Aligning pangenomes with hierarchical wavefront algorithm

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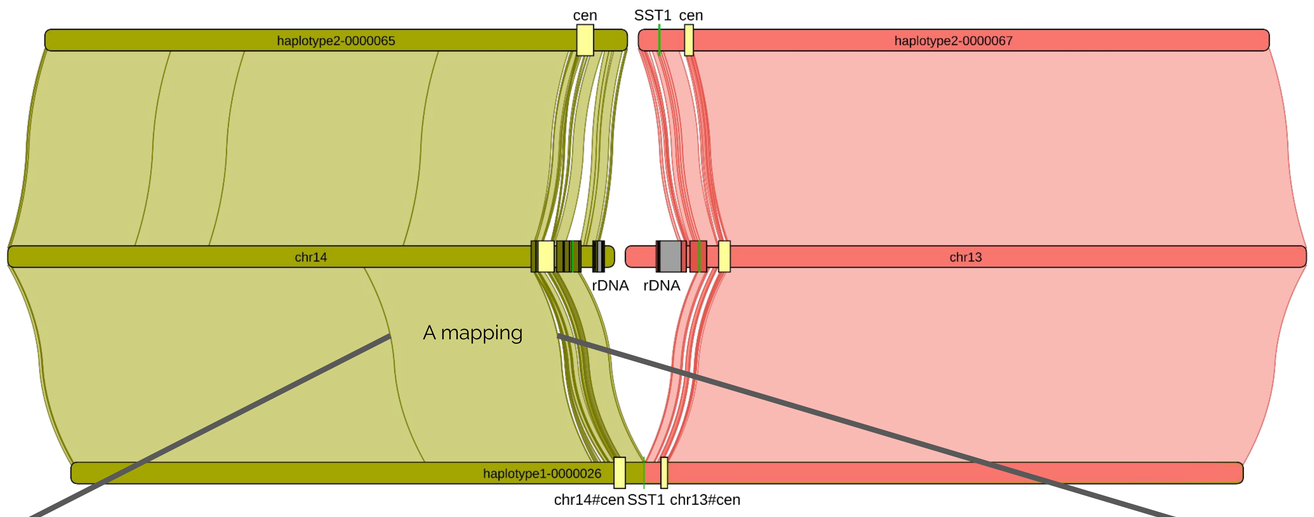
1) Introduction

- **Sequence alignment** is a core task in bioinformatics.
- Due to the computational complexity of exact alignment, **heuristic methods** are closely tied to the sequence types being considered.
- **Seeding and extension** strategies are driven by seeds that are chained and filtered to find candidate regions for base-level alignment.
- Increasing read lengths and availability of big whole-genome assemblies rendered such approaches **overly sensitive**.
- The dramatic **increase in scale** poses significant challenges for current methods.

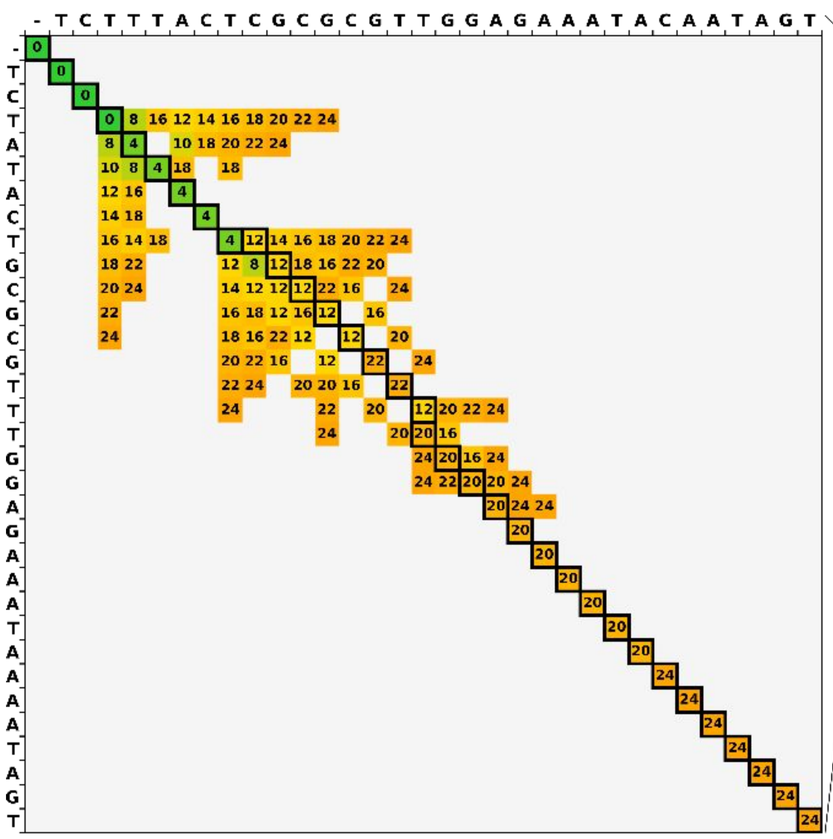
Sequence mappings between human acrocentric chromosomes

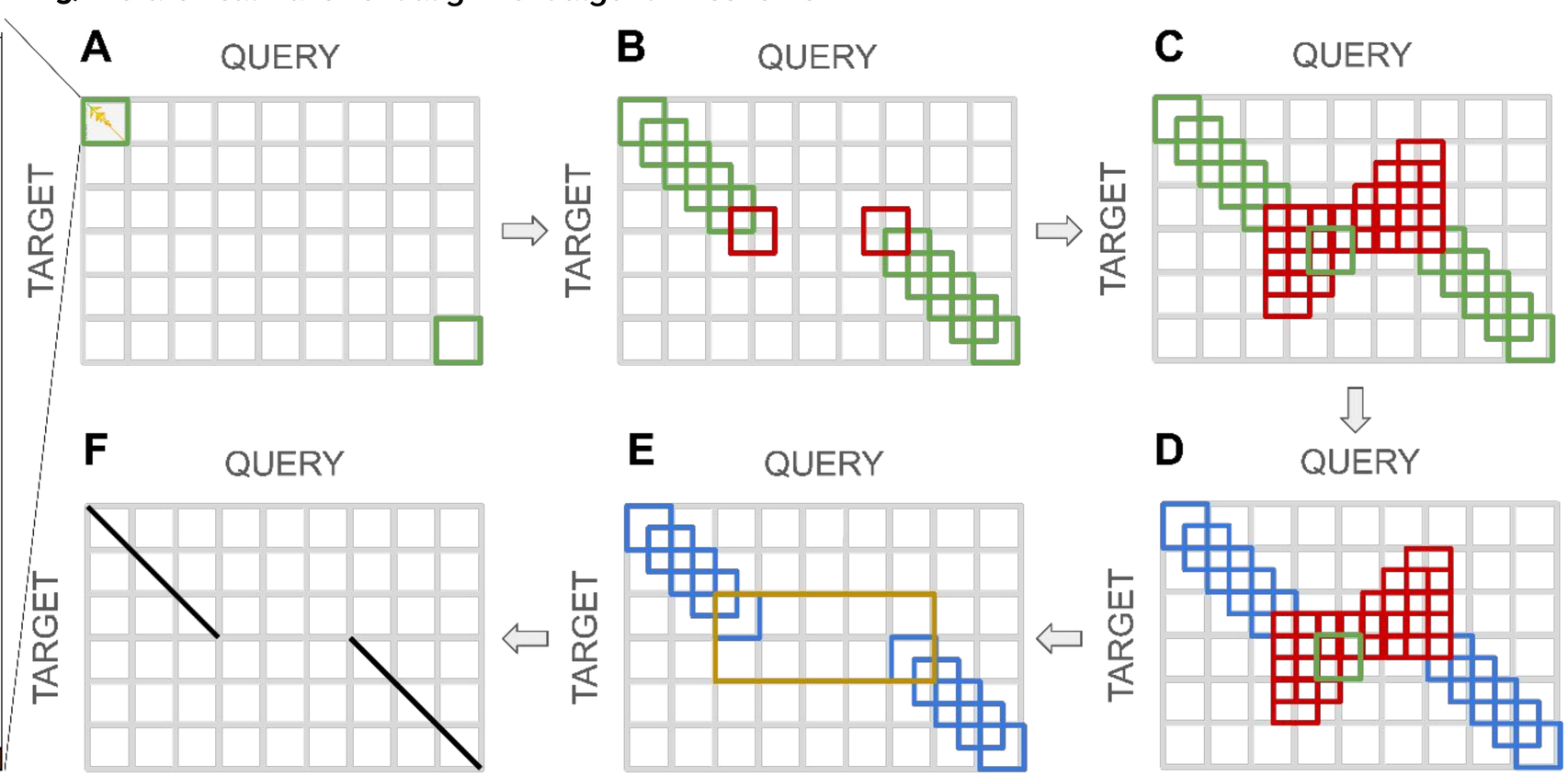


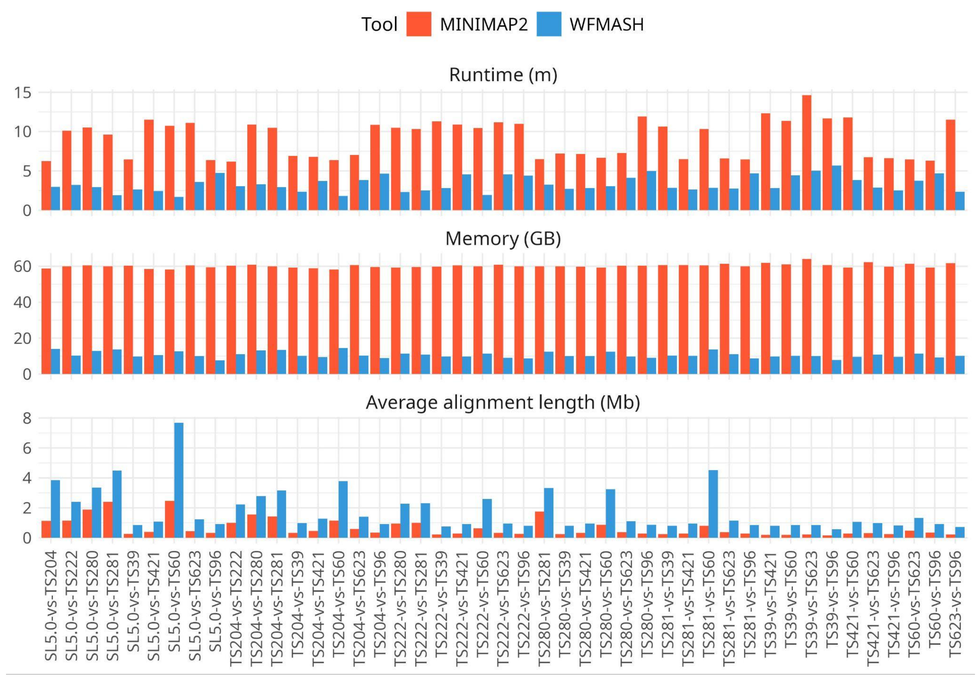
2) Method

- We improve alignment performance for this new scale by **sparsifying** key information that drives mapping and alignment.
- We present **WFMASH**[1], a **sequence aligner** for large pangenomes.
- WFMASH leverages a 2-step strategy:
  a) It first applies a locality-sensitive hashing algorithm, adapted from MashMap[2,3], to determine **syntenic region boundaries** (aka mappings) between long DNA sequences;
  b) Then, a **hierarchical implementation of the wavefront alignment (WFA) algorithm**[4,5] allows computing the base-level alignment of the identified regions.

3) Hierarchical wavefront alignment algorithm scheme

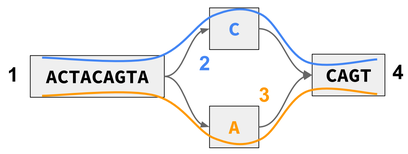




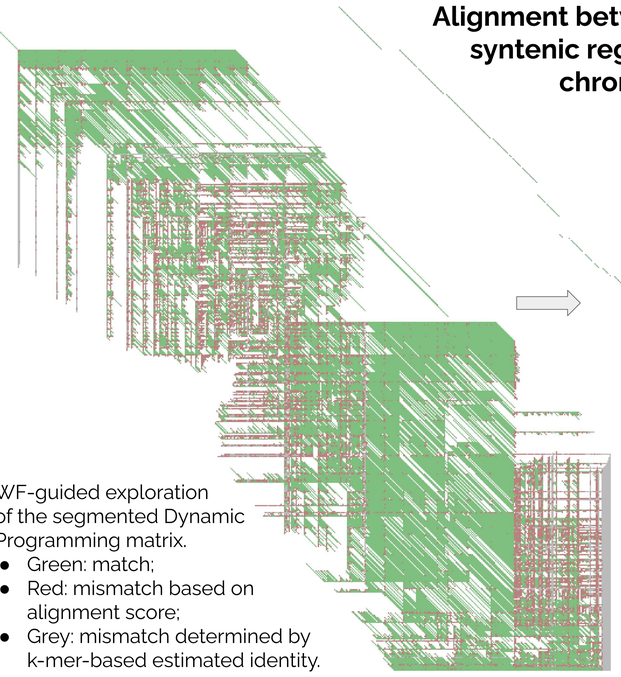


4) Results

- With a **plant pangenome** made with 10 **tomato** haploid assemblies, WFMASH computes the all-vs-all alignment ~2.7X faster than MINIMAP2[6], on average, while requiring ~5.6X less memory and aligning longer sequences.
- With an **inter-species pangenome** made with 16 **primates** assemblies (from *Homo sapiens*, *Gorilla gorilla*, *Pan paniscus*, *Pan troglodytes*, *Pongo abelii*, *Pongo pygmaeus*, *Symphalangus syndactylus*), WFMASH computes the all-vs-all alignment in 70 hours using 128 threads on an AMD EPYC 7742 64-Core processor, with a memory peak of 202 GB.
- We use WFMASH in the Pangenome Graph Building (PGGB) pipeline[7,8] to build unbiased **pangenome variation graphs**.



Alignment between two 70 kbp long syntenic regions of two human chromosomes 13



Segments belonging to the final optimal alignment.

WF-guided exploration of the segmented Dynamic Programming matrix.

- Green: match;
- Red: mismatch based on alignment score;
- Grey: mismatch determined by k-mer-based estimated identity.

1. WFMASH GitHub repository: https://github.com/waveygang/wfmash
2. Chirag Jain et al., 2018. A fast adaptive algorithm for computing whole-genome homology maps. Bioinformatics
3. Bryce Kille et al., 2023. Minmers are a generalization of minimizers that enable unbiased local Jaccard estimation. Bioinformatics
4. Santiago Marco-Sola et al., 2020. Fast gap-affine pairwise alignment using the wavefront algorithm
5. Santiago Marco-Sola, et al., 2023. Optimal gap-affine alignment in O(s) space. Bioinformatics
6. Heng Li, 2018. Minimap2: pairwise alignment for nucleotide sequences. Bioinformatics
7. Erik Garrison and Andrea Guarracino, 2023. Unbiased pangenome graphs. Bioinformatics
8. Erik Garrison, Andrea Guarracino et al., 2024. Building pangenome graphs, bioRxiv

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