

Pangenome-based characterization of novel genetic variants



Background

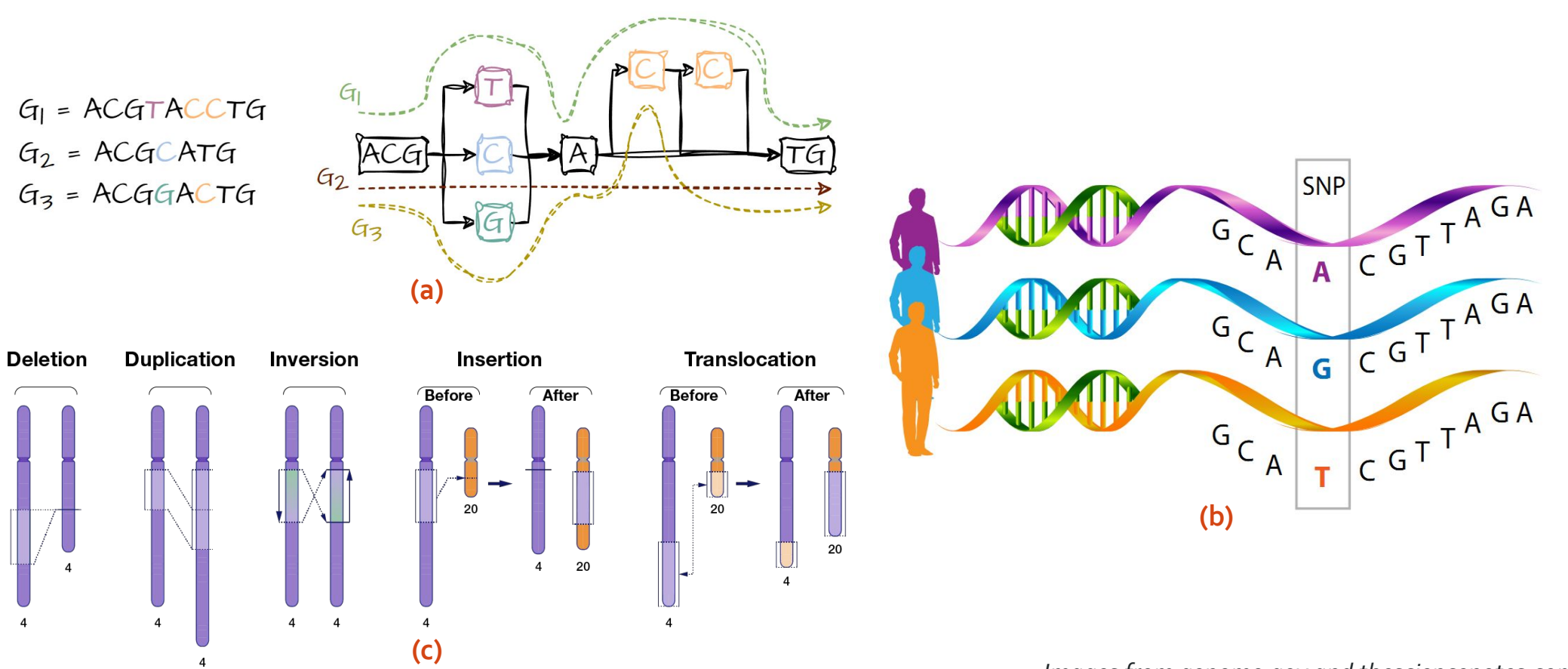
(a) **Pangenome**: collection of genomes from a population
→ helps in reducing the "reference-bias"

(b) **Short Variants**: SNPs/indels

- health and disease (e.g., diabetes)
- drug response
- other phenotypic traits

(c) **Structural Variants**: big (≥ 50 bp) rearrangements

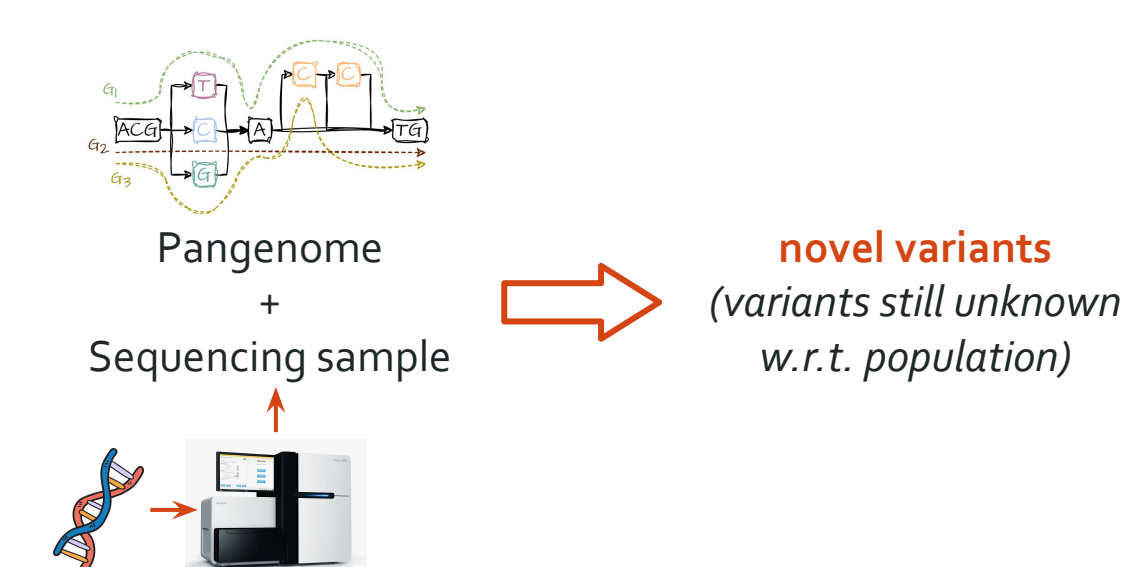
- genetic disorders (e.g., autism, schizophrenia...)
- cancer (e.g., melanoma, breast, prostate...)



Images from [genome.gov](https://www.genome.gov) and [thesciencenotes.com](https://www.thesciencenotes.com)

Goal

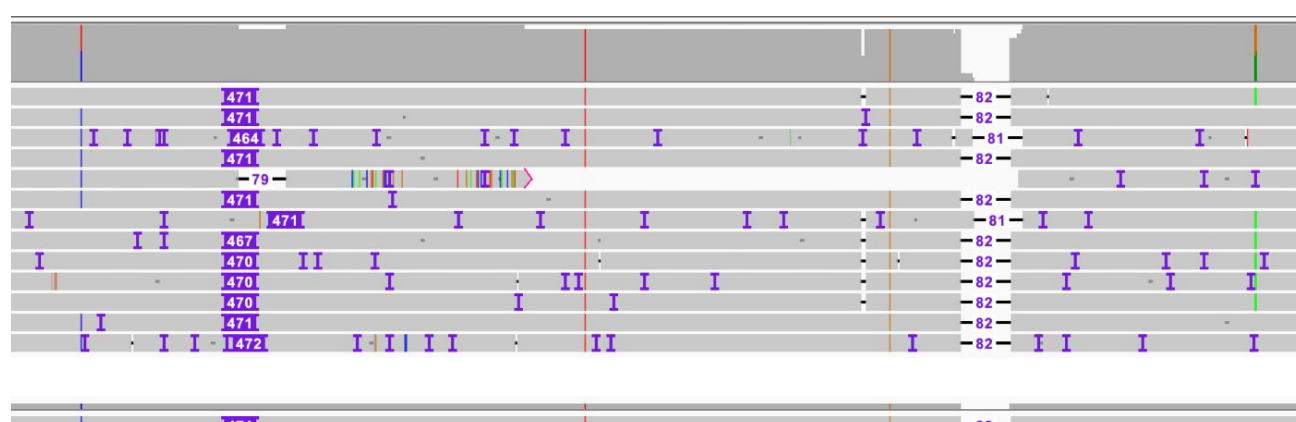
"Joint variant calling and pangenome augmentation"
pangenome-based, assembly-free, and mapping-free



State-of-the-art

A lot of **reference-based** approaches

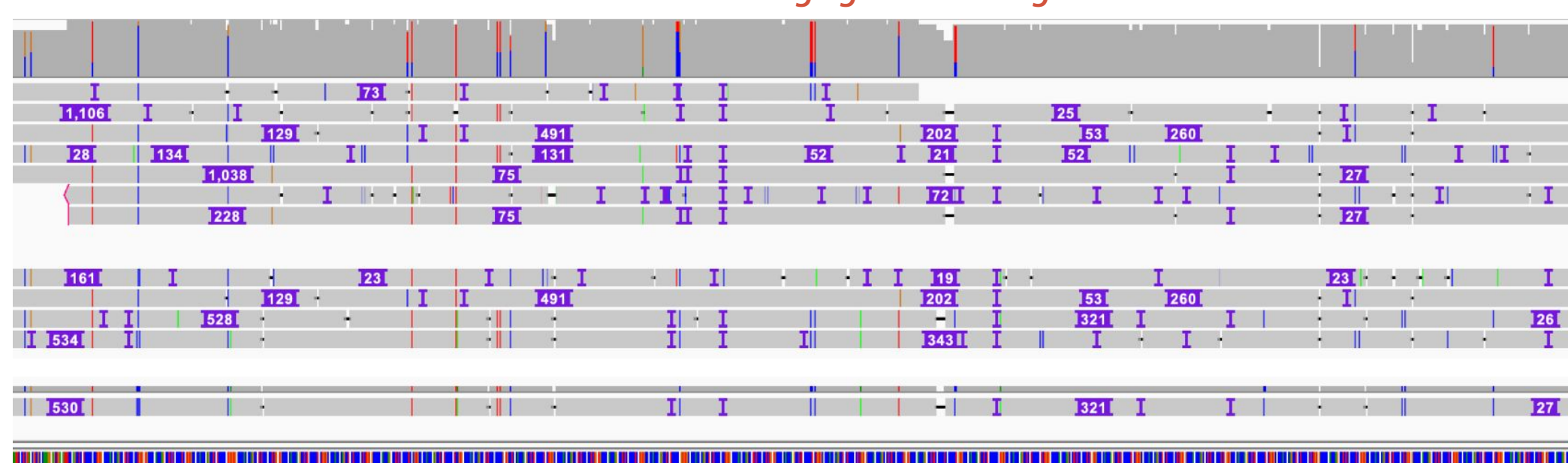
- short reads alignment (X inaccurate)
 - ...
- long reads alignment (X "inaccurate")
 - SVIM [Bioinformatics, 2019]
 - cuteSV [Genome Biology, 2020]
 - SVDSS [Nature Methods, 2023]
 - sniffles2 [Nature Biotechnology, 2024]
 - ...
- genome assembly (X expensive)
 - dipcall [Nature Methods, 2018]
 - PAV [Science, 2021]
 - VolcanoSV [Nature Communication, 2024]
 - ...



Few **pangenome-based** approaches (X expensive) [bioRxiv, 2024]

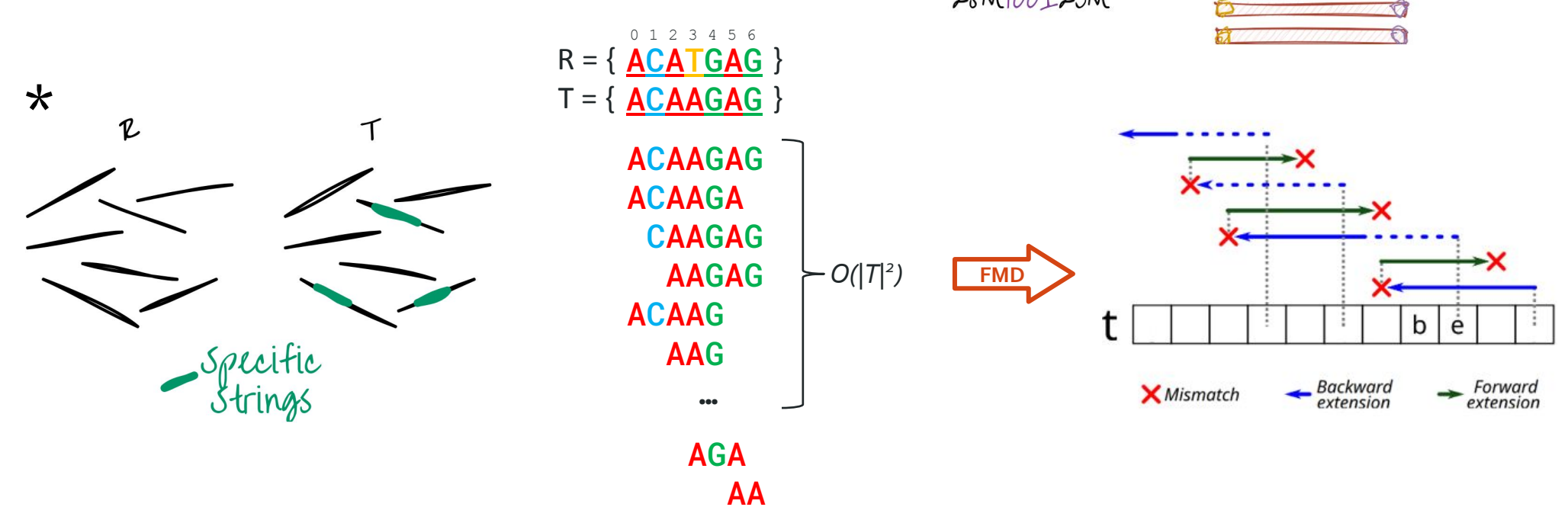
- based on genome assembly and read alignments to graphs

But what about Challenging Genomic Regions?



Approach

- index pangenome
- compute **specific strings**
- anchor specific strings to graph
- cluster specific strings
- "summarize" clusters
- realign consensus back to local graph
- augment graph and get variations

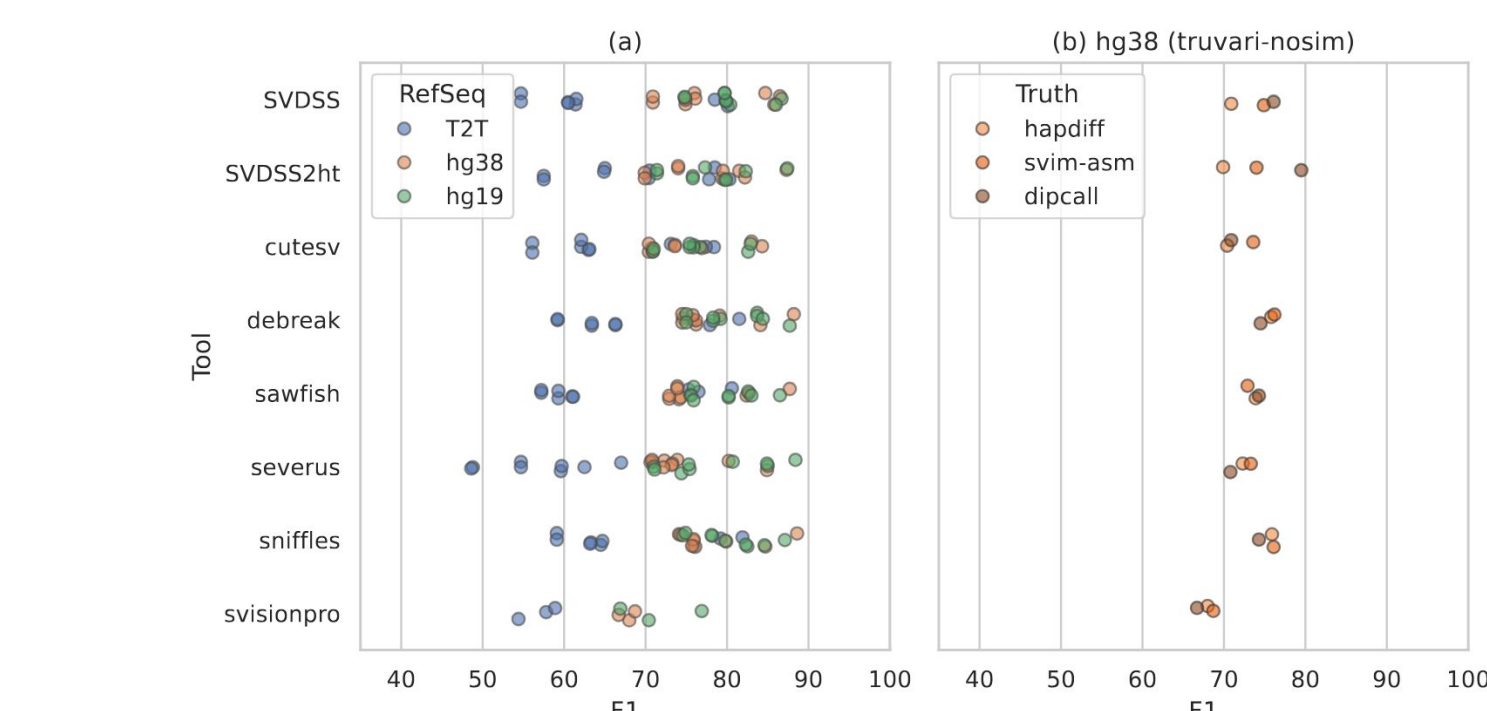


Denti et al. Pangenome graph augmentation from unassembled long reads. bioRxiv (2025)

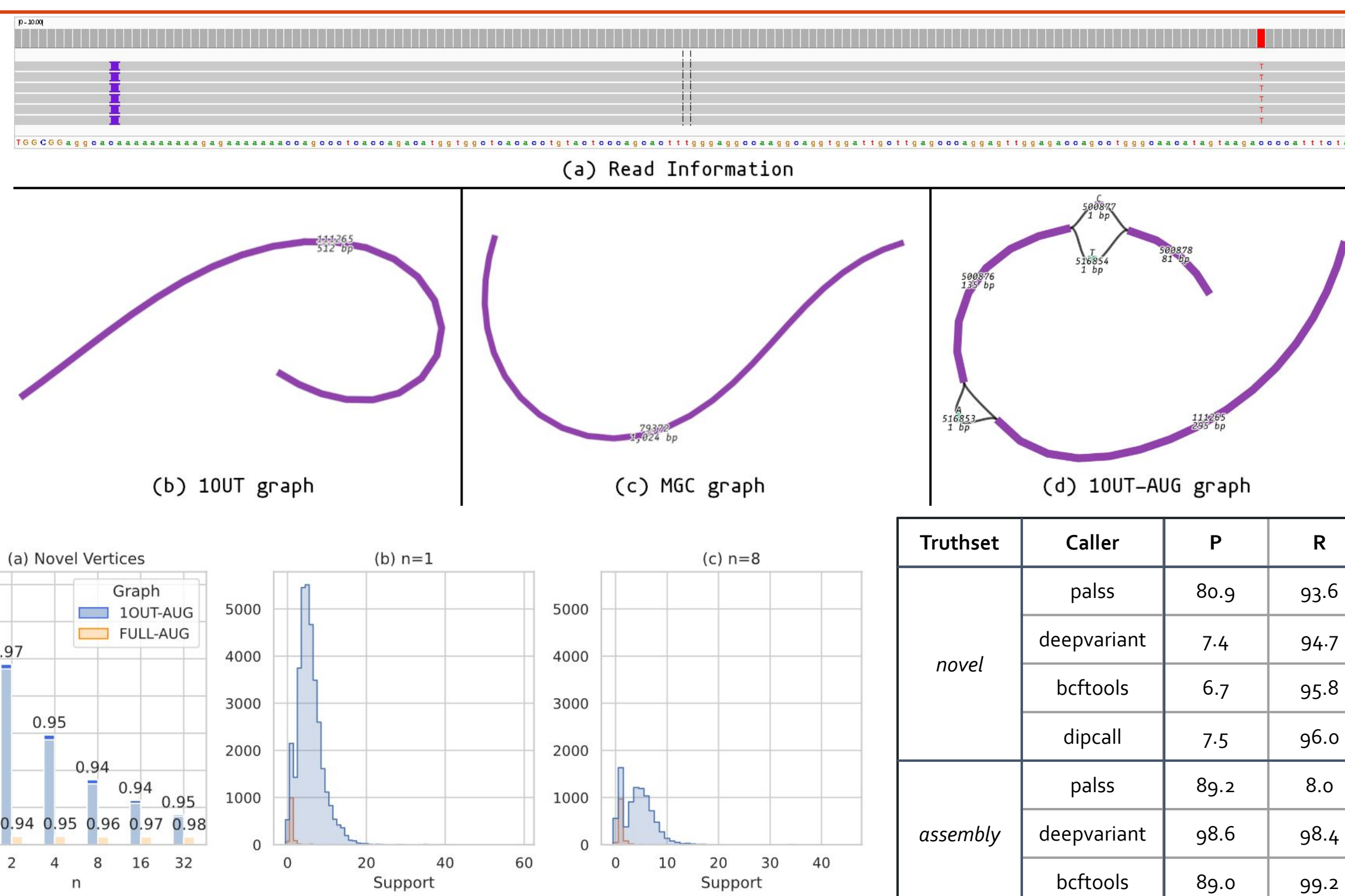
Results

Currently testing C++ implementation on HPRC pangenomes and simulated PacBio HiFi data

- ⇒ augmentation is effective (+15 challenging regions with 65 specific variants w.r.t. assembly-based)
- ⇒ good precision (although there is still room for improvements)
- ⇒ promising results on novel SNP calling
- ⇒ SVs evaluation under investigation (although particularly complex*)



*Denti et al. Anyone can be the best: Impact of diverse methodologies on the evaluation of structural variant callers. bioRxiv (2025)



Truthset	Caller	P	R	F1
novel	palss	80.9	93.6	86.8
	deepvariant	7.4	94.7	13.7
	bcftools	6.7	95.8	12.6
	dipcall	7.5	96.0	13.9
assembly	palss	89.2	8.0	14.7
	deepvariant	98.6	98.4	98.5
	bcftools	89.0	99.2	93.8

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