# Accelerating Genome Sequence Analysis via Efficient Hardware/Algorithm Co-Design

**Damla Senol Cali**

Staff Software Engineer, Hardware Acceleration

Bionano Genomics

Email: damlasenolcali@gmail.com

Website: https://damlasenolcali.github.io

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# Genome Sequencing

- **Genome sequencing:** Enables us to determine the order of the DNA sequence in an organism's genome
  - Plays a pivotal role in:
    - Personalized medicine
    - Outbreak tracing
    - Understanding of evolution

Genome

DNA

- **Challenges:**
  - There is no sequencing machine that takes long DNA as an input, and gives the complete sequence as output
  - Sequencing machines extract small randomized fragments of the original DNA sequence

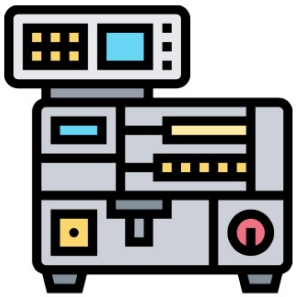
# Genome Sequencing (cont'd.)

Sample Collection

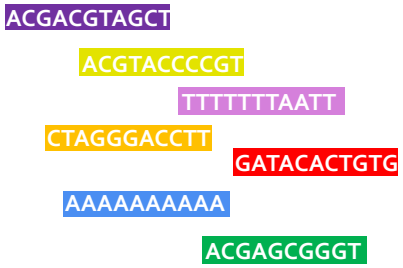
Large DNA molecule

Chopped DNA fragments

Preparation



Sequencing




Sequenced reads

Genome Sequence Analysis

# Sequencing Technologies

Oxford Nanopore (ONT)

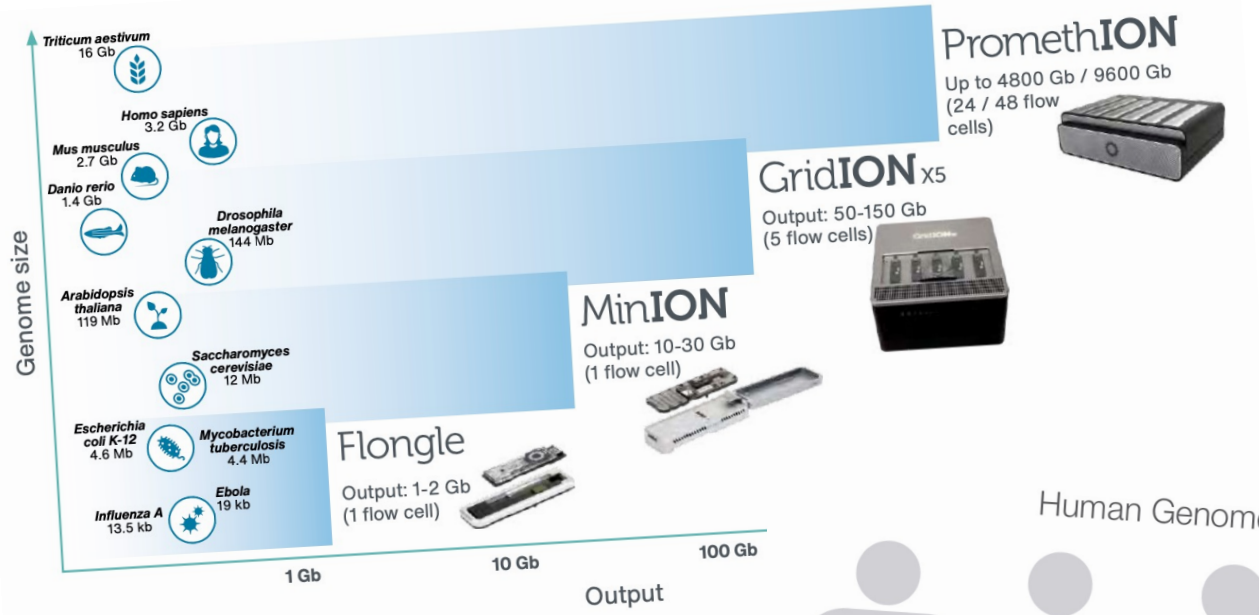
PacBio

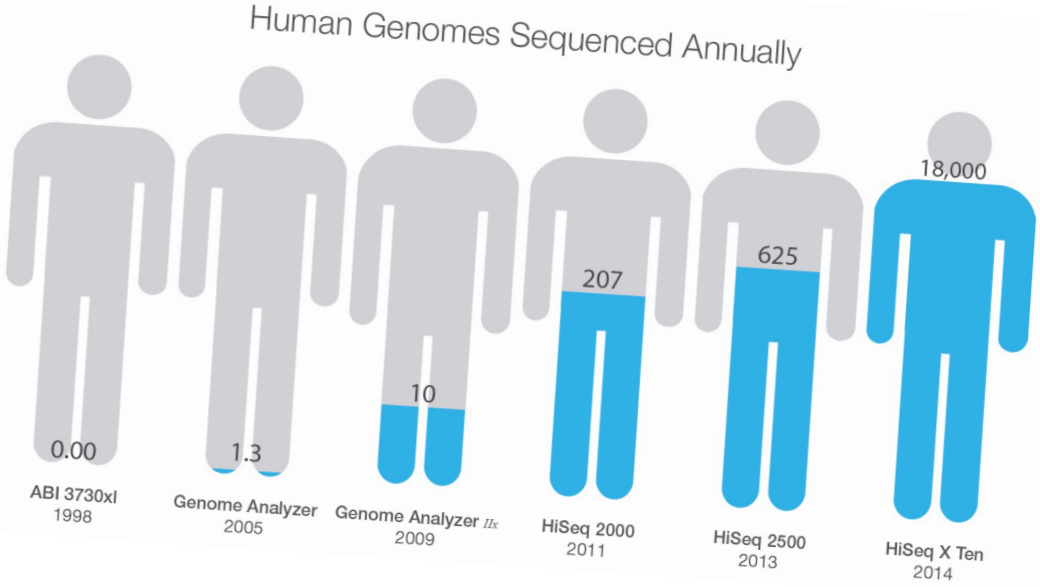
Illumina

***Short reads:*** **a few hundred base pairs** and **error rate of ~0.1%**

***Long reads:*** **thousands to millions of base pairs** and **error rate of 5–10%**

# Current State of Sequencing



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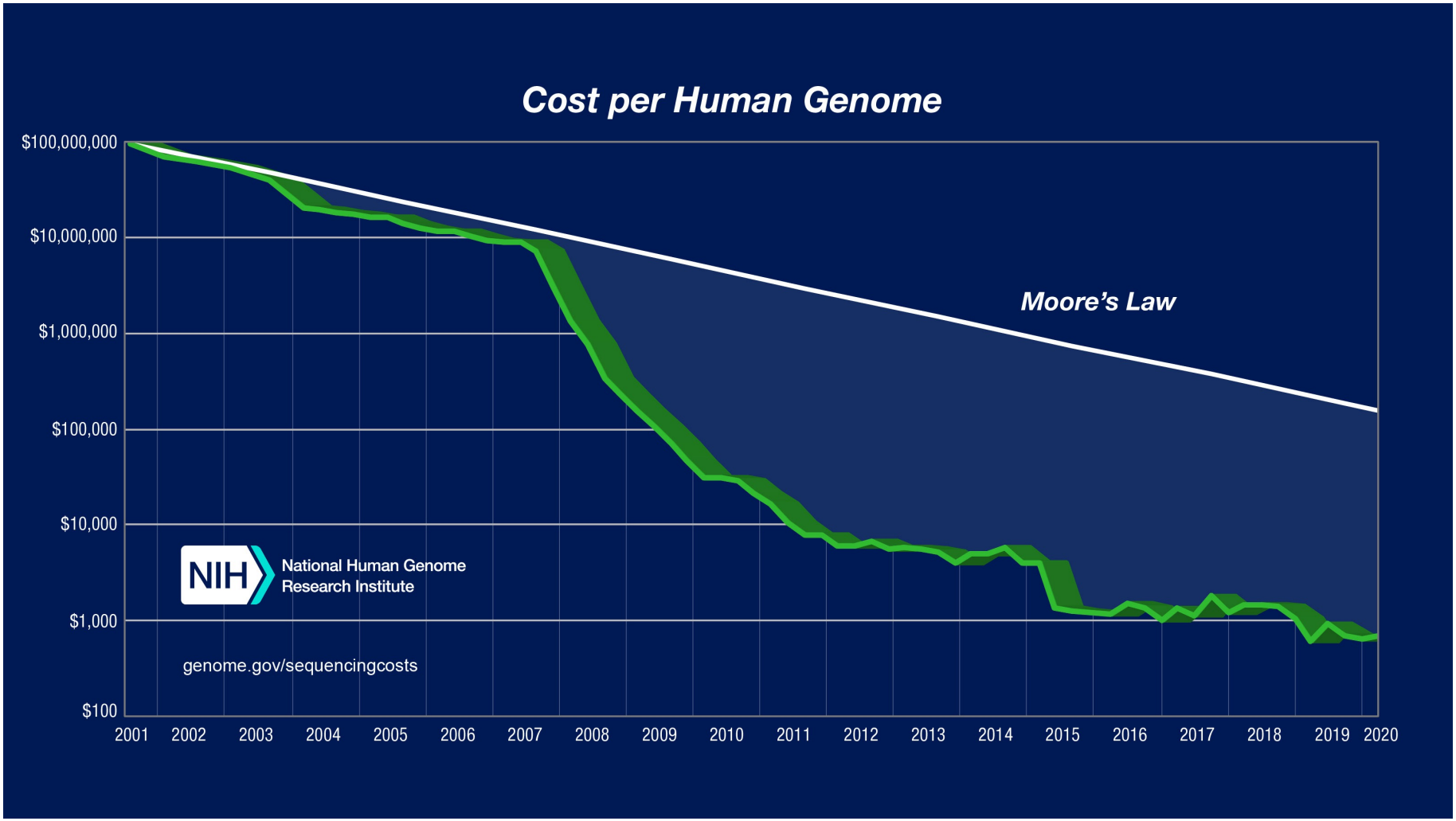


*From NIH (https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data)

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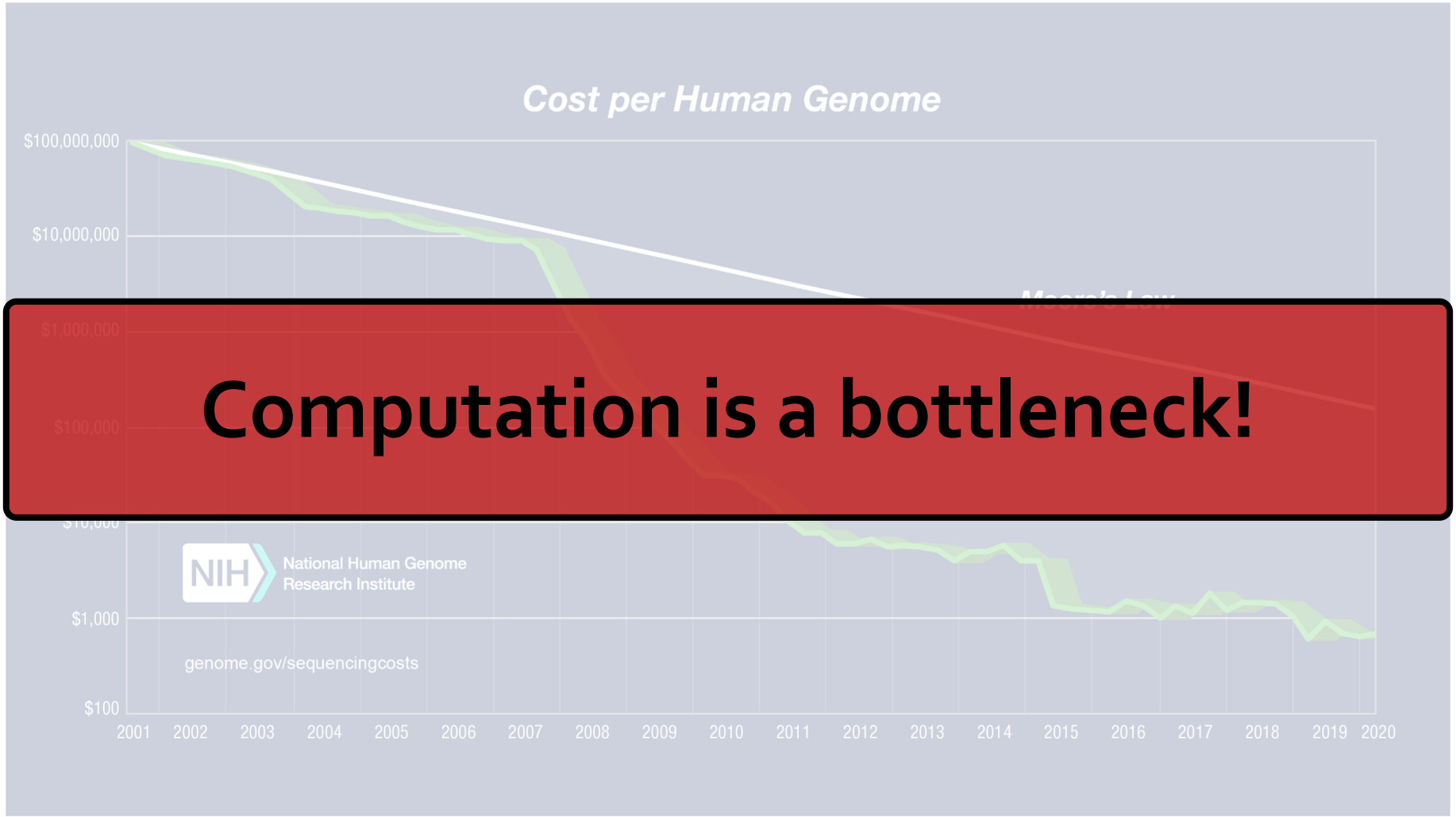


**Computation is a bottleneck!**

*From NIH (https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data)

# Problem Statement

**Rapid genome sequence analysis** is currently bottlenecked by **the computational power and memory bandwidth limitations of existing systems**, as many of the steps in genome sequence analysis must process **a large amount of data**

# Our Goal & Approach

- **Our Goal:**

  Accelerating genome sequence analysis by **efficient hardware/algorithm co-design**

- **Our Approach:**
  (1) Analyze the multiple steps and the associated tools in the genome sequence analysis pipeline,
  (2) Expose the tradeoffs between accuracy, performance, memory usage and scalability, and
  (3) Co-design fast and efficient algorithms along with scalable and energy-efficient customized hardware accelerators for the key bottleneck steps of the pipeline

# Research Statement

Genome sequence analysis

can be accelerated by co-designing

**fast and efficient algorithms** along with

**scalable and energy-efficient customized**

**hardware accelerators** for the

**key bottleneck steps of the pipeline**

# Research Contributions

Bottleneck analysis of genome assembly pipeline for long reads

*[Briefings in Bioinformatics, 2018]*

GenASM: Approximate string matching framework for genome sequence analysis

*[MICRO 2020]*

BitMAc: FPGA-based near-memory acceleration of bitvector-based sequence alignment

**[Ongoing]**

SeGraM: Hardware acceleration framework for sequence-to-graph mapping

**[Ongoing]**

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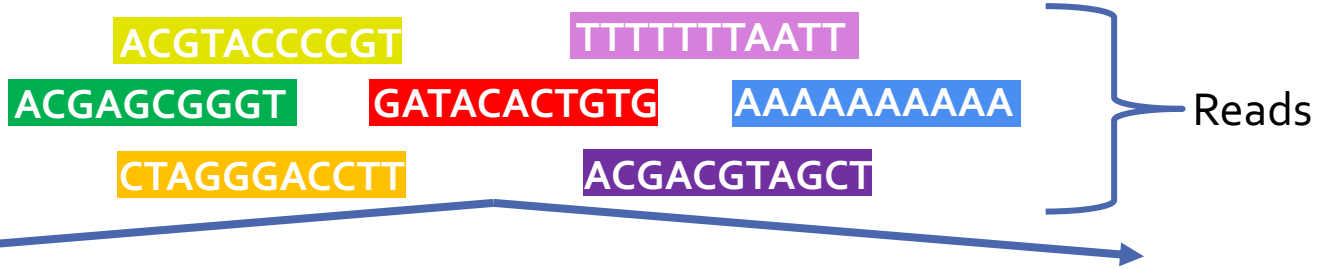
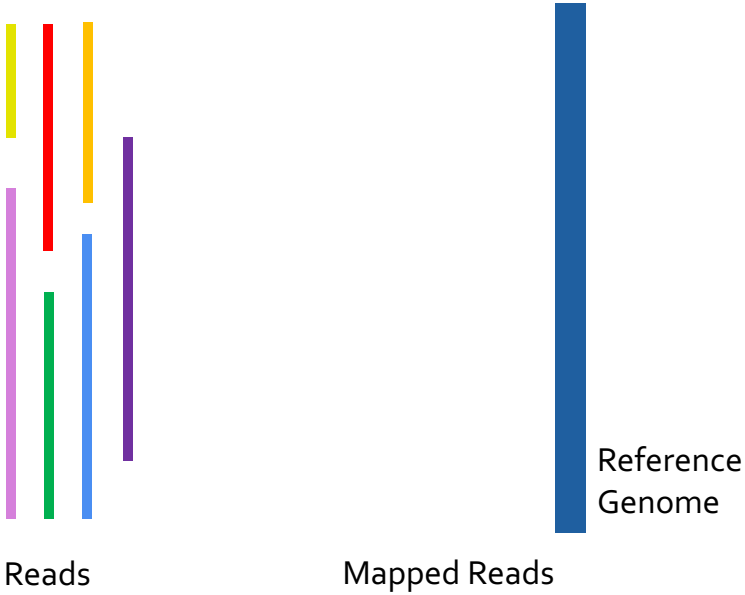
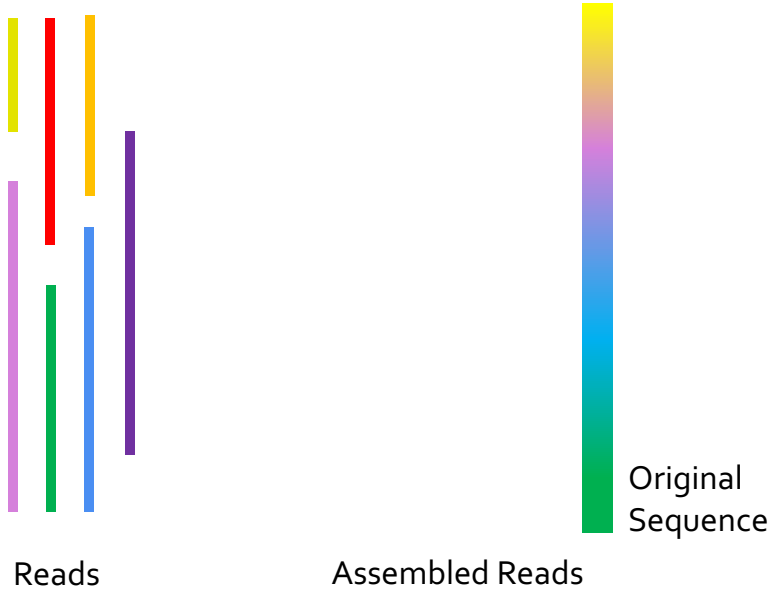
# Genome Sequence Analysis




**Read Mapping,** method of aligning the reads against the reference genome in order to **detect matches and variations.**

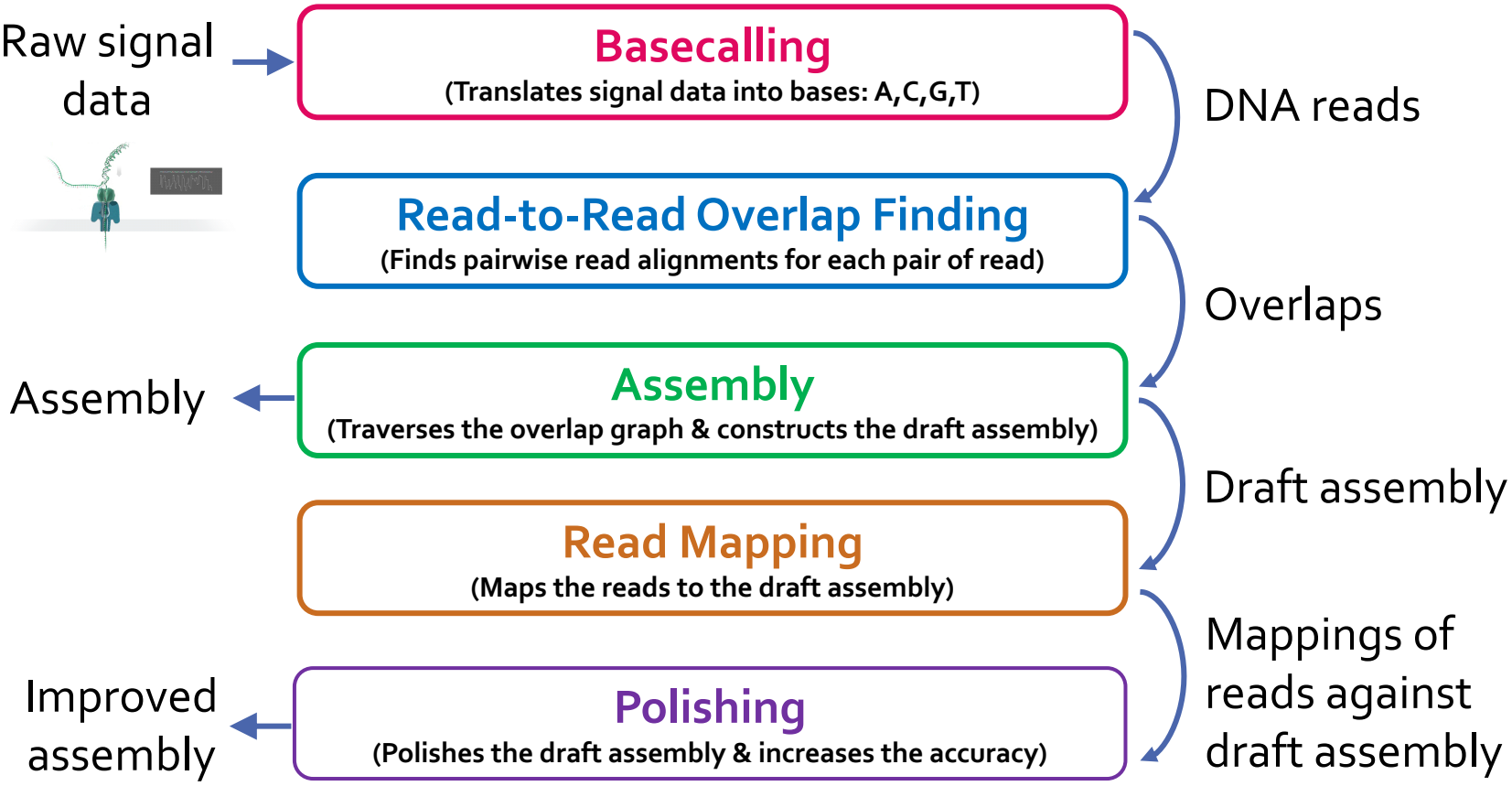
***De novo* Assembly,** method of merging the reads in order to **construct** the original sequence.



# Genome Assembly Pipeline Using Long Reads

- With the emergence of long read sequencing technologies, *de novo* assembly becomes a promising way of constructing the original genome.



# Our Contributions

- Analyze the tools in multiple dimensions: accuracy, performance, memory usage, and scalability
- Reveal new bottlenecks and trade-offs
- First study on bottleneck analysis of nanopore sequence analysis pipeline on real machines
- Provide guidelines for practitioners
- Provide guidelines for tool developers

# Key Findings

- Laptops are becoming a popular platform for running genome assembly tools, as the portability of a laptop makes it a good fit for in-field analysis
  - Greater memory constraints
  - Lower computational power
  - Limited battery life

- Memory usage is an important factor that greatly affects the performance and the usability of the tool
  - Data structure choices that increase the memory requirements
  - Algorithms that are not cache-efficient
  - Not keeping memory usage in check with the number of threads

- Scalability of the tool with the number of cores is an important requirement. However, parallelizing the tool can increase the memory usage
  - Not dividing the input data into batches
  - Not limiting the memory usage of each thread
  - Dividing the dataset instead of the computation between simultaneous threads

# Key Findings

## Goal 1: High-performance and low-power

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# Key Findings

**Goal 1:**
**High-performance and low-power**

**Goal 2:**
**Memory-efficient**

- Scalability of the tool with the number of cores is an important requirement. However, parallelizing the tool can increase the memory usage
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# Key Findings

**Goal 1:**
**High-performance and low-power**

**Goal 2:**
**Memory-efficient**

**Goal 3:**
**Scalable/highly-parallel**

# Nanopore Sequencing & Tools [BiB 2018]

Damla Senol Cali, Jeremie S. Kim, Saugata Ghose, Can Alkan, and Onur Mutlu, **"Nanopore Sequencing Technology and Tools for Genome Assembly: Computational Analysis of the Current State, Bottlenecks and Future Directions"**

*Briefings in Bioinformatics*, April 2018.

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

**Damla Senol Cali [1,*], Jeremie S. 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

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*[Ongoing]*

SeGraM: Hardware acceleration framework for sequence-to-graph mapping

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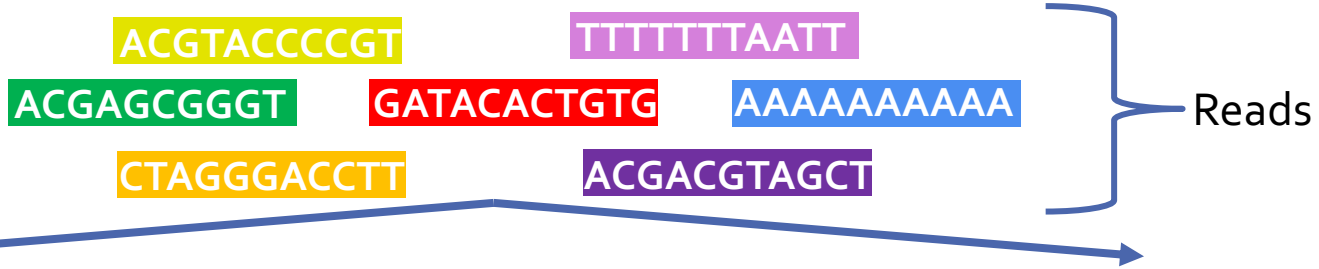
# Recall: Genome Sequence Analysis

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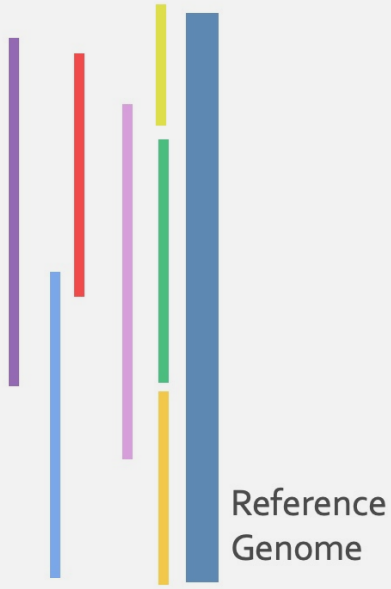
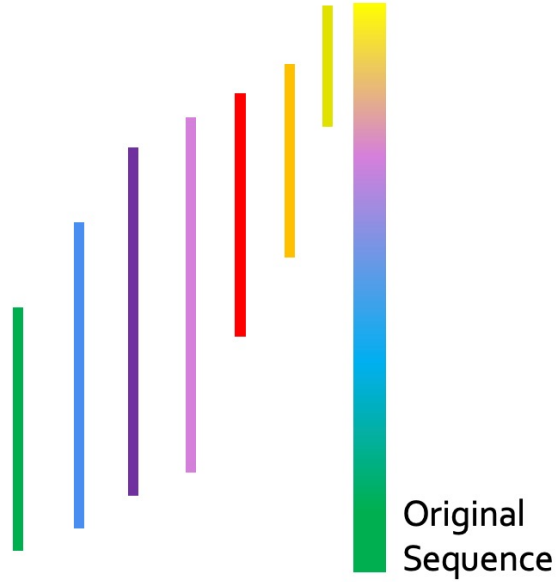
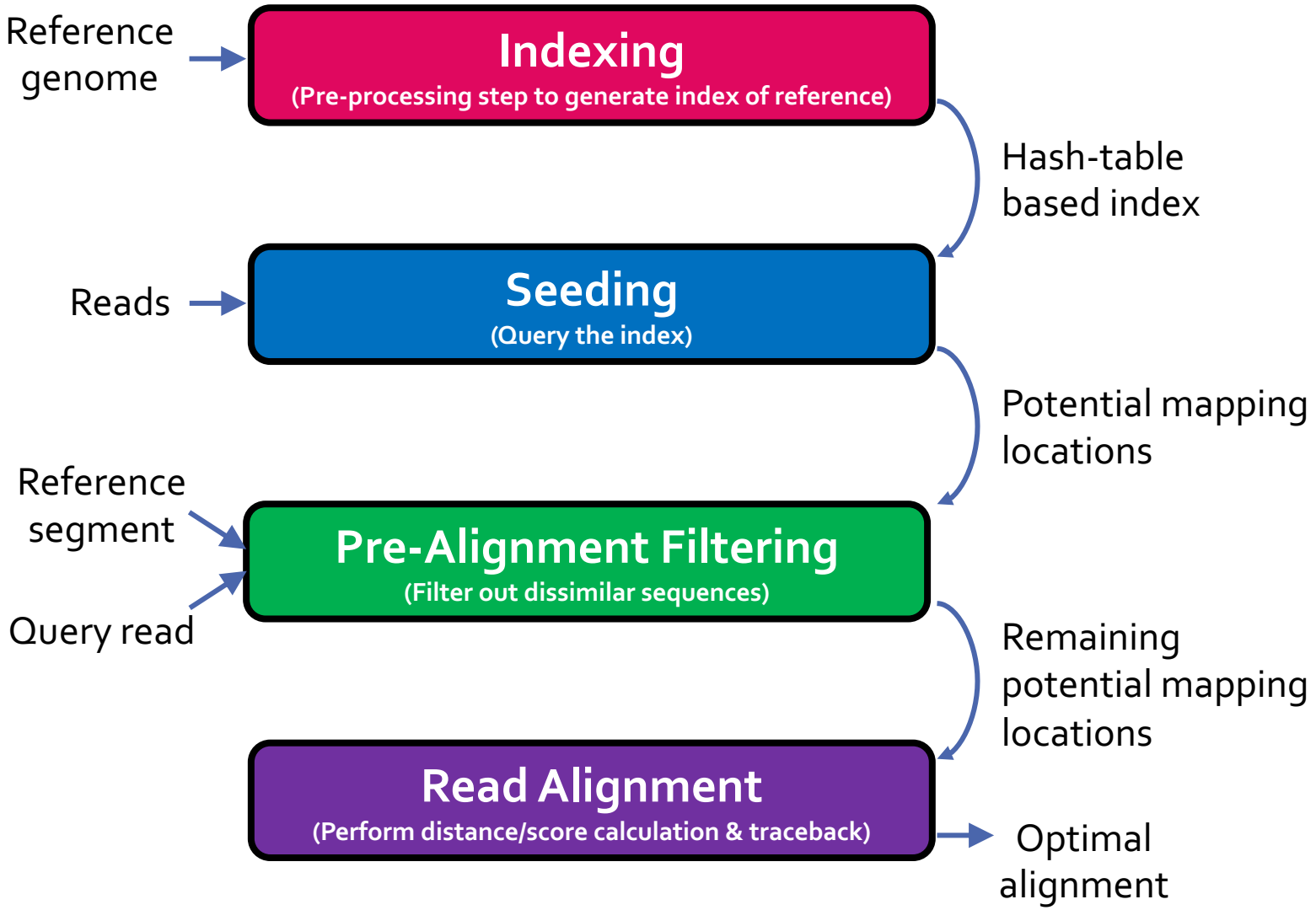



***De novo* Assembly,** method of merging the reads in order to **construct** the original sequence.



# Read Mapping Pipeline



# GSA with Read Mapping

- **Read mapping:** *First key step* in genome sequence analysis (GSA)
  - Aligns reads to one or more possible locations within the reference genome, and
  - Finds the matches and differences between the read and the reference genome segment at that location

- Multiple steps of read mapping require ***approximate string matching***
  - Approximate string matching (ASM) enables read mapping to account for sequencing errors and genetic variations in the reads

- Bottlenecked by the computational power and memory bandwidth limitations of existing systems

# GenASM: ASM Framework for GSA

**Our Goal:**

Accelerate approximate string matching
by designing a fast and flexible framework,
which can accelerate *multiple steps* of genome sequence analysis

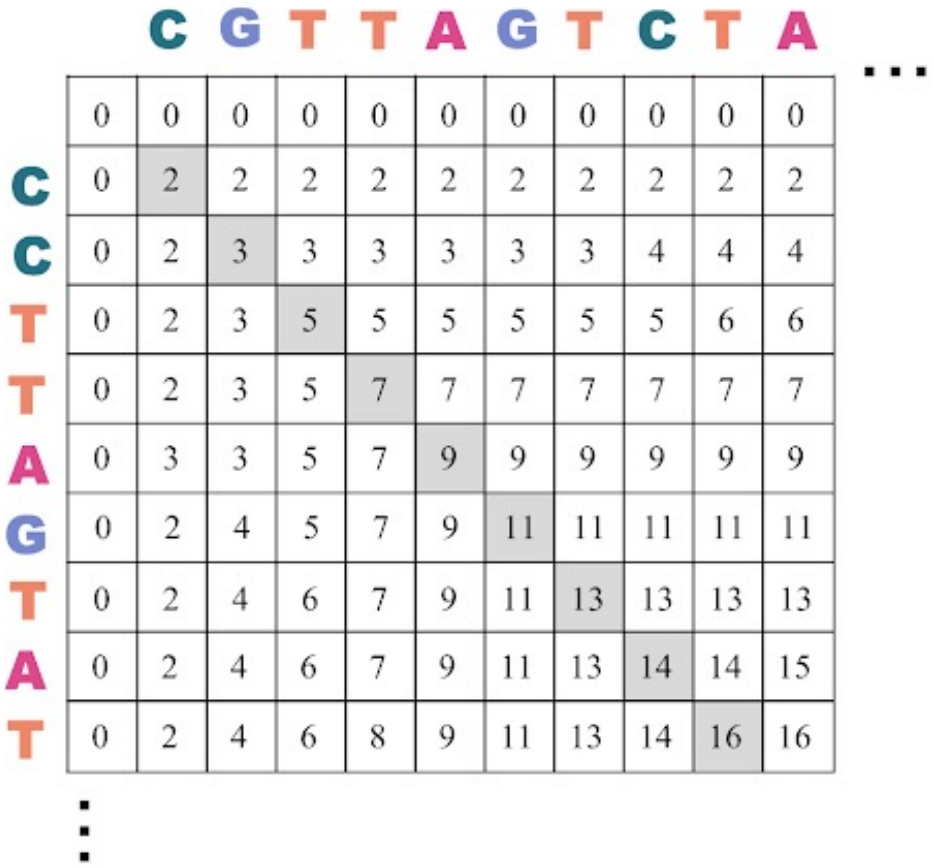
- **GenASM:** *First* ASM acceleration framework for GSA
  - Based upon the *Bitap* algorithm
    - Uses fast and simple bitwise operations to perform ASM
  - Modified and extended ASM algorithm
    - Highly-parallel Bitap with long read support
    - Novel bitvector-based algorithm to perform *traceback*
  - Co-design of our modified scalable and memory-efficient algorithms with low-power and area-efficient hardware accelerators

# Approximate String Matching

- Sequenced genome may not exactly map to the reference genome due to genetic variations and sequencing errors


- **Approximate string matching (ASM):**
  - Detect the differences and similarities between two sequences
  - In genomics, ASM is required to:
    - Find the *minimum edit distance* (i.e., total number of differences)
    - Find the *optimal alignment* with a *traceback* step
      - Sequence of matches, substitutions, insertions and deletions, along with their positions
  - Usually implemented as a dynamic programming (DP) based algorithm

# DP-based ASM



| | | C | G | T | T | A | G | T | C | T | A | … |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| C | 0 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | |
| C | 0 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | |
| T | 0 | 2 | 3 | 5 | 5 | 5 | 5 | 5 | 5 | 6 | 6 | |
| T | 0 | 2 | 3 | 5 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | |
| A | 0 | 3 | 3 | 5 | 7 | 9 | 9 | 9 | 9 | 9 | 9 | |
| G | 0 | 2 | 4 | 5 | 7 | 9 | 11 | 11 | 11 | 11 | 11 | |
| T | 0 | 2 | 4 | 6 | 7 | 9 | 11 | 13 | 13 | 13 | 13 | |
| A | 0 | 2 | 4 | 6 | 7 | 9 | 11 | 13 | 14 | 14 | 15 | |
| T | 0 | 2 | 4 | 6 | 8 | 9 | 11 | 13 | 14 | 16 | 16 | |
| ⋮ | | | | | | | | | | | | |

Commonly-used algorithm for ASM in genomics…

…with quadratic time and space complexity

# Bitap Algorithm

- Bitap[1,2] performs ASM with fast and simple bitwise operations
  - Amenable to efficient hardware acceleration
  - Computes the **minimum edit distance** between a **text** (e.g., reference genome) and a **pattern** (e.g., read) with a maximum of ***k*** errors
- **Step 1: Pre-processing (per pattern)**
  - Generate a pattern bitmask (PM) for each character in the alphabet (A, C, G, T)
  - Each PM indicates if character exists at each position of the pattern
- **Step 2: Searching (Edit Distance Calculation)**
  - Compare all characters of the text with the pattern by using:
    - Pattern bitmasks
    - Status bitvectors that hold the partial matches
    - Bitwise operations

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

# Limitations of Bitap

1) **Data Dependency Between Iterations:**
   - Two-level data dependency forces the consecutive iterations to take place sequentially

# Bitap Algorithm (cont'd.)

- **Step 2: Edit Distance Calculation**

For each character of the text (char):

Copy previous R bitvectors as oldR

R[0] = (oldR[0] << 1) | PM [char]

For d = 1…k:

deletion = oldR[d-1]

substitution = oldR[d-1] << 1

insertion = R[d-1] << 1

match = (oldR[d] << 1) | PM [char]

R[d] = deletion & mismatch & insertion & match

Check MSB of R[d]:

If 1, no match.

If 0, match with *d* many errors.

Large number of iterations

# Bitap Algorithm (cont'd.)

- **Step 2: Edit Distance Calculation**

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Data dependency between iterations (i.e., no parallelization)

R[d] = deletion & mismatch & insertion & match

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# Limitations of Bitap

1) **Data Dependency Between Iterations:**
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2) **No Support for Traceback:**
   - Bitap does not include any support for optimal alignment identification

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  R[d] = deletion & mismatch & insertion & match

  Check MSB of R[d]:

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Does *not* store and process these intermediate bitvectors to find the optimal alignment (i.e., no traceback)

# Limitations of Bitap

**Algorithm**

1) **Data Dependency Between Iterations:**
   - Two-level data dependency forces the consecutive iterations to take place sequentially
2) **No Support for Traceback:**
   - Bitap does not include any support for optimal alignment identification
3) **No Support for Long Reads:**
   - Each bitvector has a length equal to the length of the pattern
   - Bitwise operations are performed on these bitvectors

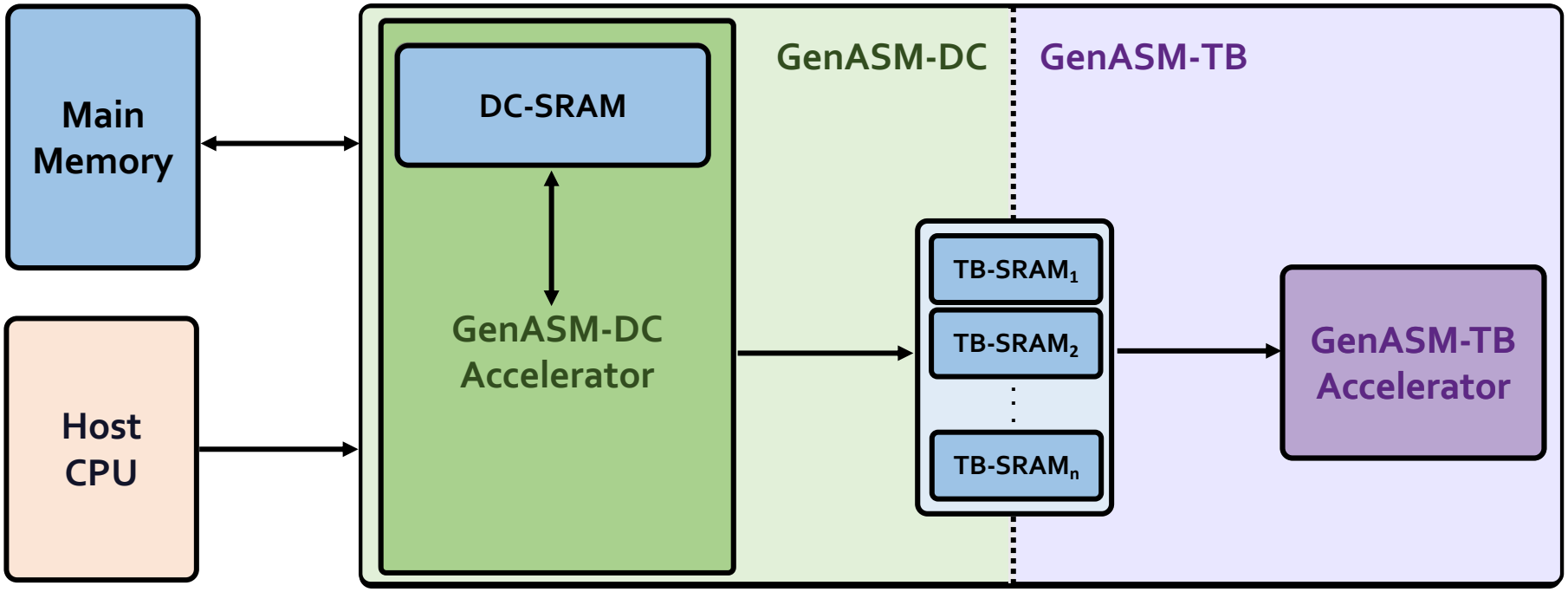
**Hardware**

4) **Limited Compute Parallelism:**
   - Text-level parallelism
   - Limited by the number of compute units in existing systems
5) **Limited Memory Bandwidth:**
   - High memory bandwidth required to read and write the computed bitvectors to memory

# GenASM: ASM Framework for GSA

- Approximate string matching (ASM) acceleration framework based on the Bitap algorithm
- *First* ASM acceleration framework for genome sequence analysis
- We overcome the five limitations that hinder Bitap's use in genome sequence analysis:
  - Modified and extended ASM algorithm **SW**
    - Highly-parallel Bitap with long read support
    - Novel bitvector-based algorithm to perform *traceback*
  - Specialized, low-power and area-efficient hardware for both modified Bitap and novel traceback algorithms **HW**

# GenASM Hardware Design




**GenASM-DC:** generates bitvectors and performs edit **D**istance **C**alculation

**GenASM-TB:** performs **T**race**B**ack and assembles the optimal alignment

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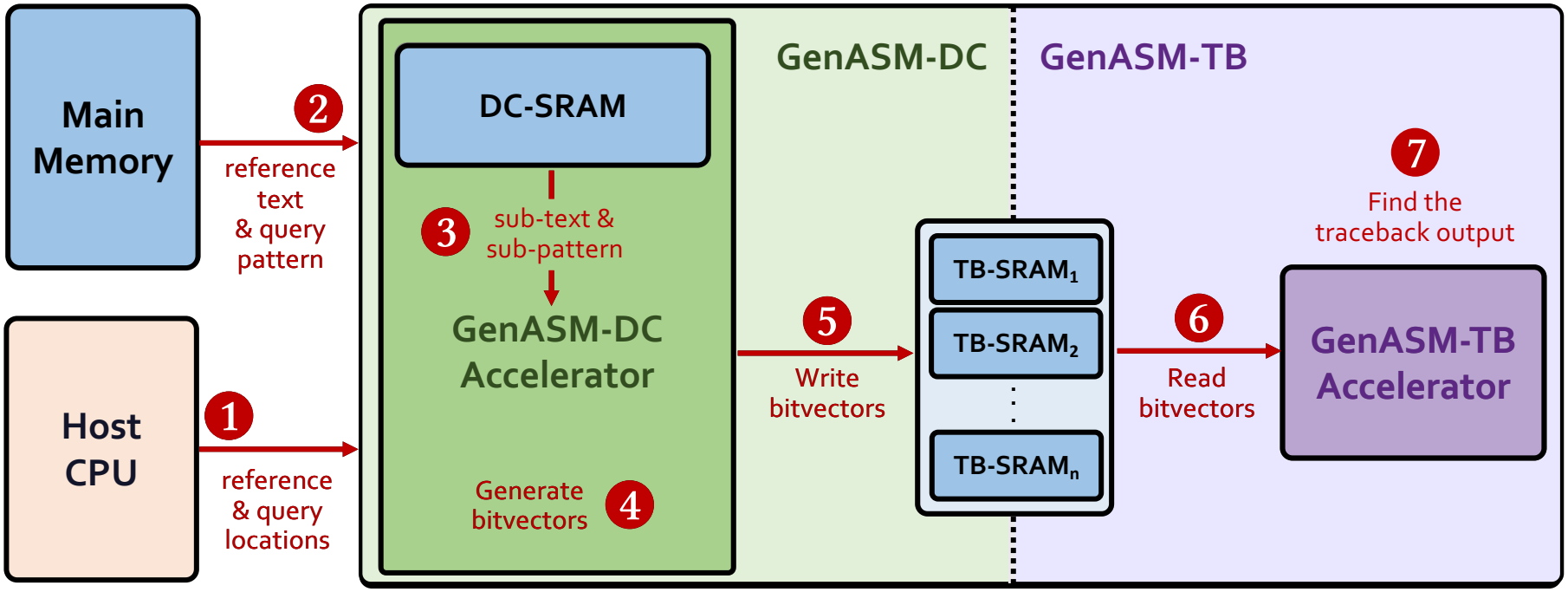


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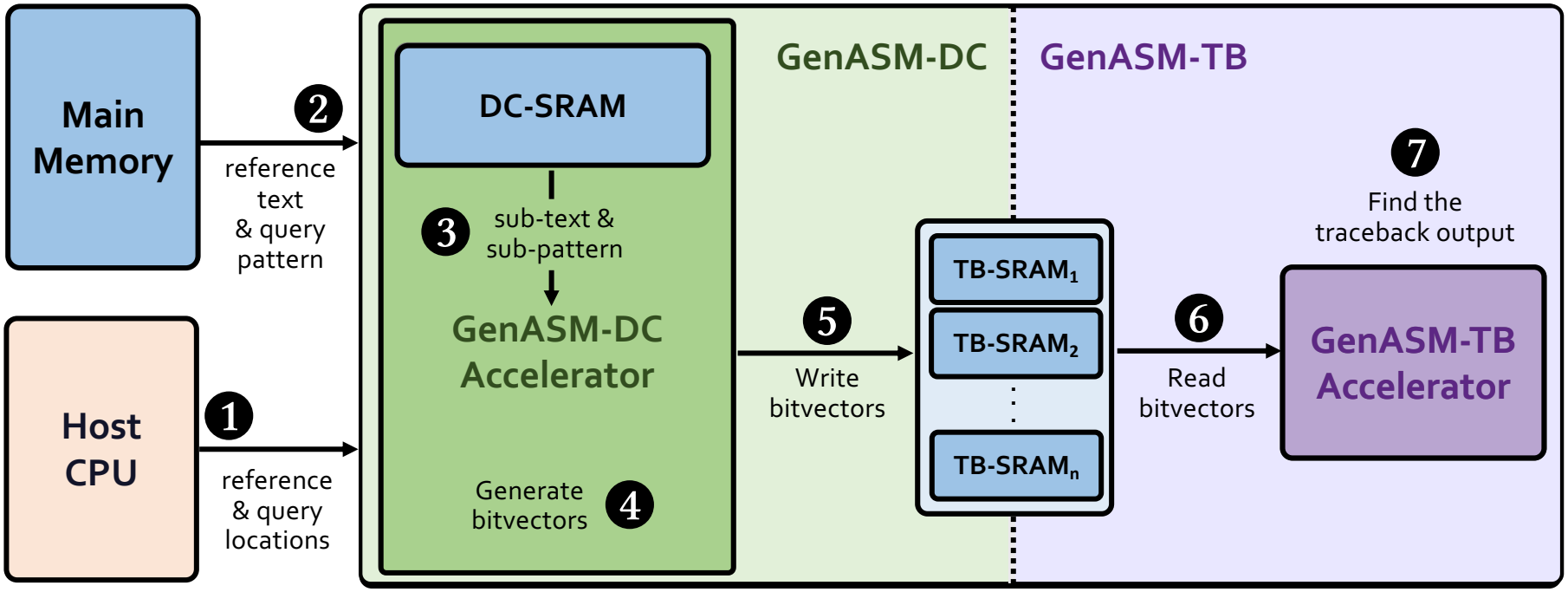



**Our *specialized compute units* and *on-chip SRAMs* help us to:**

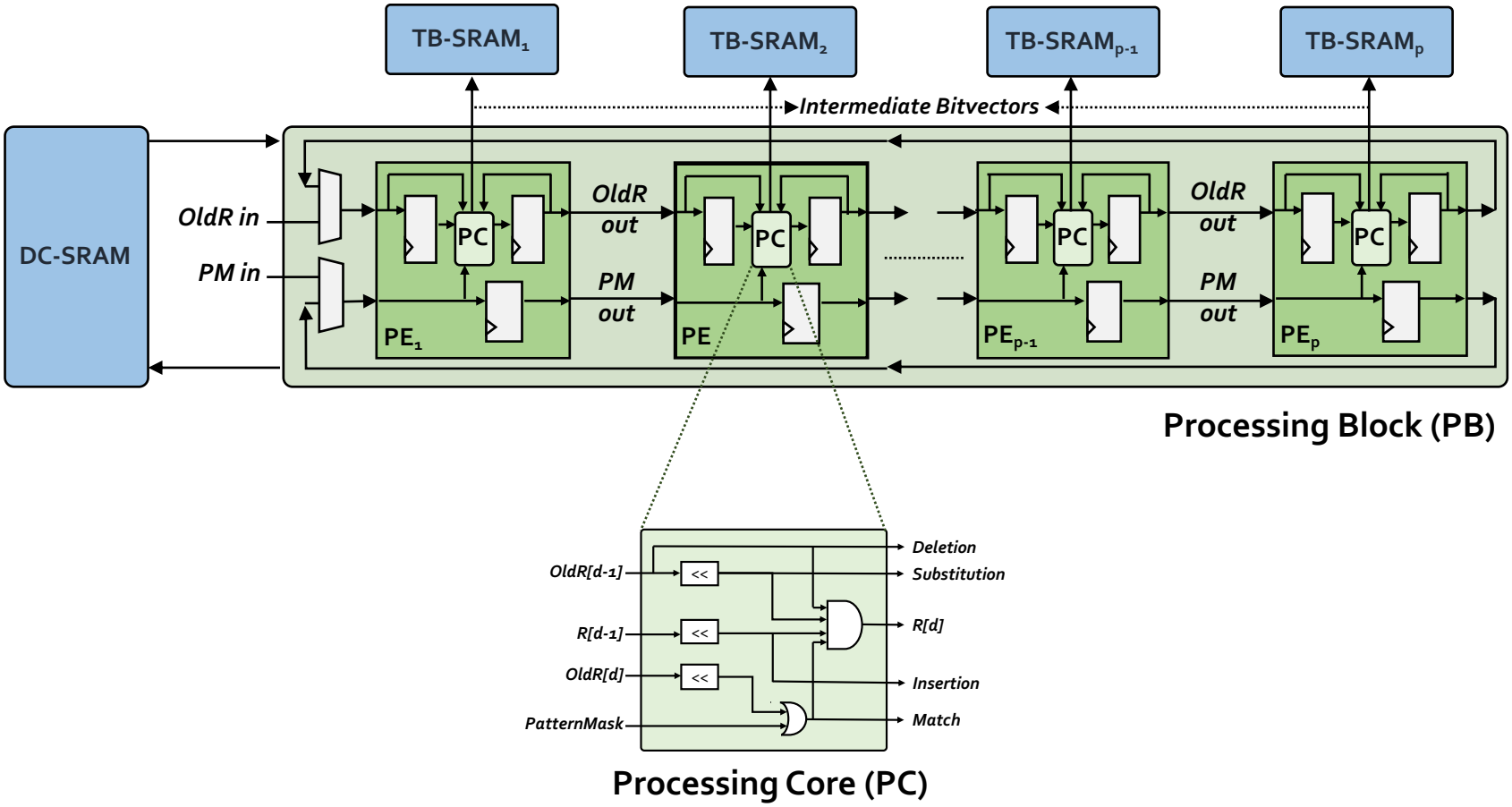
**→ Match the rate of computation with memory capacity and bandwidth**

**→ Achieve high performance and power efficiency**

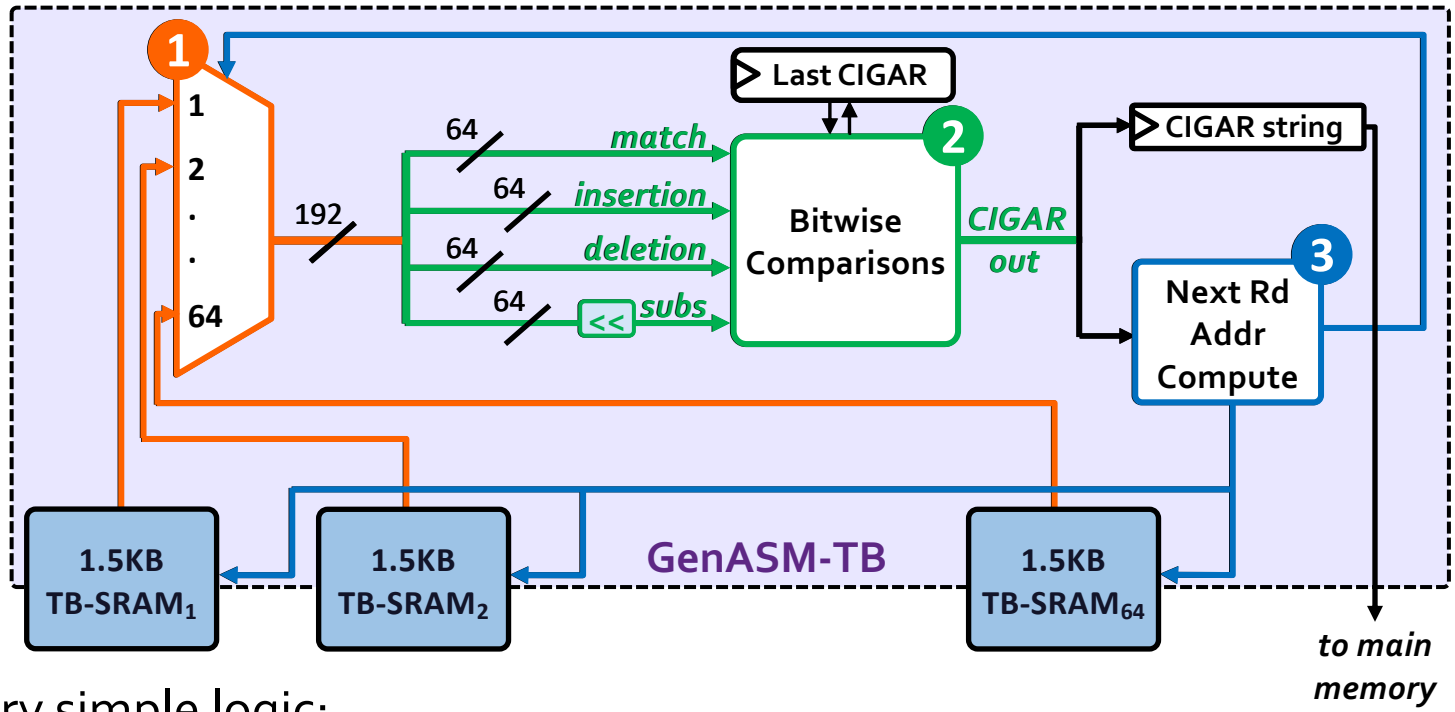
**→ Scale linearly in performance with the number of parallel compute units that we add to the system**

# GenASM-DC: Hardware Design

- **Linear cyclic systolic array-**based accelerator
  - Designed to maximize parallelism and minimize memory bandwidth and memory footprint



# GenASM-TB: Hardware Design




- Very simple logic:
  - 1 Reads the bitvectors from one of the TB-SRAMs using the computed address
  - 2 Performs the required bitwise comparisons to find the traceback output for the current position
  - 3 Computes the next TB-SRAM address to read the new set of bitvectors

# Use Cases of GenASM

**(1) Read Alignment Step of Read Mapping**

- Find the optimal alignment of how reads map to candidate reference regions

**(2) Pre-Alignment Filtering for Short Reads**

- Quickly identify and filter out the unlikely candidate reference regions for each read

**(3) Edit Distance Calculation**

- Measure the similarity or distance between two sequences

- We also discuss other possible use cases of GenASM in our paper:
  - Read-to-read overlap finding, hash-table based indexing, whole genome alignment, generic text search

# Evaluation Methodology

- We evaluate GenASM using:
  - Synthesized SystemVerilog models of the GenASM-DC and GenASM-TB accelerator datapaths
  - Detailed simulation-based performance modeling

- 16GB HMC-like 3D-stacked DRAM architecture
  - 32 vaults
  - 256GB/s of internal bandwidth, clock frequency of 1.25GHz
  - In order to achieve high parallelism and low power-consumption
  - Within each vault, the logic layer contains a GenASM-DC accelerator, its associated DC-SRAM, a GenASM-TB accelerator, and TB-SRAMs.

# Evaluation Methodology (cont'd.)

| | SW Baselines | HW Baselines |
|---|---|---|
| Read Alignment | Minimap2[1]<br>BWA-MEM[2] | GACT (Darwin)[3]<br>SillaX (GenAx)[4] |
| Pre-Alignment Filtering | – | Shouji[5] |
| Edit Distance Calculation | Edlib[6] | ASAP[7] |


[1] H. Li. "Minimap2: Pairwise Alignment for Nucleotide Sequences." In *Bioinformatics,* 2018.
[2] H. Li. "Aligning sequence reads, clone sequences and assembly contigs with BWA-MEM." In *arXiv,* 2013.
[3] Y. Turakhia et al. "Darwin: A genomics co-processor provides up to 15,000 x acceleration on long read assembly." In *ASPLOS,* 2018.
[4] D. Fujiki et al. "GenAx: A genome sequencing accelerator." In *ISCA*, 2018.
[5] M. Alser. "Shouji: A fast and efficient pre-alignment filter for sequence alignment." In *Bioinformatics,* 2019.
[6] M. Šošić et al. "Edlib: A C/C++ library for fast, exact sequence alignment using edit distance." In *Bioinformatics,* 2017.
[7] S.S. Banerjee et al. "ASAP: Accelerated short-read alignment on programmable hardware." In *TC*, 2018.

# Evaluation Methodology (cont'd.)

- **For Use Case 1: Read Alignment**, we compare GenASM with:
  - Minimap2 and BWA-MEM (state-of-the-art **SW**)
    - Running on Intel® Xeon® Gold 6126 CPU (12-core) operating @2.60GHz with 64GB DDR4 memory
    - Using two simulated datasets:
      - Long ONT and PacBio reads: 10Kbp reads, 10-15% error rate
      - Short Illumina reads: 100-250bp reads, 5% error rate
  - GACT of Darwin and SillaX of GenAx (state-of-the-art **HW**)
    - Open-source RTL for GACT
    - Data reported by the original work for SillaX
    - GACT is best for long reads, SillaX is best for short reads

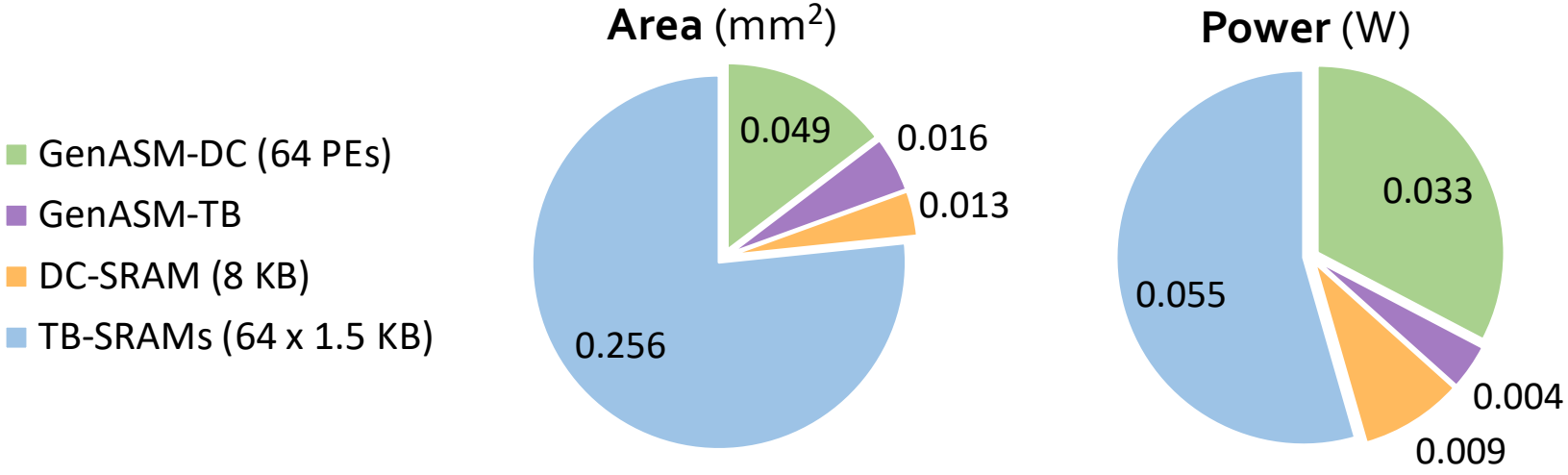
# Evaluation Methodology (cont'd.)

- **For Use Case 2: Pre-Alignment Filtering,** we compare GenASM with:
  - Shouji (state-of-the-art **HW** – FPGA-based filter)
    - Using two datasets provided as test cases:
      - 100bp reference-read pairs with an edit distance threshold of 5
      - 250bp reference-read pairs with an edit distance threshold of 15

- **For Use Case 3: Edit Distance Calculation,** we compare GenASM with:
  - Edlib (state-of-the-art **SW**)
    - Using two 100Kbp and 1Mbp sequences with similarity ranging between 60%-99%
  - ASAP (state-of-the-art **HW** – FPGA-based accelerator)
    - Using data reported by the original work

# Key Results – Area and Power

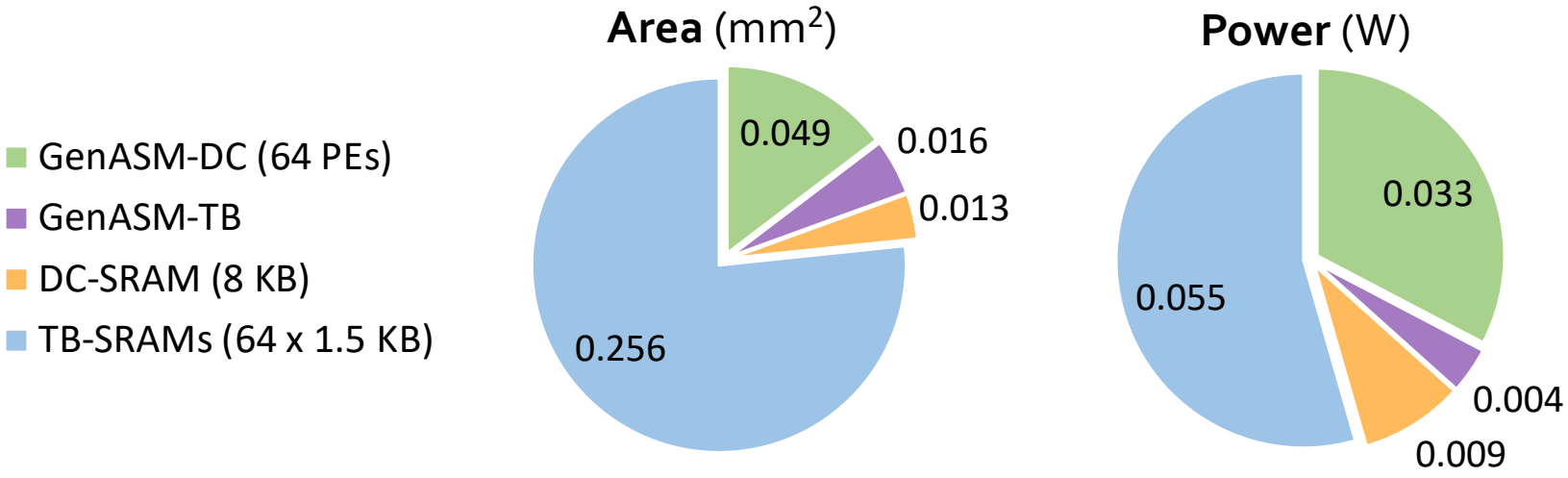
- Based on our **synthesis** of **GenASM-DC** and **GenASM-TB** accelerator datapaths using the Synopsys Design Compiler with a **28nm** process:
  - Both GenASM-DC and GenASM-TB operate **@ 1GHz**




| | | |
|---|---|---|
| **Total (1 vault):** | 0.334 $mm^2$ | 0.101 W |
| **Total (32 vaults):** | 10.69 $mm^2$ | 3.23 W |
| **% of a Xeon CPU core:** | **1%** | **1%** |

# Key Results – Area and Power

- Based on our **synthesis** of **GenASM-DC** and **GenASM-TB** accelerator datapaths using the Synopsys Design Compiler with a **28nm** LP process:
  - Both GenASM-DC and GenASM-TB operate **@ 1GHz**




**GenASM has low area and power overheads**

# Key Results – Use Case 1

**(1) Read Alignment Step of Read Mapping**

- Find the optimal alignment of how reads map to candidate reference regions

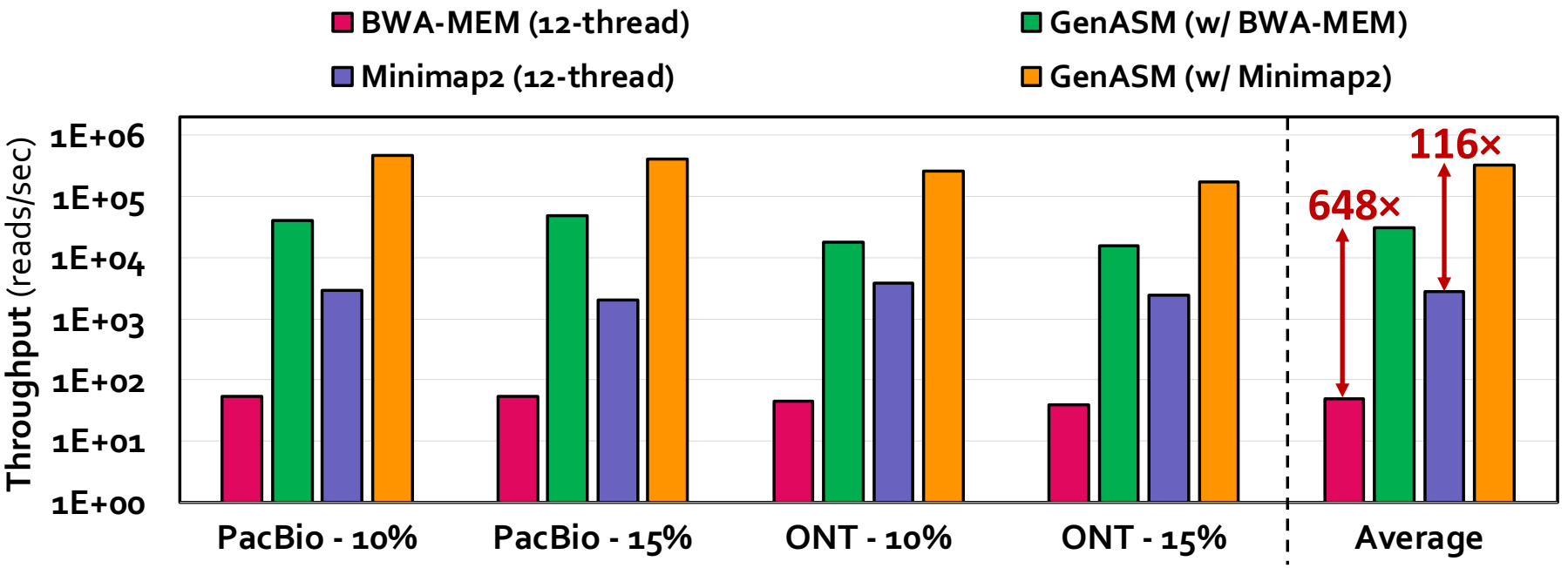
**(2) Pre-Alignment Filtering for Short Reads**

- Quickly identify and filter out the unlikely candidate reference regions for each read

**(3) Edit Distance Calculation**

- Measure the similarity or distance between two sequences

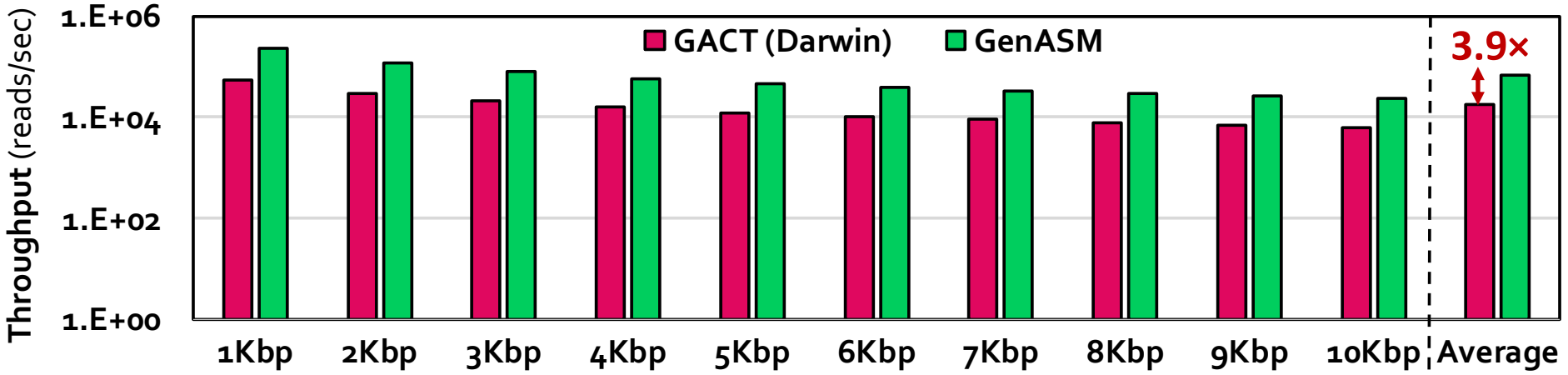
# Key Results – Use Case 1 (Long Reads)




**SW**

GenASM **achieves 648× and 116× speedup** over 12-thread runs of BWA-MEM and Minimap2, while **reducing power consumption by 34× and 37×**

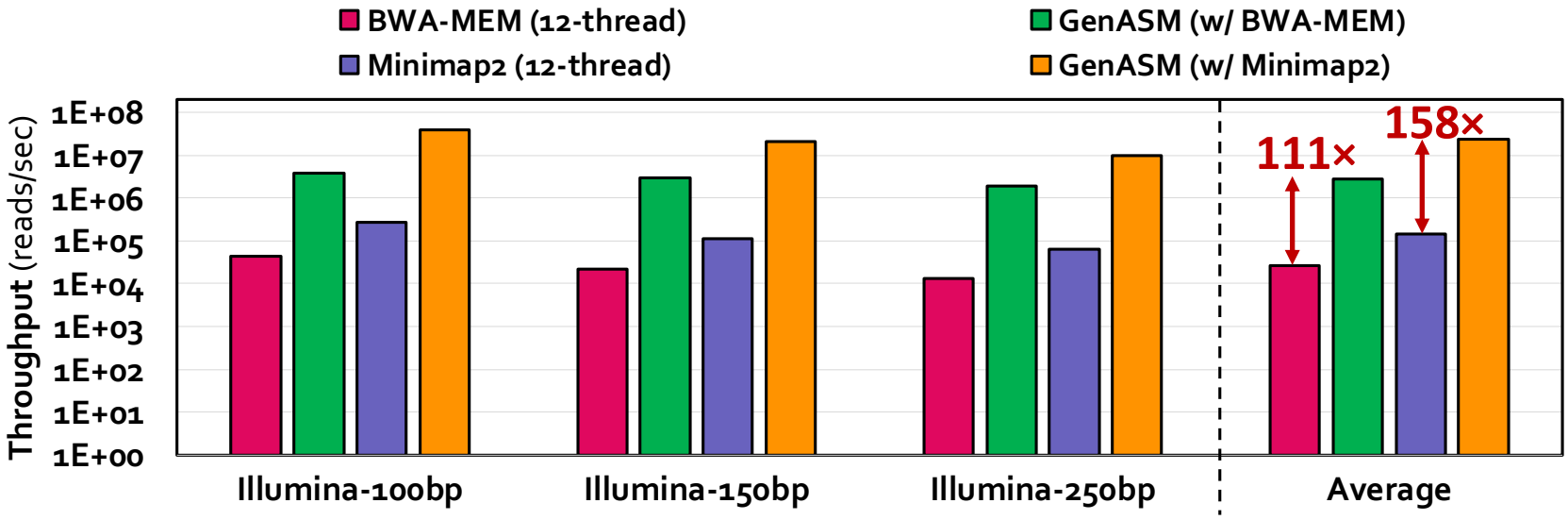
# Key Results – Use Case 1 (Long Reads)




**HW**

GenASM provides **3.9× better throughput**,
**6.6× the throughput per unit area**, and
**10.5× the throughput per unit power**,
compared to GACT of Darwin

# Key Results – Use Case 1 (Short Reads)




**SW** GenASM **achieves 111× and 158× speedup** over 12-thread runs of BWA-MEM and Minimap2, while **reducing power consumption by 33× and 31×**

**HW** GenASM provides **1.9× better throughput** and uses **63% less logic area** and **82% less logic power**, compared to SillaX of GenAx

# Key Results – Use Case 2

**(1) Read Alignment Step of Read Mapping**

- Find the optimal alignment of how reads map to candidate reference regions

**(2) Pre-Alignment Filtering for Short Reads**

- Quickly identify and filter out the unlikely candidate reference regions for each read

**(3) Edit Distance Calculation**

- Measure the similarity or distance between two sequences

# Key Results – Use Case 2

- Compared to Shouji:
  - **3.7×** speedup
  - **1.7×** less power consumption
  - **False accept rate of 0.02%** for GenASM vs. 4% for Shouji
  - **False reject rate of 0%** for both GenASM and Shouji

**HW**

GenASM is **more efficient in terms of both speed and power consumption**, while **significantly improving the accuracy** of pre-alignment filtering

# Key Results – Use Case 3

**(1) Read Alignment Step of Read Mapping**

- Find the optimal alignment of how reads map to candidate reference regions

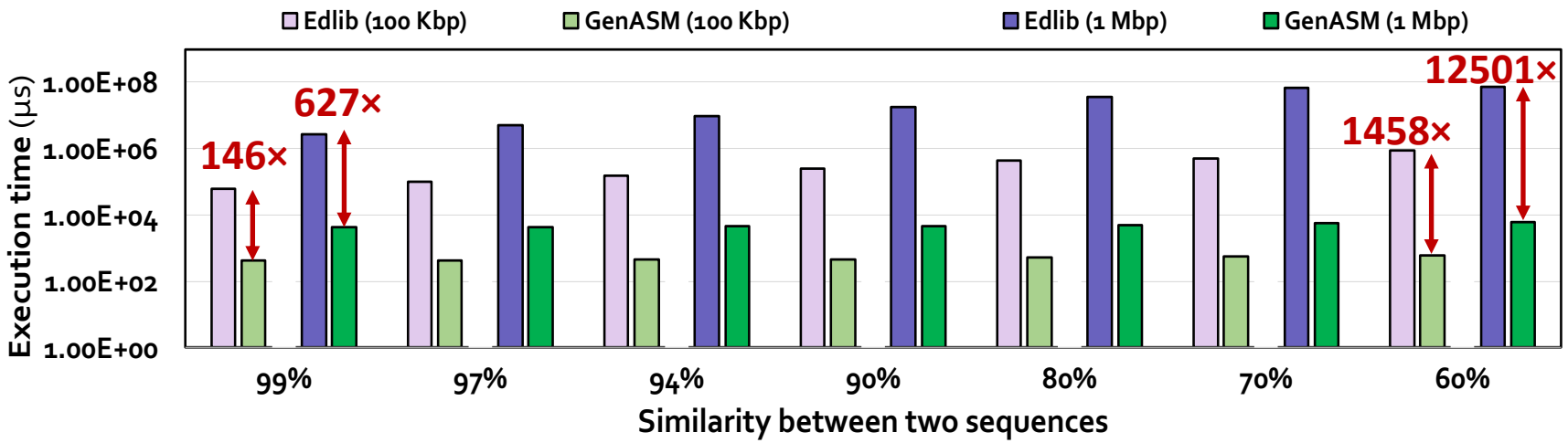
**(2) Pre-Alignment Filtering for Short Reads**

- Quickly identify and filter out the unlikely candidate reference regions for each read

**(3) Edit Distance Calculation**

- Measure the similarity or distance between two sequences

# Key Results – Use Case 3




**SW**

GenASM provides **146 – 1458×** and **627 – 12501× speedup, while reducing power consumption by 548×** and **582×** for 100Kbp and 1Mbp sequences, respectively, compared to Edlib

**HW**

GenASM provides **9.3 – 400× speedup** over ASAP, while consuming **67× less power**

# Additional Details in the Paper

- Details of the **GenASM-DC and GenASM-TB algorithms**
- **Big-O analysis** of the algorithms
- Detailed explanation of **evaluated use cases**
- **Evaluation methodology details**
  (datasets, baselines, performance model)
- **Additional results** for the three evaluated use cases
- **Sources of improvements in GenASM**
  (algorithm-level, hardware-level, technology-level)
- Discussion of **four other potential use cases** of GenASM

# Summary of GenASM

- **Problem:**
  - Genome sequence analysis is bottlenecked by the computational power and memory bandwidth limitations of existing systems
  - This bottleneck is particularly an issue for *approximate string matching*

- **Key Contributions:**
  - GenASM: An approximate string matching (ASM) acceleration framework to accelerate multiple steps of genome sequence analysis
    - *First* to enhance and accelerate Bitap for ASM with genomic sequences
    - *Co-design* of our modified scalable and memory-efficient algorithms with low-power and area-efficient hardware accelerators
    - Evaluation of three different use cases: read alignment, pre-alignment filtering, edit distance calculation

- **Key Results:** GenASM is significantly more efficient for all the three use cases (in terms of throughput and throughput per unit power) than state-of-the-art software and hardware baselines

# GenASM [MICRO 2020]

Damla Senol Cali, Gurpreet S. Kalsi, Zulal Bingol, Can Firtina, Lavanya Subramanian, Jeremie S. Kim, Rachata Ausavarungnirun, Mohammed Alser, Juan Gomez-Luna, Amirali Boroumand, Anant Nori, Allison Scibisz, Sreenivas Subramoney, Can Alkan, Saugata Ghose, and Onur Mutlu,

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

*Proceedings of the 53rd International Symposium on Microarchitecture (**MICRO**)*, Virtual, October 2020.

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

Damla Senol Cali[†⋈] Gurpreet S. Kalsi[⋈] Zülal Bingöl[▽] Can Firtina[◇] Lavanya Subramanian[‡] Jeremie S. Kim[◇†]
Rachata Ausavarungnirun[⊙] Mohammed Alser[◇] Juan Gomez-Luna[◇] Amirali Boroumand[†] Anant Nori[⋈]
Allison Scibisz[†] Sreenivas Subramoney[⋈] Can Alkan[▽] Saugata Ghose[⋆†] Onur Mutlu[◇†▽]
[†]*Carnegie Mellon University* [⋈]*Processor Architecture Research Lab, Intel Labs* [▽]*Bilkent University* [◇]*ETH Zürich*
[‡]*Facebook* [⊙]*King Mongkut's University of Technology North Bangkok* [⋆]*University of Illinois at Urbana–Champaign*

# Research Contributions

Bottleneck analysis of genome assembly pipeline for long reads

*[Briefings in Bioinformatics, 2018]*

GenASM: Approximate string matching framework for genome sequence analysis

*[MICRO 2020]*

BitMAc: FPGA-based near-memory acceleration of bitvector-based sequence alignment

*[Ongoing]*

SeGraM: Hardware acceleration framework for sequence-to-graph mapping

*[Ongoing]*

# BitMAc: FPGA-based GenASM

**Our Goal:**

Map GenASM accelerators to an FPGA with HBM2, where **HBM2 offers high memory bandwidth** and **FPGA resources offer high parallelism** by instantiating multiple copies of the GenASM accelerators

- **Re-modified GenASM algorithms** for a better mapping to the FPGA resources
- **Intra-level parallelism** by instantiating multiple processing elements (PEs) for the DC execution
- **Inter-level parallelism** by running multiple independent GenASM executions in parallel

# Key Findings

- Based on the FPGA resources, **the complete BitMAc design:**
  - 4 BitMAc accelerators connected to each pseudo-channel (128 in total)
  - Each BitMAc accelerator contains a DC accelerator with 16 PEs, a TB accelerator, an FSM, and 13.2KB of M20Ks
  - Clocked at 200MHz

- BitMAc provides:
  - **136× – 761× speedup** over the state-of-the-art CPU baselines
  - **6.8× – 19.4× speedup** over the state-of-the-art GPU baseline

# Key Findings (cont'd.)

- BitMAc has:
  - **64% logic utilization** and **90% on-chip memory utilization**
  - Total power consumption of **48.9W**, where **59% accounts for the M20Ks**

- **Bottlenecked by the amount of on-chip memory** (i.e., M20Ks)
- **Cannot saturate the high bandwidth** that multiple HBM2 stacks on the FPGA provide
- Need (1) **algorithm-level modifications** to decrease the amount of data that need to be stored in M20Ks, and (2) **newer FPGA chips that provide a higher amount of on-chip memory capacity**

# Research Contributions

Bottleneck analysis of genome assembly pipeline for long reads

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GenASM: Approximate string matching framework for genome sequence analysis

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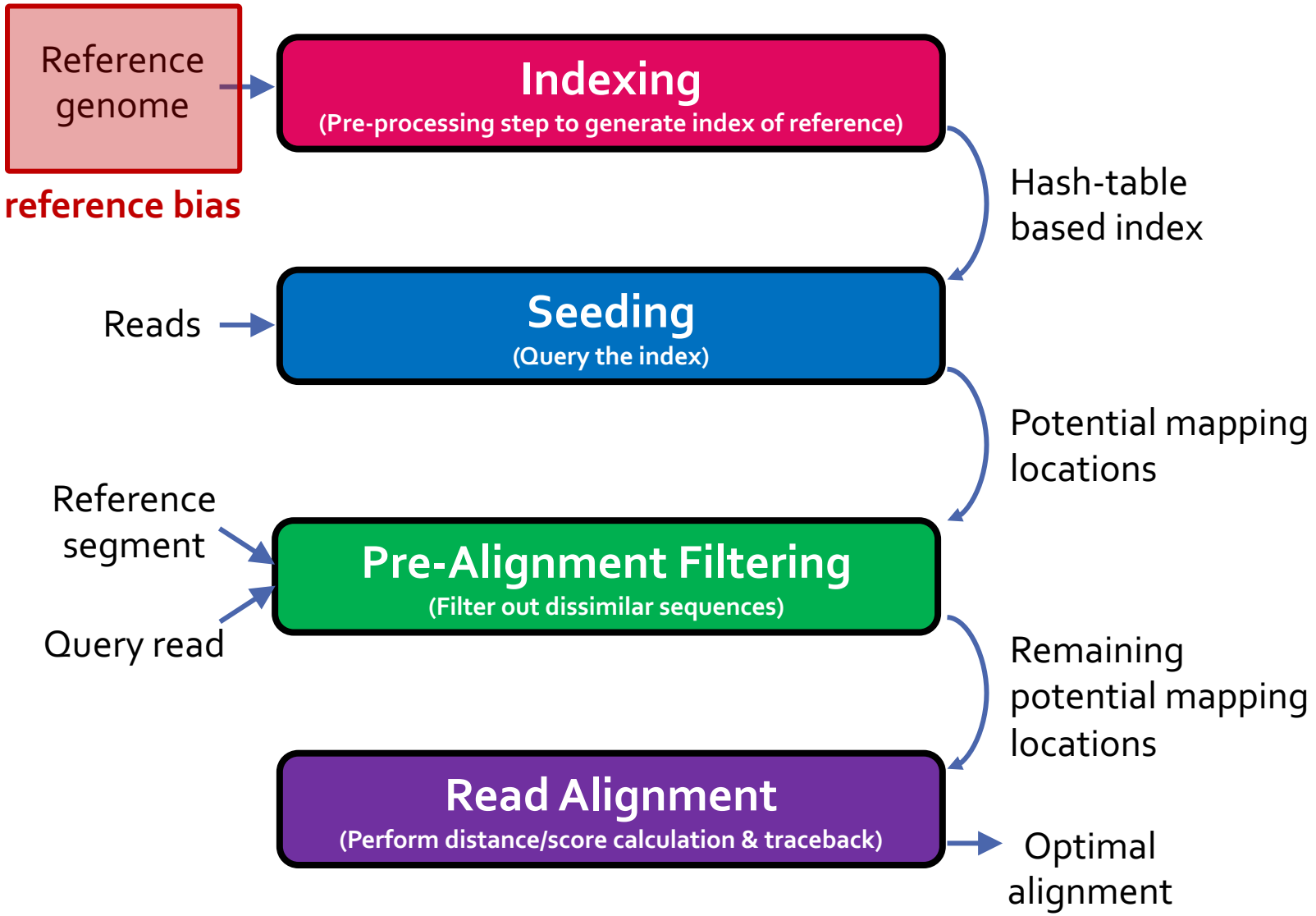
BitMAc: FPGA-based near-memory acceleration of bitvector-based sequence alignment

*[Ongoing]*

SeGraM: Hardware acceleration framework for sequence-to-graph mapping

*[Ongoing]*

# Recall: Read Mapping Pipeline



# Genome Graphs

Genome graphs:

- Include the reference genome together with genetic variations
- Provide a compact representation
- Enable us to move away from aligning with single reference genome (reference bias) and toward using the sequence diversity

**Reference #1:** ACGTACGT

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**Reference #2:** ACGGACGT

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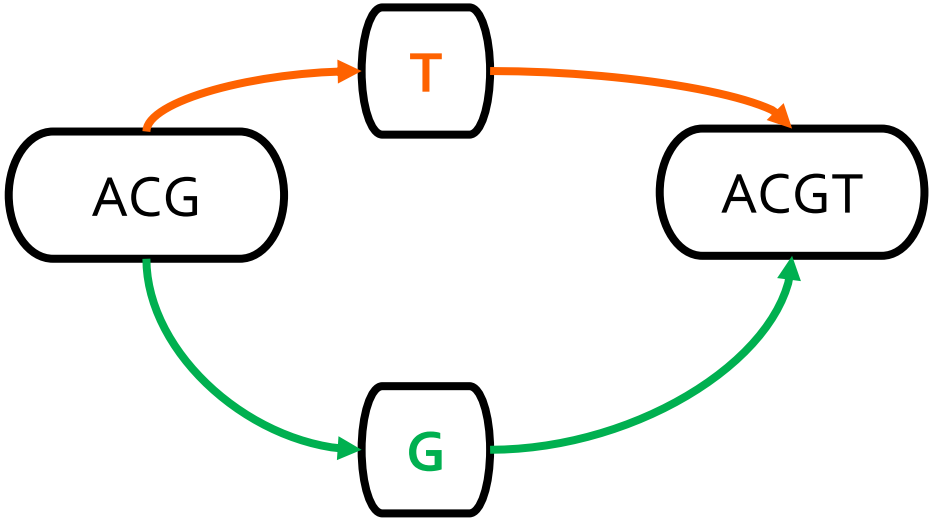
**Reference #2:** ACG**G**ACGT



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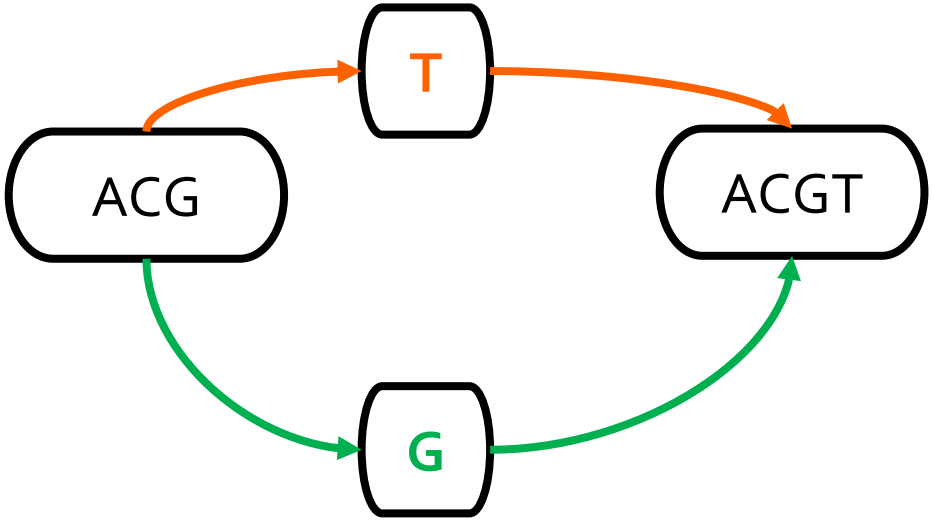

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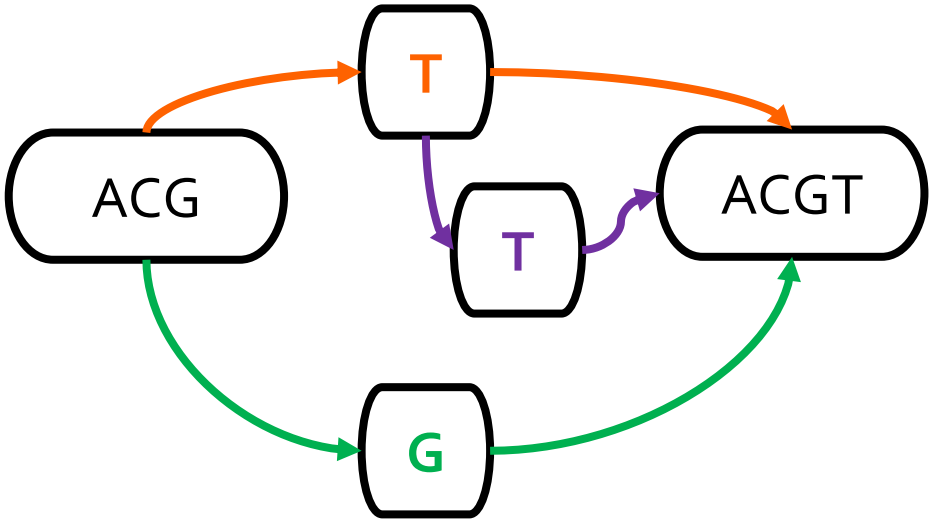

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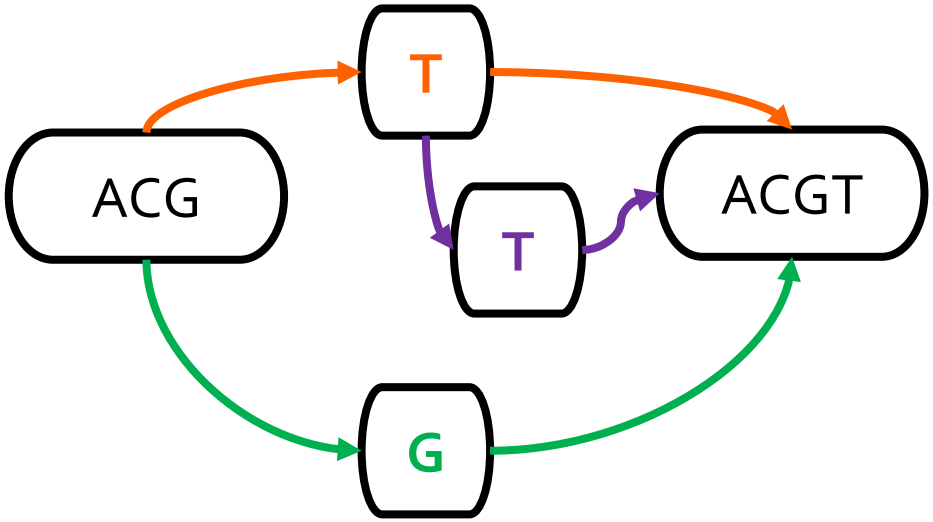
**Reference #2:** ACGGACGT

**Reference #3:** ACGTTACGT

**Reference #4:** ACGACGT



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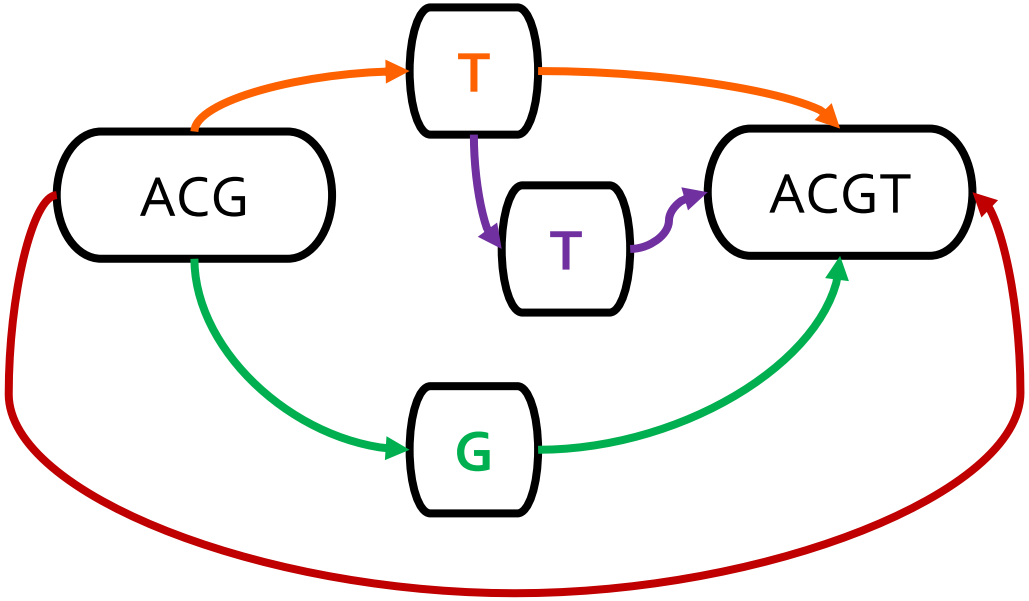


# Problem & Motivation

- Traditional read mapping causes reference bias
- Aligning sequences to graphs is a newer field and only a few software tools exist for graph-based GSA
- Graph-based analysis exacerbates mapping's bottlenecks
- Hardware acceleration of sequence-to-graph mapping: important but unexplored research problem

# SeGraM: First Graph Mapping Accelerator

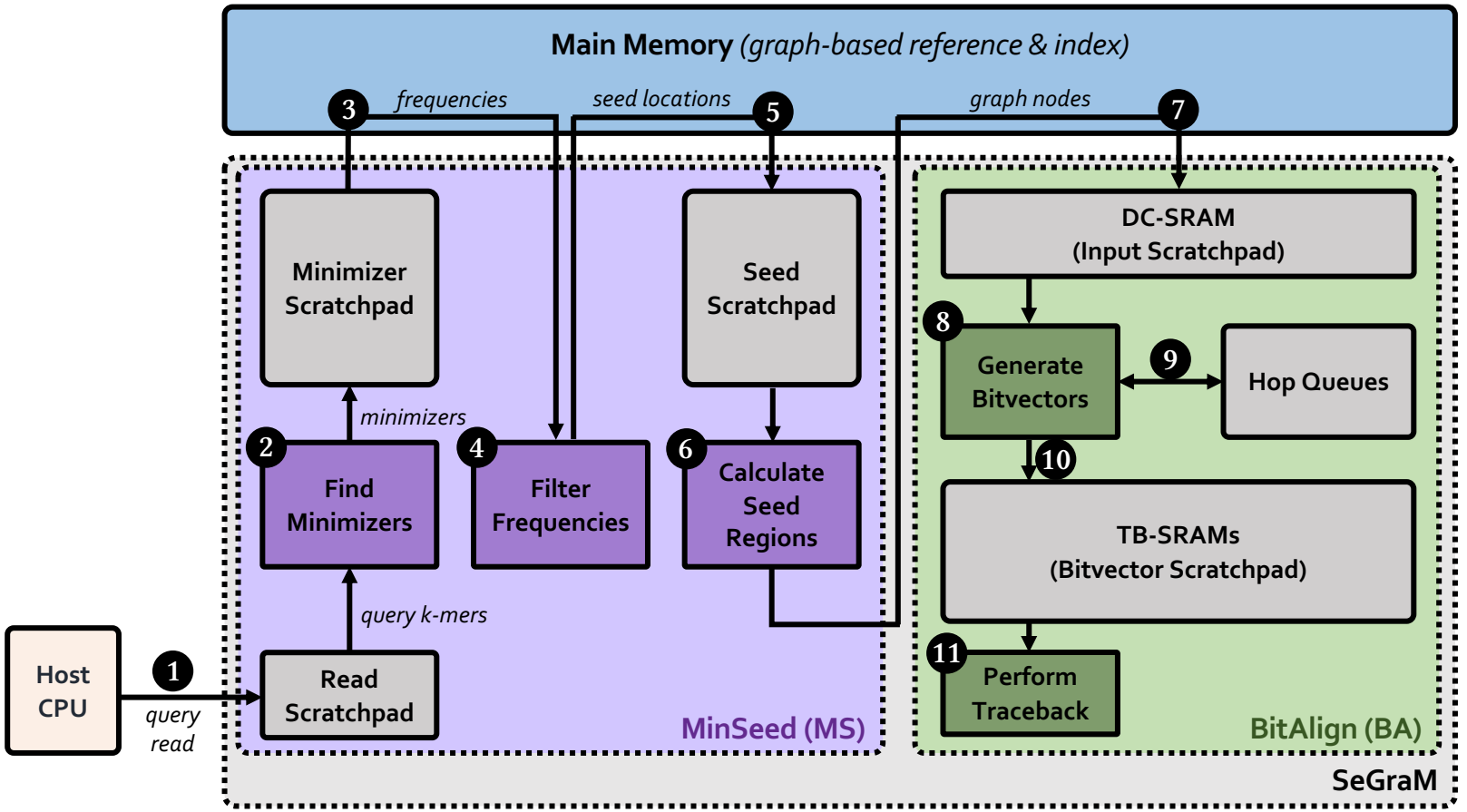
**Our Goal:**

Design high-performance, scalable, power- and area-efficient hardware accelerators that alleviate bottlenecks in both the seeding and alignment steps of sequence-to-graph mapping with support for both short and long reads

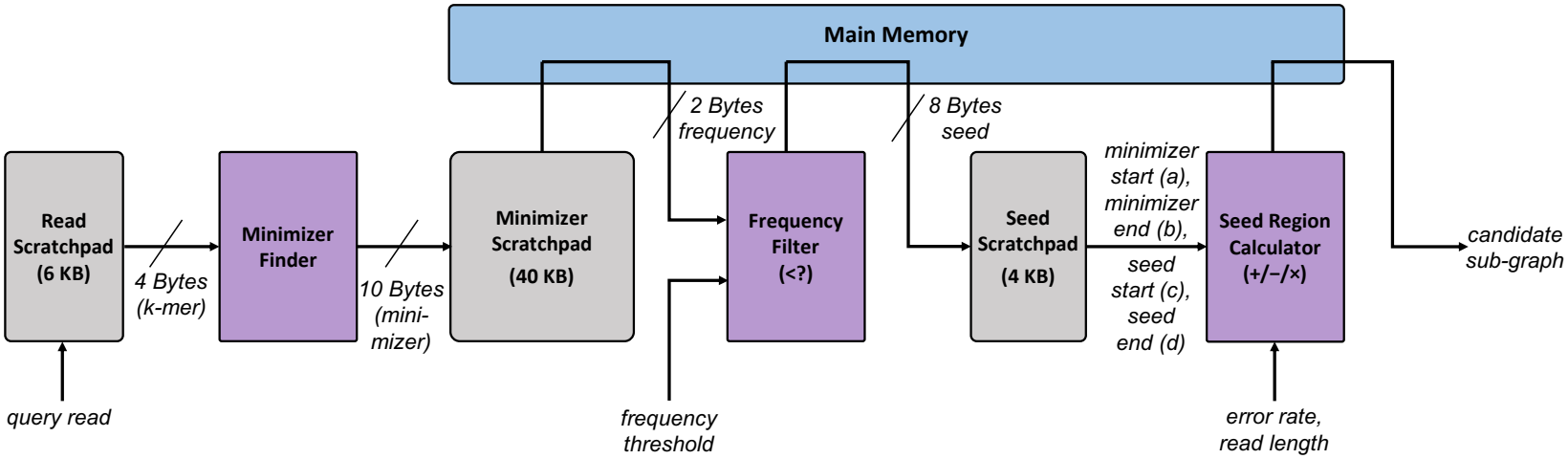
**SeGraM:**

- *MinSeed:* The *first* minimizer-based seeding hardware
- *BitAlign:* The *first* sequence-to-graph alignment hardware based on modified GenASM algorithms and accelerators

# Overview of SeGraM



# MinSeed HW



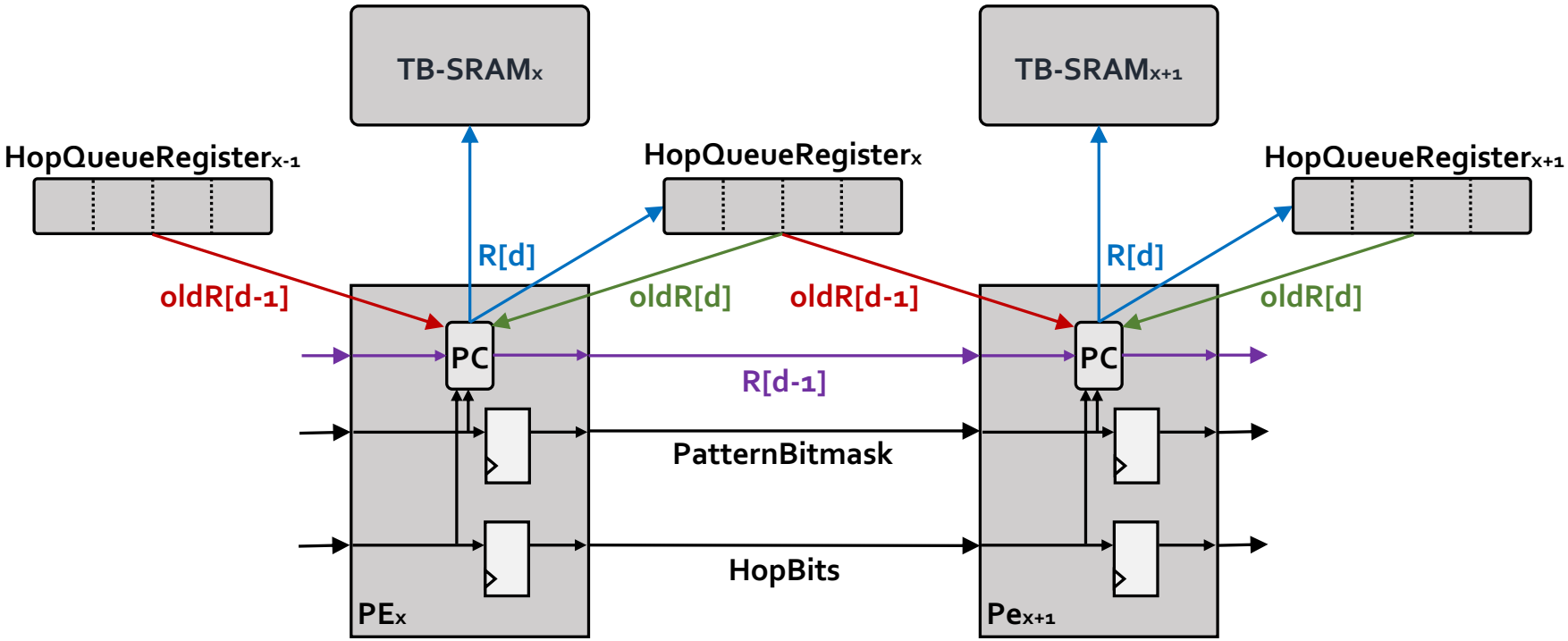

(1) **Three computation modules** responsible for finding the minimizers, filtering the frequencies of minimizers, and finding the associated regions of every seed location

(2) **Three scratchpads** for storing the query read, its minimizers, and seed locations

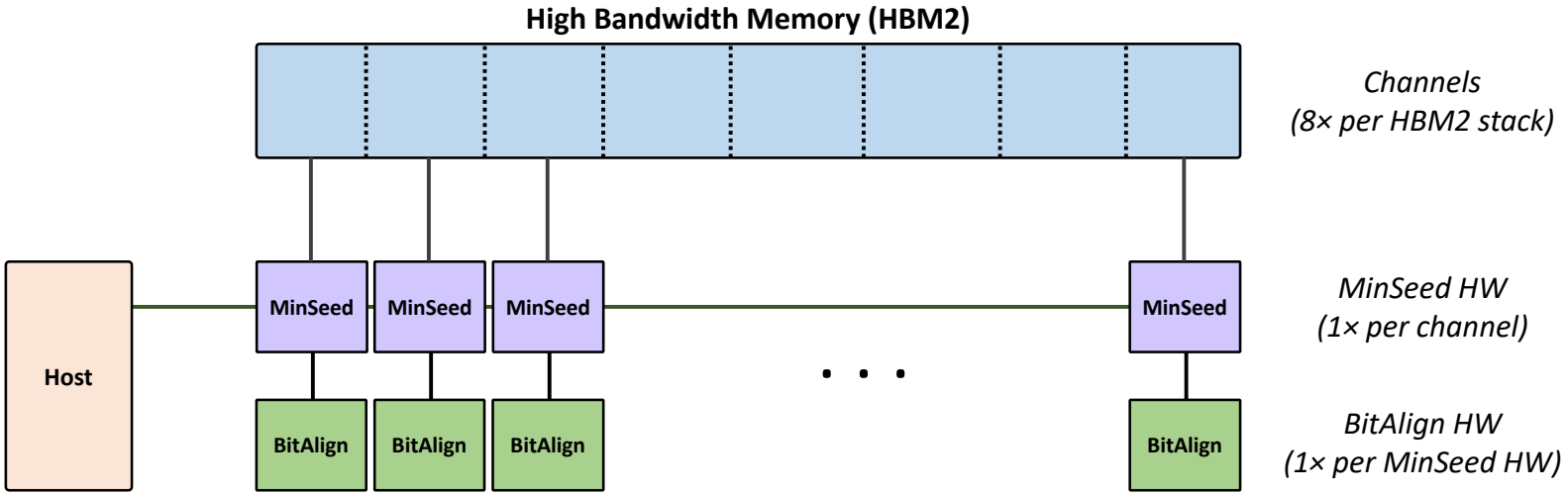
(3) **The memory interface**, which handles the frequency, seed location, and subgraph accesses

# BitAlign HW

- **Linear cyclic systolic array-based accelerator**
- ***Hop queue registers*** to incorporate the hops by feeding the bitvectors of non-neighbor characters/nodes



# Overall System of SeGraM




- A single SeGraM consists of **8 MinSeed modules** that exploit data-level parallelism when performing seeding
- Each MinSeed module has **exclusive access to one HBM2E channel**
- Each MinSeed module is connected to **a single BitAlign module**
- We **hide the latency of MinSeed** when performing seeding while running sequence-to-graph alignment with BitAlign

# Use Cases of SeGraM

**(1) End-to-End Sequence-to-Graph Mapping**

- The whole SeGraM design (MinSeed + BitAlign) should be executed
- We support both short and long reads

**(2) Sequence-to-Graph Alignment**

- BitAlign can be executed by itself without the need of an initial seeding tool/accelerator
- BitAlign can also be used for sequence-to-sequence alignment since it is a special and simpler variant of sequence-to-graph alignment

**(3) Seeding**

- MinSeed only can be used as the seeding module for both graph-based mapping and linear traditional mapping
- MinSeed is orthogonal to be coupled with any alignment tool or accelerator

# Evaluation Methodology

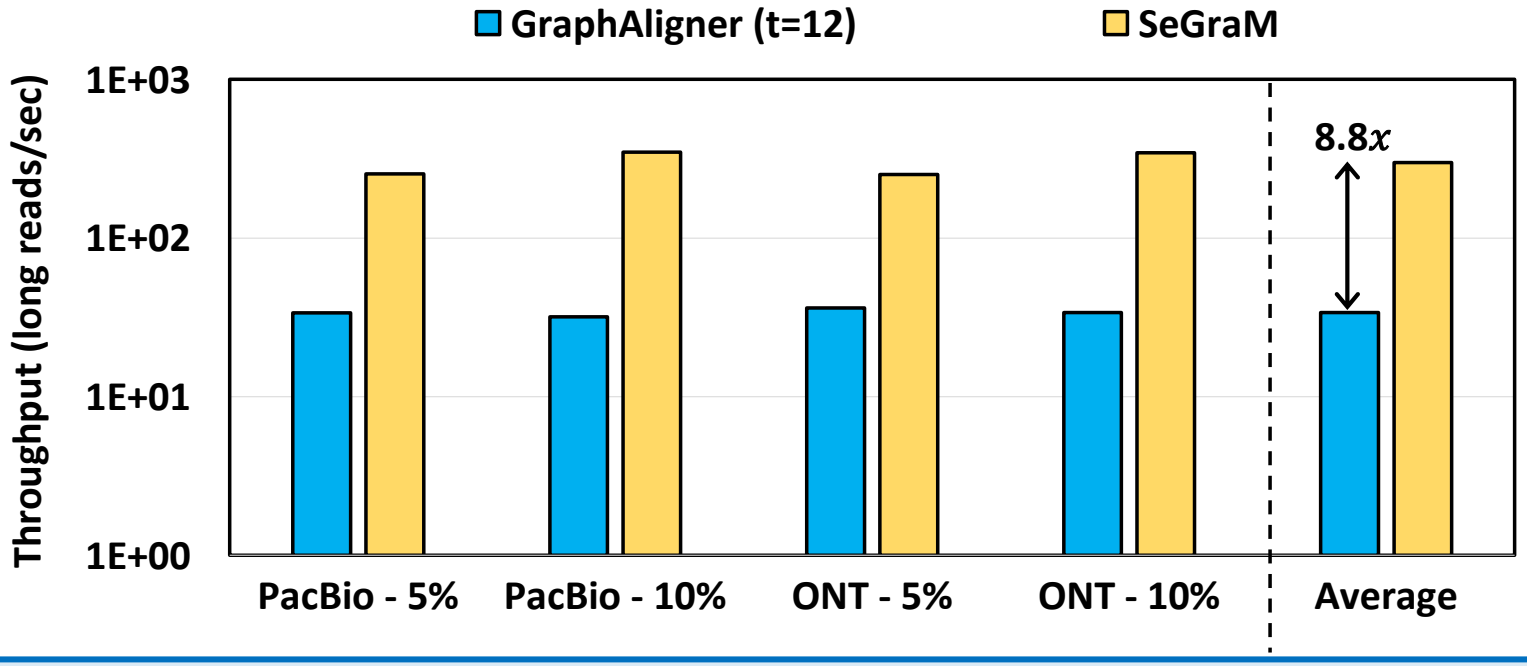
- We evaluate SeGraM using:
  - **Synthesized** SystemVerilog models of the MinSeed and BitAlign accelerator datapaths
  - **Simulation-** and **spreadsheet-based** performance modeling
- **4 x 24GB HBM2E stacks, each with 8 independent channels**
  - 1 MinSeed and 1 BitAlign HW per each channel **(32 in total)**
- Baseline tools:
  - **GraphAligner** and **vg** for sequence-to-graph mapping
  - **PaSGAL** for sequence-to-graph alignment
  - **Darwin**, **GenAx**, and **GenASM** for sequence-to-sequence alignment
- **Simulated datasets** for both short and long reads

# Key Results – Area & Power

- Based on our **synthesis** of **MinSeed** and **BitAlign** accelerator datapaths using the Synopsys Design Compiler with a **28nm** process (**@ 1GHz):**

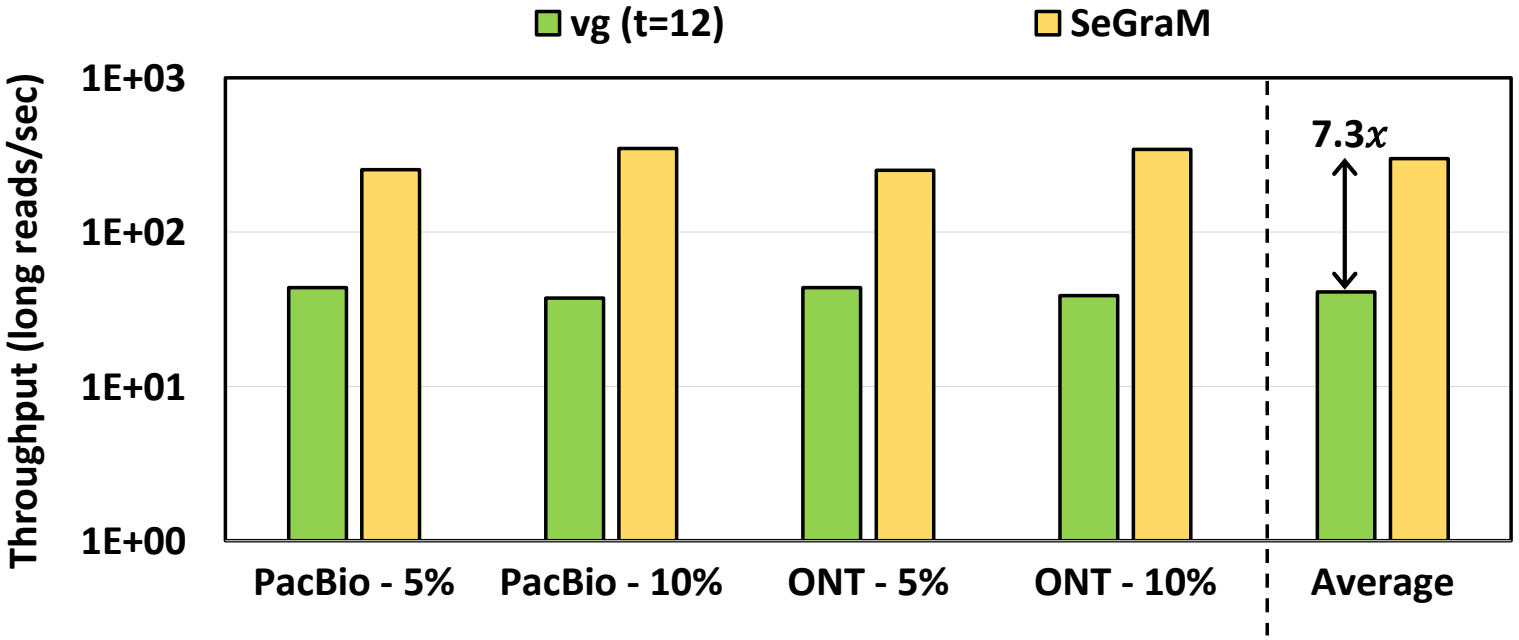
| Component | Area ($mm^2$) | Power (mW) |
|---|---|---|
| MinSeed – Logic | 0.017 | 10.8 |
| Read Scratchpad (6 KB) | 0.009 | 1.9 |
| Minimizer Scratchpad (40 KB) | 0.061 | 6.9 |
| Seed Scratchpad (4 KB) | 0.006 | 2.5 |
| BitAlign – DC Logic with HopQueueRegisters (64 PEs) | 0.393 | 378.0 |
| BitAlign – TB Logic | 0.020 | 2.7 |
| Input Scratchpad (DC-SRAM; 24 KB) | 0.034 | 8.4 |
| Bitvector Scratchpad (TB-SRAMs; 128 KB) | 0.233 | 115.1 |
| **Total – 1 x SeGraM** | **0.773** | **526.3 (0.5 W)** |
| **Total – 8 x SeGraM** | **6.184** | **4210.4 (4.2 W)** |
| **Total – 32 x SeGraM** | **24.736** | **16841.6 (16.8 W)** |

# Key Results – SeGraM with Long Reads (I)



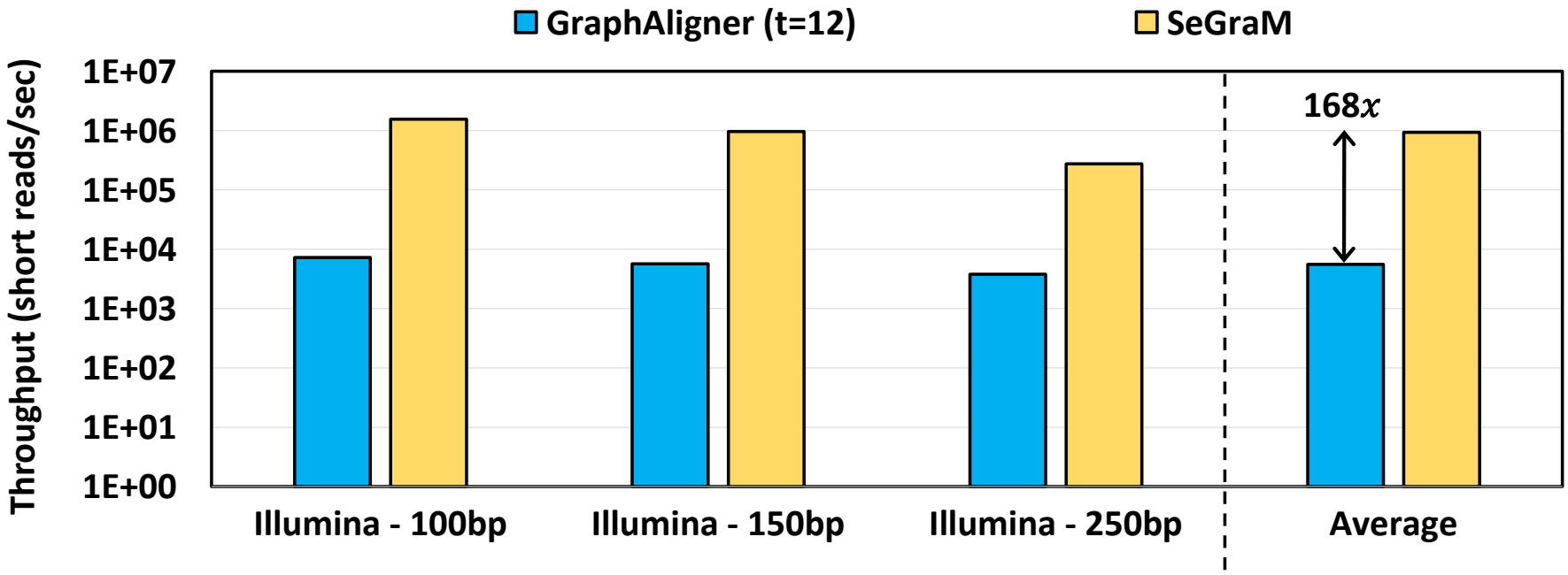

SeGraM provides **8.8× throughput improvement** over GraphAligner's 12-thread execution, while **reducing the power consumption by 4.9×**

# Key Results – SeGraM with Long Reads (II)



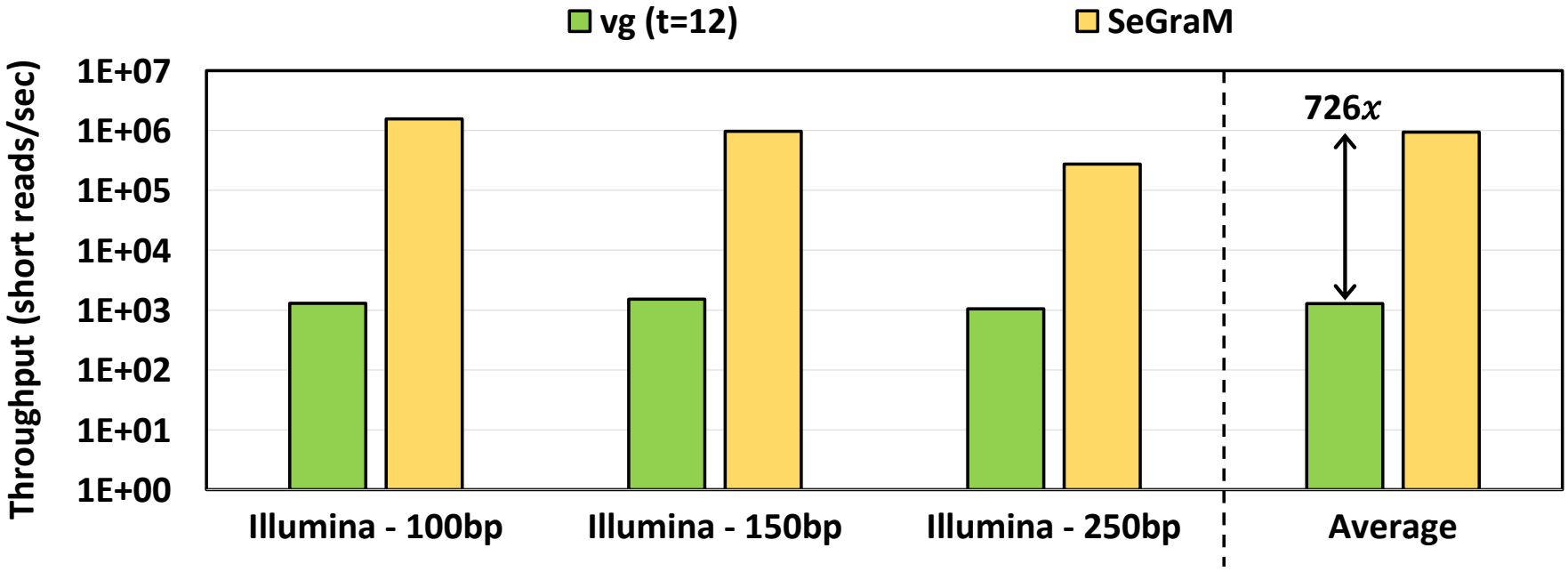

SeGraM provides **7.3× throughput improvement** over vg's 12-thread execution,
while **reducing the power consumption by 6.5×**

# Key Results – SeGraM with Short Reads (I)



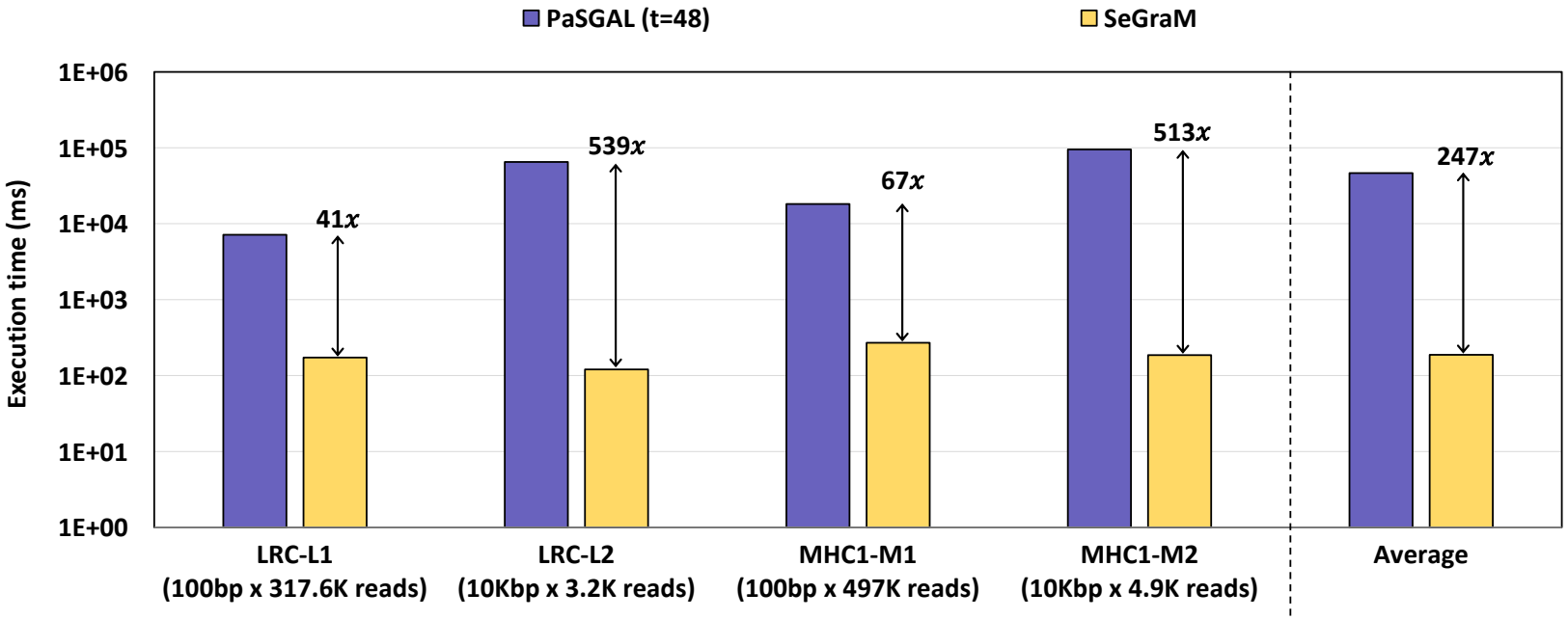

SeGraM provides **168× throughput improvement** over GraphAligner's 12-thread execution, while **reducing the power consumption by 4.7×**

# Key Results – SeGraM with Short Reads (II)




SeGraM provides **726× throughput improvement** over vg's 12-thread execution,
while **reducing the power consumption by 4.9×**

# Key Results – BitAlign (Graph Alignment)




BitAlign provides **41×-539× speedup** over the 48-thread AVX512-supported execution of PaSGAL

# Key Results – BitAlign (Linear Alignment)

- BitAlign can be used for both sequence-to-sequence alignment and sequence-to-graph alignment
  - The cost of more functionality: Extra hop queue registers in BitAlign
  - However, we do *not* sacrifice any performance
- **For long reads (over GACT of Darwin and GenASM):**
  - 4.8× and 1.2× throughput improvement,
  - 1.9× and 5.2× higher power consumption, and
  - 1.4× and 2.3× higher area overhead
- **For short reads (over SillaX of GenAx and GenASM):**
  - 2.4× and 1.3× throughput improvement

# Summary of SeGraM

**Problem:**

- Traditional read mapping causes reference bias
- Aligning sequences to graphs is a newer field and only a few software tools exist for graph-based GSA
- Graph-based analysis exacerbates mapping's bottlenecks
- Hardware acceleration of sequence-to-graph mapping: important but unexplored research problem

**Key Contributions:**

- SeGraM: *First* acceleration framework for sequence-to-graph mapping
  - MinSeed: *First* minimizer-based seeding accelerator
  - BitAlign: *First* sequence-to-graph alignment accelerator based upon our new bitvector-based, highly-parallel algorithm

**Key Results:** SeGraM and BitAlign provide significant speedups compared to the software baselines, while reducing the power consumption

# Research Contributions

Bottleneck analysis of genome assembly pipeline for long reads

***[Briefings in Bioinformatics, 2018]***

GenASM: Approximate string matching framework for genome sequence analysis

***[MICRO 2020]***

BitMAc: FPGA-based near-memory acceleration of bitvector-based sequence alignment

***[Ongoing]***

SeGraM: Hardware acceleration framework for sequence-to-graph mapping

***[Ongoing]***

# Conclusion

Rapid genome sequence analysis is bottlenecked by **the computational power and memory bandwidth limitations of existing systems**, as many of the steps in genome sequence analysis must process **a large amount of data**

# Conclusion (cont'd.)

Genome sequence analysis can be accelerated by co-designing **fast and efficient algorithms** along with **scalable and energy-efficient customized hardware accelerators** for the key bottleneck steps of the pipeline

# Conclusion (cont'd.)

Bottleneck analysis of genome assembly pipeline for long reads

*[Briefings in Bioinformatics, 2018]*

GenASM: Approximate string matching framework for genome sequence analysis

*[MICRO 2020]*

BitMAc: FPGA-based near-memory acceleration of bitvector-based sequence alignment

**[Ongoing]**

SeGraM: Hardware acceleration framework for sequence-to-graph mapping

**[Ongoing]**

# Future Work

- Incorporating a Filtering Approach for SeGraM
- GenASM-based Algorithm for Sequence Alignment with the Affine Gap Model
- End-to-End Acceleration of the Mapping Pipeline
- Accelerating Assembly with Long Reads

# Accelerating Genome Sequence Analysis via Efficient Hardware/Algorithm Co-Design

**Damla Senol Cali**

Staff Software Engineer, Hardware Acceleration

Bionano Genomics

Email: damlasenolcali@gmail.com

Website: https://damlasenolcali.github.io

**SAFARI Live Seminar**

November 7, 2021

Carnegie Mellon ETH zürich SAFARI

# Other Publications @ SAFARI

*FPGA-based Near-Memory Acceleration of Modern Data-Intensive Applications (IEEE Micro, 2021)*

Gagandeep Singh, Mohammed Alser, Damla Senol Cali, Dionysios Diamantopoulos, Juan Gomez-Luna, Henk Corporaal, and Onur Mutlu.

*Accelerating Genome Analysis: A Primer on an Ongoing Journey (IEEE Micro, 2020)*

Mohammed Alser, Zulal Bingol, Damla Senol Cali, Jeremie S. Kim, Saugata Ghose, Can Alkan, and Onur Mutlu.

*Apollo: A Sequencing-Technology-Independent, Scalable, and Accurate Assembly Polishing Algorithm (Bioinformatics, 2020)*

Can Firtina, Jeremie S. Kim, Mohammed Alser, Damla Senol Cali, A. Ercument Cicek, Can Alkan, and Onur Mutlu.

*Demystifying Workload–DRAM Interactions: An Experimental Study (ACM SIGMETRICS, 2019)*

Saugata Ghose, Tianshi Li, Nastaran Hajinazar, Damla Senol Cali, and Onur Mutlu.

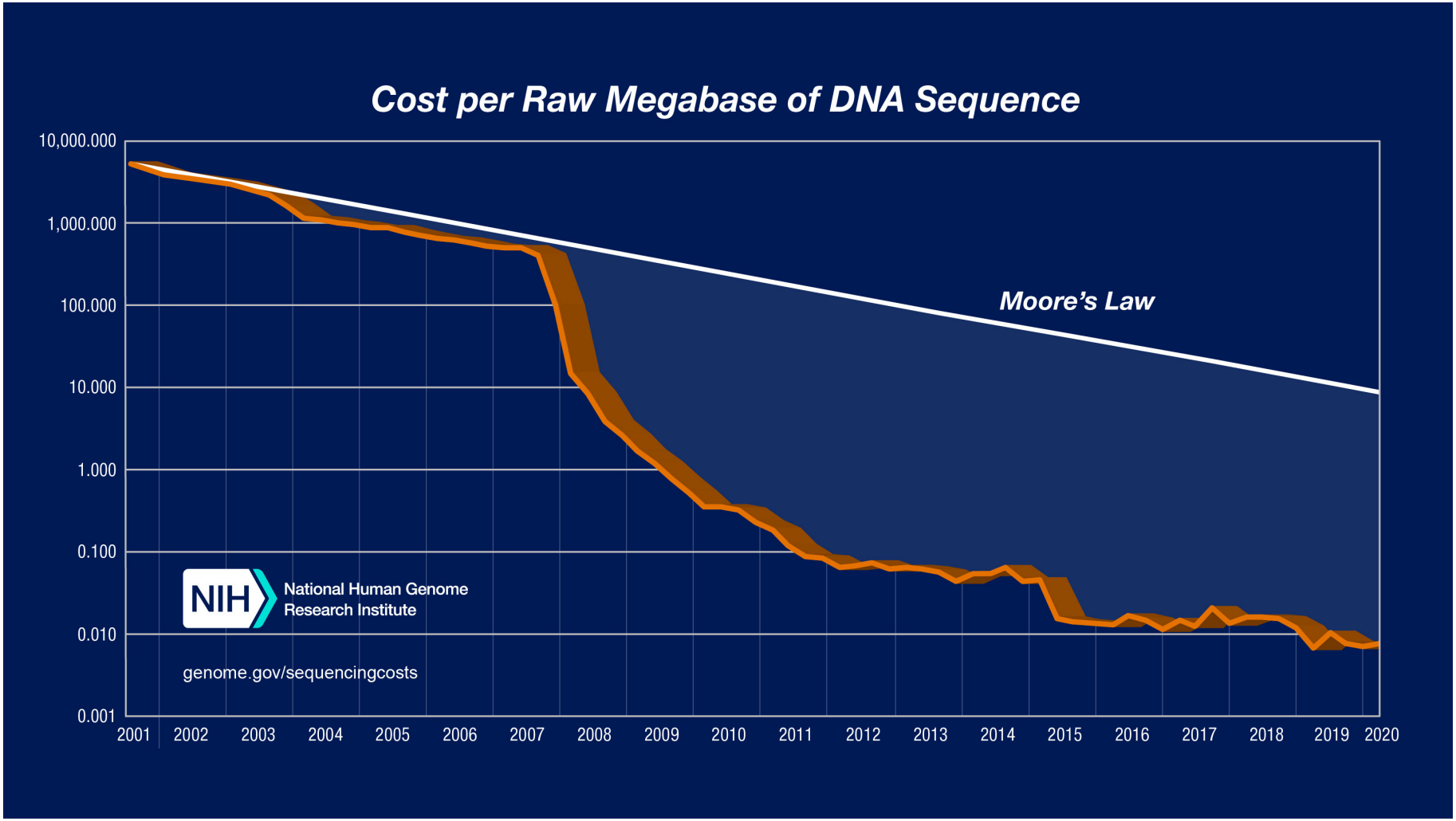
*GRIM-Filter: Fast Seed Location Filtering in DNA Read Mapping Using Processing-in-Memory Technologies (BMC Genomics, 2018)*

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

# Backup Slides

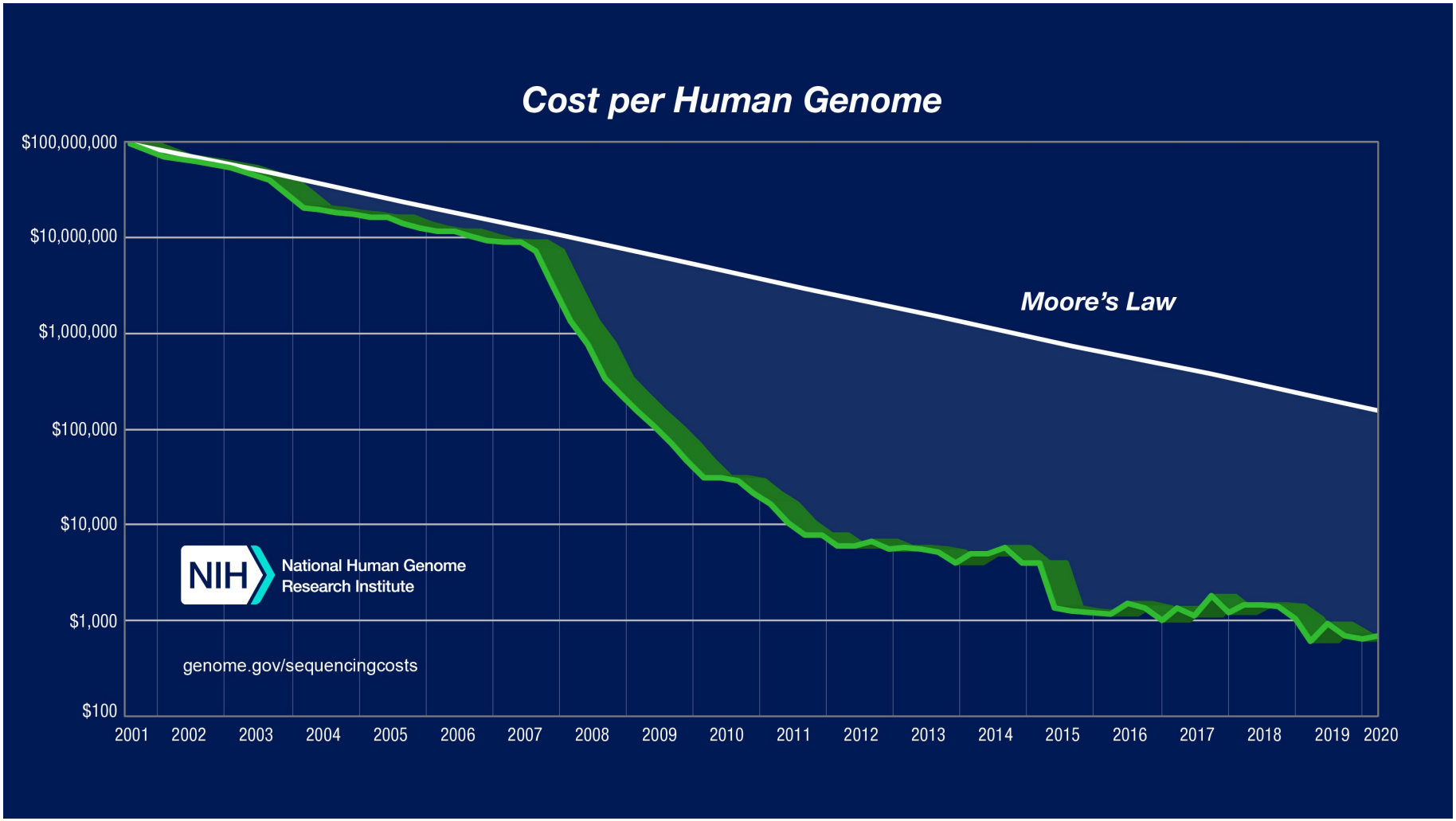
(Sequencing)

# Cost of Sequencing




*From NIH (https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data)

# Cost of Sequencing (cont'd.)



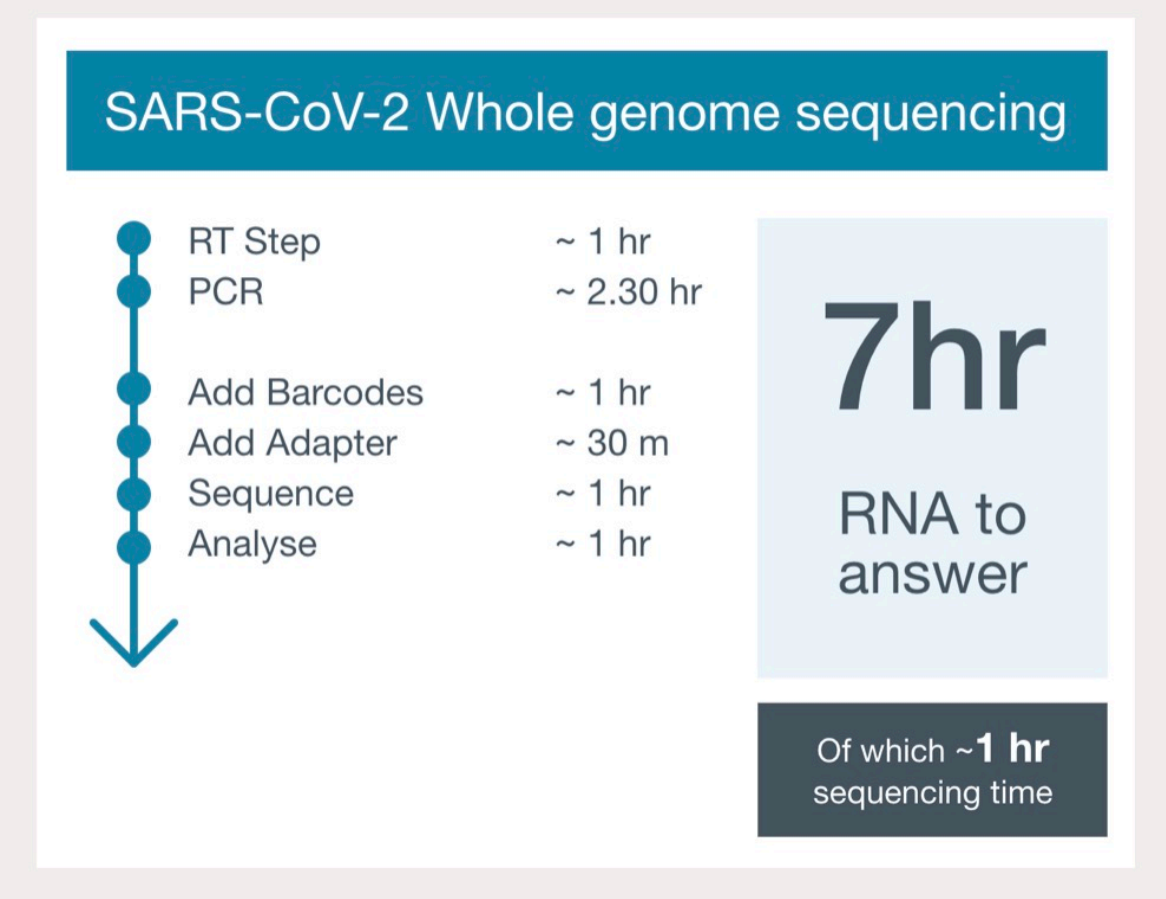

*From NIH (https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data)

# Sequencing of SARS-CoV-2

**Why genome sequencing and sequence data analysis are important?**

- To detect the virus from a human sample
- To understand the sources and modes of transmission of the virus
- To sequence the genome of the virus itself, COVID-19, in order to track the mutations in the virus
- To explore the genes of infected patients
  - To understand why some people get more severe symptoms than others
  - To help with the development of new treatments

# COVID-19 Research with ONT



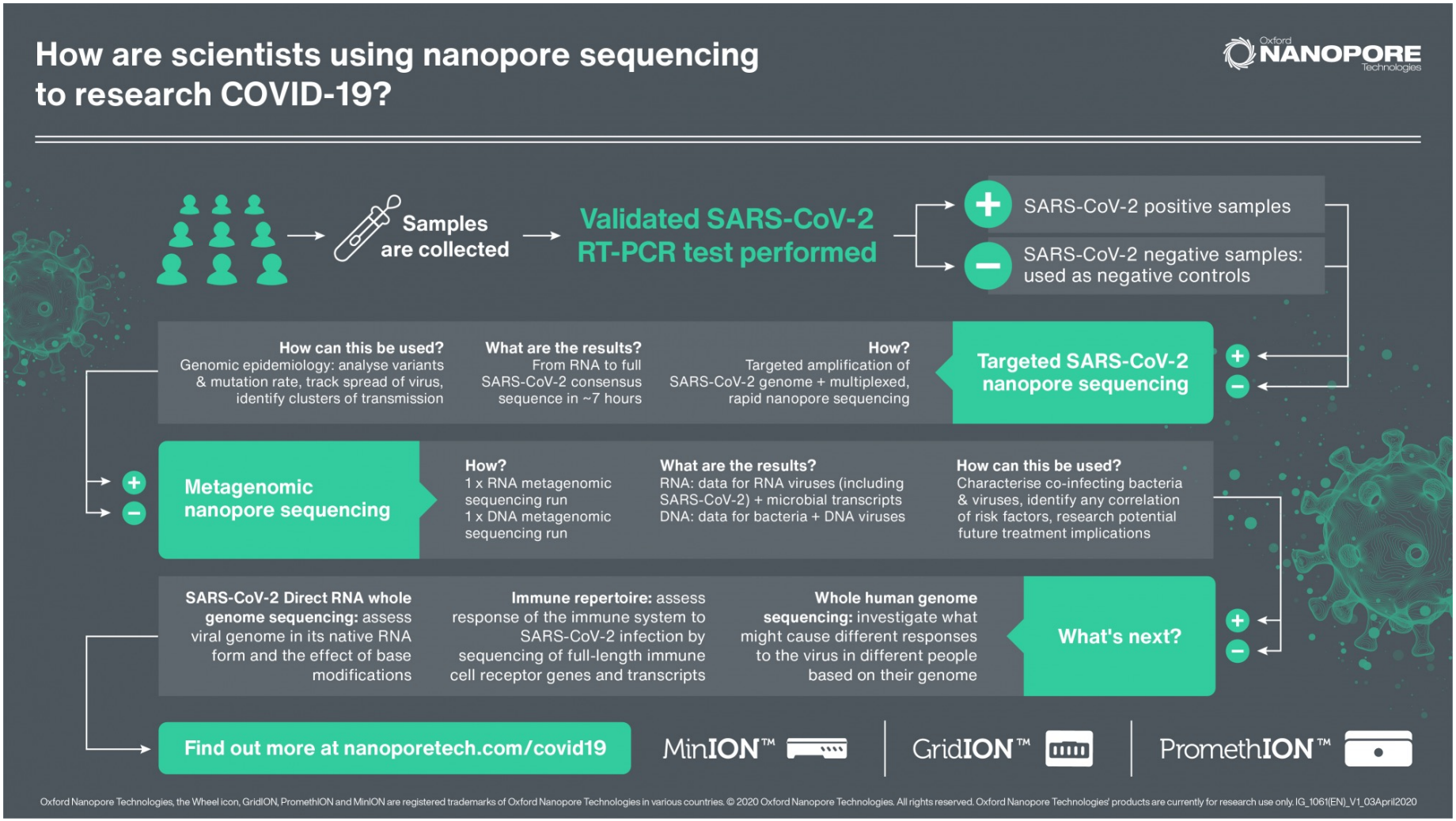

- From ONT (https://nanoporetech.com/covid-19/overview)

# Future of Genome Sequencing & Analysis

MinION from ONT

SmidgION from ONT

# COVID-19 Research with ONT (cont'd.)




- From ONT (https://nanoporetech.com/covid-19/overview)

# Backup Slides

## (Nanopore)

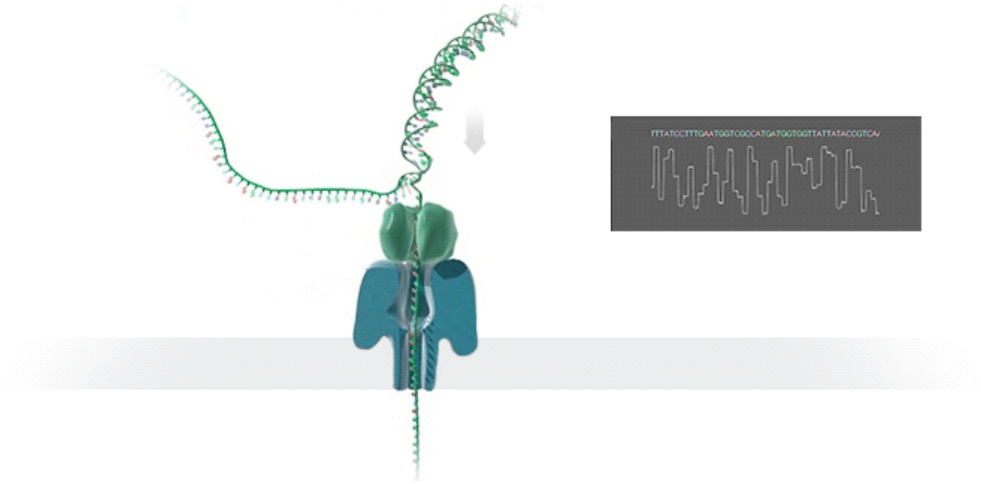
# Nanopore Sequencing Technology

- **Nanopore sequencing** is an emerging and a promising single-molecule DNA sequencing technology.

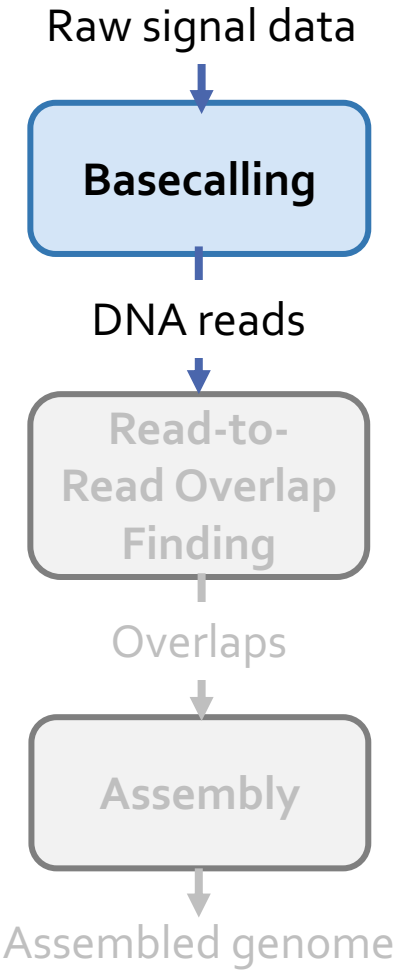
- First nanopore sequencing device, **MinION**, made commercially available by **Oxford Nanopore Technologies** (ONT) in **May 2014.**
  - Inexpensive
  - Long read length (>882Kbp)
  - Produces data in real time
  - Pocket-sized and portable

# Nanopore Sequencing

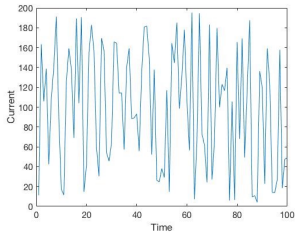
- **Nanopore** is a nano-scale hole.
- In nanopore sequencers, an **ionic current** passes through the nanopores.
- When the DNA strand passes through the nanopore, the sequencer measures the **change in current**.
- This change is used to identify the bases in the strand with the help of **different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



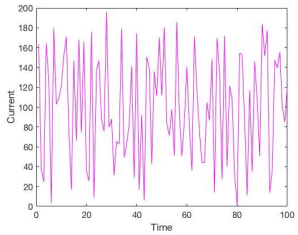
# Step 1: Basecalling



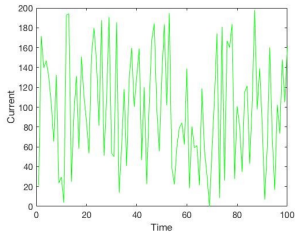

Translates the **raw signal** output into bases to generate **DNA reads**.




ACTGTCGAGTCGTAGAGA…TTT

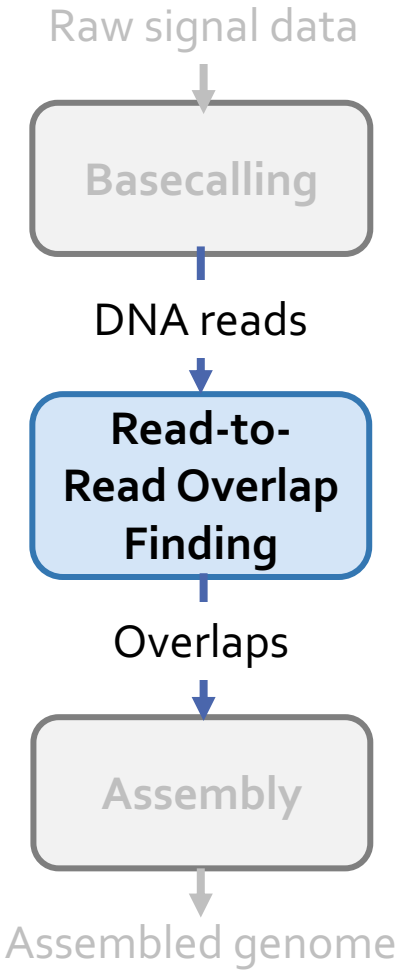



TTTGTCGAGTCGTAGAGA…TAG



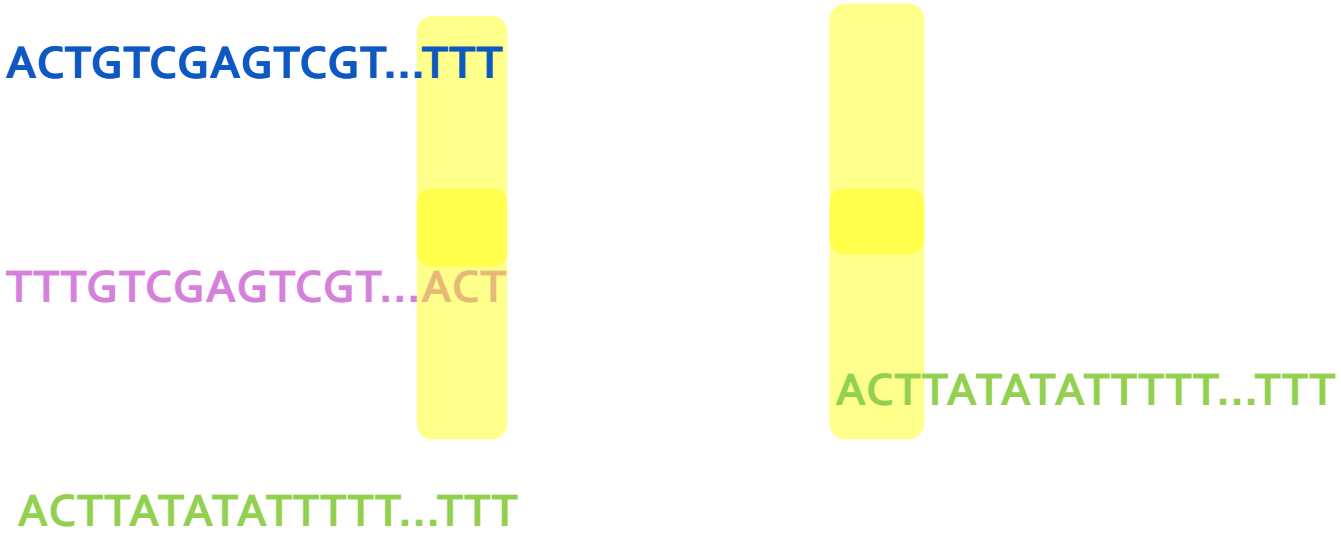

TAGTATATATTTTGGGGT…TAA

# Step 2: Read-to-Read Overlap Finding

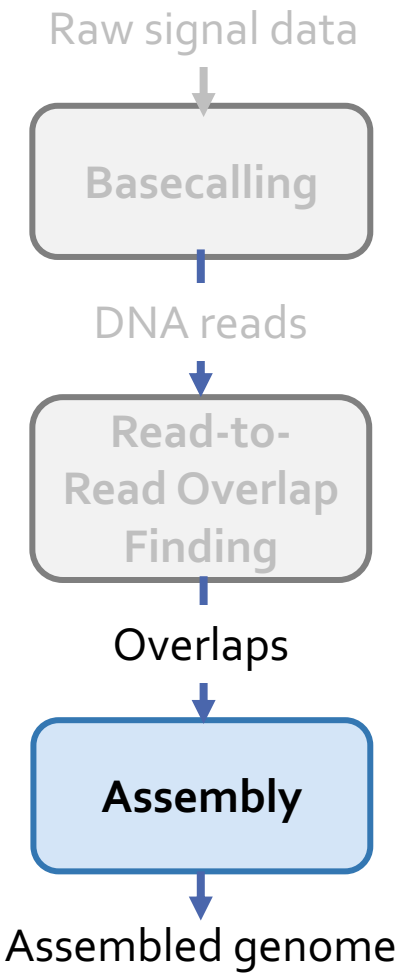



Read-to-read overlap

- is a **common sequence between two reads,** and
- occurs when the matched regions of these reads **originate from the same part of the complete genome.**



# Step 3: Assembly




Assembly algorithms,

- generate an **overlap graph** with the overlaps from the previous step,
- **traverse** this graph, then
- **construct** the assembled genome.


**Which one is correct?**

# Experimental Methodology

| Name | Model | CPU specifications | Main memory specifications |
|---|---|---|---|
| System 1 | 40-core Intel® Xeon® E5-2630 v4 CPU @ 2.20GHz | 20 physical cores 2 threads per core 40 logical cores with hyper-threading** | 128GB DDR4 2 channels, 2 ranks/channel Speed: 2400MHz |
| System 2 (desktop) | 8-core Intel® Core i7-2600 CPU @ 3.40GHz | 4 physical cores 2 threads per core 8 logical cores with hyper-threading** | 16GB DDR3 2 channels, 2 ranks/channel Speed: 1333MHz |
| System 3 (big-mem) | 80-core Intel® Xeon® E7-4850 CPU @ 2.00GHz | 40 physical cores 2 threads per core 80 logical cores with hyper-threading** | 1TB DDR3 8 channels, 4 ranks/channel Speed: 1066MHz |

# Experimental Methodology (cont'd.)

**Accuracy Metrics**

- Average Identity : Percentage **similarity** between the assembly and the reference genome
- Coverage: **Ratio of the #aligned bases** in the reference genome to the length of reference genome
- Number of mismatches: Total number of **single-base differences** between the assembly and the reference genome
- Number of indels: Total number of **insertions and deletions** between the assembly and the reference genome

**Performance Metrics**

- Wall clock time
- Peak memory usage
- Parallel speedup

} Using **/usr/bin/time** & **perf**

# Experimental Methodology

**Basecalling**

| Tool | Strategy |
|---|---|
| Metrichor | RNN |
| Nanonet | RNN |
| Scrappie | RNN |
| Nanocall | HMM |
| DeepNano | RNN |

**Read-to-Read Overlap Finding**

| Tool | Strategy |
|---|---|
| GraphMap | *k*-mer similarity |
| Minimap | Minimizer similarity |

**Assembly**

| Tool | Strategy |
|---|---|
| Canu | OLC with error correction |
| Miniasm | OLC without error correction |

**Read Mapping**

| Tool | Strategy |
|---|---|
| BWA-MEM | Burrows–Wheeler Transform |
| GraphMap | *k*-mer similarity |
| Minimap | Minimizer similarity |

**Polishing**

| Tool | Strategy |
|---|---|
| Nanopolish | HMM |
| Racon | Partial order alignment graph |

# Nanopore Basecalling Tools

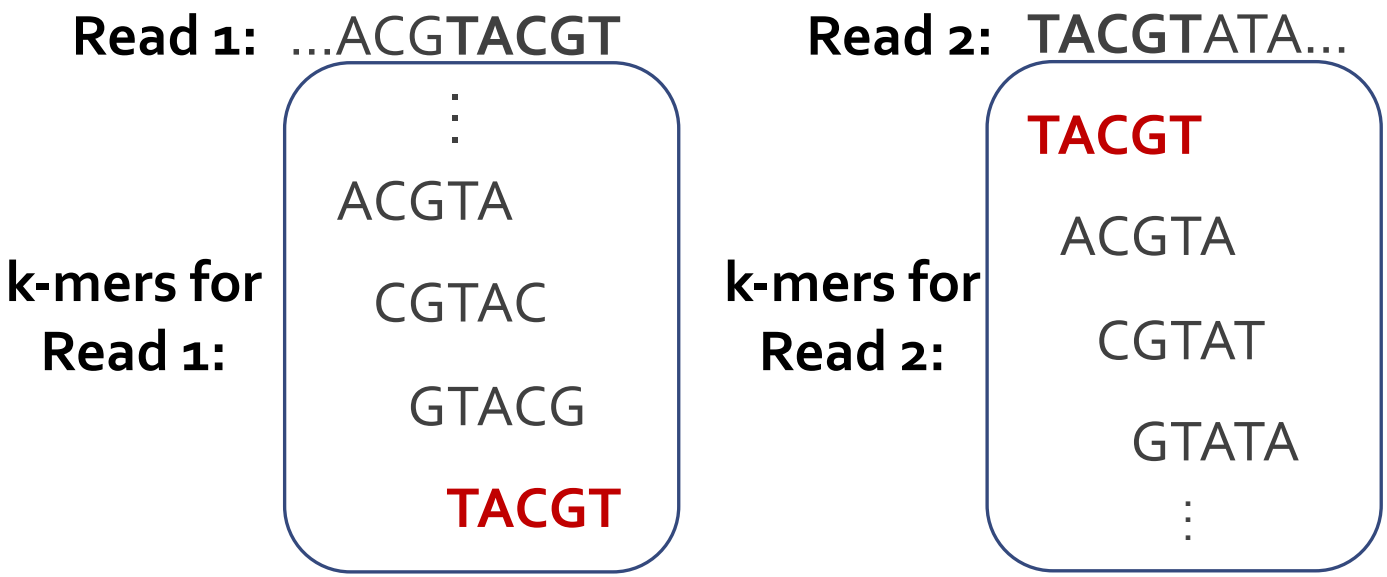
- Metrichor
  - ONT's cloud-based basecaller
  - Uses recurrent neural networks (**RNN**) for basecalling
- Nanonet
  - ONT's offline and open-source alternative for Metrichor
  - Uses **RNN** for basecalling
- Scrappie
  - ONT's newest basecaller that explicitly addresses basecalling errors in homopolymer regions
- Nanocall [David+, Bioinformatics 2016]
  - Uses Hidden Markov Models (**HMM**) for basecalling
- DeepNano [Boža+, PloS One 2017]
  - Uses **RNN** for basecalling

# Read-to-Read Overlap Finding Tools

- GraphMap [Sović+, Nature Communications 2016]
  - First partitions the entire read data set into *k*-length substrings (i.e., *k*-mers), and then stores them in a hash table with the positions.
  - Detects the overlaps by finding the *k*-mer similarity between any two given reads, using the generated hash table.
- Minimap [Li+, Bioinformatics 2016]
  - Partitions the entire read data set into *k*-mers, but instead of creating a hash table for the full set of *k*-mers, finds the minimum representative set of *k*-mers, called *minimizers*, and creates a hash table with only these minimizers.
  - Finds the overlaps between two reads by finding minimizer similarity.

# GraphMap vs. Minimap

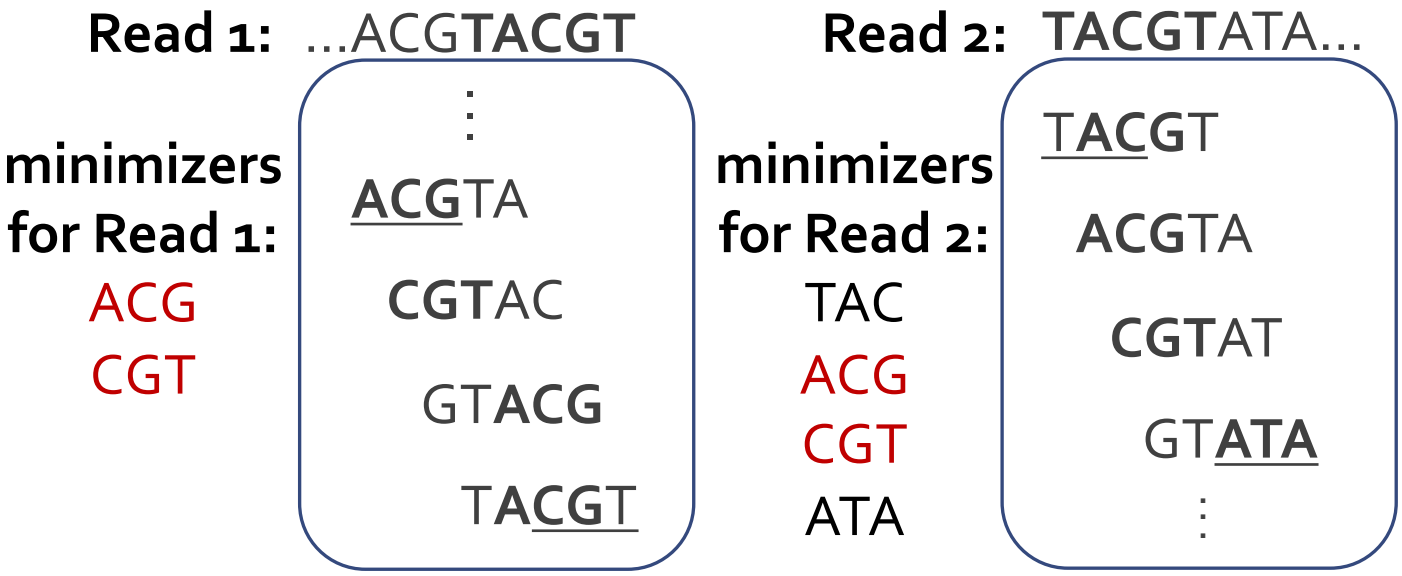
- **GraphMap**
  - Finds **k-mers** and store them in hash table with the positions.




  - Finds overlaps between two reads by **k-mer similarity**.

# GraphMap vs. Minimap

- **Minimap**
  - Finds minimum representative set of k-mers, i.e. **minimizers** and store them in hash table, instead of storing all k-mers.




  - Finds overlaps between two reads by **minimizer similarity**.

# Assembly Tools

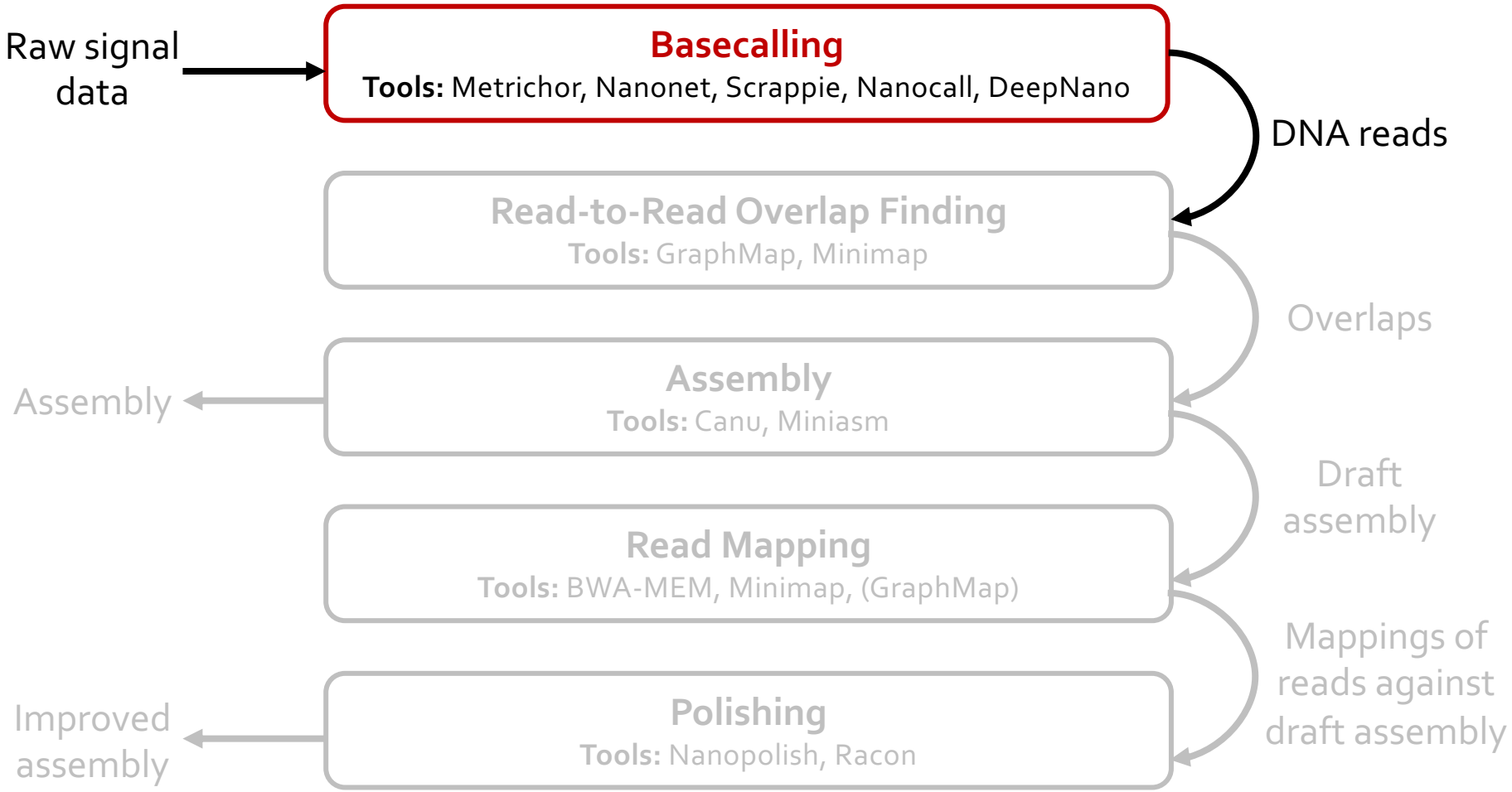
- Canu [Koren+, Genome Research 2017]
  - Performs error-correction as the initial step of its own pipeline
    - Improves the accuracy of the bases in the reads
    - Computationally-expensive
  - After the error-correction step, finds overlaps between corrected reads and constructs a draft assembly
- Miniasm [Li+, Bioinformatics 2016]
  - Skips the error-correction step, and constructs the draft assembly from the uncorrected read overlaps computed in the previous step.
  - Lowers computational cost but the accuracy of the draft assembly depends directly on the accuracy of the uncorrected basecalled reads.

# Read Mapping & Polishing Tools

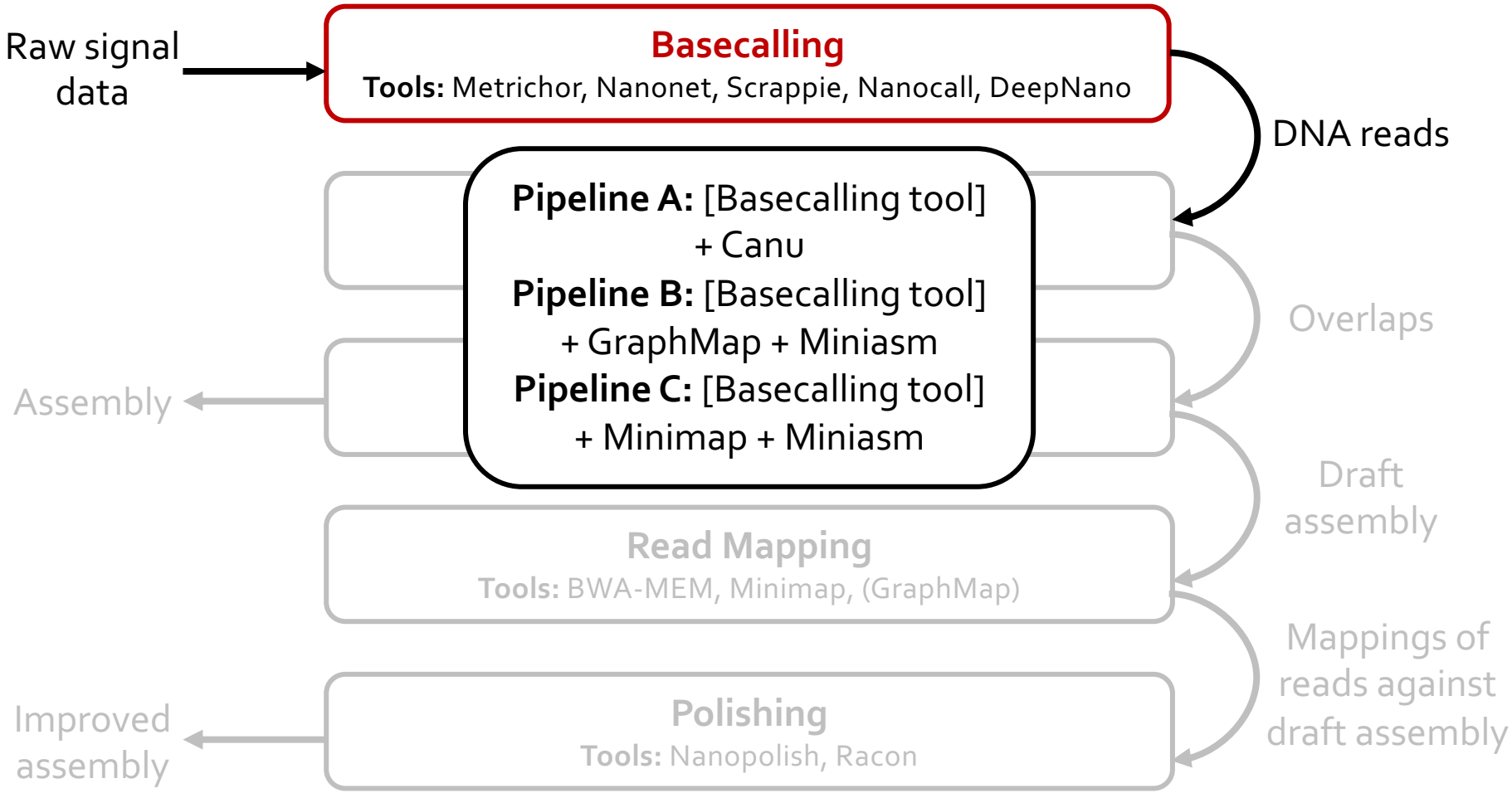
- **Read Mapping tools**
  - BWA-MEM [Li, arXiv 2013]
    - Commonly used long-read mapper
  - GraphMap and Minimap (from Step 2)

- **Polishing tools**
  - Nanopolish [Loman+, Nature Methods 2015]
    - HMM-based approach for polishing
  - Racon [Vaser+, Genome Research 2017]
    - Alignment graph-based approach for polishing

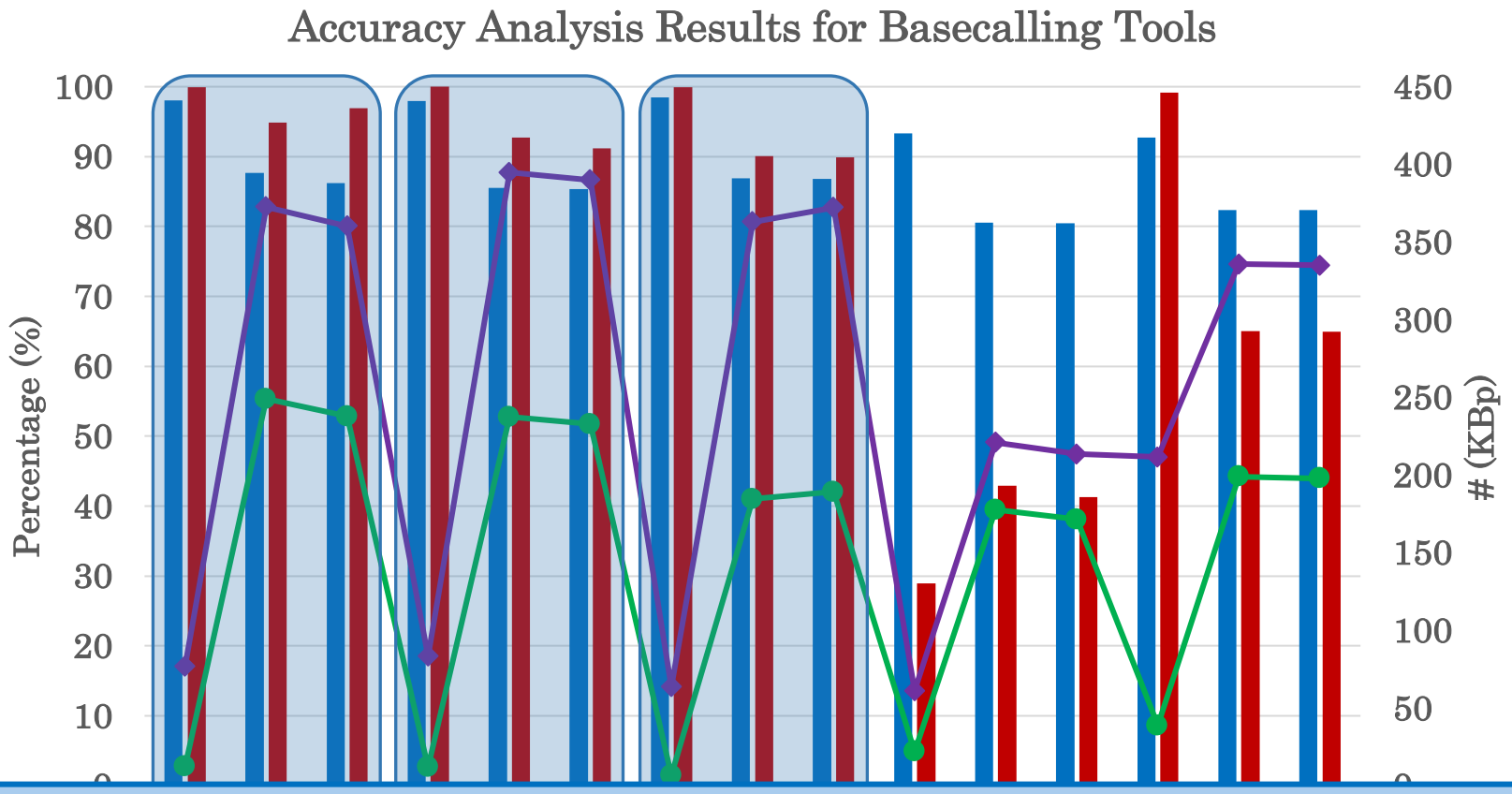
# Nanopore Genome Assembly Pipeline



# Nanopore Genome Assembly Pipeline

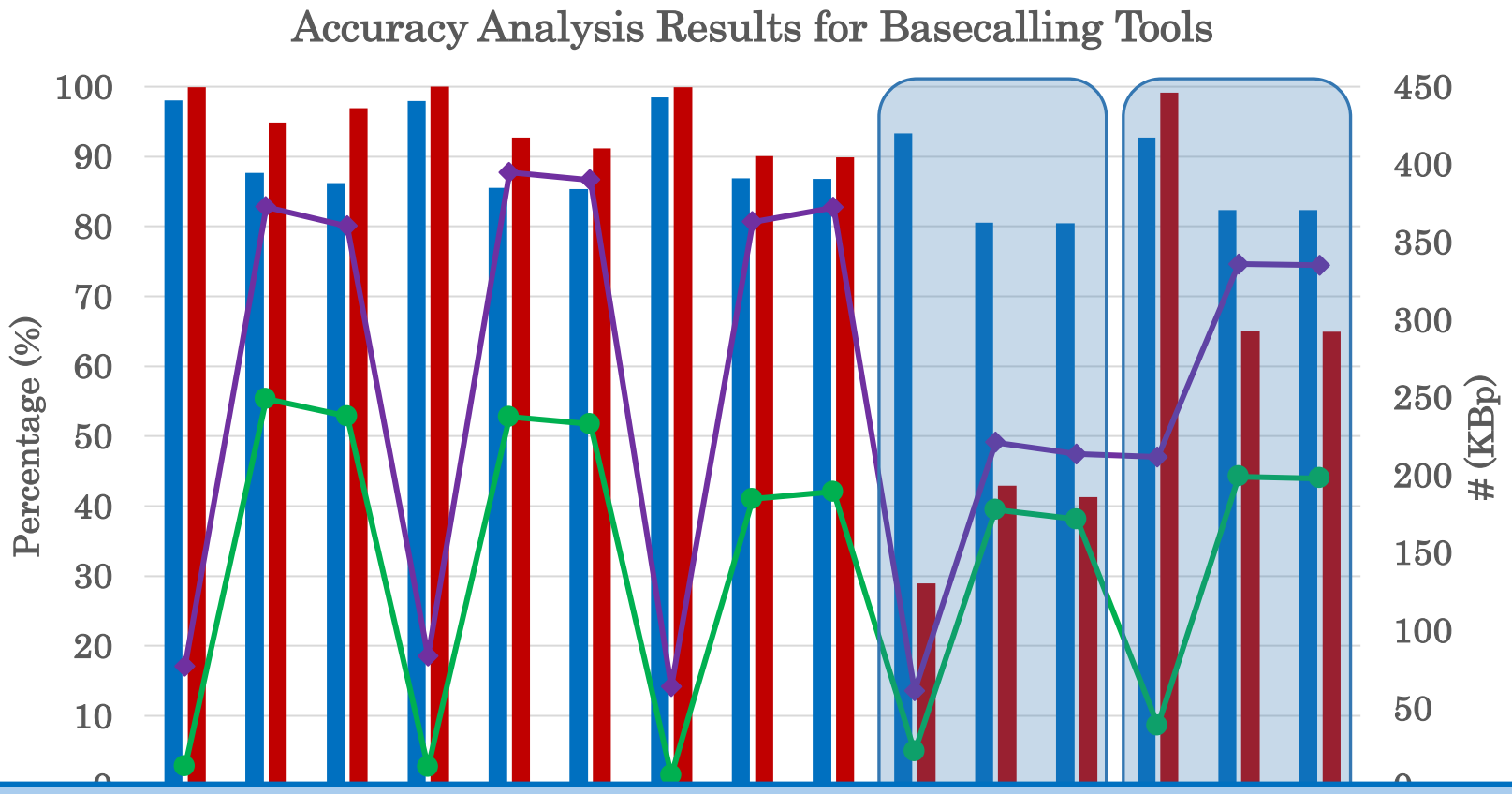


# Basecalling – Accuracy



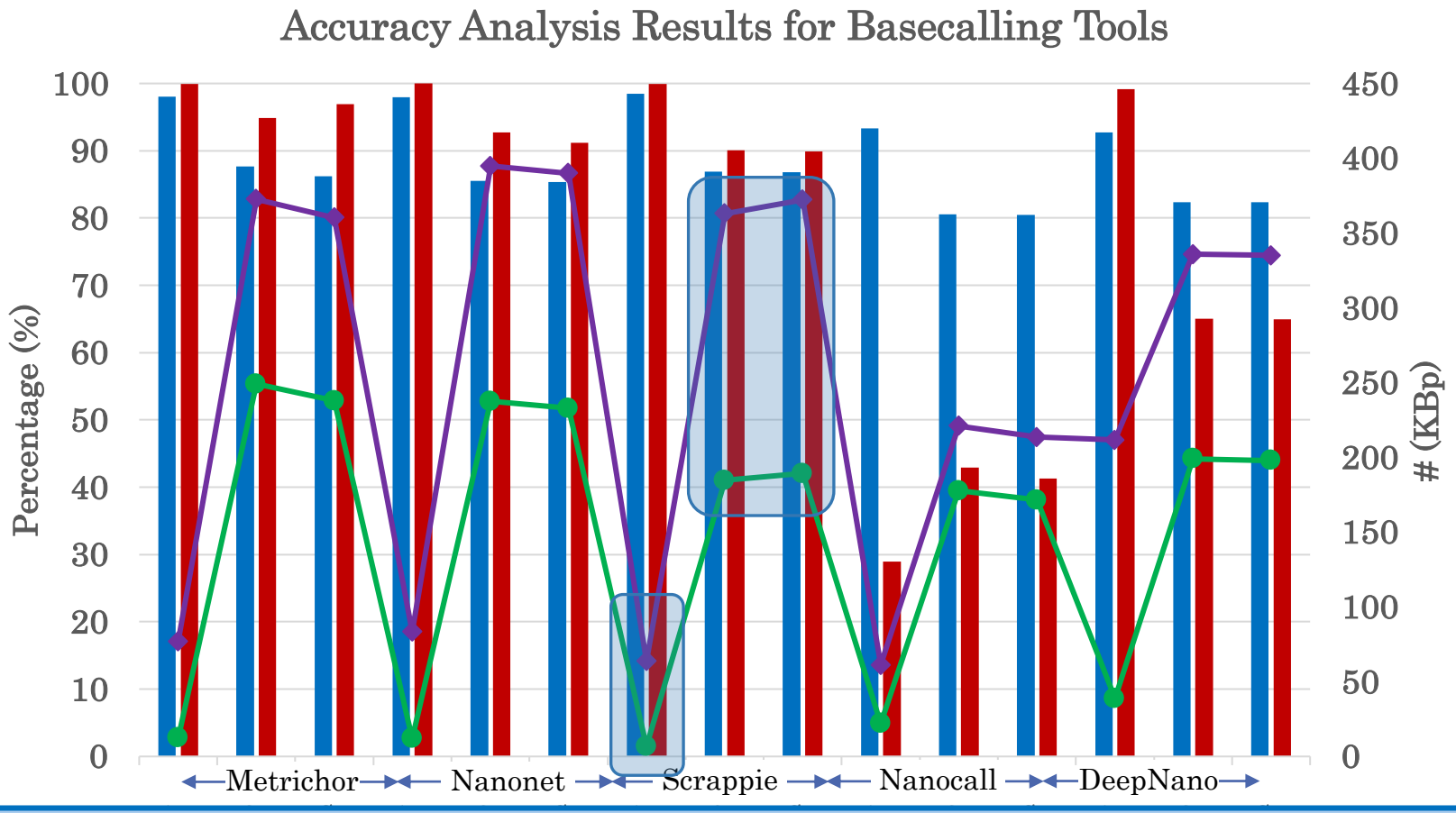

**Observation 1-a:** *Metrichor, Nanonet and Scrappie have similar identity and coverage trends among all of the evaluated scenarios.*

# Basecalling – Accuracy



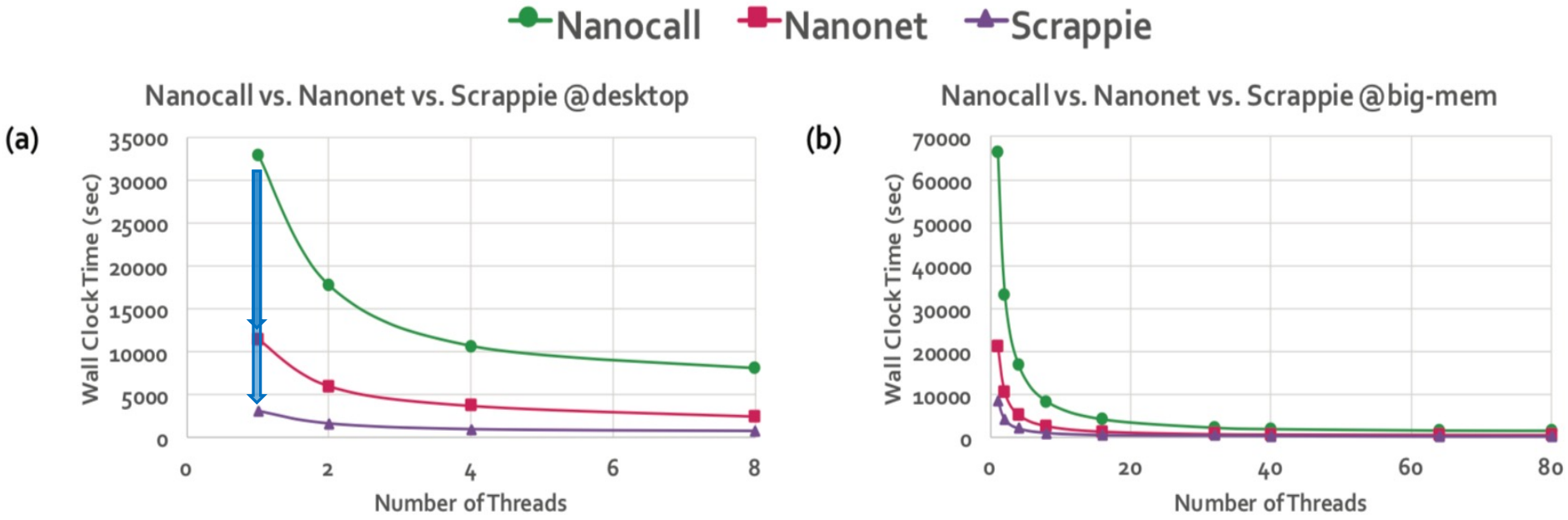

**Observation 1-b:** *However, Nanocall and DeepNano cannot reach these three basecallers' accuracies: they have lower identity and lower coverage.*

# Basecalling – Accuracy



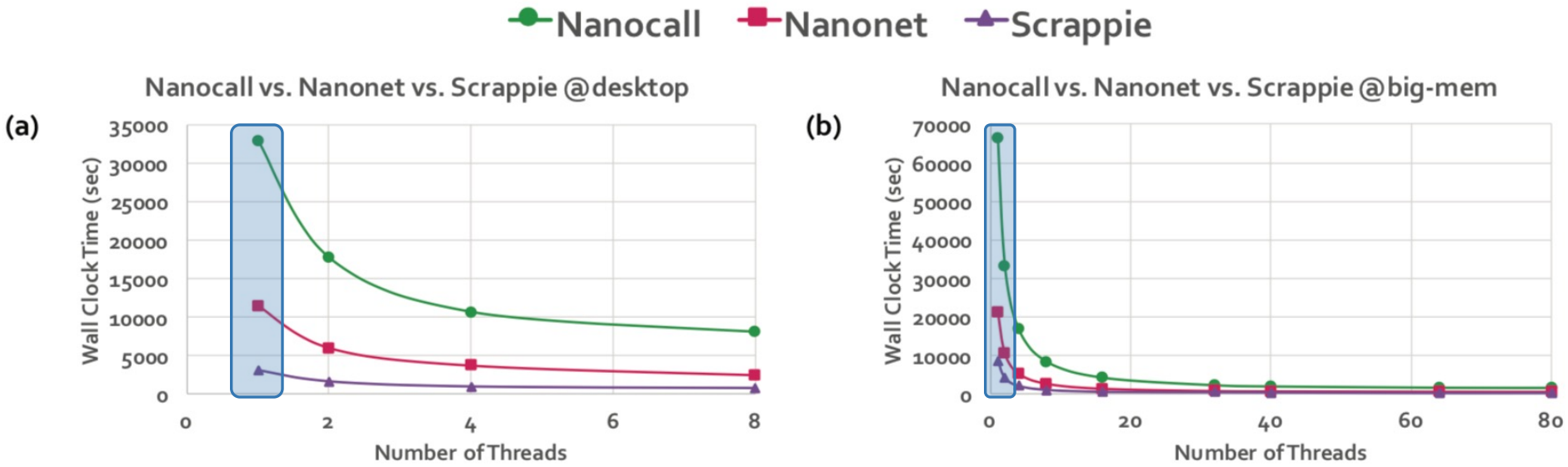

**Observation 1-c:** *Scrappie has the highest accuracy with the lowest number of mismatches and indels.*

# Basecalling – Speed



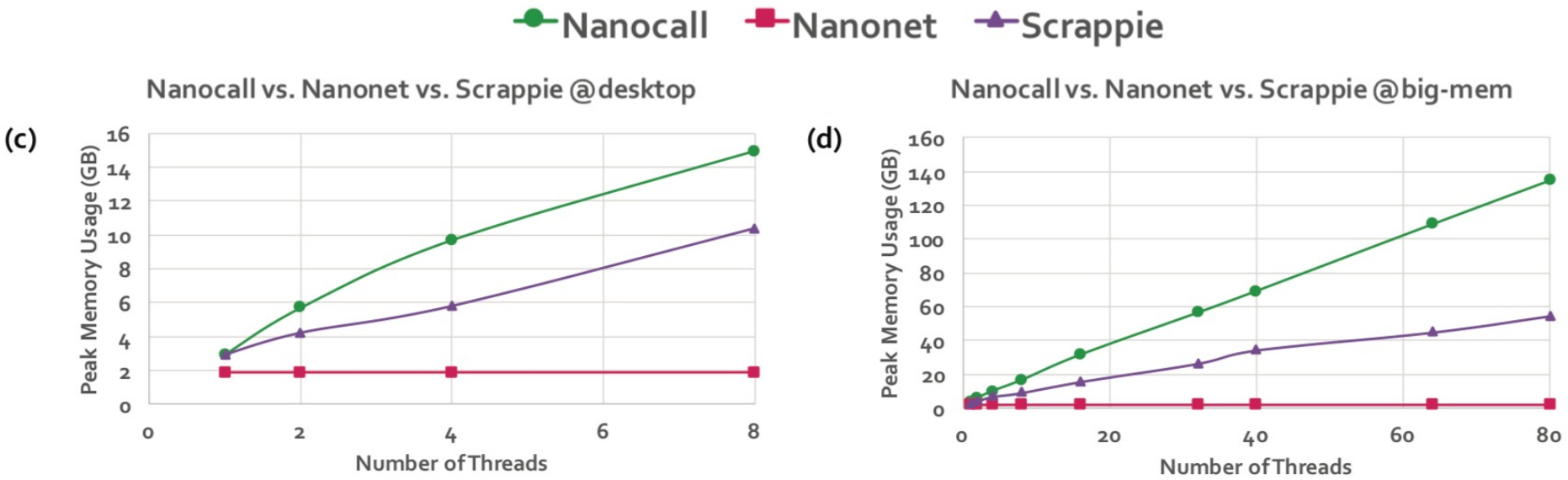

**Observation 2:** *RNN-based basecallers, Nanonet and Scrappie are faster than HMM-based basecaller, Nanocall.*

# Basecalling – Speed



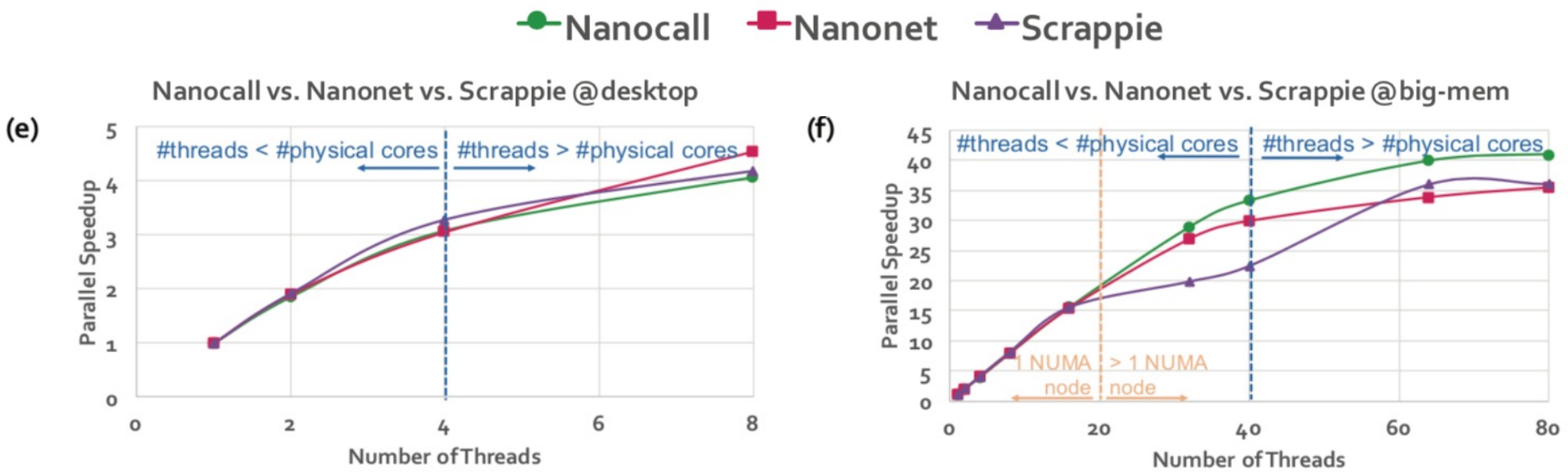

**Observation 3:** *When #threads=1, desktop is approximately 2x faster than big-mem because of desktop's higher CPU frequency. It is an indication that all of these three tools are computationally expensive.*

# Basecalling – Memory




**Observation 4:** *Scrappie and Nanocall have a linear increase in memory usage when number of threads increases. In contrast, Nanonet has a constant memory usage for all evaluated thread units.*

# Basecalling – Speedup




**Observation 5:** *When the number of threads exceeds the number of physical cores, the simultaneous multithreading overhead prevents continued linear speedup of Nanonet, Scrappie and Nanocall because of the CPU-intensive workload of these tools.*

# Basecalling – Key Observations

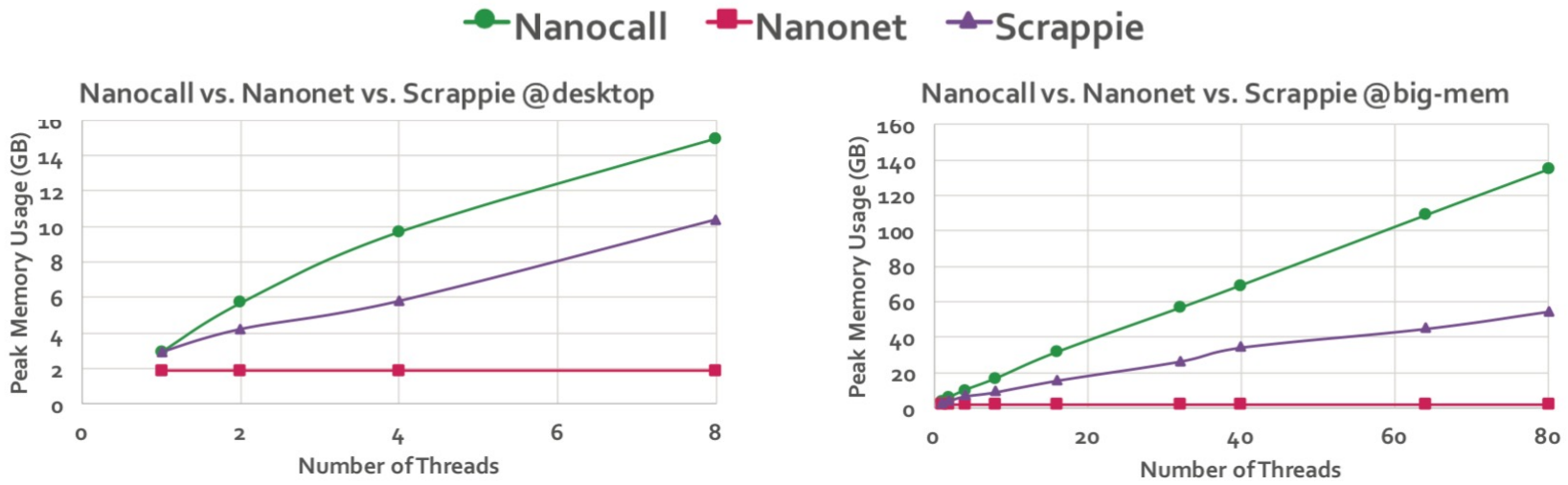
**Accuracy:**

- ONT's basecallers (i.e., Metrichor, Nanonet and Scrappie) have similar identity and coverage trends among all of the evaluated scenarios. However, other two basecallers (i.e., Nanocall and DeepNano) cannot reach these three basecallers' accuracies: they have lower identity and lower coverage
- Scrappie has the highest accuracy with the lowest number of mismatches and indels

**Performance:**

- RNN-based basecallers are faster than HMM-based basecaller

# Basecalling – Key Observations




## Memory Usage:

- Scrappie and Nanocall have a linear increase in memory usage when number of threads increases. In contrast, Nanonet has a constant memory usage for all evaluated thread units

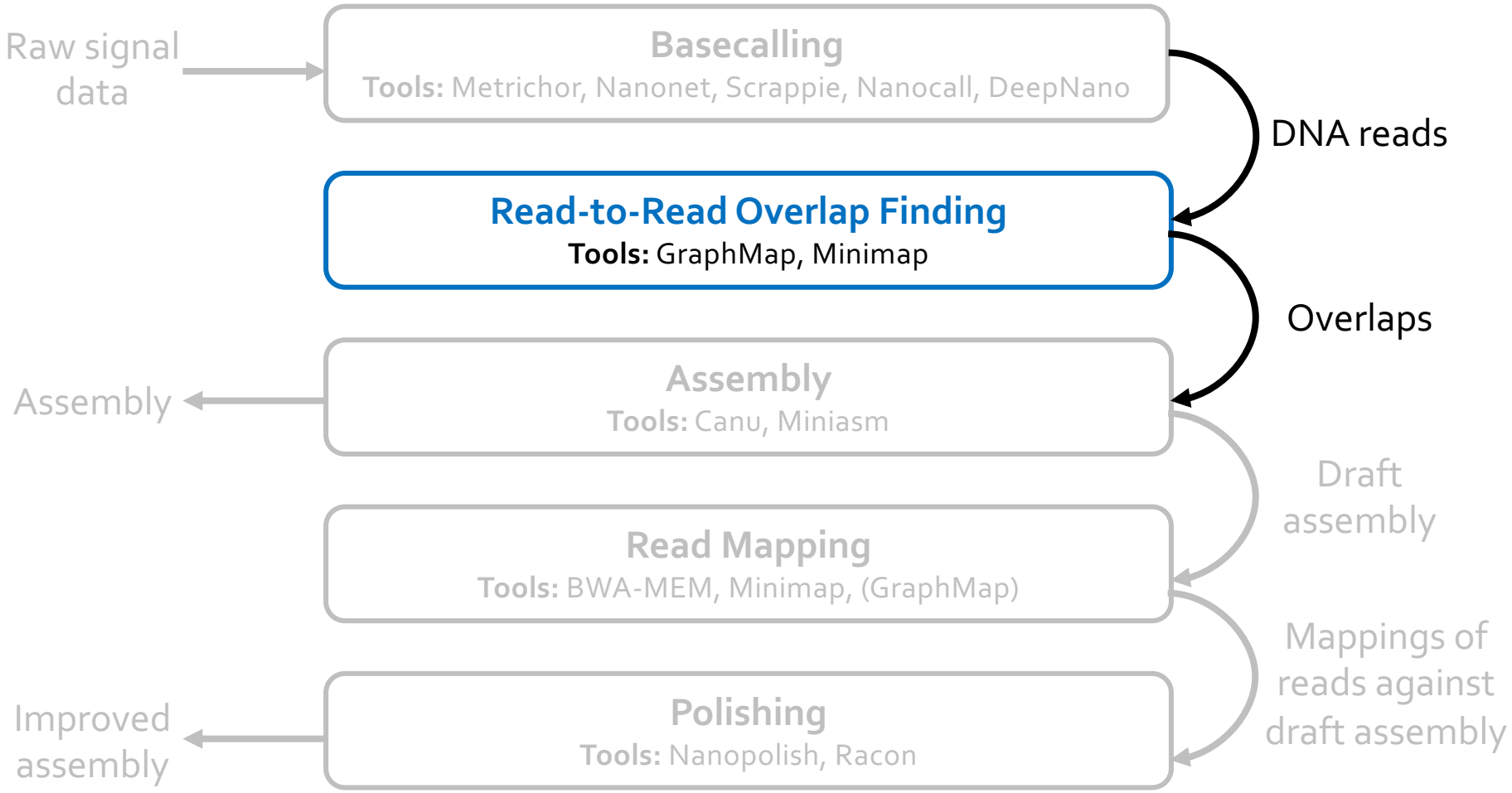
## Scalability:

- Data sharing between threads degrades the parallel speedup of Nanonet when cores from multiple NUMA nodes take role in the computation

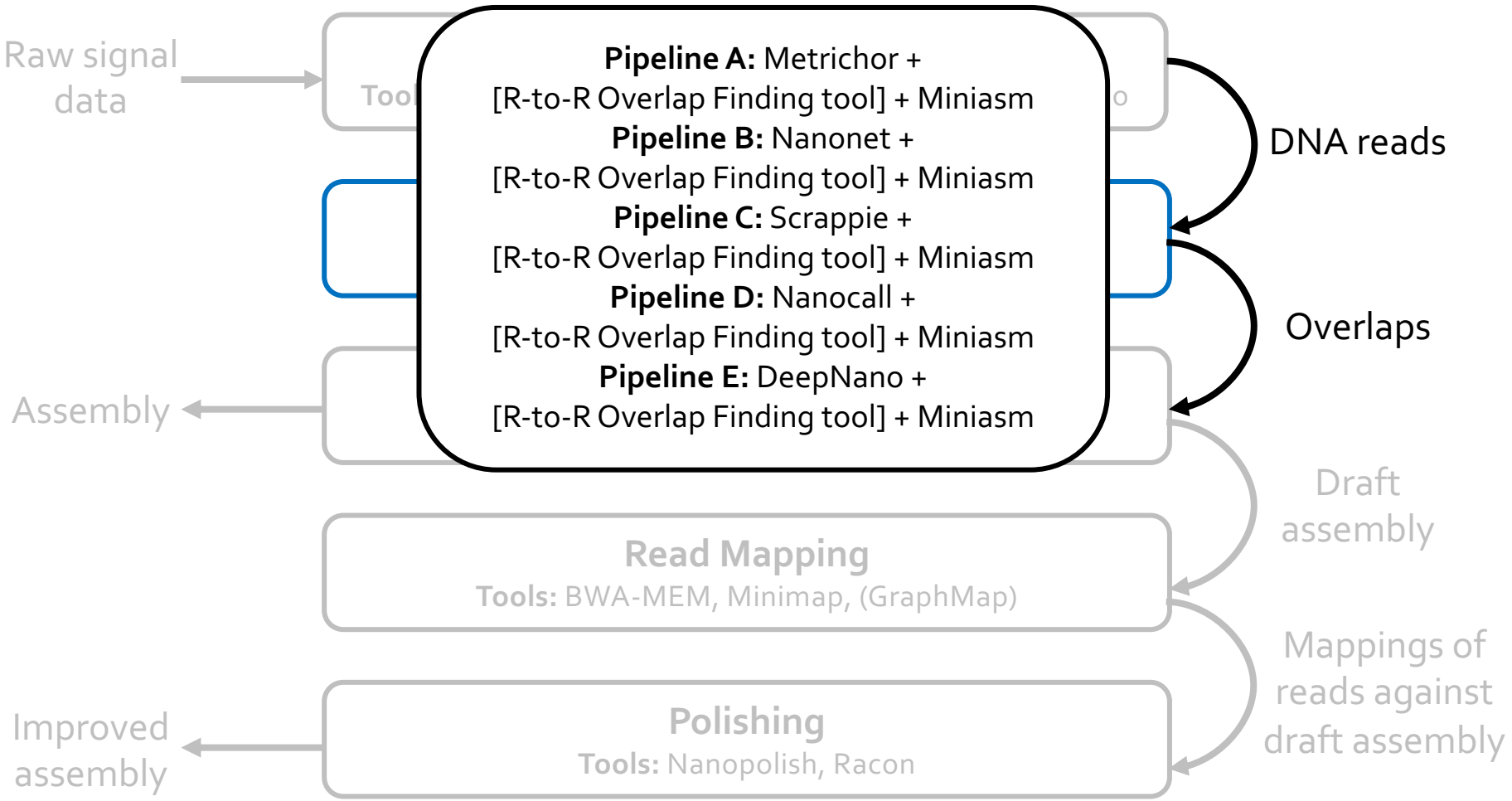
# Basecalling – Summary

- The choice of the tool for the basecalling step plays an important role to overcome the high error rates of nanopore sequencing technology.
- Basecalling with RNNs (e.g. Metrichor, Nanonet, Scrappie) provides higher accuracy and higher speed than basecalling with HMMs.
- The newest basecaller of ONT, Scrappie, also has the potential to overcome the homopolymer basecalling problem.

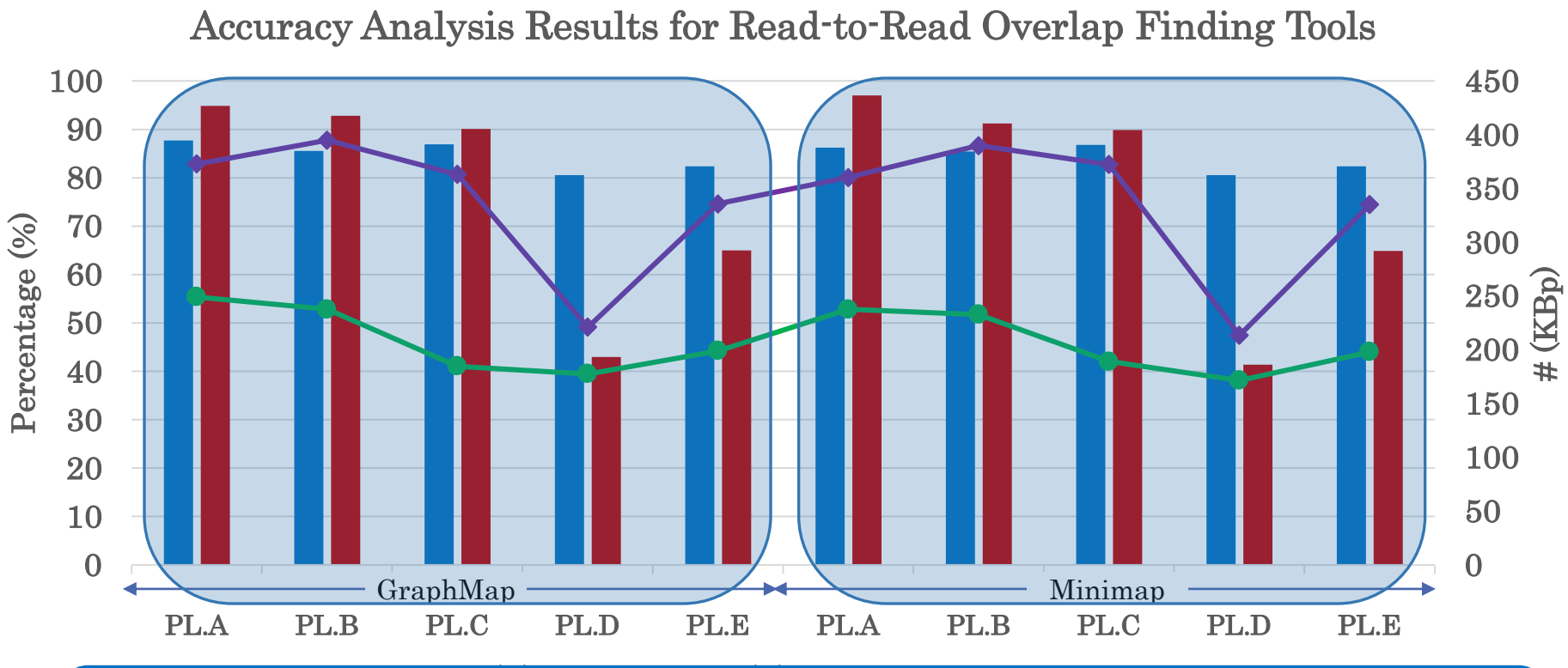
# Nanopore Genome Assembly Pipeline



# Nanopore Genome Assembly Pipeline

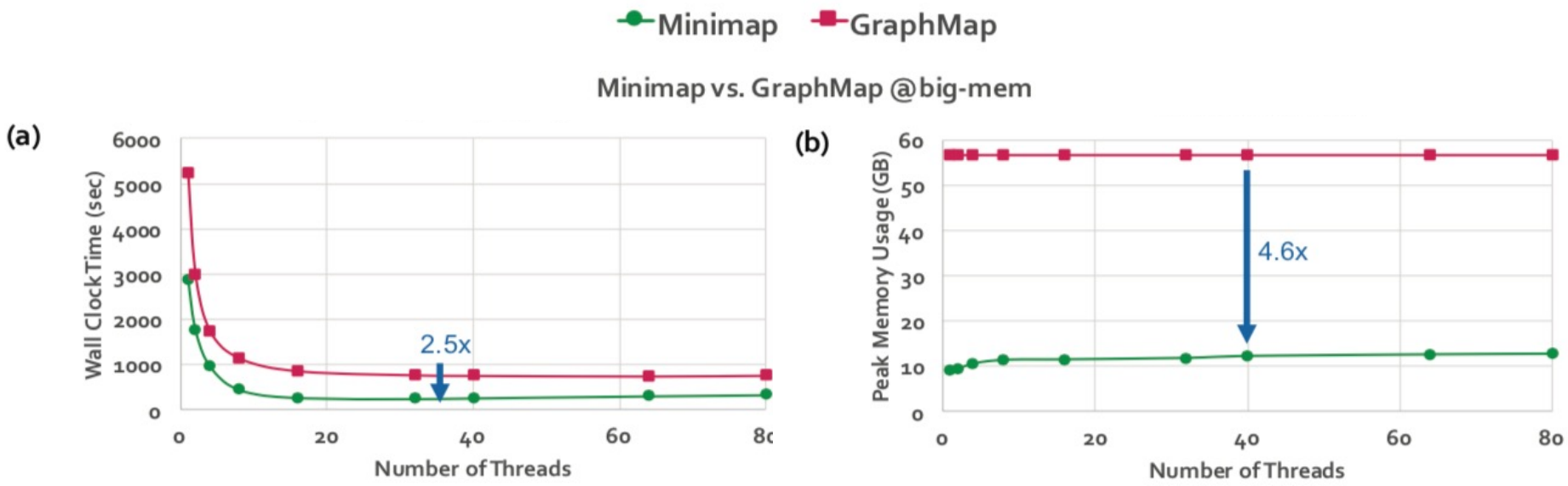


# R-to-R Overlap Finding – Accuracy



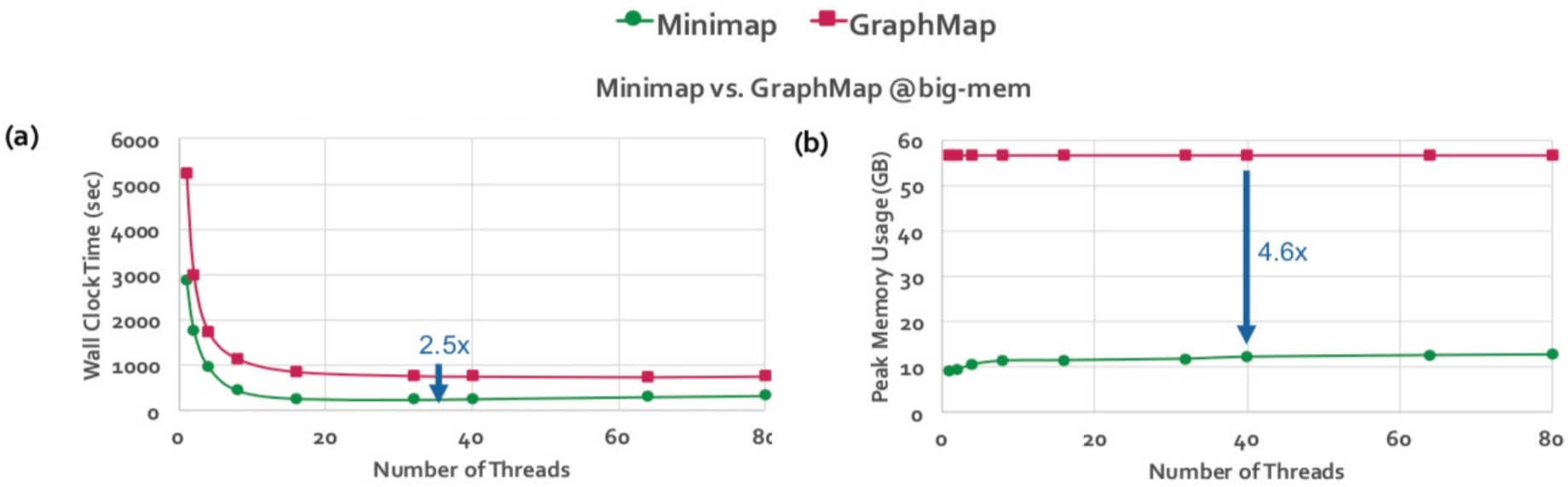

**Observation 5:** *Pipelines with GraphMap or Minimap end up with similar accuracy results.*

# R-to-R Overlap Finding – Performance



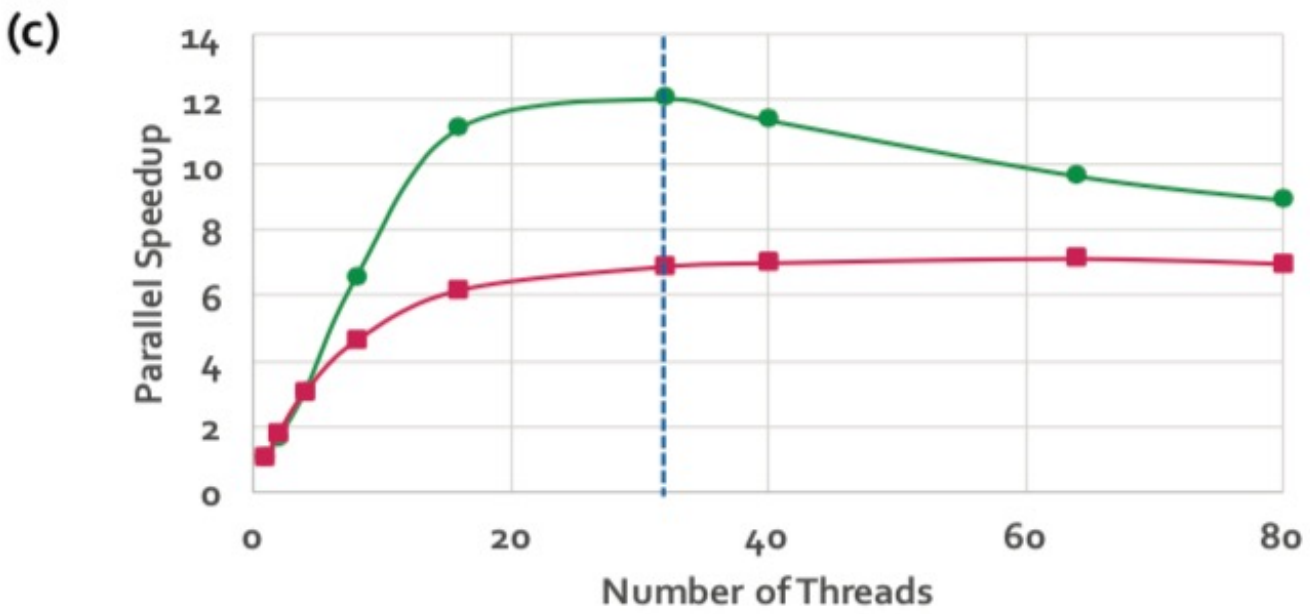

**Observation 6:** *The memory usage of both GraphMap and Minimap is dependent on the hash table size but independent of number of threads. Minimap requires 4.6x less memory than GraphMap, on average.*

# R-to-R Overlap Finding – Performance

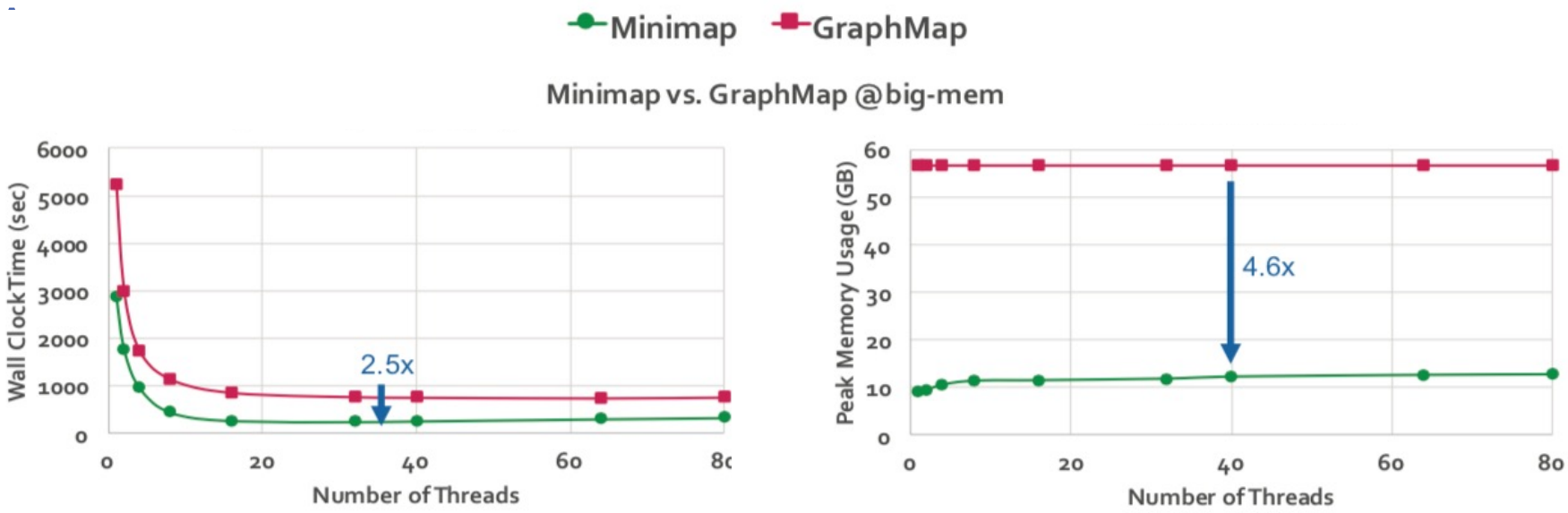



**Observation 7:** *Minimap is 2.5x faster than GraphMap, on average. Since in Minimap, the size of dataset that needs to be scanned is greatly shrunk by storing minimizers instead of k-mers, it performs much less computation than GraphMap.*

# R-to-R Overlap Finding – Speedup



# R-to-R Overlap Finding – Key Observations




## Memory Usage:

- The memory usage of both GraphMap and Minimap is dependent on the hash table size but independent of number of threads. Minimap requires 4.6x less memory than GraphMap, on average.

## Performance:

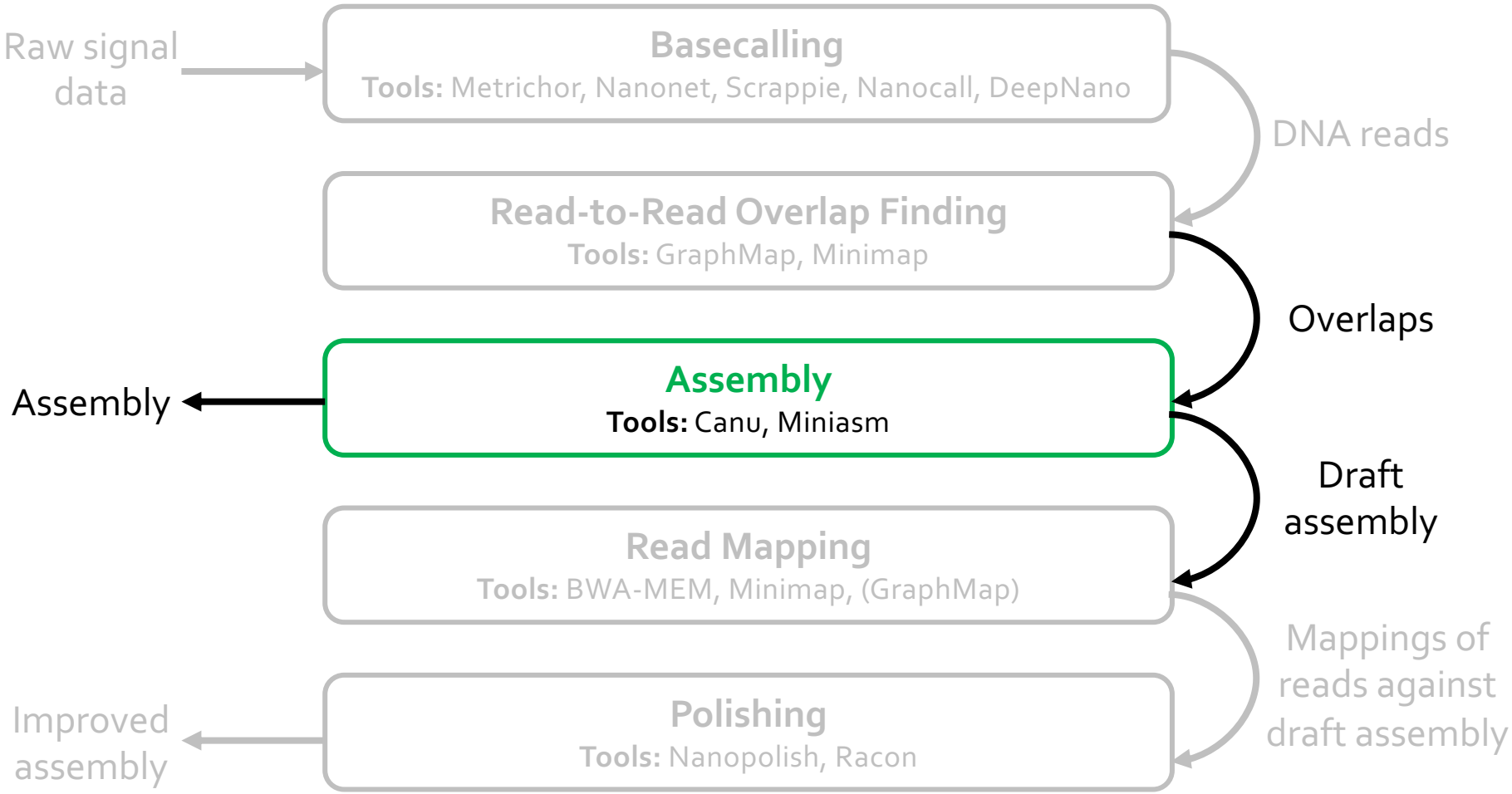
- Minimap is 2.5x faster than GraphMap, on average.

# R-to-R Overlap Finding – Summary

- Storing minimizers instead of all *k*-mers, as done by Minimap, does *not* affect the overall accuracy of the first three steps of the pipeline.

- By storing minimizers, Minimap has a much lower memory usage and thus much higher performance than GraphMap.

# Nanopore Genome Assembly Pipeline



# Assembly – Accuracy & Performance

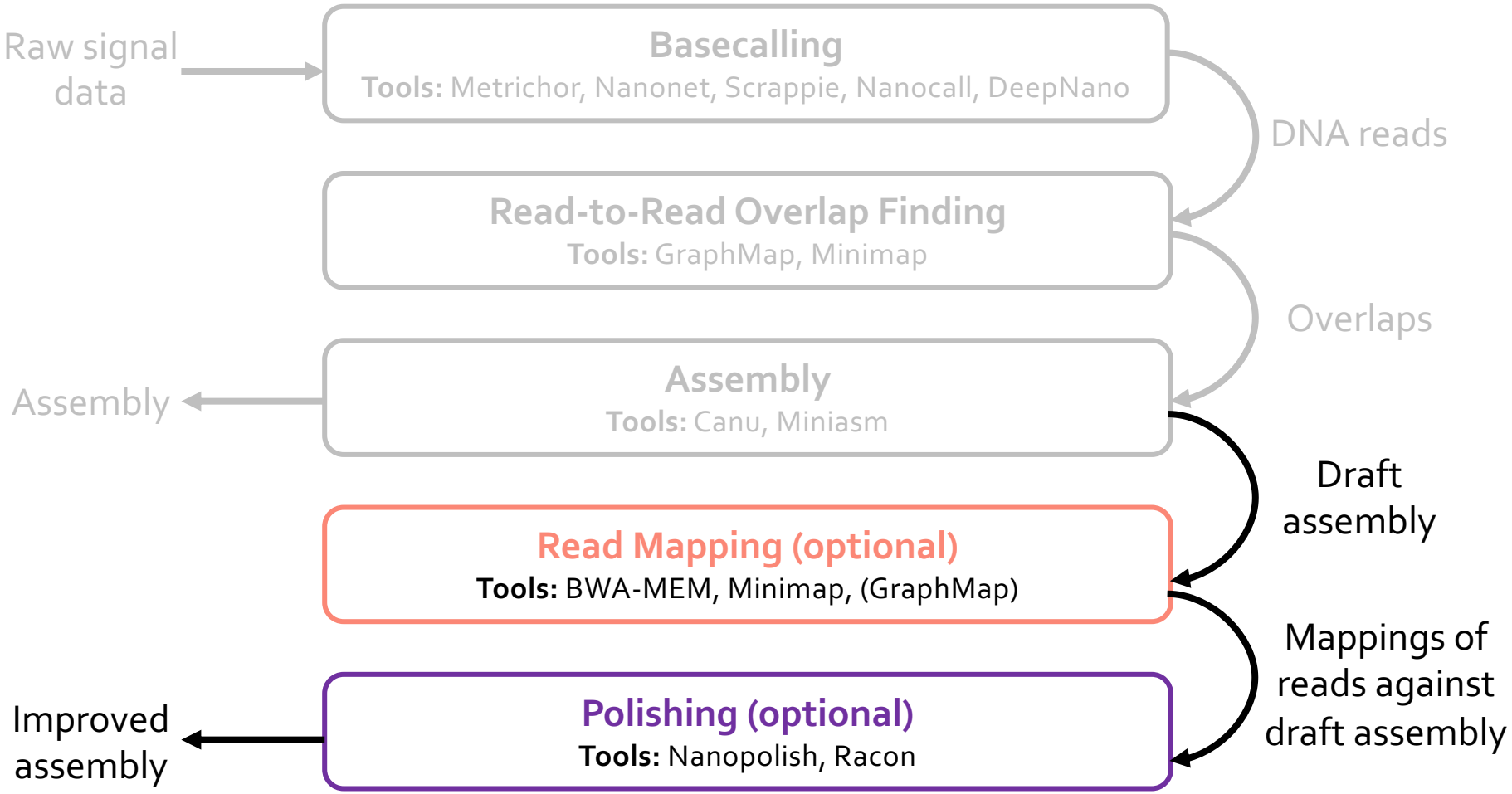
**Observation 8:** *Canu provides higher accuracy than Miniasm, with the help of the error-correction step that is present in its own pipeline. On average, Canu provides 96.1% identity whereas Miniasm provides 84.4% identity.*

**Observation 9:** *Canu is much more computationally intensive and greatly (i.e., by 1096.3x) slower than Miniasm, because of its very expensive error-correction step.*

# Assembly – Summary

- There is a trade-off between accuracy and performance when deciding on the appropriate tool for the assembly step.
- Canu produces highly accurate assemblies, but it is resource intensive and slow. In contrast, Miniasm is a fast assembler, but it cannot produce as accurate draft assemblies as Canu.
- Miniasm can potentially be used for fast initial analysis and then further polishing can be applied in the next step to produce higher-quality assemblies.

# Nanopore Genome Assembly Pipeline



# Read Mapping & Polishing – Accuracy

**Observation 11:** *Both Nanopolish and Racon significantly increase the accuracy of the draft assemblies.*

For example, Nanopolish increases the identity and coverage of the draft assembly generated with the Metrichor+Minimap+Miniasm pipeline from 87.71% and 94.85%, respectively, to 92.33% and 96.31%.
Similarly, Racon increases them to 97.70% and 99.91%, respectively.

**Observation 12:** *For Racon, the choice of read mapper does not affect the accuracy of the polishing step.*

# Read Mapping & Polishing – Speed

**Observation 13:** *Nanopolish is computationally much more intensive and thus greatly slower than Racon.*

Nanopolish runs take days to complete whereas Racon runs take minutes. This is mainly because Nanopolish works on each base individually, whereas Racon works on the windows. Since each window is much longer (i.e., 20kb) than a single base, the computational workload is greatly smaller in Racon.

**Observation 14:** *BWA-MEM is computationally more expensive than Minimap.*

Although the choice of BWA-MEM and Minimap for the read mapping step does not affect the accuracy of the polishing step, these two tools have a significant difference in performance.

# Read Mapping & Polishing – Summary

- Further polishing can significantly increase the accuracy of the assemblies.

- Pipelines with Minimap and Racon can provide a significant speedup compared with the pipelines with BWA-MEM and Nanopolish, while resulting with high-quality consensus sequences.

# Nanopore Sequencing & Tools [BiB 2018]

Damla Senol Cali, Jeremie S. Kim, Saugata Ghose, Can Alkan, and Onur Mutlu, **"Nanopore Sequencing Technology and Tools for Genome Assembly: Computational Analysis of the Current State, Bottlenecks and Future Directions."**

*Briefings in Bioinformatics*, April 2018.

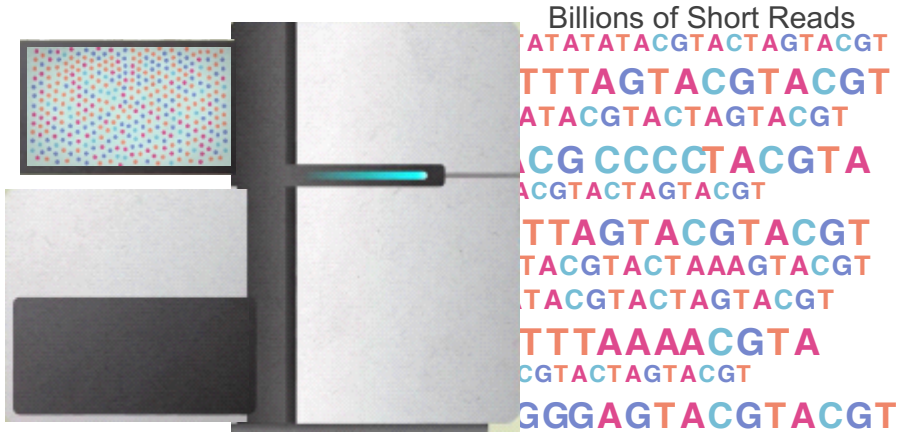
**Nanopore Sequencing Technology and Tools for Genome Assembly: Computational Analysis of the Current State, Bottlenecks and Future Directions**

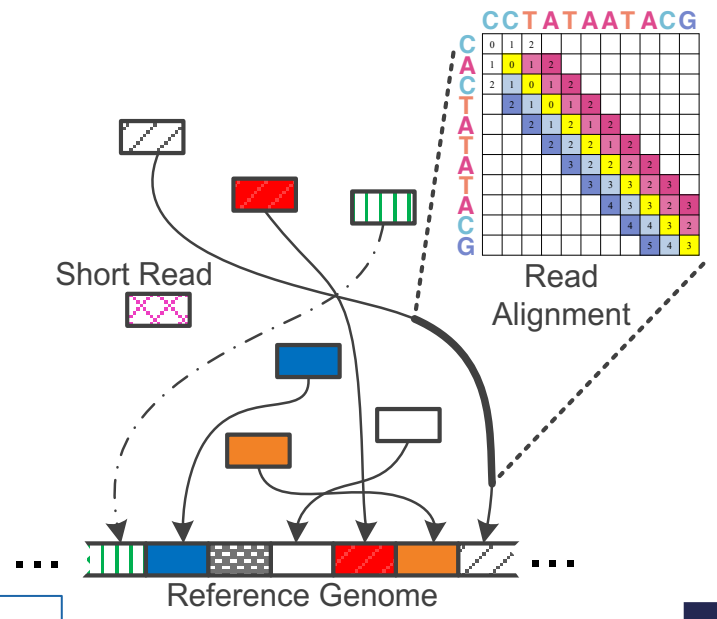
**Damla Senol Cali [1,*], Jeremie S. Kim [1,3], Saugata Ghose [1], Can Alkan [2*] and Onur Mutlu [3,1*]**

[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

# Backup Slides
## (GenASM)

Source: Prof. Onur Mutlu's lecture slides




# 1 Sequencing

# Genome Analysis

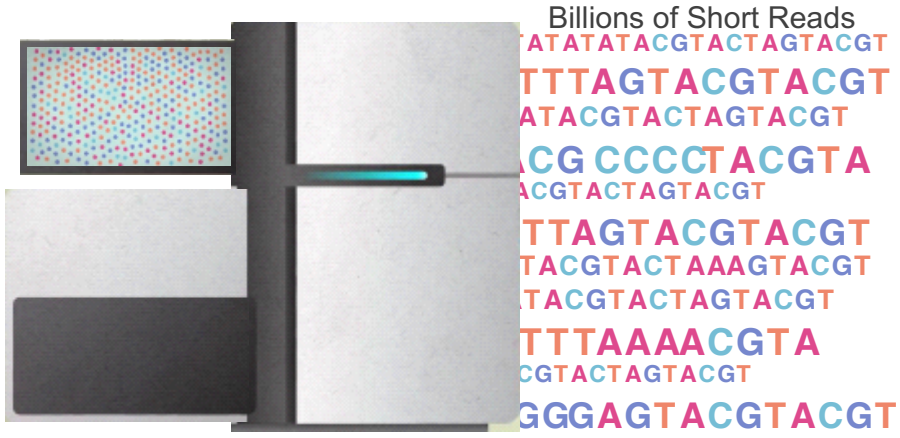
# Read Mapping 2

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

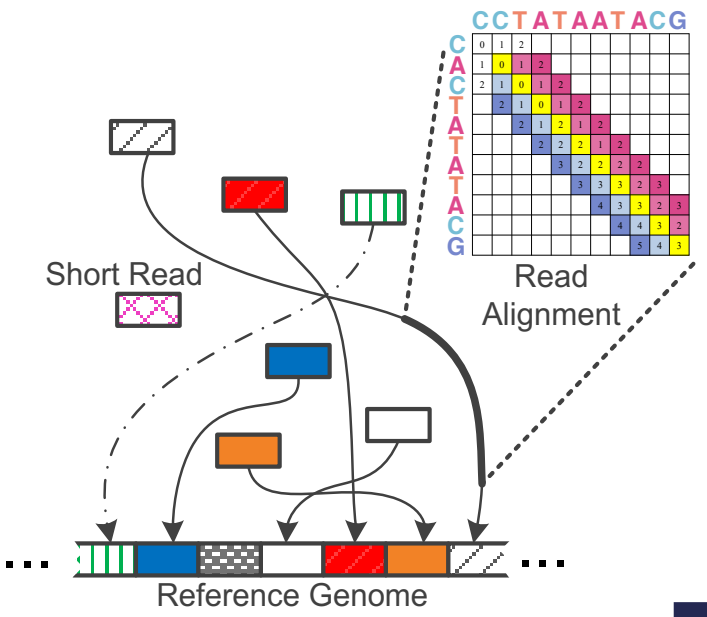
# 3 Variant Calling


# Scientific Discovery 4

Source: Prof. Onur Mutlu's lecture slides

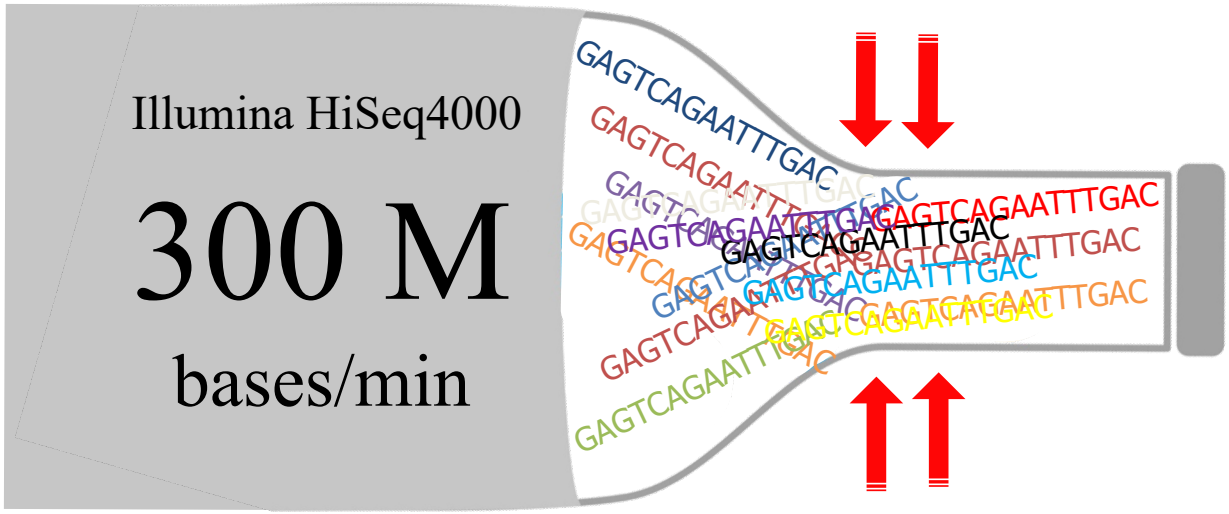



## 1 Sequencing




## Read Mapping 2

**Bottlenecked in Mapping!!**



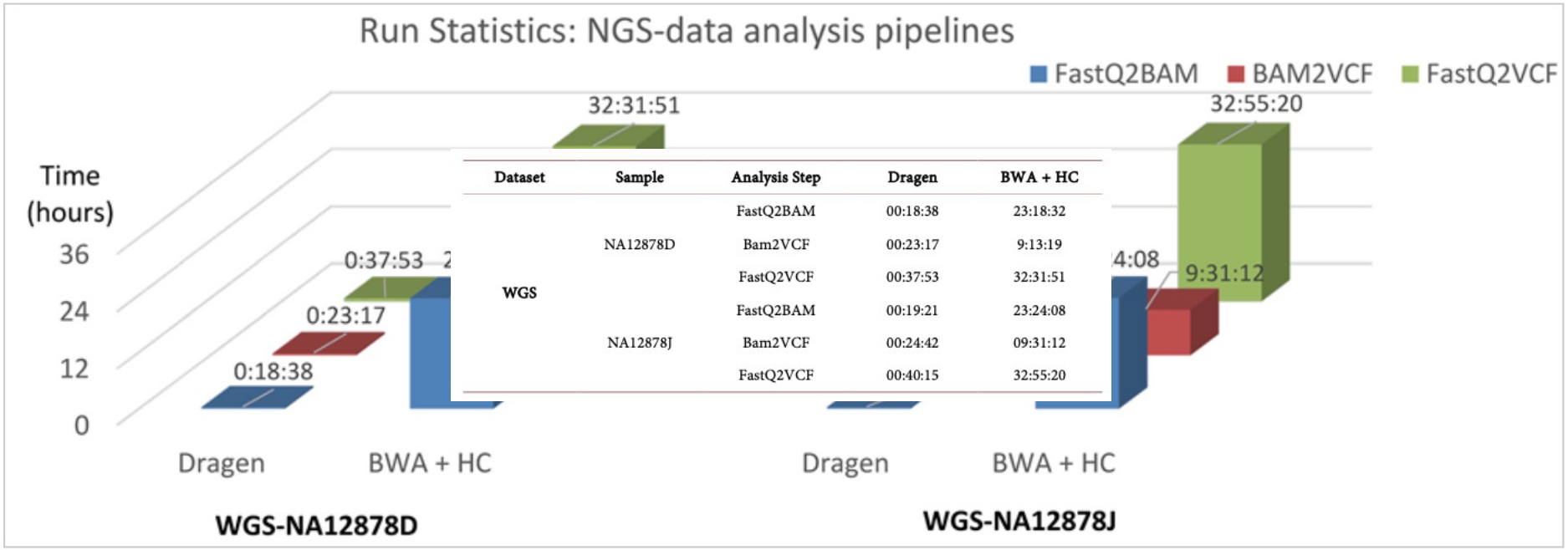

on average

2 M

bases/min

(0.6%)

# Illumina's DRAGEN




| Dataset | Sample | Analysis Step | Dragen | BWA + HC |
|---|---|---|---|---|
| WGS | NA12878D | FastQ2BAM | 00:18:38 | 23:18:32 |
| | | Bam2VCF | 00:23:17 | 9:13:19 |
| | | FastQ2VCF | 00:37:53 | 32:31:51 |
| | NA12878J | FastQ2BAM | 00:19:21 | 23:24:08 |
| | | Bam2VCF | 00:24:42 | 09:31:12 |
| | | FastQ2VCF | 00:40:15 | 32:55:20 |

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

# Illumina's DRAGEN

| Dataset | Sample | Analysis Step | Dragen | BWA + HC |
|---|---|---|---|---|
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Goyal+, "Ultra-fast next generation human genome sequencing data processing using DRAGENTM bio-IT processor for precision medicine", *Open Journal of Genetics,* 2017.

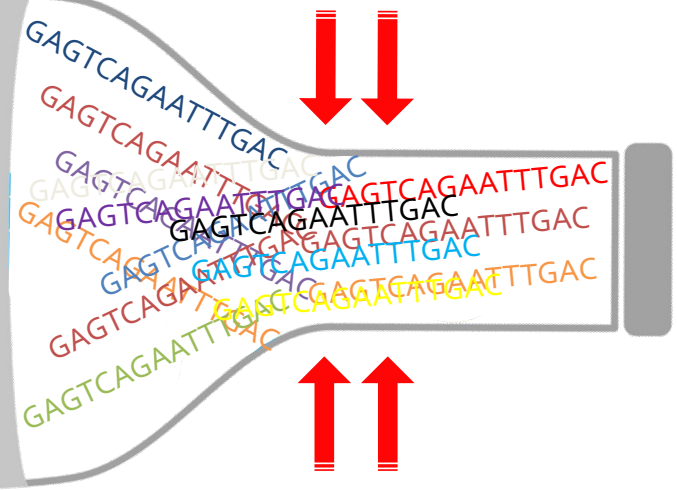
# Bottlenecked in Read Mapping!!

48 Human whole genomes

at 30× coverage

**in about 2 days**

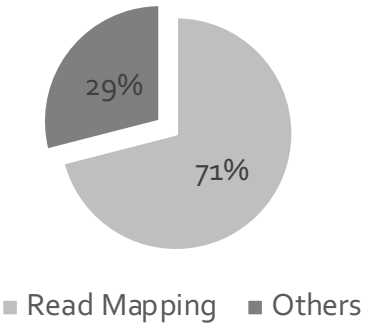
Illumina NovaSeq 6000




1 Human genome

**32 CPU hours**

on a 48-core processor

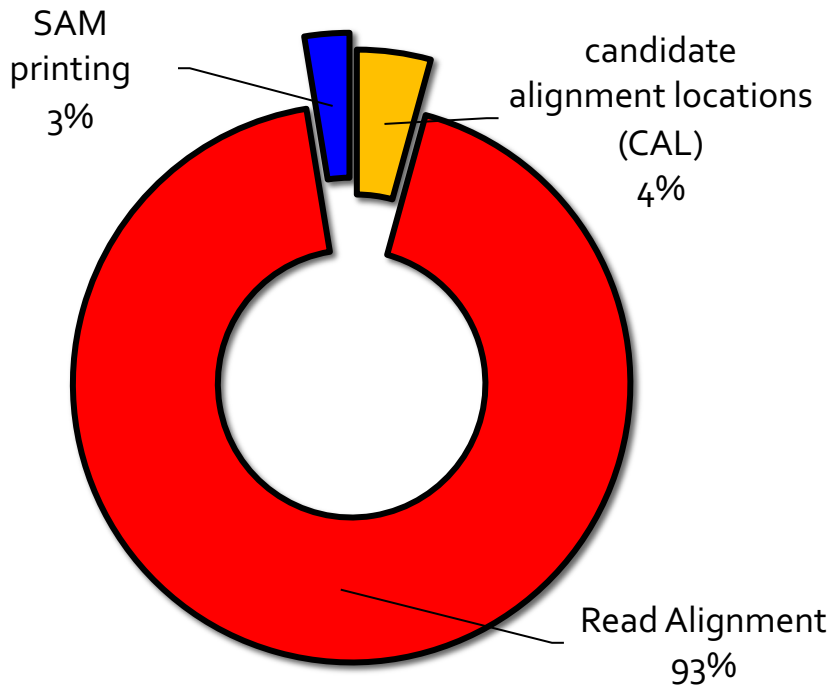



Goyal+, "Ultra-fast next generation human genome sequencing data processing using DRAGENTM bio-IT processor for precision medicine", *Open Journal of Genetics,* 2017.

# What Makes Read Mapper Slow?

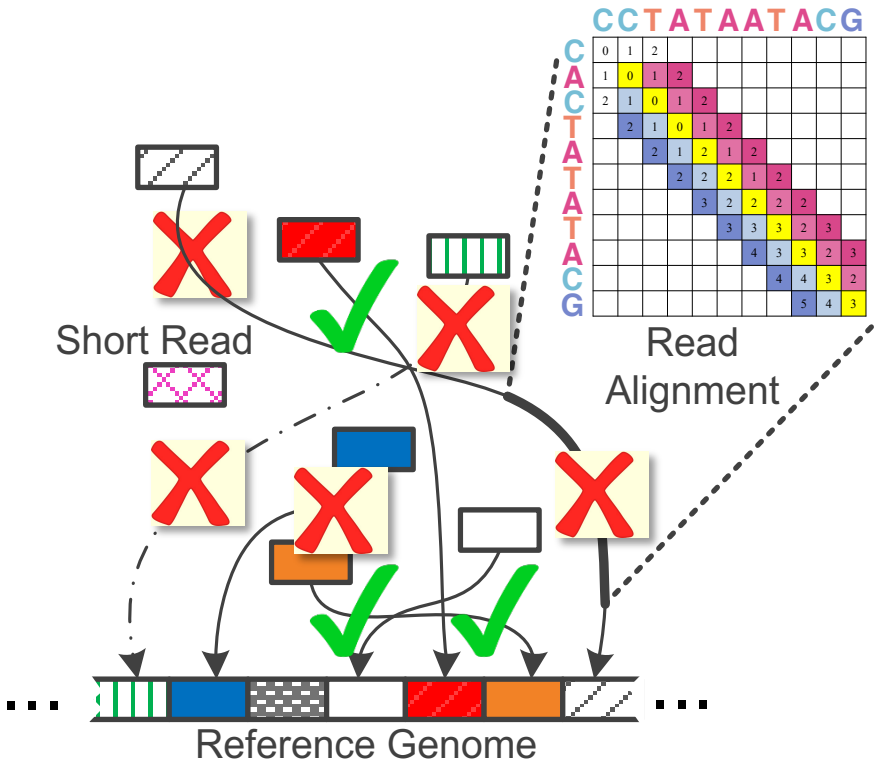
**93%**

**of the read mapper's execution time is spent in read alignment.**




*Alser et al, Bioinformatics (2017)*

# What Makes Read Mapper Slow? (cont'd.)




**98%**

**of candidate locations have high dissimilarity with a given read.**

Cheng *et al*, *BMC bioinformatics* (2015)
Xin *et al*, *BMC genomics* (2013)

# What Makes Read Mapper Slow? (cont'd.)

- **Quadratic-time** dynamic-programming algorithm

  Enumerating all possible prefixes

| | | N | E | T | H | E | R | L | A | N | D | S |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| S | 1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 10 |
| W | 2 | 2 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| I | 3 | 3 | 3 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| T | 4 | 4 | 4 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| Z | 5 | 5 | 5 | 4 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| E | 6 | 6 | 5 | 5 | 5 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| R | 7 | 7 | 6 | 6 | 6 | 5 | 4 | 5 | 6 | 7 | 8 | 9 |
| L | 8 | 8 | 7 | 7 | 7 | 6 | 5 | 4 | 5 | 6 | 7 | 8 |
| A | 9 | 9 | 8 | 8 | 8 | 7 | 6 | 5 | 4 | 5 | 6 | 7 |
| N | 10 | 9 | 9 | 9 | 9 | 8 | 7 | 6 | 5 | 4 | 5 | 6 |
| D | 11 | 10 | 10 | 10 | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 5 |

- **Data dependencies** limit the computation parallelism

  Processing row (or column) after another

- **Entire matrix** is computed even though strings can be dissimilar.

  Number of differences is computed only at the backtraking step.

# Approximate String Matching (ASM)

**Approximate string matching algorithms:**

- *Smith-Waterman (SW)* algorithm [Smith+, Advances in Applied Mathematics 1981]
  - Dynamic programming (DP) algorithm, with quadratic time and space complexity
  - Common algorithm used by read mappers

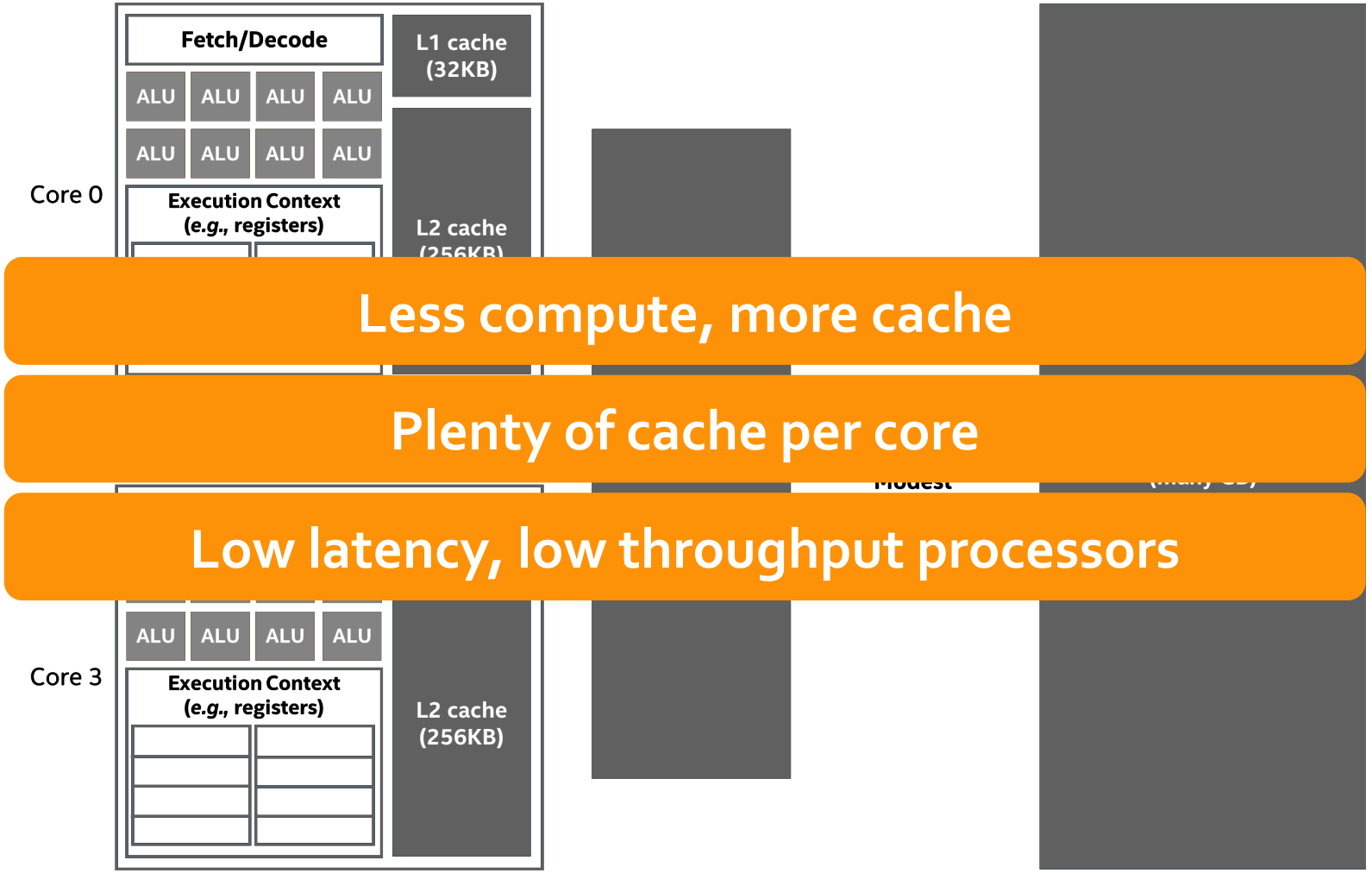
- *Myers' bitvector* algorithm [Myers, Journal of the ACM 1999]
  - Transformed version of SW algorithm into bitvectors and bitwise operations

- *Bitap* algorithm [Baeza-Yates+, Communications of the ACM 1992]
  - [Wu+, Communications of the ACM 1992] extended *Bitap* to perform approximate string matching
  - Bitvectors and bitwise operations

We have focused on the *Bitap* algorithm.

→ Reason: *Bitap* algorithm can perform ASM with fast and simple bitwise operations, which makes it amenable to efficient hardware acceleration.

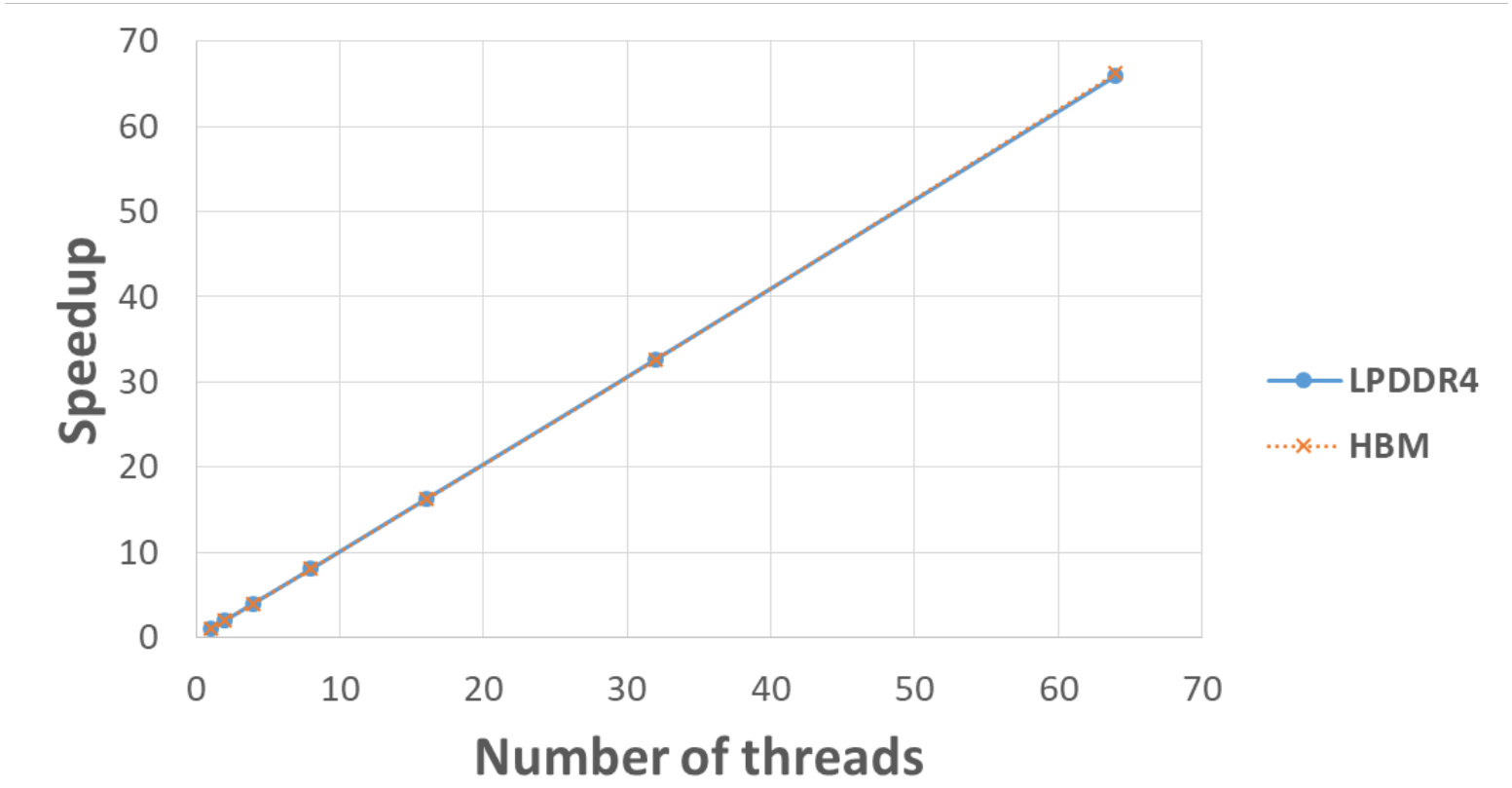
# CPU Systems


Fetch/Decode
L1 cache (32KB)
ALU
ALU
ALU
ALU
ALU
ALU
ALU
ALU
Core 0
Execution Context (e.g., registers)
L2 cache
Less compute, more cache
Plenty of cache per core
Low latency, low throughput processors
Core 3
Execution Context (e.g., registers)
L2 cache (256KB)

# Evaluation Methodology (CPU-bitap)

- **Vtune analysis on a real system**
  - **System Configuration:**
    - Intel Core i5-6600K CPU @ 3.50GHz (Skylake)
    - Single socket, 4 physical cores, 1 thread per core
    - 32KB L1 private caches, 256KB L2 private caches, 6MB shared LLC
    - 32GB main memory
  - **Analysis Details:**
    - HPC performance characterization
    - Hardware events for MPKIs and cache hit/miss rates of each level of cache
    - Hotspot analysis
- **Gem5 + Ramulator Simulations**
  - **Gem5 Configuration:**
    - CPU type: O3 (detailed)
    - Number of cores= Number of threads = 1, 2, 4, 8, 16, 32, 64
    - Private L1 size = 64KB each
    - Private L2 size = 512KB each
    - Shared L3 size = # cores * 1MB
    - Main memory type = LPDDR4 vs. HBM
    - Main memory size = 16GB
  - **Analysis Details:**
    - Execution-driven simulation
    - Scalability, memory-intensity (cache usage, memory bandwidth, and memory latency) and possible bottlenecks analysis
      - With and without L2/L3 caches

# Results (CPU-bitap)



# Results (CPU-bitap)

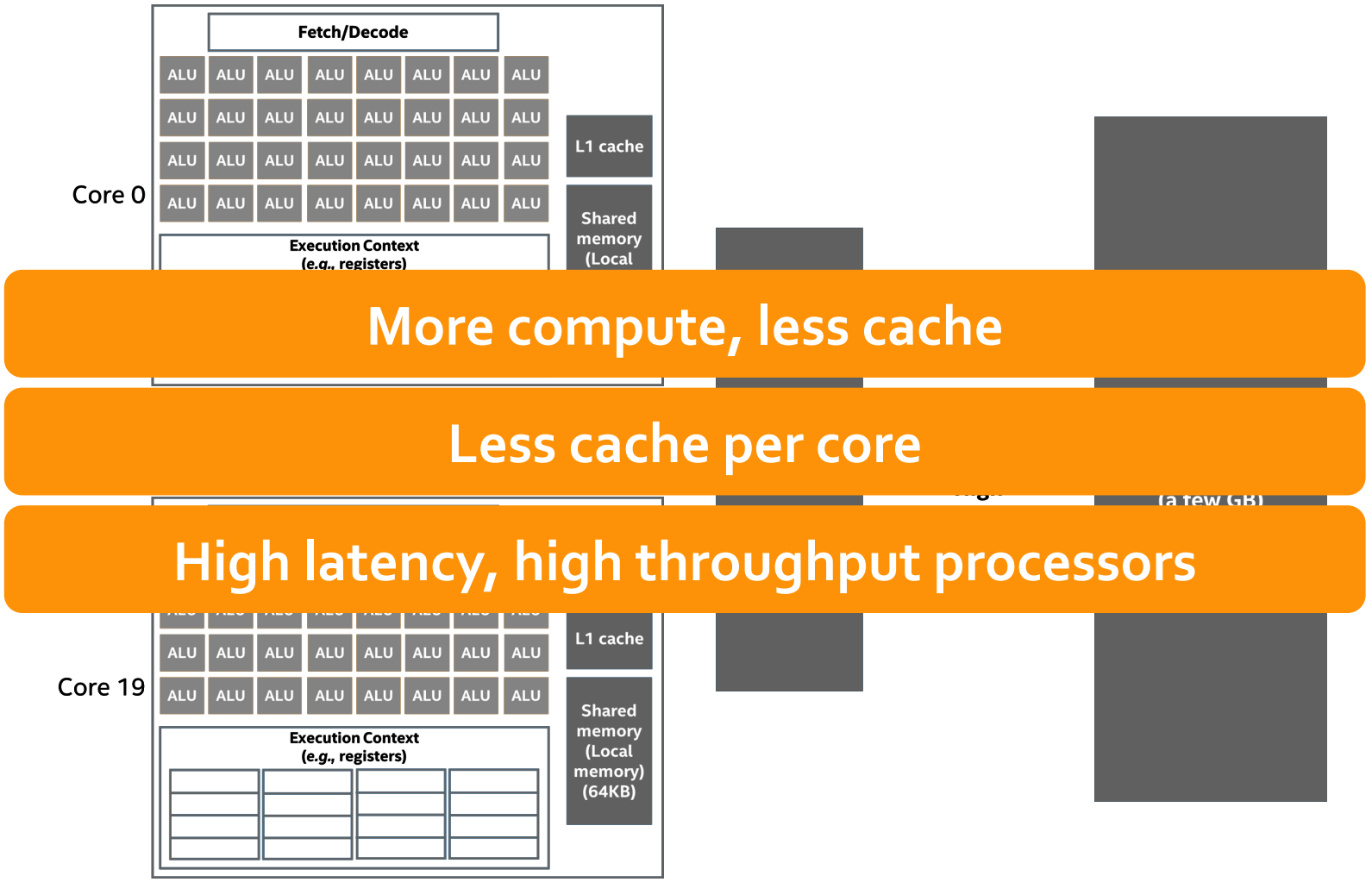
- *CPU-bitap* is very compute-intensive and not memory-bound.

- Lots of computation for one byte of data movement
  - L1-MPKI: 0.196, L2-MPKI: 0.086, LLC-MPKI: 0.037, and
  - Very high L1-hit rate (99.895%)

- Adding more cores provides a linear speedup

- Since the working set fits within the registers and the L1 cache and the number of memory requests is very low:
  - No performance difference without L2 and L3 caches
  - No performance difference between LPDDR4 or HBM as the memory

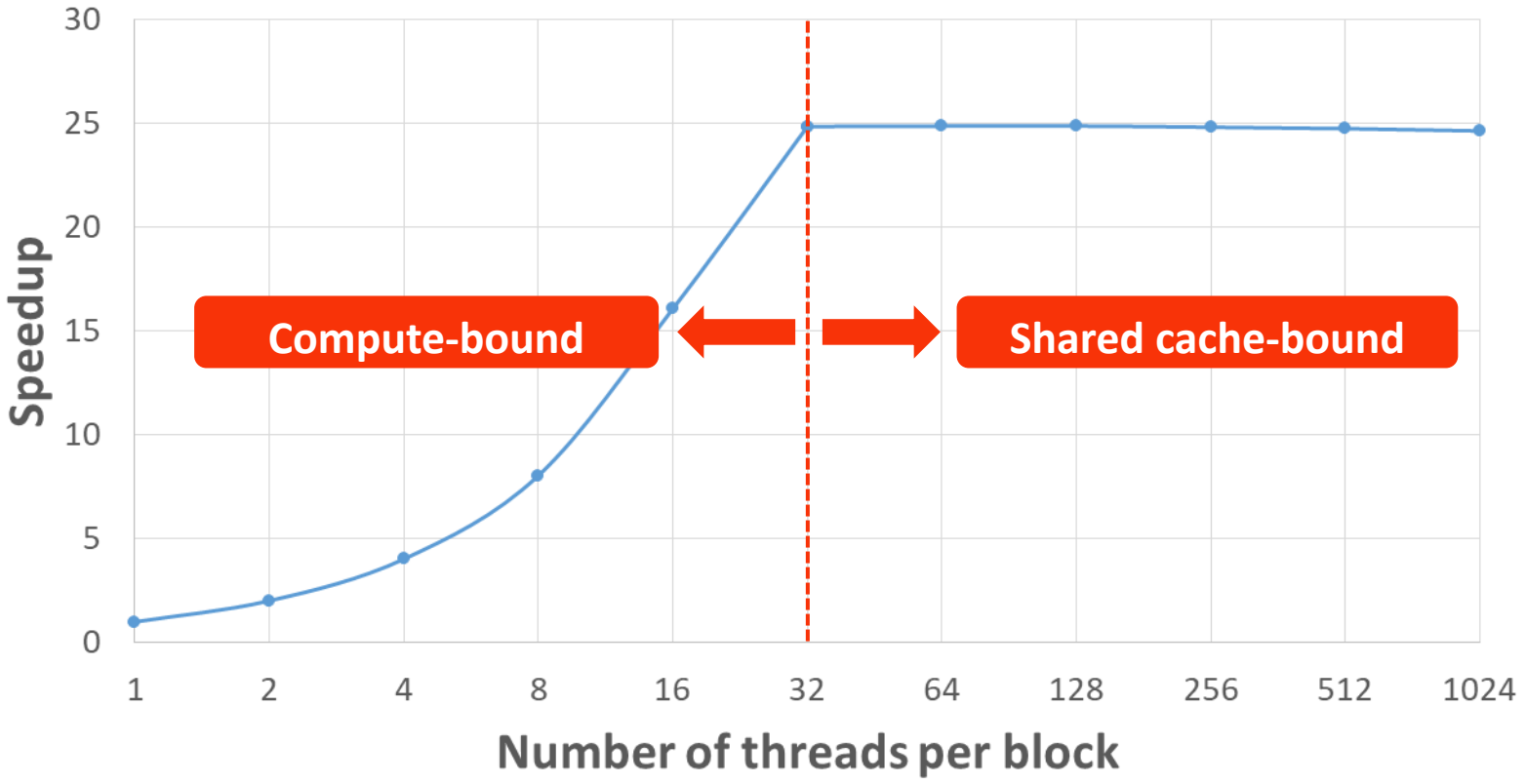
# GPU Systems


Fetch/Decode
ALU
L1 cache
Core 0
Shared memory (Local
Execution Context (e.g., registers)
More compute, less cache
Less cache per core
High latency, high throughput processors
Core 19
Shared memory (Local memory) (64KB)
Execution Context (e.g., registers)

# Evaluation Methodology (GPU-bitap)

- **nvprof analysis on a real system**
  - **System Configuration:**
    - Nvidia Titan V GPU (Volta)
    - 80 multiprocessors * 64 CUDA cores per MP = 5120 CUDA cores
    - L2 cache size = 4.5MB
    - Warp size = 32
    - 12GB HBM2 memory
  - **Analysis Details:**
    - Events:
      - Elapsed and active cycles
    - Metrics:
      - Branch and warp execution efficiency
      - L2 read/write transactions and throughput
      - DRAM read/write transactions and throughput
      - Stalls (*i.e.*, instruction fetch, execution dependency, memory dependency, and busy compute pipeline)

# Results (GPU-bitap)



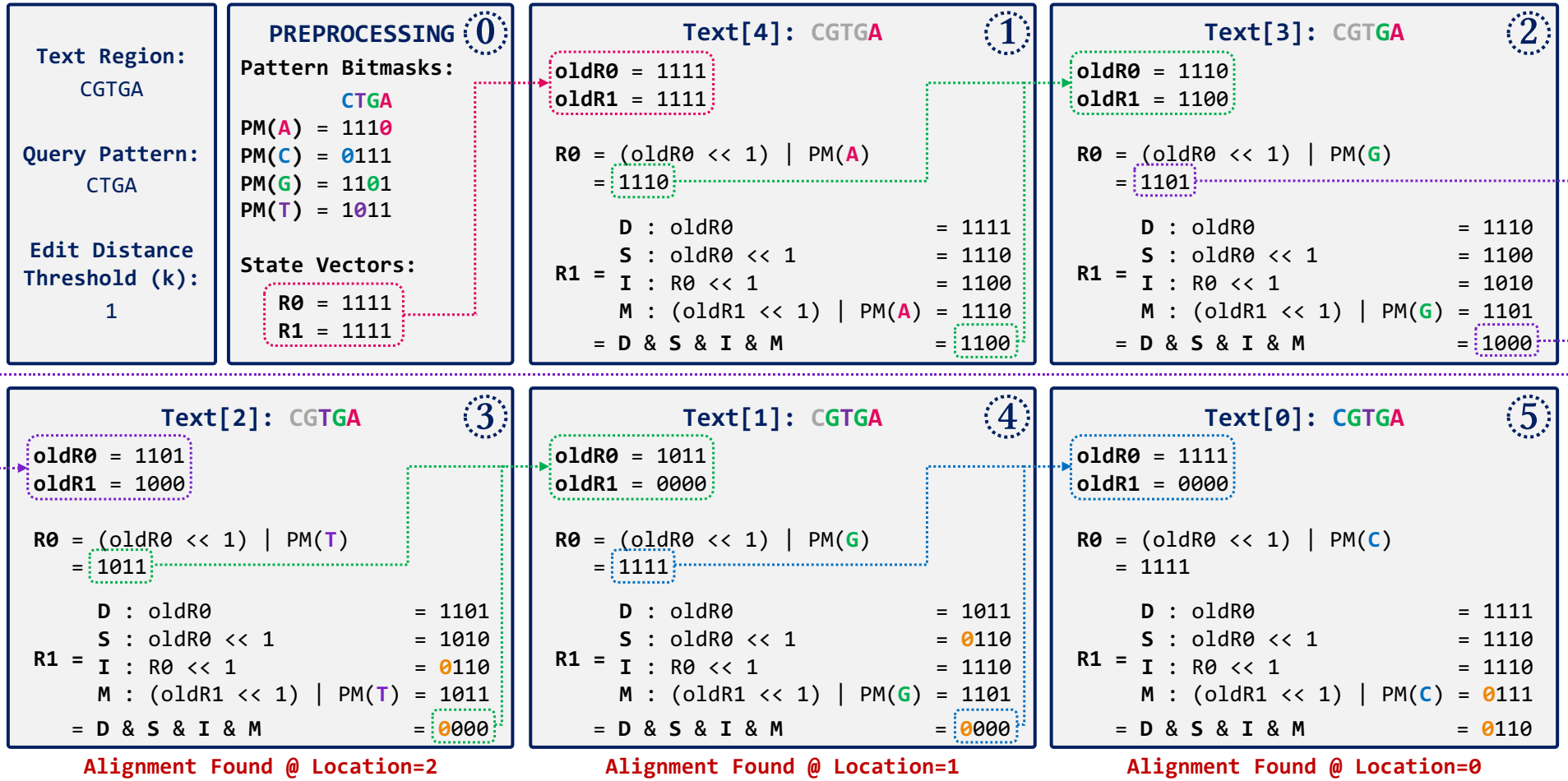
# Results (GPU-bitap)

- From 1 thread per block to 32 threads per block,
  - *GPU-bitap* is compute-bound, and
  - Warp execution efficiency increases from 3% to 100%, linearly.

- *GPU-bitap* is shared cache-bound (*i.e.*, on-GPU L2 cache-bound) after number of threads per block reaches 32.
  - Small number of registers → not enough to hold the frequently used data
  - Number of L2 read transactions stops decreasing and becomes stable

- Bottlenecks:
  - Shared memory and L2 cache accesses
  - Destructive interference of threads

# Example for the Bitap Algorithm



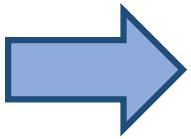
# GenASM Algorithm

- **GenASM-DC Algorithm:**
  - Modified Bitap for Distance Calculation
  - Extended for efficient long read support
  - Besides bit-parallelism that Bitap has, extended for parallelism:
    - Loop unrolling
    - Text-level parallelism

- **GenASM-TB Algorithm:**
  - Novel Bitap-compatible TraceBack algorithm
  - Walks through the intermediate bitvectors (match, deletion, substitution, insertion) generated by GenASM-DC
  - Follows a divide-and-conquer approach to decrease the memory footprint

# Loop Unrolling in GenASM-DC

| Cycle# | Thread$_1$ *R0/1/2/..* |
|---|---|
| #1 | T0-R0 |
| … | … |
| #8 | T0-R7 |
| #9 | T1-R0 |
| … | … |
| #16 | T1-R7 |
| #17 | T2-R0 |
| … | … |
| #24 | T2-R7 |
| #25 | T3-R0 |
| … | … |
| #32 | T3-R7 |



| Cycle# | Thread$_1$ *R0/4* | Thread$_2$ *R1/5* | Thread$_3$ *R2/6* | Thread$_4$ *R3/7* |
|---|---|---|---|---|
| #1 | T0-R0 | – | – | – |
| #2 | T1-R0 | T0-R1 | – | – |
| #3 | T2-R0 | T1-R1 | T0-R2 | – |
| #4 | T3-R0 | T2-R1 | T1-R2 | T0-R3 |
| #5 | T0-R4 | T3-R1 | T2-R2 | T1-R3 |
| #6 | T1-R4 | T0-R5 | T3-R2 | T2-R3 |
| #7 | T2-R4 | T1-R5 | T0-R6 | T3-R3 |
| #8 | T3-R4 | T2-R5 | T1-R6 | T0-R7 |
| #9 | – | T3-R5 | T2-R6 | T1-R7 |
| #10 | – | – | T3-R6 | T2-R7 |
| #11 | – | – | – | T3-R7 |

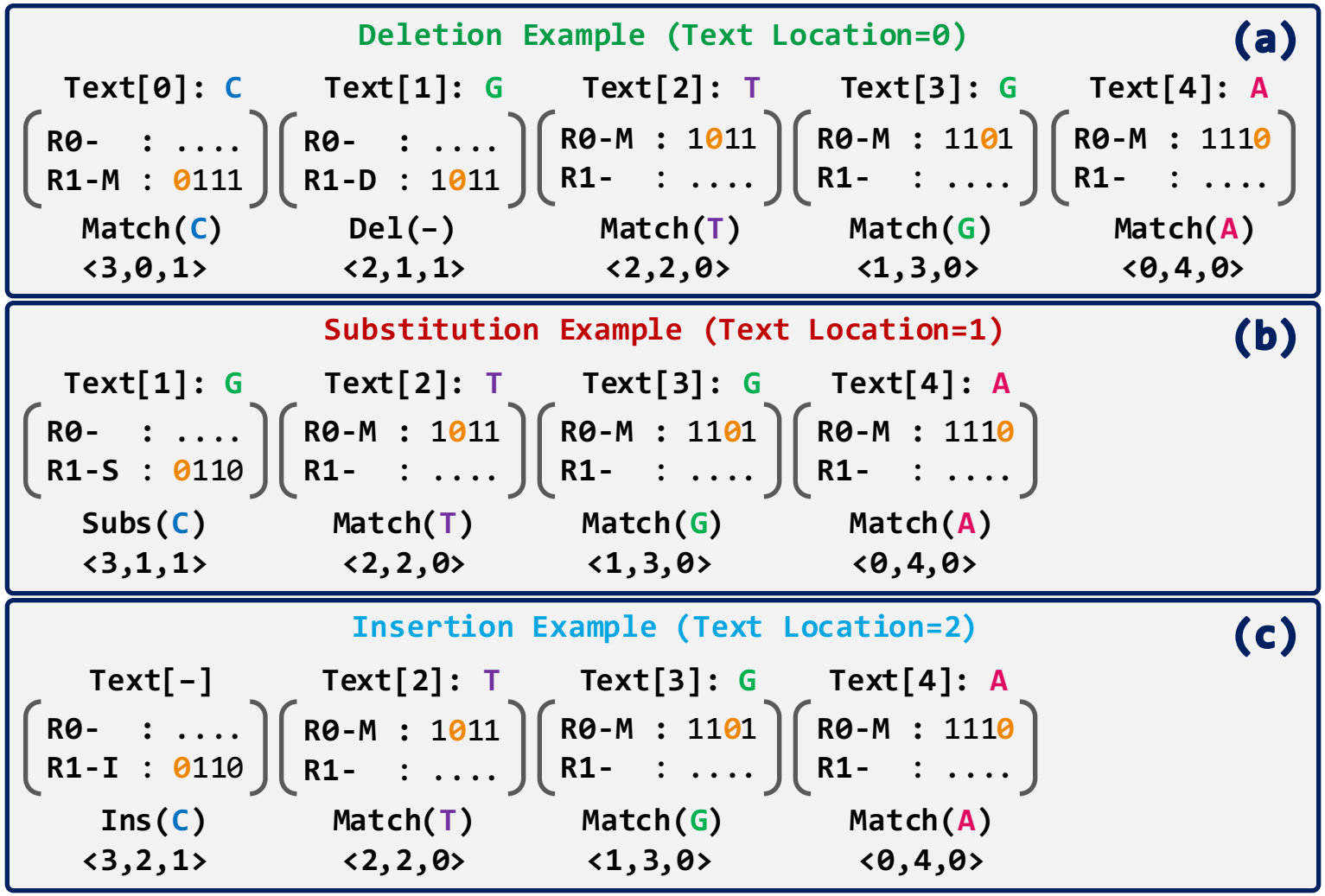
data ***written to memory***

data ***read from memory***

target cell ($R_d$)

cells target cell depends on ($oldR_d$, $R_{d-1}$, $oldR_{d-1}$)

# Traceback Example with GenASM-TB



# GenASM [MICRO 2020]

Damla Senol Cali, Gurpreet S. Kalsi, Zulal Bingol, Can Firtina, Lavanya Subramanian, Jeremie S. Kim, Rachata Ausavarungnirun, Mohammed Alser, Juan Gomez-Luna, Amirali Boroumand, Anant Nori, Allison Scibisz, Sreenivas Subramoney, Can Alkan, Saugata Ghose, and Onur Mutlu,

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

*Proceedings of the 53rd International Symposium on Microarchitecture (**MICRO**)*, Virtual, October 2020.

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

Damla Senol Cali[†⋈] Gurpreet S. Kalsi[⋈] Zülal Bingöl[▽] Can Firtina[◇] Lavanya Subramanian[‡] Jeremie S. Kim[◇†]
Rachata Ausavarungnirun[⊙] Mohammed Alser[◇] Juan Gomez-Luna[◇] Amirali Boroumand[†] Anant Nori[⋈]
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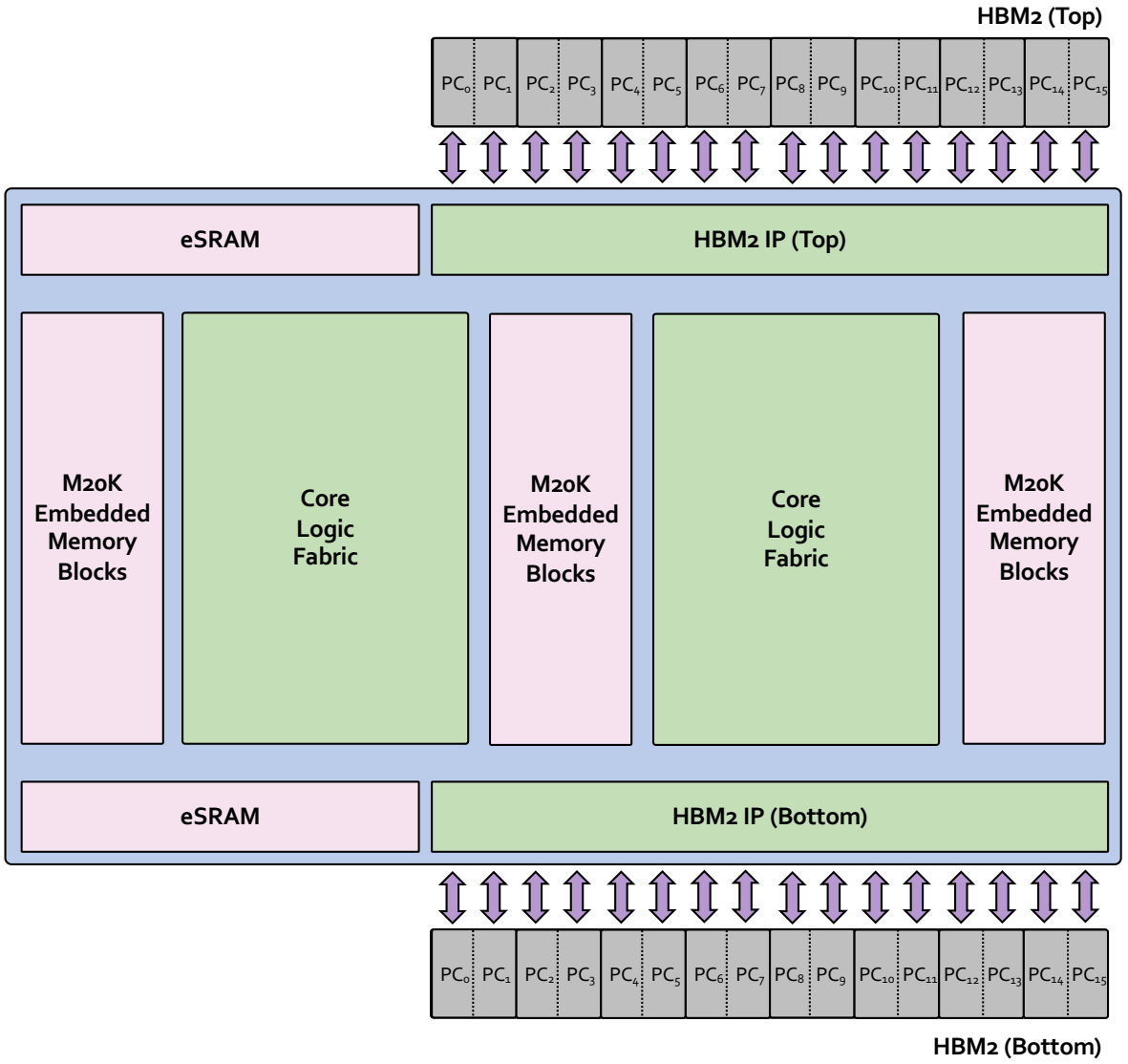
[†]*Carnegie Mellon University* [⋈]*Processor Architecture Research Lab, Intel Labs* [▽]*Bilkent University* [◇]*ETH Zürich*
[‡]*Facebook* [⊙]*King Mongkut's University of Technology North Bangkok* [⋆]*University of Illinois at Urbana–Champaign*

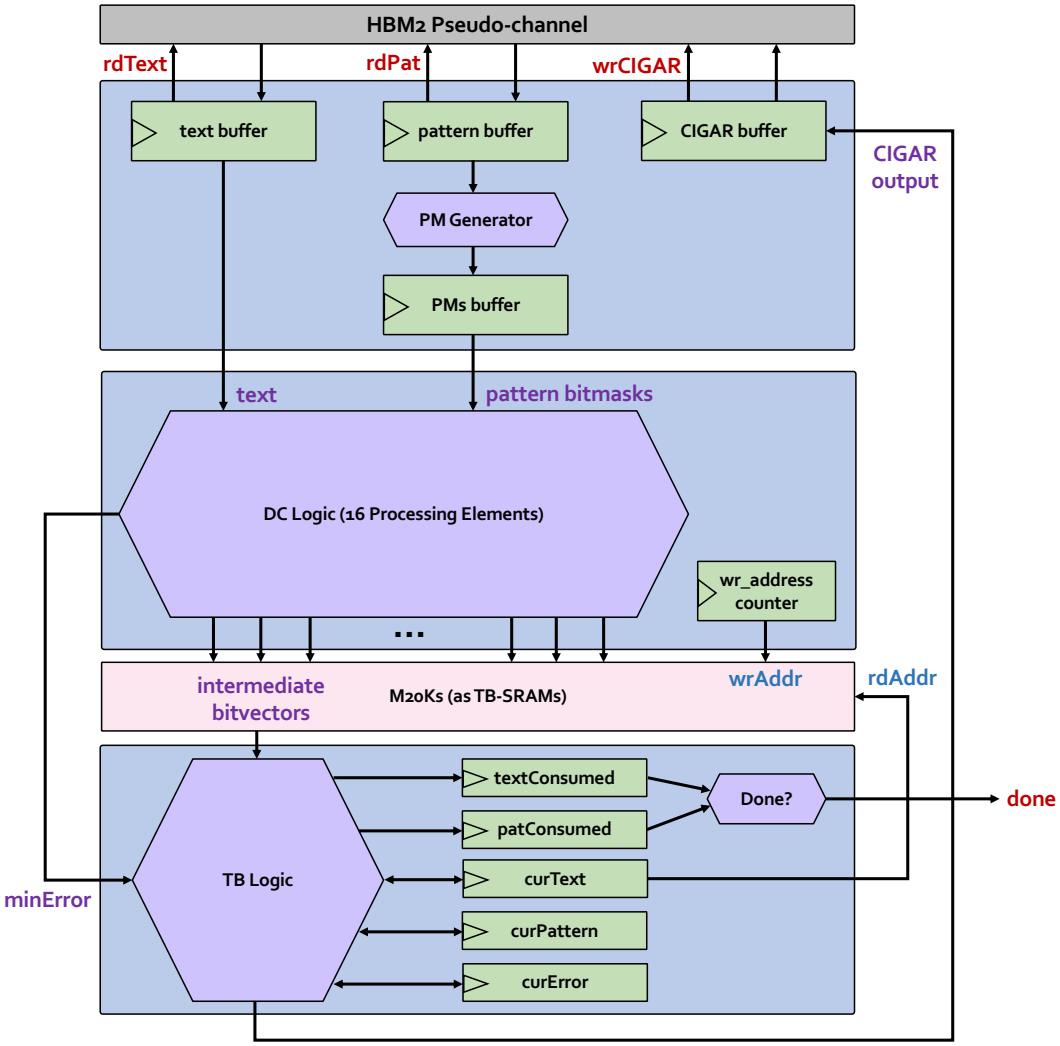
# Backup Slides

(BitMAc)

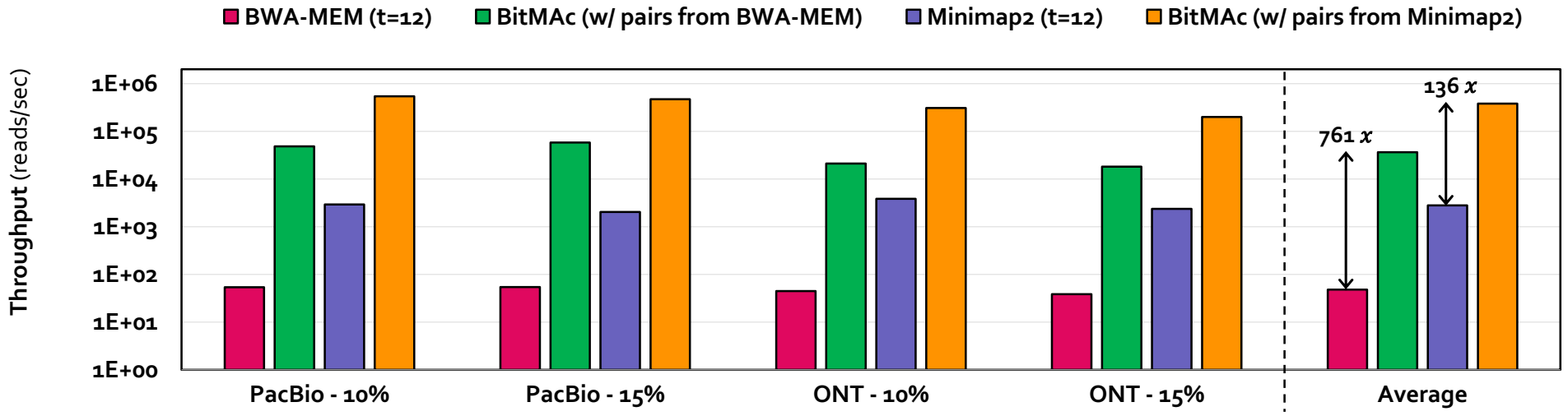
# Intel Stratix 10 MX

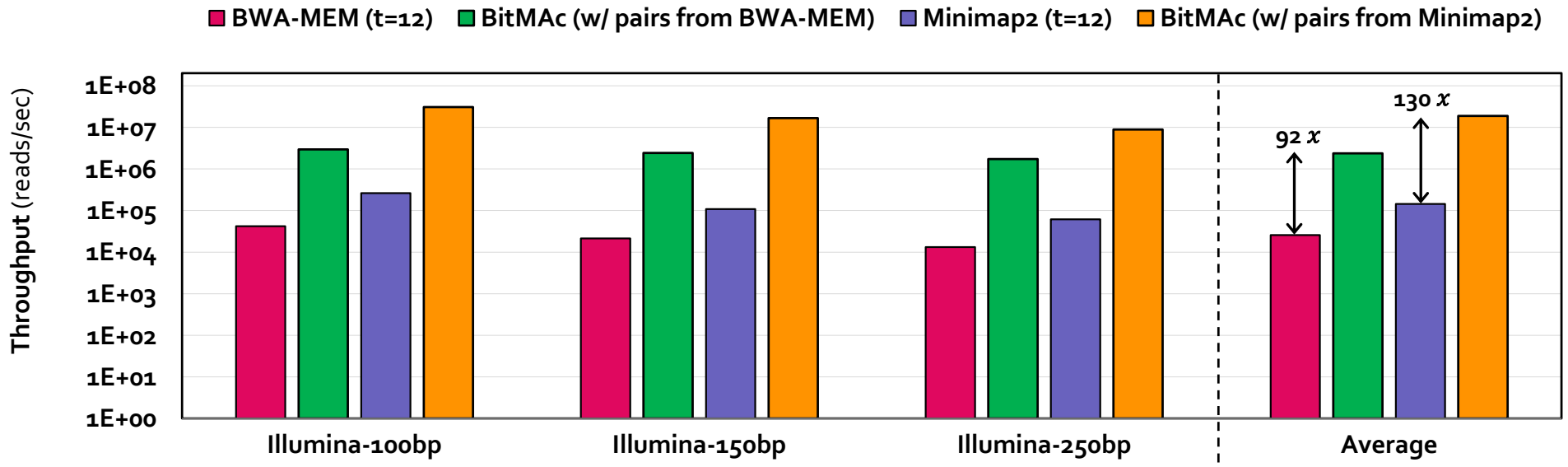


# BitMAc Design



# BitMAc – Results



# BitMAc – Results

| Component | Dynamic On-Chip Power Dissipation | Total On-Chip Power Dissipation |
|---|---|---|
| DC Logic (16 PEs) | 128.57 mW | |
| TB Logic | 10.24 mW | |
| FSM Logic | 3.15 mW | |
| M20Ks | 211.61 mW | |
| Other | 15.72 mW | |
| **Total – 1 BitMAc Accelerator** | **369.29 mW (0.4 W)** | **6043.24 mW (6.0 W)** |
| **Total – 32 BitMAc Accelerators (1 per each pseudo-channel)** | **11569.92 mW (11.6 W)** | **17234.67 mW (17.2 W)** |
| **Total – 128 BitMAc Accelerators (4 per each pseudo-channel)** | **43042.90 mW (43 W)** | **48935.65 mW (48.9 W)** |

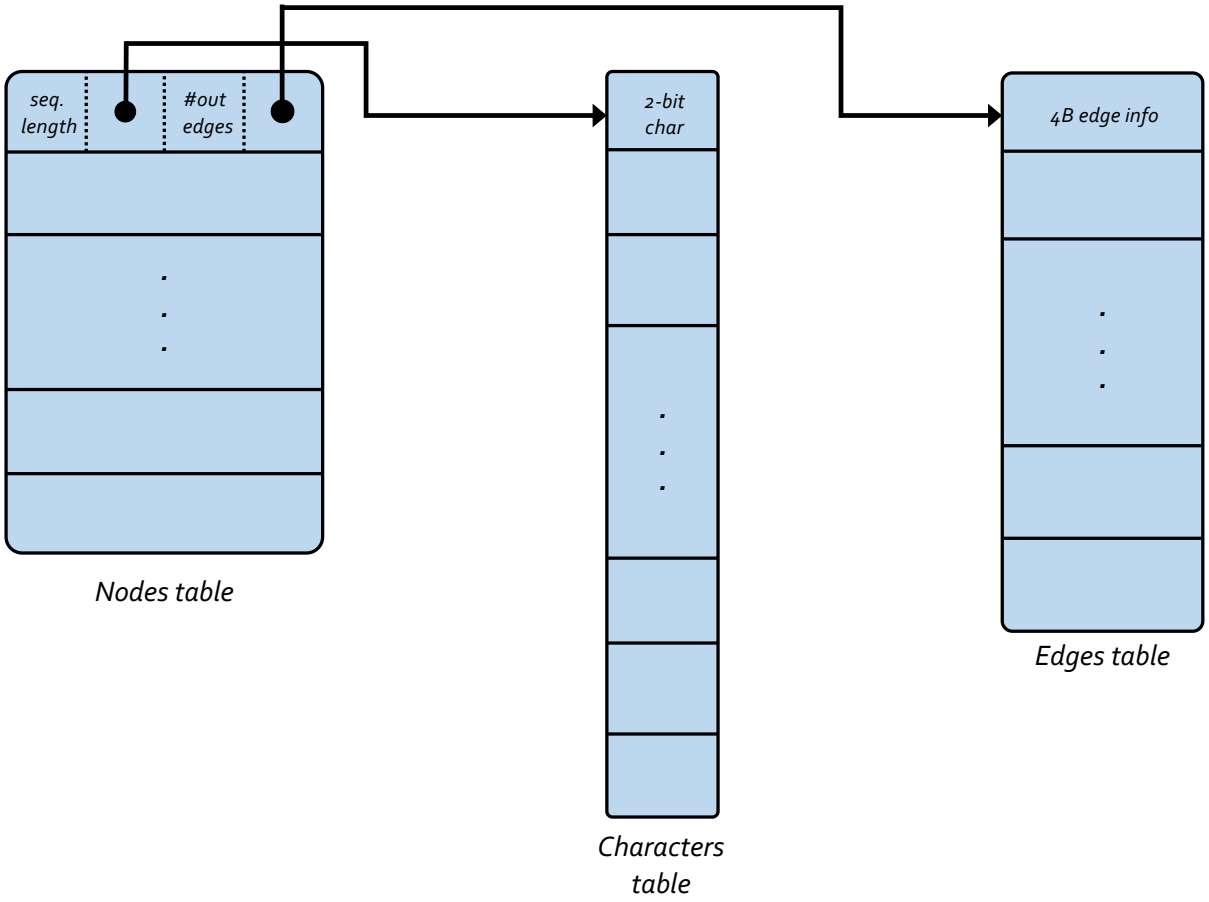
# BitMAc – Results

| Configuration | Logic Utilization | M20K | eSRAM | DSP |
|---|---|---|---|---|
| 1 BitMAc Accelerator | 0.5% | 0.7% | 0% | 0% |
| 32 BitMAc Accelerators (1 per each pseudo-channel) | 17.7% | 22.4% | 0% | 0% |
| 128 BitMAc Accelerators (4 per each pseudo-channel) | 64.3% | 89.7% | 0% | 0% |

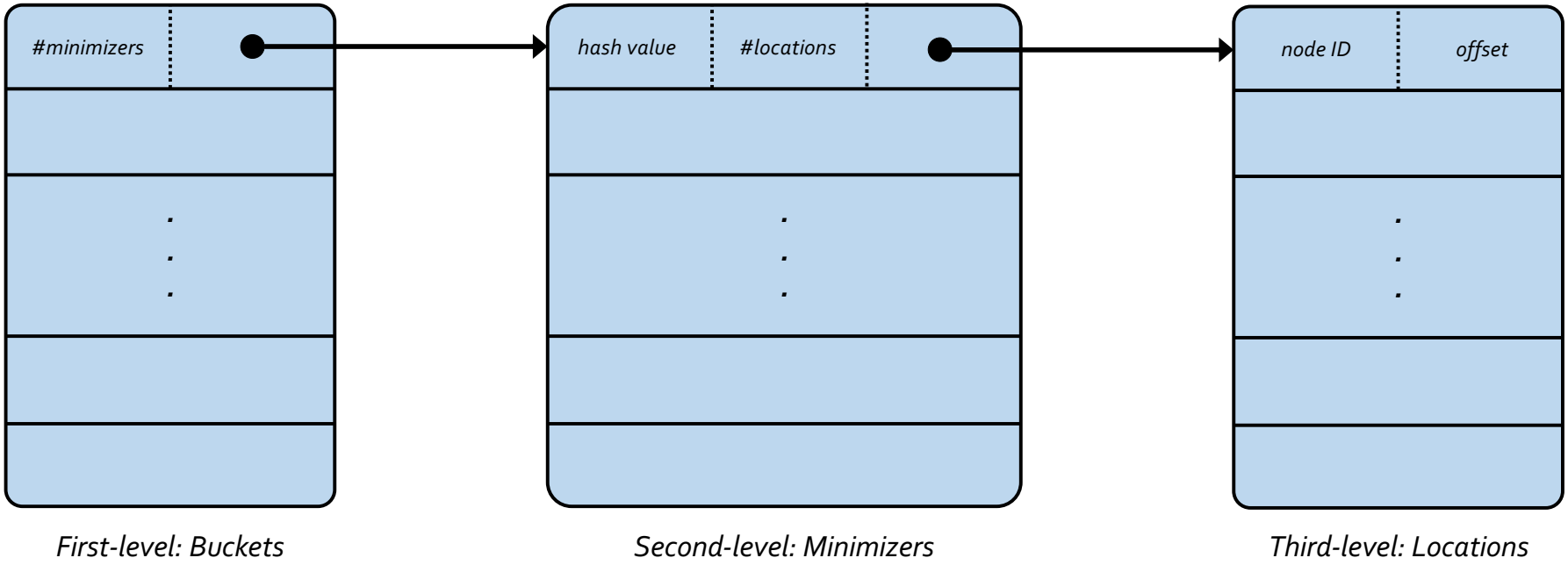
# Backup Slides

(SeGraM)

# SeGraM – Graph Structure



# SeGraM – Index Structure



# Minimizers

| Position | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| Sequence | A | G | T | A | G | C | A |
| Full set of k-mers with minimizer in **red** | A | G | T | | | | |
| | | G | T | A | | | |
| | | | T | A | G | | |
| | | | | **A** | **G** | **C** | |
| | | | | | G | C | A |

# BitAlign Algorithm

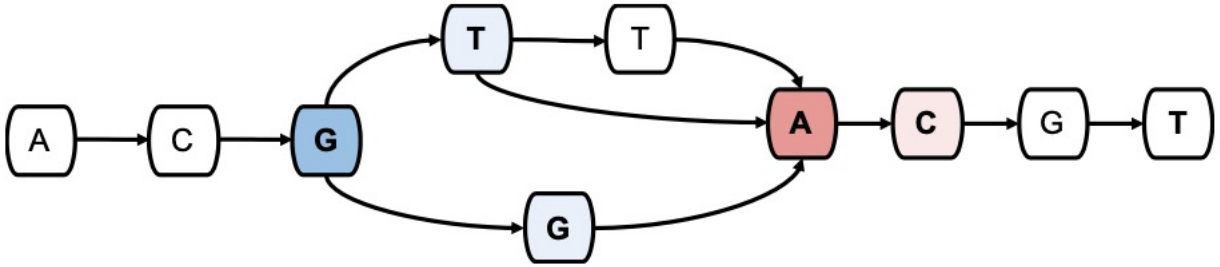
**Algorithm 1** BitAlign Algorithm

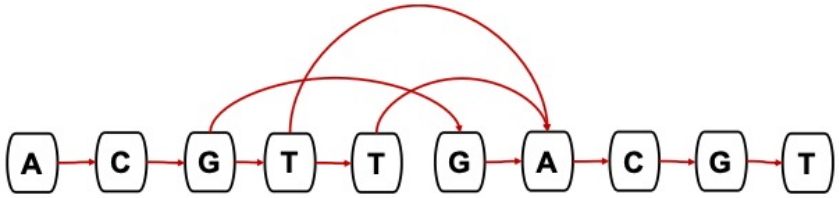
**Inputs:** `graph-nodes` (reference), `pattern` (query), `k` (edit distance threshold)

**Outputs:** `editDist` (minimum edit distance), `CIGARstr` (traceback output)

```
1: n ← length of linearized reference subgraph
2: m ← length of query pattern
3: PM ←genPatternBitmasks(pattern)   ▷ pre-process the pattern
4:
5: allR[n][d] ← 111.111      ▷ init R[d] bitvectors for all characters
6:
7: for i in (n-1):-1:0 do          ▷ iterate over each graph node
8:    curChar ← graph-nodes[i].char
9:    curPM ← PM[curChar]          ▷ retrieve the pattern bitmask
10:
11:   R0 ← 111...111            ▷ status bitvector for exact match
12:   for j in graph-nodes[i].successors do
13:      R0 ← ((R[j][0]<<1) | curPM) & R0
14:   allR[i][0] ← R0
15:
16:   for d in 1:k  do
17:      I ← (allR[i][d-1]<<1)                          ▷ insertion
18:      Rd ← I                        ▷ status bitvector for d errors
19:      for j in graph-nodes[i].successors do
20:         D ← allR[j][d-1]                            ▷ deletion
21:         S ← allR[j][d-1]<<1                      ▷ substitution
22:         M ← (allR[j][d]<<1) | curPM                 ▷ match
23:         Rd ← D & S & M & Rd
24:      allR[i][d] ← Rd
25: <editDist, CIGAR> ← traceback(allR, graph-nodes,
26: pattern)
```

# SeGraM – Hops



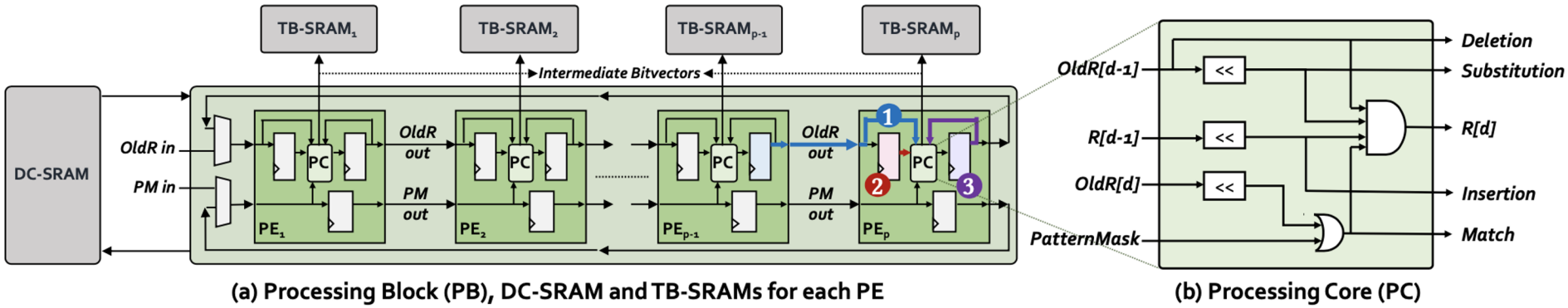




| NodeID | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| HopBits | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 |
| | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 |
| | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 5 |
| | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 6 |
| | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 7 |
| | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 8 |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 9 |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 10 |

# Recall: GenASM-DC's HW Design

| Cycle# | Thread$_1$ *R0/4* | Thread$_2$ *R1/5* | Thread$_3$ *R2/6* | Thread$_4$ *R3/7* |
|---|---|---|---|---|
| #1 | T0-R0 | – | – | – |
| #2 | T1-R0 | T0-R1 | – | – |
| #3 | T2-R0 | T1-R1 | T0-R2 | – |
| #4 | T3-R0 | T2-R1 | T1-R2 | T0-R3 |
| #5 | T0-R4 | T3-R1 | T2-R2 | T1-R3 |
| #6 | T1-R4 | T0-R5 | T3-R2 | T2-R3 |
| #7 | T2-R4 | T1-R5 | T0-R6 | T3-R3 |
| #8 | T3-R4 | T2-R5 | T1-R6 | T0-R7 |
| #9 | – | T3-R5 | T2-R6 | T1-R7 |
| #10 | – | – | T3-R6 | T2-R7 |
| #11 | – | – | – | T3-R7 |

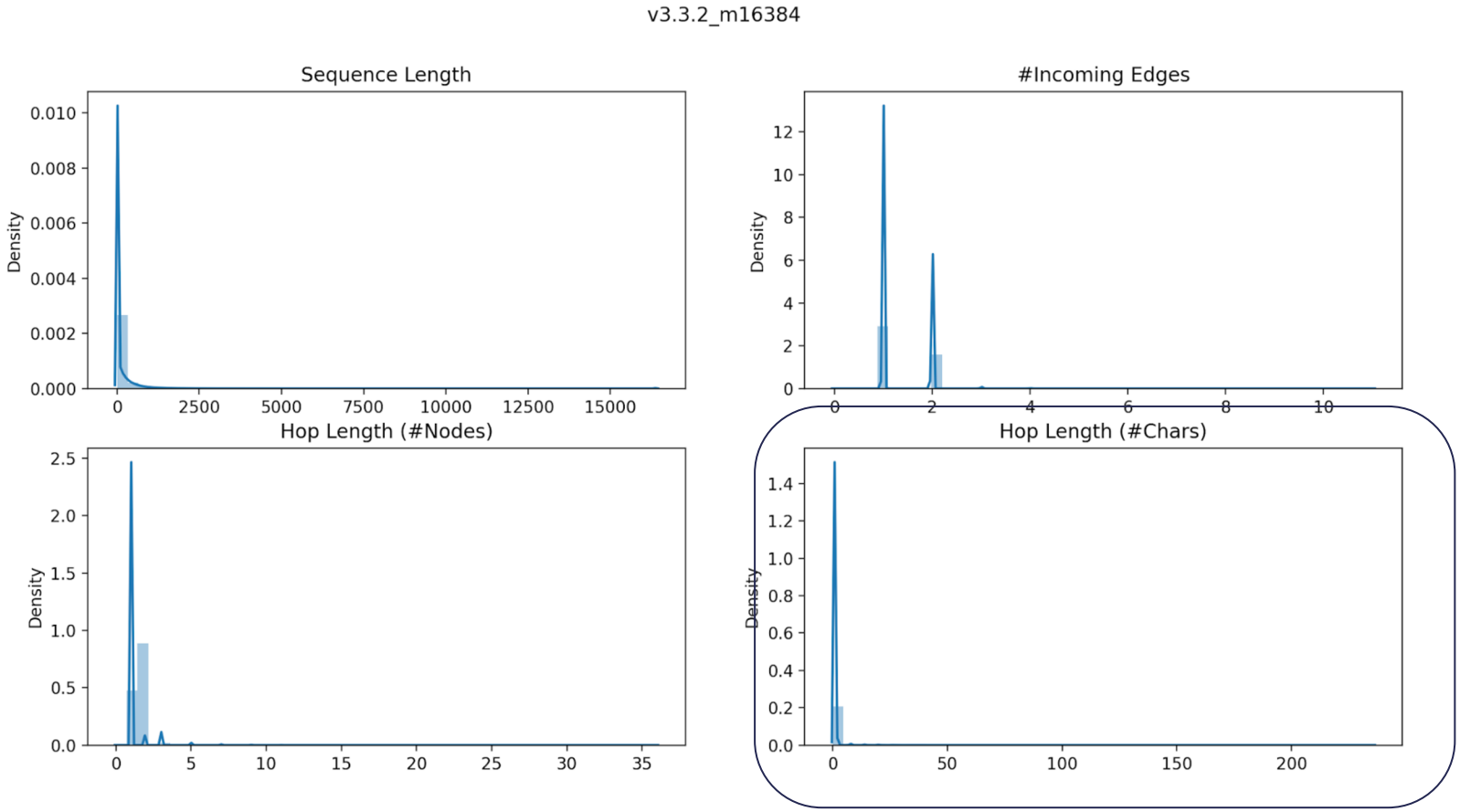
```
deletion (D) ← oldR[d-1]
substitution (S) ← (oldR[d-1]<<1)
insertion (I) ← (R[d-1]<<1)
match (M) ← (oldR[d]<<1) | curPM
```



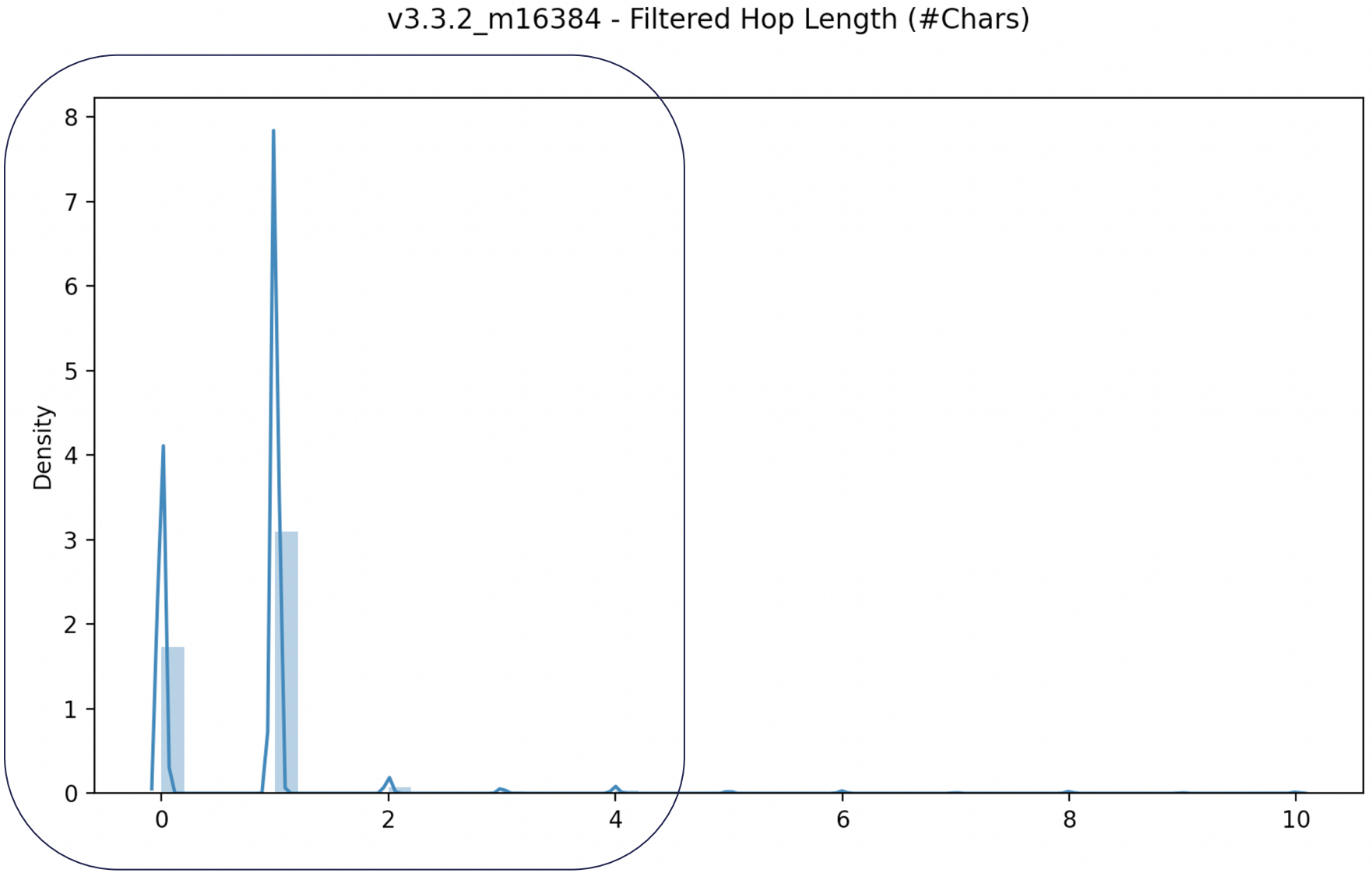

(a) Processing Block (PB), DC-SRAM and TB-SRAMs for each PE

(b) Processing Core (PC)

# BitAlign – Hop Length Dist Plots



# Hop Length Dist Plots (cont'd.)



# DP-based Graph Alignment

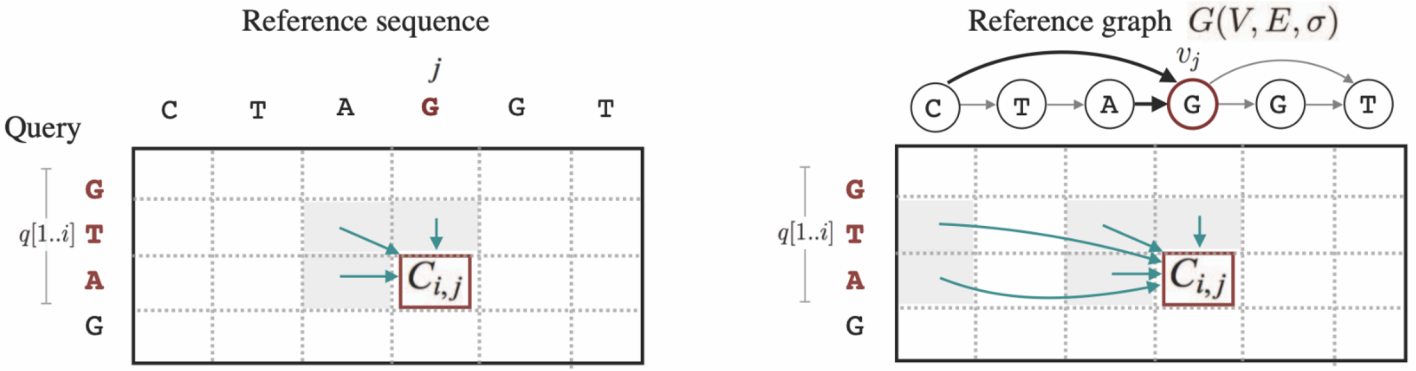


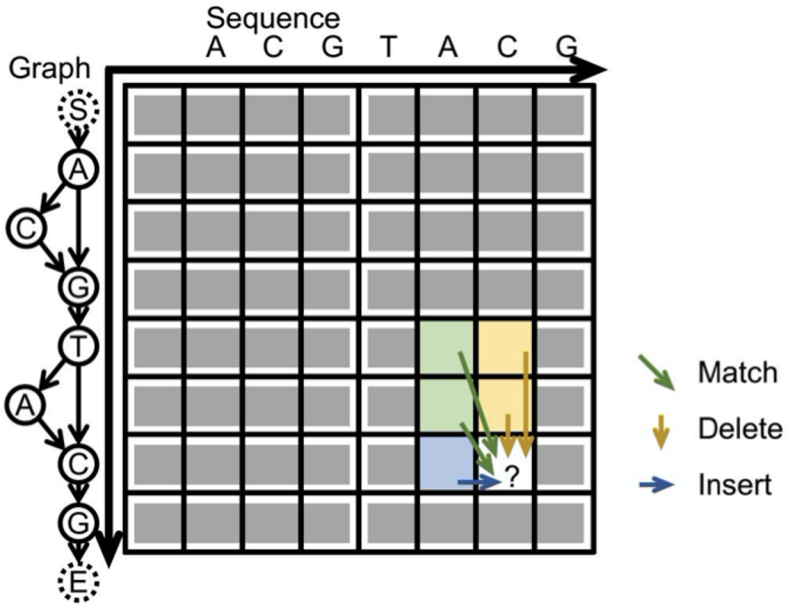

Fig. 2: Example to illustrate difference between Smith-Waterman sequence to sequence alignment and sequence to DAG alignment procedures.

$$C_{0,j} = 0$$

$$C_{i,j} = \max \begin{cases} 0 & \\ \Delta_{i,j} & \\ C_{i-1,k} + \Delta_{i,j} & \forall k : (v_k, v_j) \in E \\ C_{i,k} - \Delta_{ins} & \forall k : (v_k, v_j) \in E \\ C_{i-1,j} - \Delta_{del} & \end{cases} \quad (1)$$

From *PaSGAL paper*

# DP-based Graph Alignment (cont'd.)




"abPOA processes all the vectors in a row-by-row manner following the partial order of the graph. During the DP process, for "match" and "delete" operations (diagonal and vertical moves in the DP matrix), all scores stored in each SIMD vector can be updated in parallel as they only rely on scores in the predecessor rows. For "insert" operations (horizontal moves in the DP matrix), sequential non-parallel updating of scores in the same SIMD vector is needed, as the score of each cell depends on the score of the cell on the left."

From *abPOA paper*

"A region of a yeast genome variation graph"
from *vg* paper [Garrison et al., Nature Biotechnology, 2018]