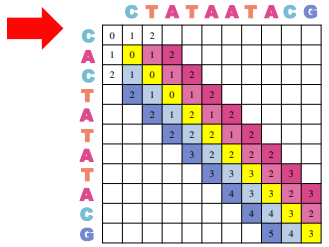
$x10^{12}$ mappings



Billions of Short Reads



$x10^{3}$ 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

GateKeeper Walkthrough

Generate 2E+1 masks → Amend random zeros: 101 → 111 & 1001 → 1111 → AND all masks, ACCEPT iff number of '1' ≤ Threshold

```
                Query :GAGAGAGATATTTAGTGTTGCAGCACTACAACACAAAAGAGGACCAACTTACGTGTCTAAAAGGGGGAACATTGTTGGGCCGGA
            Reference :GAGAGAGATAGTTAGTGTTGCAGCCACTACAACACAAAAGAGGACCAACTTACGTGTCTAAAAGGGGAGACATTGTTGGGCCGG

          Hamming Mask :00000000001000000000000111111101111000111011010110111111111000100000111101101001010
    1-Deletion Mask :11111111111001111101111100000000000000000000000000000000000000000011000000000000000
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    3-Deletion Mask :11111111111011101100110111011101100010010011111111111111100101100110010110111011101111
  1-Insertion Mask :11111111111011111011111011101100010010011111111111111100101100110001010111011101110
  2-Insertion Mask :00000010011111001111111110010001101010100110101111111111111011100111111100011110110
  3-Insertion Mask :11111111011101100110001111111110101101111110011001011101111111101110111010111001000

                                                --- Masks after amendment ---

          Hamming Mask :00000000001000000000000111111111111000111111110111111111111000100000111111111111111
    1-Deletion Mask :11111111111111111111111100000000000000000000000000000000000000000011000000000000000
    2-Deletion Mask :00000000111111111111111111111111111111000111111111111111111111000100011111111111111
    3-Deletion Mask :11111111111111111111111111111111111000111111111111111111111111111111111111111111111
  1-Insertion Mask :11111111111111111111111111111111000111111111111111111111111111000111111111111111110
  2-Insertion Mask :00000011111111111111111111111000111111111111111111111111111111111111111000111111100
  3-Insertion Mask :11111111111111111111000111111111111111111111111111111111111111111111111111111111000

           AND Mask :00000000001000000000000100000000000000000000000000000000000000000001000000000000000

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

GateKeeper Walkthrough (cont'd)

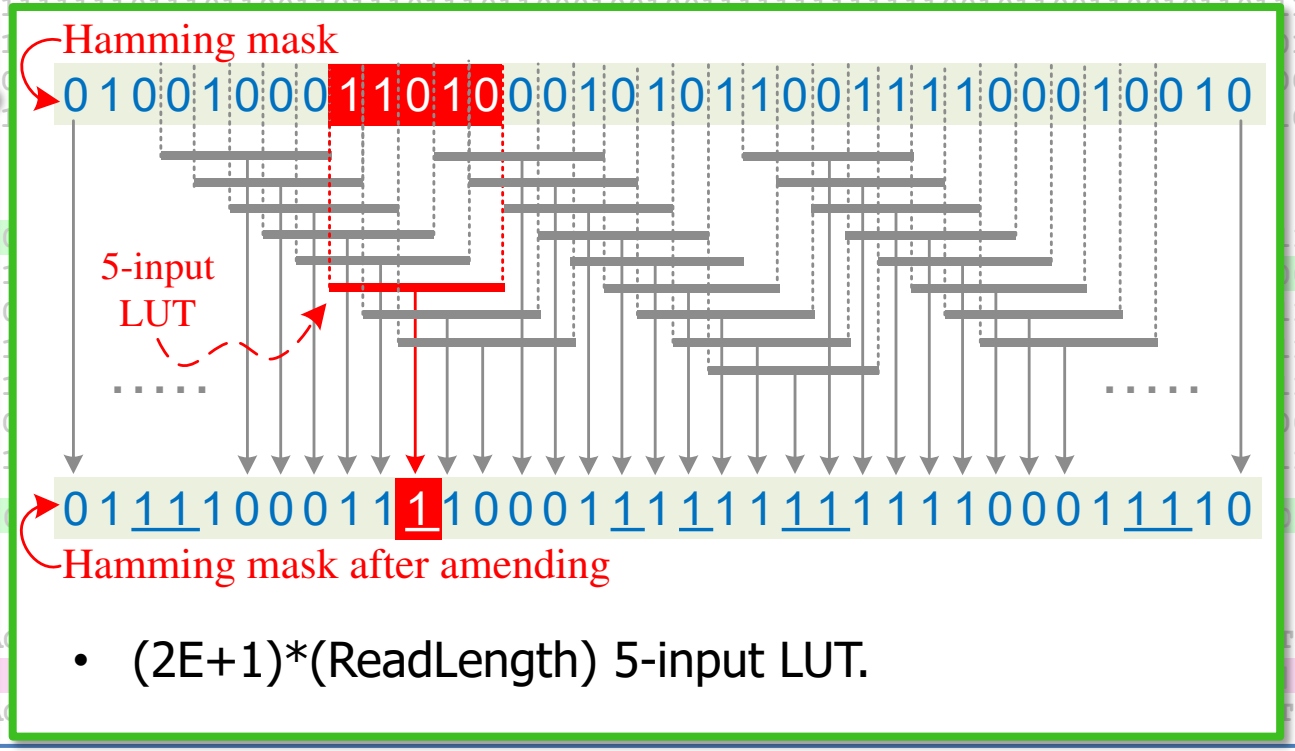
Generate 2E+1 masks

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.

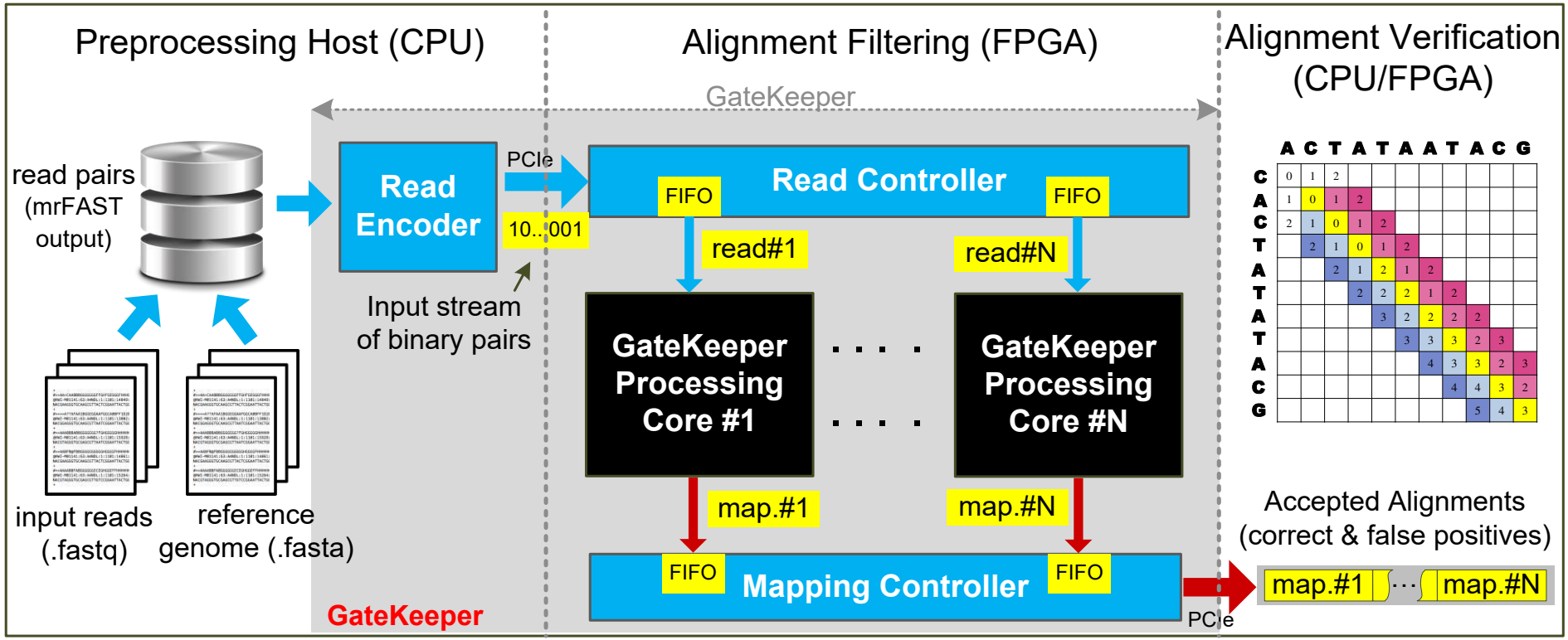
- (2E)*(ReadLength) 2-AND operations.
- (ReadLength/4) 5-input LUT.
- log_2ReadLength-bit counter.



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

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



GateKeeper vs. SHD

GateKeeper	SHD

▪ FPGA (Xilinx VC709)
▪ Multi-core (parallel)
▪ Examines a single mapping @ 125 MHz
▪ Limited to PCIe Gen3(4x) transfer rate (128 bits @ 250MHz)
▪ Amending requires:
  ❑ (2E+1) 5-input LUT.
	▪ Intel SIMD
	▪ Single-core (sequential)
	▪ Examines a single mapping @ ~2MHz
	▪ Limited to a read length of 128 bp (SSE register size)
	▪ Amending requires:
	  ❑ 4(2E+1) bitwise OR.
	  ❑ 4(2E+1) packed shuffle.
	  ❑ 3(2E+1) shift.

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

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 GateKeeper

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

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

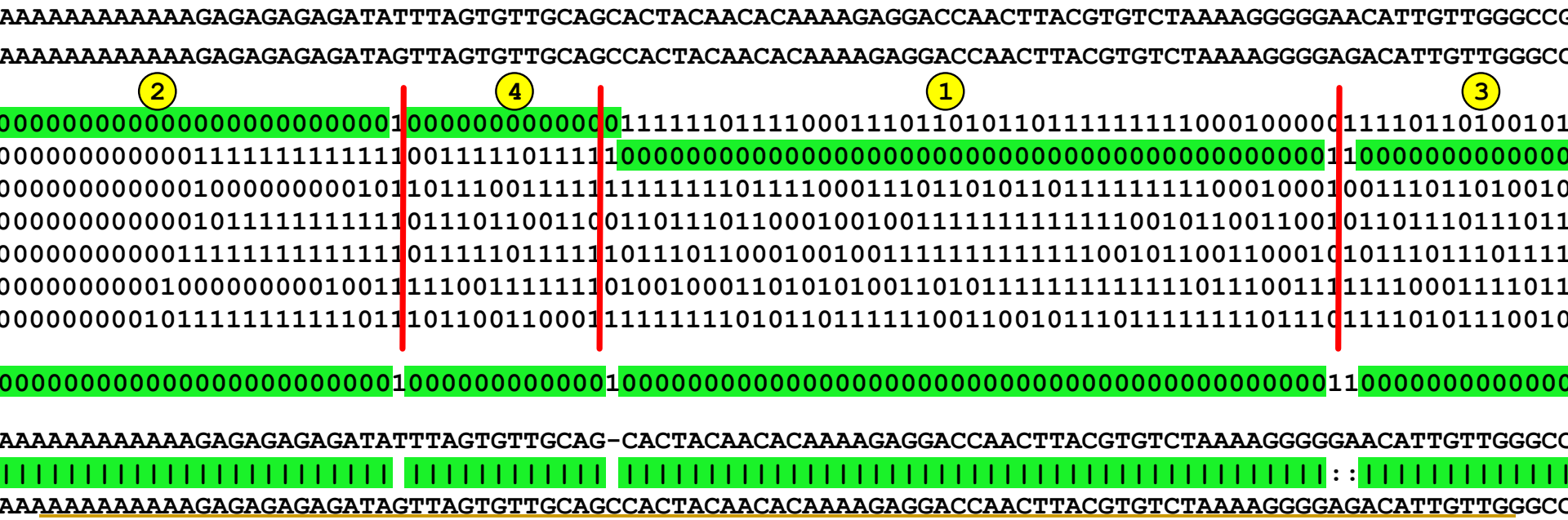
Sequence analysis

GateKeeper: A New Hardware Architecture for Accelerating Pre-Alignment in DNA Short Read Mapping

Mohammed Alser[1,*], Hasan Hassan[2], Hongyi Xin[3], Oğuz Ergin[2], Onur Mutlu[4,*], and Can Alkan[1,*]

Next Talk: MAGNET (AACBB 2018)

- Key observation: the use of **AND operation** to check if a zero (match) exists in a column introduces filtering inaccuracy.
- Key Idea: count the **consecutive zeros** in each mask and select the longest in a divide-and-conquer approach.
- **MAGNET** is **17x to 105x more accurate** than GateKeeper and SHD.



Agenda

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  - State-of-the-art Read Mapper Design
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  - Exploiting Structure of the Genome
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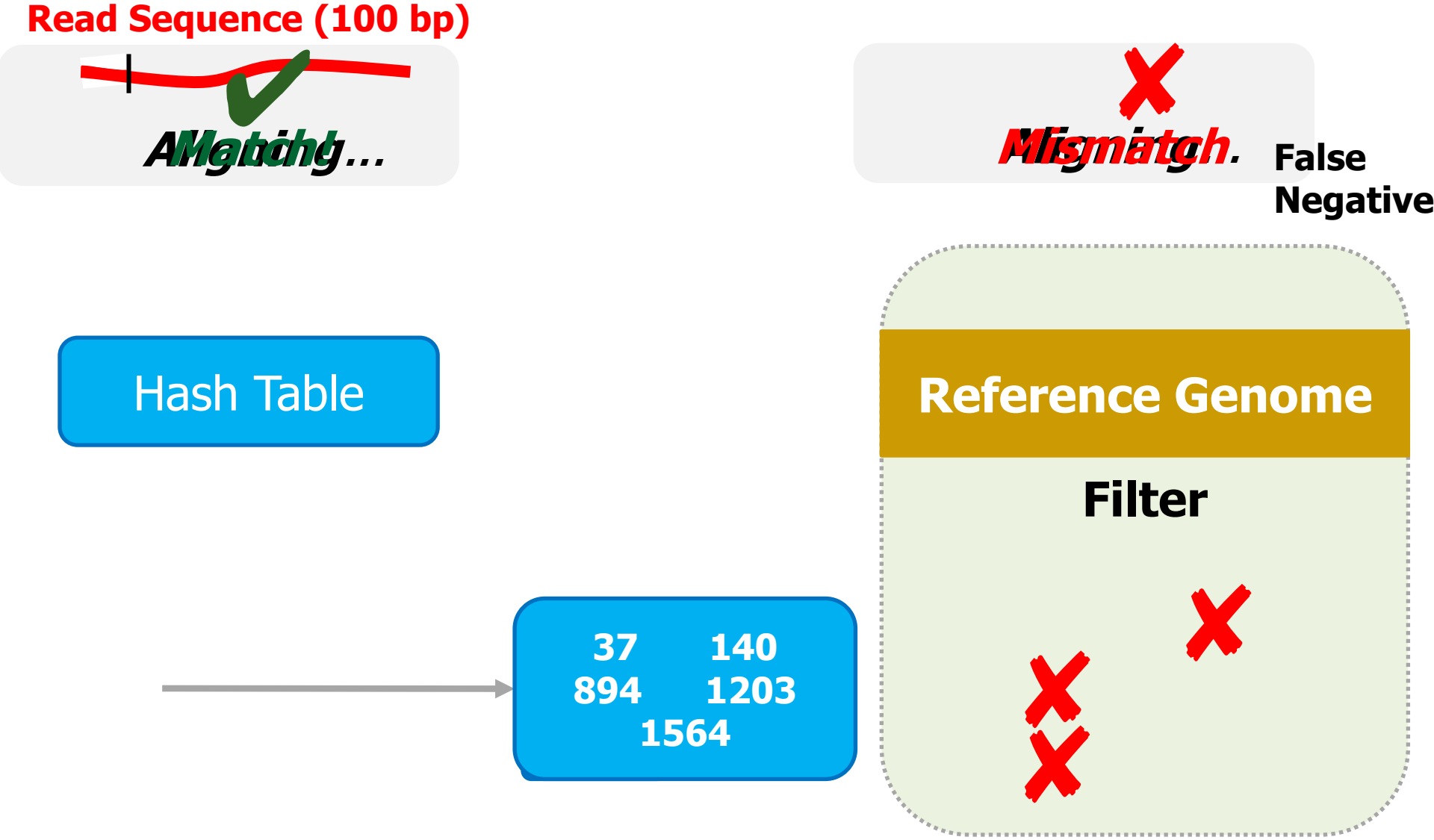
- Hardware Acceleration
  - Specialized Architectures
  - Processing in Memory
- Future Opportunities: New Sequencing Technologies

Read Mapping & Filtering

- Problem: Heavily bottlenecked by Data Movement
- GateKeeper performance limited by DRAM bandwidth [Alser+, Bioinformatics 2017]
- Ditto for SHD [Xin+, Bioinformatics 2015]
- Solution: Processing-in-memory can alleviate the bottleneck
- However, we need to design mapping & filtering algorithms to fit processing-in-memory

Hash Tables in Read Mapping



Read Mapping & Filtering in Memory

We need to design

mapping & filtering algorithms

that fit processing-in-memory

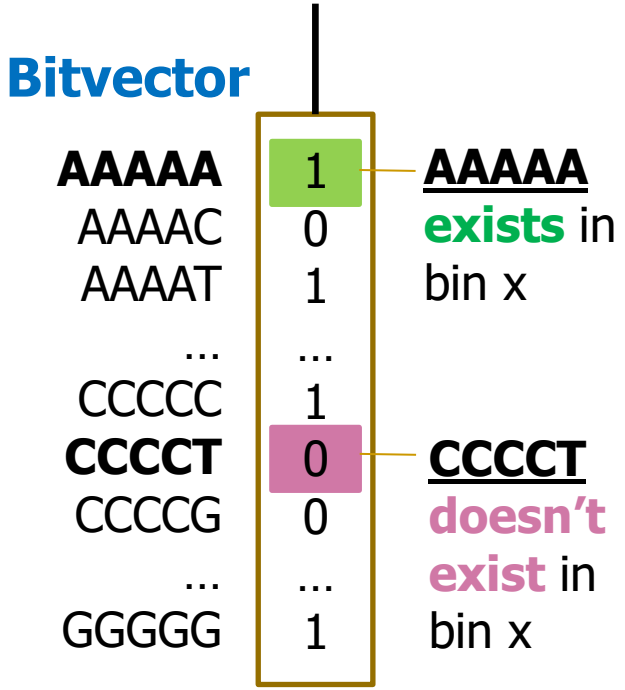
Our Proposal: GRIM-Filter

1. **Data Structures: Bins & Bitvectors**
2. Checking a Bin
3. Integrating GRIM-Filter into a Mapper

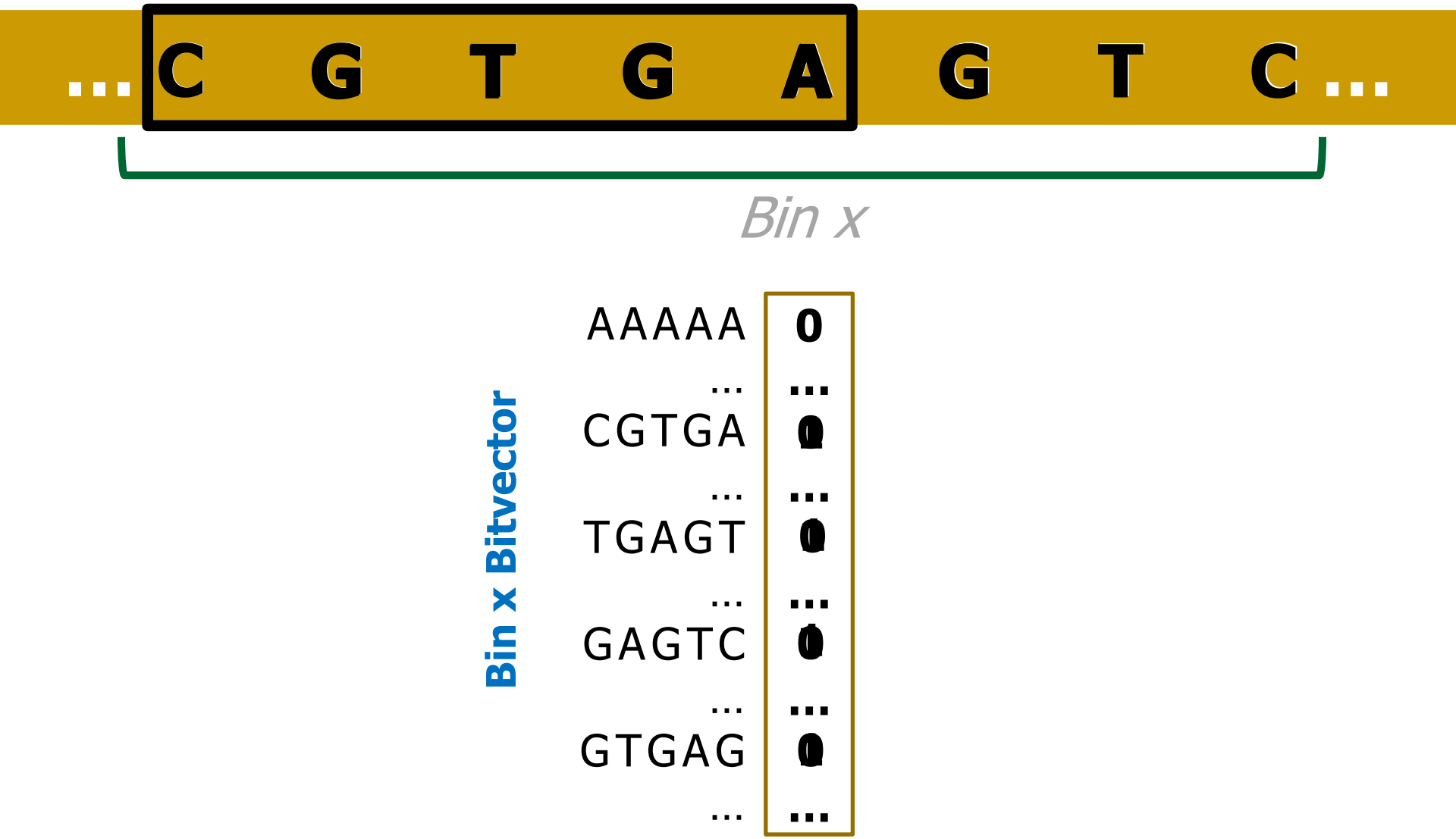
GRIM-Filter: Bins

- We partition the genome into large sequences (**bins**).

- 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



GRIM-Filter: Bitvectors

Storing all bitvectors requires $4^n * t$ bits in memory, where t = number of bins.

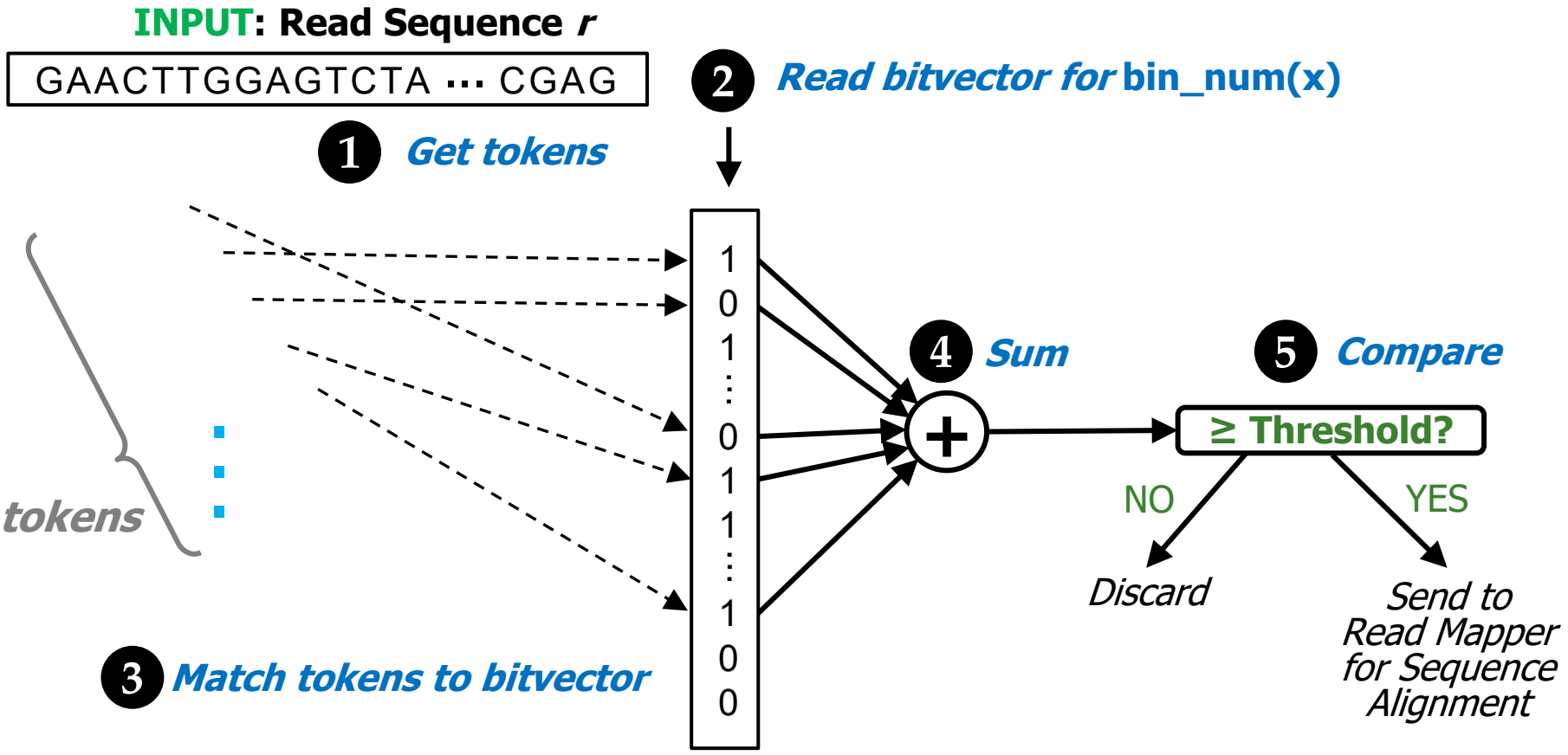
For **bin size** ~200, and **n** = 5, **memory footprint** ~3.8 GB

Our Proposal: GRIM-Filter

1. Data Structures: Bins & Bitvectors
2. **Checking a Bin**
3. Integrating GRIM-Filter into a Mapper

GRIM-Filter: Checking a Bin

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



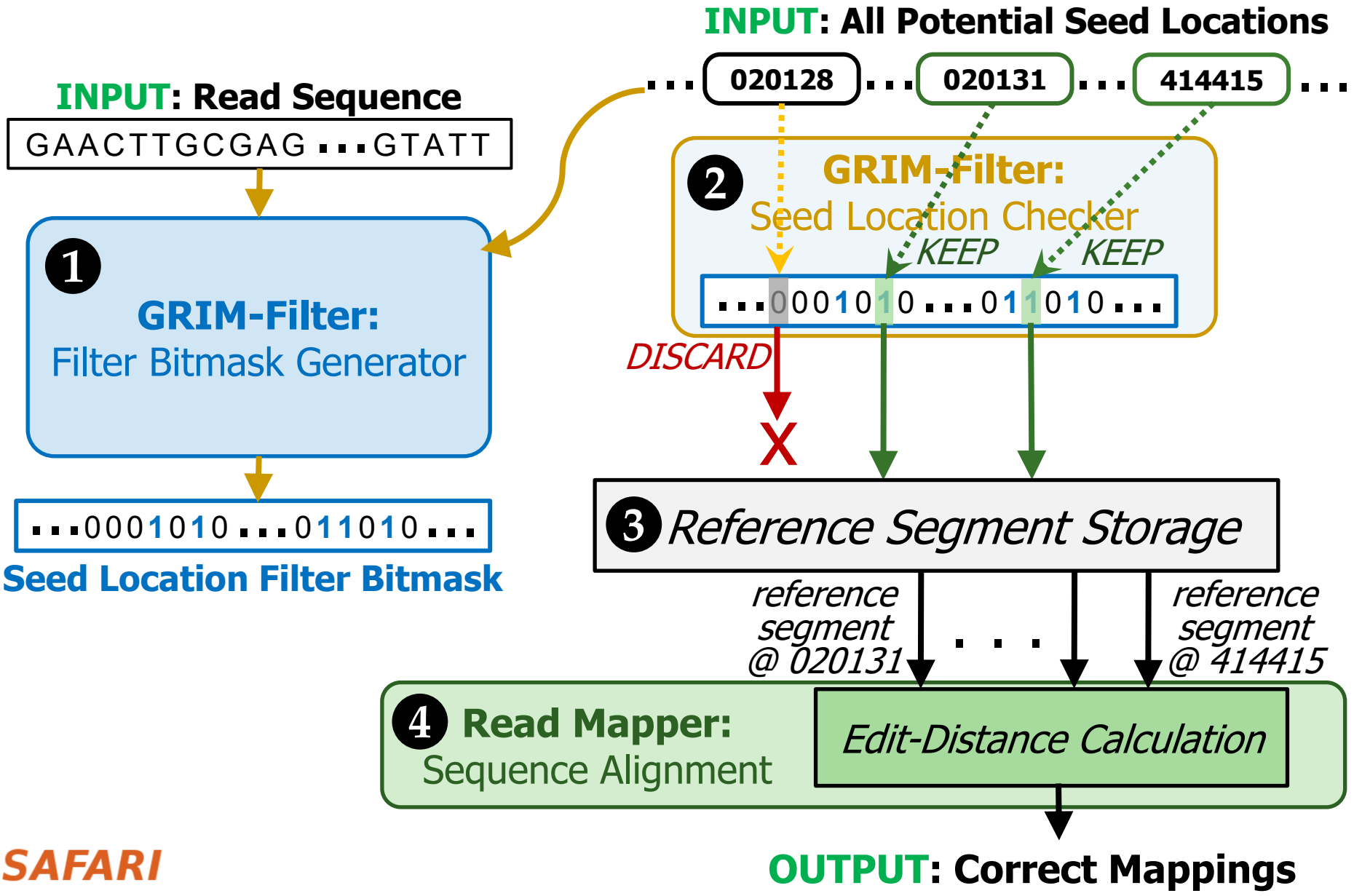
Our Proposal: GRIM-Filter

1. Data Structures: Bins & Bitvectors
2. Checking a Bin
3. Integrating GRIM-Filter into a Mapper

Our Proposal: GRIM-Filter

1. Data Structures: Bins & Bitvectors
2. Checking a Bin
3. **Integrating GRIM-Filter into a Mapper**

Integrating GRIM-Filter into a Read Mapper



SAFARI

Key Properties of GRIM-Filter

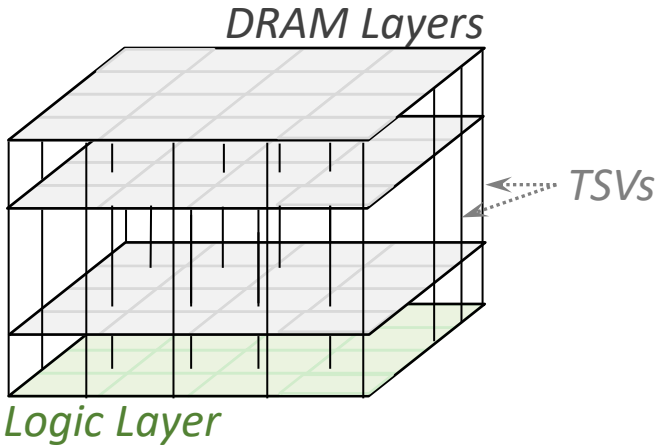
1. **Simple Operations**:
   - To check a given bin, find the **sum** of all bits corresponding to each token in the read
   - **Compare** against threshold to determine whether to align

2. **Highly Parallel**: Each bin is operated on independently and there are many many bins

3. **Memory Bound**: Given the frequent accesses to the large bitvectors, we find that GRIM-Filter is memory bound

These properties together make GRIM-Filter a good algorithm to be run in 3D-Stacked DRAM

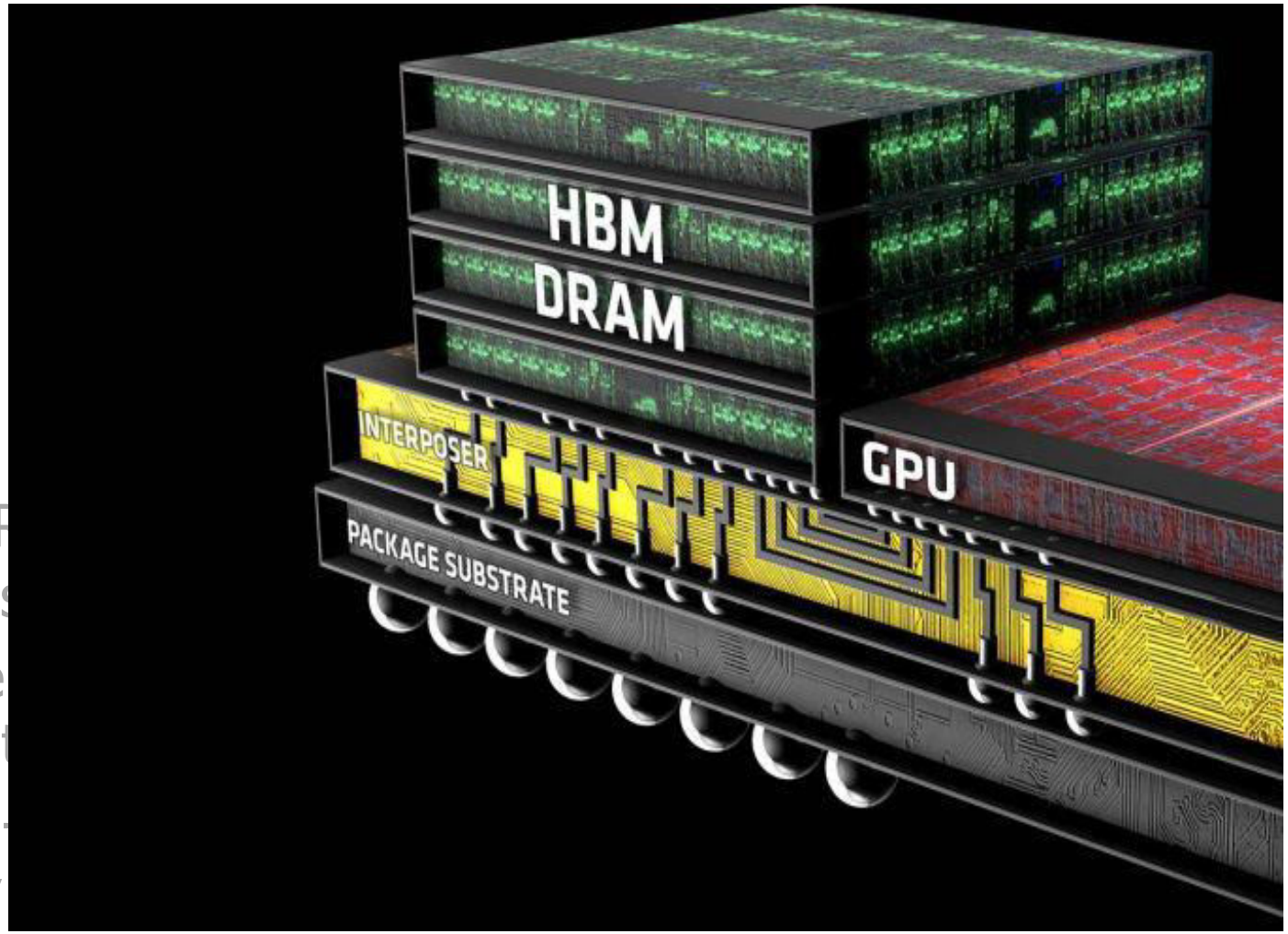
3D-Stacked Memory



- 3D-Stacked DRAM architecture has **extremely high bandwidth** as well as a stacked customizable logic layer
  - Logic Layer enables **Processing-in-Memory**, via high-bandwidth low-latency access to DRAM layers
  - Embed GRIM-Filter operations into **DRAM logic layer** and appropriately distribute bitvectors throughout memory

3D-Stacked Memory

- 3D-Stacked DR
  bandwidth as
  - Logic Layer e
    computation t
  - Embed GRIM-
    appropriately



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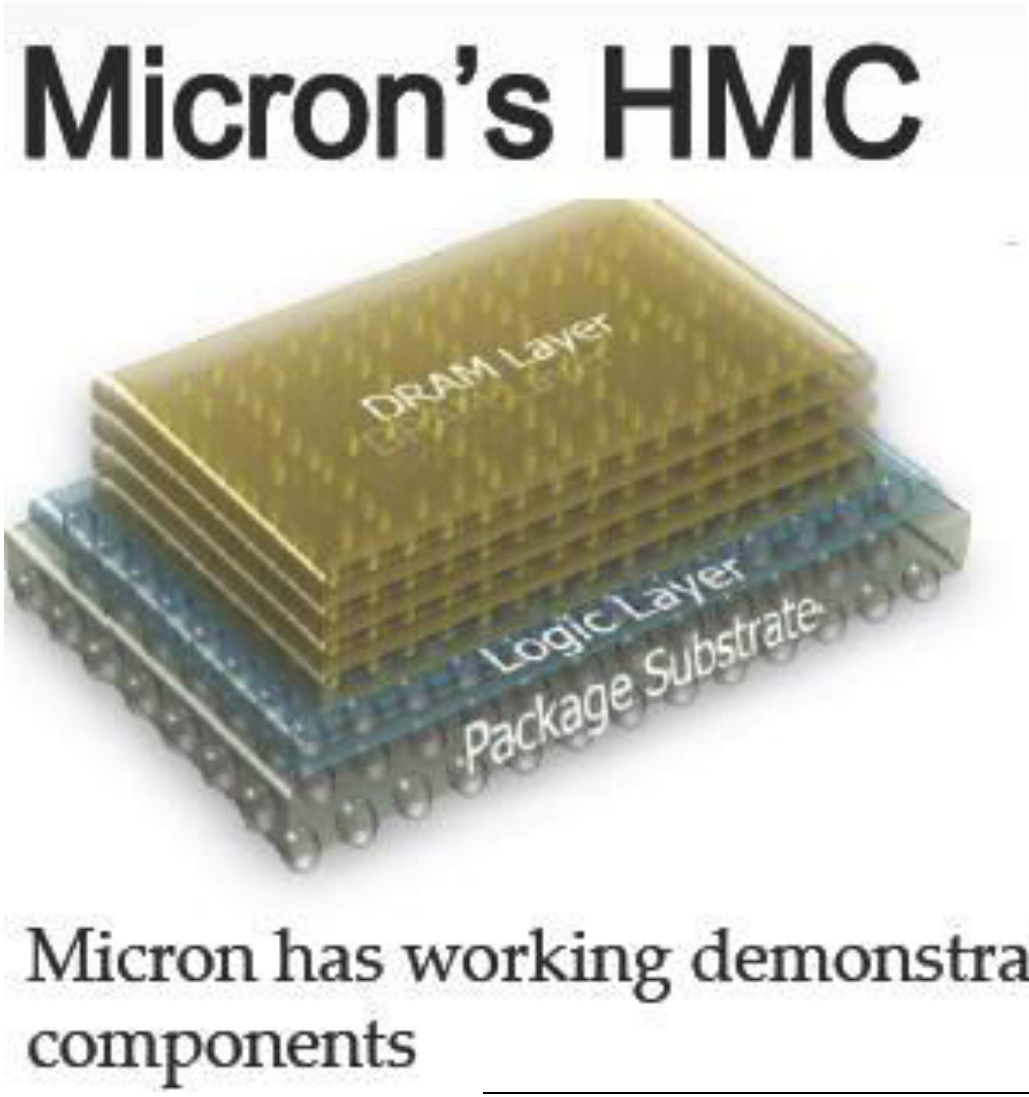
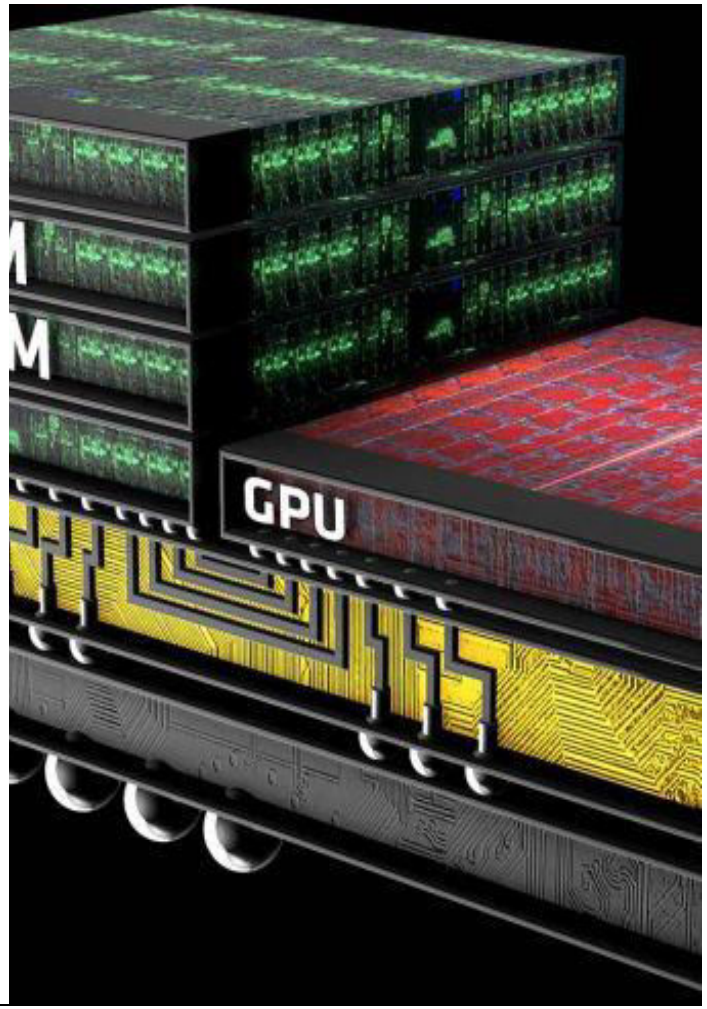
3D-Stacked Memory

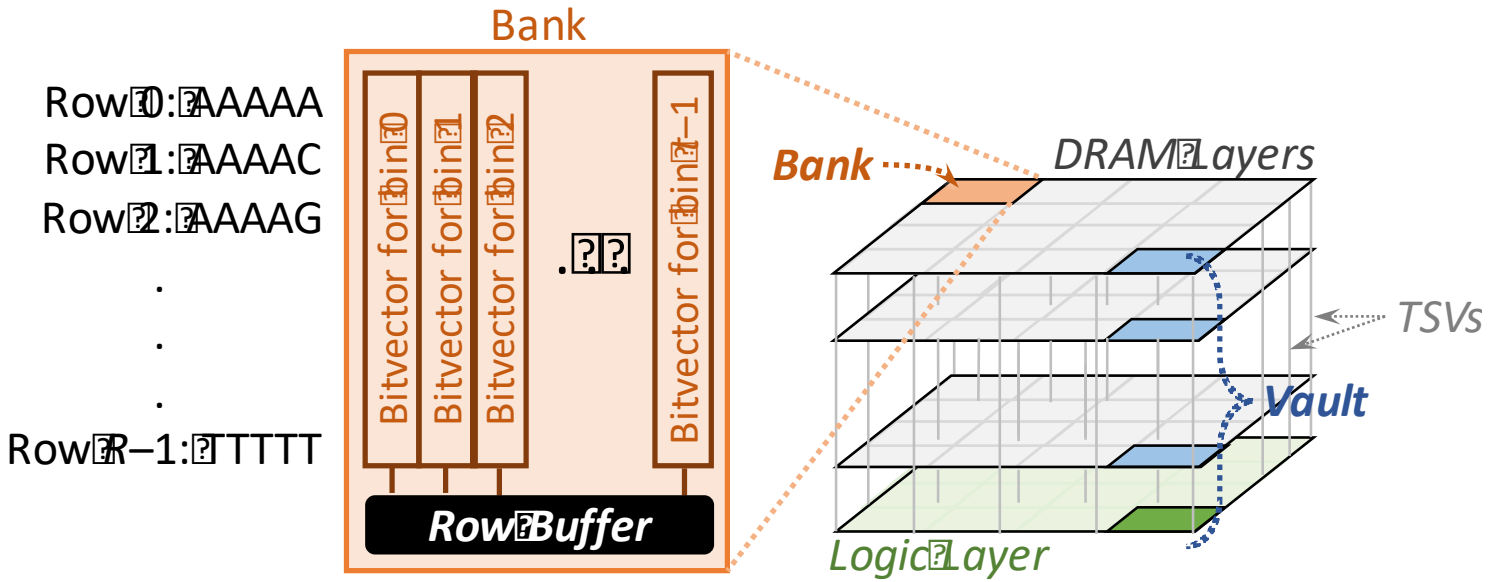




http://images.anandtech.com/doci/9266/HBMCar_678x452.jpg

http://i1-news.softpedia-static.com/images/news2/Micron-and-Samsung-Join-Force-to-Create-Next-Gen-Hybrid-Memory-2.png

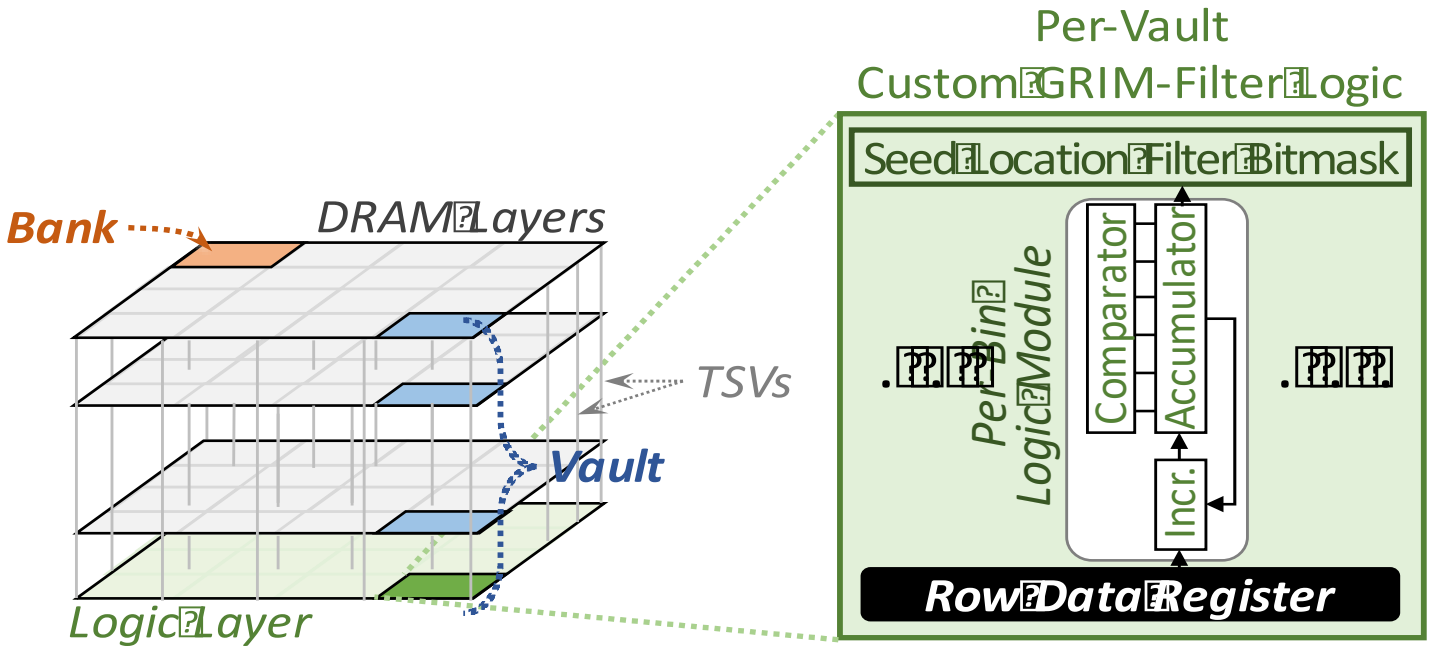
GRIM-Filter in 3D-Stacked DRAM



- 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 in 3D-Stacked DRAM



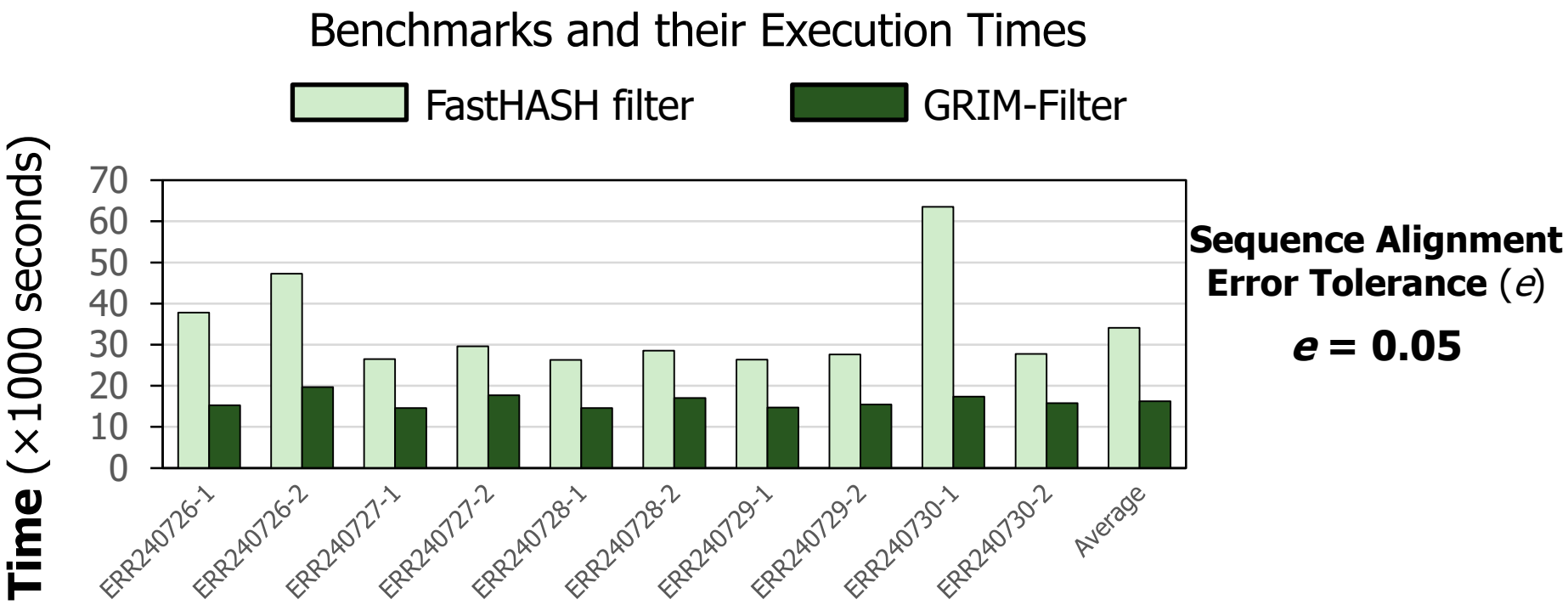
- Customized logic for accumulation and comparison per genome segment
  - Low area overhead, simple implementation
  - For HBM2, we use 4096 incrementer LUTs, 7-bit counters, and comparators in logic layer

Details are in [Kim+, BMC Genomics 2018]

Methodology

- Performance simulated using an in-house 3D-Stacked DRAM simulator
- Evaluate 10 real read data sets (From the 1000 Genomes Project)
  - Each data set consists of 4 million reads of length 100
- Evaluate two key metrics
  - Performance
  - False negative rate
    - The fraction of locations that pass the filter but result in a mismatch
- Compare against a state-of-the-art filter, FastHASH **[Xin+, BMC Genomics 2013]** when using mrFAST, but **GRIM-Filter can be used with ANY read mapper**

GRIM-Filter Performance

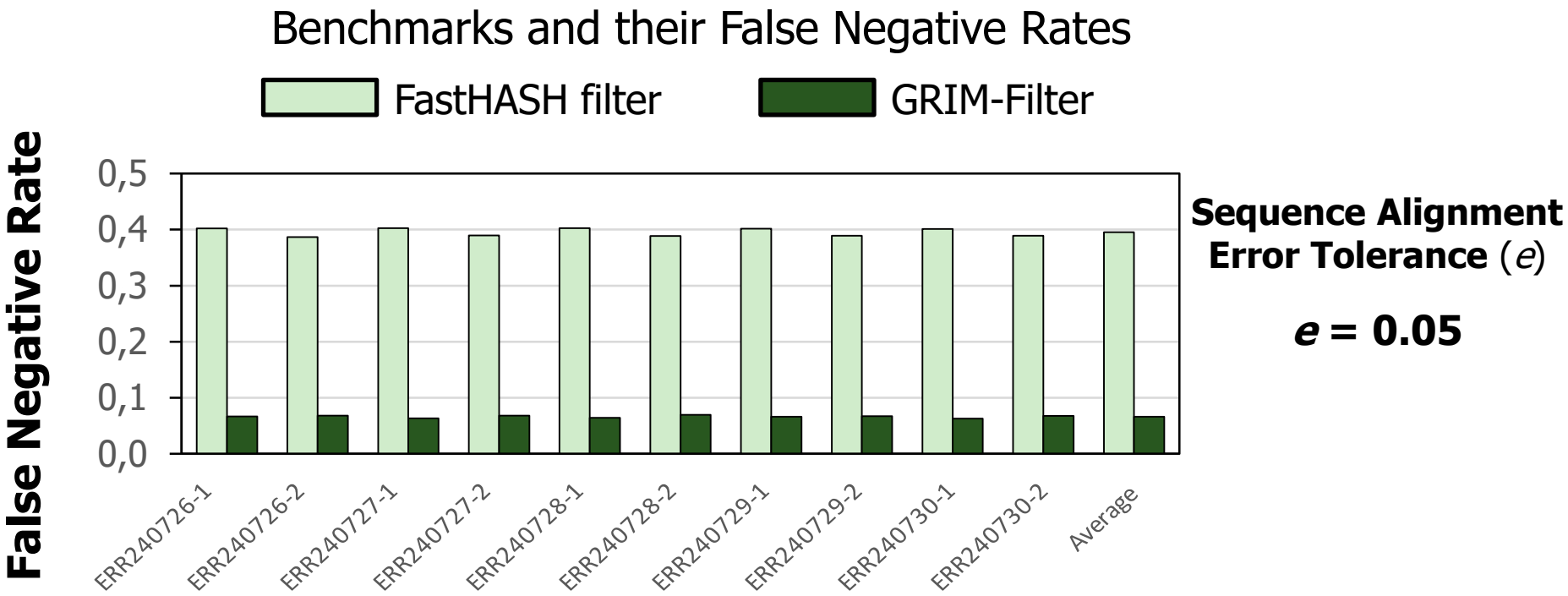


1.8x-3.7x performance benefit across real data sets

2.1x average performance benefit

GRIM-Filter gets performance due to its hardware-software co-design

GRIM-Filter False Negative Rate



5.6x-6.4x False Negative reduction across real data sets

6.0x average reduction in False Negative Rate

GRIM-Filter utilizes more information available in the read to filter

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"
  to appear in ***BMC Genomics***, 2018.
  Proceedings of the 16th Asia Pacific Bioinformatics Conference (***APBC***),
  Yokohama, Japan, January 2018.
  arxiv.org Version (pdf)

GRIM-Filter: Fast Seed Location Filtering in DNA Read Mapping Using Processing-in-Memory Technologies

Jeremie S. Kim[1,6*], Damla Senol Cali[1], Hongyi Xin[2], Donghyuk Lee[3], Saugata Ghose[1], Mohammed Alser[4], Hasan Hassan[6], Oguz Ergin[5], Can Alkan*[4], and Onur Mutlu*[6,1]

Agenda

- The Problem: DNA Read Mapping
  - State-of-the-art Read Mapper Design
- Algorithmic Acceleration
  - Exploiting Structure of the Genome
  - Exploiting SIMD Instructions
- Hardware Acceleration
  - Specialized Architectures
  - Processing in Memory
- Future Opportunities: New Sequencing Technologies

Recall: High-Throughput Sequencing

- Massively parallel sequencing technology
  - Illumina, Roche 454, Ion Torrent, SOLID…
- Small DNA fragments are first amplified and then sequenced in parallel, leading to
  - High throughput
  - High speed
  - Low cost
  - Short reads
    - Amplification step limits the read length since too short or too long fragments are not amplified well.
- Sequencing is done by either reading optical signals as each base is added, or by detecting hydrogen ions instead of light, leading to:
  - Low error rates (relatively)
  - Reads lack information about their order and which part of genome they are originated from

Nanopore Sequencing Technology

- **Nanopore sequencing** is an emerging and a promising single-molecule DNA sequencing technology
  - No amplification → Less limit on read length → Longer read length

- First nanopore sequencing device, **MinION**, made commercially available by **Oxford Nanopore Technologies** (ONT) in **May 2014.**
  - Inexpensive
  - Long read length (> 882K bp)
  - Portable: Pocket-sized
  - Produces data in real-time

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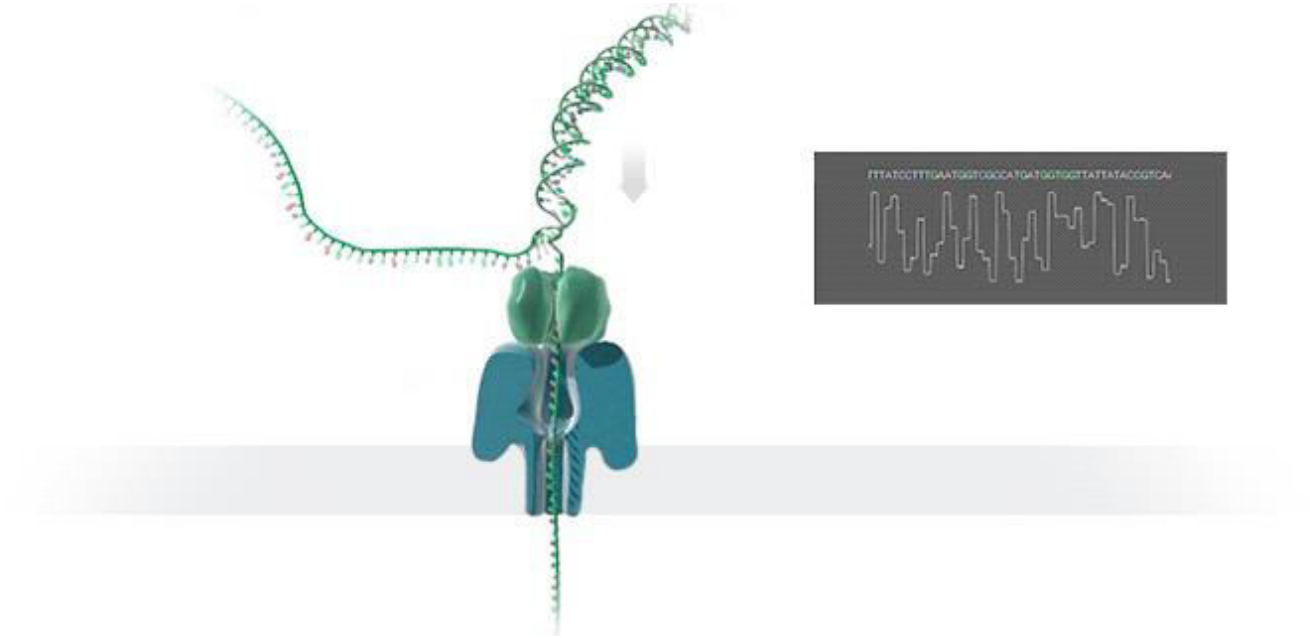
Nanopore Sequencing



- **Nanopore** is a nano-scale hole
- 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

Advantages of Nanopore Sequencing

Nanopores:

- Do *not* require any labeling of the DNA or nucleotide for detection during sequencing
- Rely on the electronic or chemical structure of the different nucleotides for identification
- Allow sequencing very long reads, and
- Provide portability, low cost, and high throughput.

Challenges of Nanopore Sequencing

- One major drawback: high error rates
- Nanopore sequence analysis tools have a critical role to:
  - overcome high error rates
  - take better advantage of the technology
- Faster tools are critically needed to:
  - Take better advantage of the real-time data production capability of MinION
  - Enable fast, real-time data analysis

Nanopore Genome Assembly Pipeline

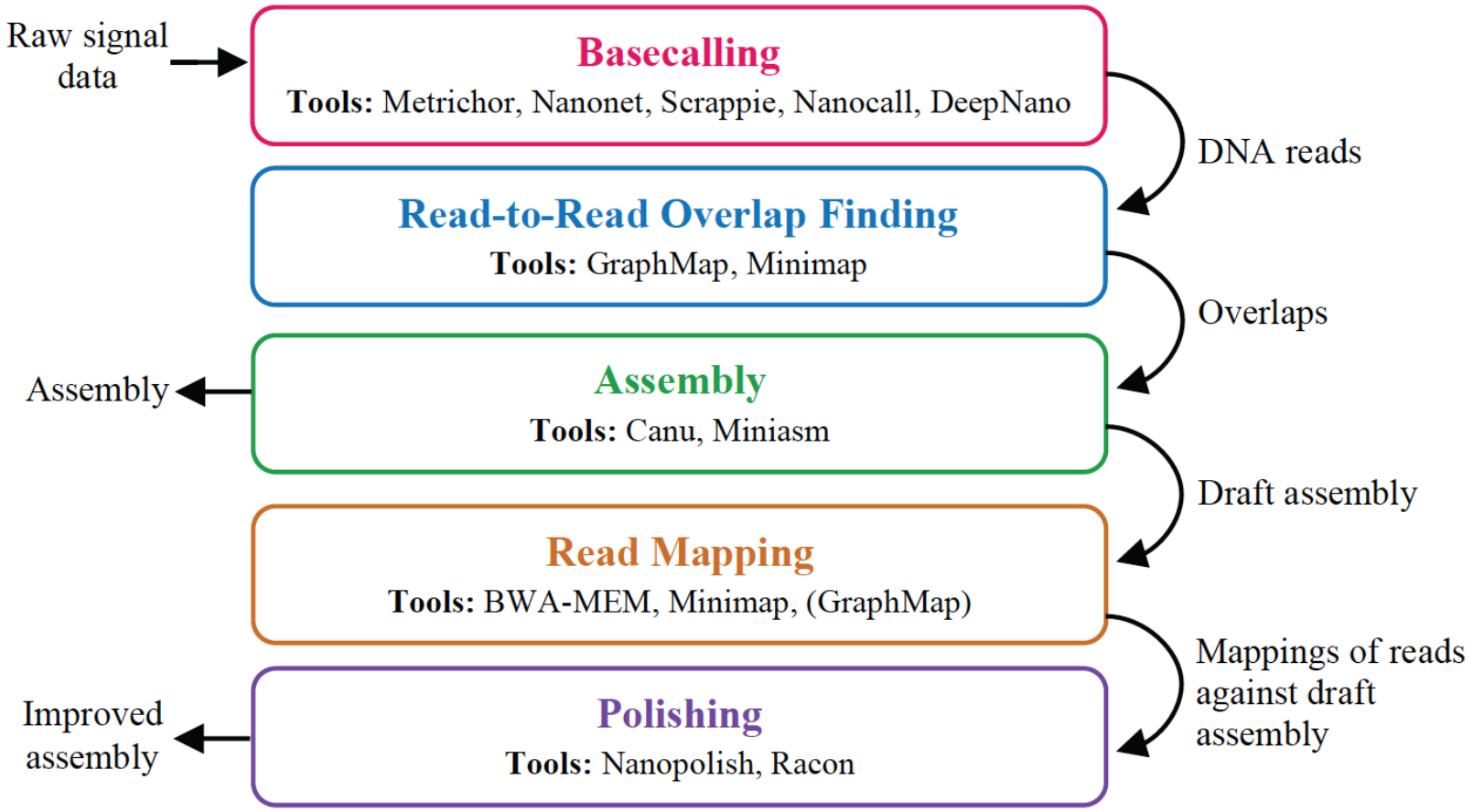


Figure 1. The analyzed genome assembly pipeline using nanopore sequence data, with its five steps and the associated tools for each step.

Senol Cali+, "**Nanopore Sequencing Technology and Tools for Genome Assembly**" to appear in Briefings in Bioinformatics, 2018.

More on Nanopore Sequencing & Tools

Nanopore Sequencing Technology and Tools for Genome Assembly: Computational Analysis of the Current State, Bottlenecks, and Future Directions

Damla Senol Cali [1,*], Jeremie Kim [1,3], Saugata Ghose [1], Can Alkan [2*] and Onur Mutlu [3,1*]

[1]Department of Electrical and Computer Engineering, Carnegie Mellon University, Pittsburgh, PA, USA
[2]Department of Computer Engineering, Bilkent University, Bilkent, Ankara,Turkey
[3]Department of Computer Science, Systems Group, ETH Zürich, Zürich, Switzerland

Senol Cali+, "**Nanopore Sequencing Technology and Tools for Genome Assembly: Computational Analysis of the Current State, Bottlenecks and Future Directions**," to appear in Briefings in Bioinformatics, 2018. [Preliminary arxiv.org version]

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  - Exploiting SIMD Instructions
- Hardware Acceleration
  - Specialized Architectures
  - Processing in Memory
- Future Opportunities: New Sequencing Technologies

Conclusion

- System design for bioinformatics is a critical problem
  - It has large scientific, medical, societal, personal implications
- This talk is about accelerating a key step in bioinformatics: genome sequence analysis
  - In particular, read mapping
- We covered various recent ideas to accelerate read mapping
  - My personal journey since September 2006
- **Many future opportunities exist**
  - **Especially with new sequencing technologies**

Acknowledgments

- Prof. Can Alkan, Bilkent University

- Many students
  - Mohammed Alser, Damla Senol Cali, Jeremie Kim
  - Hasan Hassan
  - Hongyi Xin
  - …

- All papers, source code, and more are at:
  - https://people.inf.ethz.ch/omutlu/projects.htm

Accelerating Genome Analysis

A Primer on an Ongoing Journey

Onur Mutlu
omutlu@gmail.com
https://people.inf.ethz.ch/omutlu

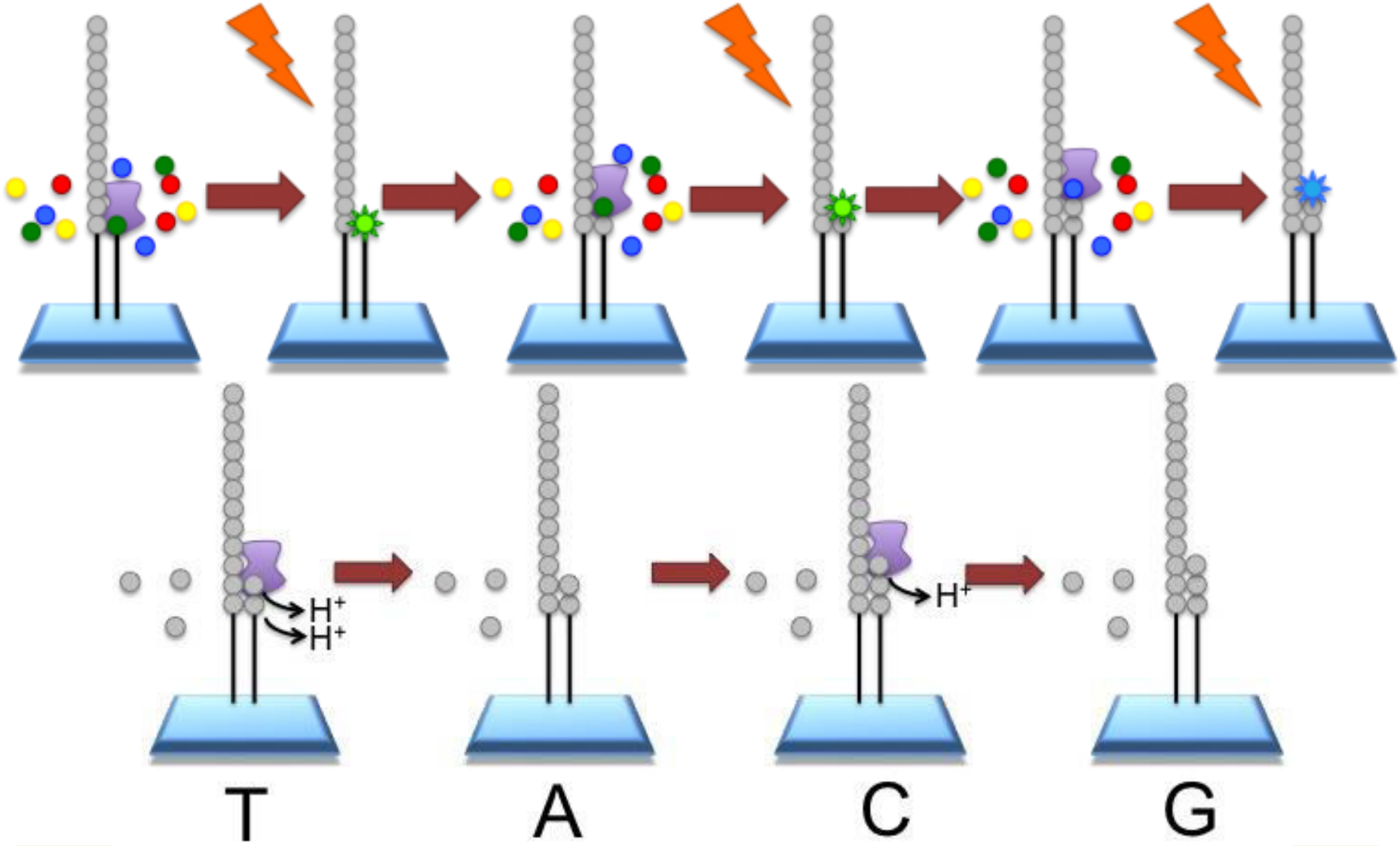
March 8, 2018

ETH HAML Seminar

SAFARI

ETH zürich

High-Throughput Sequencing



Nanopore Sequencing

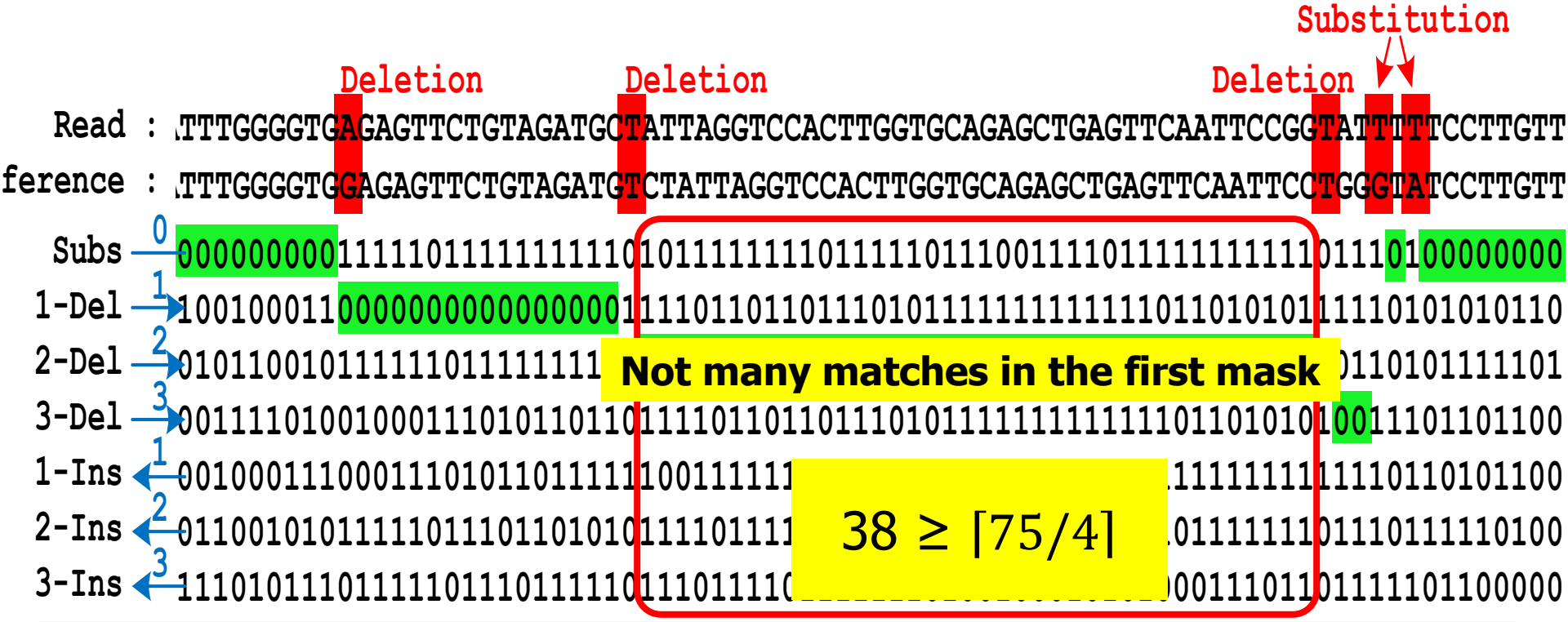
- **Basecalling** translates the raw signal output of the nanopore sequencer into bases (A, C, G, T) to generate DNA reads.
  - 1) The raw current signal is divided into discrete blocks (events).
  - 2) Each event is decoded into a most-likely set of bases.

- **Deletions** are the dominant error of nanopore sequencing.
  - In the ideal case, each consecutive event should differ by one base. However, in practice, this is not the case because of the non-stable speed of the translocation.
  - Determining the correct length of the homopolymers (*i.e.*, repeating stretches of one kind of base, *e.g.*, AAAAAAA) is challenging.

3- Highly Accurate Filtering Algorithm (cont'd)

MAGNET

- Check for substitutions.
- The longest identical subsequence ≥ $\lceil (m - E)/(E + 1) \rceil$.
- Extraction & Encapsulation (divide-and-Conquer fashion).



3- Highly Accurate Filtering Algorithm (cont'd)

MAGNET

- Check for substitutions.
- The longest identical subsequence ≥ $\lceil (m - E)/(E + 1) \rceil$.
- Extraction & Encapsulation (divide-and-Conquer fashion).

Now divide the problem into two subproblems and repeat

3- Highly Accurate Filtering Algorithm (cont'd)

MAGNET

- Check for substitutions.
- The longest identical subsequence ≥ $\lceil (m - E)/(E + 1) \rceil$.
- Extraction & Encapsulation (divide-and-Conquer fashion).

SA Counting the encapsulation bits reveals the number of edits

MAGNET Accelerator