Algorithms for Pan-genome Computational Analysis

Founder set construction under allelic and non-allelic homologous recombination

Konstantinn Bonnet, Daniel Dörr, Tobias Marschall
Institute for Medical Biometry and Bioinformatics
Düsseldorf, Germany

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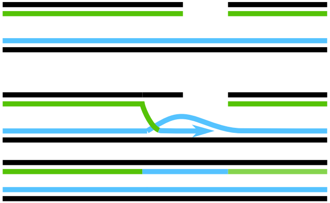
Outline

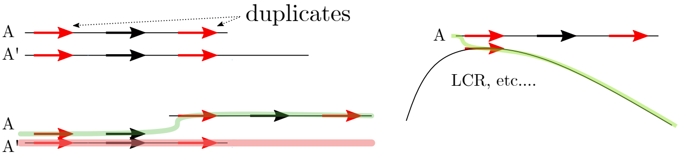
- Homologous recombinations
- A recombination model
- The Founder Set problem
- Minimizing recombinations in founder sets
- Results

EU's Horizon 2020 / ITN MCSA GA No 956229

Homologous recombination



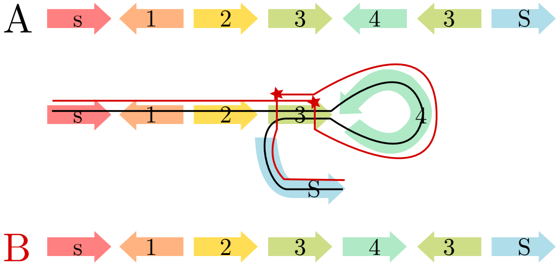
Allelic HR



Non-allelic HR

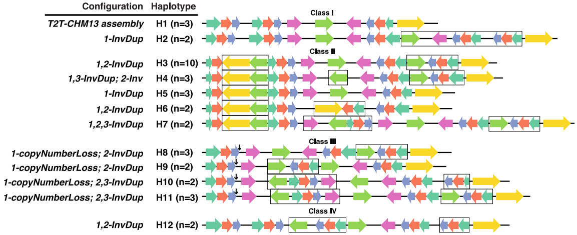
- Double strand-breaks during DNA replication
- Repair: highly similar segments picked by mistake
- Leads to duplications, deletions, and other complex rearrangements

Modeling inversions



- Can be modeled with HR
- Using flanking inverted repeats

Rearrangements in 1p36.13



Configuration	Haplotype
T2T-CHM13 assembly	H1 (n=3)
1-InvDup	H2 (n=2)
1,2-InvDup	H3 (n=10)
1,3-InvDup; 2-Inv	H4 (n=3)
1-InvDup	H5 (n=3)
1,2-InvDup	H6 (n=2)
1,2,3-InvDup	H7 (n=2)
1-copyNumberLoss; 2-InvDup	H8 (n=3)
1-copyNumberLoss; 2-InvDup	H9 (n=2)
1-copyNumberLoss; 2,3-InvDup	H10 (n=2)
1-copyNumberLoss; 2,3-InvDup	H11 (n=3)
1,2-InvDup	H12 (n=2)

- AHR and NAHR play a major role in genomic rearrangements
- Important targets for study in complex loci

→ New model handling both AHR and NAHR, and which can represent complex rearrangements

[2] Porubsky, Höps, Ashraf et al. Haplotype-resolved inversion landscape reveals hotspots of mutational recurrence associated with genomic disorders Cell, 2022

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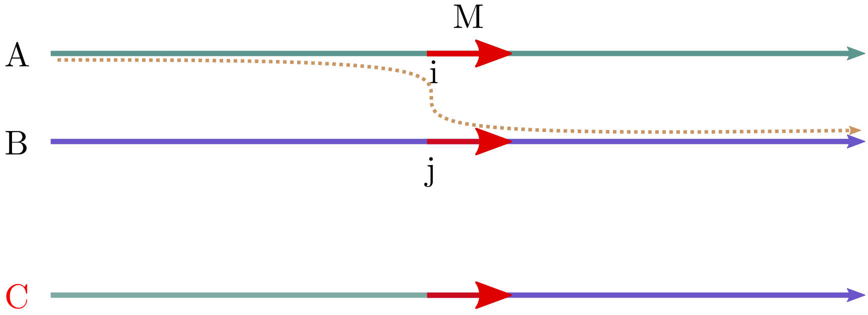
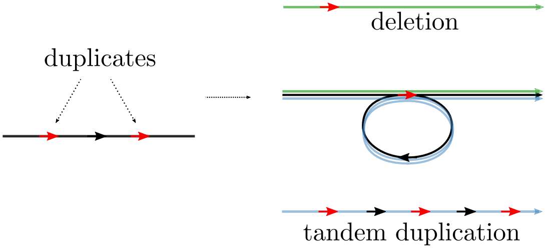
The homologous recombination operation



Acts between **two haplotypes** on a **shared segment**
→ Result: **concatenation** of the **suffix** of one and **prefix** of the other

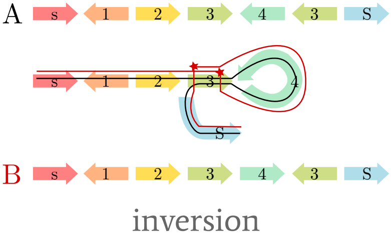
Modeling rearrangements



duplicates

deletion

tandem duplication



inversion

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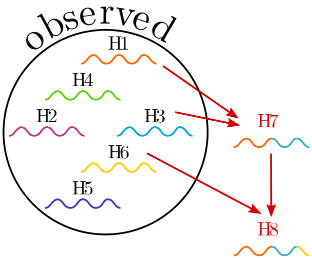
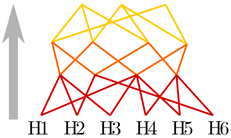
Recombining in a sample



Recombining pairs
to construct **new haplotypes**



Recombining pairs
to construct **observed haplotypes**

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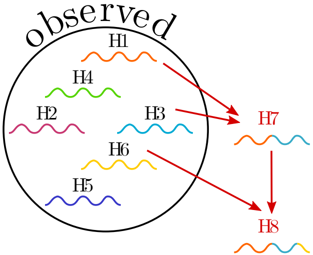
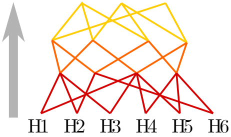
Recombining in a sample

Founder Set problem: find a **generator of minimal size** of the set of haplotypes





Recombining pairs to construct **new haplotypes**

Recombining pairs to construct **observed haplotypes**

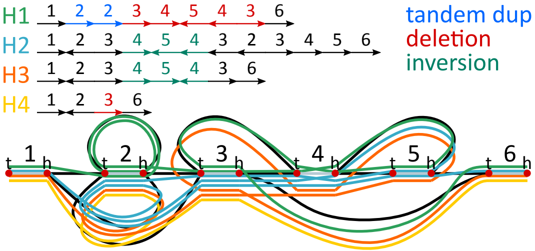
Full algorithmic details: paper

Constructing founder sets under allelic and non-allelic homologous recombination

https://doi.org/10.1101/2022.05.27.493721

Variation graphs

Input: set of haplotypes + their variation graph

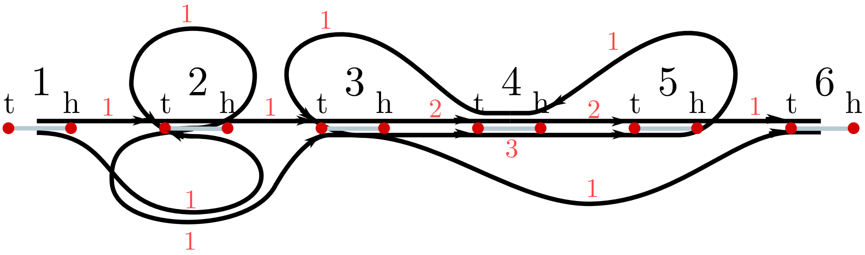


- Nodes and edges: homologous DNA segments and their adjacencies
- Haplotypes: walks from one extremity to the other (source, sink)
- Every edge of the graph is covered by at least one haplotype (by constrution)

A network flow solution

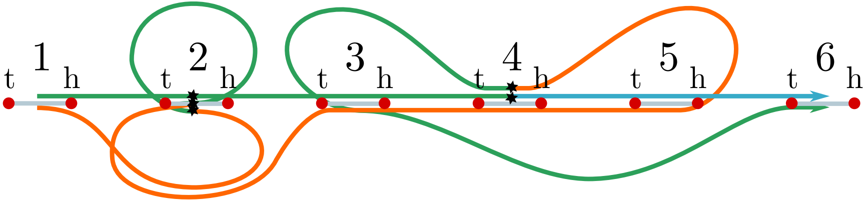
→ Formulation as a network flow problem:
Minimize total flow + constraints to ensure valid haplotypes

Total (incoming) flow at (the tail of) the sink = minimal founder set size



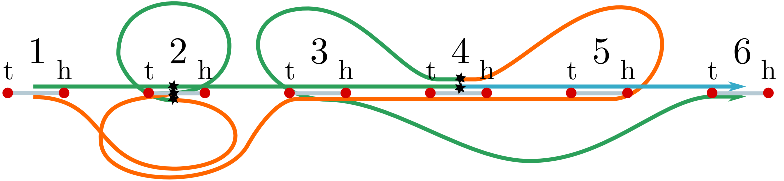
Solution to the Founder Set problem

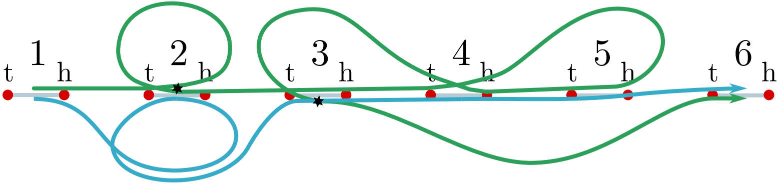
Once founder sequences are constructed → minimal set of founders



Solution to the Founder Set problem

But... is it good enough?





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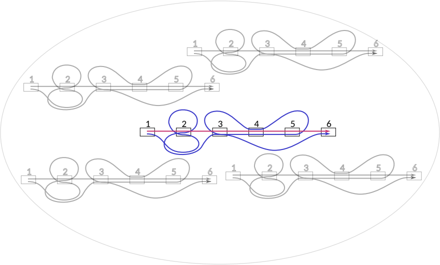
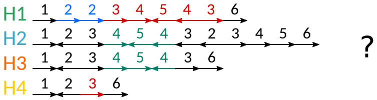
One does not simply construct founder sequences...





Structure, number of recombinations?

Haplotype information?

Next question: what is the most parsimonious founder set?

→ Given a flow solution:

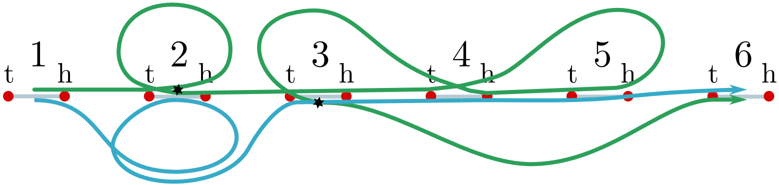
Derive a founder set that **minimizes the recombinations** wrt. the set of haplotypes.

Proposed solution: ILP

Define **minimization problem** on a given flow solution

- Add nodes to the flow graph for marker multiplicities
- Constraints for validity + recombination detection
- Once a solution is computed, extract founder sequences

Solution: **haplotype coloring** and a **minimal number of recombinations**



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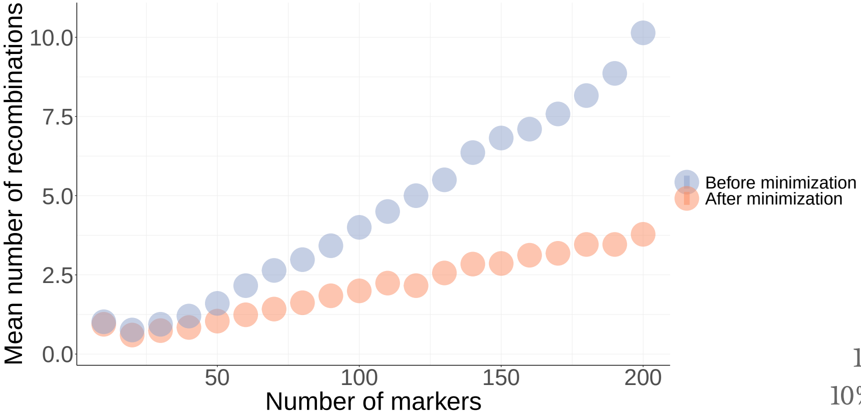
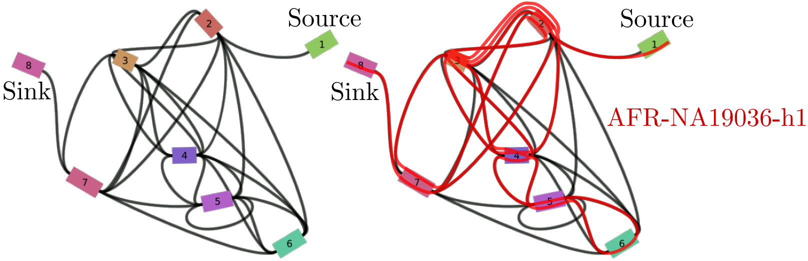
Number of recombinations

Experiments: simulated arbitrary graph (parameterizable) + haplotypes



10 haplotypes
10% dup. and inv.

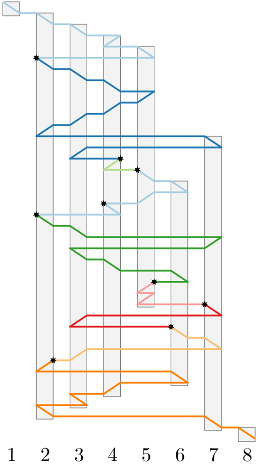
Application: 1p36.13



Visualization with Bandage:
8 nodes, 26 edges, 68 haplotypes + CHM13 reference

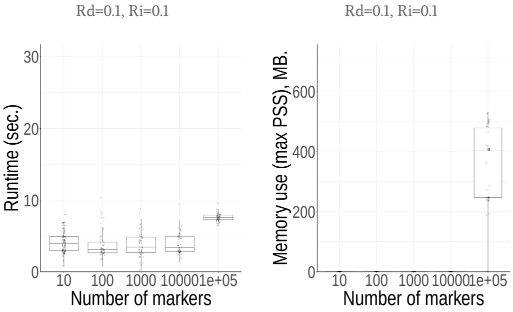
Data provided by Feyza Yilmaz (Jackson Labs).

Application: 1p36.13

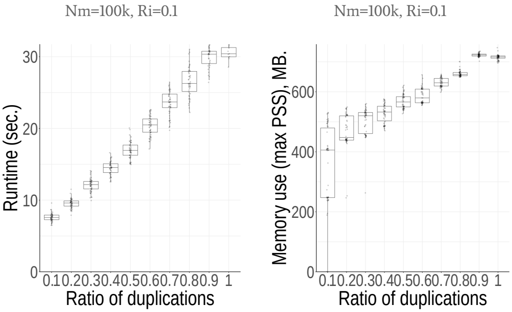


- Single founder sequence
- 9 recombinations between 8 haplotypes
- Minimization time: 60.3 seconds, peak PSS of 225MB.

Benchmark: flow solution

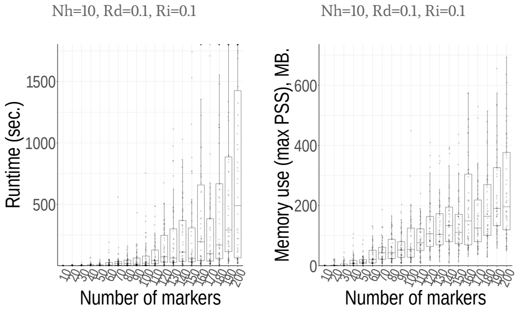


Number of markers

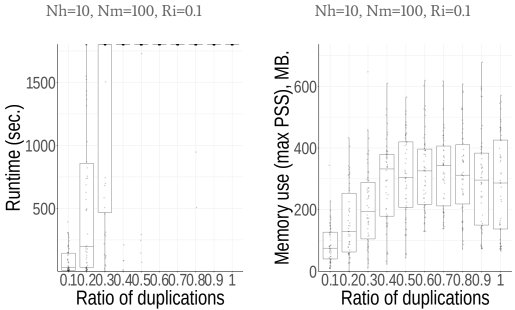


Ratio of duplications

Benchmark: minimization



Number of markers



Ratio of duplications

Conclusion and outlook

A new framework to solve a biologically relevant problem

- A solution to the founder set problem, and a decent one for minimizing the number of recombinations
- Work in progress, but promising with real biological data

Next step:

Find a founder set st. the number of recombinations **within the haplotypes** is minimal wrt. the founder sequences

Availability: `https://github.com/marschall-lab/hrfs`
written in Rust, experiments available as snakemake workflows.

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Thank you!

Bibliography

[1] R. R. Wick et al. ``Bandage: interactive visualization of de novo genome assemblies''. In: Bioinformatics 31.20 (June 2015), pp. 3350–3352. ISSN: 1367-4803. DOI: 10.1093/bioinformatics/btv383. eprint: https://academic.oup.com/bioinformatics/article-pdf/31/20/3350/17088082/btv383.pdf. URL: https://doi.org/10.1093/bioinformatics/btv383.

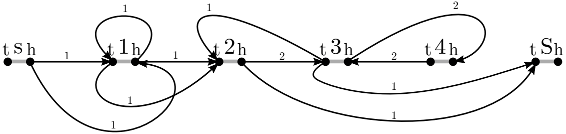
[2] D. Porubsky et al. ``Recurrent inversion polymorphisms in humans associate with genetic instability and genomic disorders''. In: Cell 185.11 (2022), 1986–2005.e26. ISSN: 0092-8674. DOI: https://doi.org/10.1016/j.cell.2022.04.017. URL: https://www.sciencedirect.com/science/article/pii/S0092867422004640.

A network flow solution

Note: condense both algo slides into one
Part 1: Given a haplotype variation graph, what is the size of the smallest set of founder sequences? → Formulation as a network flow problem:

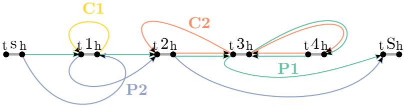
- Total flow of each edge ≥ 1
- Prohibit backtracking to the source ($f_{out_{s^t}} = 0$)

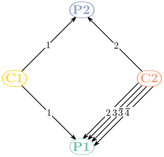
Integer flow at the sink: size of a minimal founder set.

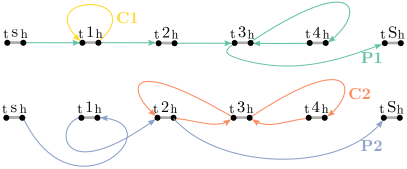


Founder sequences construction

Part 2: Given a solution to the network flow problem, construct a founder set.
→ Idea: decomposition into a component graph







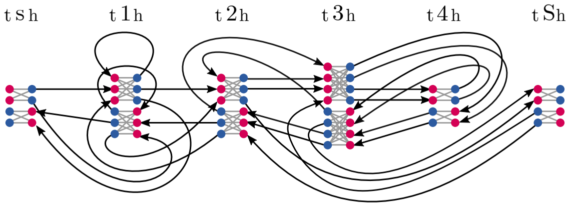
Integrate cycles into paths to obtain a smallest set of founder sequences.

Proposed solution: ILP

Using a previously obtained flow solution:

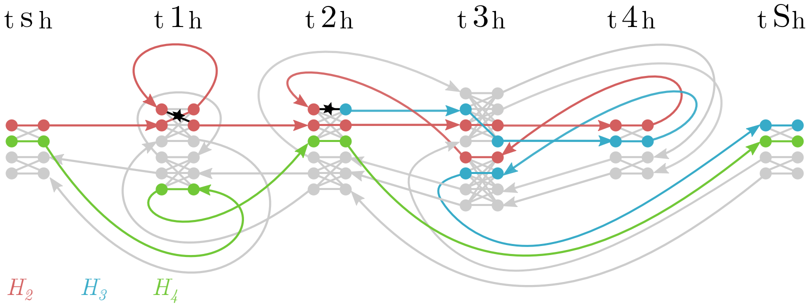
- matching constraints: recombination detected → force a boolean switch on
- flow constraints: push flow from source to sink

Minimize the number of toggled switches, integrating all cycles into valid paths.



ILP solution

Obtained directly from the matchings:


t s h
t 1 h
t 2 h
t 3 h
t 4 h
t S h
H_2
H_3
H_4