

Enabling Fast and Accurate Real-Time Analysis of Raw Nanopore Signals for Large Genomes

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Paper



Code





Nanopore Sequencing

Nanopore Sequencing: a widely used sequencing technology

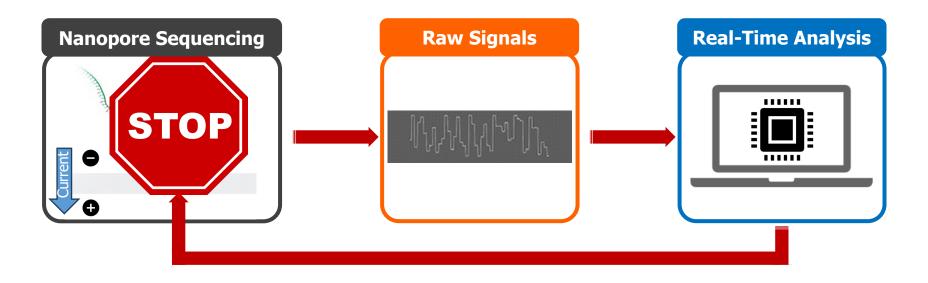
- Can sequence large fragments of nucleic acid molecules (up to >2Mbp)
- Offers high throughput
- Cost-effective

Enables real-time genome analysis





Real-Time Analysis with Nanopore Sequencing



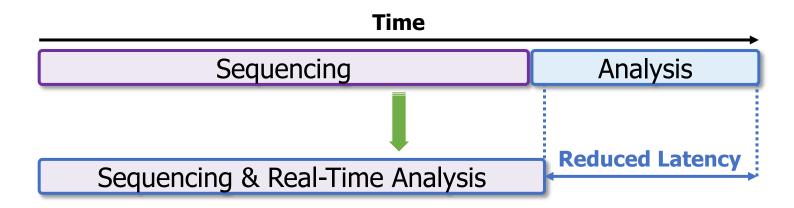
Raw Signals: Ionic current measurements generated at a certain throughput

Real-Time Analysis: Analyzing all raw signals by matching the throughput

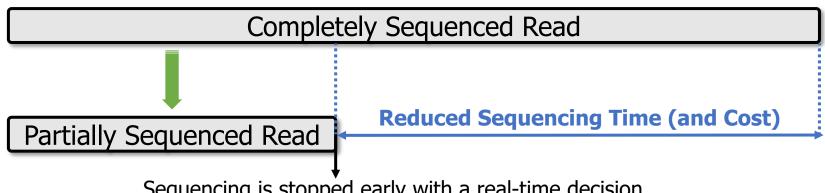
Real-Time Decisions: Stopping sequencing early based on real-time analysis

Benefits of Real-Time Genome Analysis

Reducing latency by overlapping the sequencing and analysis steps



Reducing sequencing time and cost by stopping sequencing early



Sequencing is stopped early with a real-time decision

Challenges in Real-Time Genome Analysis

Rapid analysis to match the nanopore sequencer throughput

Timely decisions to stop sequencing as early as possible

Accurate analysis from noisy raw signal data

Power-efficient computation for scalability and portability

Executive Summary

Problem: Real-time analysis of nanopore raw signals is **inaccurate** and **inefficient for large genomes**

Goal: Enable fast and accurate real-time analysis of raw signals for large genomes

Key Contributions:

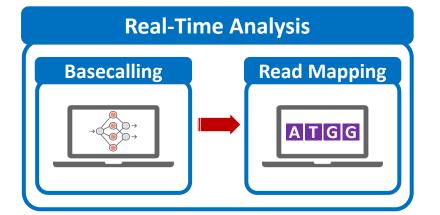
- 1) The first hash-based mechanism that can quickly and accurately analyze raw nanopore signals for large genomes
- 2) The novel **Sequence Until** technique can accurately and **dynamically stop the entire sequencing of all reads at once** if further sequencing is not necessary

Key Results: Across 3 use cases and 5 genomes of varying sizes, RawHash provides

- 25.8× and 3.4× better average throughput compared to two state-of-the-art works
- − 1.14× − 2.13× more accurate mapping results for large genomes
- Sequence Until reduces the sequencing time and cost by 15×

Existing Solutions

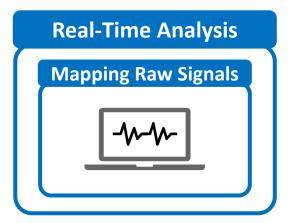
1. Deep neural networks (**DNNs**) for translating **signals** to **bases**



Less noisy analysis from basecalled sequences

Costly and power-hungry computational requirements

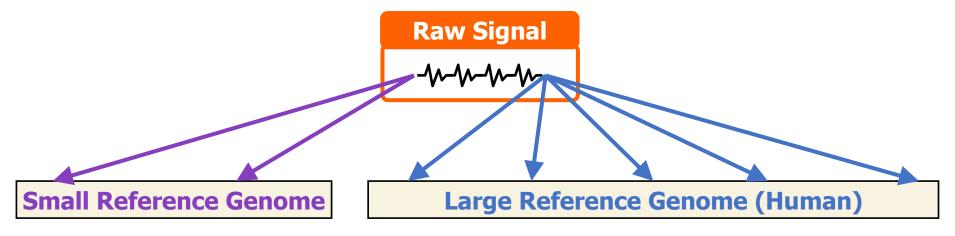
Mapping signals to reference genomes without basecalling



Raw signals contain richer information than bases

Efficient analysis with better scalability and portability

The Problem - Mapping Raw Signals



Fewer candidate regions in **small genomes**

Substantially **larger number of regions** to check **per read** as the genome size increases

Accurate mapping

Problem: Probabilistic mechanisms on many regions → inaccurate mapping

High throughput

Problem: Distance calculation on many regions → reduced throughput

The Problem - Mapping Raw Signals

Raw Signal

Existing solutions are inaccurate or inefficient for large genomes

Accurate mapping

on many regions -> inaccurate mapping

High throughput

on many regions → reduced throughput

Outline

Background

RawHash

Evaluation

Conclusion

Goal

Enable fast and accurate real-time analysis of raw nanopore signals for large genomes





The first hash-based search mechanism to quickly and accurately map raw nanopore signals to reference genomes

Sequence Until can accurately and dynamically stop
the entire sequencing run at once
if further sequencing is unnecessary

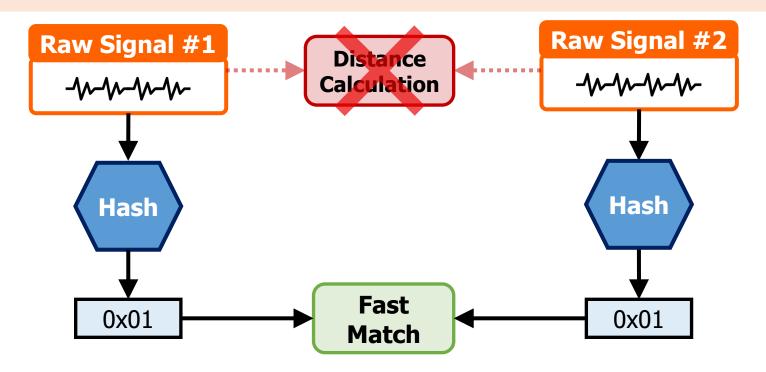


The first hash-based search mechanism to quickly and accurately map raw nanopore signals to reference genomes

Sequence Until can accurately and dynamically stop the entire sequencing run at once if further sequencing is unnecessary

RawHash – Key Idea

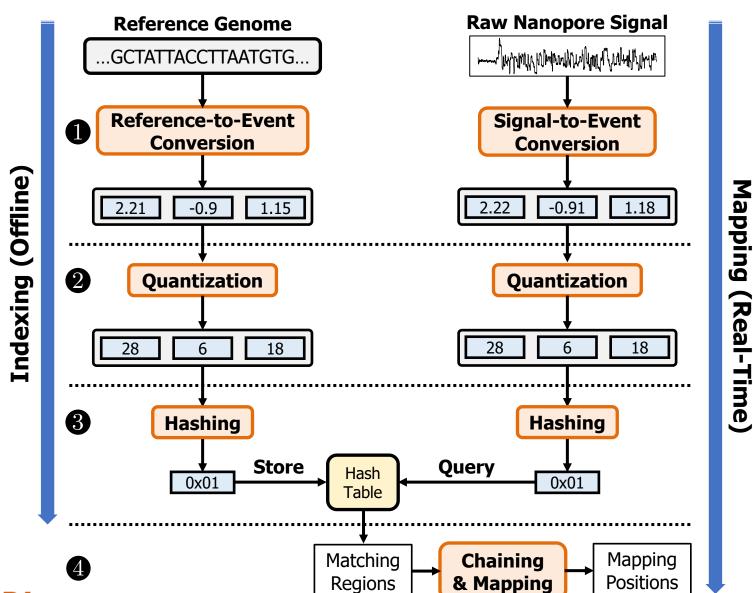
Key Observation: Identical nucleotides generate **similar** raw signals



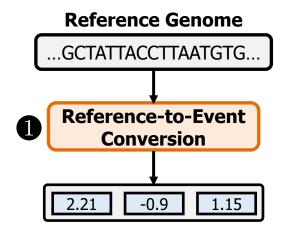
Challenge #1: Generating the **same** hash value for **similar enough** signals

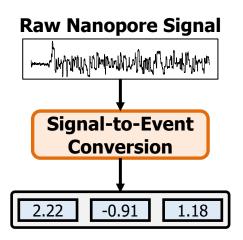
Challenge #2: Accurately finding similar regions as few as possible

RawHash Overview



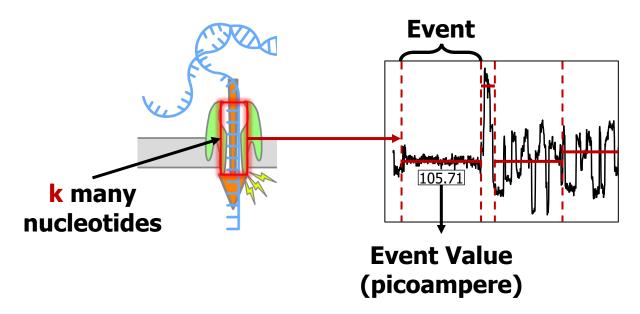
RawHash Overview





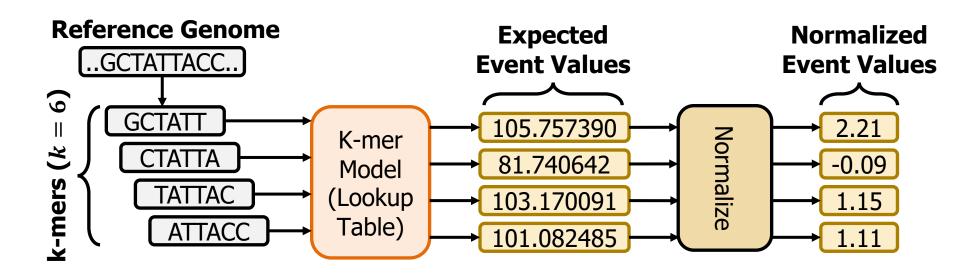
Events in Raw Nanopore Signals

- Event: A segment of the raw signal
 - Corresponds to a **particular k**-mer
- Event detection finds these segments to identify k-mers
 - Start and end positions are marked by abrupt signal changes
 - Statistical methods identify these abrupt changes
 - Event value: average of signals within an event



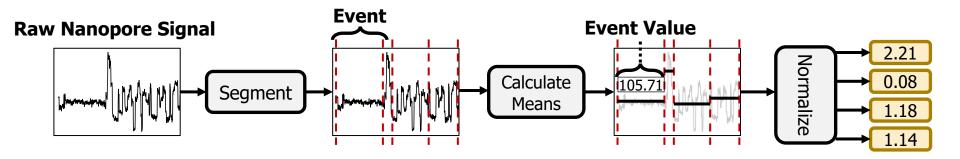
Reference-to-Event Conversion

- K-mer model: Provides expected event values for each k-mer
 - Preconstructed based on nanopore sequencer characteristics
- Use the k-mer model to convert all k-mers
 of a reference genome to their expected event values



Signal-to-Event Conversion

- **Event detection:** Identifies signal regions corresponding to specific k-mers
 - Uses statistical test (**segmentation**) to spot abrupt signal changes



Consecutive events → consecutive k-mers

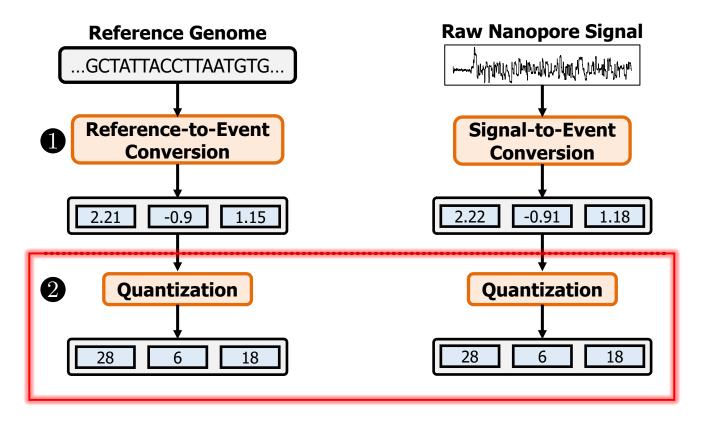
Signal-to-Event Conversion

- Event detection: Identifies signal regions corresponding to specific k-mers
 - Uses statistical test (segmentation) to spot abrupt signal changes

Can we match events (k-mers) between reference genome and raw signals?

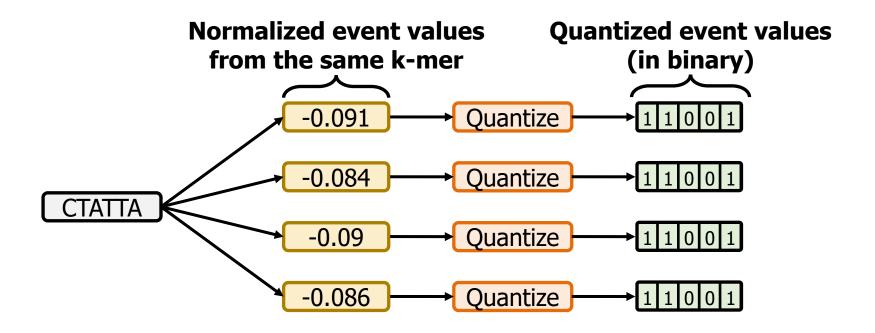
Consecutive events → consecutive k-mers

RawHash Overview

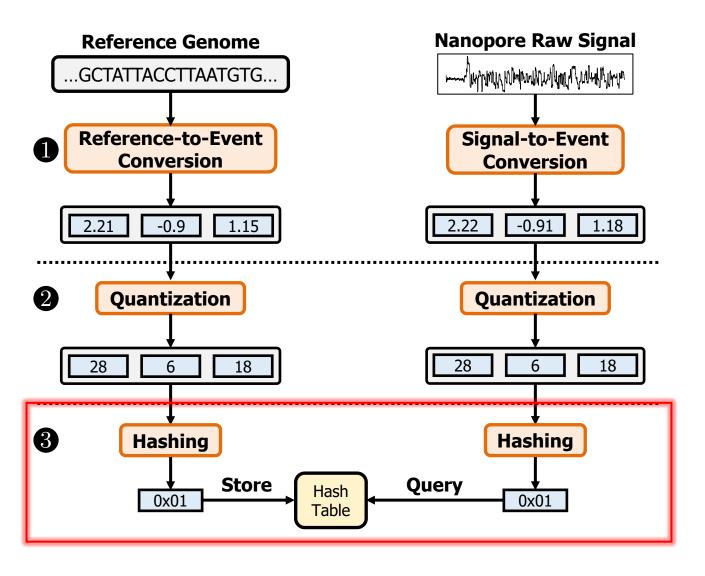


Quantizing the Event Values

- Observation: Slight differences in raw signals from identical k-mers
 - Challenge: Direct event value matching is not feasible and accurate
- **Key Idea:** Quantize the event values
 - Enables assigning identical quantized values to similar event values



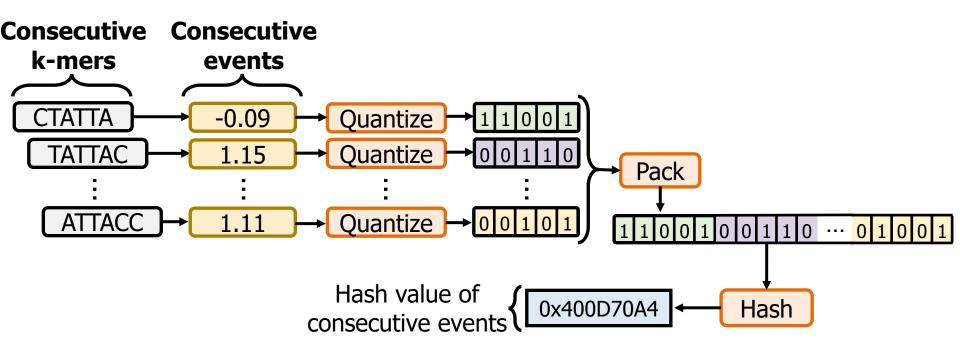
RawHash Overview



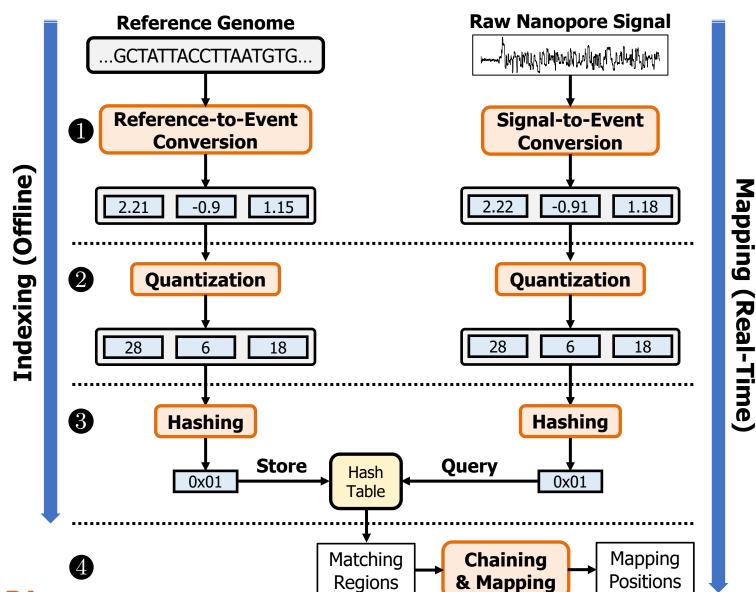


Hashing for Fast Similarity Search

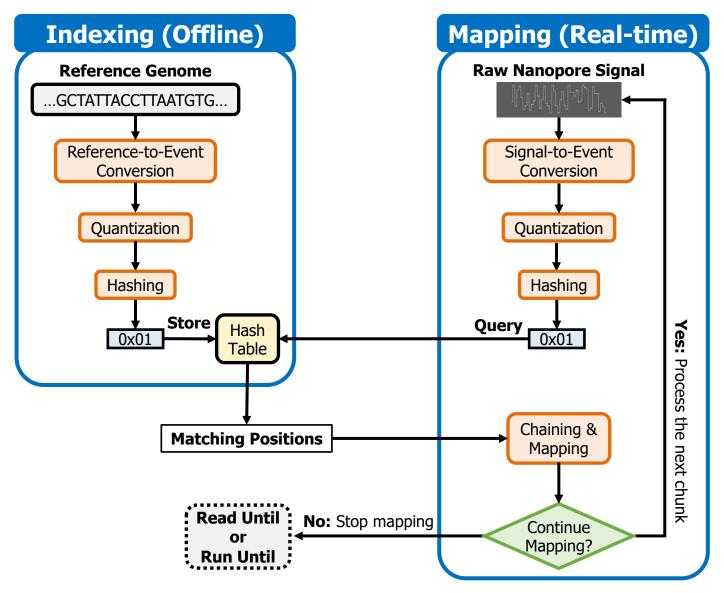
- Each event usually represents a very small k-mer (6 to 9 characters)
 - **Challenge:** Short k-mers are likely to appear in many locations
- Key Idea: Create longer k-mers from many consecutive events
- Key Benefit: Directly match hash values to quickly identify similarities



RawHash Overview



Real-Time Mapping using Hash-based Indexing





The first hash-based search mechanism to quickly and accurately map raw nanopore signals to reference genomes

Sequence Until can accurately and dynamically stop the entire sequencing run at once if further sequencing is unnecessary



The first hash-based search mechanism to quickly and accurately map raw nanopore signals to reference genomes

Sequence Until can accurately and dynamically stop
the entire sequencing run at once
if further sequencing is unnecessary

The Sequence Until Mechanism

Problem:

- Unnecessary sequencing waste time, power and money

Key Idea:

- **Dynamically** decide if further sequencing of the entire sample is necessary to achieve high accuracy
- Stop sequencing early without sacrificing accuracy

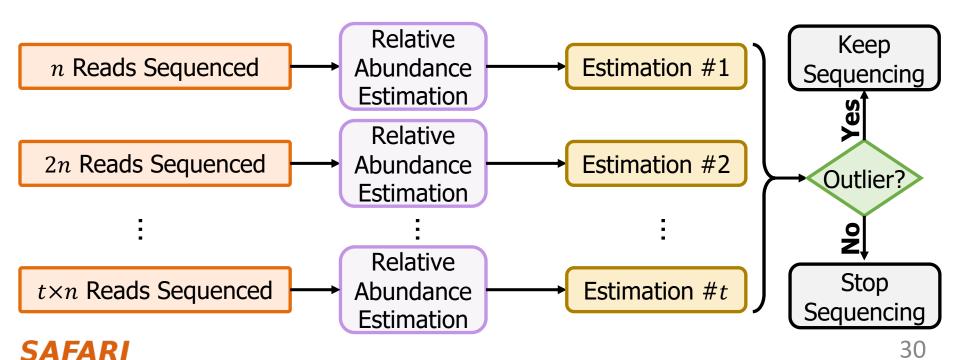
Potential Benefits:

- Significant reduction in sequencing time and cost
- Example real-time genome analysis use case:
 - Relative abundance estimation

The Sequence Until Mechanism

Key Steps:

- 1. Continuously generate relative abundance estimation after every n reads
- 2. Keep the last t estimation results
- 3. **Detect outliers** in the results via **cross-correlation** of the recent t results
- 4. Absence of outliers indicates **consistent results**
 - Further sequencing is likely to generate consistent results → Stop the sequencing



Outline

Background

RawHash

Evaluation

Conclusion

Evaluation Methodology

- Compared to UNCALLED [Kovaka+, Nat. Biotech. 2021]
 and Sigmap [Zhang+, ISMB/ECCB 2021]
 - CPU baseline: AMD EPYC 7742 @2.26GHz
 - **32 threads** for each tool

- Use cases for real-time genome analysis:
 - 1. Read mapping
 - 2. Relative abundance estimation
 - Benefits of Sequence Until
 - 3. Contamination analysis

Evaluation Methodology

- Evaluation metrics:
 - Throughput (bases processed per second)
 - Potential reduction in **sequencing time and cost**
 - Accuracy
 - **Baseline:** Mapping basecalled reads using minimap2
 - Precision, recall, and F1 scores
 - Relative abundance estimation distance to ground truth

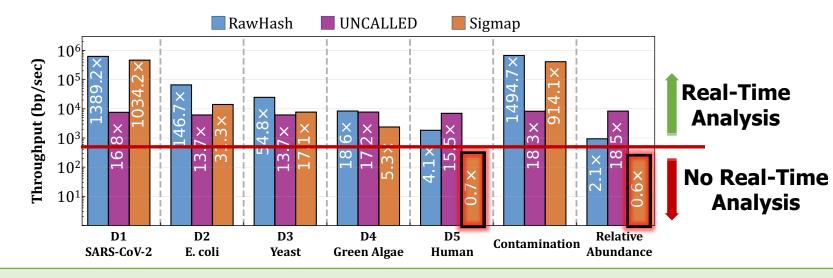
Datasets:

	Organism	Reads (#)	Bases (#)	Genome Size				
Read Mapping								
D1	SARS-CoV-2	1,382,016	594M	29,903				
D2	E. coli	353,317	2,365M	5M				
D3	Yeast	49,989	380M	12M				
D4	Green Algae	29,933	609M	111M				
D5	Human HG001	269,507	1,584M	3,117M				
Relative Abundance Estimation								
	D1-D5	2,084,762	5,531M	3,246M				
Contamination Analysis								
	D1 and D5	1,651,523	2,178M	29,903				



Throughput

- Real-time analysis requires faster throughput than sequencer
 - Throughput of a nanopore sequencer: ~450 bp/sec (data generation speed)



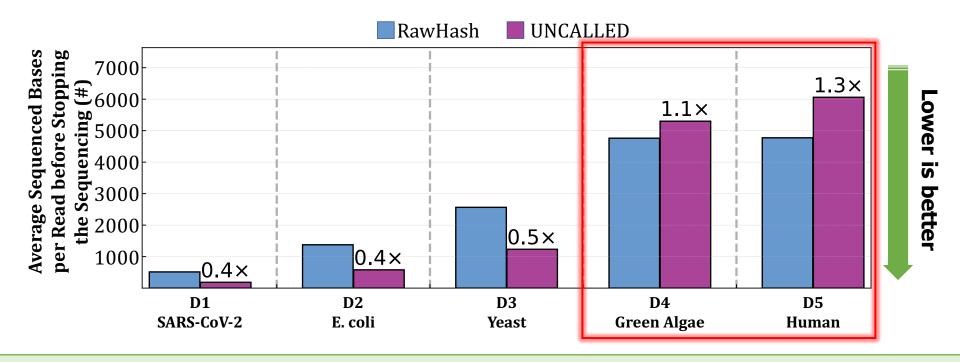
25.8× and **3.4**× better average throughput compared to

UNCALLED and Sigmap, respectively

Sigmap cannot perform real-time analysis for large genomes

Sequencing Time

- Fewer bases to sequence →
 - Reduction in sequencing time and cost



RawHash reduces sequencing time and cost

for large genomes up to 1.3× compared to UNCALLED

Mapping Accuracy

Read mapping accuracy of each tool and each use case

Dataset		UNCALLED	Sigmap	RawHash					
Read Mapping									
D1	Precision	0.9547	0.9929	0.9868					
SARS-CoV-2	Recall	0.9910	0.5540	0.8735					
	F_1	0.9725	0.7112	0.9267					
D2	Precision	0.9816	0.9842	0.9573					
E. coli	Recall	0.9647	0.9504	0.9009					
	F_1	0.9731	0.9670	0.9282					
D3	Precision	0.9459	0.9856	0.9862					
Yeast	Recall	0.9366	0.9123	0.8412					
	F_1	0.9412	0.9475	0.9079					
D4	Precision	0.8836	0.9741	0.9691					
Green Algae	Recall	0.7778	0.8987	0.7015					
_	F_1	0.8273	0.9349	0.8139					
D5	Precision	0.4867	0.4287	0.8959					
Human HG001	Recall	0.2379	0.2641	0.4054					
	F_1	0.3196	0.3268	0.5582					

Dataset	U	NCALLED	Sigmap	RawHash				
Relative Abundance Estimation								
	Precision	0.7683	0.7928	0.9484				
D1-D5	Recall	0.1273	0.2739	0.3076				
	F_1	0.2184	0.4072	0.4645				
	Contamina	ation Analysis	5					
	Precision	0.9378	0.7856	0.8733				
D1, D5	Recall	0.9910	0.5540	0.8735				
	F_1	0.9637	0.6498	0.8734				

For Large Genomes: RawHash provides the best accuracy

in all metrics, resulting in $\mathbf{1.14} \times \mathbf{-2.13} \times \mathbf{improvement}$ in F_1 score

Relative Abundance Estimation Accuracy

- Estimating the ratio of genomes in a sample in real-time
 - **Distance:** Euclidean distance compared to the ground truth distance
 - The dataset includes a large reference genome

		Estimated Relative Abundance Ratios					
Tool	SARS-CoV-2	E. coli	Yeast	Green Algae	Human	Distance	
Ground Truth	0.0929	0.4365	0.0698	0.1179	0.2828	N/A	
UNCALLED	0.0026	0.5884	0.0615	0.1313	0.2161	0.1895	
Sigmap	0.0419	0.4191	0.1038	0.0962	0.3390	0.0877	
RawHash	0.1249	0.4701	0.0957	0.0629	0.2464	0.0847	

RawHash provides the **best relative abundance estimation**closest to the ground truth estimation

Real Implementation of Sequence Until

- Running RawHash by using
 - RawHash (100%): The entire sample without Sequence Until
 - RawHash (7%): RawHash with Sequence Until where Sequence Until dynamically stops the entire sequencing after sequencing 7% of the sample

	Estimated Relative Abundance Ratios in 50,000 Random Reads					
Tool	SARS-CoV-2	E. coli	Yeast	Green Algae	Human	Distance
RawHash (100%)	0.0270	0.3636	0.3062	0.1951	0.1081	N/A
RawHash + Sequence Until (7%)	0.0283	0.3539	0.3100	0.1946	0.1133	0.0118

Sequence Until enables sequencing **only 7%** (~1/15) of the entire sample **with high accuracy**

Simulating Sequence Until

Real relative abundance results using the entire set of reads

	Estimated Relative Abundance Ratios					
Tool	SARS-CoV-2	E. coli	Yeast	Green Algae	Human	Distance
Ground Truth	0.0929	0.4365	0.0698	0.1179	0.2828	N/A
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- Simulating the benefits of Sequence Until by
 - Using a random portion (25%, 10%, 1%, ...) of the sample

	Estimated Relative Abundance Ratios					
Tool	SARS-CoV-2	E. coli	Yeast	Green Algae	Human	Distance
Ground Truth	0.0929	0.4365	0.0698	0.1179	0.2828	N/A
UNCALLED (25%)	0.0026	0.5890	0.0613	0.1332	0.2139	0.1910
RawHash (25%)	0.0271	0.4853	0.0920	0.0786	0.3170	0.0995
UNCALLED (10%)	0.0026	0.5906	0.0611	0.1316	0.2141	0.1920
RawHash (10%)	0.0273	0.4869	0.0963	0.0772	0.3124	0.1004
UNCALLED (1%)	0.0026	0.5750	0.0616	0.1506	0.2103	0.1836
RawHash (1%)	0.0259	0.4783	0.0987	0.0882	0.3088	0.0928
UNCALLED (0.1%)	0.0040	0.4565	0.0380	0.1910	0.3105	0.1242
RawHash (0.1%)	0.0212	0.5045	0.1120	0.0810	0.2814	0.1136
UNCALLED (0.01%)	0.0000	0.5551	0.0000	0.0000	0.4449	0.2602
RawHash (0.01%)	0.0906	0.6122		0.0000	0.2972	0.2232



Simulating Sequence Until

Real relative abundance results using the entire set of reads

		Estimated Relative Abundance Ratios					
Tool	SARS-CoV-2	E. coli	Yeast	Green Algae	Human	Distance	
Ground Truth	0.0929	0.4365	0.0698	0.1179	0.2828	N/A	
UNCALLED	0.0026	0.5884	0.0615	0.1313	0.2161	0.1895	
Sigmap	0.0419	0.4191	0.1038	0.0962	0.3390	0.0877	

UNCALLED and RawHash benefit from Sequence Until

significantly **by up to 100**× reductions in

sequencing time and costs

1001	SAKS-COV-Z	E. con	reasi	Green Aigae	питап	Distance
Ground Truth	0.0929	0.4365	0.0698	0.1179	0.2828	N/A
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UNCALLED (0.01%)	0.0000	0.5551	0.0000	0.0000	0.4449	0.2602
RawHash (0.01%)	0.0906	0.6122		0.0000	0.2972	0.2232



More in the Paper

More Results

- Mapping time per read
- Overall **computational resources** required by each tool
 - Peak memory usage, CPU time and real time in the indexing and mapping steps
- Performance breakdown of the steps in RawHash

Details of all mechanisms and configurations

- Details of the quantization and hashing mechanism
- Details of the **parameter configurations**
- Trade-offs between the **DNN-based approaches** and raw signal mapping approaches

RawHash

 <u>Can Firtina</u>, Nika Mansouri Ghiasi, Joel Lindegger, Gagandeep Singh, Meryem Banu Cavlak, Haiyu Mao, and Onur Mutlu,

"RawHash: Enabling Fast and Accurate Real-Time Analysis of Raw Nanopore Signals for Large Genomes"

Proceedings of the <u>31st Annual Conference on Intelligent Systems for Molecular Biology (ISMB)</u> and the <u>22nd European Conference on Computational Biology</u> (**ECCB**), Jul 2023

[arXiv preprint] [Source Code]

> *Bioinformatics*, 2023, **39**, i297–i307 https://doi.org/10.1093/bioinformatics/btad272 ISMB/ECCB 2023





RawHash: enabling fast and accurate real-time analysis of raw nanopore signals for large genomes

Can Firtina (b) 1,*, Nika Mansouri Ghiasi (b) 1, Joel Lindegger (b) 1, Gagandeep Singh (b) 1, Meryem Banu Cavlak (b) 1, Haiyu Mao (b) 1, Onur Mutlu (b) 1,*

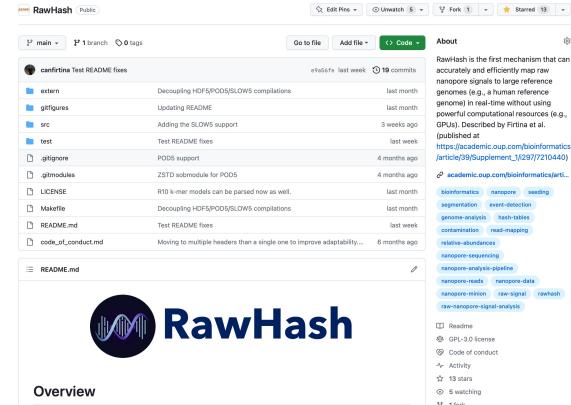
^{*}Corresponding author. Department of Information Technology and Electrical Engineering, ETH Zurich, Gloriastrasse 35, 8092 Zurich, Switzerland. E-mail: firtinac@ethz.ch (C.F.), omutlu@ethz.ch (O.M.)



¹Department of Information Technology and Electrical Engineering, ETH Zurich, 8092 Zurich, Switzerland

RawHash Source Code

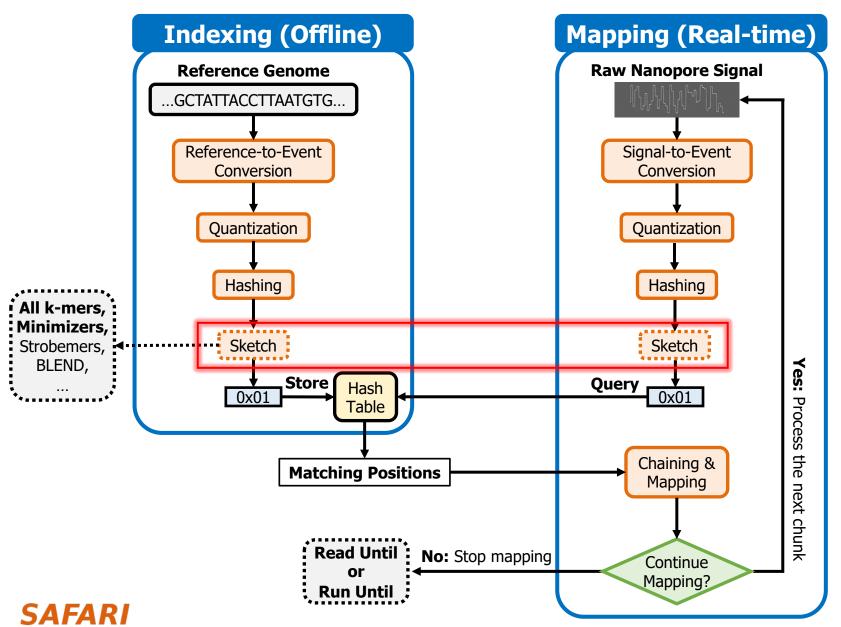
- Supports all major raw signal file formats and flow cell versions
 - FAST5, POD5, S/BLOW5 file formats
- Easy-to-use scripts
 - To download all the datasets
 - To reproduce all of our results
- You can write your outlier function for Sequence Until
 - Easily integrate Sequence Until
- Upcoming Feature:
 - Integrating the MinKNOW API



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



Sketching with Hash-based Indexing



Outline

Background

RawHash

Evaluation

Conclusion

Conclusion

Key Contributions:

- 1) The first hash-based mechanism that can quickly and accurately analyze raw nanopore signals for large genomes
- 2) The novel Sequence Until technique can accurately and dynamically stop the entire sequencing of all reads at once if further sequencing is not necessary

Key Results: Across 3 use cases and 5 genomes of varying sizes, RawHash provides

- 25.8× and 3.4× better average throughput compared to two state-of-the-art works
- 1.14x 2.13x more accurate mapping results for large genomes
- Sequence Until reduces the sequencing time and cost by 15×

Many opportunities for analyzing raw nanopore signals in real-time:

- Many hash-based sketching techniques can now be used for raw signals
- Indexing is very cheap: Many future use cases with the on-the-fly index construction
- We should rethink the algorithms to perform downstream analysis fully using raw signals



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Paper



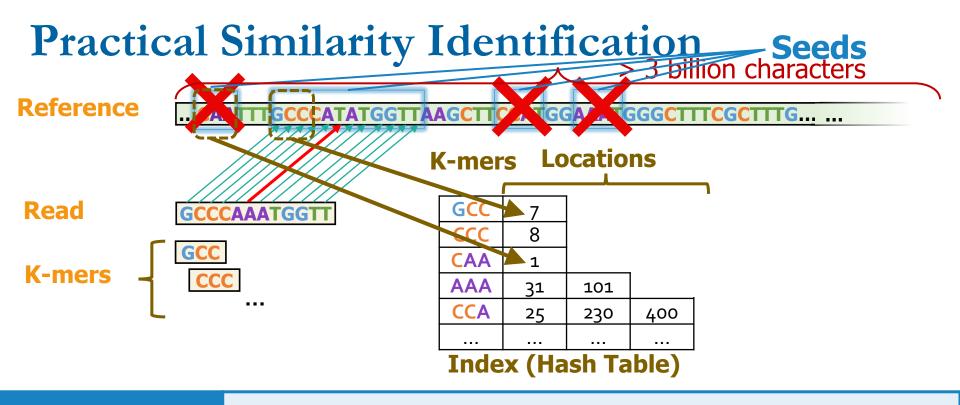
Code





Backup Slides





Seeding

Determine potential matching regions (seeds) in the reference genome

Seed Filtering (e.g., Chaining)

Prune some seeds in the reference genome

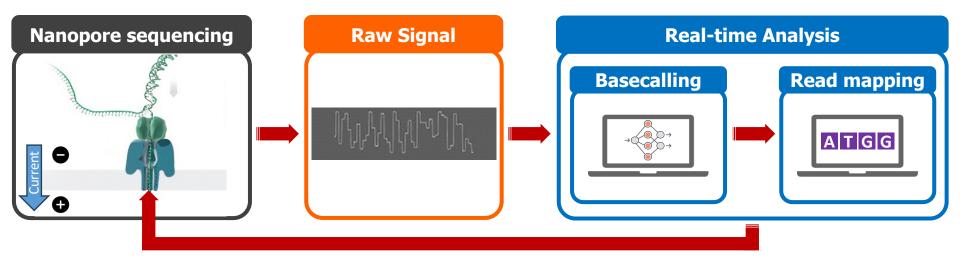
Alignment

Determine the exact differences between the read and the reference genome

SAFARI

Existing Solutions – Real-time Basecalling

Deep neural networks (**DNNs**) for translating **signals** to **bases**

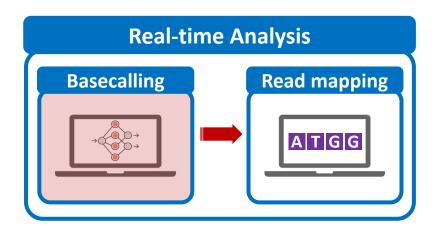


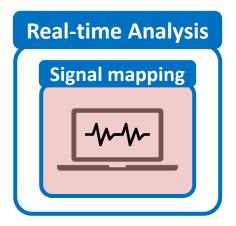
DNNs provide less noisy analysis from basecalled sequences

Costly and power-hungry computational requirements

The Problem

The existing solutions are ineffective for large genomes





Costly and energy-hungry computations to basecall each read:

Portable sequencing becomes challenging with resource-constrained devices

Larger number of reference regions cannot be handled accurately or quickly, rendering existing solutions ineffective for large genomes

Applications of Read Until

Depletion: Reads mapping to a particular reference genome is ejected

- Removing contaminated reads from a sample
- Relative abundance estimation
- Controlling low/high-abundance genomes in a sample
- Controlling the sequencing of depth of a genome

Enrichment: Reads **not** mapping to a particular reference genome is ejected

- Purifying the sample to ensure it contains only the selected genomes
- Removing the host genome (e.g., human) in contamination analysis

Applications of Run Until and Sequence Until

Run Until: Stopping the sequencing without informative decision from analysis

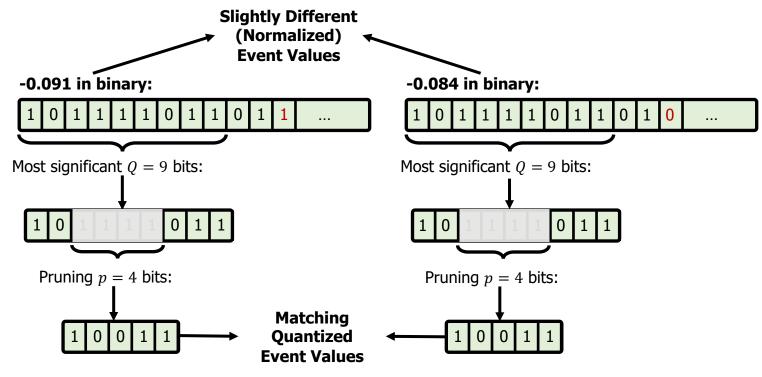
- Stopping when reads reach to a particular depth of coverage
- Stopping when the abundance of all genomes reach a particular threshold

Sequence Until: Stopping the sequencing based on information decision

- Stopping when relative abundance estimations do not change substantially (for high-abundance genomes)
- Stopping when finding that the sample is contaminated with a particular set of genomes
- •

Details: Quantizing the Event Values

- Observation: Identical k-mers generate similar raw signals
 - **Challenge:** Their corresponding event values can be slightly different
- **Key Idea:** Quantize the event values
 - To enable assigning the **same quantized value** to the **similar event values**



Average Sequenced Bases and Chunks

Tool	SARS-CoV-2	E. coli	Yeast	Green Algae	Human
	Average se	equenced ba	se length pe	r read	
UNCALLED	184.51	580.52	1,233.20	5,300.15	6,060.23
RawHash	513.95	1,376.14	2,565.09	4,760.59	4,773.58
	Average seque	enced numb	er of chunks	s per read	
Sigmap	1.01	2.11	4.14	5.76	10.40
RawHash	1.24	3.20	5.83	10.72	10.70

RawHash reduces sequencing time and cost for large genomes

up to **1.3**× compared to UNCALLED

Although Sigmap processes less number of chunks than RawHash, it fails to provide real-time analysis capabilities for large genomes

Breakdown Analysis of the RawHash Steps

	Fraction of entire runtime (%)							
Tool	SARS-CoV-2	E. coli	Yeast	Green Algae	Human			
File I/O	0.00	0.00	0.00	0.00	0.00			
Signal-to-Event	21.75	1.86	1.01	0.53	0.02			
Sketching	0.74	0.06	0.04	0.03	0.00			
Seeding	3.86	4.14	3.52	6.70	5.39			
Chaining	73.50	93.92	95.42	92.43	94.46			
Seeding + Chaining	77.36	98.06	98.94	99.14	99.86			

The entire runtime is **bottlenecked by the chaining step**

Required Computation Resources in Indexing

Tool	Contamination	SARS-CoV-2	E. coli	Yeast	Green Algae	Human	Relative Abundance
			CPU Ti	me (sec)			
UNCALLED	8.72	9.00	11.08	18.62	285.88	4,148.10	4,382.38
Sigmap	0.02	0.04	8.66	24.57	449.29	36,765.24	40,926.76
RawHash	0.18	0.13	2.62	4.48	34.18	1,184.42	788.88
			Real tir	ne (sec)			
UNCALLED	1.01	1.04	2.67	7.79	280.27	4,190.00	4,471.82
Sigmap	0.13	0.25	9.31	25.86	458.46	37,136.61	41,340.16
RawHash	0.14	0.10	1.70	2.06	15.82	278.69	154.68
			Peak men	nory (GE	3)		
UNCALLED	0.07	0.07	0.13	0.31	11.96	48.44	47.81
Sigmap	0.01	0.01	0.40	1.04	8.63	227.77	238.32
RawHash	0.01	0.01	0.35	0.76	5.33	83.09	152.80

The indexing step of RawHash is **orders of magnitude faster** than the indexing steps of UNCALLED and Sigmap, especially **for large genomes**

RawHash requires larger memory space than UNCALLED

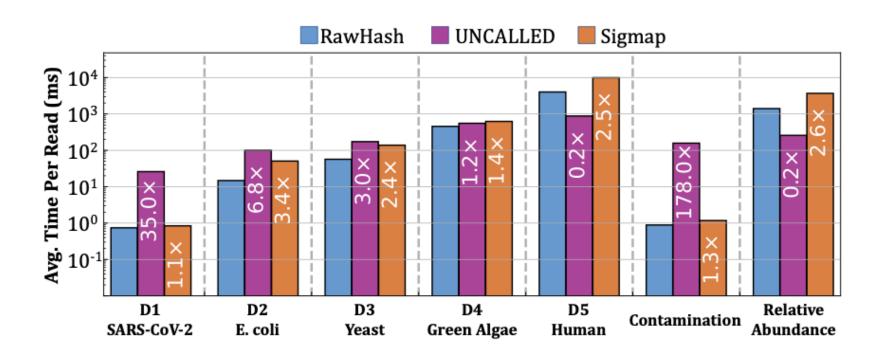
Required Computation Resources in Mapping

Tool	Contamination	SARS-CoV-2	E. coli	Yeast	Green Algae	Human	Relative Abundance
			CPU '	Time (sec)			
UNCALLED	265,902.26	36,667.26	35,821.14	8,933.52	16,769.09	262,597.83	586,561.54
Sigmap	4,573.18	1,997.84	23,894.70	11,168.96	31,544.55	4,837,058.90	11,027,652.91
RawHash	3,721.62	1,832.56	8,212.17	4,906.70	25,215.23	2,022,521.48	4,738,961.77
			Real	time (sec)			
UNCALLED	20,628.57	2,794.76	1,544.68	285.42	2,138.91	8,794.30	19,409.71
Sigmap	6,725.26	3,222.32	2,067.02	1,167.08	2,398.83	158,904.69	361,443.88
RawHash	3,917.49	1,949.53	957.13	215.68	1,804.96	65,411.43	152,280.26
			Peak m	emory (GB)			
UNCALLED	0.65	0.19	0.52	0.37	0.81	9.46	9.10
Sigmap	111.69	28.26	111.11	14.65	29.18	311.89	489.89
RawHash	4.13	4.20	4.16	4.37	11.75	52.21	55.31

The mapping step of RawHash is **significantly faster than Sigmap** for all genomes, and **faster than UNCALLED for small genomes**

RawHash requires larger memory space than UNCALLED

Average Mapping Time per Read



The mapping step of RawHash is **significantly faster than Sigmap** for all genomes, and **faster than UNCALLED for small genomes**



Parameter Configurations

Tool	Contamination	SARS-CoV-2	E. coli	Yeast	Green Algae	Human	Relative Abundance
RawHash	-x viral -t 32	-x viral -t 32	-x sensitive -t 32	-x sensitive -t 32	-x fast -t 32	-x fast -t 32	-x fast -t 32
UNCALLED		map -t 32					
Sigmap	-m -t 32						
Minimap2	-x map-ont -t 32						

Preset (-x)	Corresponding parameters	Usage
viral	-e 5 -q 9 -1 3	Viral genomes
sensitive	-e 6 -q 9 -1 3	Small genomes (i.e., < 50M bases)
fast	-e 7 -q 9 -1 3	Large genomes (i.e., > 50M bases)



Versions

Tool	Version	Link to the Source Code
RawHash	0.9	https://github.com/CMU-SAFARI/RawHash/tree/8042b1728e352a28fcc79c2efd80c8b631fe7bac
UNCALLED	2.2	https://github.com/skovaka/UNCALLED/tree/74a5d4e5b5d02fb31d6e88926e8a0896dc3475cb
Sigmap	0.1	https://github.com/haowenz/sigmap/tree/c9a40483264c9514587a36555b5af48d3f054f6f
Minimap2	2.24	https://github.com/lh3/minimap2/releases/tag/v2.24
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Enabling Fast and Accurate Real-Time Analysis of Raw Nanopore Signals for Large Genomes

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Gagandeep Singh

Onur Mutlu



Paper



Code



