Hardware-Accelerated Genome Sequencing: A Co-Design Approach

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AMD
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Genome Analysis

NO machine can read the ***entire*** content of a genome

>CCTCCTCAGTGCCACCCAGCCCACTGGCAGCTCCCAAACAGGCTCTTATTAAAACACCCTGTTCCCTGCCCCTTGGAGTGAGGTGTCAAG
GACCTAAACTAAAAAAAAAAAAAGAAAAAGAAAAGAAAAAGAATTTAAAATTTAAGTAATTCTTTGAAAAAAACTAATTTCTAAGCTTCTT
CATGTCAAGGACCTAATGTGCTAAACAGCACTTTTTTGACCATTATTTTGGATCTGAAAGAAATCAAGAATAAATGAAGGACTTGATACATTG
GAAGAGGAGAGTCAAGGACCTACAGAAAAAAAAAAAAAAGAAAAAGAAAAGAAAAAGA**A**TTTAAAATTTAAGTAATTCTTTGAAAAAA
ACTAATTTCTAAGCTTCTT**C**ATGTCAAGGACCTAATGTCTGTGTTGCAGGTCTTCTTGCATTTCCCTGTCAAAAGAAAAAGAATTTAAAATTT
AAGTAATTCTTTGAAAAAAACTAATTTCTAAGCTTCTTCATGTCAAGGACCTAATGTCAGGCCAAGAGTTGCAAAAAAAAAAAAAGAAAAA
GAAAAGAAAAAGAATTTAAAATTTA**A**GTAATTCTTTGAAAAAAACTAATTTCTAAGCTTCTTCATGTCAAGGACCTAATGTAGCCAGAATGG
TTGTGGGATGGGAGCCTCTGTGGACCGACCAGGTAGCTCTCTTTTCCACACTGTAGTCTCAAAGCTTCTTCATGTGGTTTCTCTGAGTGAAA
AAAAAAAAAAGAAAAAGAAAAGAAAAAGAATTTAAAATTTAAGTAATTCTTTGAAAAAAACTAATTTCTAAGCTTT**T**TTCATGTCAAGGACC
TAATGTAGCTATACTGAACGTTATCTAGGGGAAAGATTGAAGGGGAGCTCTAAGGTCAACA……

Mohammed Alser, "Intelligent Genome Analysis", Computer Architecture, ETH Zurich, Fall 2020

Genome Sequencing Pipeline

Obtaining Genomic Sequencing Data

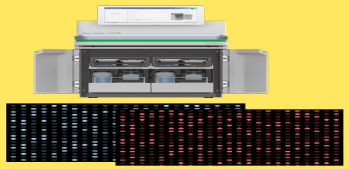
A **DNA Extraction**

DNA Fragmentation

B **Sequencing**

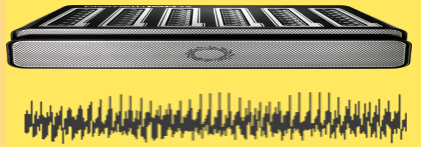
Generating Sequencing Data

Illumina



Multiple images

ONT



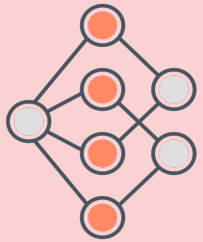
Squiggle

PacBio

30-hour movie

Basecalling

Input signal



CCGTCCCCCCGCAGTAACAT

Read Mapping

A **Indexing**

Reference Genome

Seeds

Seed content	Seed locations
	1, 4, 6
	3, 5, 12
	50, 52
	2, 100

B **Seeding**

Read

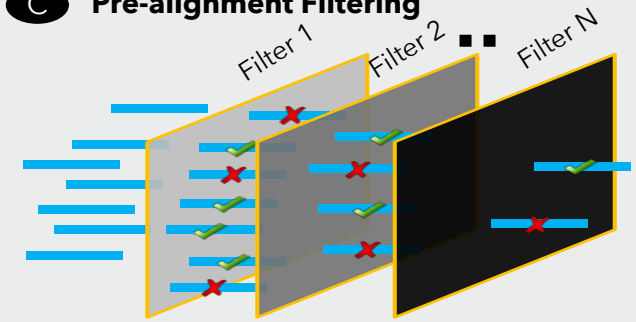
Seeds

Locating common seeds

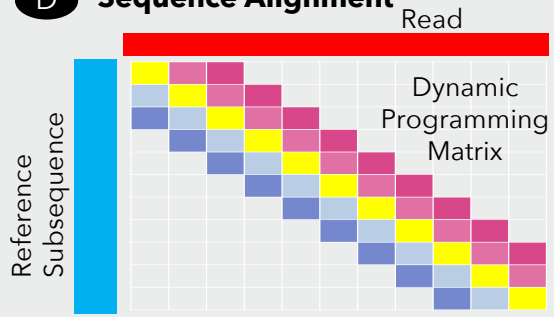
Locations of common seeds

1, 4, 6
3, 5, 12
2, 100

C **Pre-alignment Filtering**



D **Sequence Alignment**



SAFARI

Mohammed Alser et al., "From molecules to genomic variations: Accelerating genome analysis via intelligent algorithms and architectures", Computational and Structural Biotechnology Journal, Volume 20, 2022

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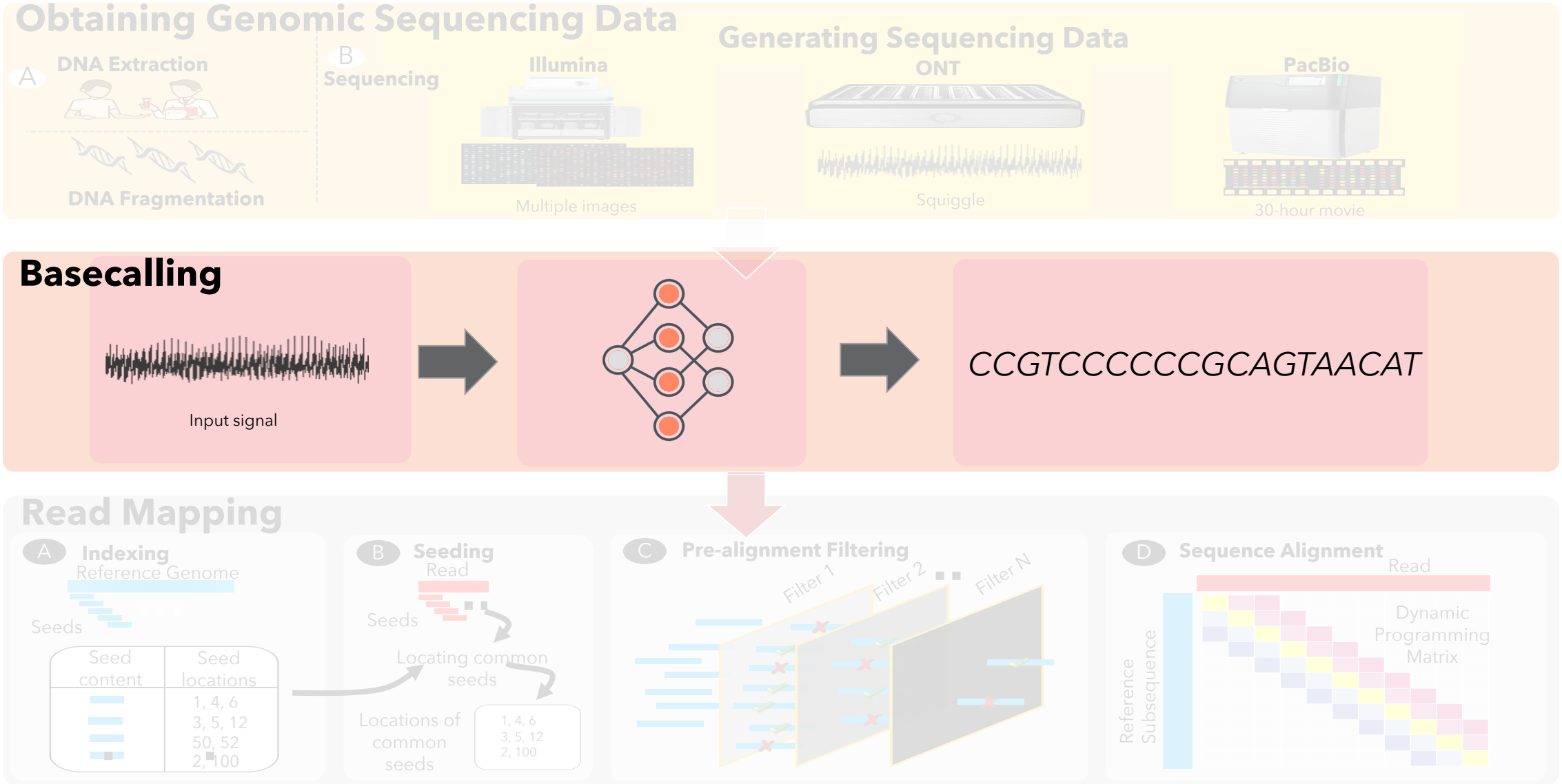
Genome Sequencing Pipeline



SAFARI

Mohammed Alser et al., "From molecules to genomic variations: Accelerating genome analysis via intelligent algorithms and architectures", Computational and Structural Biotechnology Journal, Volume 20, 2022

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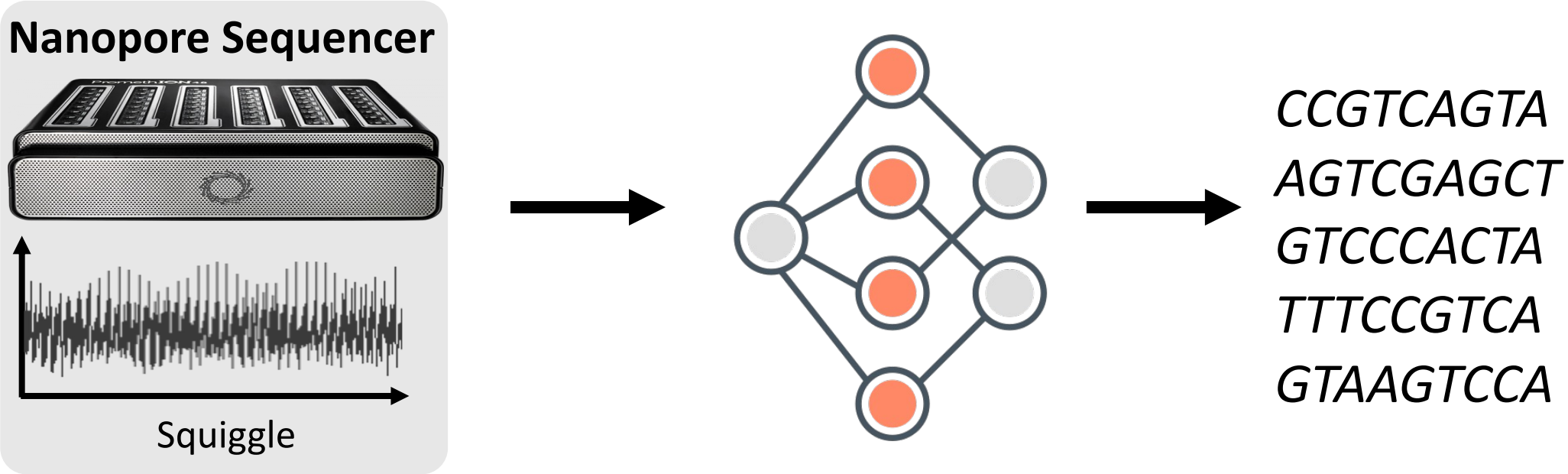
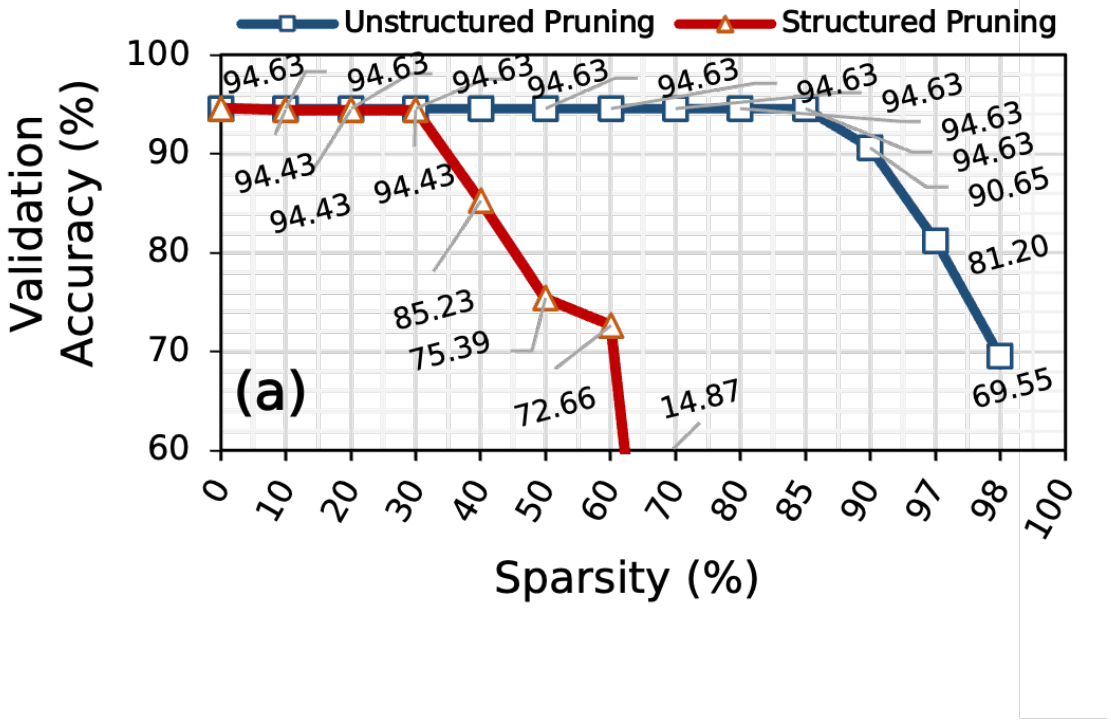
Basecalling

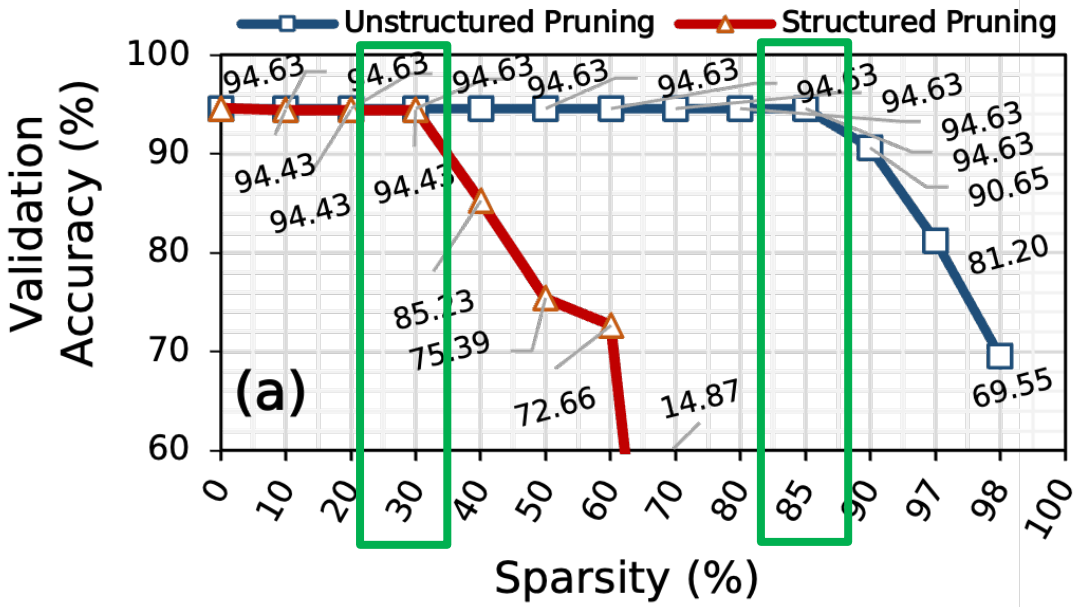
- **Basecalling is the first step in the genomics pipeline** that converts noisy electrical signals to nucleotide bases (i.e., A, C, G, T)
- Modern basecallers **use complex deep learning-based models**

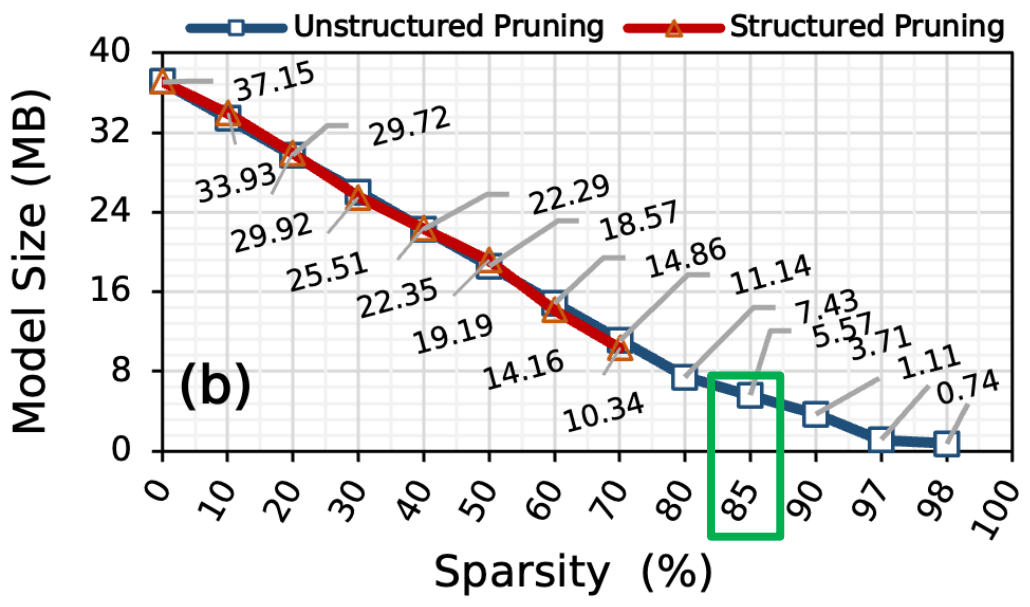


Motivation: Effect of Pruning (1/2)



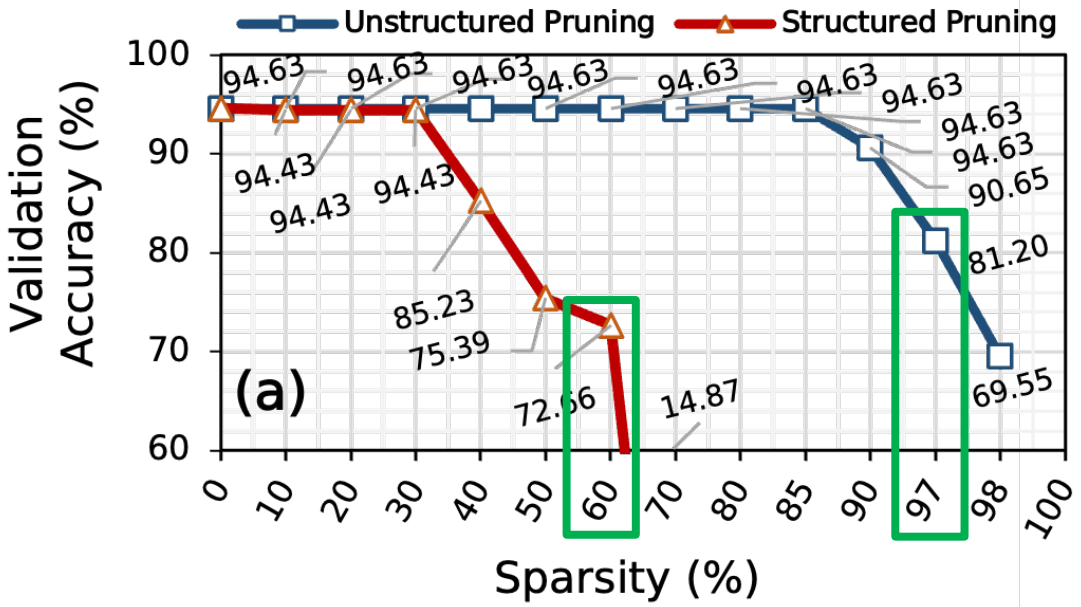
Motivation: Effect of Pruning (1/2)

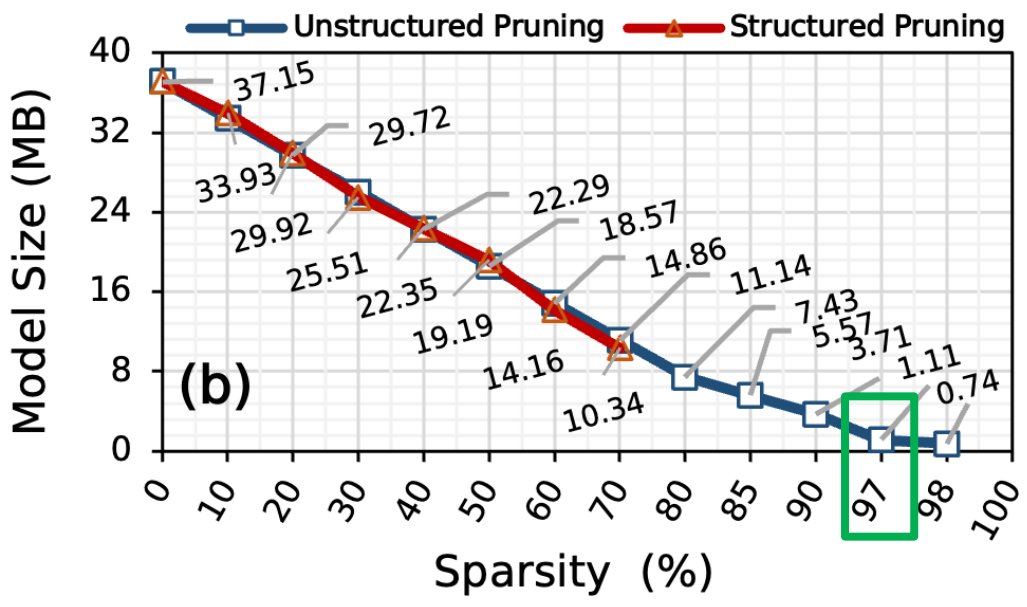




85% of weights can be pruned leading to
6.67x lower model size without any loss in accuracy

Motivation: Effect of Pruning (1/2)

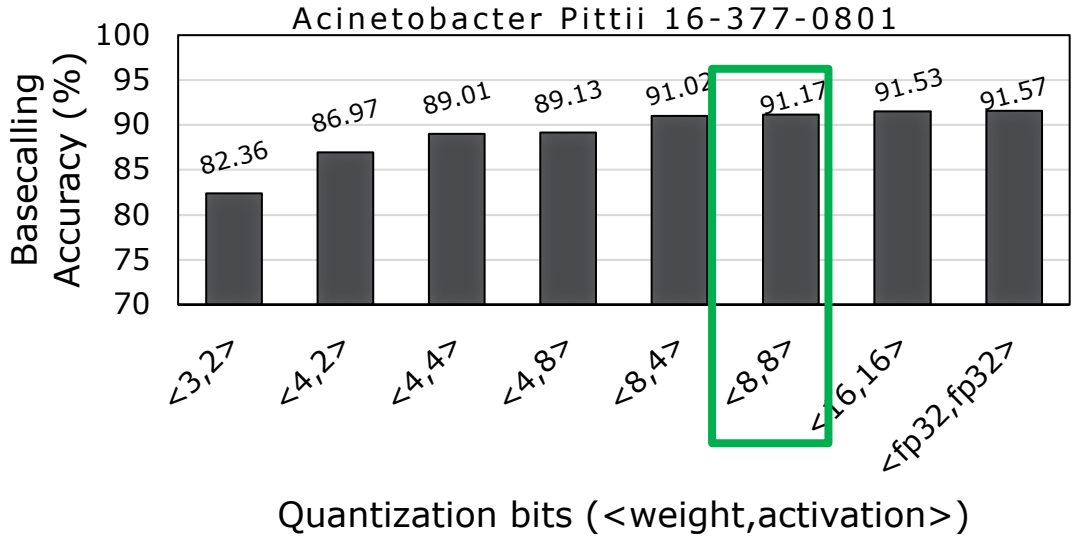


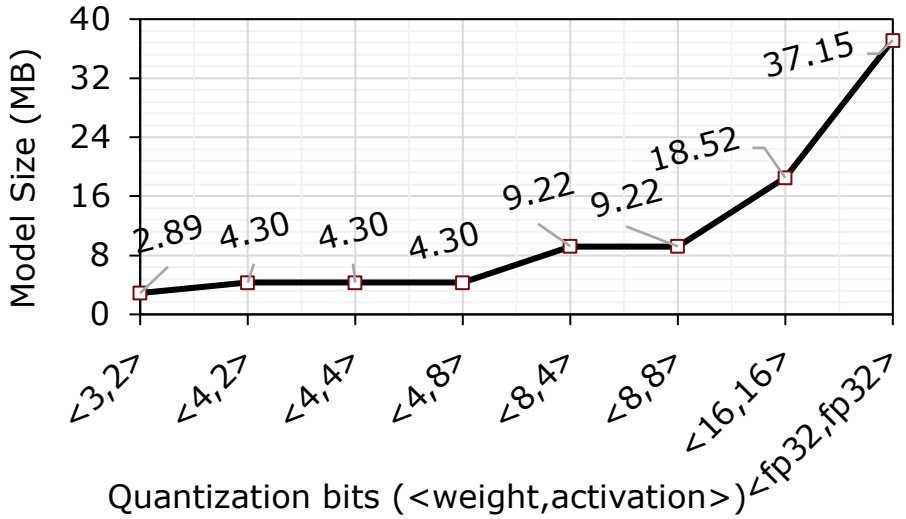


97% of weights can be pruned leading to 33.33x lower model size while providing 81.20% accuracy

Basecallers are often **adapted** from the speech recognition domain **leading to over-parametrized models**

Motivation: Effect of Quantization (2/2)





Provides full accuracy with 4x lower bits for weights and activations

Basecallers use **floating-point precision** to represent **each neural network layer**

Our Goal

Develop a comprehensive framework **for specializing and optimizing** deep learning-based basecallers that provides **high efficiency and performance**

Our Proposal

Framework for Designing Efficient Deep Learning-Based Genomic Basecallers

RUBICON Framework

RUBICON provides **two key mechanisms**

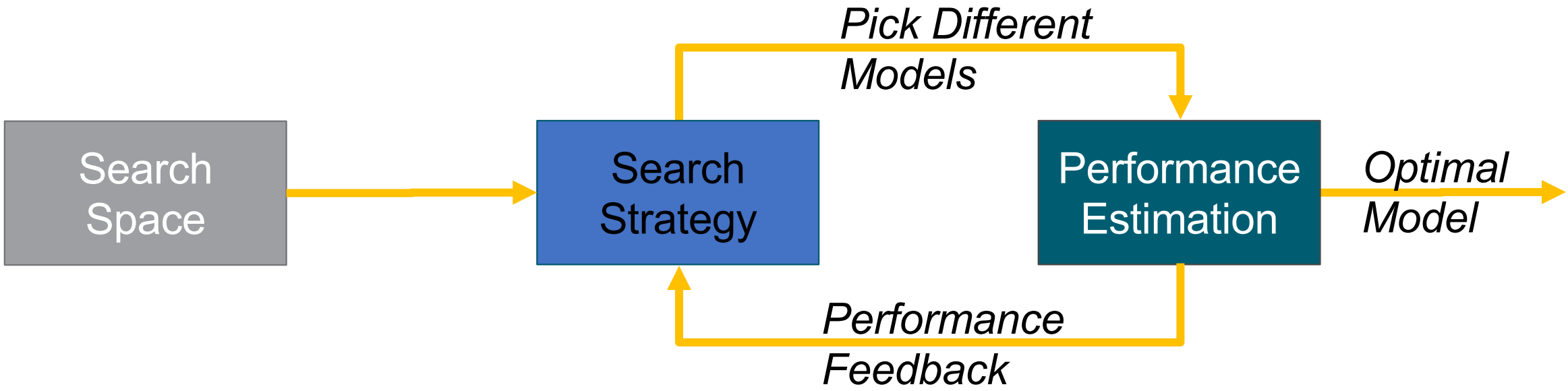
QABAS: Quantization-aware basecalling architecture search

SkipClip: Skip connection removal by teaching

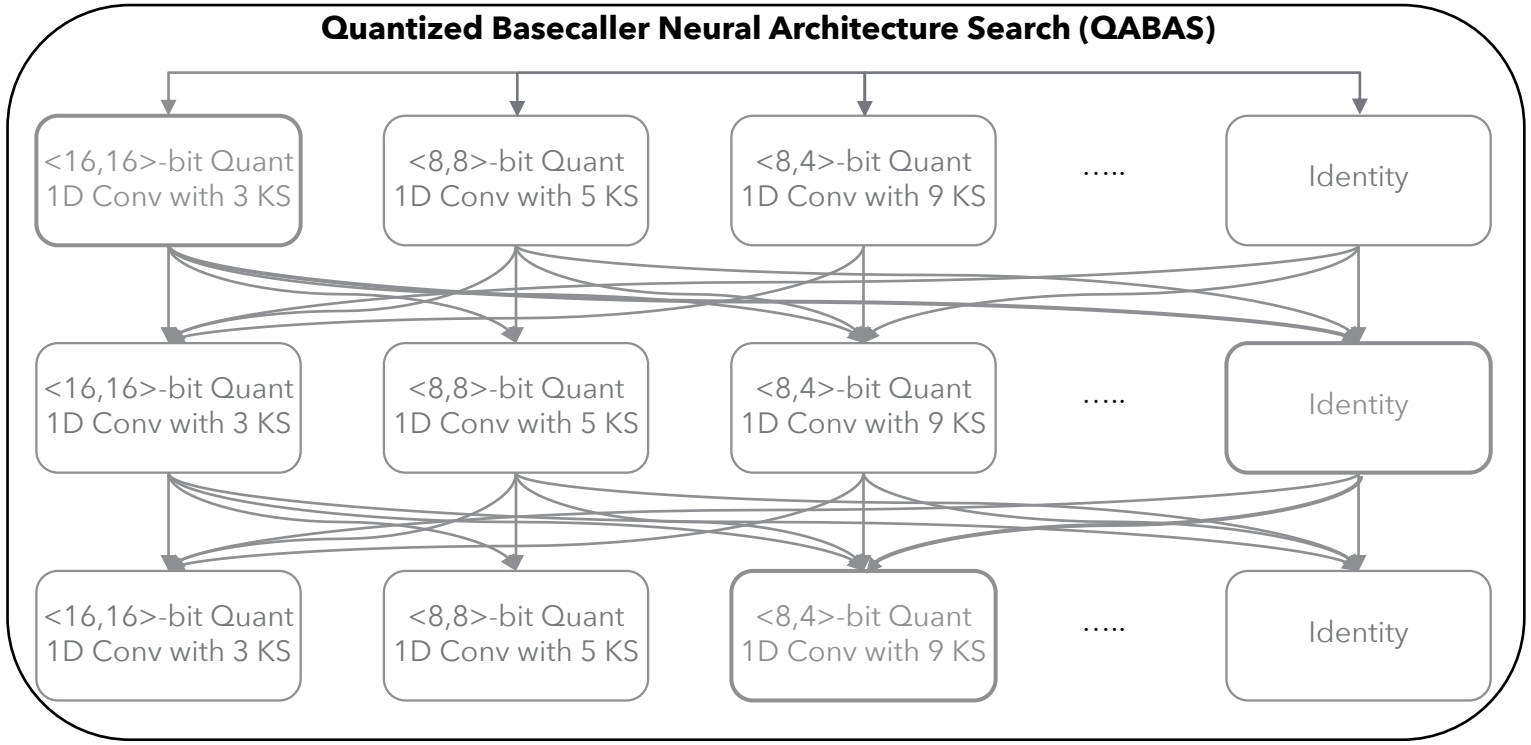
QABAS: Quantization-Aware Basecalling Architecture Search

- QABAS **automates** the process of finding efficient and high-performance hardware-aware genomics basecallers

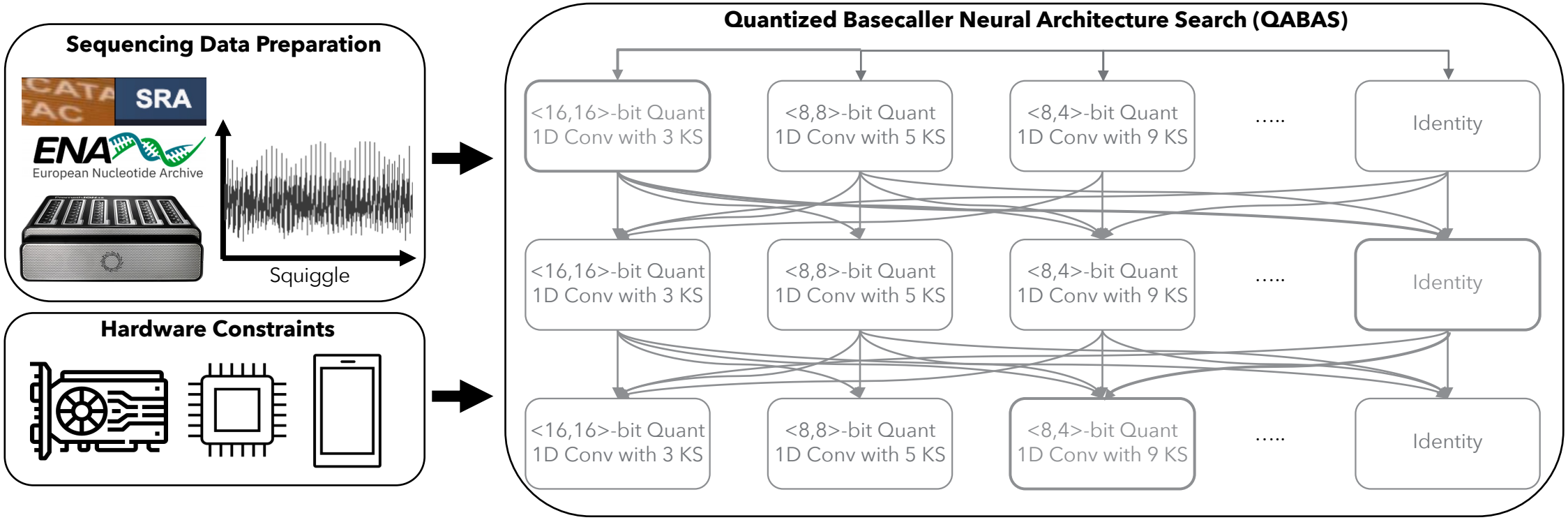
- QABAS **uses neural architecture search (NAS) to evaluate millions of different basecaller architectures**



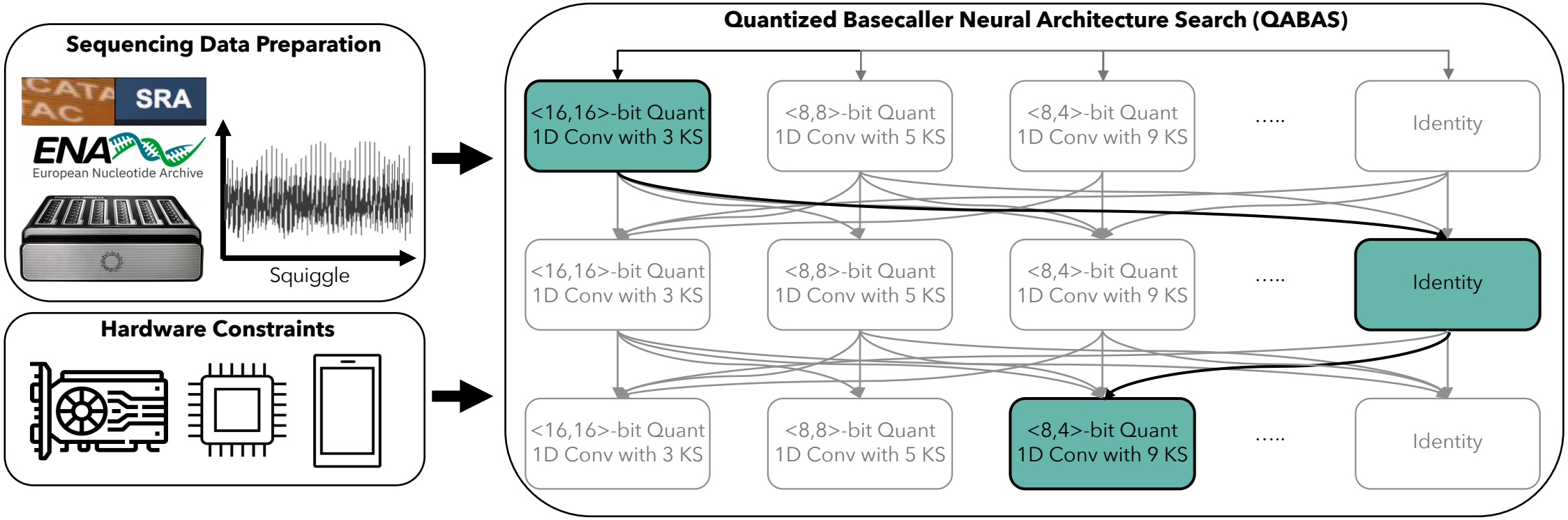
QABAS: Quantization-Aware Basecalling Architecture Search



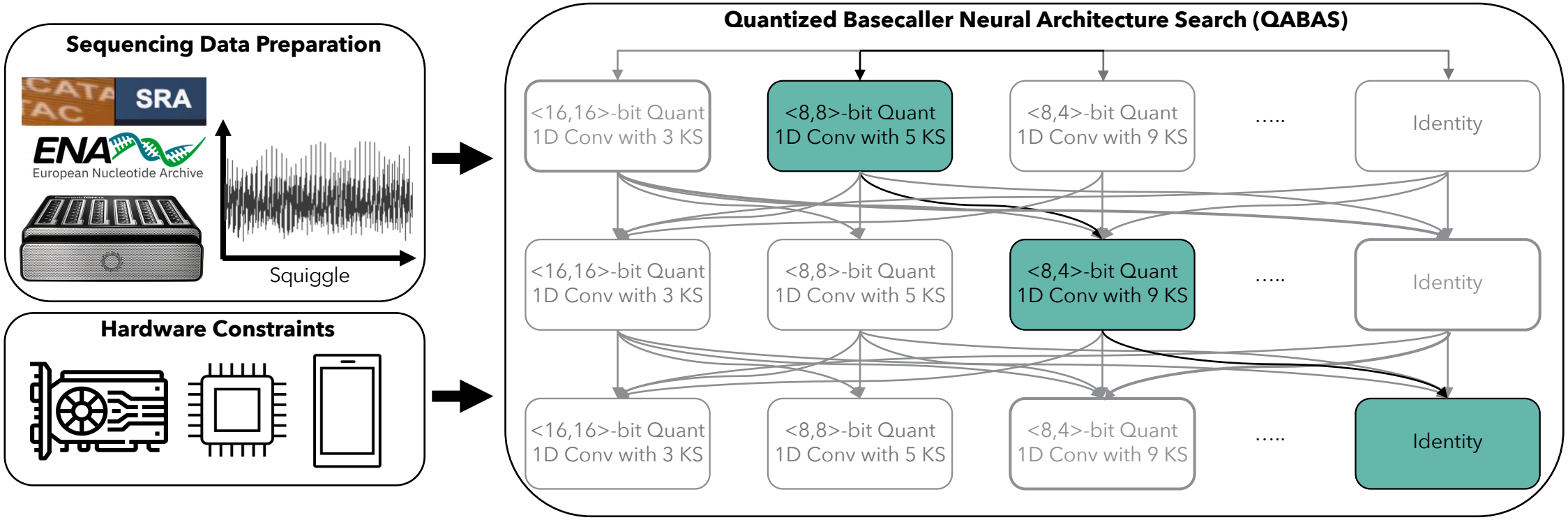
QABAS: Quantization-Aware Basecalling Architecture Search



QABAS: Quantization-Aware Basecalling Architecture Search

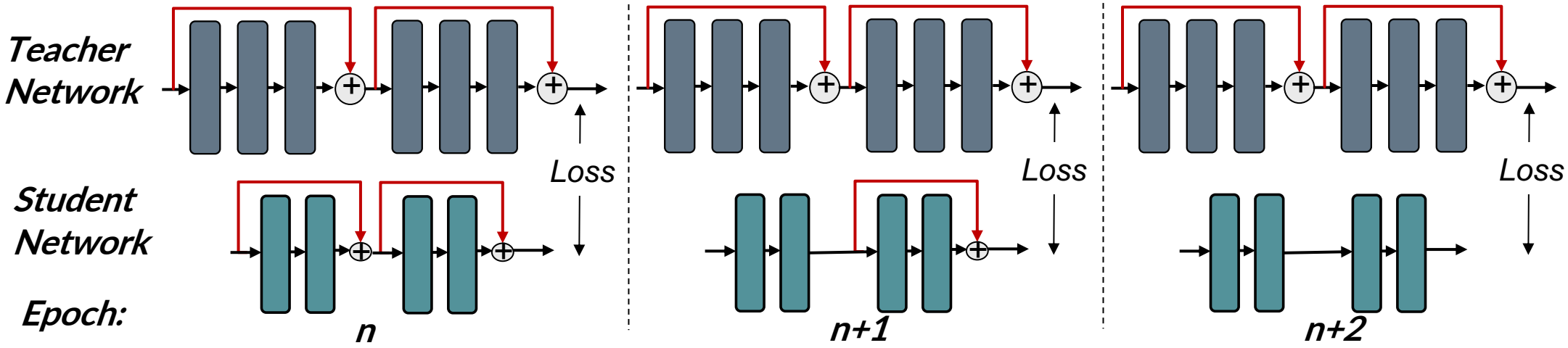


QABAS: Quantization-Aware Basecalling Architecture Search



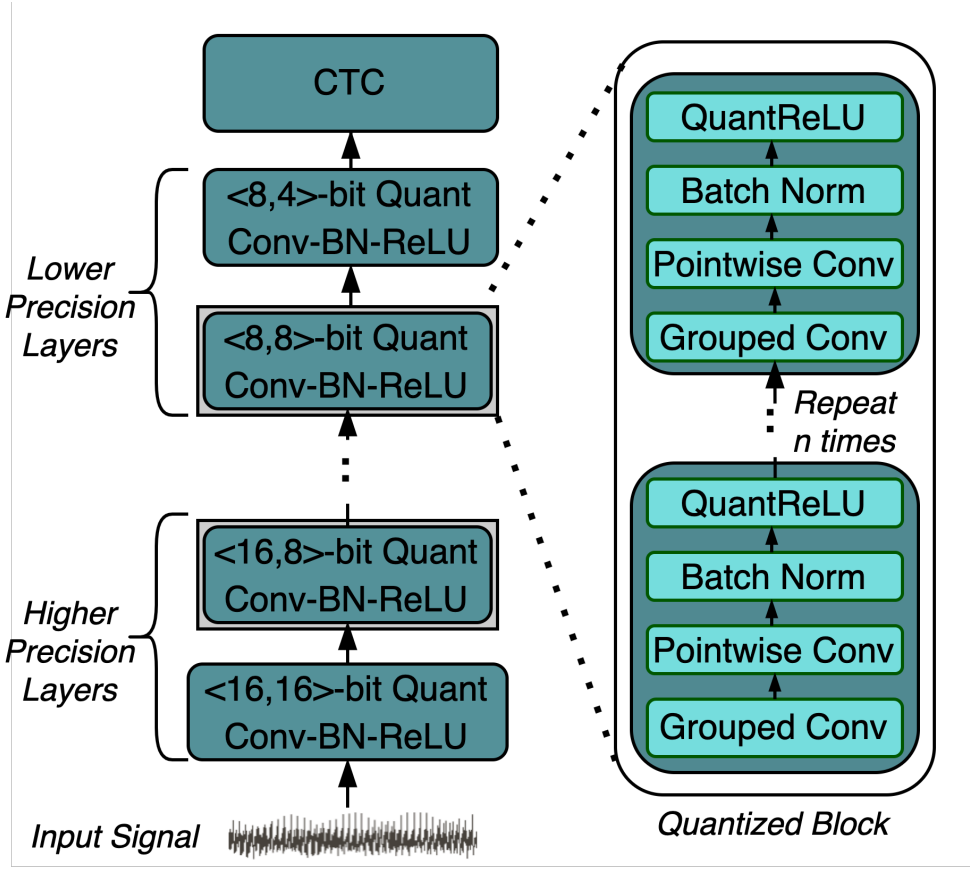
SkipClip: Skip Connection Removal by Teaching

- SkipClip removes all the skip connections present in modern **basecallers to reduce resource and storage requirements without any loss in basecalling accuracy**
- SkipClip **uses knowledge distillation**, where we train a smaller network (student) without skip connections to mimic a pre-trained bigger network (teacher) with skip connections



RUBICALL: A Hardware-Optimized Basecaller

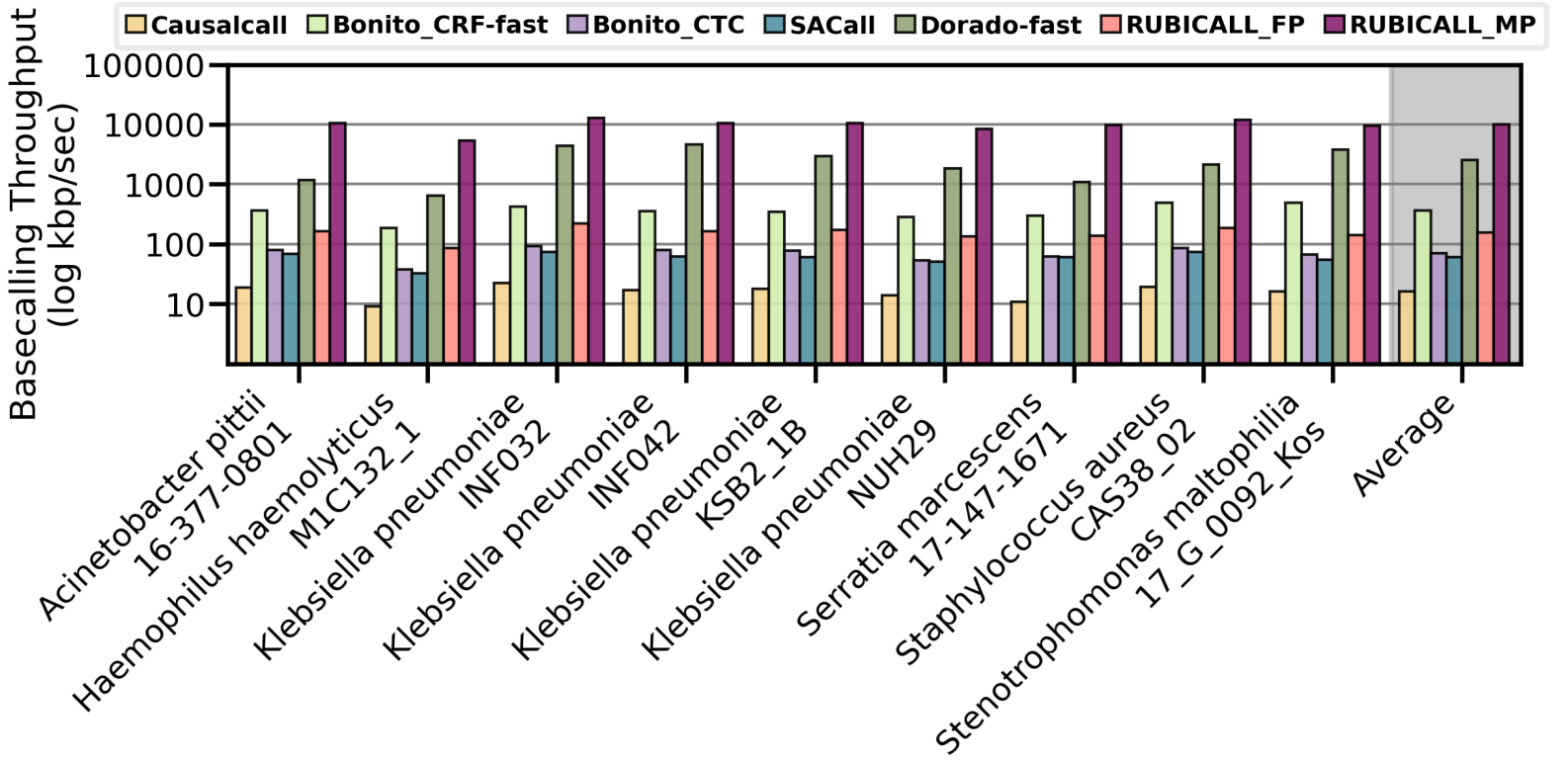
- RUBICALL is **developed using QABAS and SkipClip**
- RUBICALL is uses **mixed-precision computation**



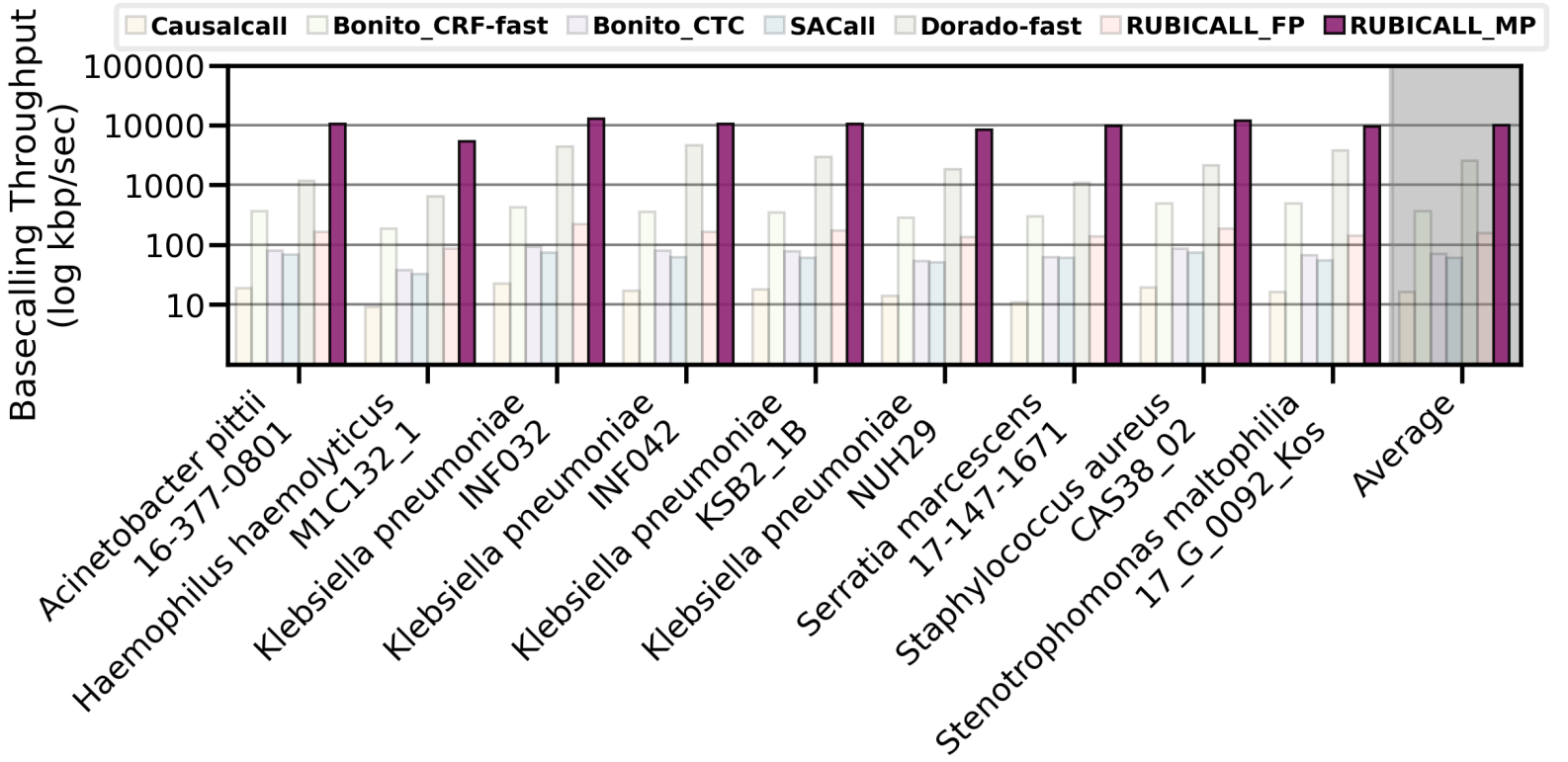
Evaluation Methodology

- Comparison to **five state-of-the-art basecallers**
  - **Bonito-CTC**, an expert-designed convolutional neural network-based basecaller from ONT
  - **Bonito-CRF-fast**, a throughput-optimized recurrent neural network-based basecaller from ONT
  - **Dorado-fast,** a LibTorch version of Bontio-CRF_fast that is optimized for low precision
  - **SACall**, a transformer-based basecaller with attention mechanism
  - **Causalcall**, a state-of-the-art hand-tuned basecaller
- We evaluate two versions of **RUBICALL**
  - **RUBICALL-MP** using mixed-precision computation
  - **RUBICALL-FP** using 32-bit floating-point precision computation

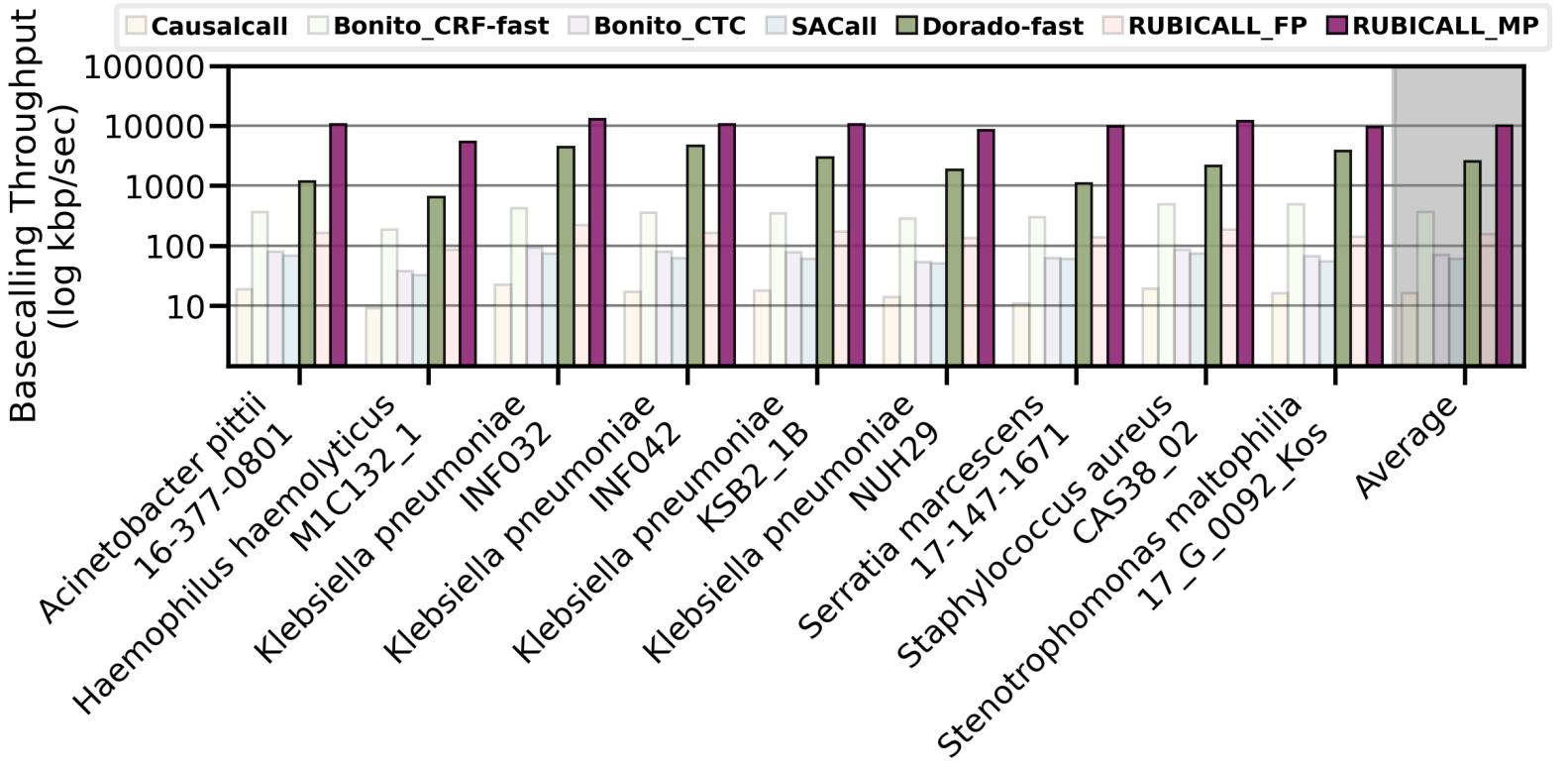
Basecalling Throughput



Basecalling Throughput

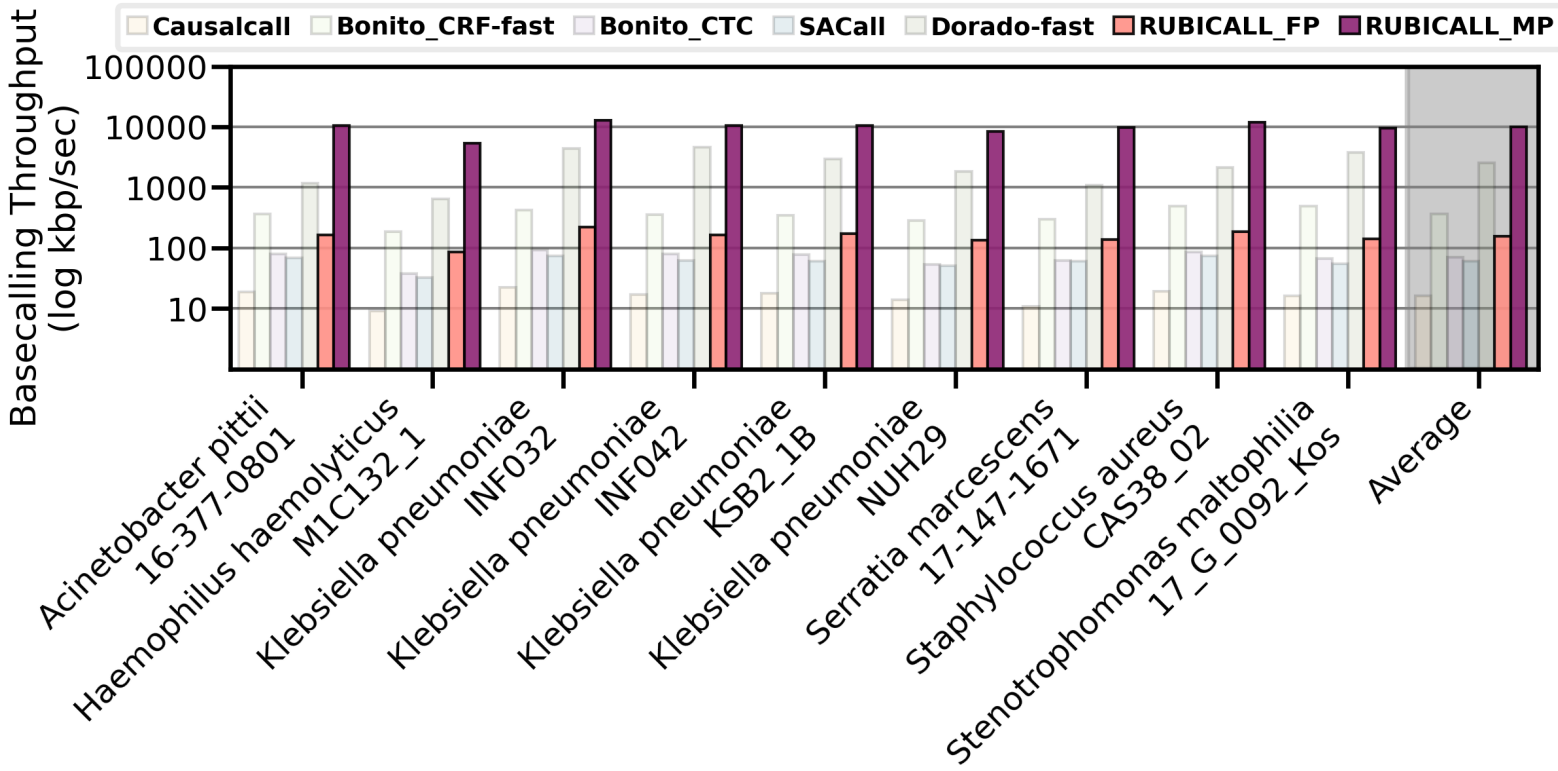


Basecalling Throughput



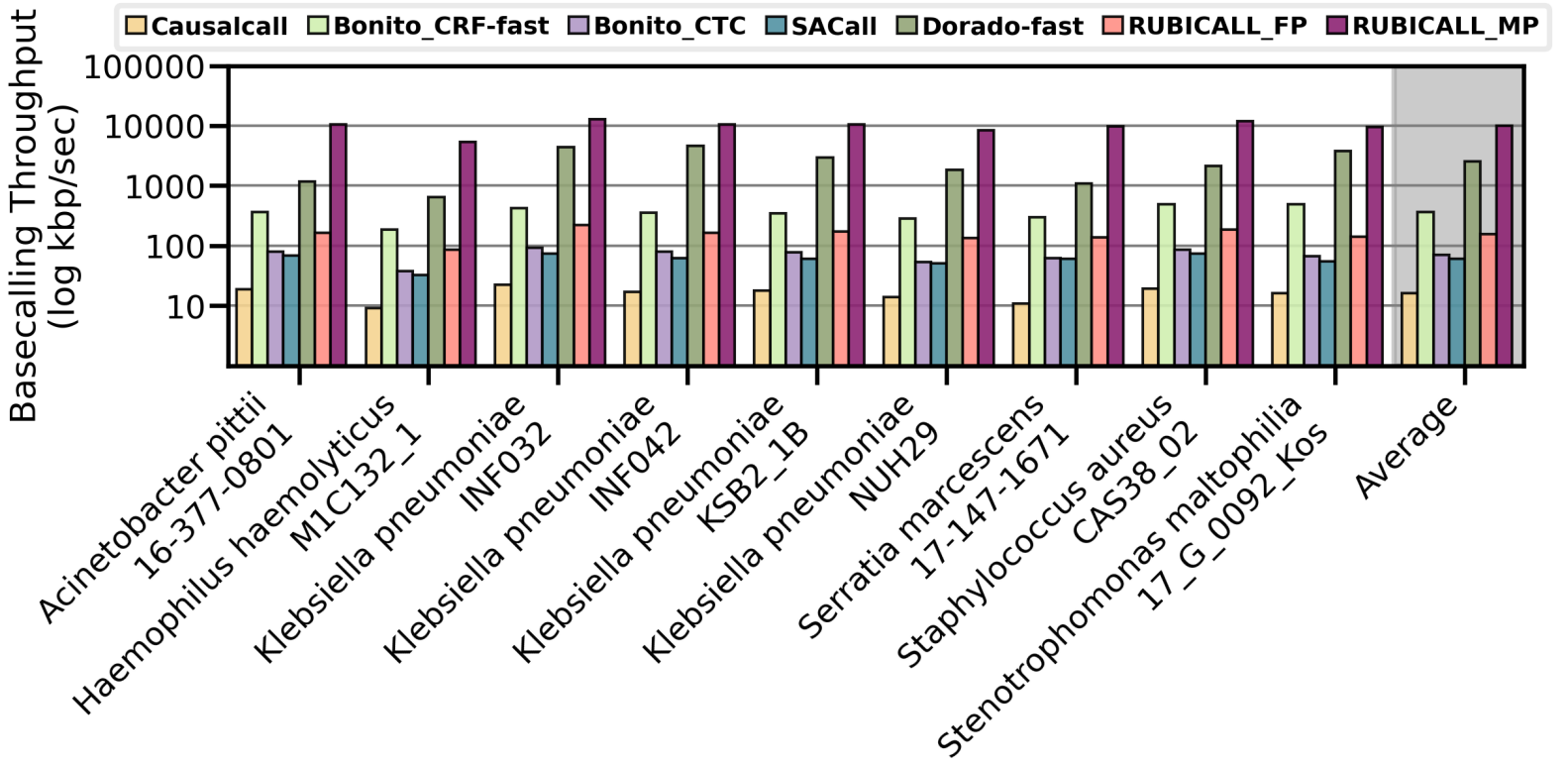
RUBICALL-MP **outperforms** Dorado-fast by **3.96x**

Basecalling Throughput



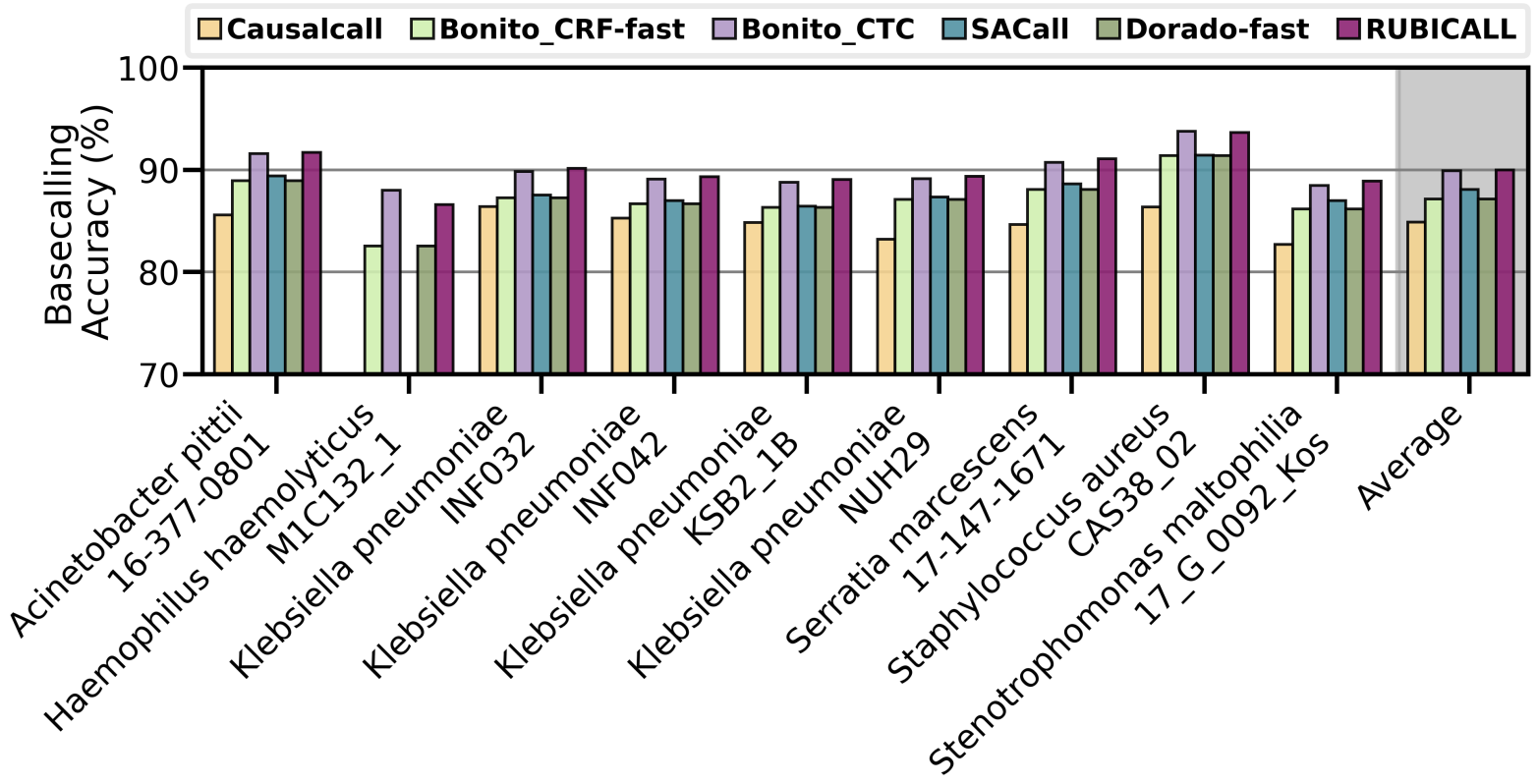
RUBICALL-MP provides **63.61x higher performance** when compared to RUBICALL-FP

Basecalling Throughput

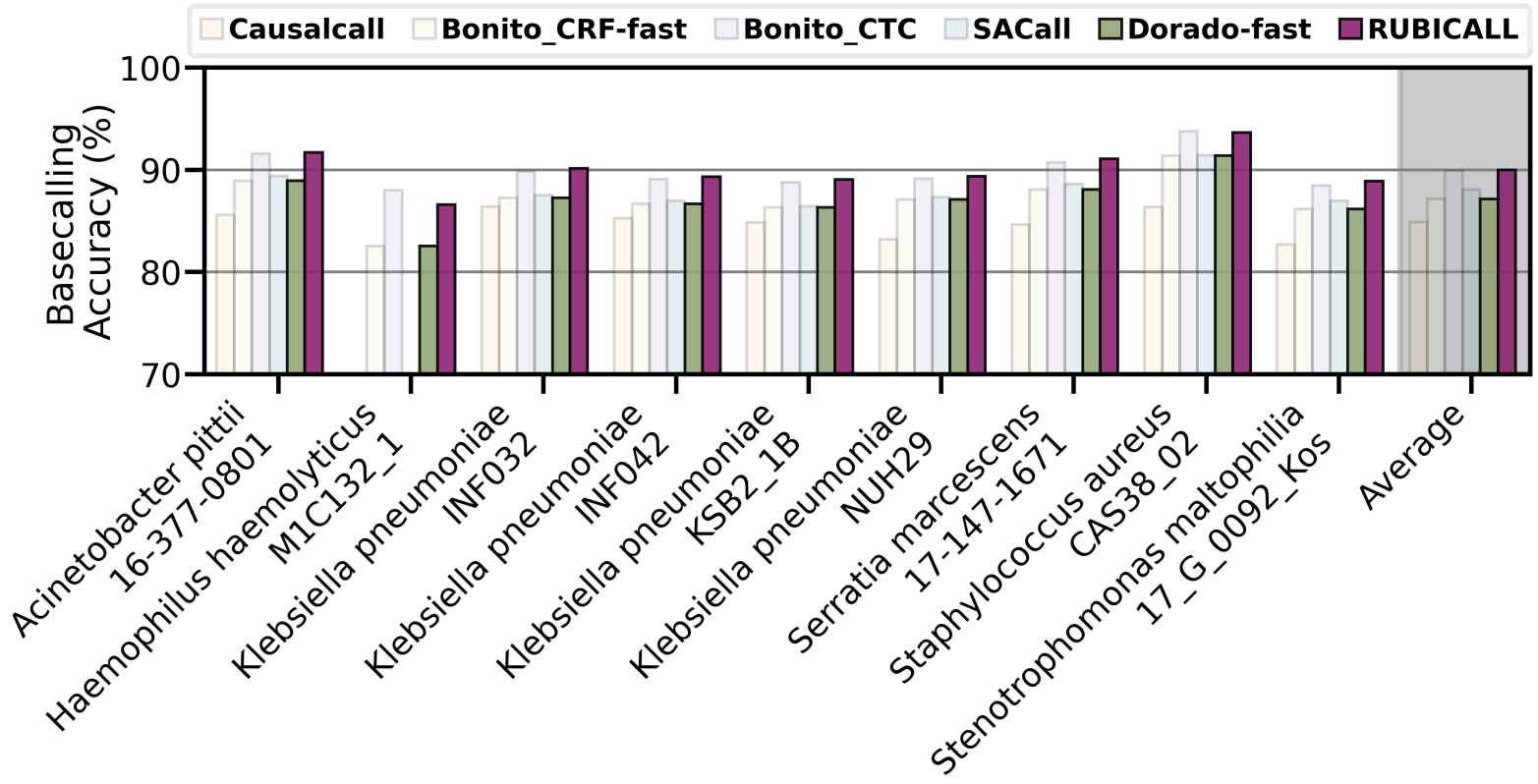


RUBICALL-MP **consistently outperforms** all the evaluated basecallers

Basecalling Accuracy

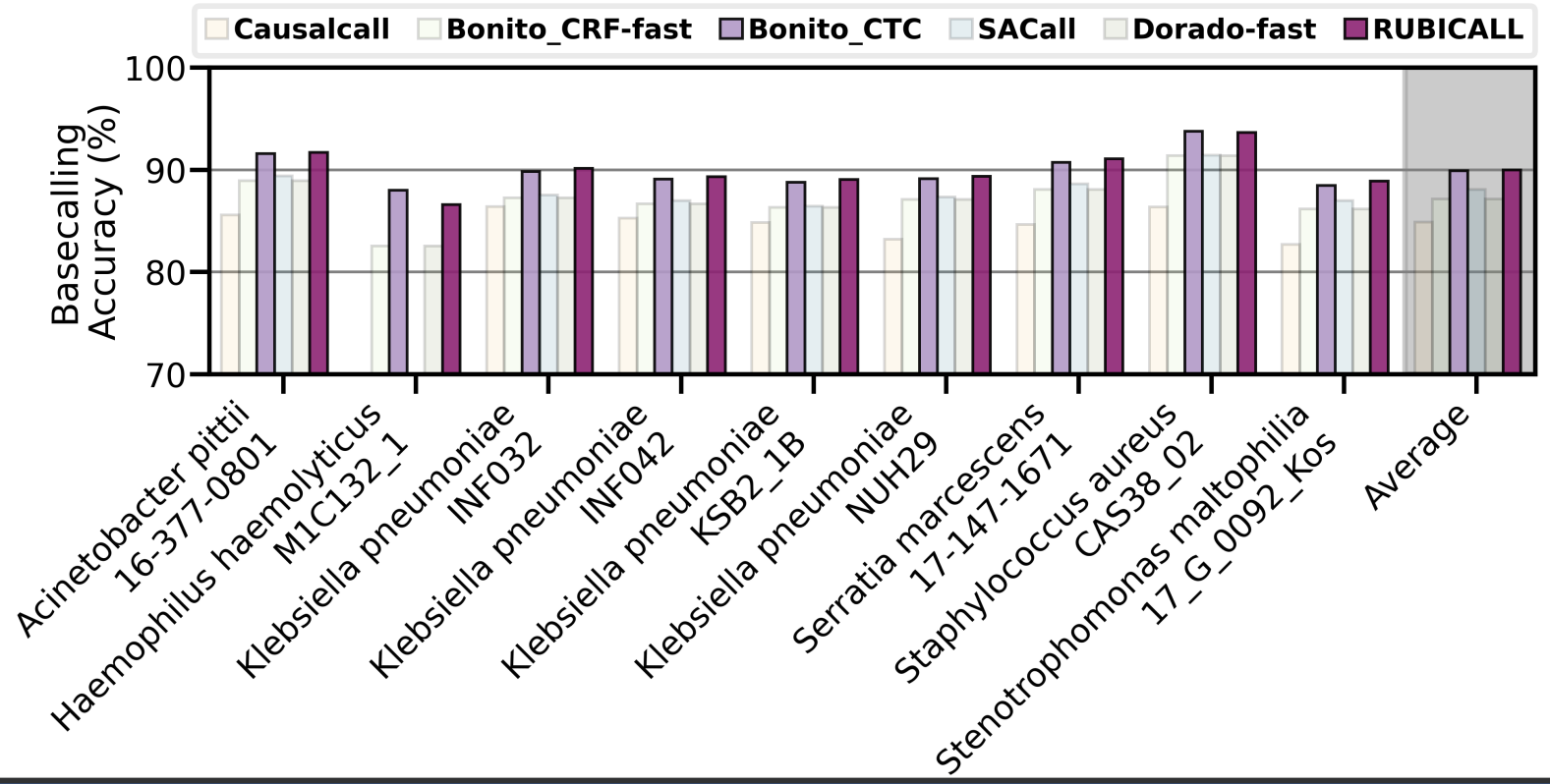


Basecalling Accuracy



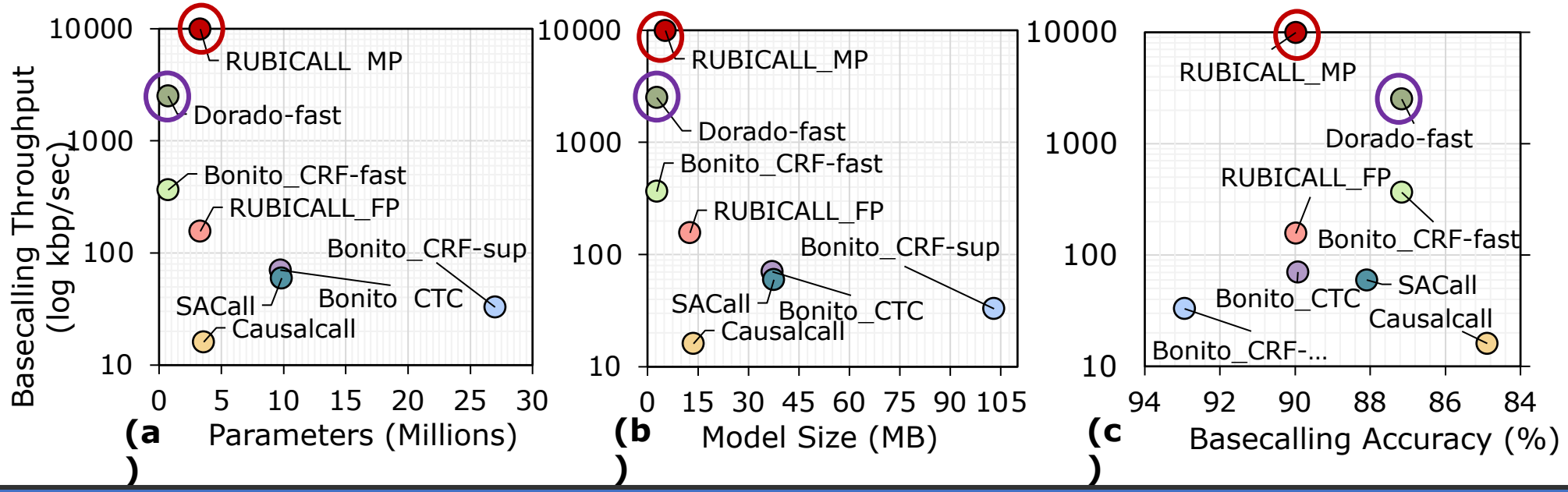
RUBICALL provides **2.97% higher accuracy** than Dorado-fast

Basecalling Accuracy



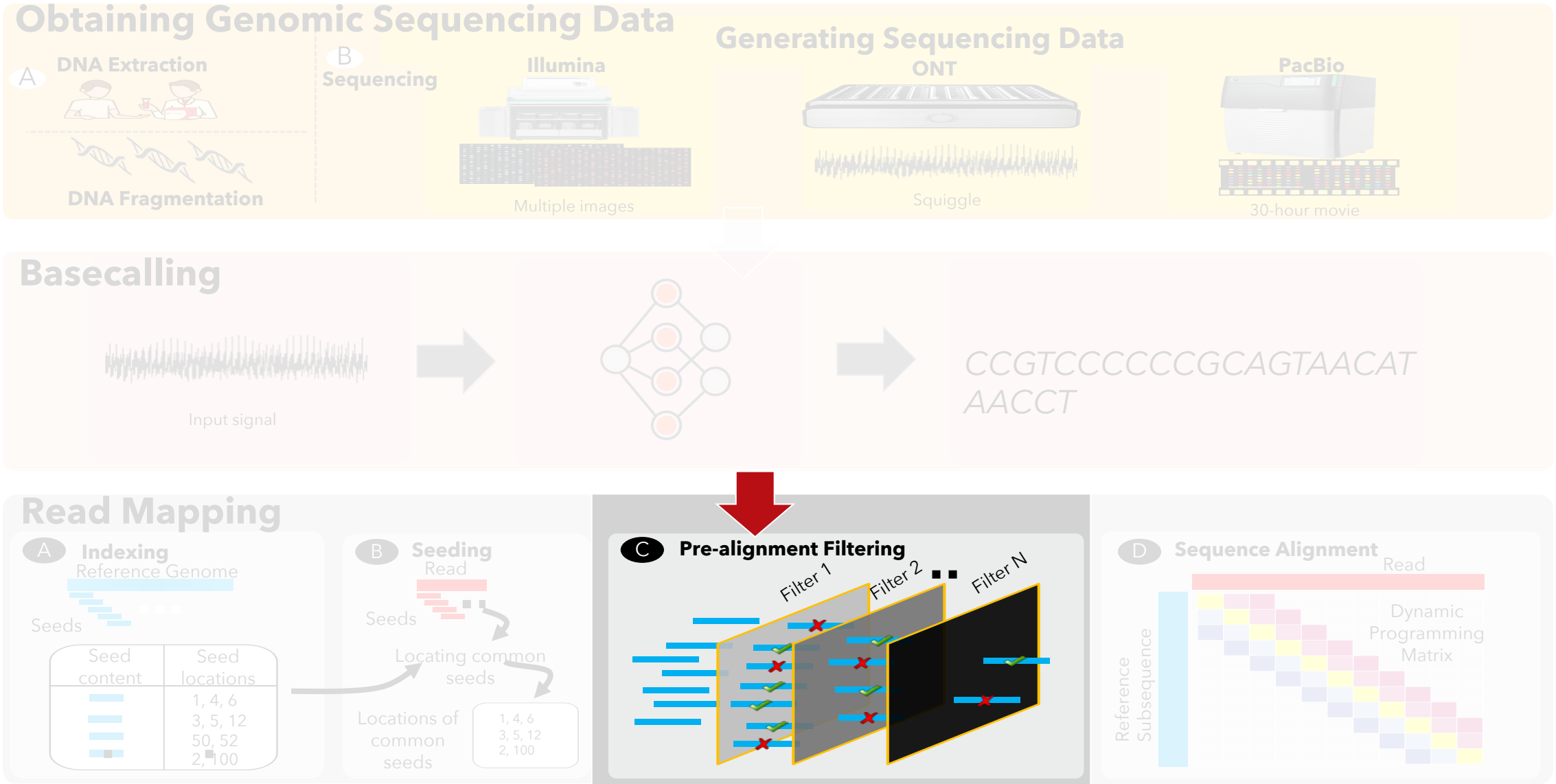
RUBICALL provides **similar accuracy** to an expert-designed basecaller while being **4.17x and 141.15x faster** with RUBICALL-FP and RUBICALL-MP, respectively

Key Results



RUBICALL-MP provides the ability to basecall **accurately, quickly, and efficiently** scale basecalling by providing **reductions in both model size and neural network model parameters**

Genome Sequencing Pipeline



SAFARI

Mohammed Alser et al., "From molecules to genomic variations: Accelerating genome analysis via intelligent algorithms and architectures", Computational and Structural Biotechnology Journal, Volume 20, 2022, Pages 4579-4599

Near-Memory Acceleration

Gagandeep Singh, Mohammed Alser, Damla Senol Cali, Dionysios Diamantopoulos, Juan Gomez-Luna, Henk Corporaal, Onur Mutlu,
FPGA-Based Near-Memory Acceleration of Modern Data-Intensive Applications
IEEE Micro, 2021.
[Source Code]

IEEE Micro

FPGA-Based Near-Memory Acceleration of Modern Data-Intensive Applications

July-Aug. 2021, pp. 39-48, vol. 41
DOI Bookmark: 10.1109/MM.2021.3088396

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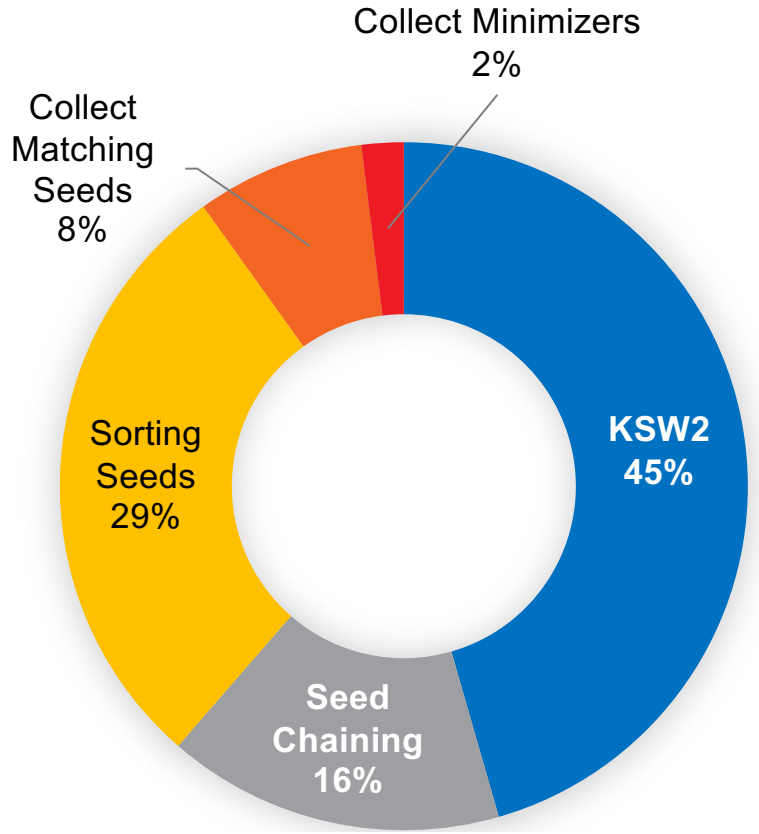
Henk Corporaal, Eindhoven University of Technology, Eindhoven, The Netherlands
Onur Mutlu, ETH Zürich, Zürich, Switzerland

Read Mapping Execution Time

>60%

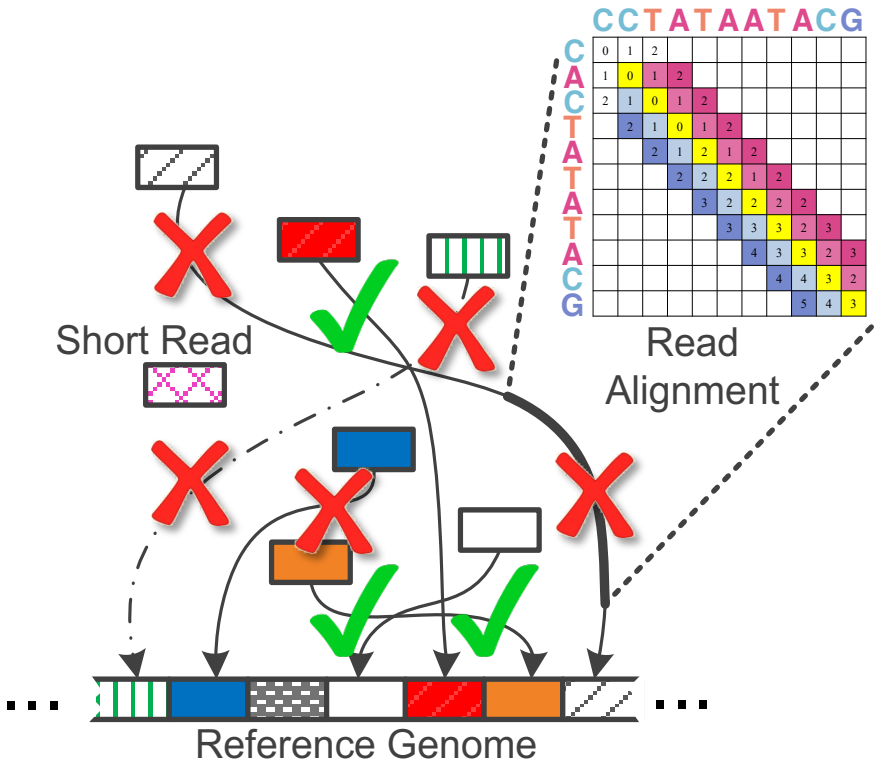
of the read mapper's execution time is spent in sequence alignment



ONT FASTQ size: 103MB (151 reads), Mean length: 356,403 bp, std: 173,168 bp, longest length: 817,917 bp

Mohammed Alser, "Intelligent Genome Analysis", Computer Architecture, ETH Zurich, Fall 2020

Large Search Space for Mapping Location



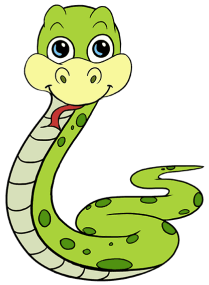
98%

of candidate locations have high dissimilarity with a given read

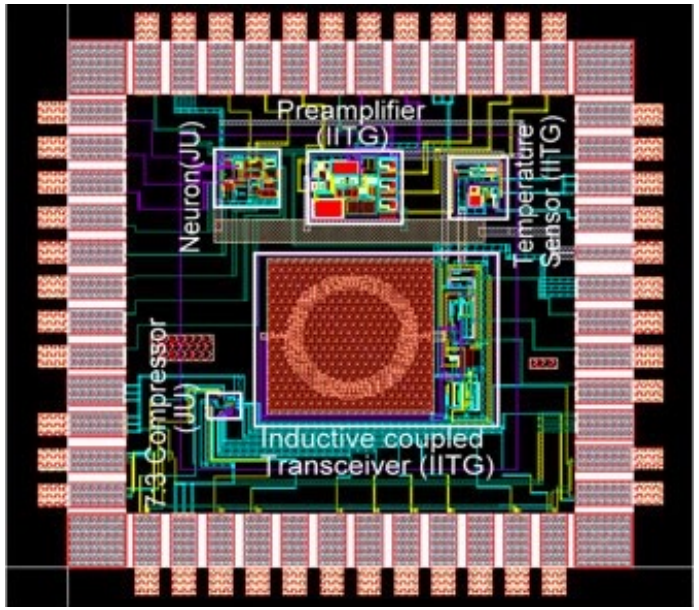
Cheng *et al*, *BMC bioinformatics* (2015)
Xin *et al*, *BMC genomics* (2013)

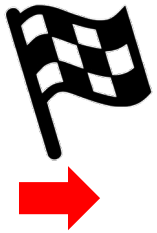
SneakySnake

- **Key idea:**
  - Approximate edit distance calculation is similar to Single Net Routing problem in VLSI chip



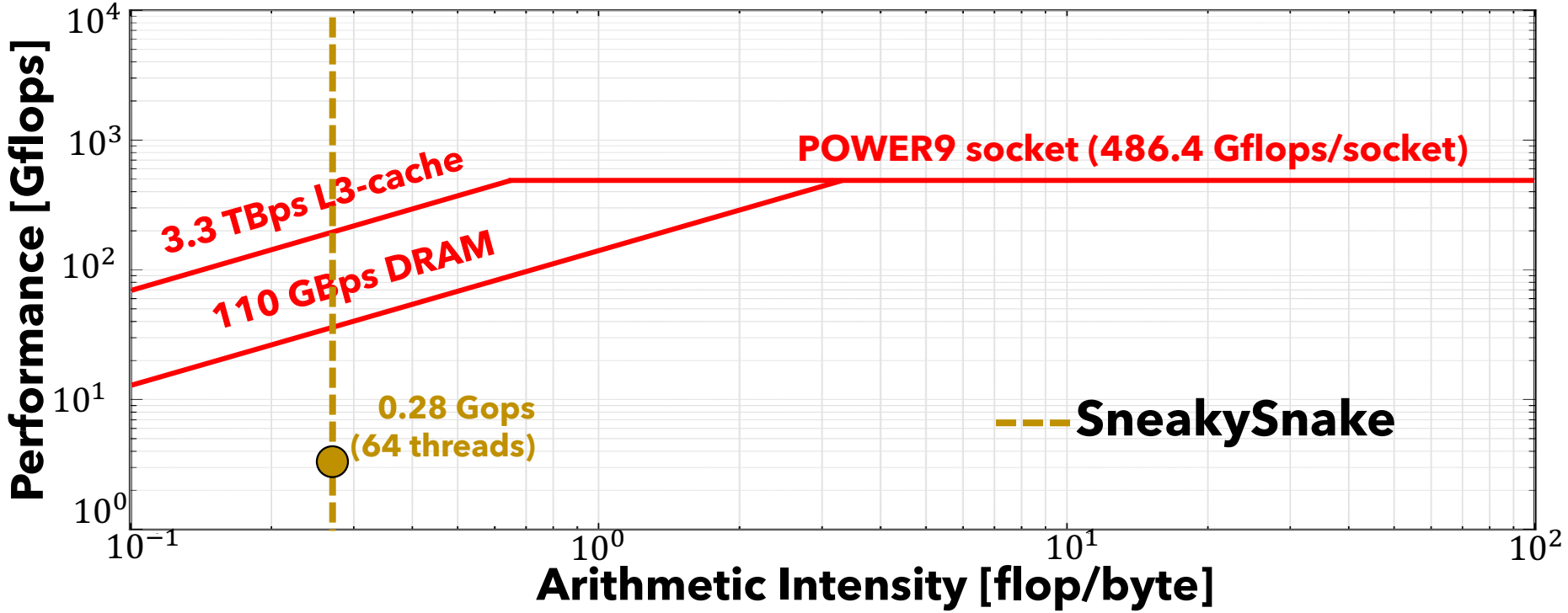
VLSI chip layout





Motivation and Goal

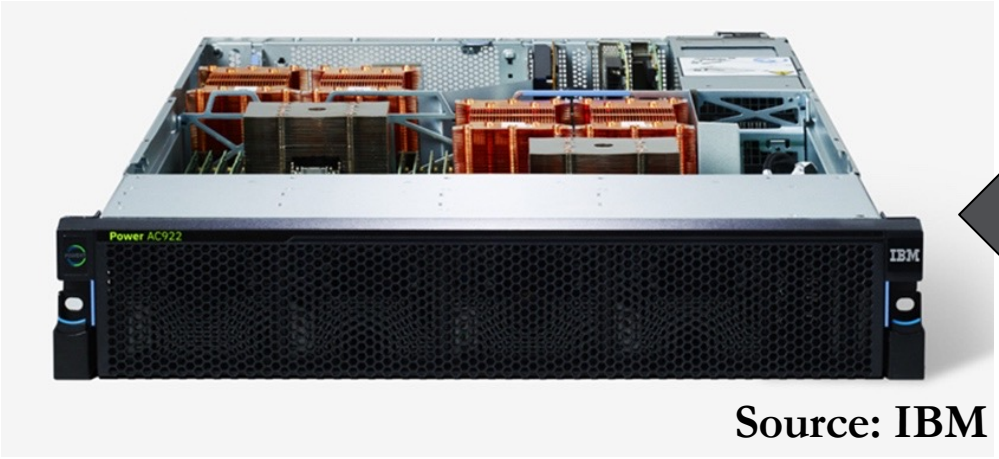
Complex memory access patterns with **limited performance** and **high energy consumption** on **CPU-based system**



Goal:

- **Mitigate** the **performance bottleneck** of modern pre-alignment filtering in an **energy-efficient way**
- Evaluate the use of **near-memory acceleration** using a **FPGA+HBM** connected through an OpenCAPI interface

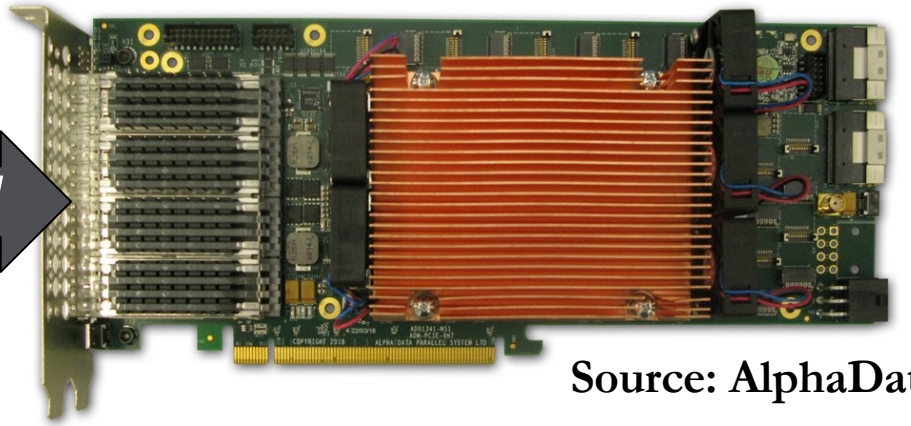
Near-Memory Acceleration



Source: IBM

POWER9 AC922

OCAPI



Source: AlphaData

HBM-based AD9H7 board

We evaluate:

I. Two POWER9+FPGA systems:

1. HBM-based AD9H7 board

Xilinx Virtex Ultrascale+™ XCVU37P-2

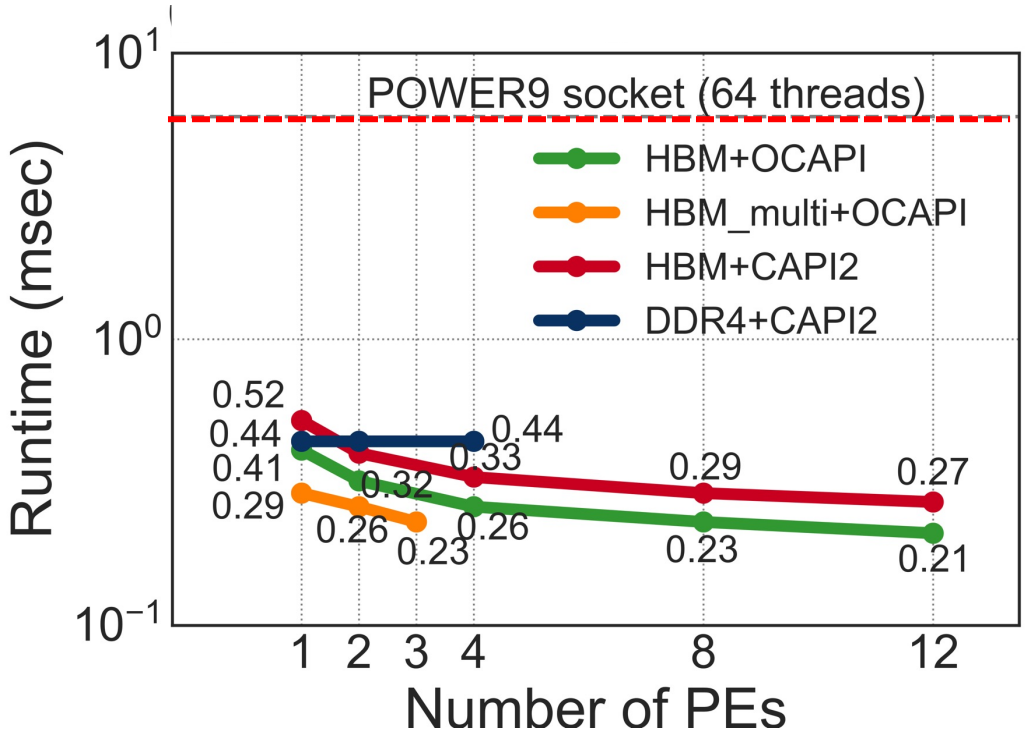
2. DDR4-based AD9V3 board

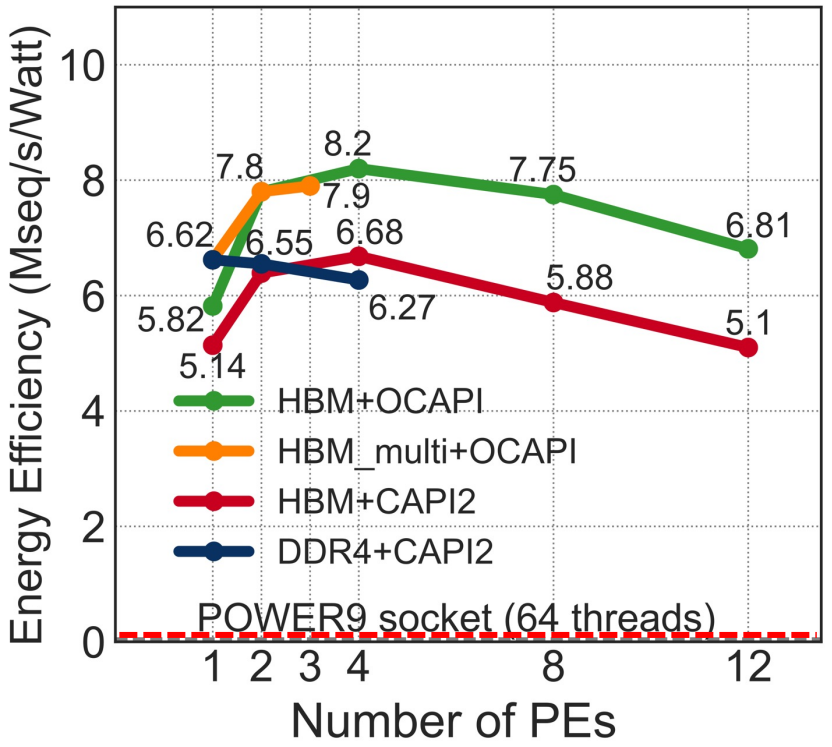
Xilinx Virtex Ultrascale+™ XCVU3P-2

II. Two interconnect technologies: **CAPI2** and **OCAPI**

III. Two processing element (PE) designs: **single channel** and **multiple channel**

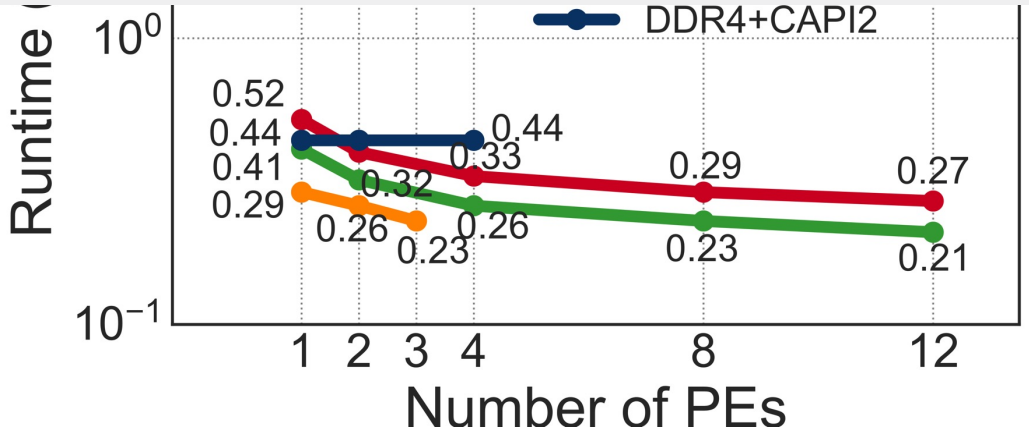
Key Results of Near-Memory Acceleration

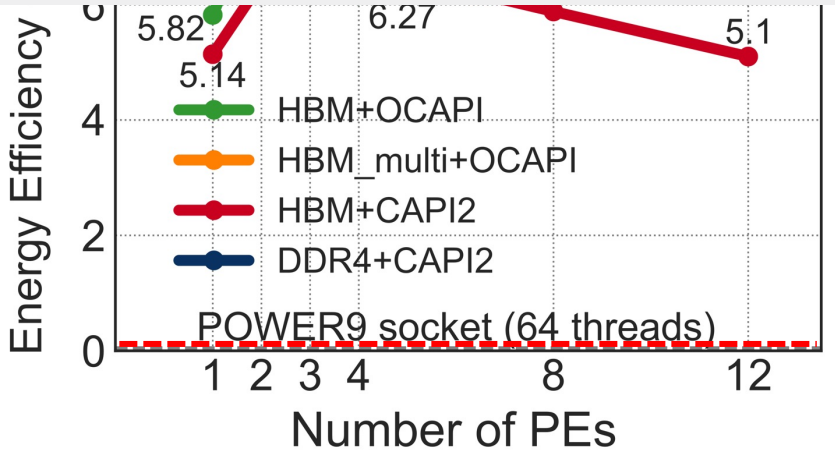




Key Results of Near-Memory Acceleration

Near-memory acceleration improves **performance** and **energy efficiency** upto 27× and 133×, respectively, over a server-grade CPU-based system





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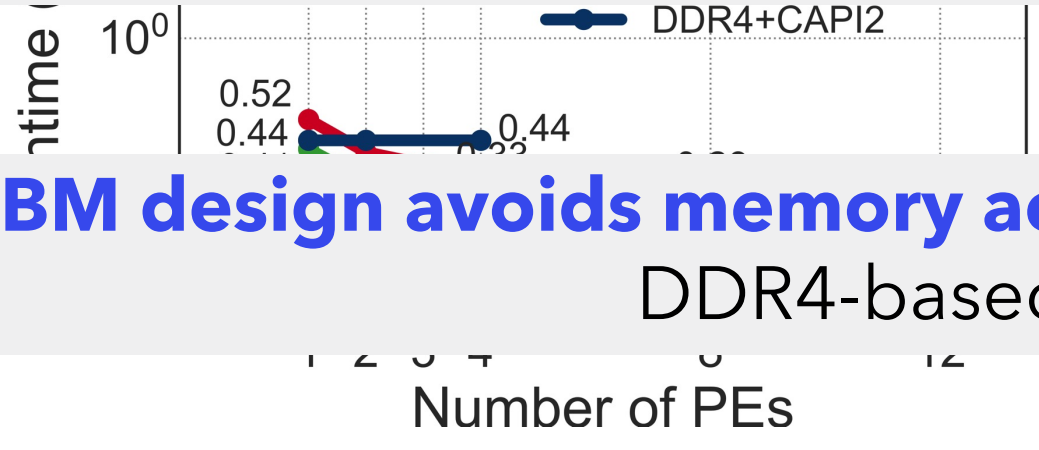

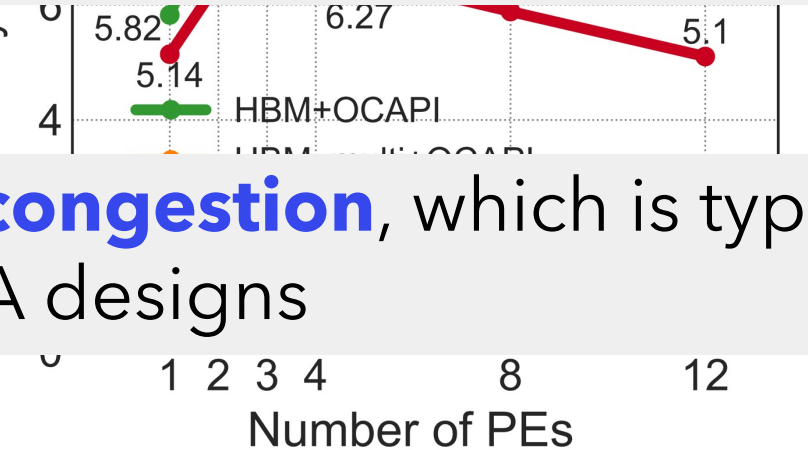

HBM design avoids memory access congestion, which is typical in DDR4-based FPGA designs

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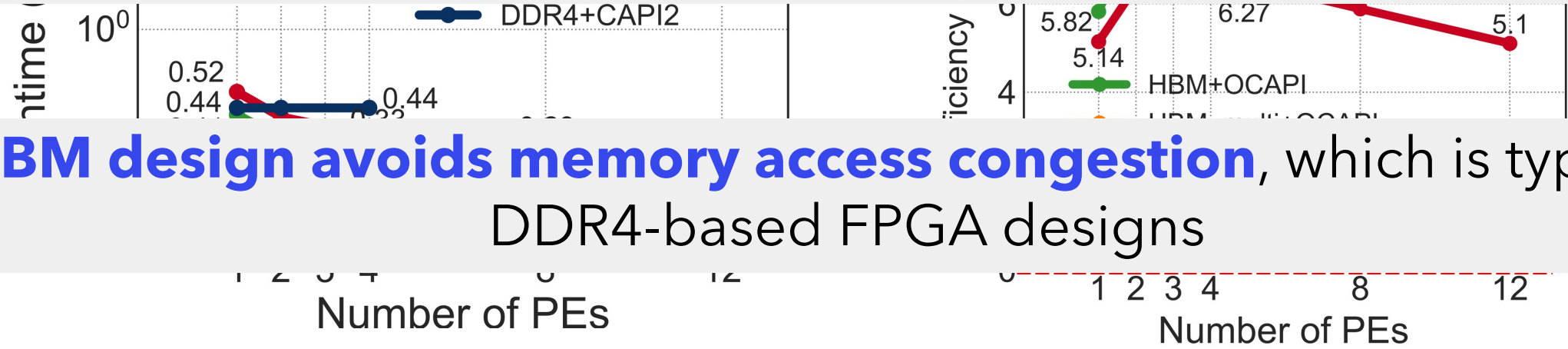

HBM design avoids memory access congestion, which is typical in DDR4-based FPGA designs

Single channel & multiple channel HBM designs
Open-source: https://github.com/CMU-SAFARI

Near-Memory Acceleration

Gagandeep Singh, Mohammed Alser, Damla Senol Cali, Dionysios Diamantopoulos, Juan Gomez-Luna, Henk Corporaal, Onur Mutlu,
FPGA-Based Near-Memory Acceleration of Modern Data-Intensive Applications
IEEE Micro, 2021.
[Source Code]

IEEE Micro

FPGA-Based Near-Memory Acceleration of Modern Data-Intensive Applications

July-Aug. 2021, pp. 39-48, vol. 41
DOI Bookmark: 10.1109/MM.2021.3088396

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Genome Sequencing Pipeline

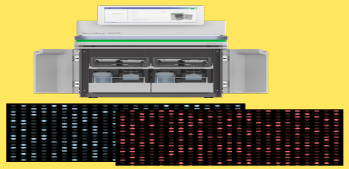
Obtaining Genomic Sequencing Data

A **DNA Extraction**

DNA Fragmentation

B **Sequencing**

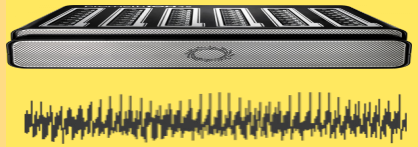
Illumina



Multiple images

Generating Sequencing Data

ONT



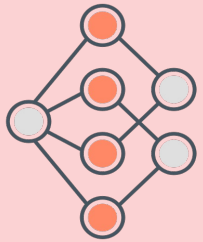
Squiggle

PacBio

30-hour movie

Basecalling

Input signal



CCGTCCCCCCGCAGTAACAT

Read Mapping

A Indexing

Reference Genome

Seeds

Seed content	Seed locations
	1, 4, 6
	3, 5, 12
	50, 52
	2, 100

B Seeding

Read

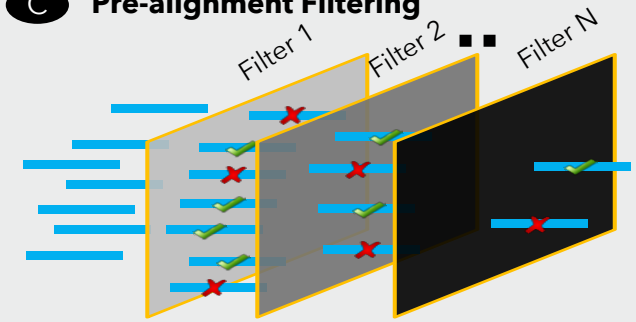
Seeds

Locating common seeds

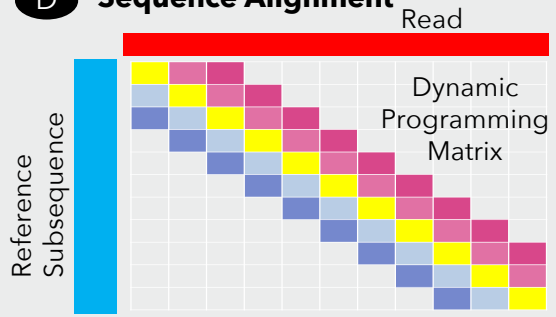
Locations of common seeds

1, 4, 6
3, 5, 12
2, 100

C Pre-alignment Filtering



D Sequence Alignment



Mohammed Alser et al., "From molecules to genomic variations: Accelerating genome analysis via intelligent algorithms and architectures", Computational and Structural Biotechnology Journal, Volume 20, 2022, Pages 4579-4599

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  - Kristof Denolf
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AMD