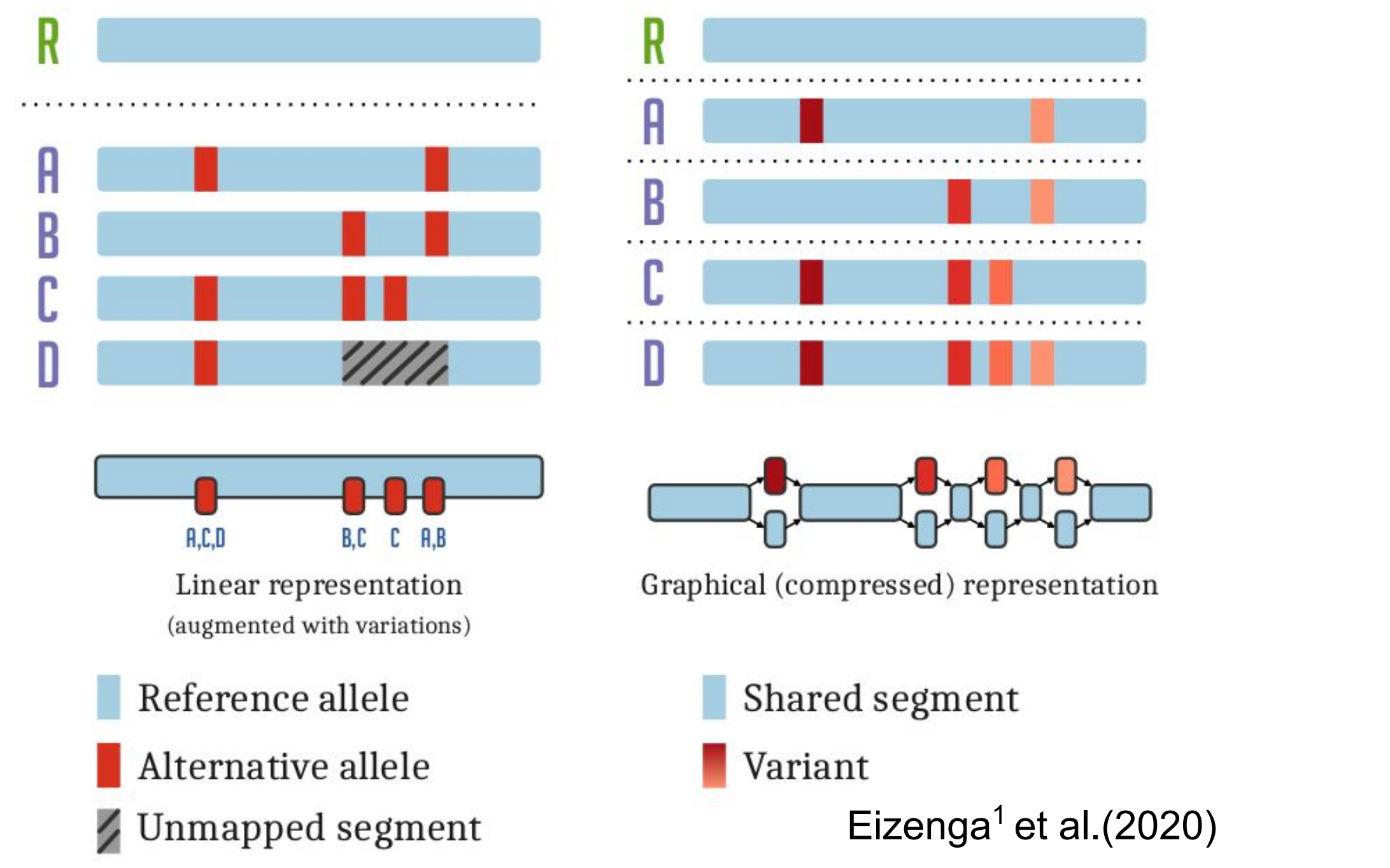
Scalable variant detection in pangenome models

Francesco Porto [a] , Flavia Villani [b], Andrea Guarracino [c], Christian Fischer [d], Hao Chen [e], Robert W. Williams [d] ,
Vincenza Colonna [b], Gianluca Della Vedova [a] , Erik Garrison [f] , and Pjotr Prins [d]

[a] Department of Informatics, Systems, and Communication, University of Milano-Bicocca, Italy, [b] National Research Council, Institute of Genetics and Biophysics 'A.Buzzati-Traverso', Naples, Italy, [c] Centre for Molecular Bioinformatics, Department of Biology, University Of Rome Tor Vergata, Rome, Italy, [d] Department of Genetics, Genomics and Informatics, College of Medicine, UTHS, [e] Department of Pharmacology, Addiction Science, and Toxicology, The University of Tennessee Health Science Center, Memphis, TN, USA, [f] Genomics Institute, University of California Santa Cruz, Santa Cruz, CA, United States.

We have implemented a two-step scalable approach to detect variants: first we construct a graph pangenome from a graphical fragment assembly (GFA) file that stores the fragments, where each fragment corresponds to a vertex of the graph, then we analyze the graph to detect all variants. We have tested our approach on a SARS-CoV-2 dataset with over 7800 fragments and on a dataset that contains all alternative sequences of the highly polymorphic human leukocyte antigen (HLA) complex.

Variation Graphs encode pangenomes



Eizenga[1] et al.(2020)

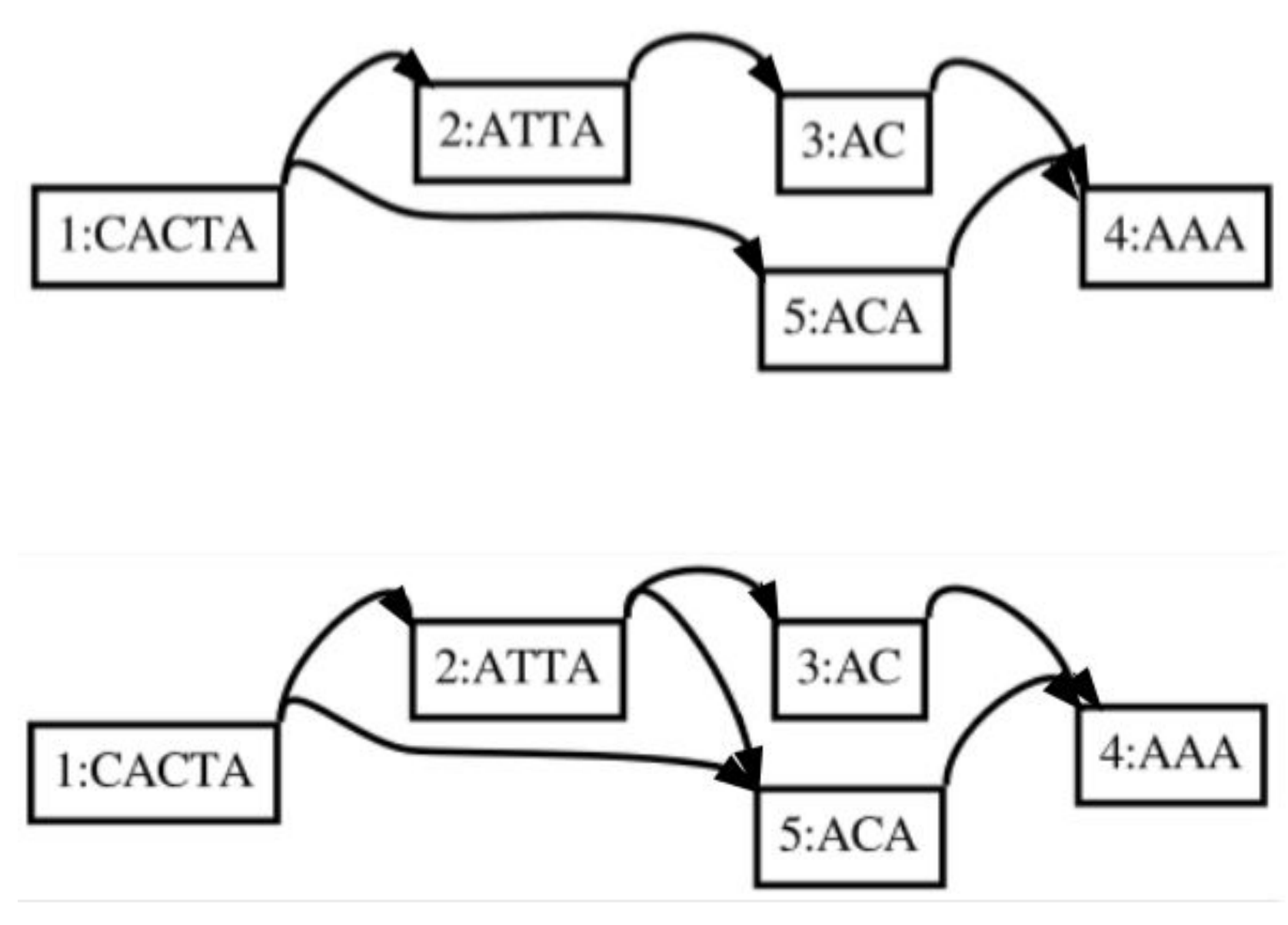
A graphical pangenome [1] models the full set of genomic elements in a given species or clade.

The *variation graph* data model describes the all-to-all alignment of many sequences (genomes or genes for instance) as walks through a graph whose nodes are labeled with DNA sequences.

Bubbles

In pangenome variation graphs, genetic variants appear as bubbles and ultrabubbles [2] (nested bubbles). These sites have a common starting context, a common exit point, and multiple possible paths that connect the two. Each path represents an allele.

Bubble



Ultrabubble

HandleGraph interface

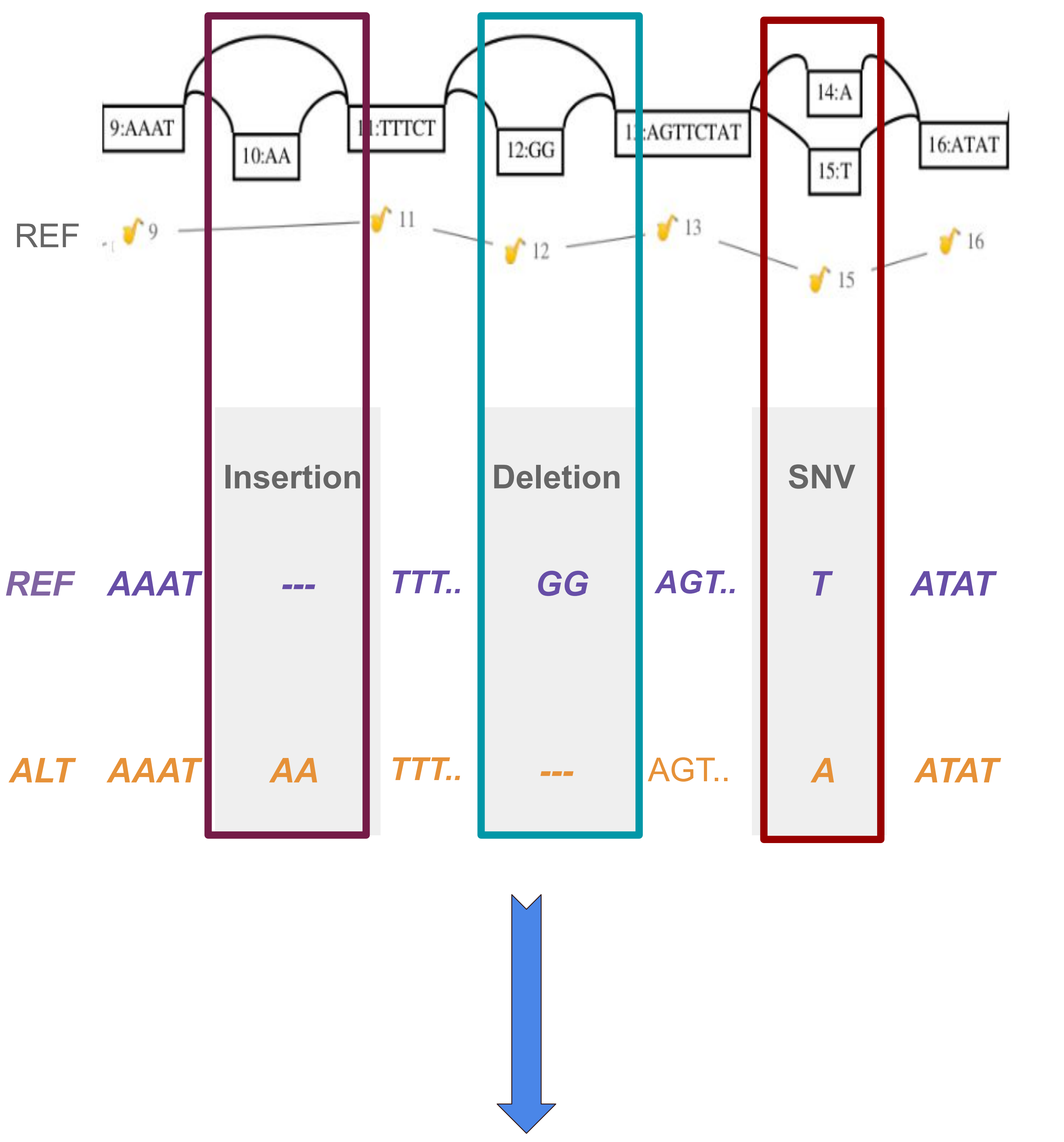
A compact and efficient data structure to represent large genomic variation graphs. ODGI (**Optimized Dynamic Graph Implementation)** is a library implementing the HandleGraph interface with minimum memory overhead. This has required a careful encoding of the graph components

Why Rust?

Rust is a programming language focused on performance and safety.

- Great ***ecosystem*** (Cargo, crates.io, docs.rs).
- Much ***safer*** than C++ while having a similar ***speed.***
- Friendly and helpful ***community.***
- Used in many open source projects, such as **Firefox.**

Variant detection in variation graphs



#CHROM	POS	ID	REF	ALT	INFO
x	6	.	--	AA	TYPE=ins
x	13	.	GG	--	TYPE=del
x	22	.	T	A	TYPE=snv

Code available at
https://github.com/HopedWall/rs-gfatovcf

Dataset HLA-DRB1-3123 Pangen]ome

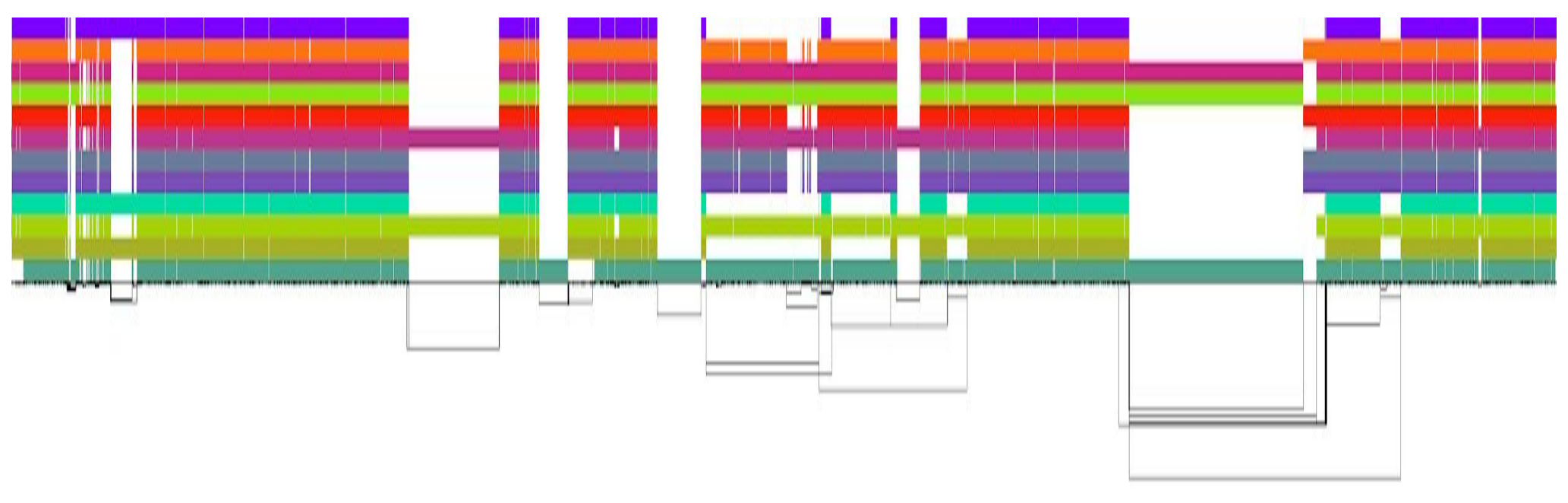


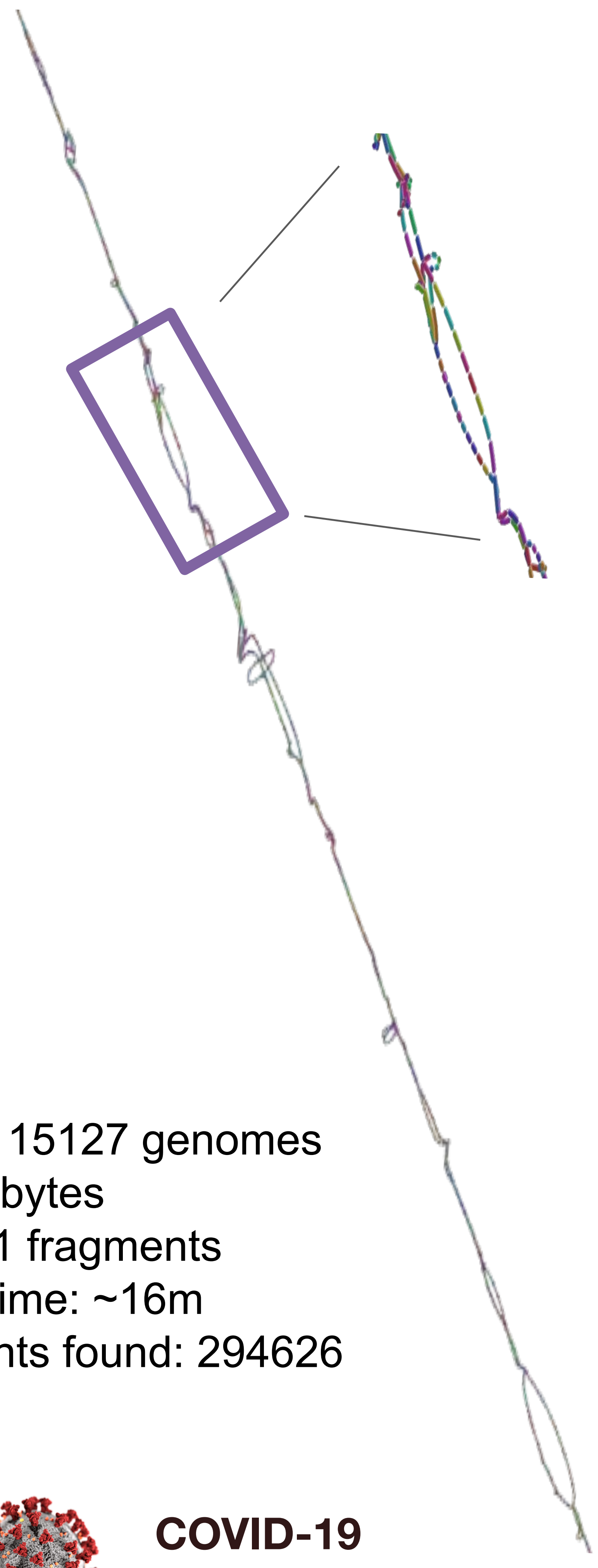
Image obtained via https://github.com/vgteam/odgi

- From 12 sequences
- Size: 163416 nucleotides
- Run time: ~0.1s
- Variants found: 7505

Data available at
https://github.com/ekg/HLA-zoo

Image obtained via
https://rrwick.github.io/Bandage/

Dataset SARS-CoV-2 Pangenome



- From 15127 genomes
- 1.2 Gbytes
- 78571 fragments
- Run time: ~16m
- Variants found: 294626

COVID-19
PubSeq

Data available at
http://covid19.genenetwork.org/

Future work

- Parallel implementation to improve its speed.
- Identification of complex bubbles (Superbubbles, Ultrabubbles, and Cacti).

References

1. Eizenga et al. (2020). Pangenome graphs. *Annual Reviews of Genomics and Human Genetics*. 21.
2. Paten, Benedict, et al. "Superbubbles, ultrabubbles, and cacti." *Journal of Computational Biology* 25.7 (2018): 649-663.