Accelerating Genome Analysis

A Primer on an Ongoing Journey

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HiCOMB-17 Keynote Talk

SAFARI

ETH zürich

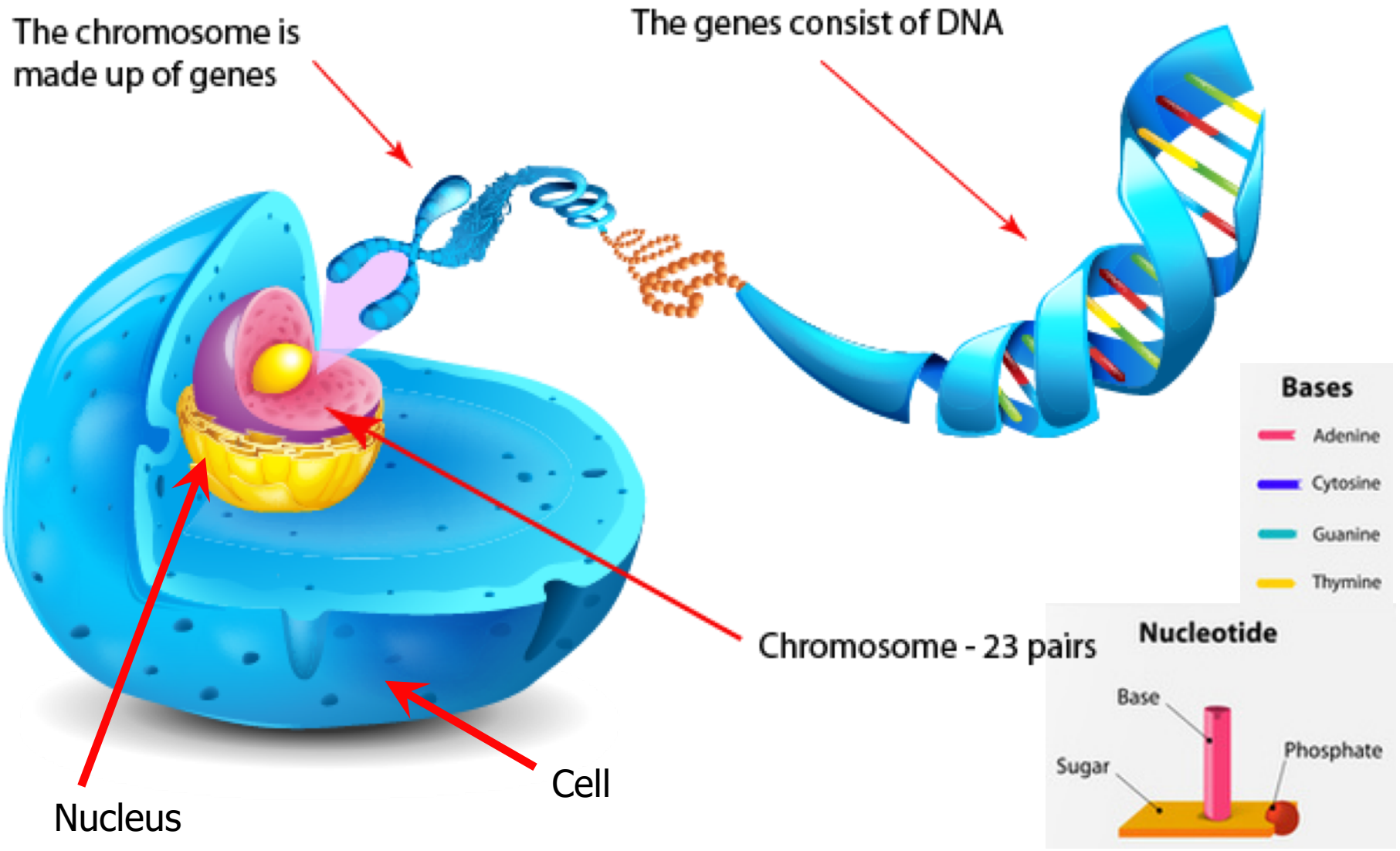
Overview

- 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

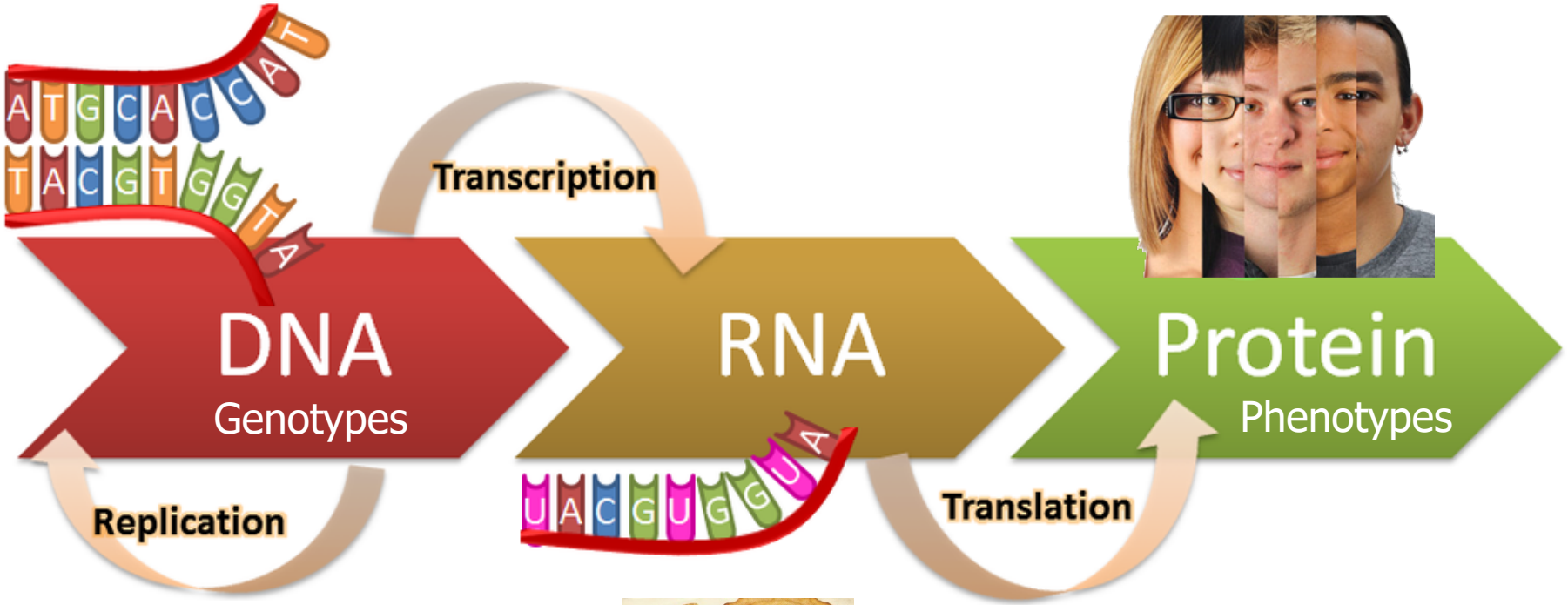
Agenda

- 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

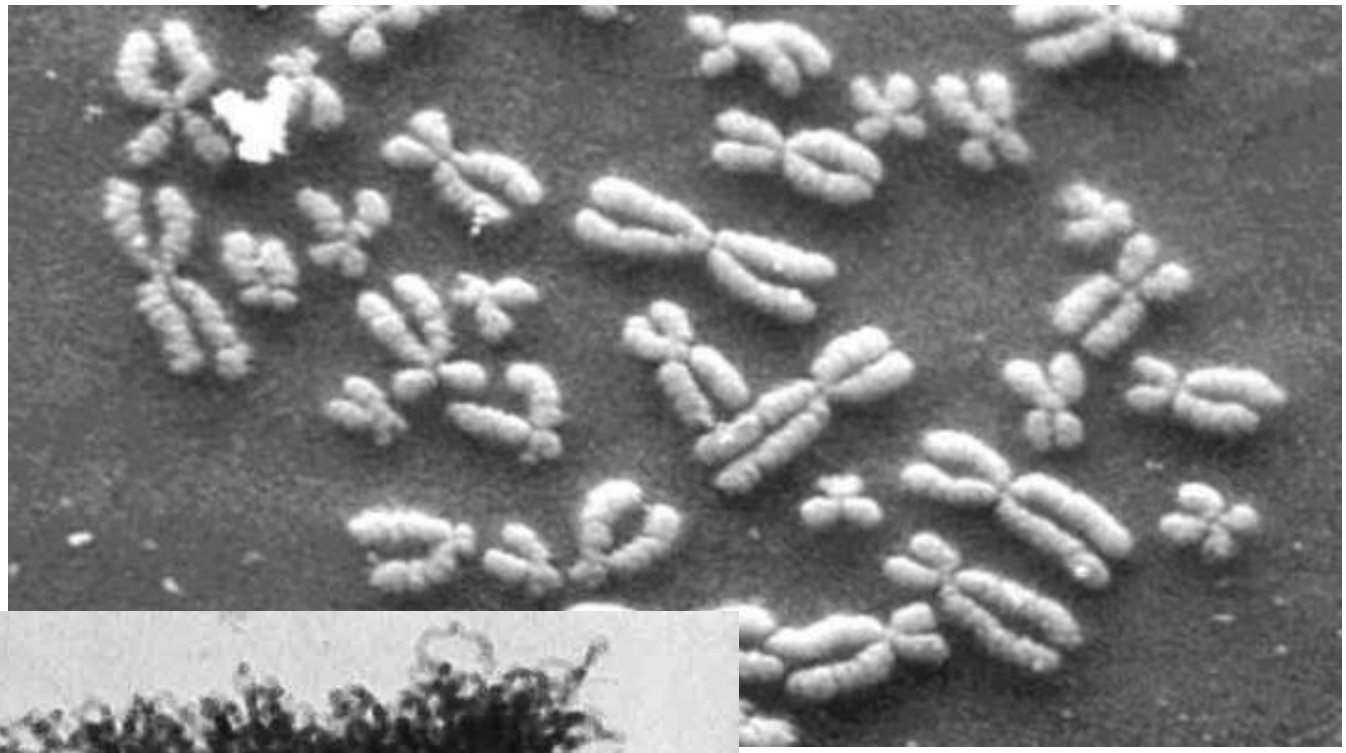
What Is a Genome Made Of?

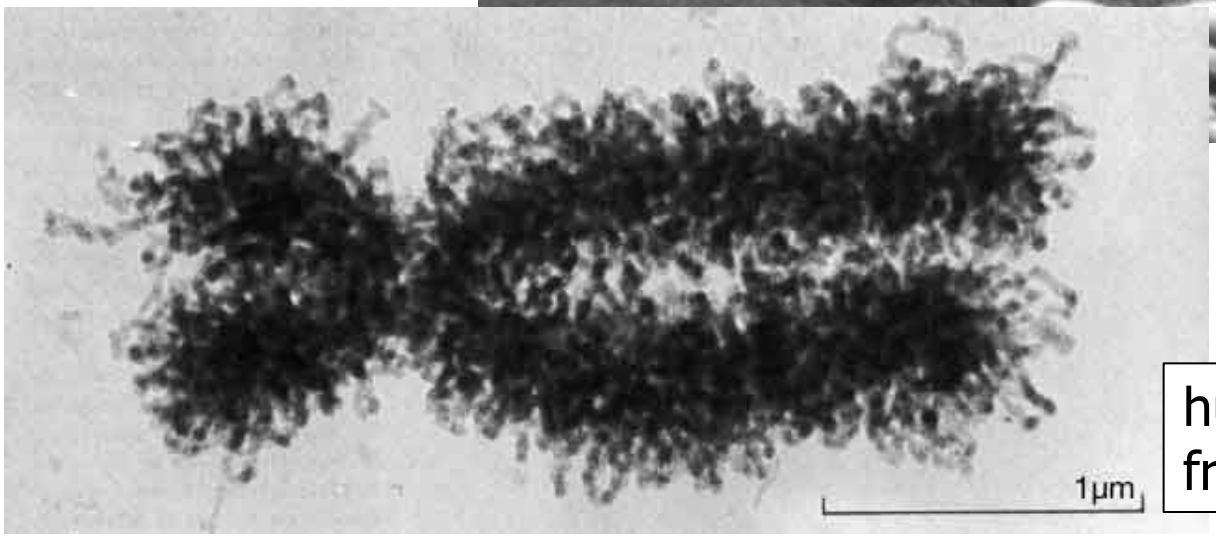


The Central Dogma of Molecular Biology



DNA Under Electron Microscope





human chromosome #12
from HeLa's cell

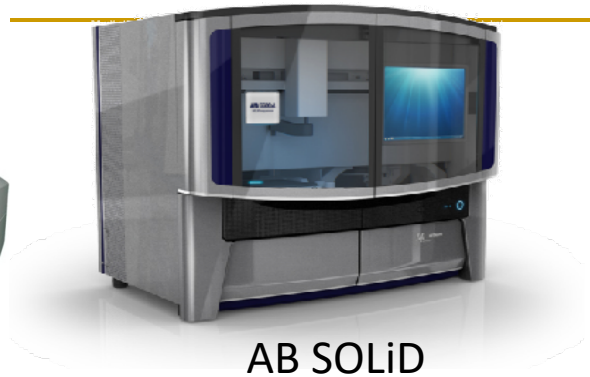
DNA Sequencing

- 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

Illumina NovaSeq 6000

Oxford Nanopore GridION

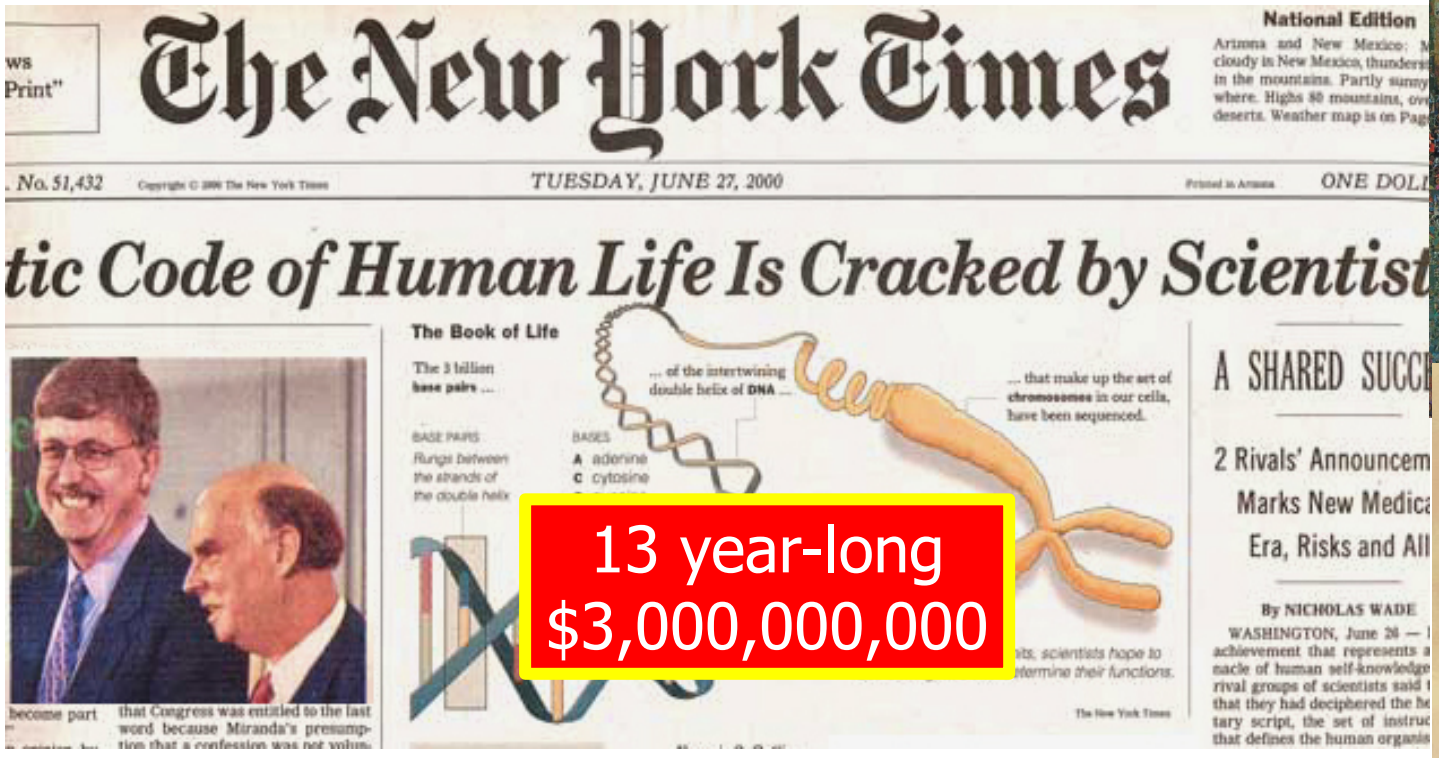
Ion Torrent PGM

Ion Torrent Proton

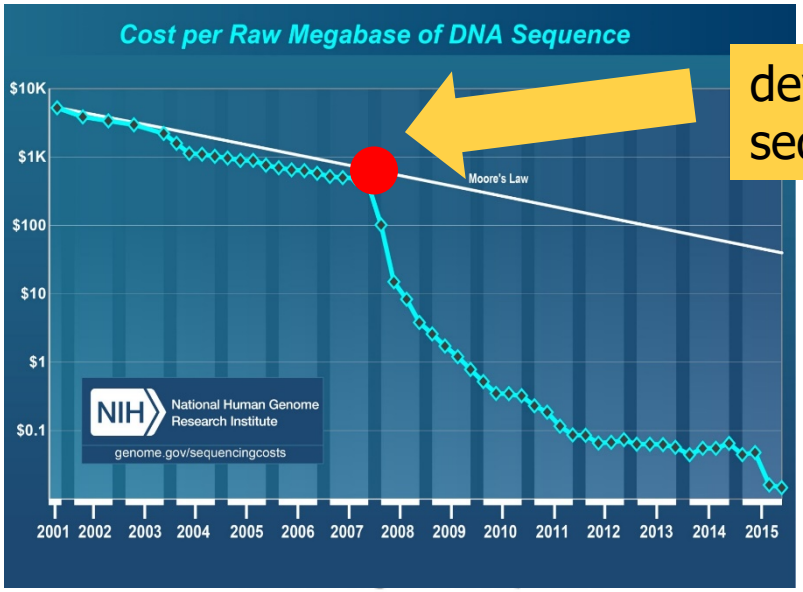
… and more! All produce data with different properties.

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.

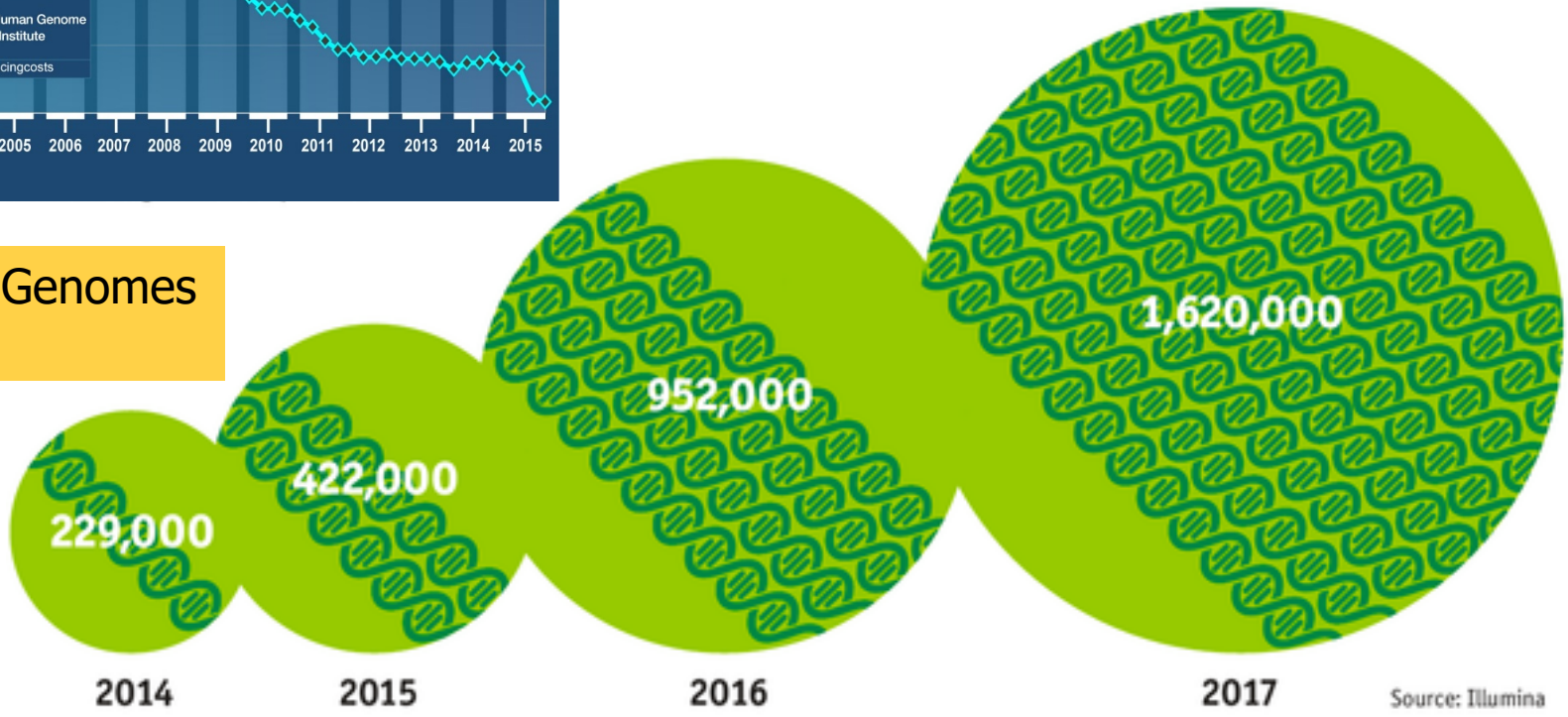


The Genomic Era (continued)



development of high-throughput sequencing (HTS) technologies

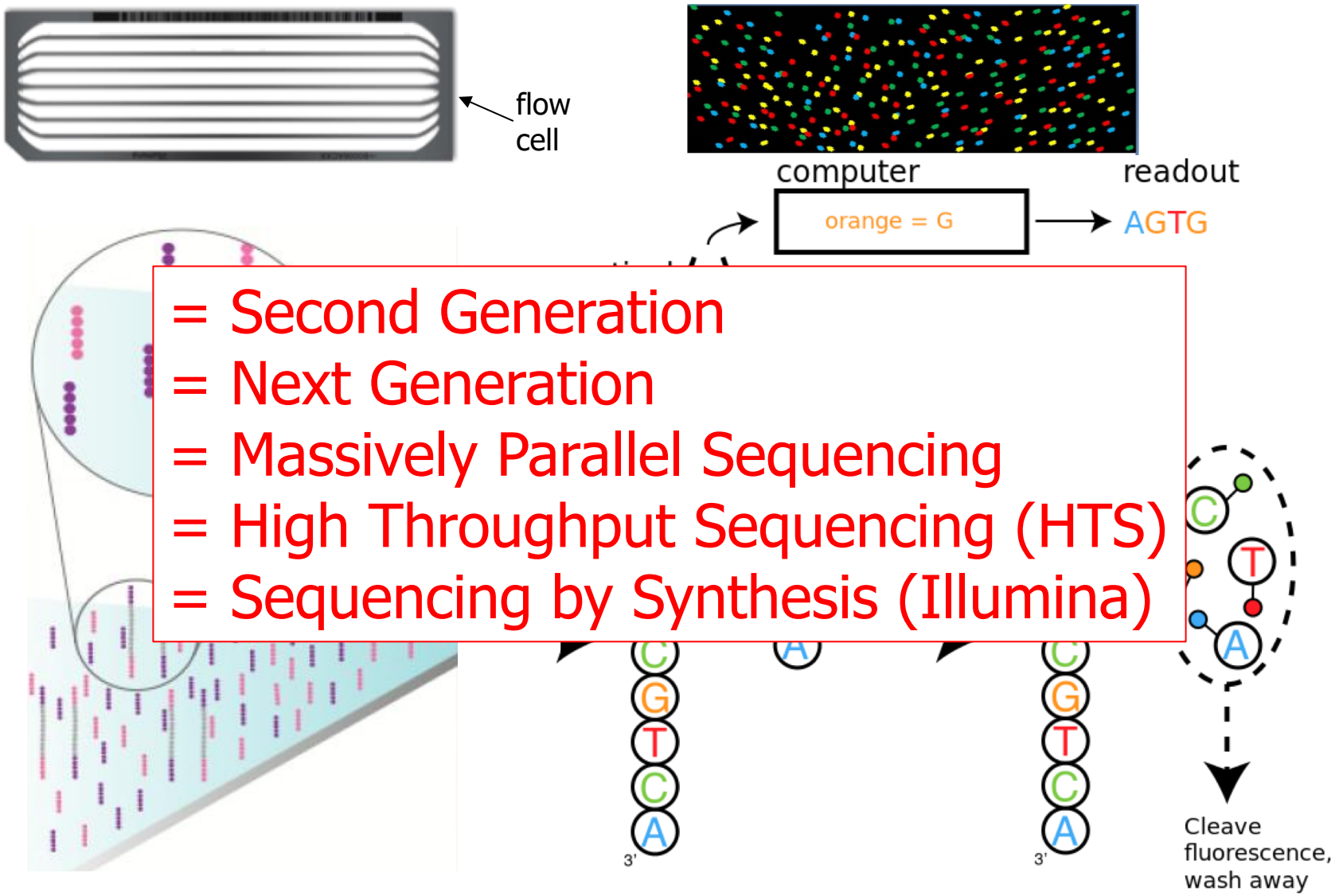
Number of Genomes Sequenced



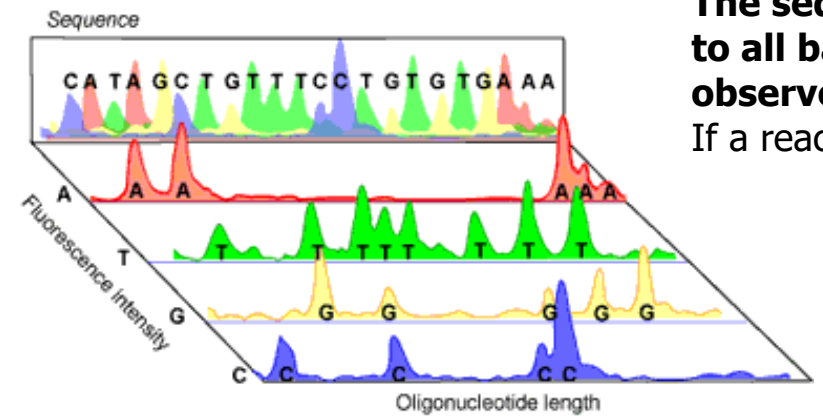
The Economist

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

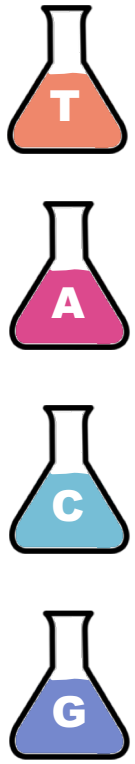
High-Throughput Sequencing (HTS)

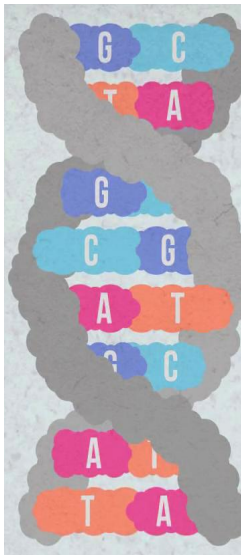


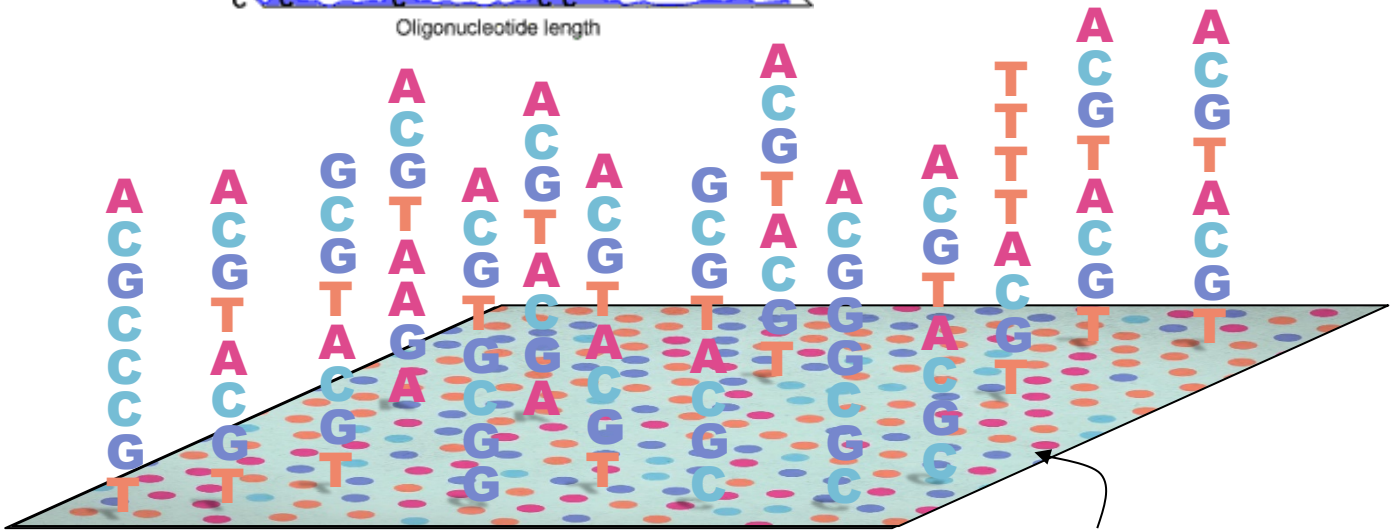
High-Throughput Sequencing (HTS)



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"



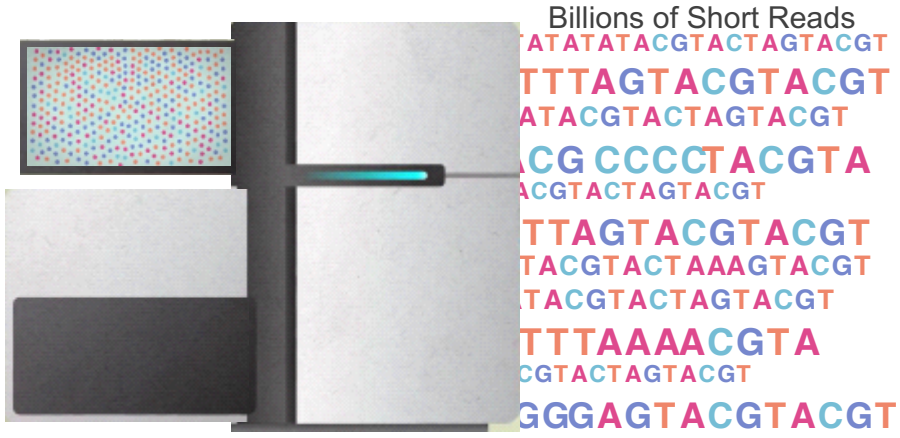




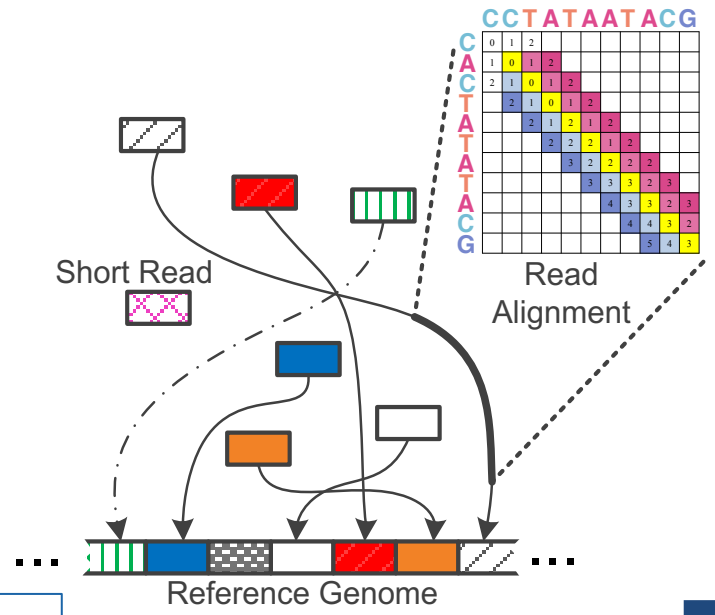
As a workaround, HTS technologies sequence random short DNA fragments (75-300 basepairs long) of copies of the original molecule.

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
- 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



1 Sequencing



Read Mapping 2

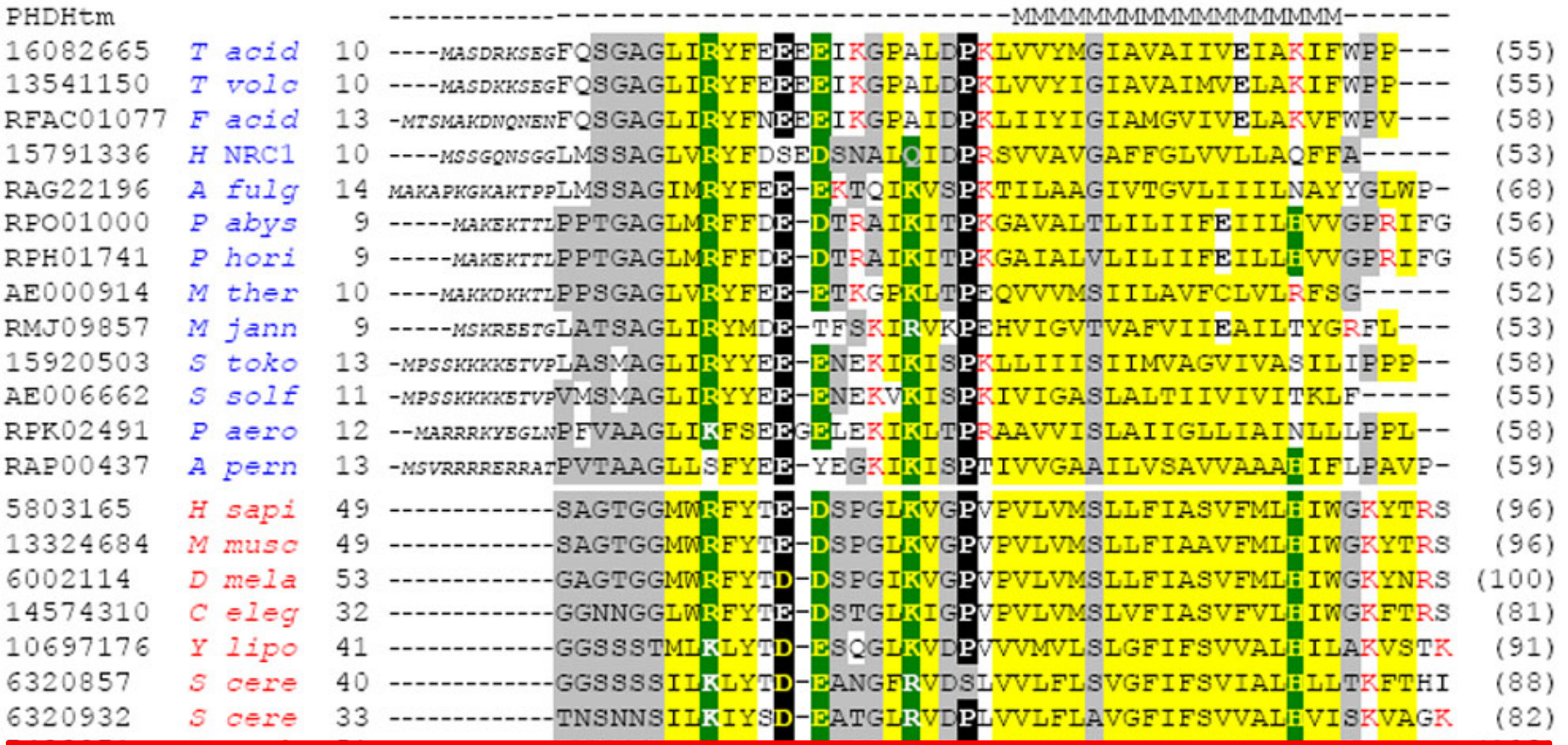
Genome Analysis

```
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%

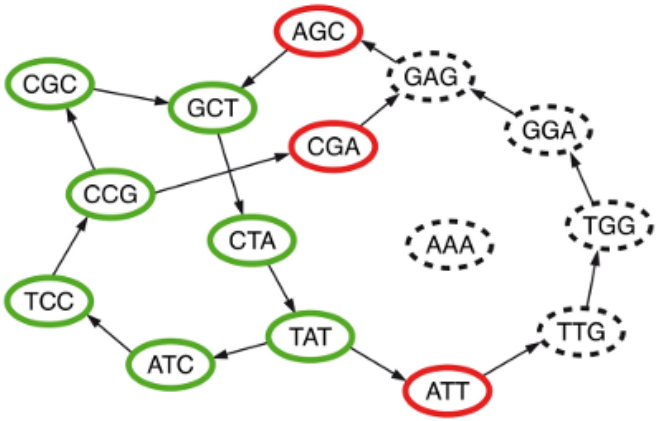
Human ~ Cow

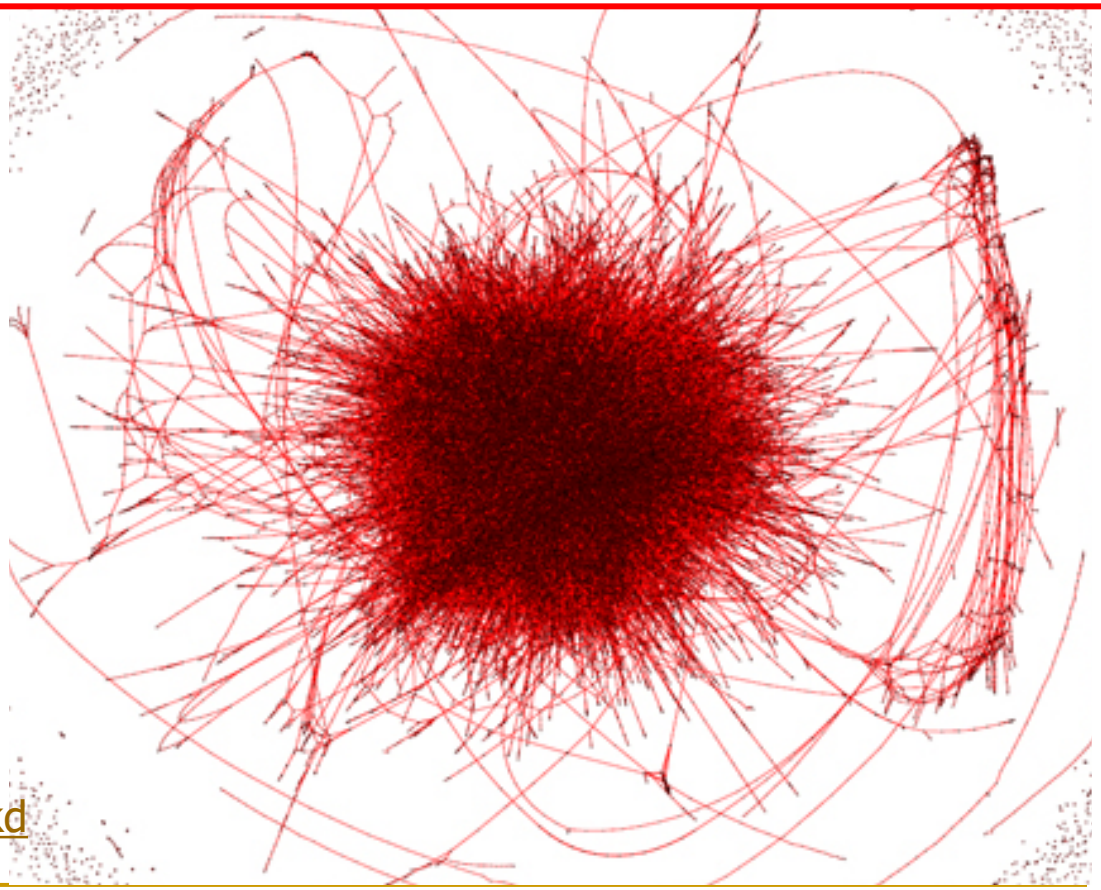
80%

Human ~ Banana

50-60%

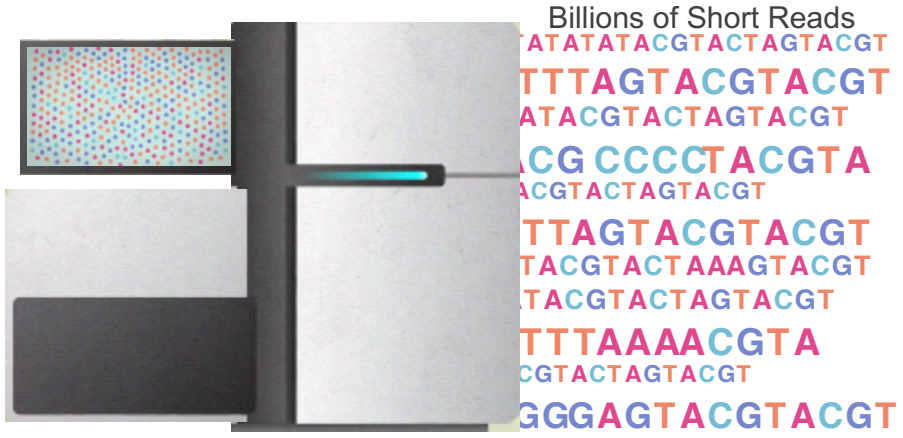
Question 2: Given a bunch of short sequences, Can you identify the approximate species cluster for genomically unknown organisms (bacteria)?





uncleaned de Bruijn graph

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



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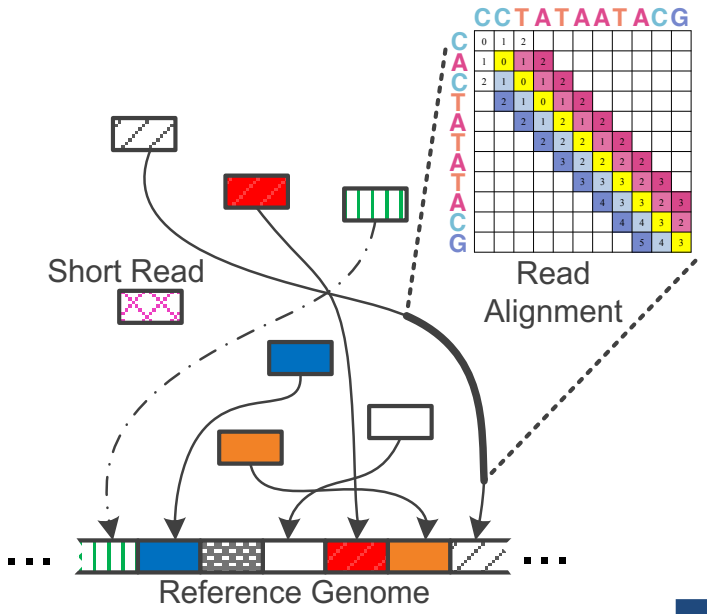
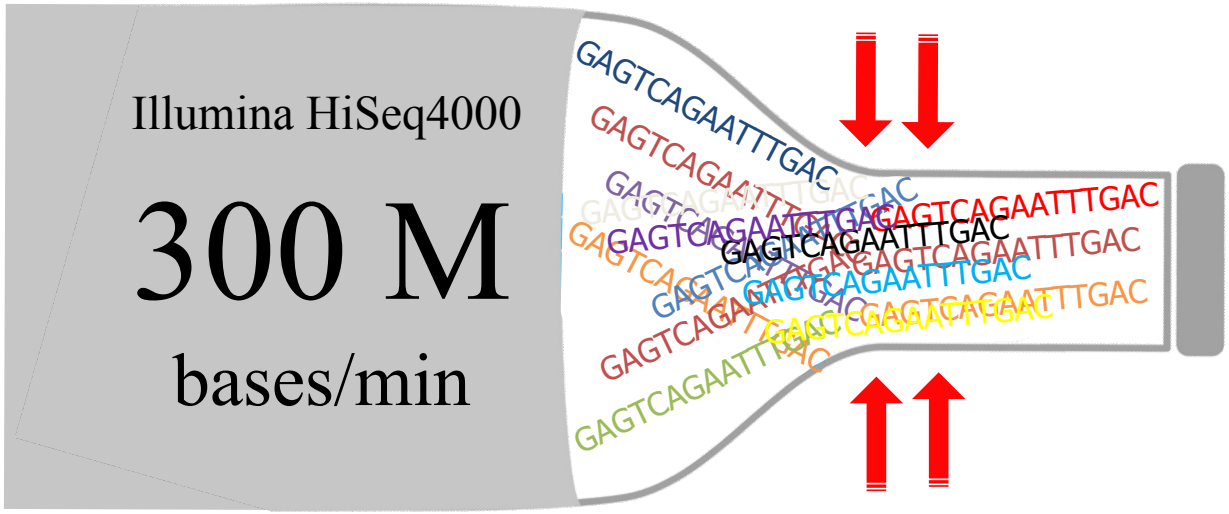


Read Mapping 2

Bottlenecked in Mapping!!



on average

2 M

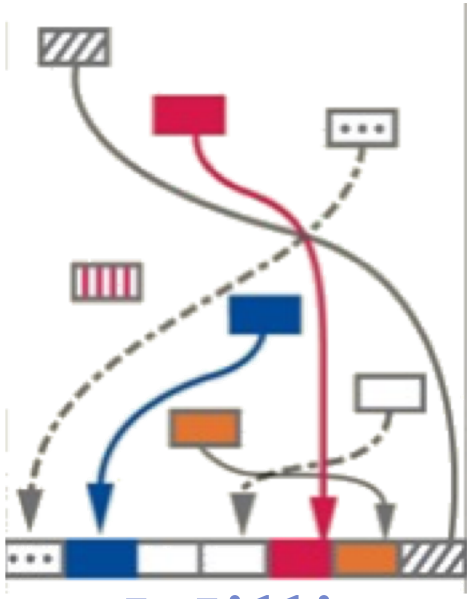
bases/min

(0.6%)

The Read Mapping Bottleneck

Illumina HiSeq4000

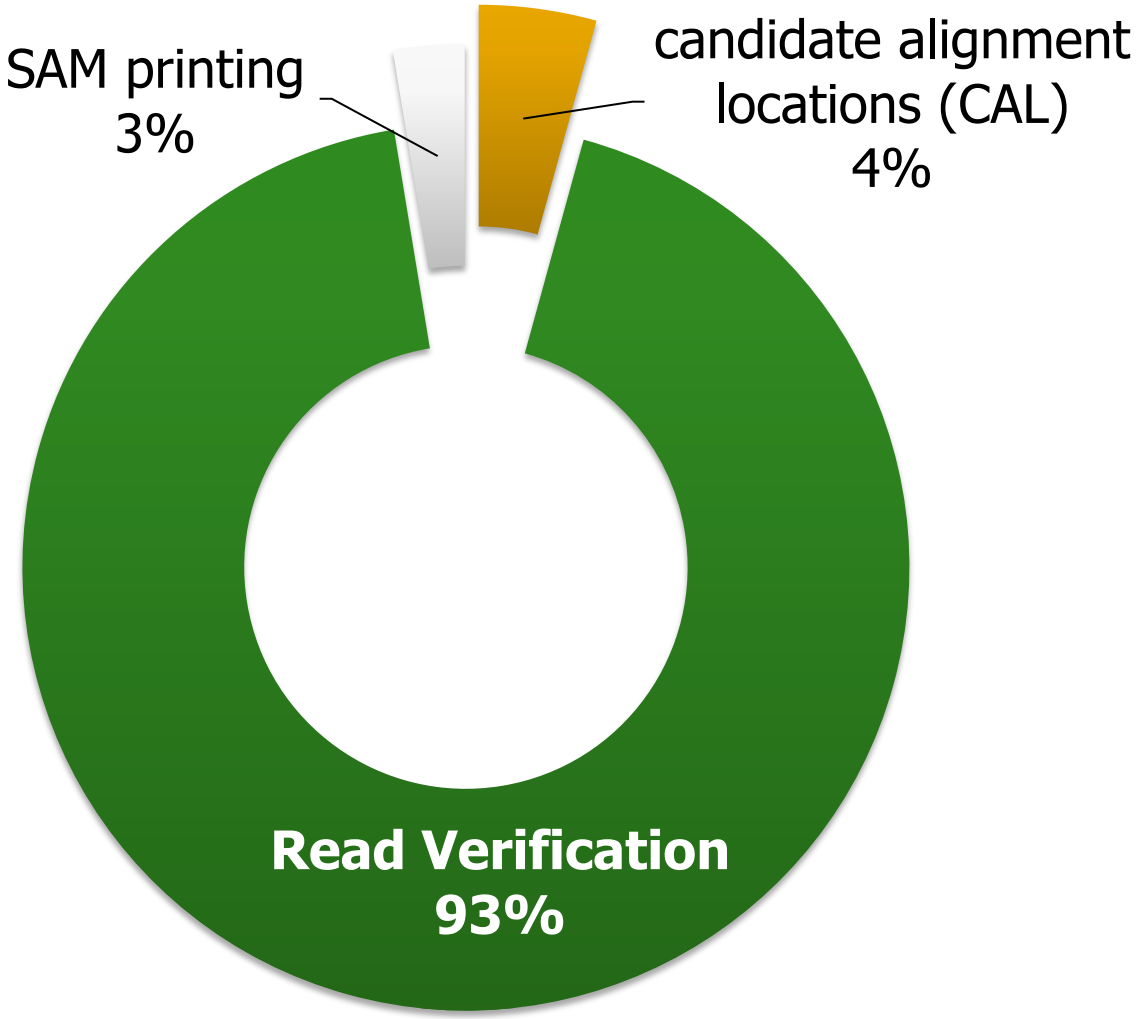
300 Million bases/minute



2 Million bases/minute

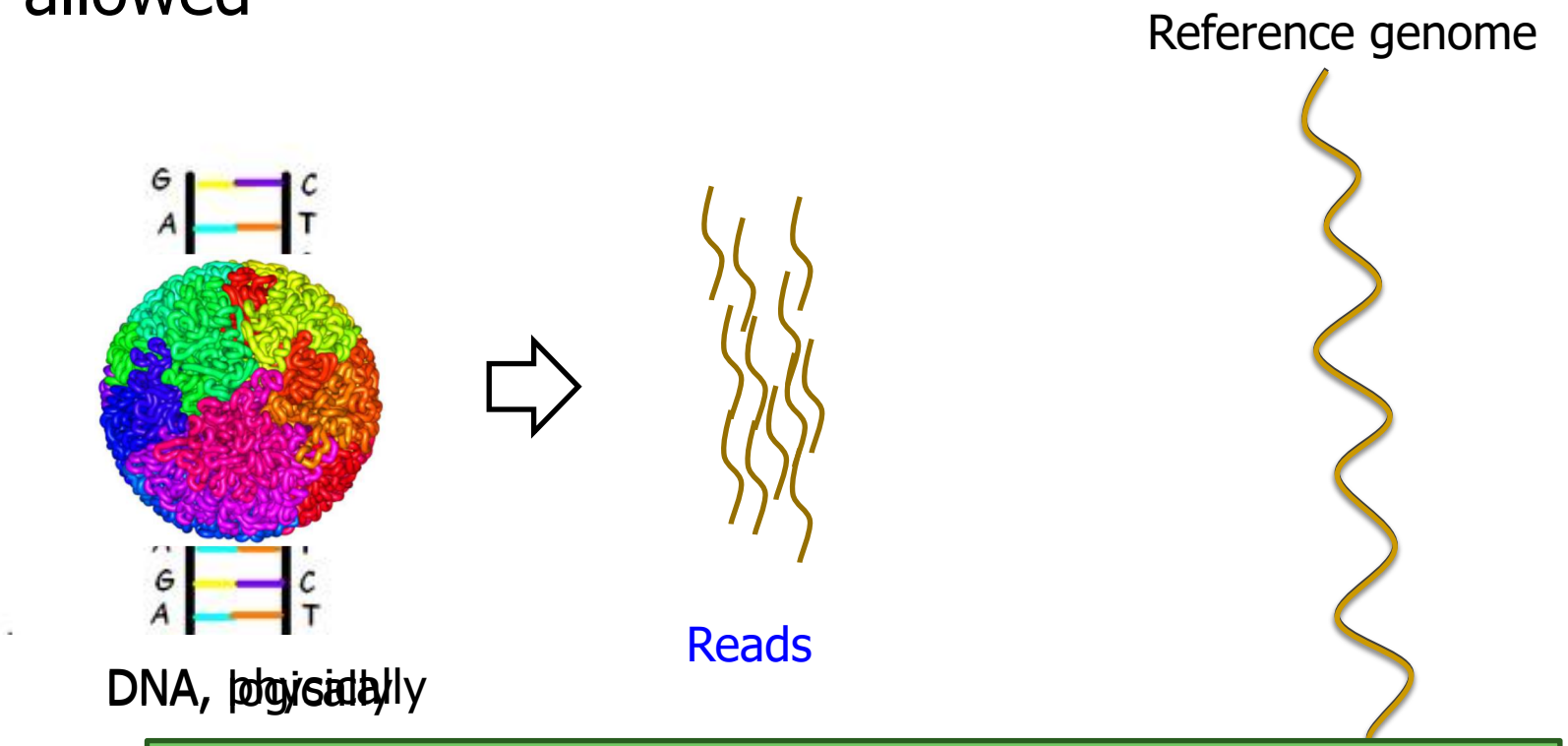
150X slower

Read Mapping Execution Time Breakdown



Read Mapping

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



Mapping short reads to reference genome is challenging (billions of 50-300 base pair reads)

Challenges in Read Mapping

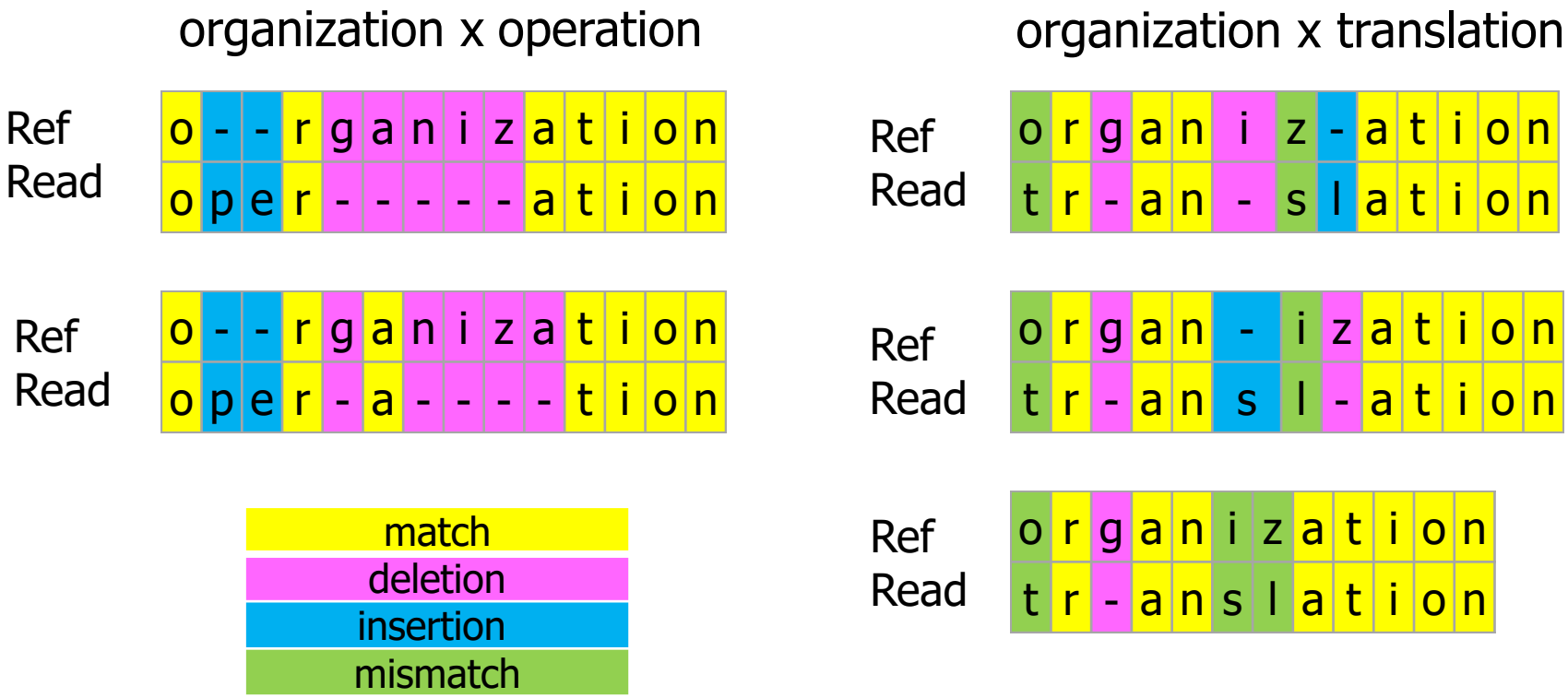
- Need to find many mappings of each read
  - A short read may map to many locations, especially with High-Throughput DNA Sequencing technologies
  - How can we find all mappings efficiently?

- 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?

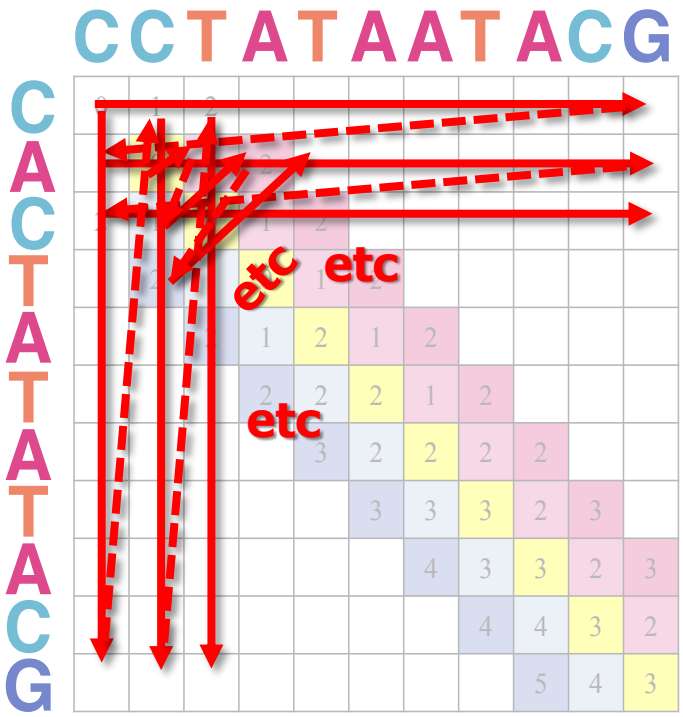
Read Alignment/Verification

- **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

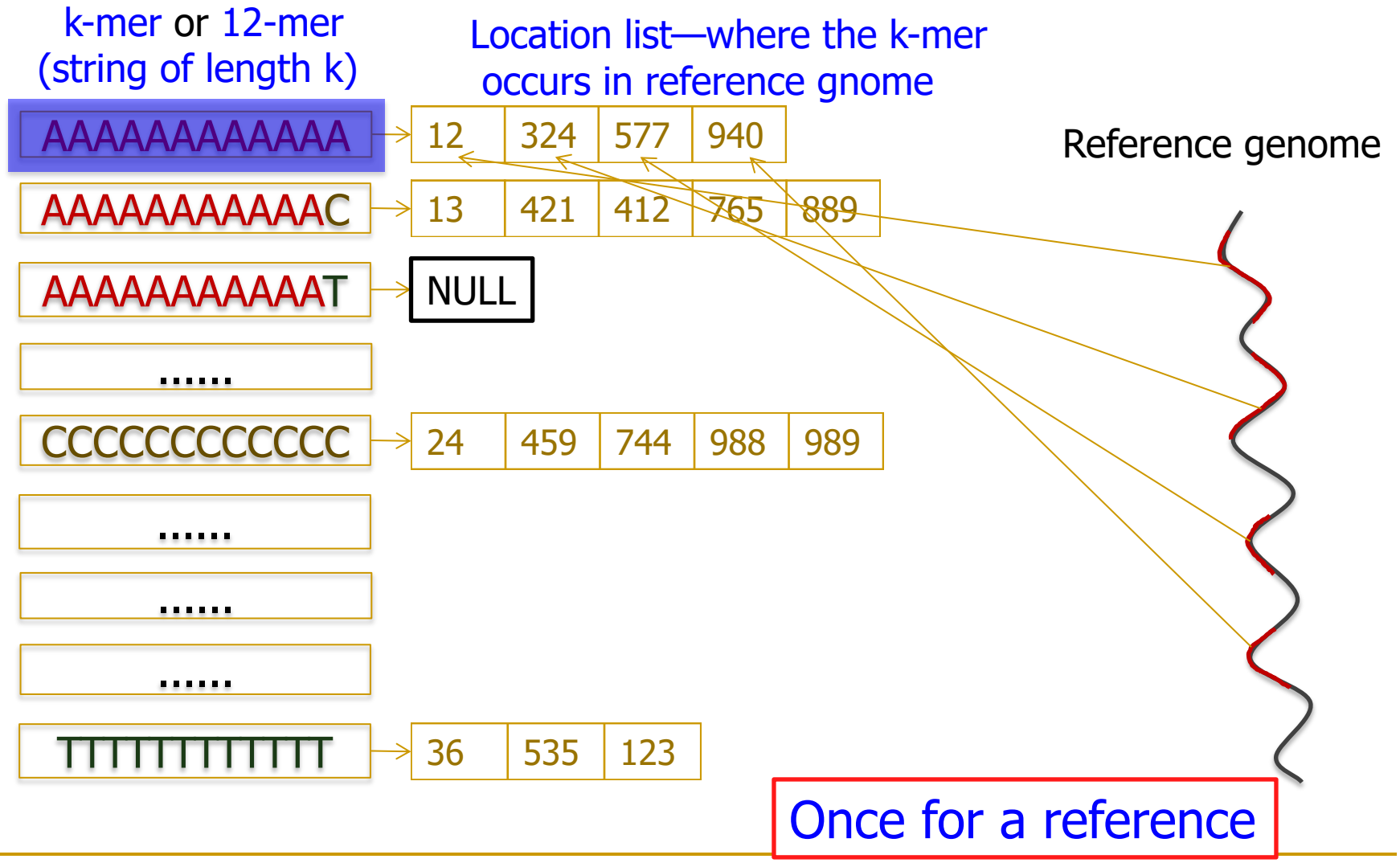
- Hash based seed-and-extend (hash table, suffix array, suffix tree)
  - Index the "k-mers" in the genome into a hash table (pre-processing)
  - When searching a read, find the location of a k-mer in the read; then extend through alignment
  - More sensitive, but slow
  - Requires large memory; this 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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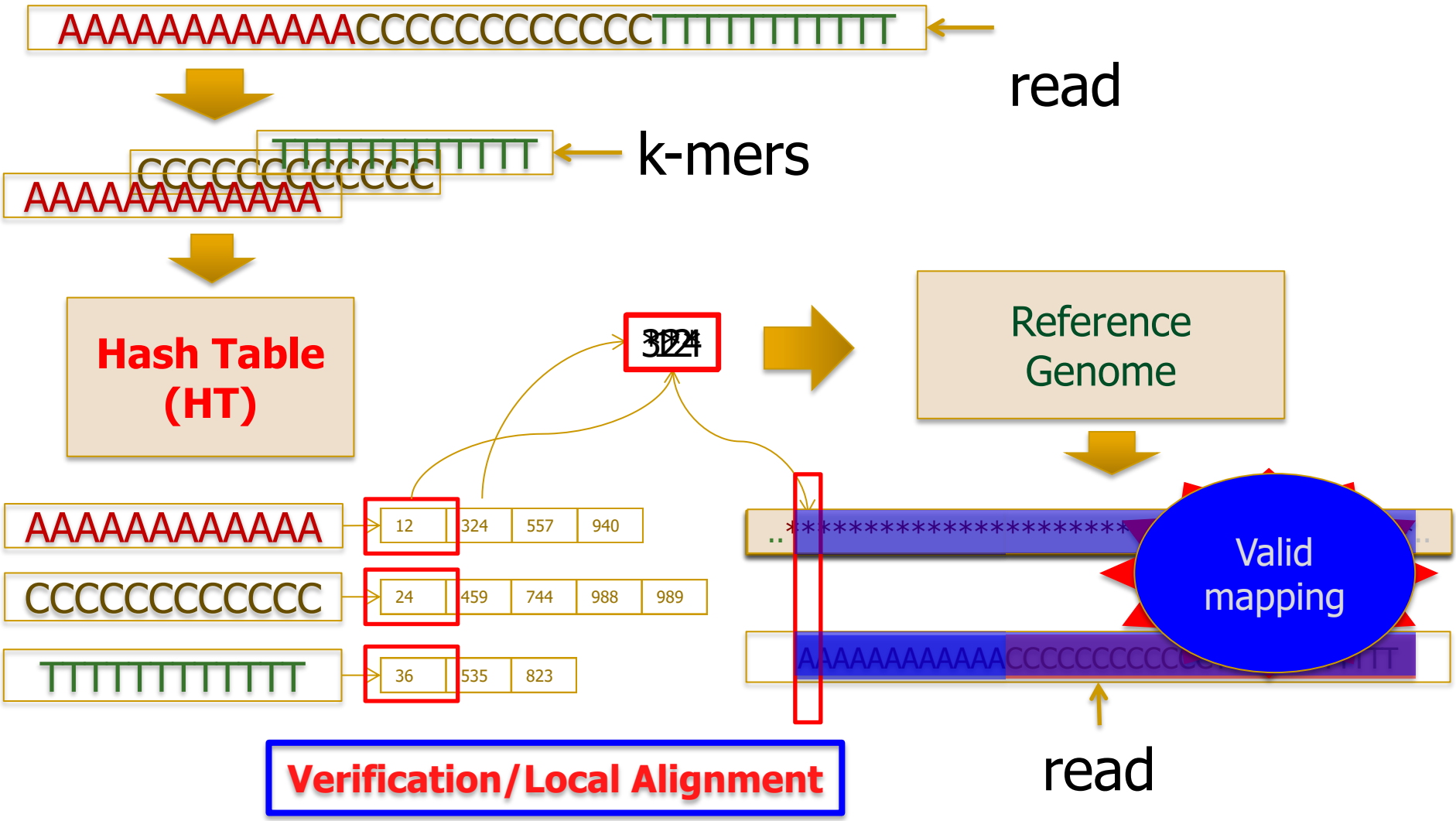


Advantages of Hash Table Based Mappers

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

nature genetics

http://mrfast.sourceforge.net/

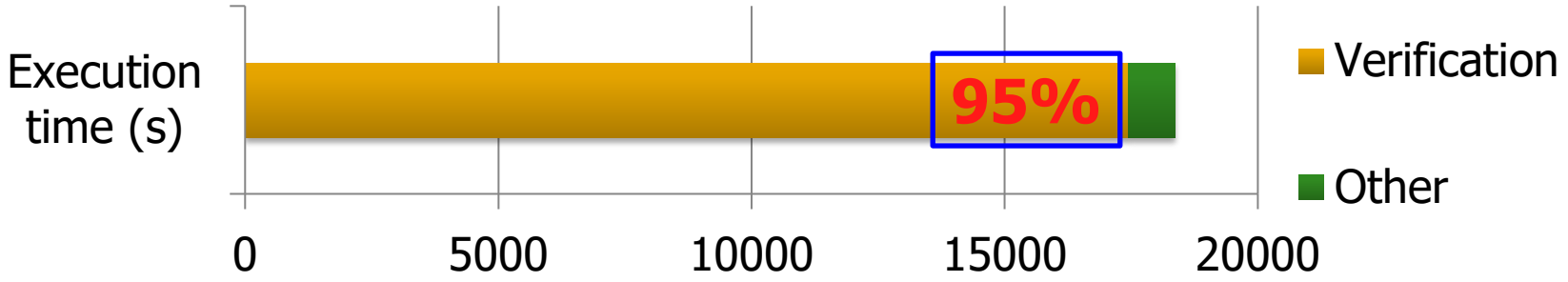
Personalized copy number and segmental duplication maps using next-generation sequencing

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

Overarching Key Idea

Filter fast before you align

Minimize costly
edit distance computations

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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

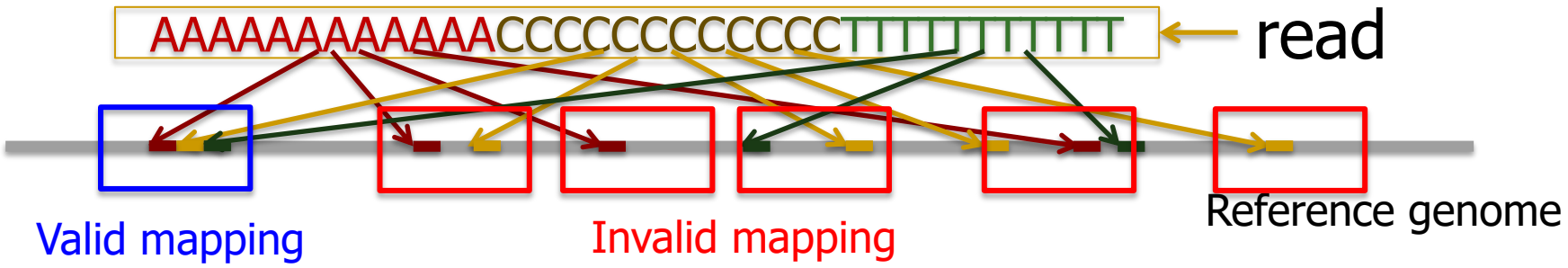
FastHASH Mechanisms [Xin+, BMC Genomics 2013]

- **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

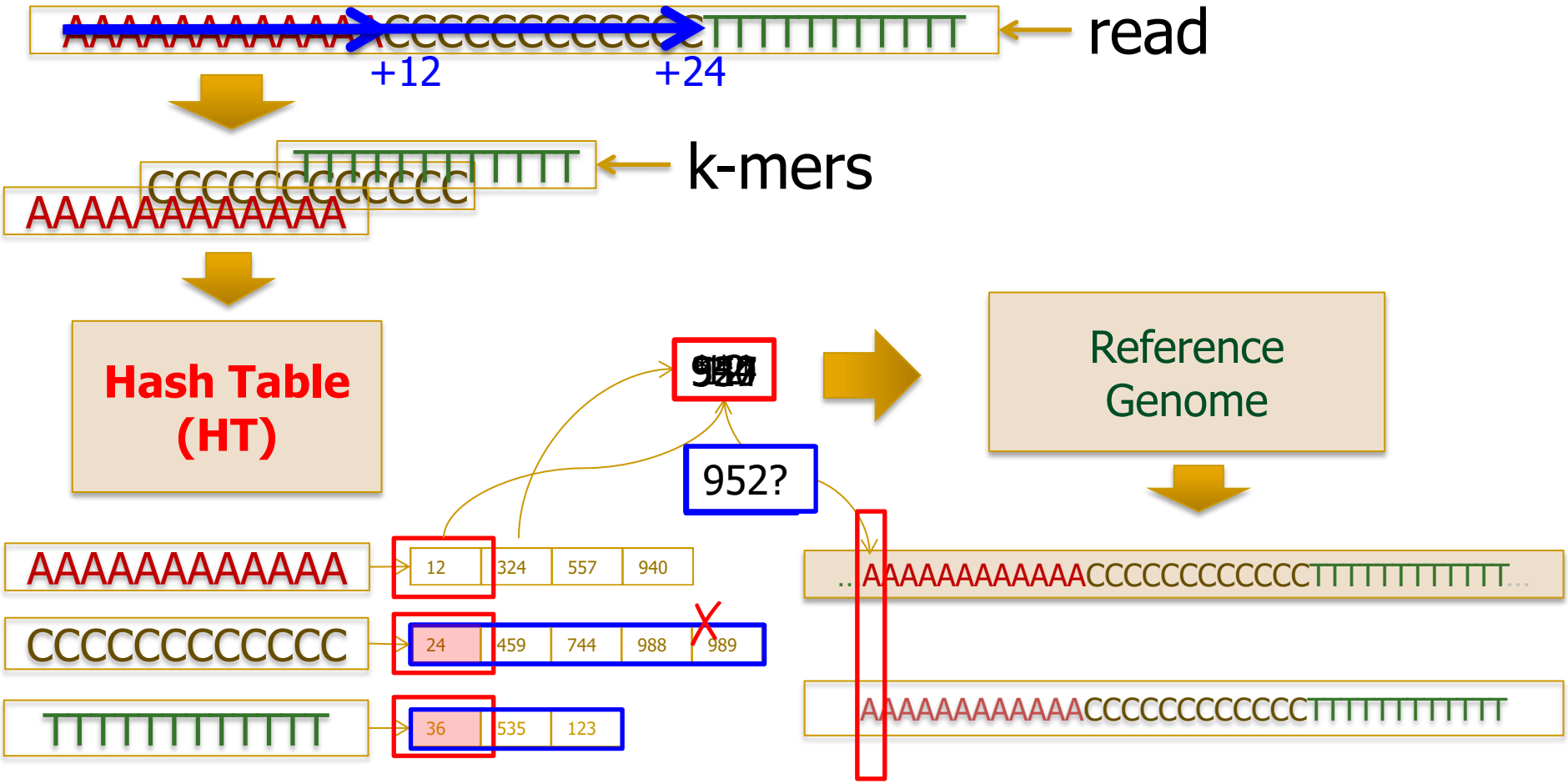
Adjacency Filtering (AF)

- **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)



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Cheap K-mer Selection (CKS)

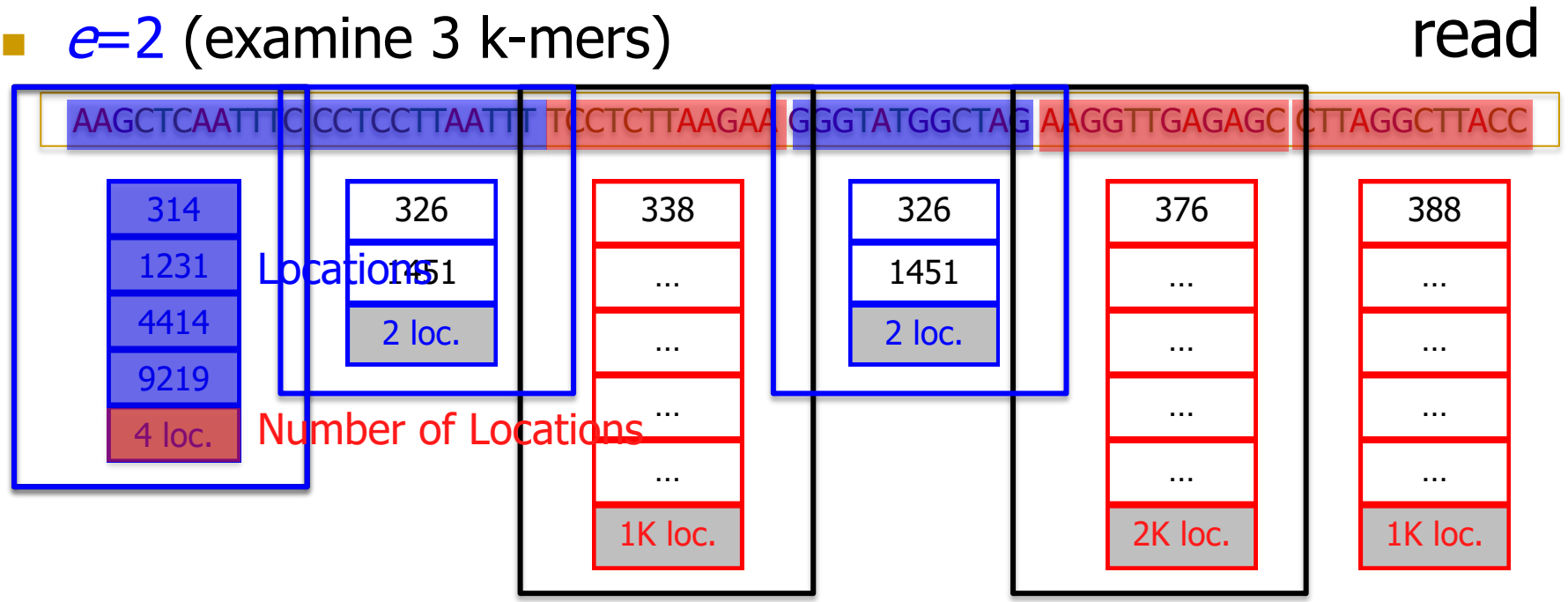
- **Goal:** Reduce the number of potential mappings

- **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

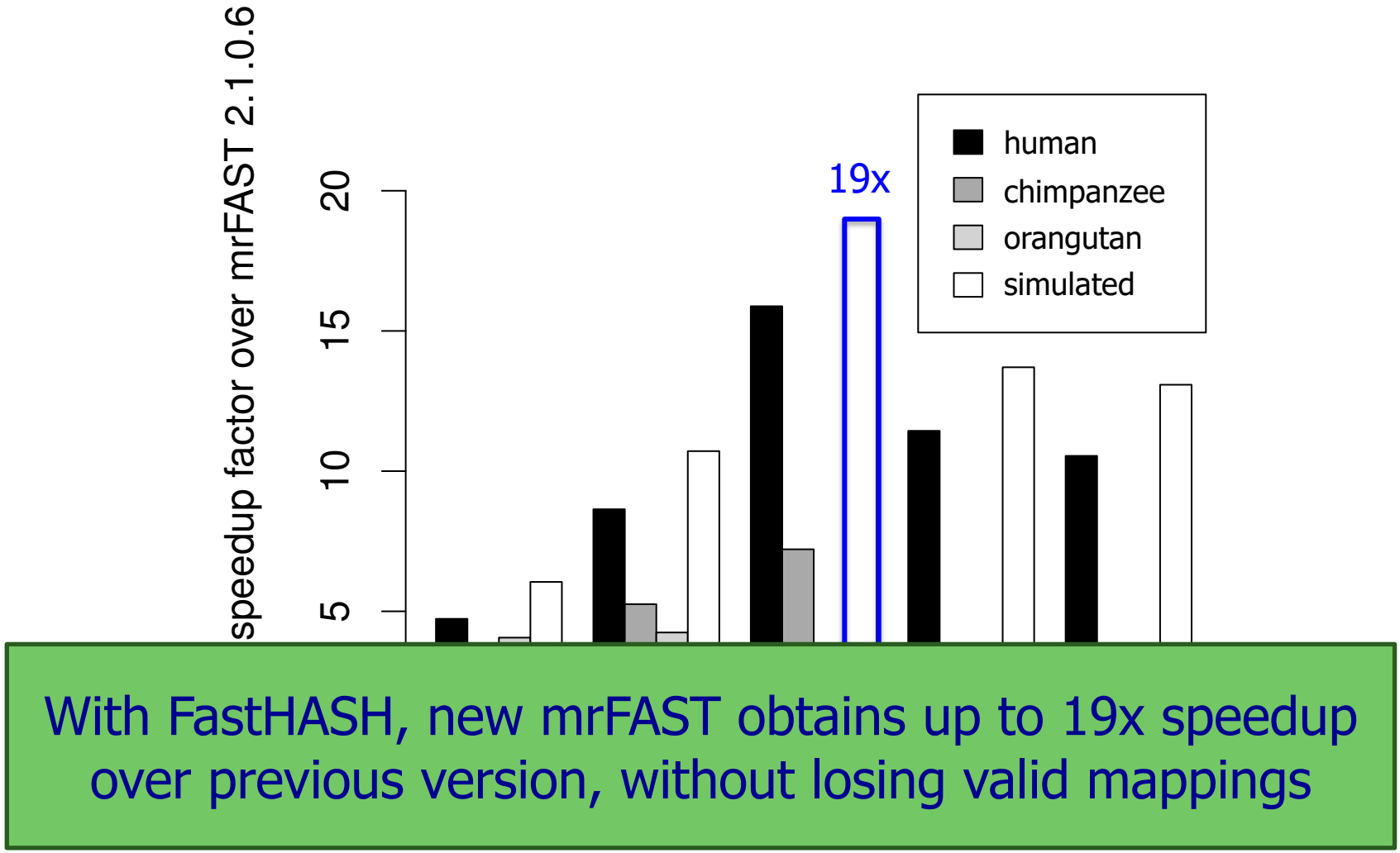
FastHASH verifies only:

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

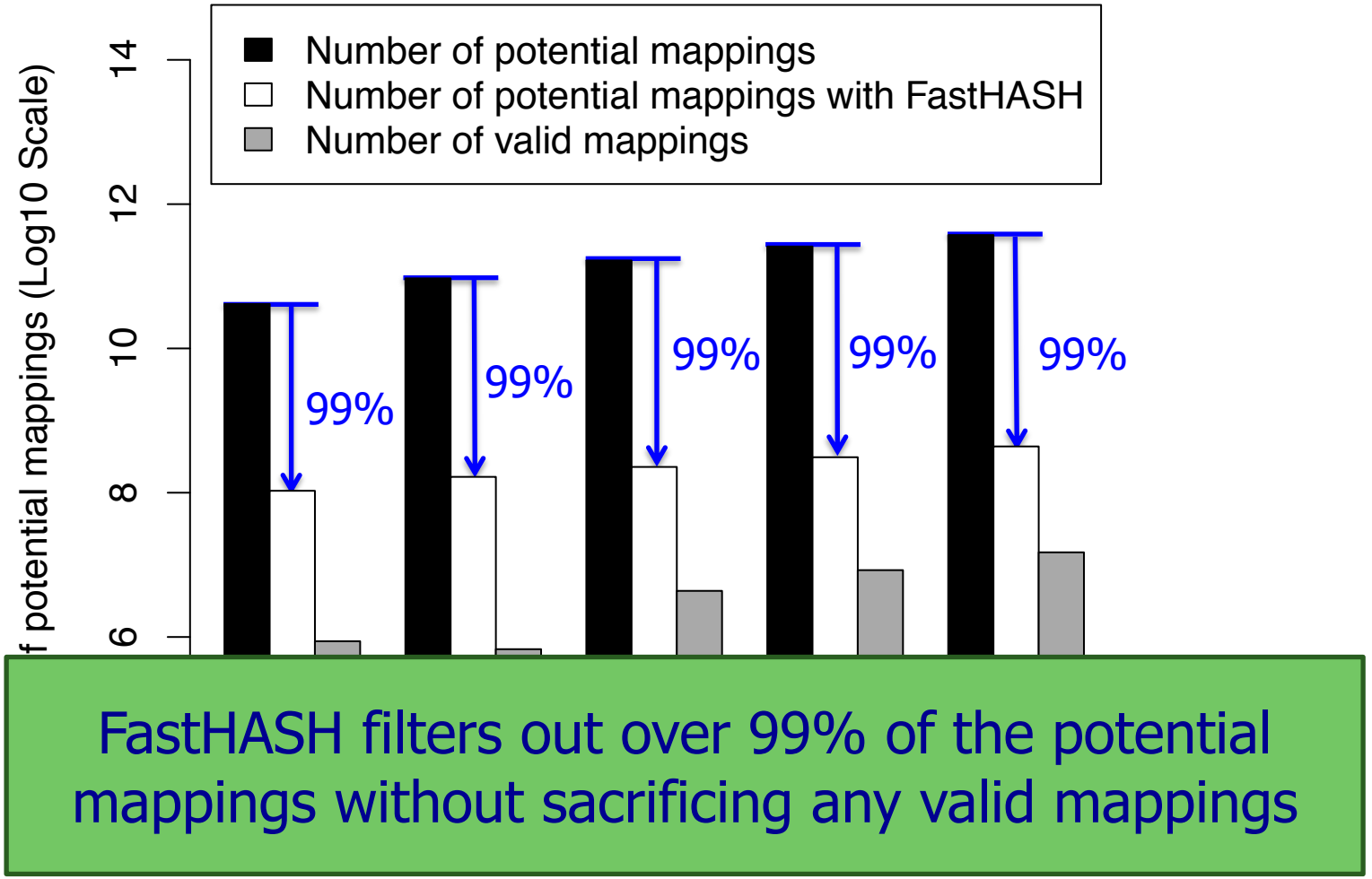


With FastHASH, new mrFAST obtains up to 19x speedup over previous version, without losing valid mappings

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

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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

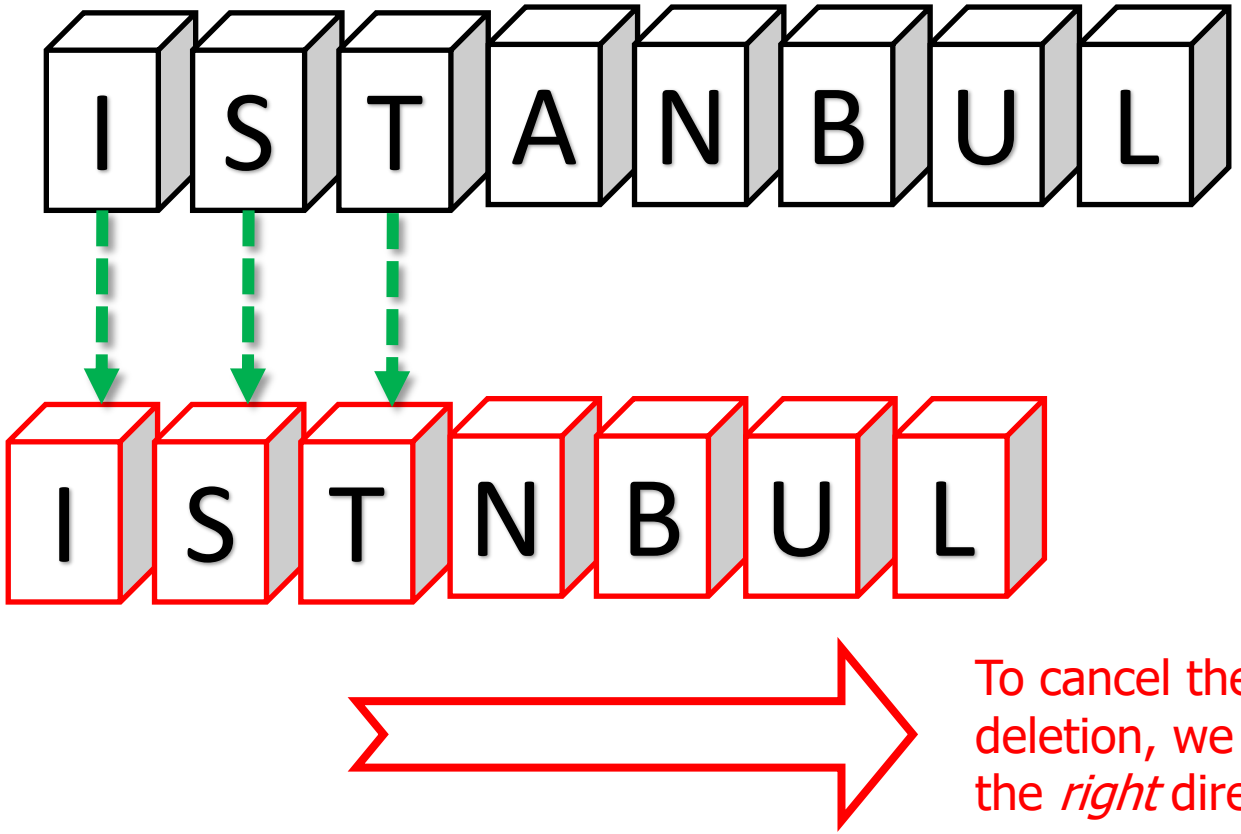
- Key observation:
  - If two strings differ by *E* edits, then every bp match can be aligned in at most *2E* shifts (of one of the strings).
    - Insight: Shifting a string by one "corrects" for one "error"

- Key idea:
  - Compute "Shifted Hamming Distance": AND of 2E Hamming Distances of two strings, to filter out invalid mappings
    - Uses bit-parallel operations that nicely map to SIMD instructions

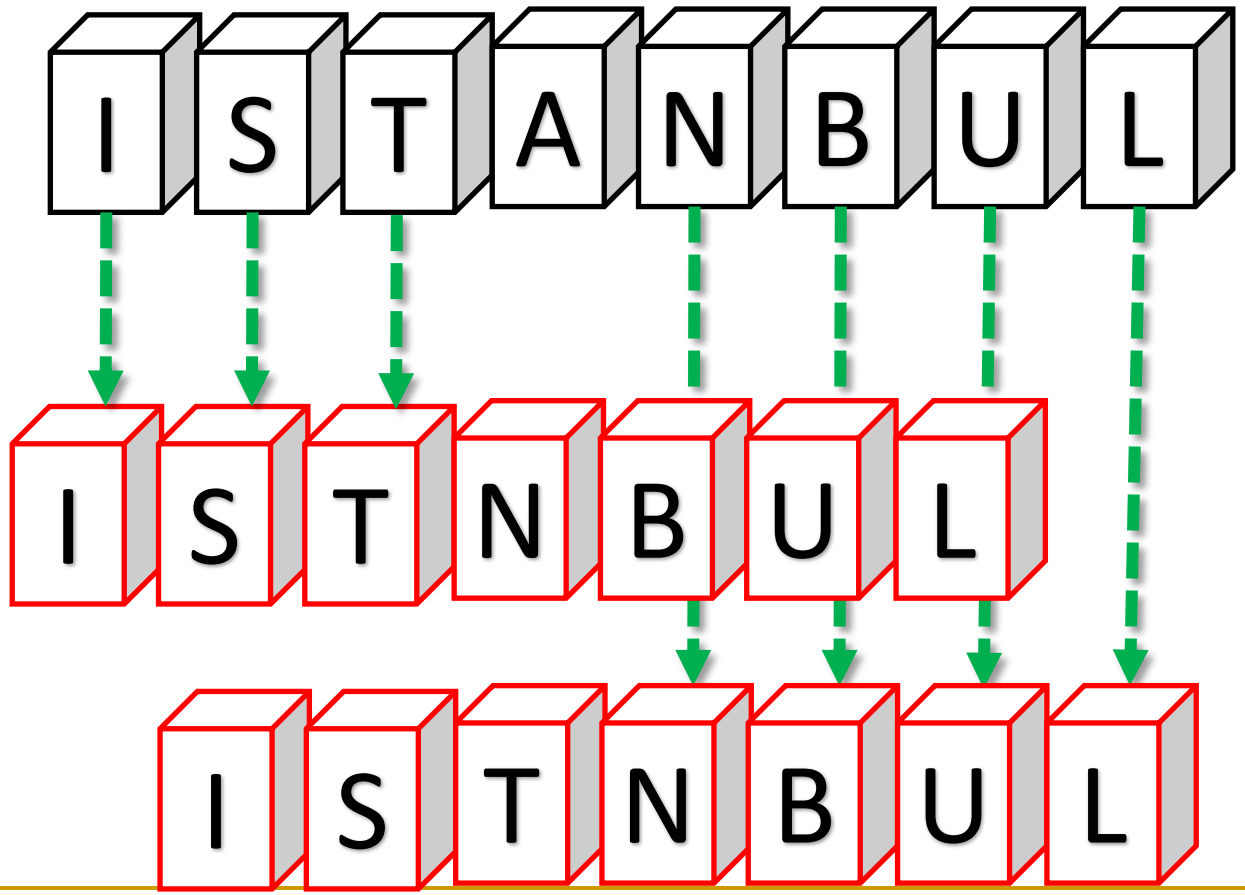
- Key result:
  - SHD is 3x faster than SeqAn (the best implementation of Gene Myers' bit-vector algorithm), with only a 7% false positive rate
  - The fastest CPU-based filtering (pre-alignment) mechanism

Insight: Shifting a String Helps Similarity Search

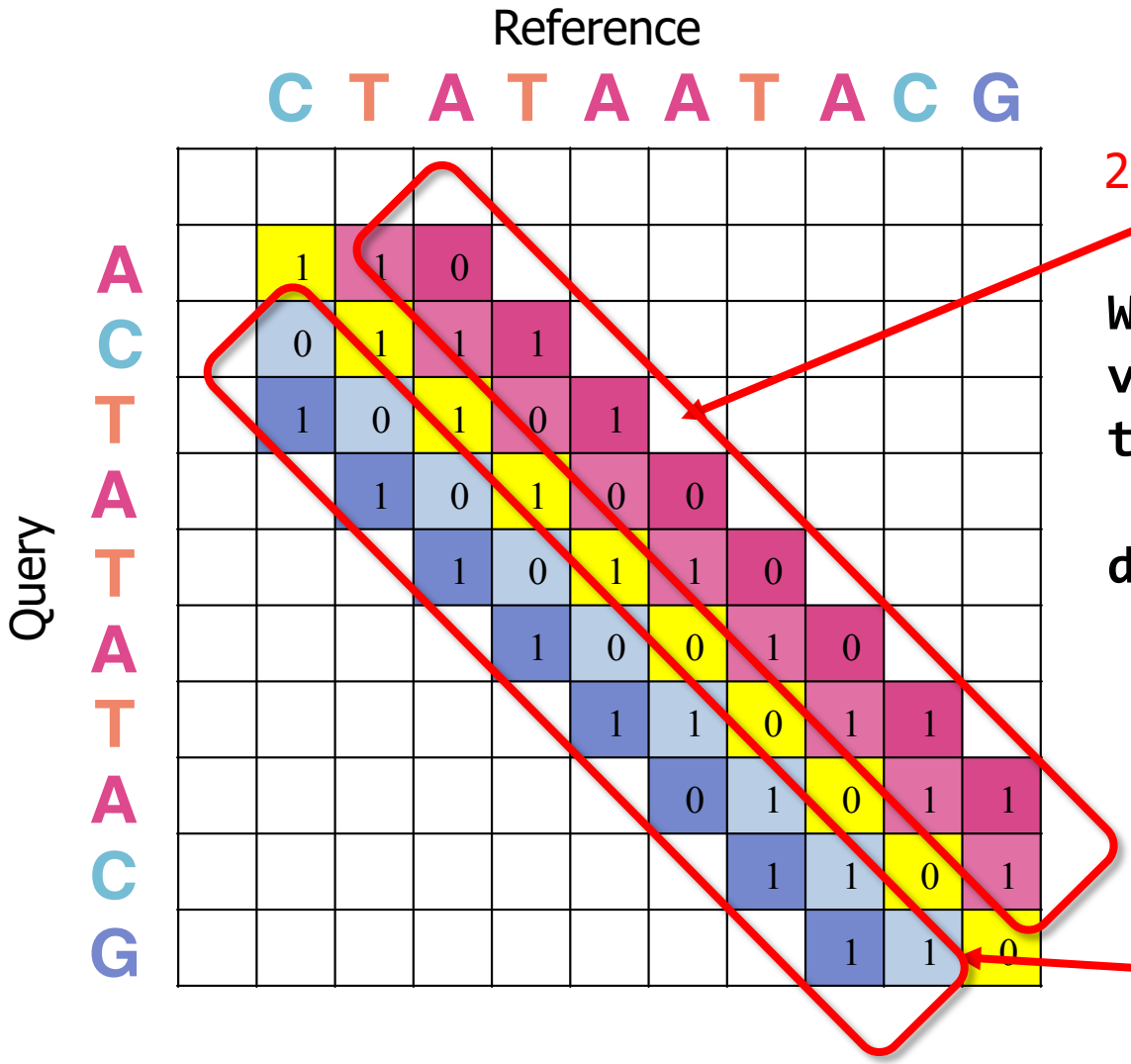
3 matches 5 mismatches



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 :0000000000100000000000011111110111100011101101011011111111100010000011110110100101
    1-Deletion Mask :1111111111100111110111110000000000000000000000000000000000000000000011000000000000000
    2-Deletion Mask :0000000010110111001111111111111011110001110110101101111111100010001001110110100101
    3-Deletion Mask :1111111111101110110011011101110110001001001111111111111100101100110010110111011101111
    1-Insertion Mask :1111111111101111101111110111011000100100111111111111100101100110001010111011101110
    2-Insertion Mask :0000001001111100111111111001000110101010011010111111111111011100111111100011101100
    3-Insertion Mask :1111111101110110011000111111111010110111111001100101110111111111011101111010111001000

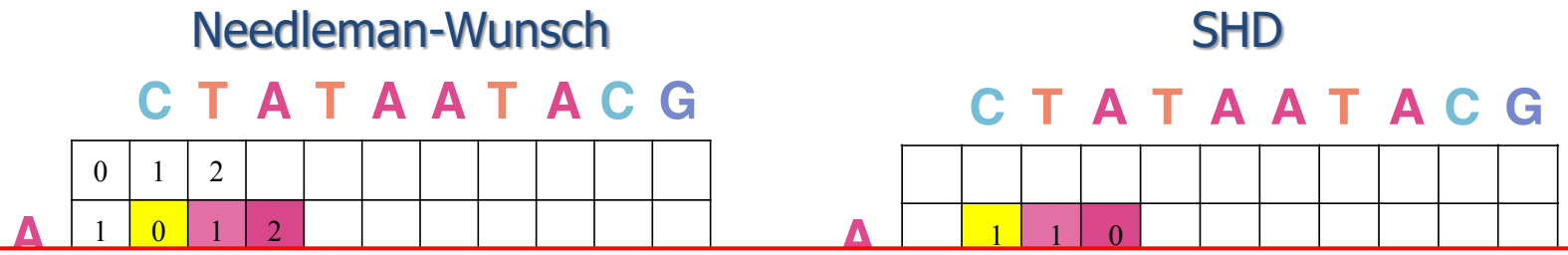
                                                --- Masks after amendment ---

          Hamming Mask :0000000000100000000000011111111111100011111111011111111111100010000011111111111111111
    1-Deletion Mask :1111111111111111111111110000000000000000000000000000000000000000000011000000000000000
    2-Deletion Mask :0000000011111111111111111111111111111100011111111111111111111100010001111111111111110
    3-Deletion Mask :1111111111111111111111111111111111111000111111111111111111111111111111111111111111111
    1-Insertion Mask :1111111111111111111111111111111111000111111111111111111111111111111000111111111111110
    2-Insertion Mask :0000001111111111111111111111000111111111111111111111111111111111111111000111111100
    3-Insertion Mask :1111111111111111111000111111111111111111111111111111111111111111111111111111111111000

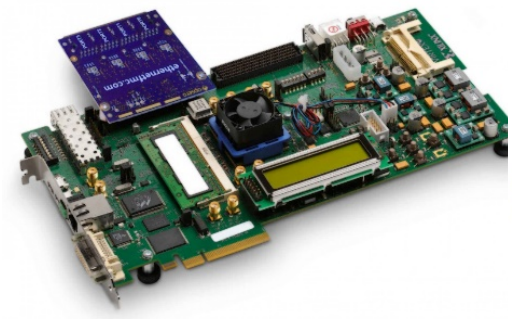
             AND Mask :0000000000100000000000010000000000000000000000000000000000000000000010000000000000000

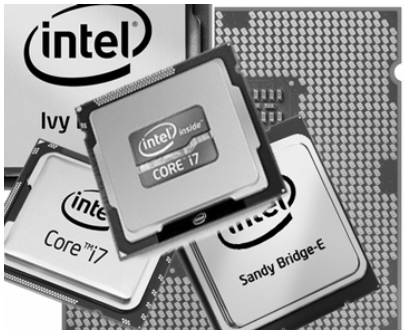
Needleman-Wunsch
        Alignment :GAGAGAGATATTTAGTGTTGCAG-CACTACAACACAAAAGAGGACCAACTTACGTGTCTAAAAGGGGGAACATTGTTGGGCCGG
                   |||||||||| ||||||||||| |||||||||||||||||||||||||||||||||||||::|||||||||||||||
                   GAGAGAGATAGTTAGTGTTGCAGCCACTACAACACAAAAGAGGACCAACTTACGTGTCTAAAAGGGGAGACATTGTTGGGCCGG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

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

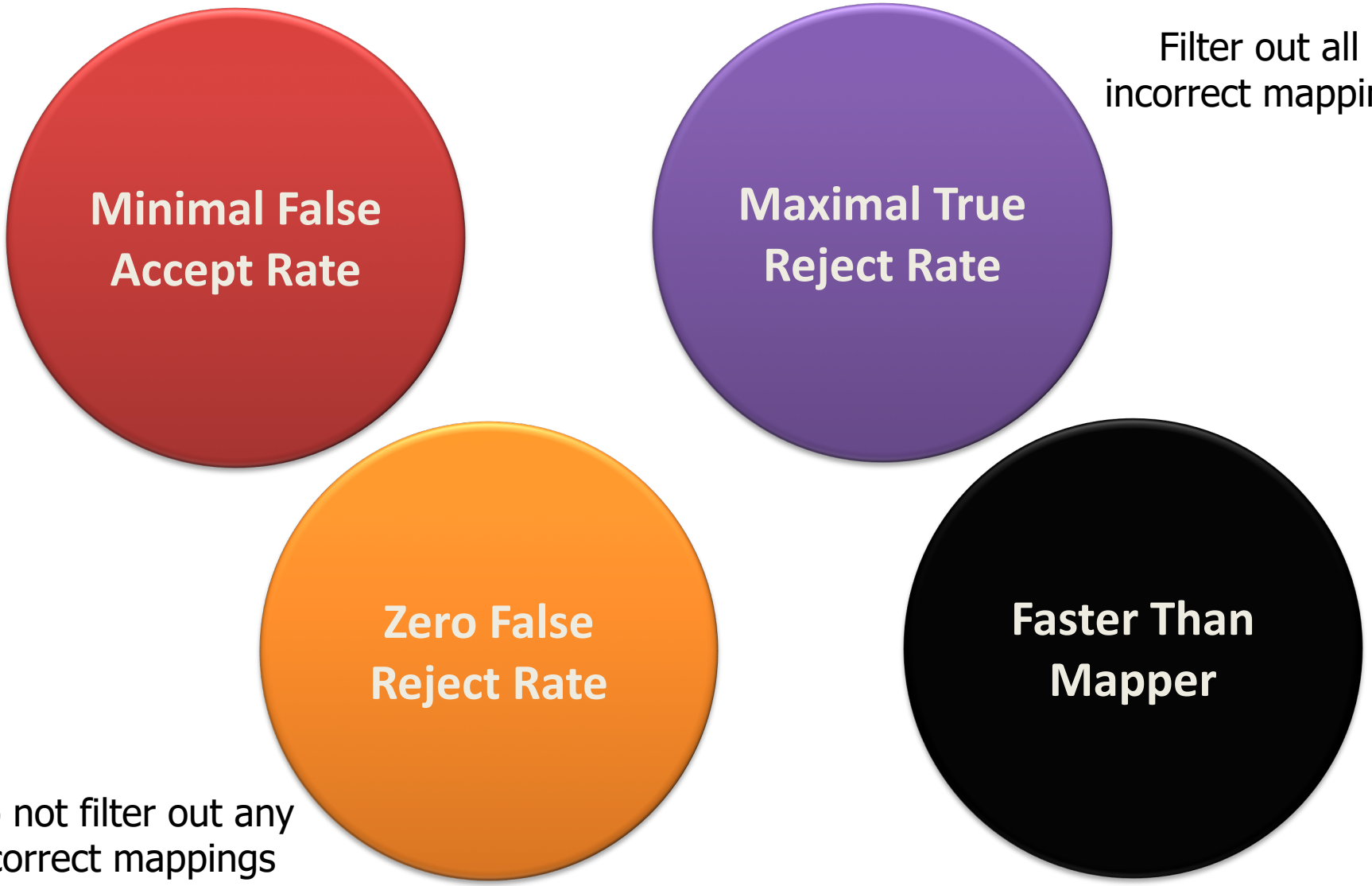
- **Alignment** is expensive
  - We need to align millions to billions of reads

- M[illegible] f[illegible]
  - [illegible]
  - [illegible]
  - [illegible]
  - [illegible] 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)

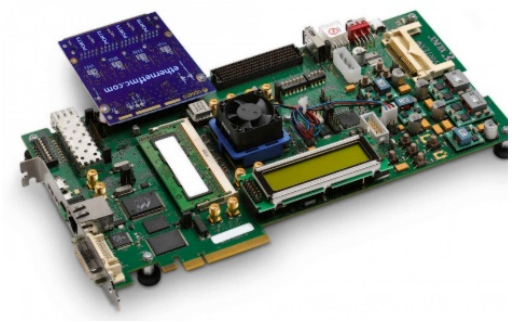
Needleman-Wunsch

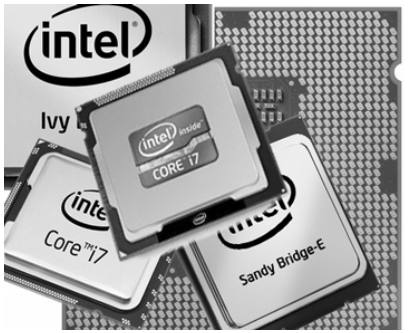
		C	T	A	T	A	A	T	A	C	G
	0	1	2								
A	1	0	1	2							

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

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

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    3-Deletion Mask :1111111111101110110011011101110110001001001111111111111100101100110010110111011101111
  1-Insertion Mask :1111111111101111101111110111011000100100111111111111100101100110001010111011101111110
  2-Insertion Mask :0000001001111100111111111001000110101010011010111111111111011100111111100011110110 0
  3-Insertion Mask :1111111101110110011000111111111010110111111001100101110111111111011101111010111001000

                                                --- Masks after amendment ---

          Hamming Mask :0000000000100000000000011111111111100011111111011111111111100010000011111111111111111
    1-Deletion Mask :1111111111111111111111110000000000000000000000000000000000000000000011000000000000000
    2-Deletion Mask :0000000011111111111111111111111111111100011111111111111111111100010001111111111111110
    3-Deletion Mask :1111111111111111111111111111111111111000111111111111111111111111111111111111111111111
  1-Insertion Mask :1111111111111111111111111111111111000111111111111111111111111111111000111111111111110
  2-Insertion Mask :0000001111111111111111111111000111111111111111111111111111111111111111000111111100
  3-Insertion Mask :1111111111111111111000111111111111111111111111111111111111111111111111111111111000

           AND Mask :0000000000100000000000010000000000000000000000000000000000000000000100000000000000

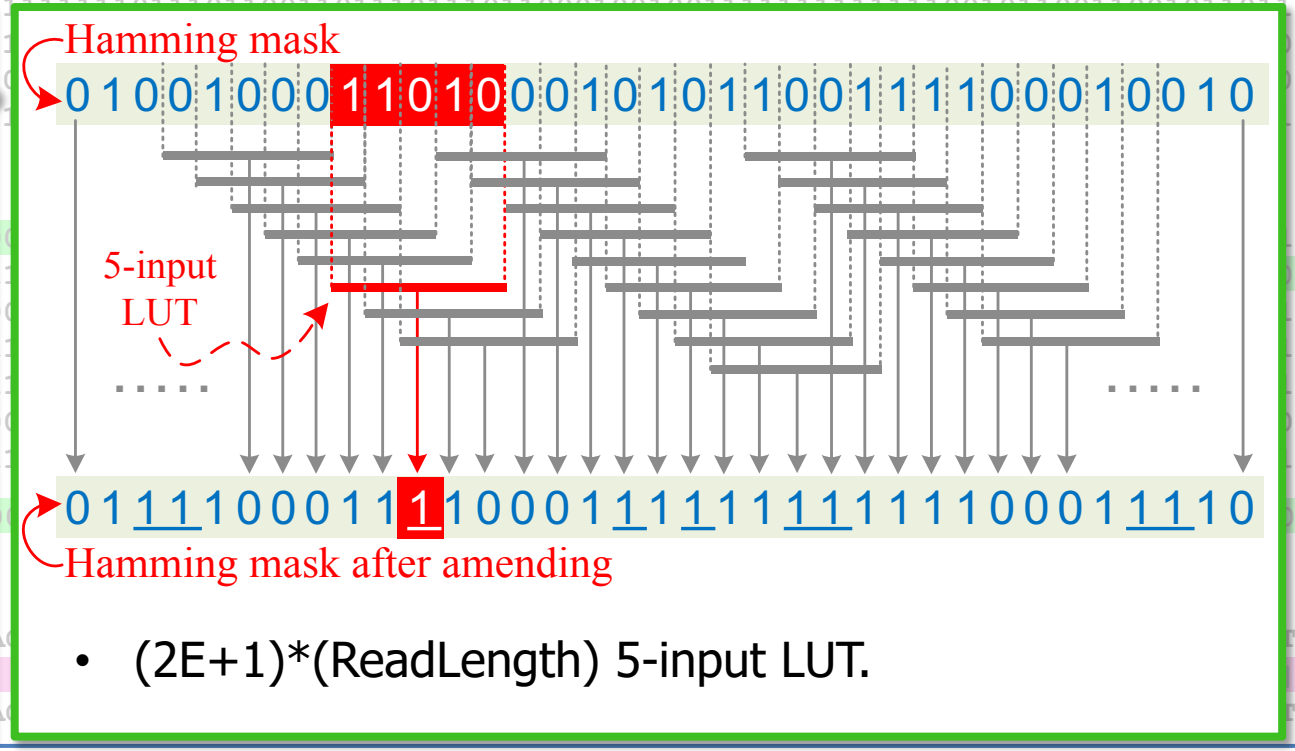
                    .GAGAGAGATATTTAGTGTTGCAG-CACTACAACACAAAAGAGGACCAACTTACGTGTCTAAAAGGGGGAACATTGTTGGGCCGG
Needleman-Wunsch
       Alignment :||||||||||| |||||||||||| ||||||||||||||||||||||||||||||||||||||||||::|||||||||||||||
                    .GAGAGAGATAGTTAGTGTTGCAGCCACTACAACACAAAAGAGGACCAACTTACGTGTCTAAAAGGGGAGACATTGTTGGGCCGG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

GateKeeper Walkthrough (cont'd)

Generate 2E+1 masks

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

Amend random zeros:
101 → 111 & 1001 → 1111



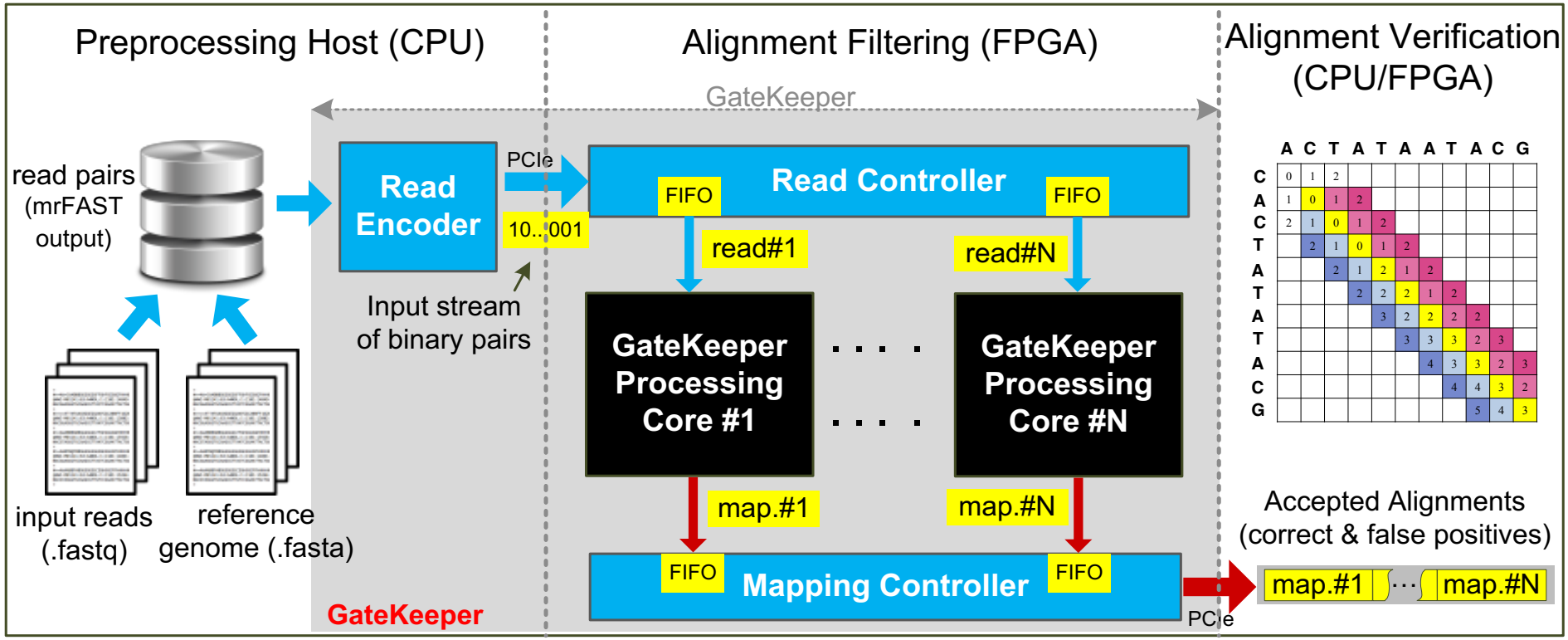
- (2E+1)*(ReadLength) 5-input LUT.

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

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

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.

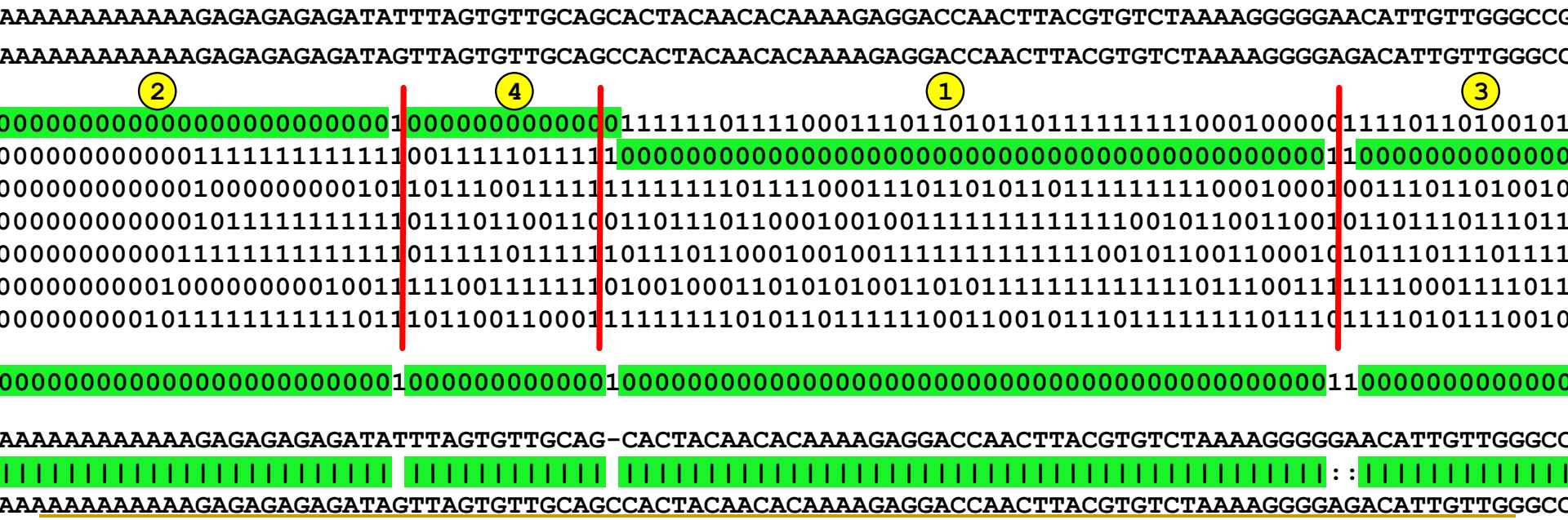
Sequence analysis

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

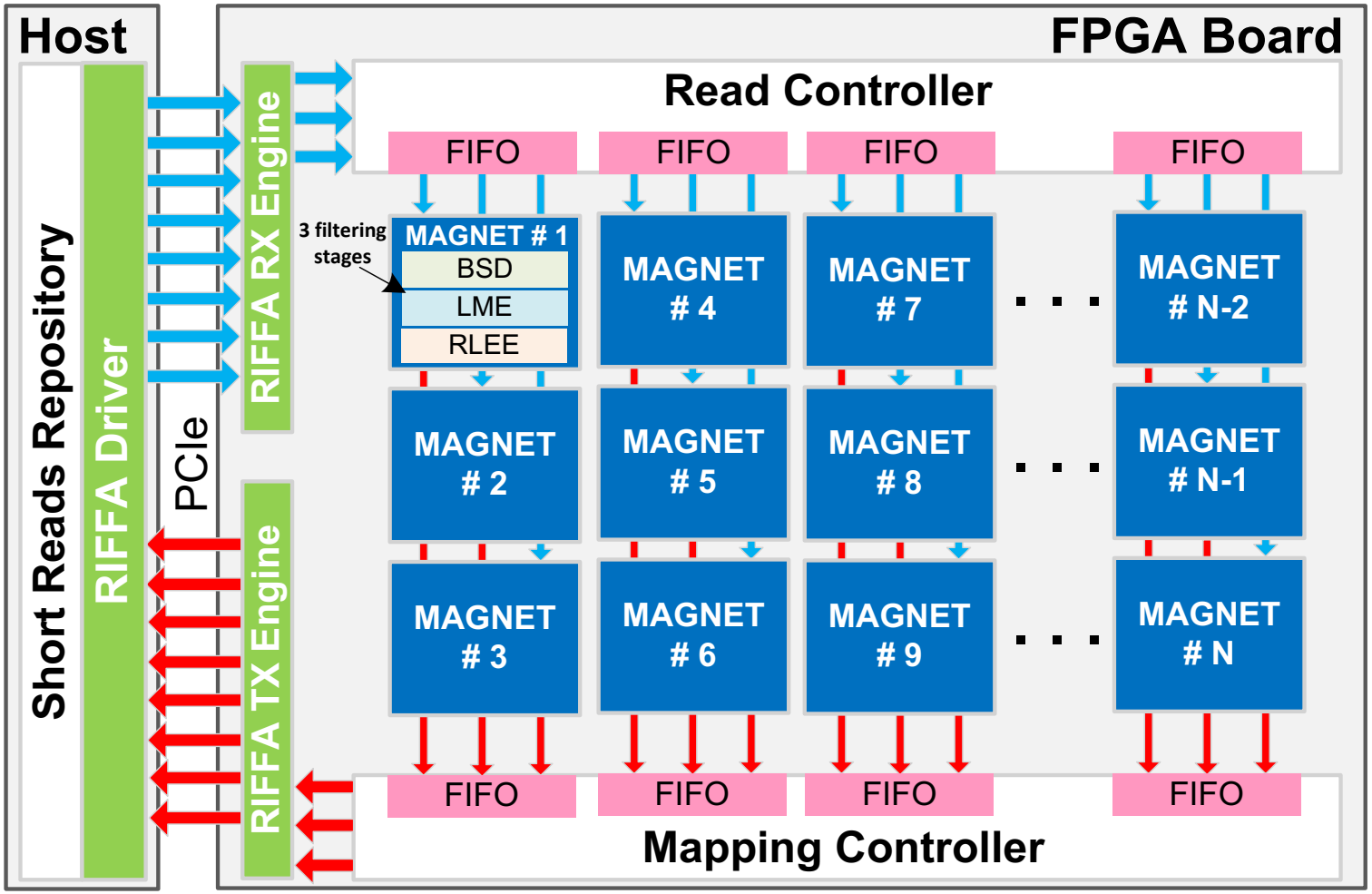
Mohammed Alser[1,*], Hasan Hassan[2], Hongyi Xin[3], Oğuz Ergin[2], Onur Mutlu[4,*], and Can Alkan[1,*]

MAGNET (AACBB 2018, TIR 2017)

- 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.



MAGNET Accelerator



Agenda

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  - State-of-the-art Read Mapper Design
- Algorithmic Acceleration
  - 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 Sequence (100 bp)

Matching…

Mismatch.

False Negative

Hash Table

Reference Genome

Filter

37 140
894 1203
1564

Read Mapping & Filtering in Memory

We need to design

mapping & filtering algorithms

that fit processing-in-memory

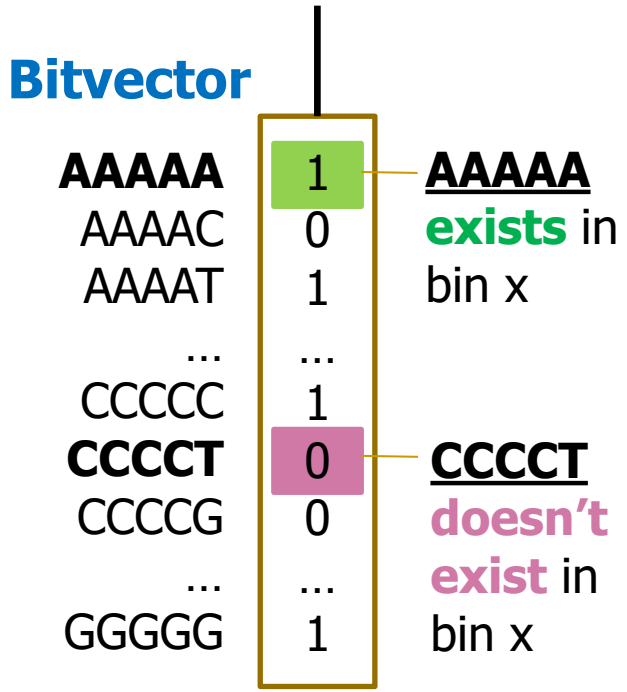
Our Proposal: GRIM-Filter

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

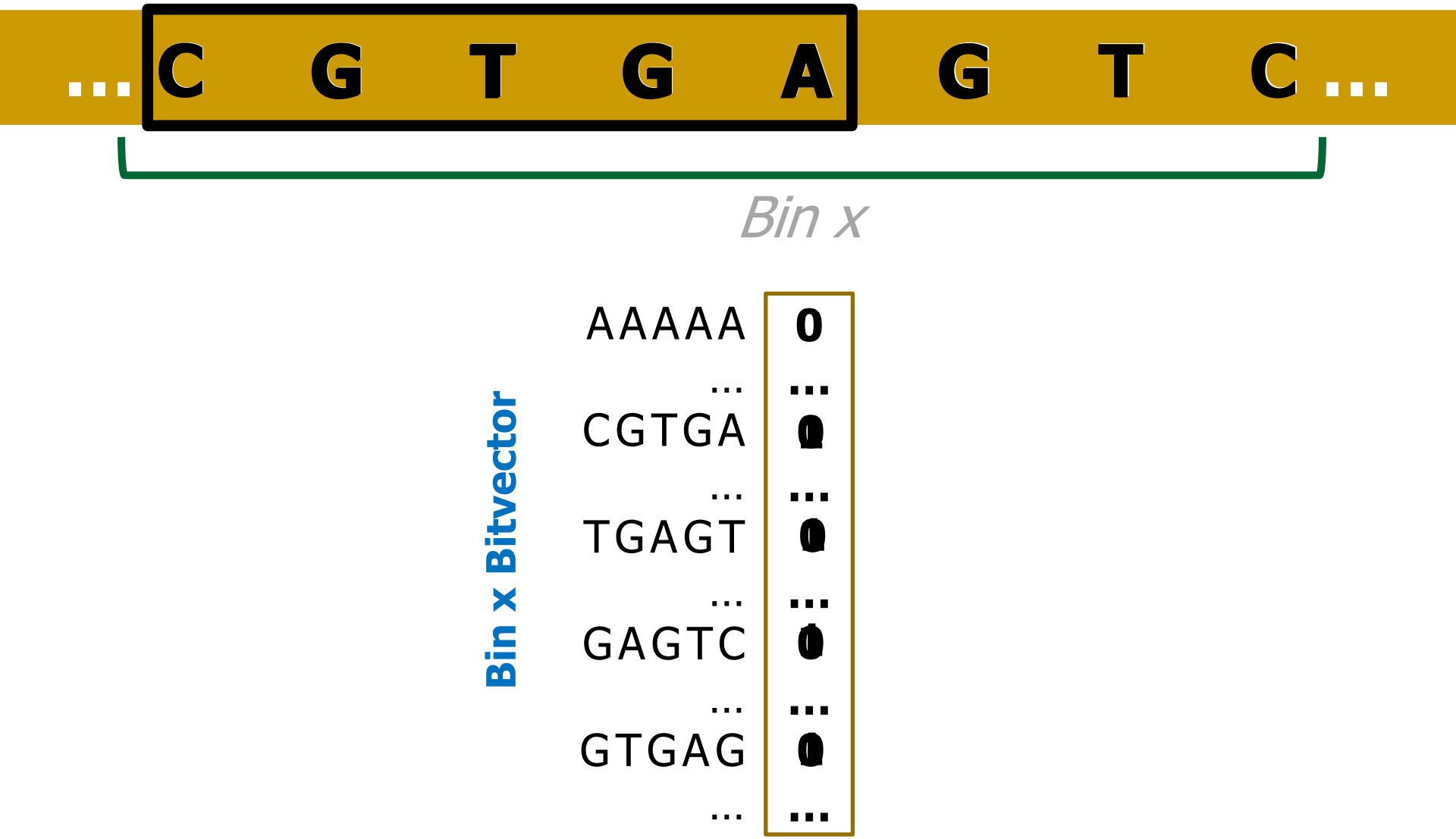
GRIM-Filter: Bins

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

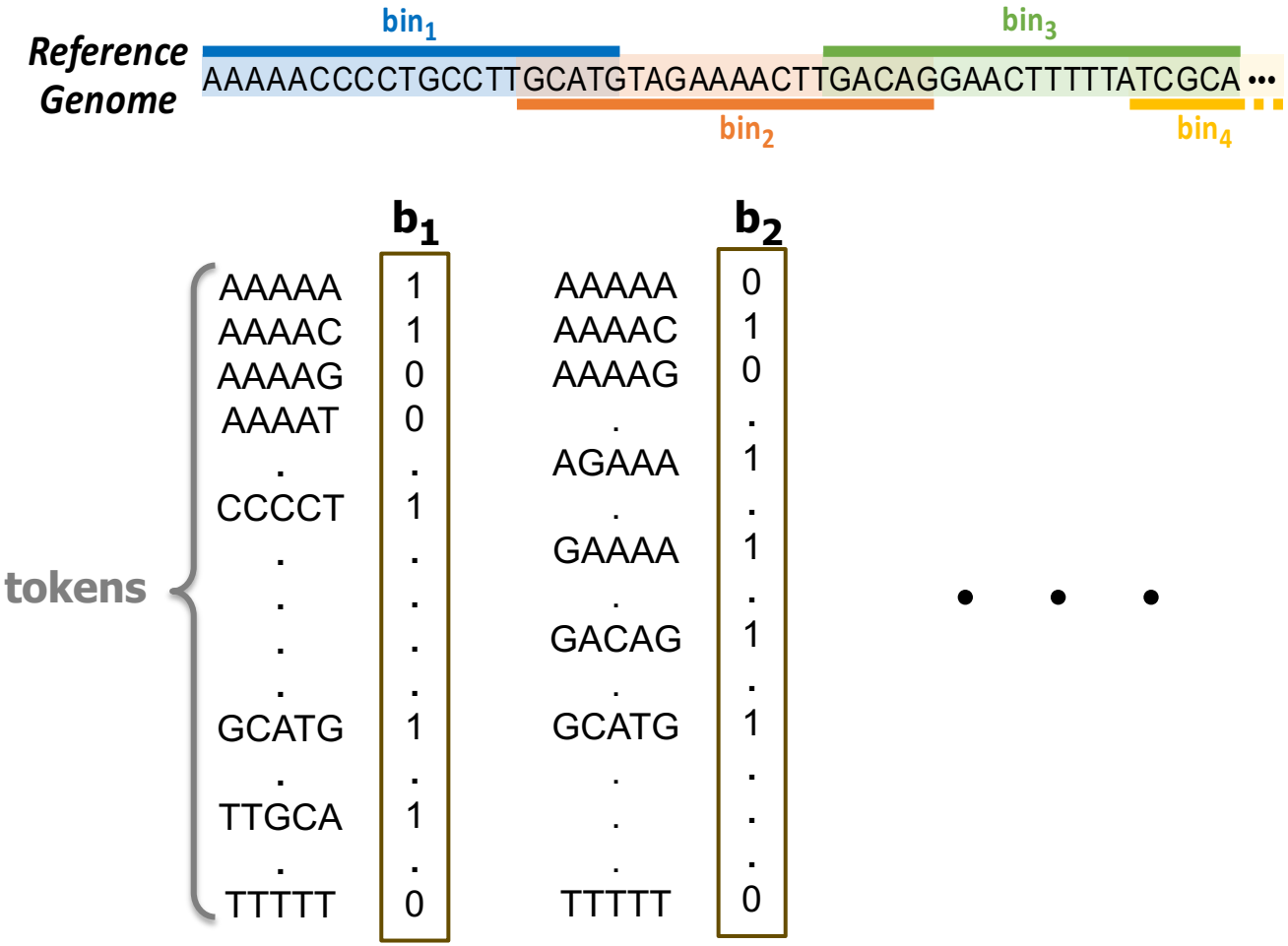
- Represent each bin with a **bitvector** that holds the occurrence of all permutations of a small string (**token**) in the bin
- To account for matches that straddle bins, we employ overlapping bins
  - A read will now always completely fall within a single bin



GRIM-Filter: Bitvectors



GRIM-Filter: Bitvectors



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

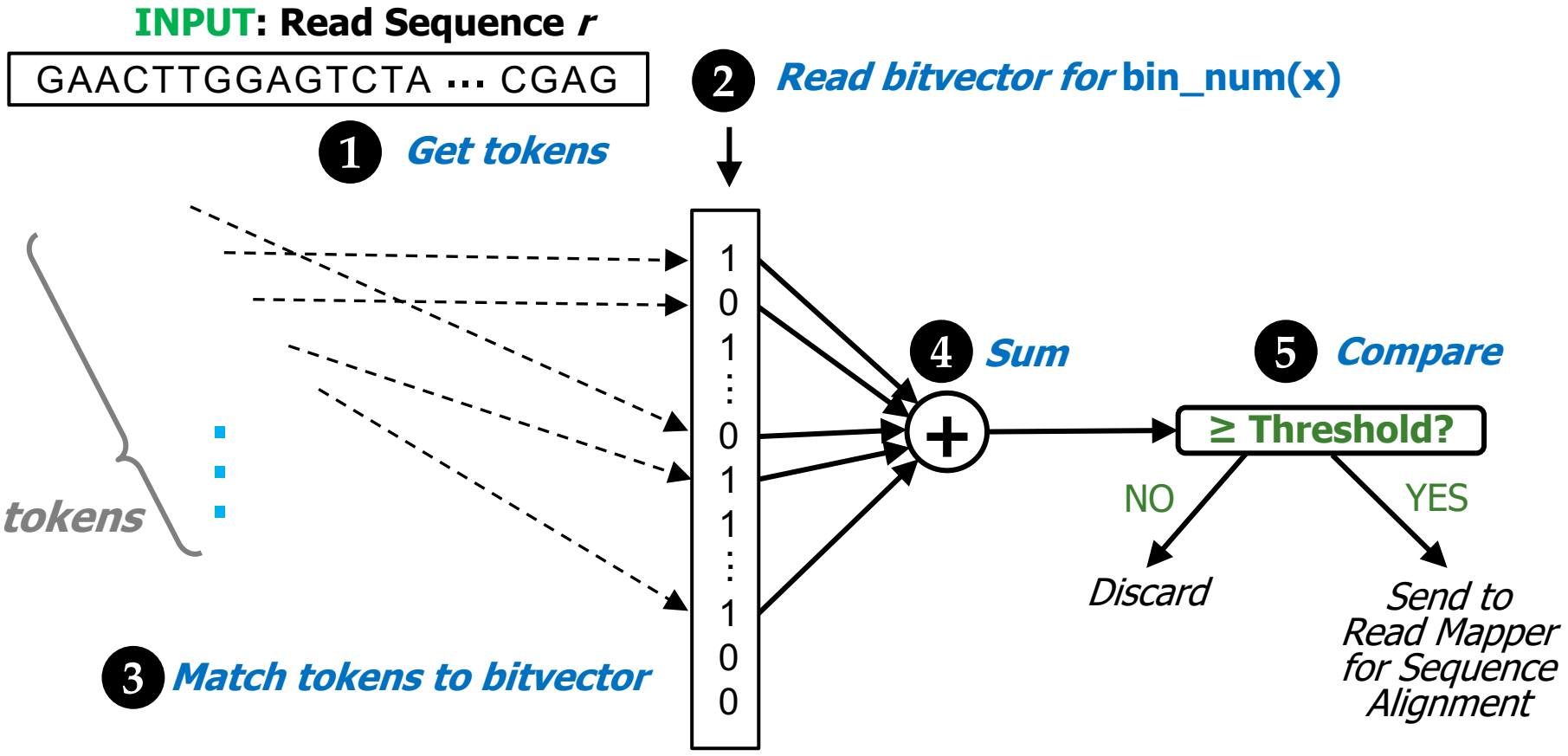
For **bin size** ~200, and **n** = 5, **memory footprint** ~3.8 GB

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
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Our Proposal: GRIM-Filter

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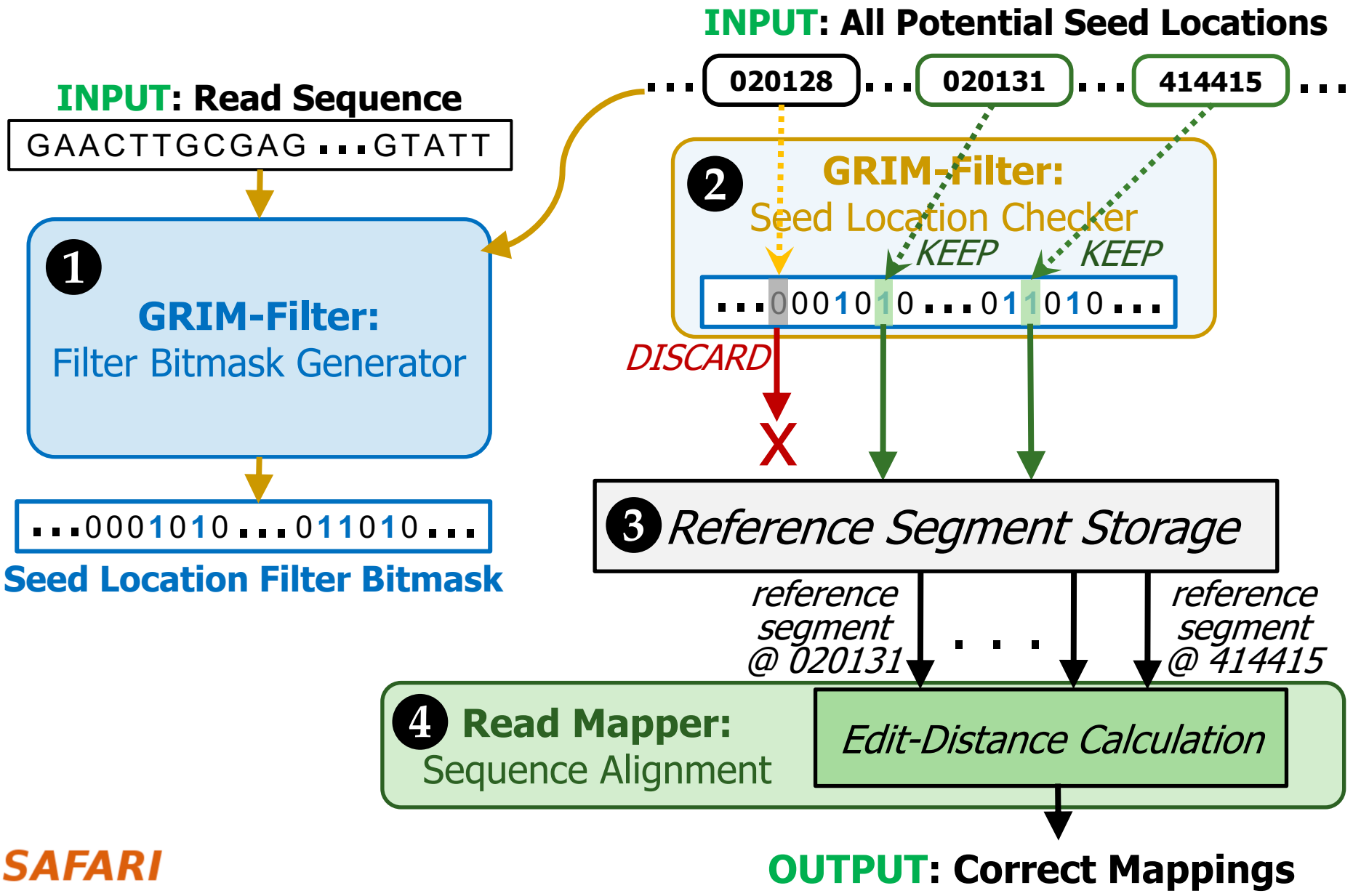
3. **Integrating GRIM-Filter into a Mapper**

Integrating GRIM-Filter into a Read Mapper



Key Properties of GRIM-Filter

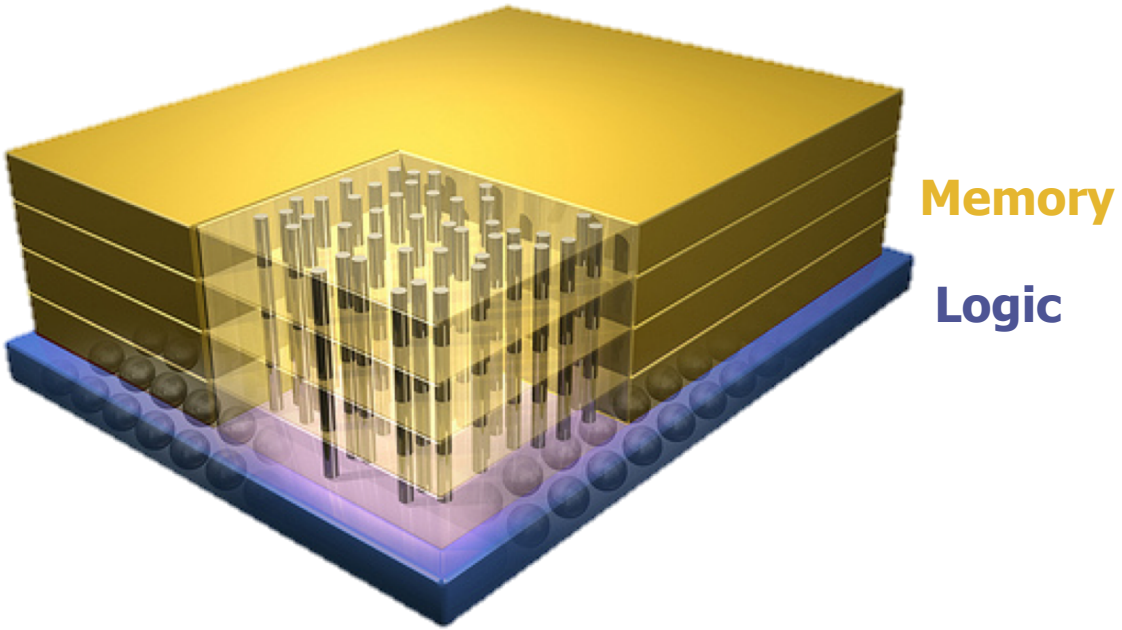
1. **Simple Operations**:
   - To check a given bin, find the **sum** of all bits corresponding to each token in the read
   - **Compare** against threshold to determine whether to align

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

Opportunity: 3D-Stacked Logic+Memory



Other "True 3D" technologies under development

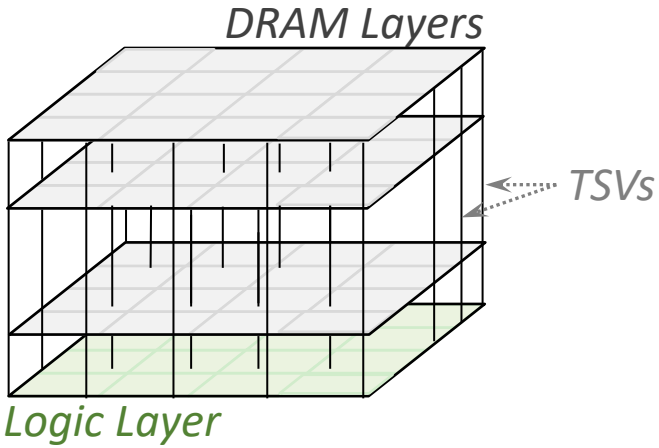
DRAM Landscape (circa 2015)

Segment	*DRAM Standards & Architectures*
Commodity	DDR3 (2007) [14]; DDR4 (2012) [18]
Low-Power	LPDDR3 (2012) [17]; LPDDR4 (2014) [20]
Graphics	GDDR5 (2009) [15]
Performance	eDRAM [28], [32]; RLDRAM3 (2011) [29]
3D-Stacked	WIO (2011) [16]; WIO2 (2014) [21]; MCDRAM (2015) [13]; HBM (2013) [19]; HMC1.0 (2013) [10]; HMC1.1 (2014) [11]
Academic	SBA/SSA (2010) [38]; Staged Reads (2012) [8]; RAIDR (2012) [27]; SALP (2012) [24]; TL-DRAM (2013) [26]; RowClone (2013) [37]; Half-DRAM (2014) [39]; Row-Buffer Decoupling (2014) [33]; SARP (2014) [6]; AL-DRAM (2015) [25]

Table 1. Landscape of DRAM-based memory

Kim+, "Ramulator: A Flexible and Extensible DRAM Simulator", IEEE CAL 2015.

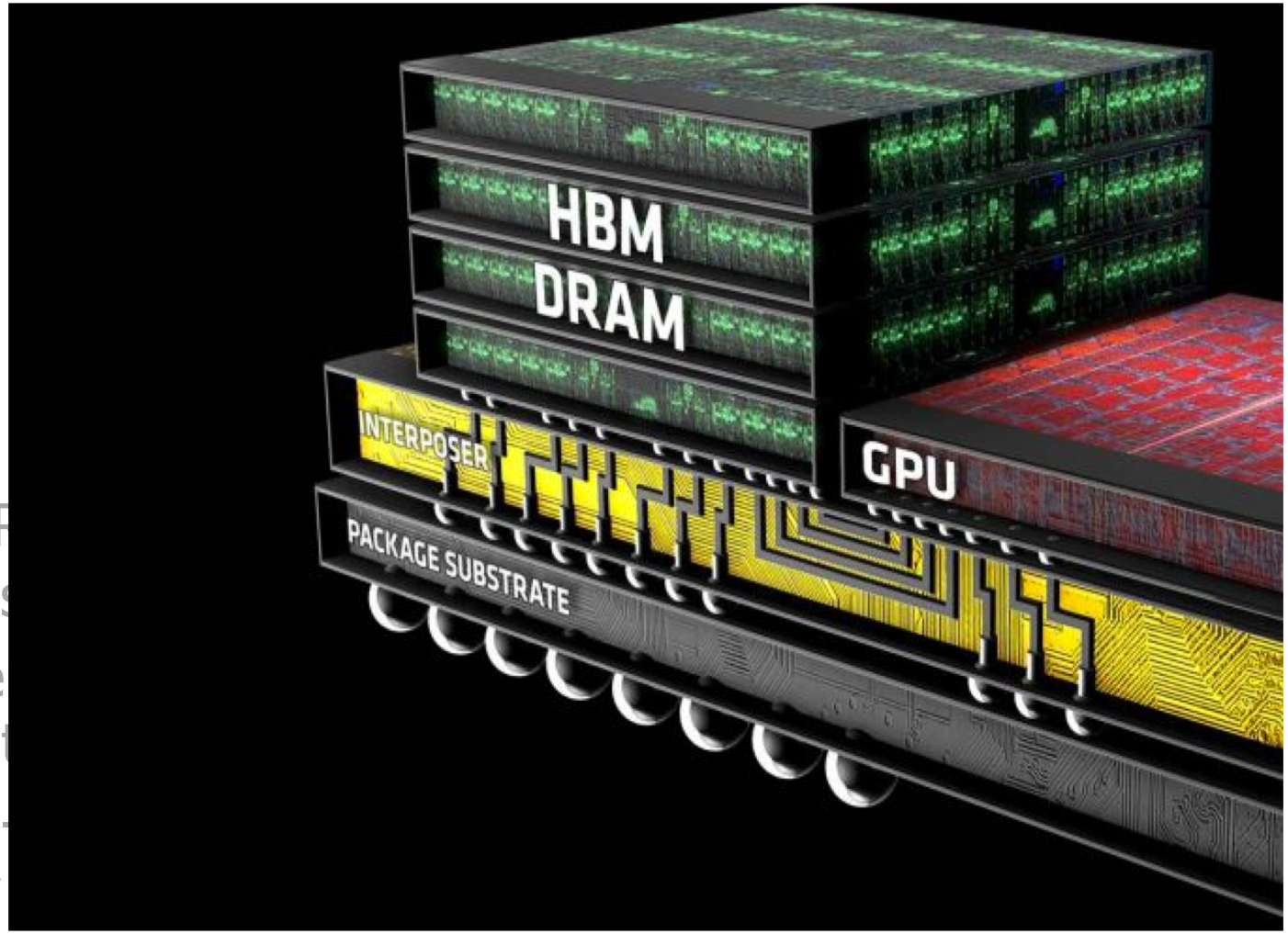
3D-Stacked Memory



- 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

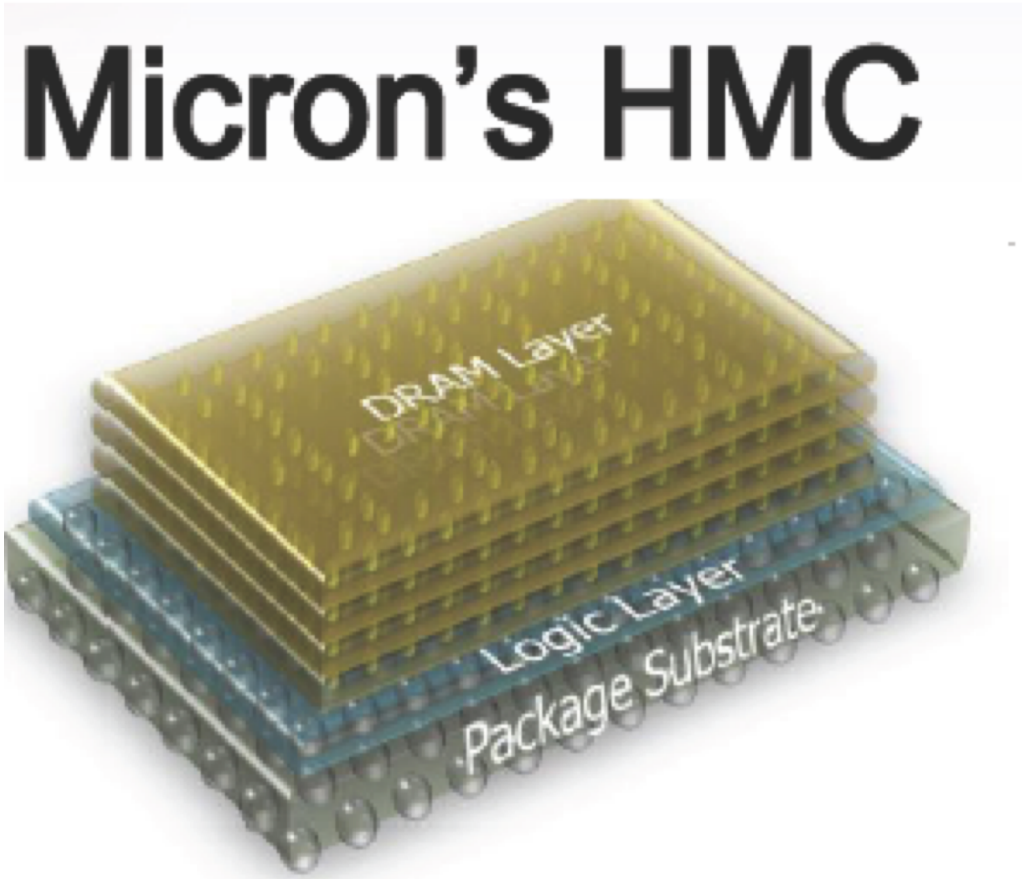
3D-Stacked Memory

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

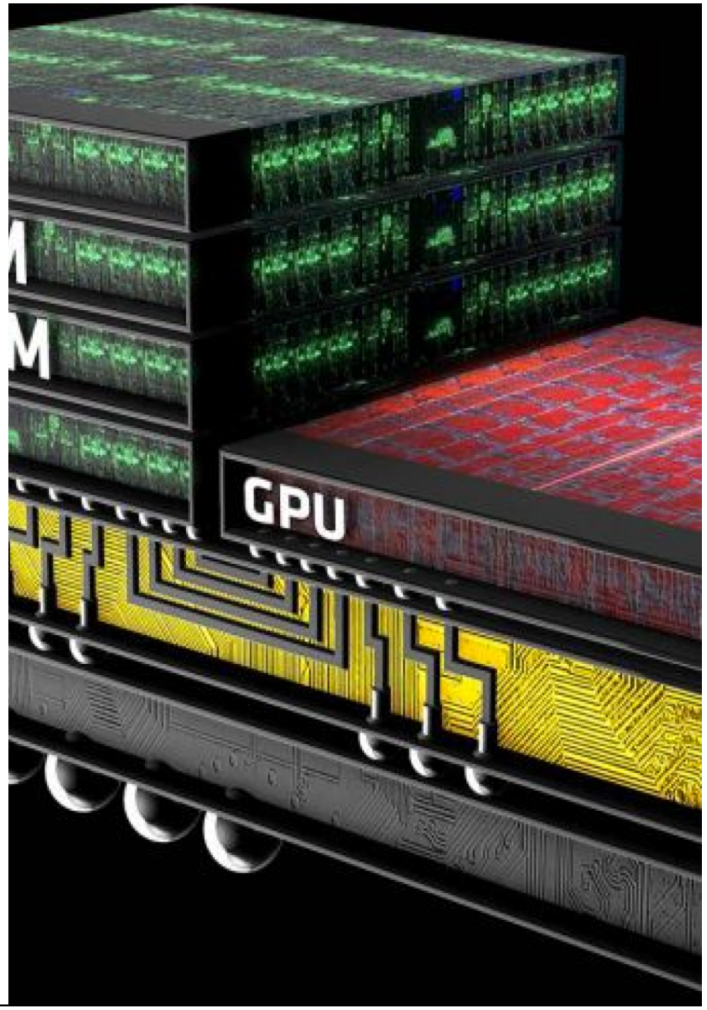


http://i1-news.softpedia-static.com/images/news2/Micron-and-Samsung-Join-Force-to-Create-Next-Gen-Hybrid-Memory-2.png

3D-Stacked Memory



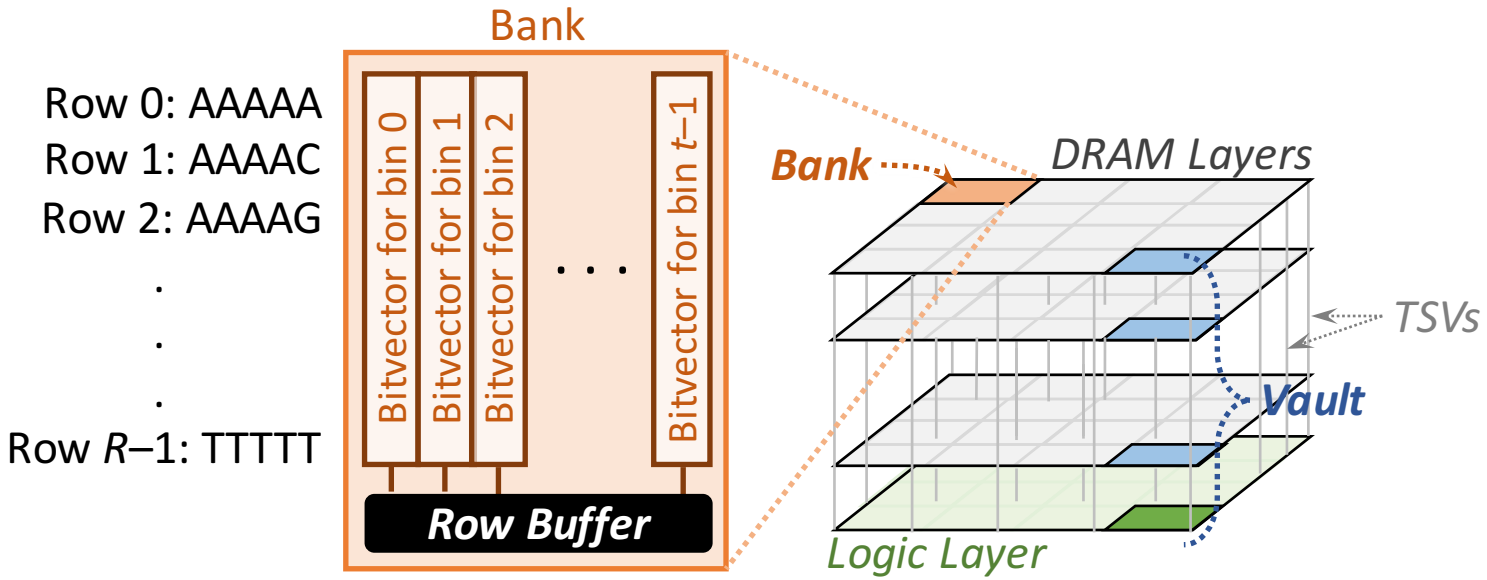
Micron has working demonstration components



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

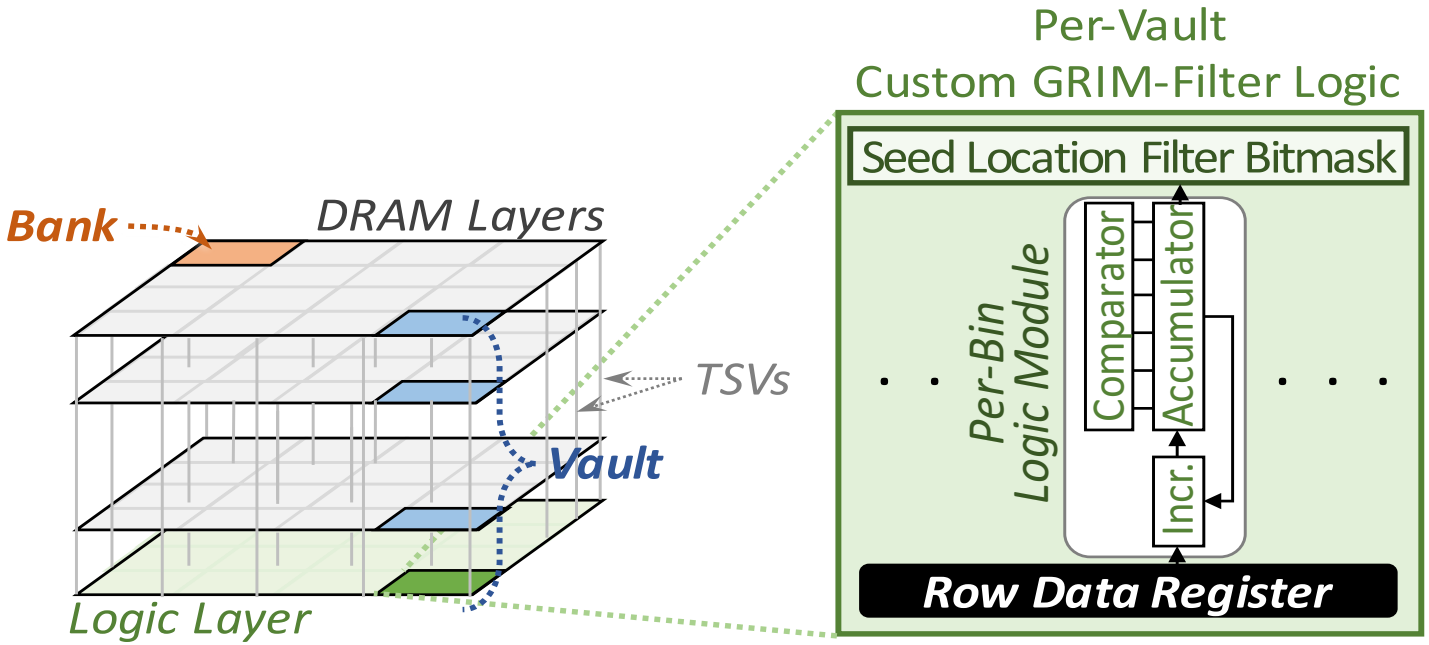
GRIM-Filter in 3D-Stacked DRAM



- 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



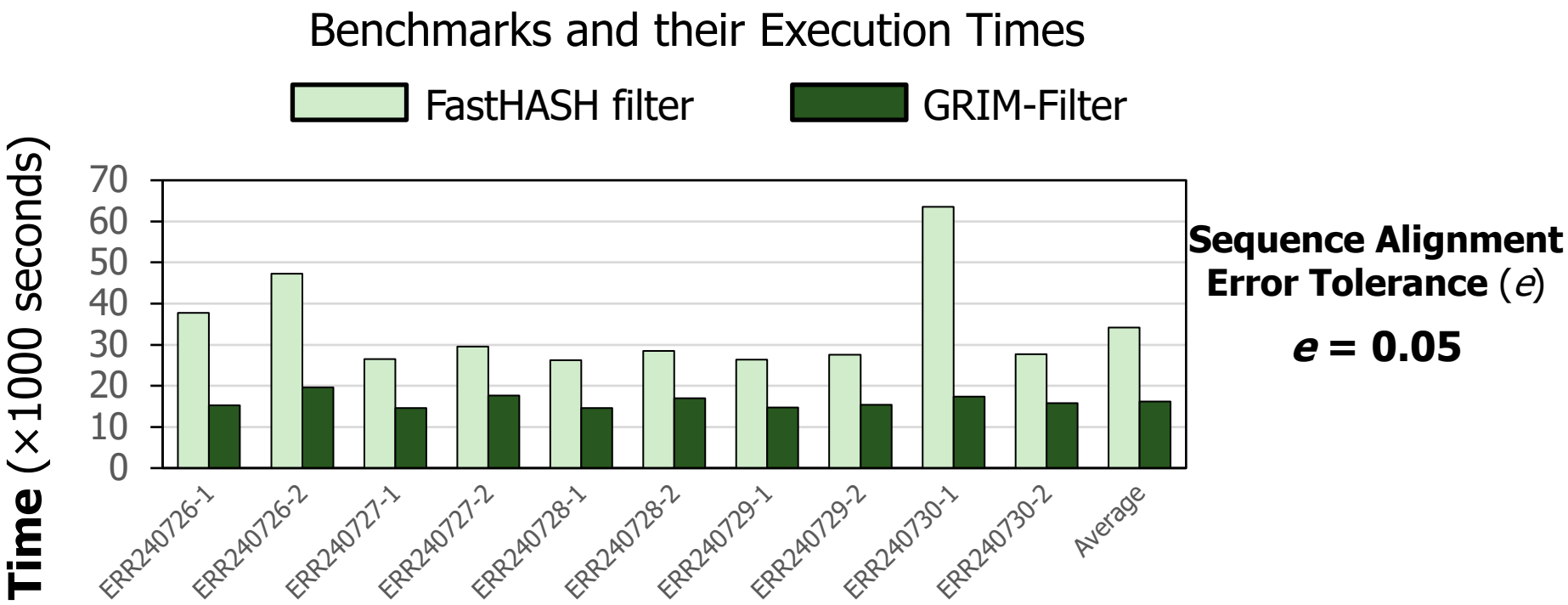
- Customized logic for accumulation and comparison per genome segment
  - Low area overhead, simple implementation
  - For HBM2, we use 4096 incrementer LUTs, 7-bit counters, and comparators in logic layer

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

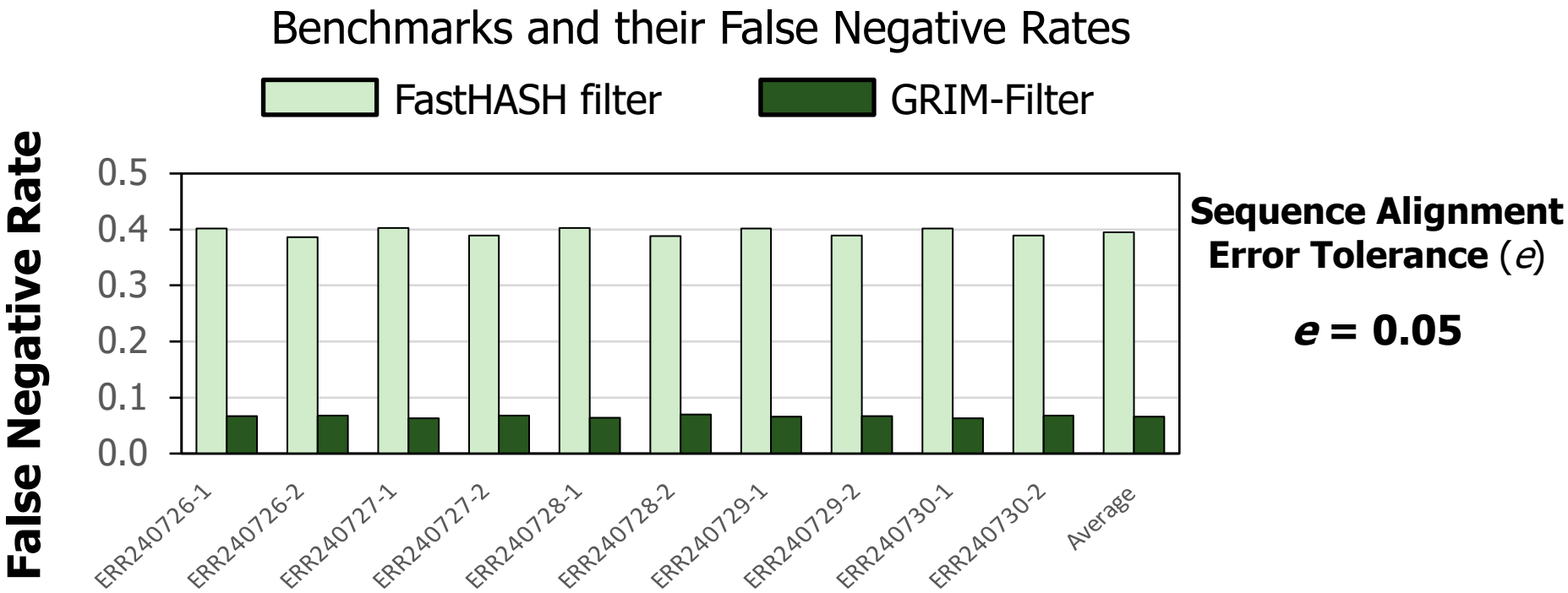


1.8x-3.7x performance benefit across real data sets

2.1x average performance benefit

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

GRIM-Filter False Negative Rate



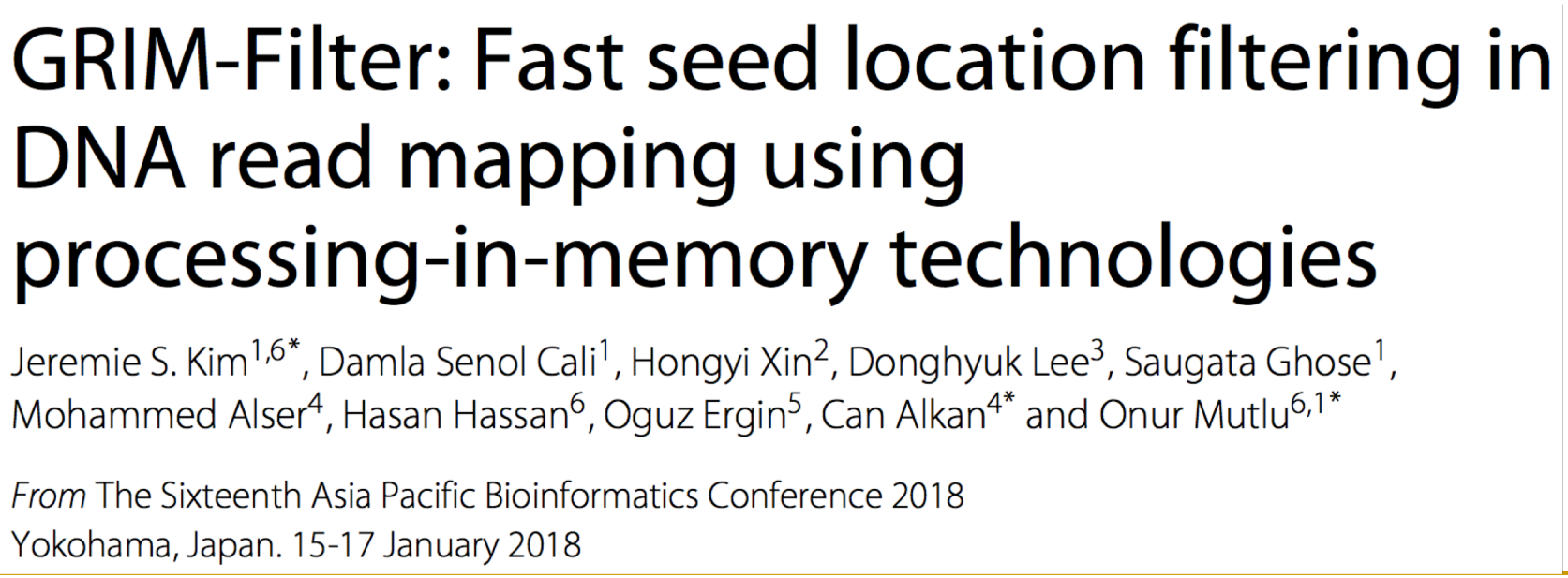
5.6x-6.4x False Negative reduction across real data sets

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"**
  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*]

From The Sixteenth Asia Pacific Bioinformatics Conference 2018
Yokohama, Japan. 15-17 January 2018

Aside: In-Memory Graph Processing

- Large graphs are everywhere (circa 2015)

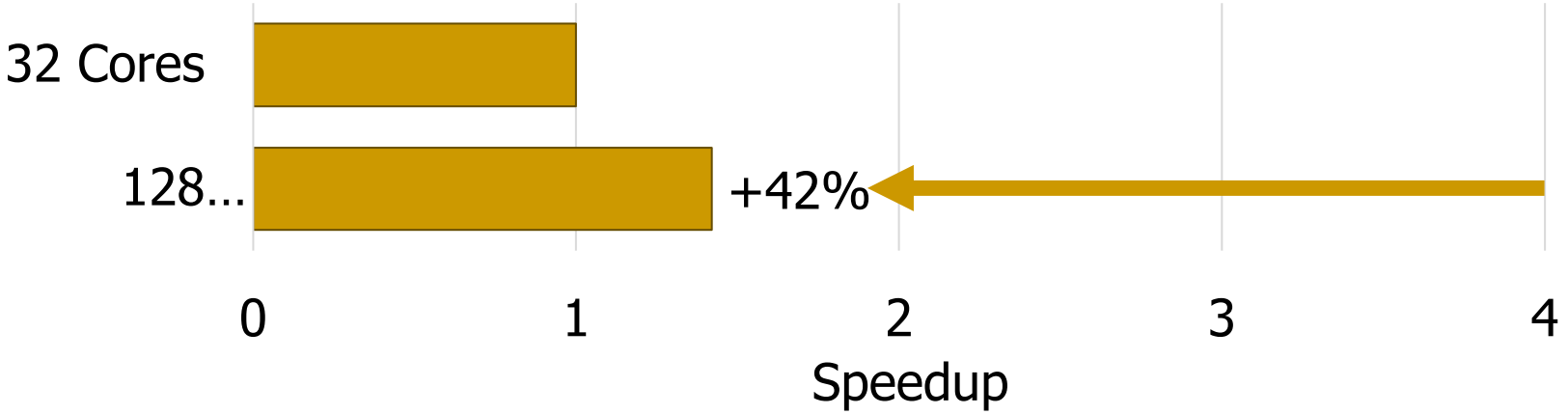
36 Million
Wikipedia Pages

1.4 Billion
Facebook Users

300 Million
Twitter Users

30 Billion
Instagram Photos

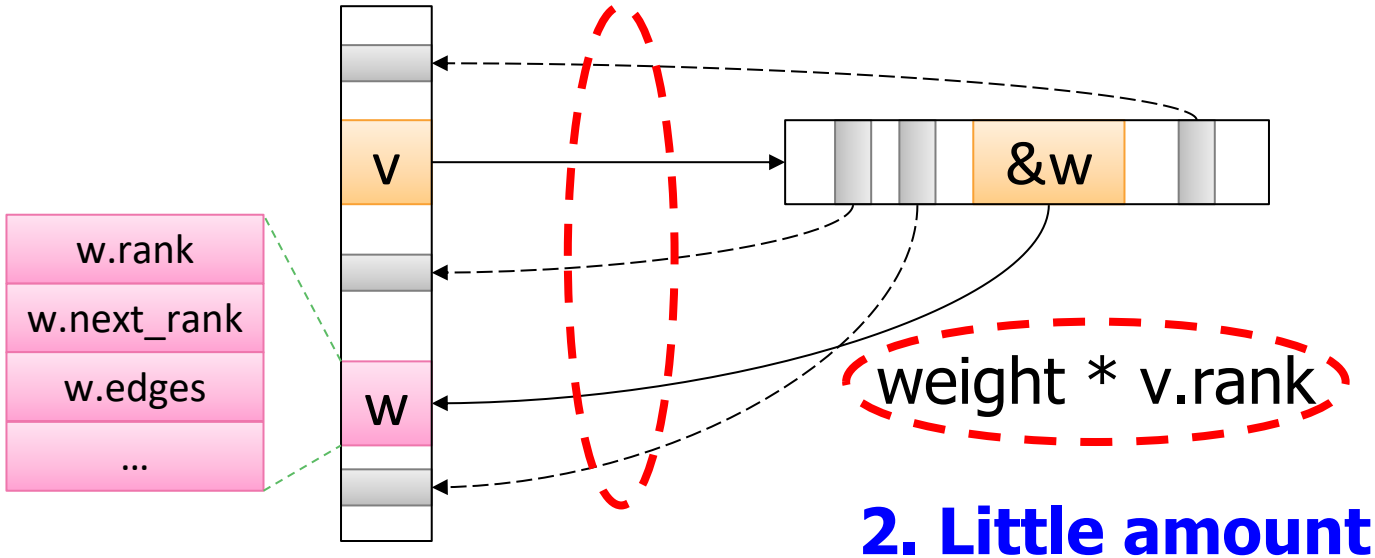
- Scalable large-scale graph processing is challenging



Key Bottlenecks in Graph Processing

```
for (v: graph.vertices) {
    for (w: v.successors) {
        w.next_rank += weight * v.rank;
    }
}
```

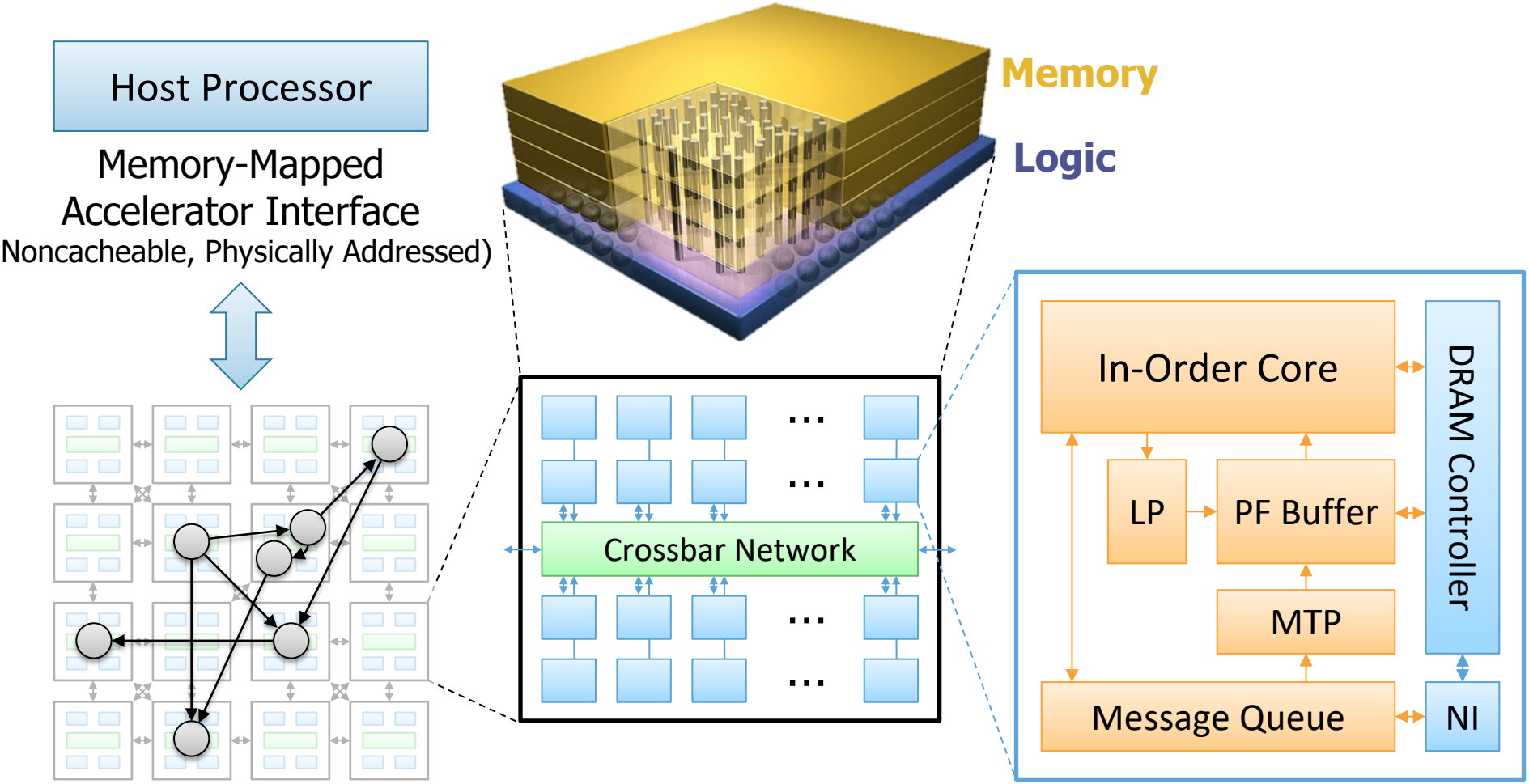
1. Frequent random memory accesses



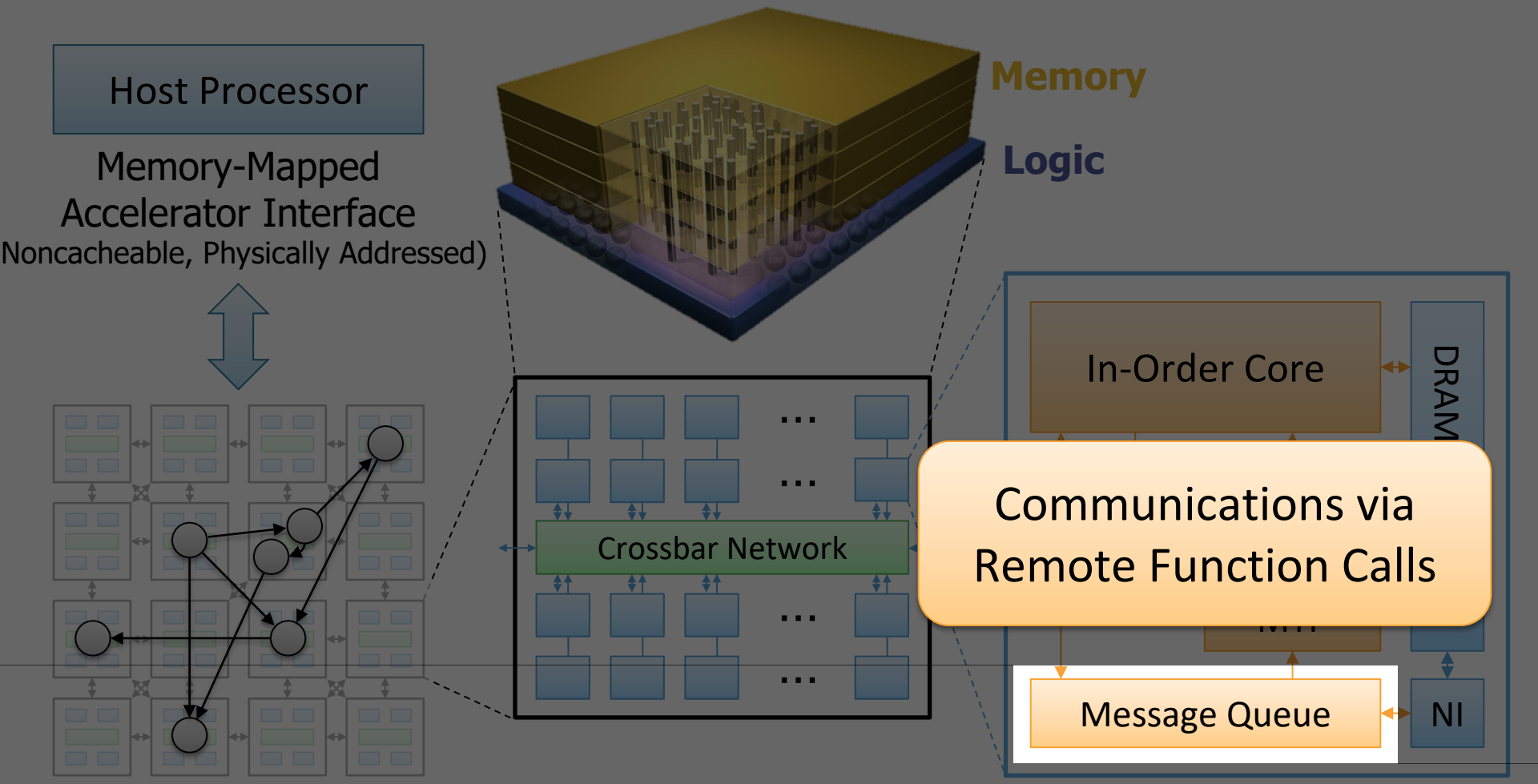
2. Little amount of computation

Tesseract System for Graph Processing

Interconnected set of 3D-stacked memory+logic chips with simple cores

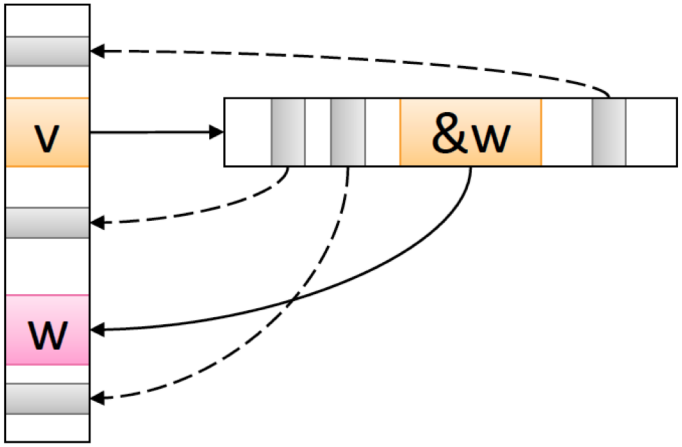


Tesseract System for Graph Processing



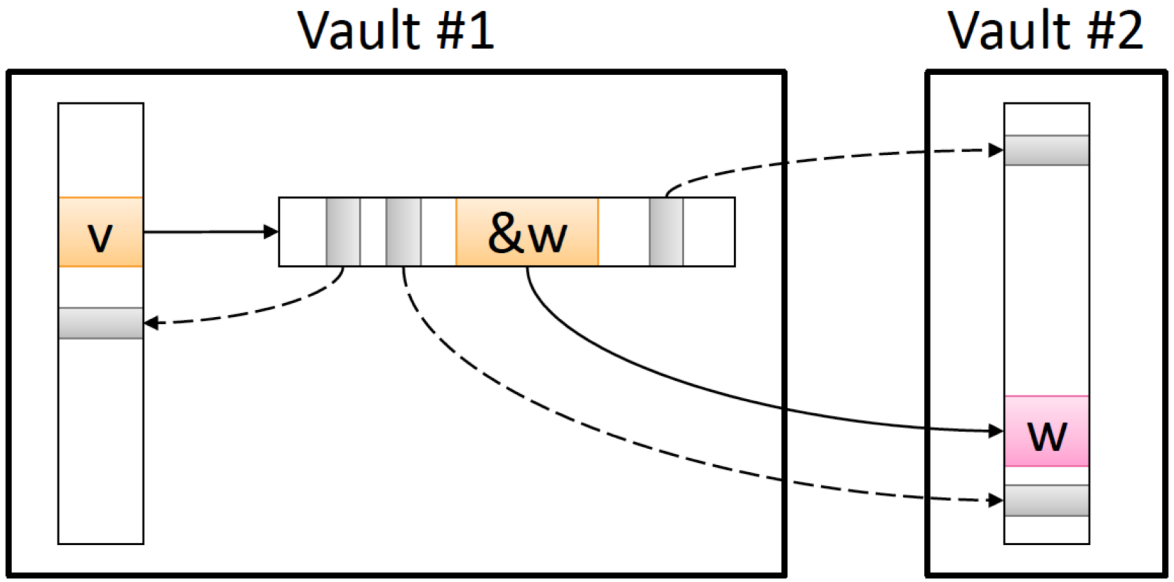
Communications In Tesseract (I)

```
for (v: graph.vertices) {
    for (w: v.successors) {
        w.next_rank += weight * v.rank;
    }
}
```



Communications In Tesseract (II)

```
for (v: graph.vertices) {
    for (w: v.successors) {
        w.next_rank += weight * v.rank;
    }
}
```

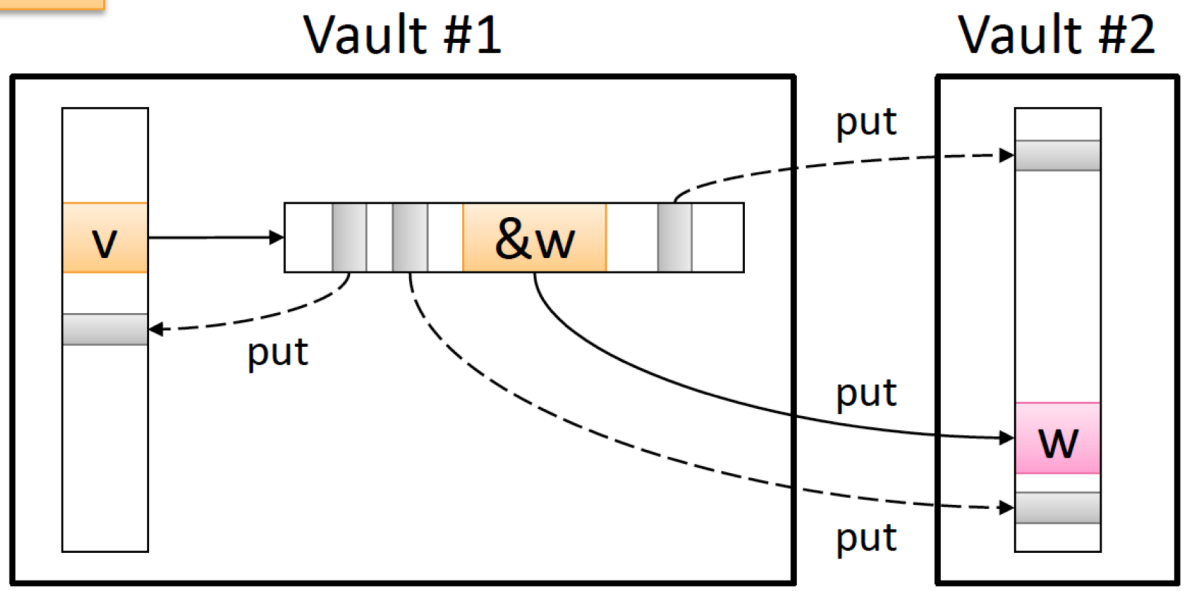


Communications In Tesseract (III)

```
for (v: graph.vertices) {
  for (w: v.successors) {
    put(w.id, function() { w.next_rank += weight * v.rank; });
  }
}
barrier();
```

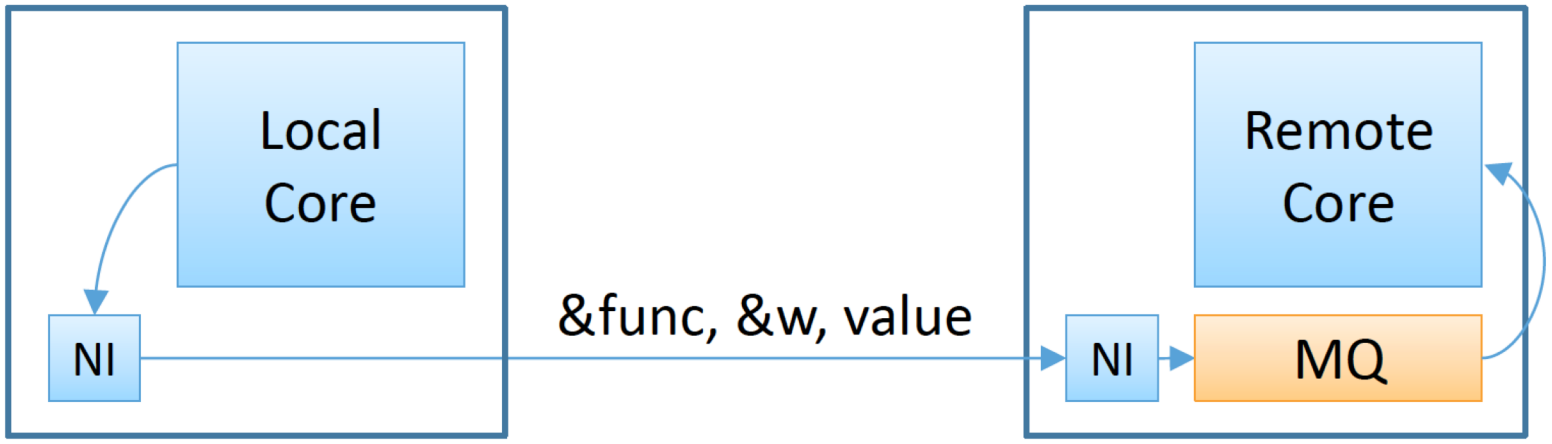
Non-blocking Remote Function Call

Can be **delayed** until the nearest barrier



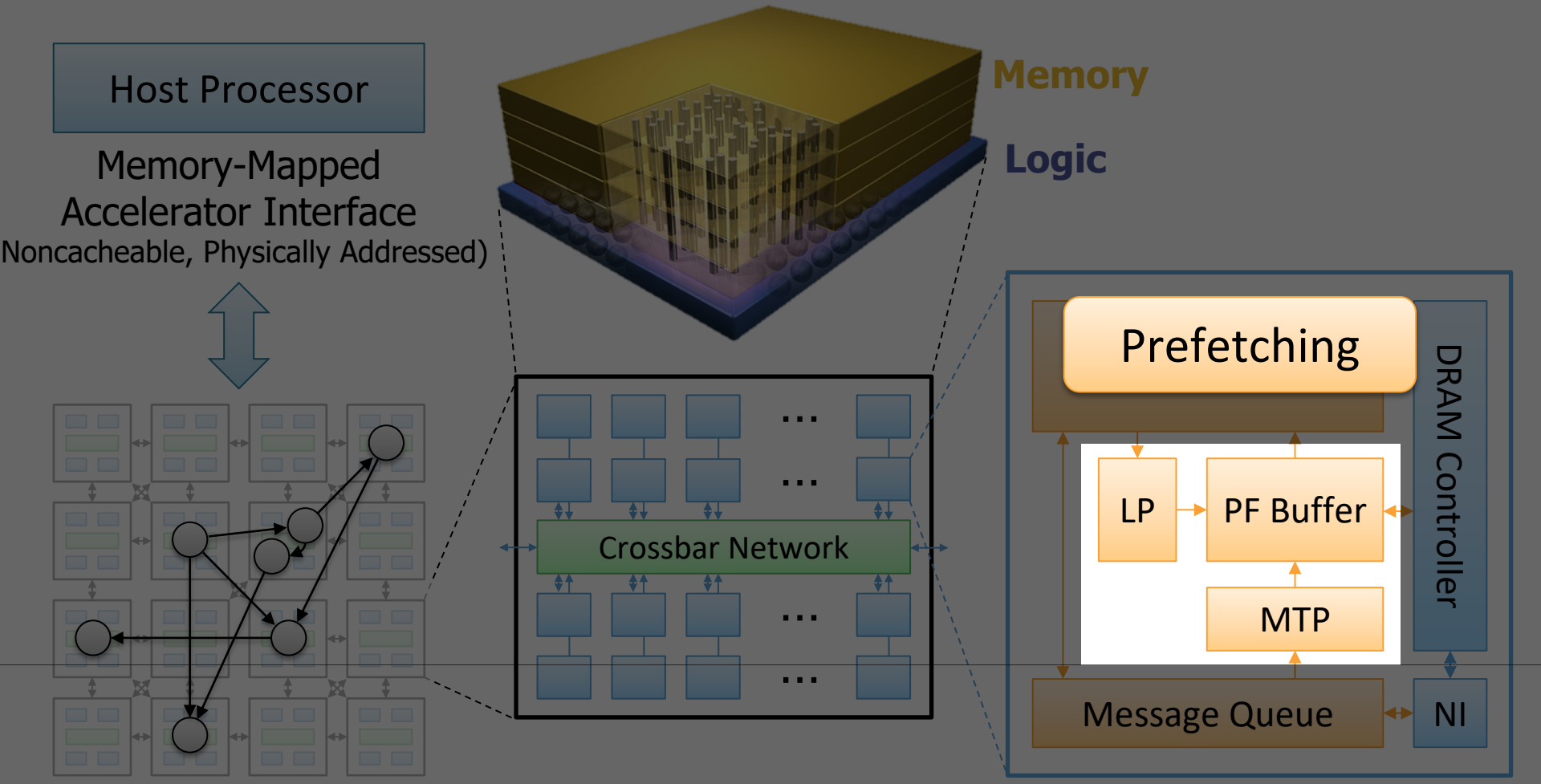
Remote Function Call (Non-Blocking)

1. Send function address & args to the remote core
2. Store the incoming message to the message queue
3. Flush the message queue when it is full or a synchronization barrier is reached

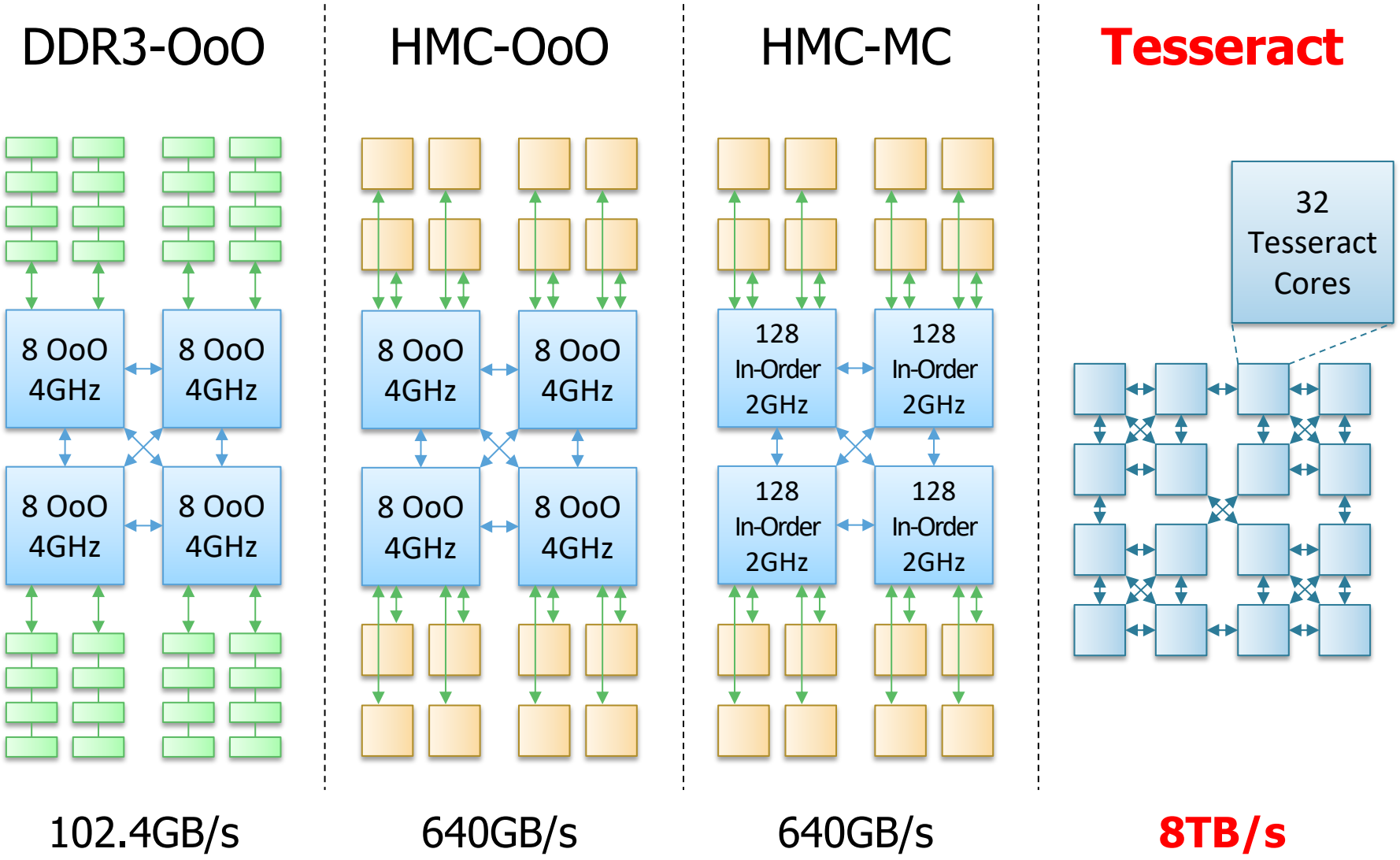


put(w.id, function() { w.next_rank += value; })

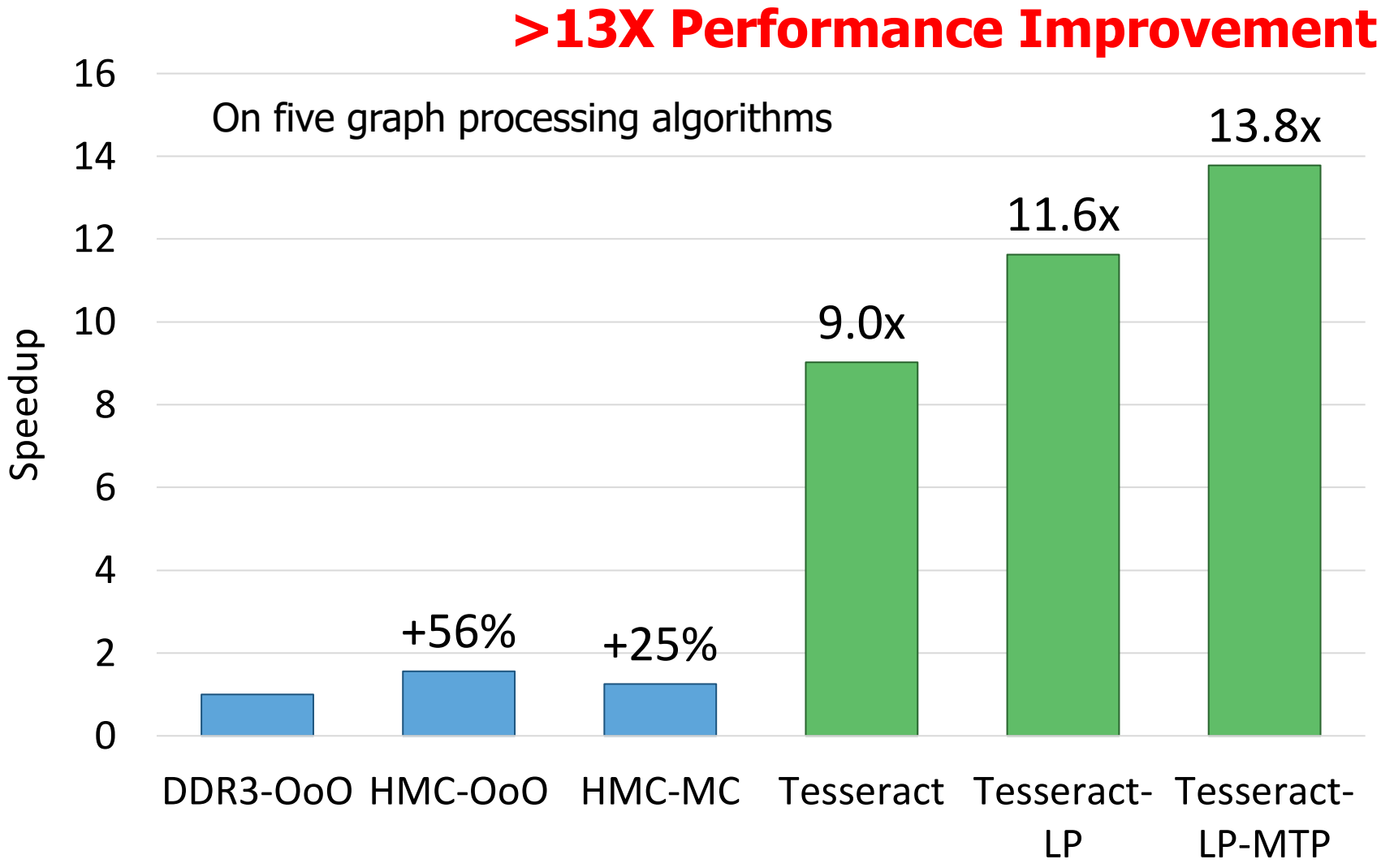
Tesseract System for Graph Processing



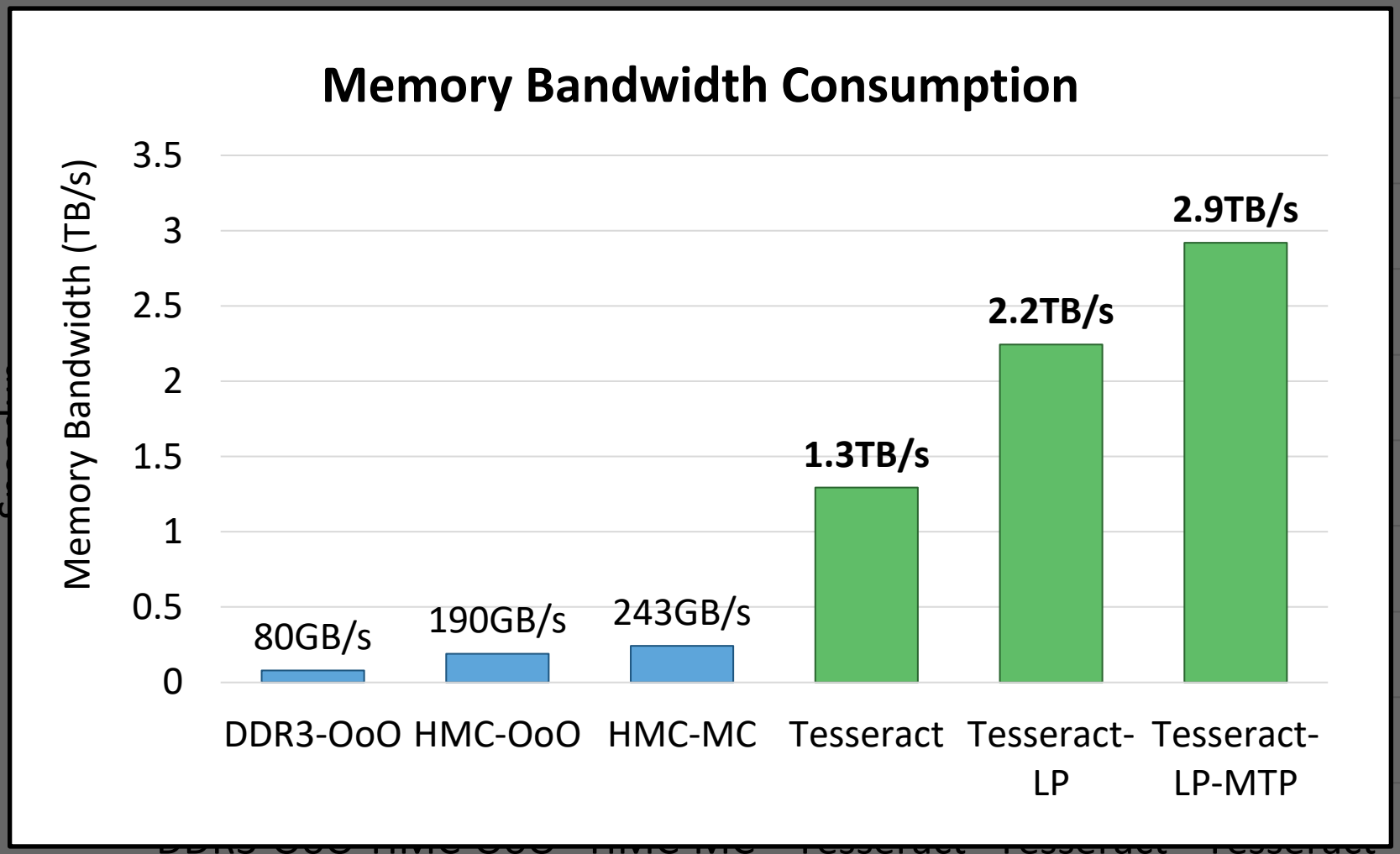
Evaluated Systems



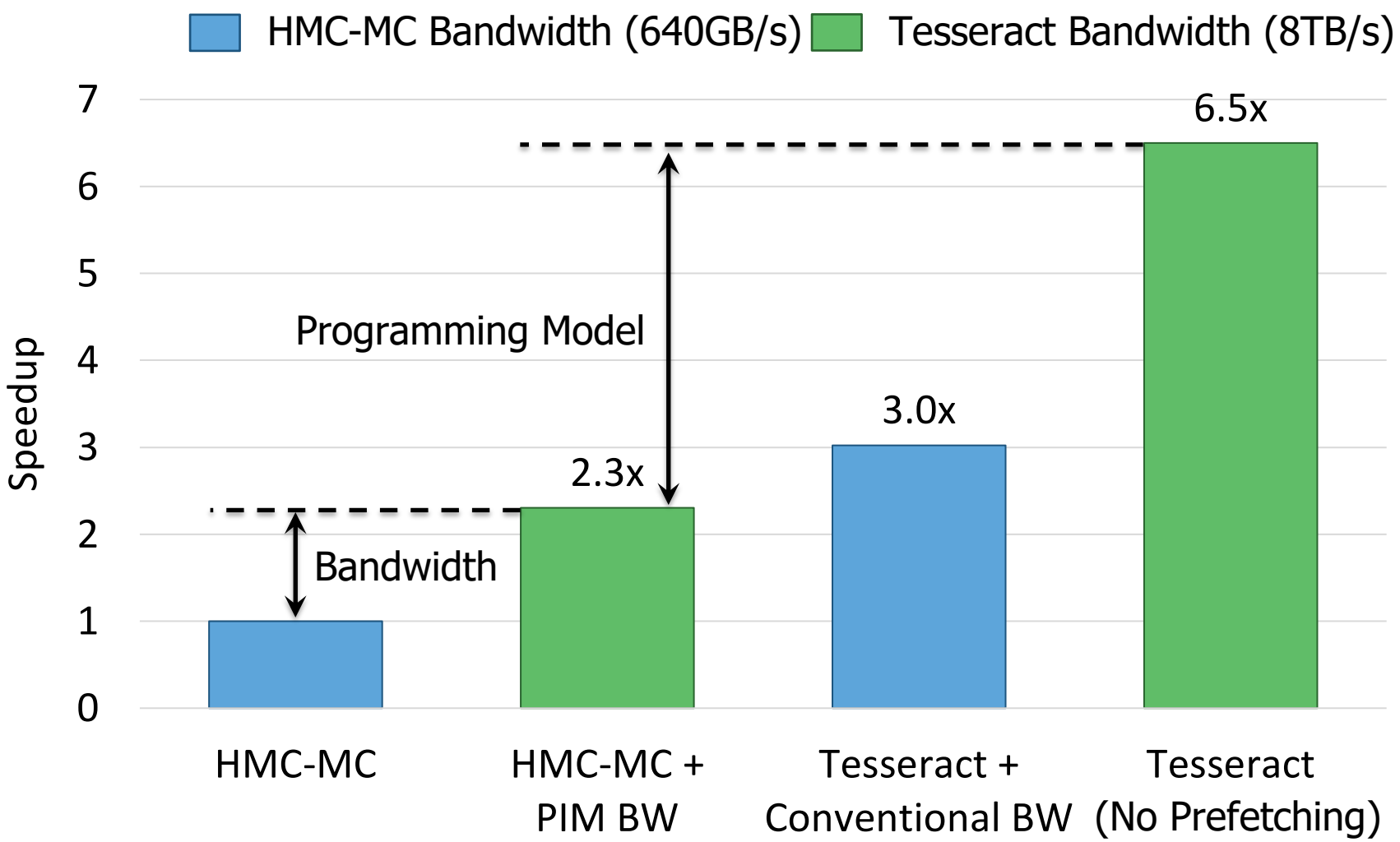
Tesseract Graph Processing Performance



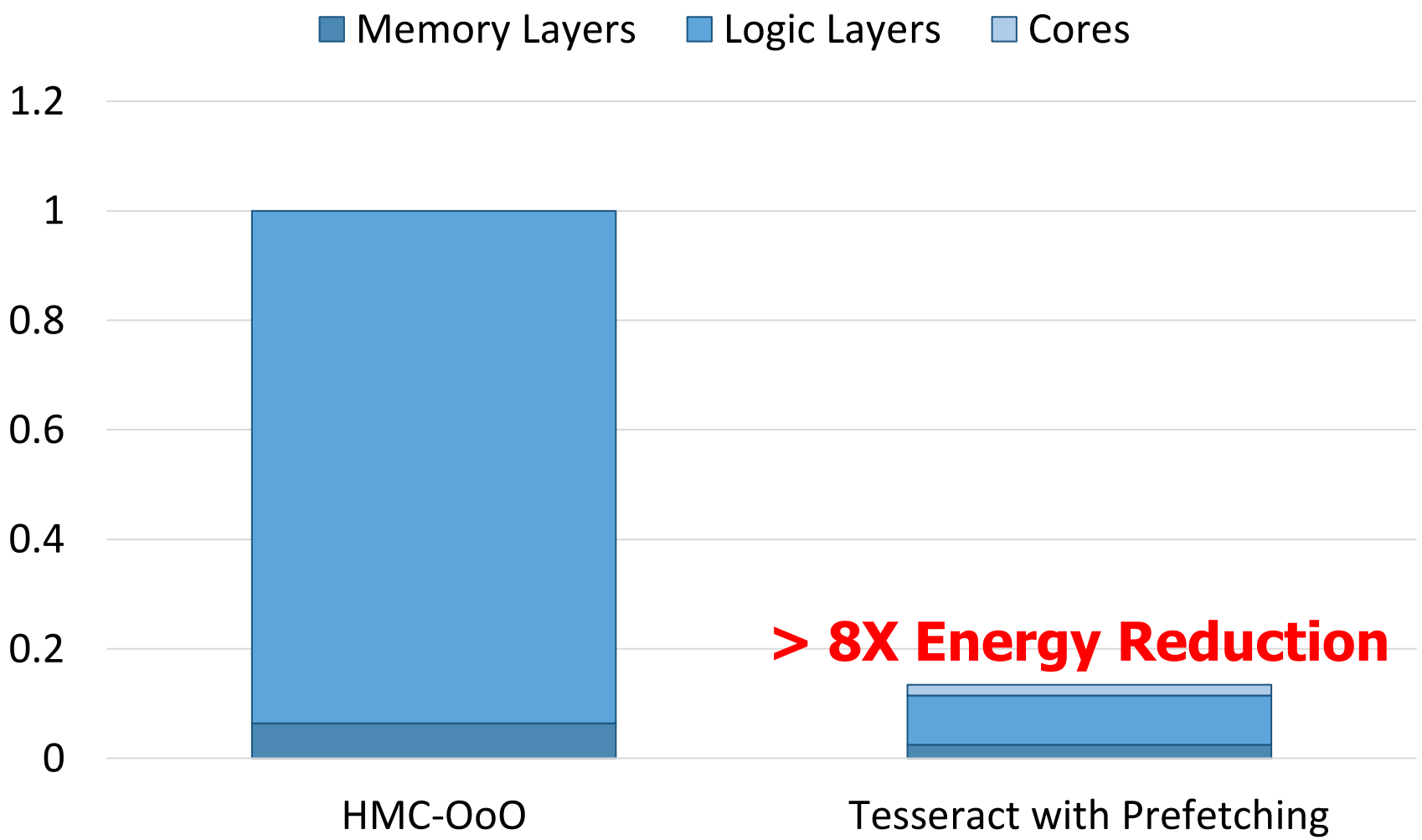
Tesseract Graph Processing Performance



Effect of Bandwidth & Programming Model



Tesseract Graph Processing System Energy



More on Tesseract

- Junwhan Ahn, Sungpack Hong, Sungjoo Yoo, Onur Mutlu, and Kiyoung Choi,
  "A Scalable Processing-in-Memory Accelerator for Parallel Graph Processing"
  *Proceedings of the 42nd International Symposium on Computer Architecture (**ISCA**)*, Portland, OR, June 2015.
  [Slides (pdf)] [Lightning Session Slides (pdf)]

A Scalable Processing-in-Memory Accelerator for Parallel Graph Processing

Junwhan Ahn Sungpack Hong[§] Sungjoo Yoo Onur Mutlu[†] Kiyoung Choi
junwhan@snu.ac.kr, sungpack.hong@oracle.com, sungjoo.yoo@gmail.com, onur@cmu.edu, kchoi@snu.ac.kr
Seoul National University [§]Oracle Labs [†]Carnegie Mellon University

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

Nanopore Sequencing Technology

an emerging and a promising
ncing technology
read length → Longer read length

- First nanopore sequencing device, **MinION**, made commercially available by **Oxford Nanopore Technologies** (ONT) in **May 2014.**
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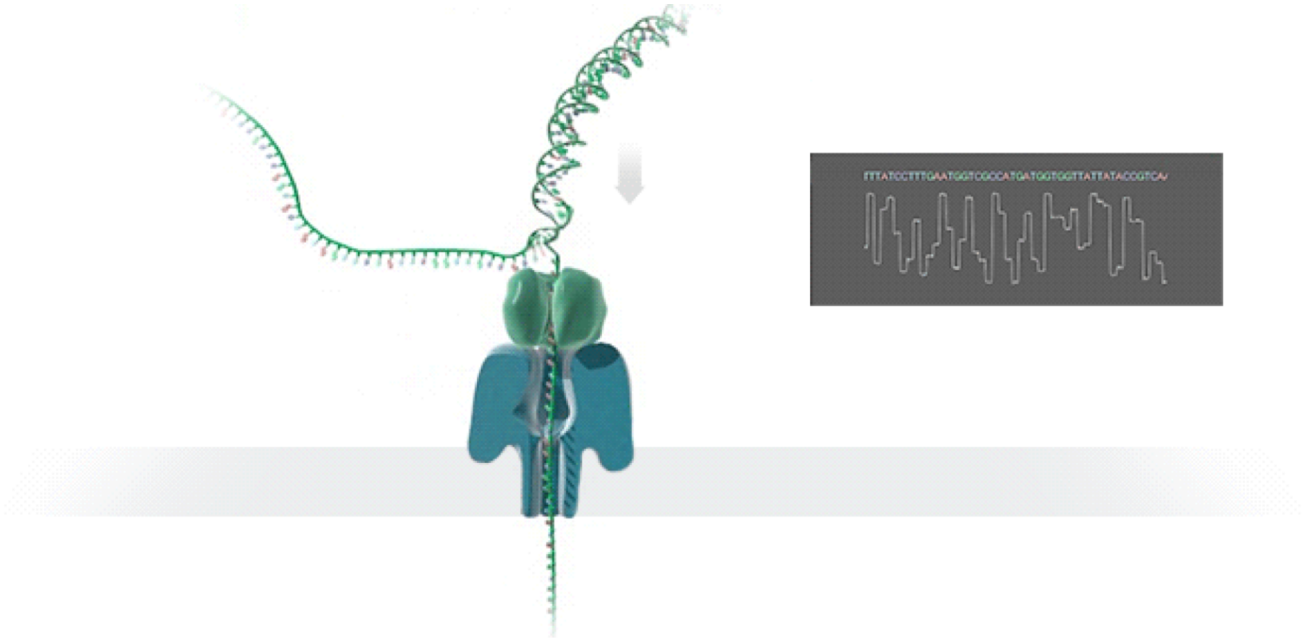
Nanopore Sequencing



- **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

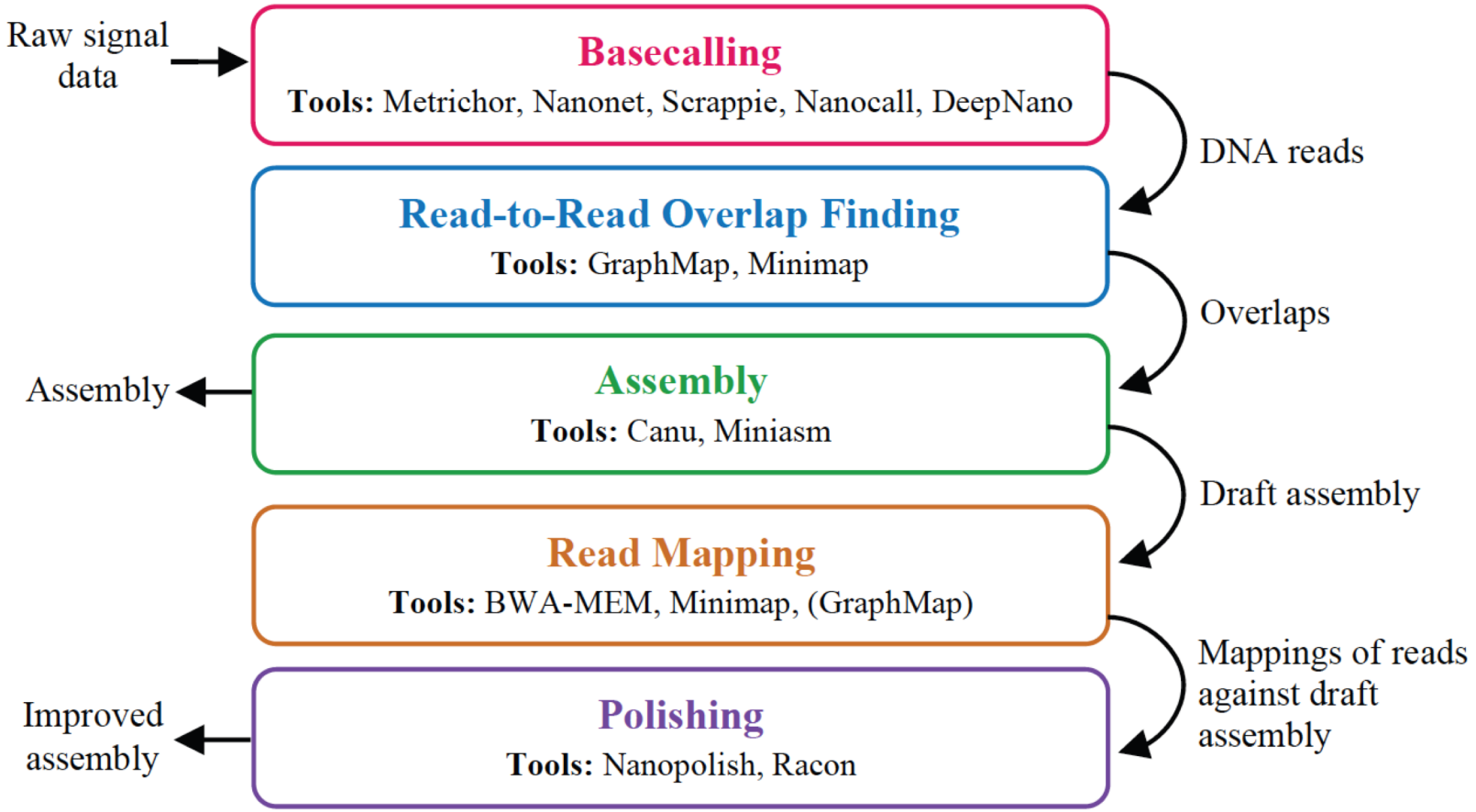


Figure 1. The analyzed genome assembly pipeline using nanopore sequence data, with its five steps and the associated tools for each step.

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

Nanopore Genome Assembly Tools (I)

Table 12. Accuracy analysis results for the full pipeline with a focus on the last two steps.

						Number of Bases	Number of Contigs	Identity (%)	Coverage (%)	Number of Mismatches	Number of Indels
1	Metrichor	+ —	+ Canu	+ BWA-MEM	+ Nanopolish	4,683,072	1	99.48	99.93	8,198	15,581
2	Metrichor	+ Minimap	+ Miniasm	+ BWA-MEM	+ Nanopolish	4,540,352	1	92.33	96.31	162,884	182,965
3	Metrichor	+ GraphMap	+ Miniasm	+ BWA-MEM	+ Nanopolish	4,637,916	2	92.38	95.80	159,206	180,603
4	Metrichor	+ —	+ Canu	+ BWA-MEM	+ Racon	4,650,502	1	98.46	100.00	18,036	51,842
5	Metrichor	+ —	+ Canu	+ Minimap	+ Racon	4,648,710	1	98.45	100.00	17,906	52,168
6	Metrichor	+ Minimap	+ Miniasm	+ BWA-MEM	+ Racon	4,598,267	1	97.70	99.91	24,014	82,906
7	Metrichor	+ Minimap	+ Miniasm	+ Minimap	+ Racon	4,600,109	1	97.78	100.00	23,339	79,721
8	Nanonet	+ —	+ Canu	+ BWA-MEM	+ Racon	4,622,285	1	98.48	100.00	16,872	52,509
9	Nanonet	+ —	+ Canu	+ Minimap	+ Racon	4,620,597	1	98.49	100.00	16,874	52,232
10	Nanonet	+ Minimap	+ Miniasm	+ BWA-MEM	+ Racon	4,593,402	1	98.01	99.97	20,322	72,284
11	Nanonet	+ Minimap	+ Miniasm	+ Minimap	+ Racon	4,592,907	1	98.04	100.00	20,170	70,705
12	Scrappie	+ —	+ Canu	+ BWA-MEM	+ Racon	4,673,871	1	98.40	99.98	13,583	60,612
13	Scrappie	+ —	+ Canu	+ Minimap	+ Racon	4,673,606	1	98.40	99.98	13,798	60,423
14	Scrappie	+ Minimap	+ Miniasm	+ BWA-MEM	+ Racon	5,157,041	8	97.87	99.80	18,085	78,492
15	Scrappie	+ Minimap	+ Miniasm	+ Minimap	+ Racon	5,156,375	8	97.87	99.94	17,922	77,807
16	Nanocall	+ —	+ Canu	+ BWA-MEM	+ Racon	1,383,851	86	93.49	28.82	19,057	65,244
17	Nanocall	+ —	+ Canu	+ Minimap	+ Racon	1,367,834	86	94.43	28.74	15,610	55,275
18	Nanocall	+ Minimap	+ Miniasm	+ BWA-MEM	+ Racon	4,707,961	5	90.75	97.11	91,502	347,005
19	Nanocall	+ Minimap	+ Miniasm	+ Minimap	+ Racon	4,673,069	5	92.23	97.10	72,646	291,918
20	DeepNano	+ —	+ Canu	+ BWA-MEM	+ Racon	7,429,290	106	96.46	99.24	27,811	102,682
21	DeepNano	+ —	+ Canu	+ Minimap	+ Racon	7,404,454	106	96.03	99.21	34,023	110,640
22	DeepNano	+ Minimap	+ Miniasm	+ BWA-MEM	+ Racon	4,566,253	1	96.76	99.86	25,791	125,386
23	DeepNano	+ Minimap	+ Miniasm	+ Minimap	+ Racon	4,571,810	1	96.90	99.97	24,994	119,519

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

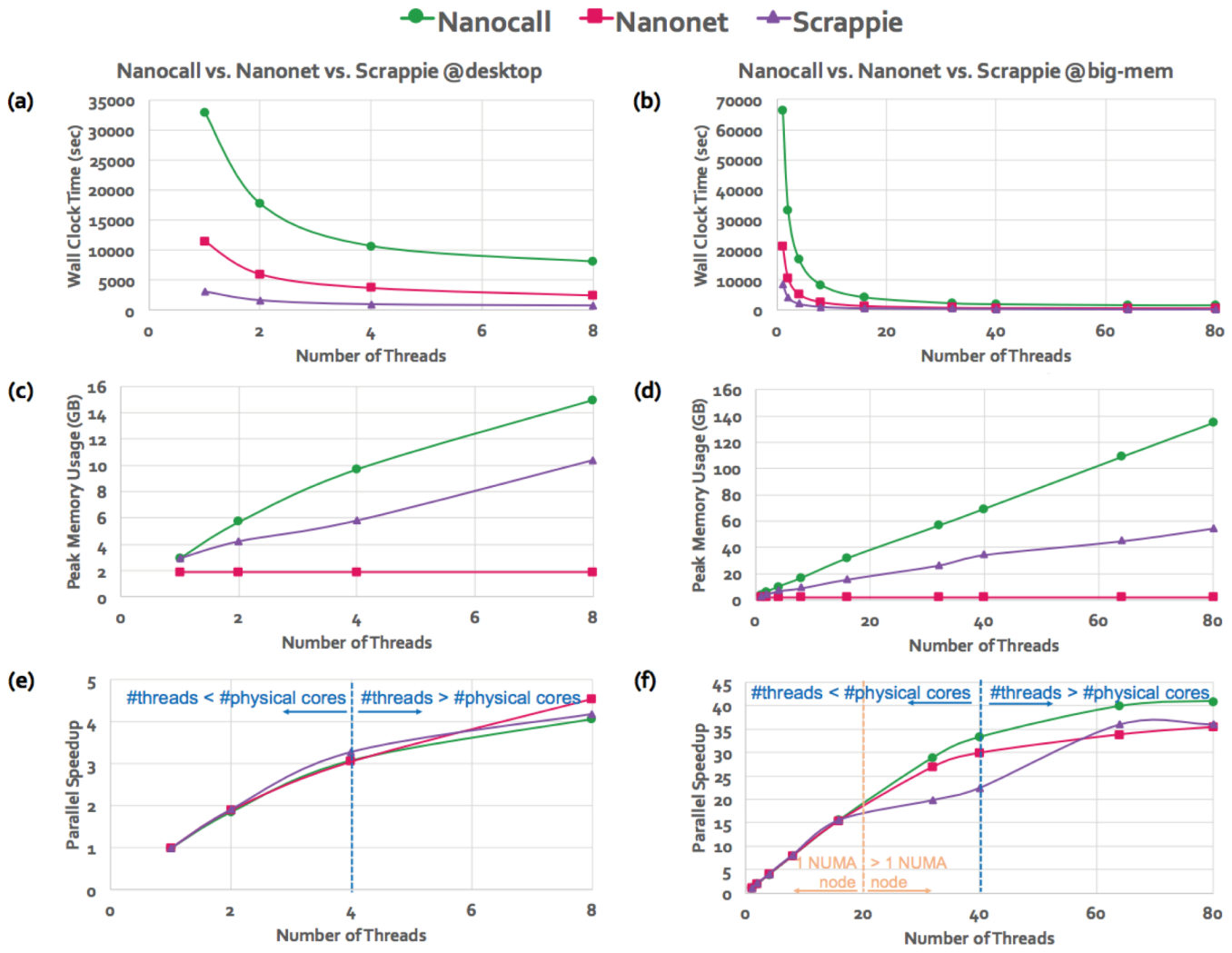
Nanopore Genome Assembly Tools (II)

Table 13. Performance analysis results for the full pipeline with a focus on the last two steps.

									Step 4: Read Mapper			Step 5: Polisher		
									Wall Clock Time (h:m:s)	CPU Time (h:m:s)	Memory Usage (GB)	Wall Clock Time (h:m:s)	CPU Time (h:m:s)	Memory Usage (GB)
1	Metrichor	+	—	+	Canu	+	BWA-MEM	+	Nanopolish	24:43	15:47:21	5.26	5:51:00	191:18:52	13.38
2	Metrichor	+	Minimap	+	Miniasm	+	BWA-MEM	+	Nanopolish	12:33	7:50:54	3.75	122:52:00	4458:36:10	31.36
3	Metrichor	+	GraphMap	+	Miniasm	+	BWA-MEM	+	Nanopolish	12:47	7:57:58	3.60	129:46:00	4799:03:51	31.31
4	Metrichor	+	—	+	Canu	+	BWA-MEM	+	Racon	24:20	15:43:40	6.60	14:44	9:09:22	8.11
5	Metrichor	+	—	+	Canu	+	Minimap	+	Racon	3	1:35	0.26	15:12	9:45:33	14.55
6	Metrichor	+	Minimap	+	Miniasm	+	BWA-MEM	+	Racon	12:10	7:48:10	5.19	15:43	9:33:39	9.98
7	Metrichor	+	Minimap	+	Miniasm	+	Minimap	+	Racon	3	1:24	0.26	20:28	8:57:40	18.24
8	Nanonet	+	—	+	Canu	+	BWA-MEM	+	Racon	9:08	5:53:18	4.84	6:33	4:02:10	4.47
9	Nanonet	+	—	+	Canu	+	Minimap	+	Racon	2	54	0.26	6:45	4:17:26	7.93
10	Nanonet	+	Minimap	+	Miniasm	+	BWA-MEM	+	Racon	4:40	2:58:02	3.88	7:08	4:19:30	5.35
11	Nanonet	+	Minimap	+	Miniasm	+	Minimap	+	Racon	2	46	0.26	7:01	4:18:48	9.53
12	Scrappie	+	—	+	Canu	+	BWA-MEM	+	Racon	33:41	21:11:06	8.66	13:32	8:24:44	7.58
13	Scrappie	+	—	+	Canu	+	Minimap	+	Racon	3	1:39	0.27	18:45	7:43:17	13.20
14	Scrappie	+	Minimap	+	Miniasm	+	BWA-MEM	+	Racon	22:41	14:31:00	6.08	14:37	8:53:59	9.50
15	Scrappie	+	Minimap	+	Miniasm	+	Minimap	+	Racon	3	1:27	0.27	15:10	9:02:45	12.72
16	Nanocall	+	—	+	Canu	+	BWA-MEM	+	Racon	4:52	3:01:15	3.80	11:07	3:26:52	5.63
17	Nanocall	+	—	+	Canu	+	Minimap	+	Racon	3	1:16	0.22	7:28	2:50:35	3.62
18	Nanocall	+	Minimap	+	Miniasm	+	BWA-MEM	+	Racon	16:06	10:27:20	5.06	18:56	11:32:45	11.47
19	Nanocall	+	Minimap	+	Miniasm	+	Minimap	+	Racon	4	1:18	0.26	11:49	7:08:59	10.98
20	DeepNano	+	—	+	Canu	+	BWA-MEM	+	Racon	17:36	11:30:20	4.43	12:48	7:13:04	8.88
21	DeepNano	+	—	+	Canu	+	Minimap	+	Racon	3	1:24	0.28	11:39	6:55:01	3.73
22	DeepNano	+	Minimap	+	Miniasm	+	BWA-MEM	+	Racon	8:15	5:22:29	4.11	14:16	8:34:32	10.30
23	DeepNano	+	Minimap	+	Miniasm	+	Minimap	+	Racon	3	1:10	0.26	12:29	7:55:32	17.11

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

Nanopore Genome Assembly Tools (III)



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 ✉, Jeremie S Kim, Saugata Ghose, Can Alkan, Onur Mutlu

Briefings in Bioinformatics, bby017, https://doi.org/10.1093/bib/bby017
Published: 02 April 2018 **Article history** ▾

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

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

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

- Can Alkan, Bilkent University

- Many students at ETH, CMU, Bilkent
  - Mohammed Alser, Damla Senol Cali, Jeremie Kim, Hasan Hassan, Donghyuk Lee, Hongyi Xin, …

- Funders:
  - NIH and Industrial Partners (Alibaba, AMD, Google, Facebook, HP Labs, Huawei, IBM, Intel, Microsoft, Nvidia, Oracle, Qualcomm, Rambus, Samsung, Seagate, VMware)

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

Accelerating Genome Analysis

A Primer on an Ongoing Journey

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

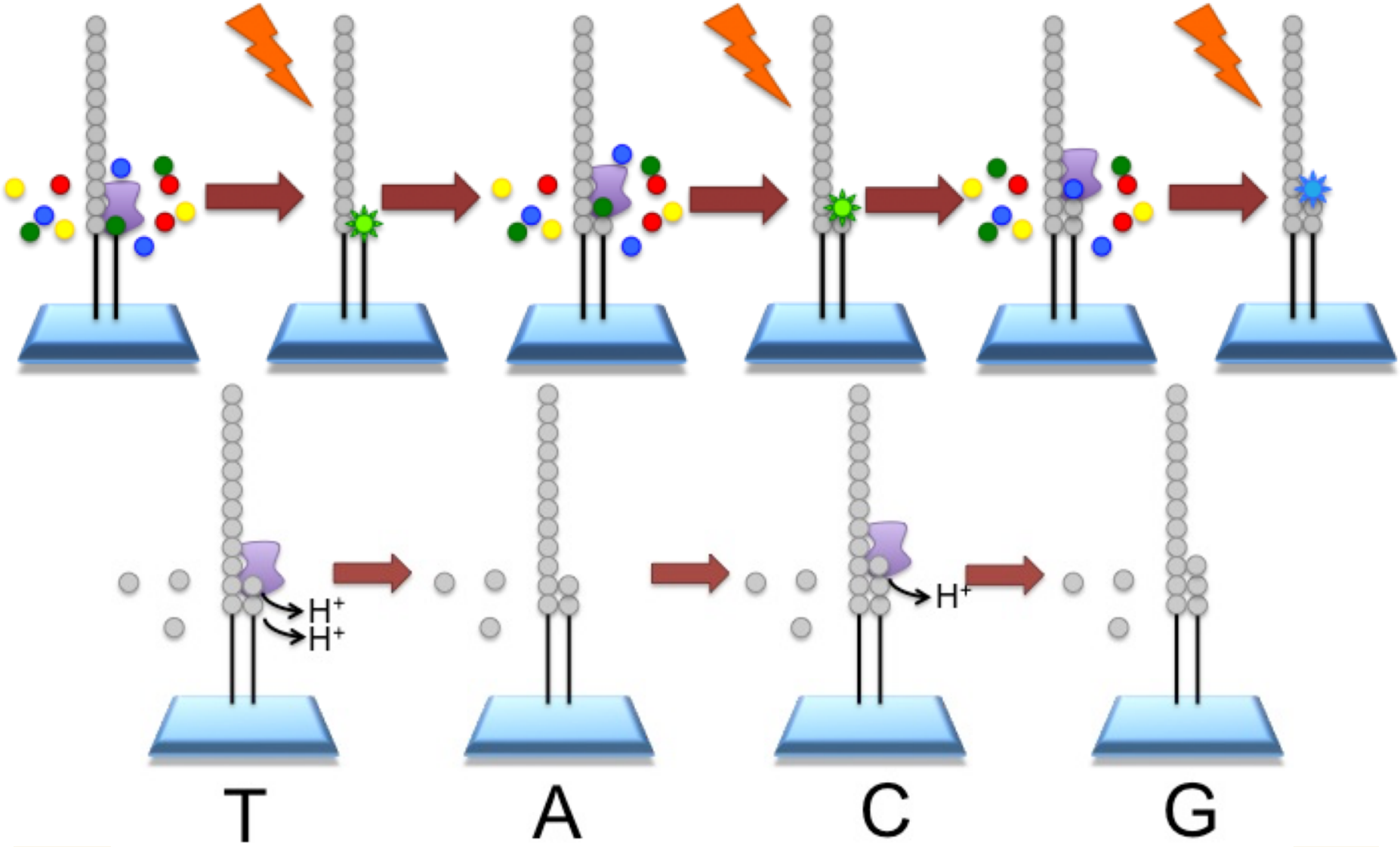
May 21, 2018

HiCOMB-17 Keynote Talk

SAFARI

ETH zürich

High-Throughput Sequencing



Nanopore Sequencing

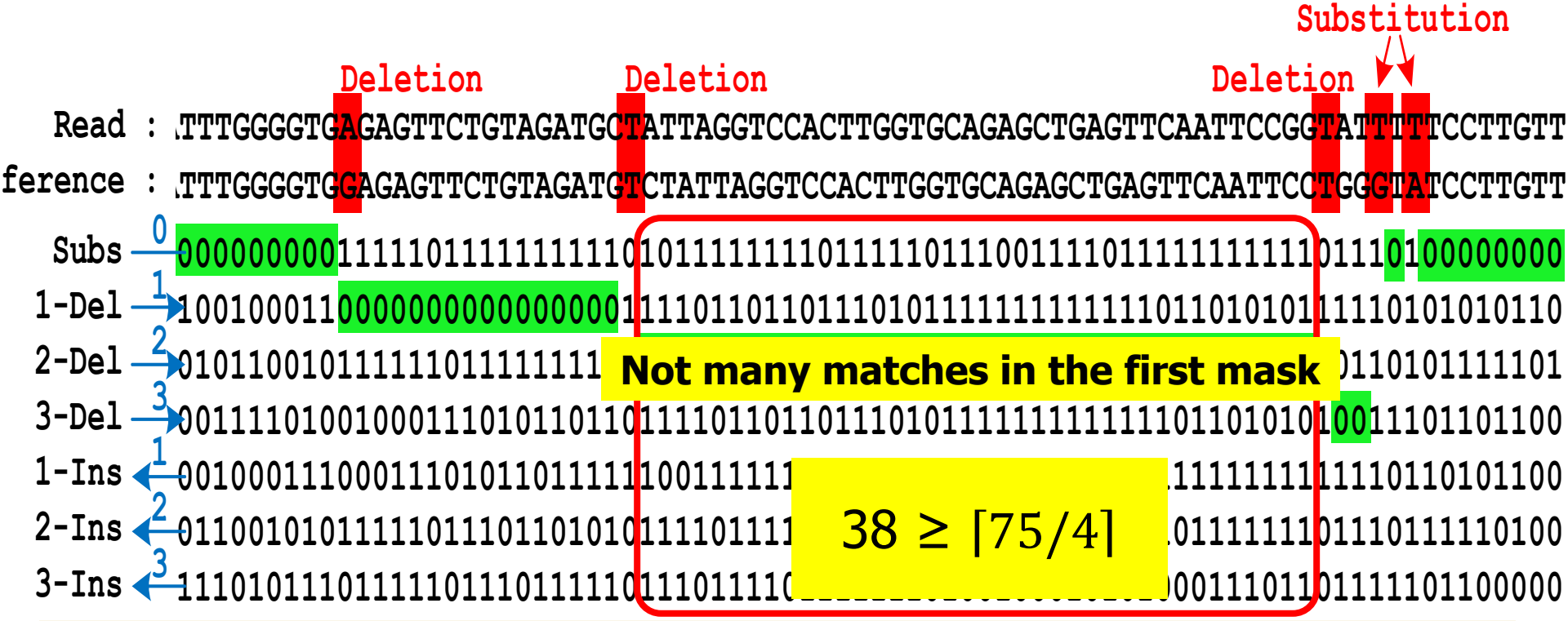
- **Basecalling** translates the raw signal output of the nanopore sequencer into bases (A, C, G, T) to generate DNA reads.
  - 1) The raw current signal is divided into discrete blocks (events).
  - 2) Each event is decoded into a most-likely set of bases.

- **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

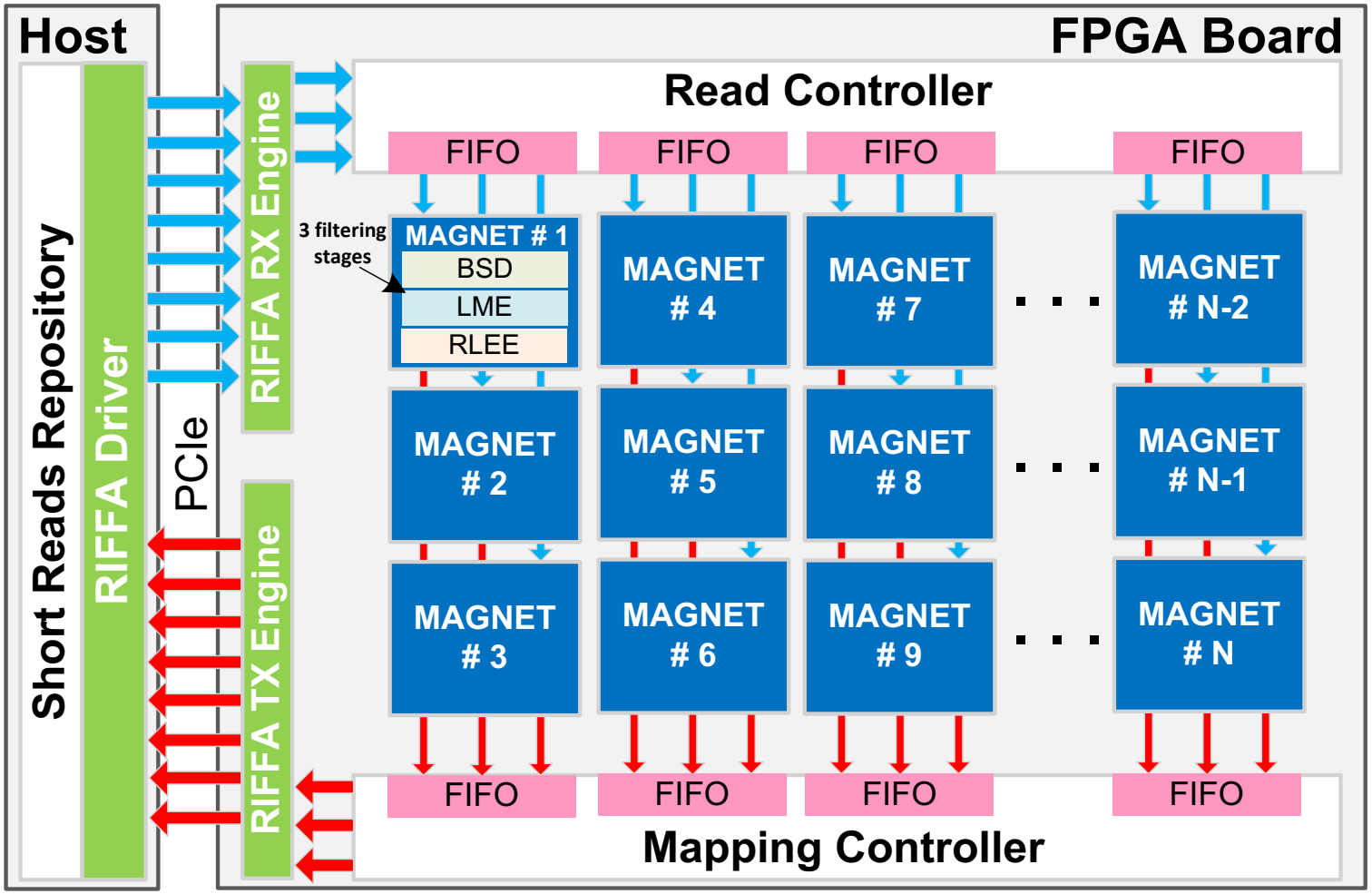
3- Highly Accurate Filtering Algorithm (cont'd)

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



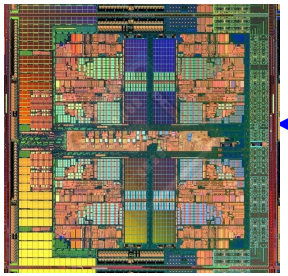
Who Am I?

- 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
  - …

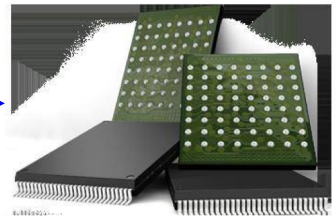
Current Research Focus Areas

***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*

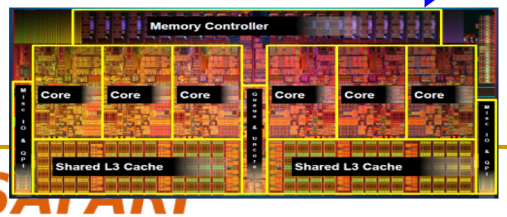


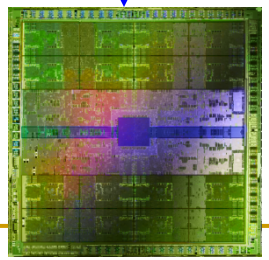
Hybrid Main Memory



Persistent Memory/Storage

Heterogeneous Processors and Accelerators





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