Universität Bielefeld

Technische Fakultät
Genominformatik

UFMS

Algorithms for Computing the Family-Free Genomic Similarity under DCJ

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joint work with

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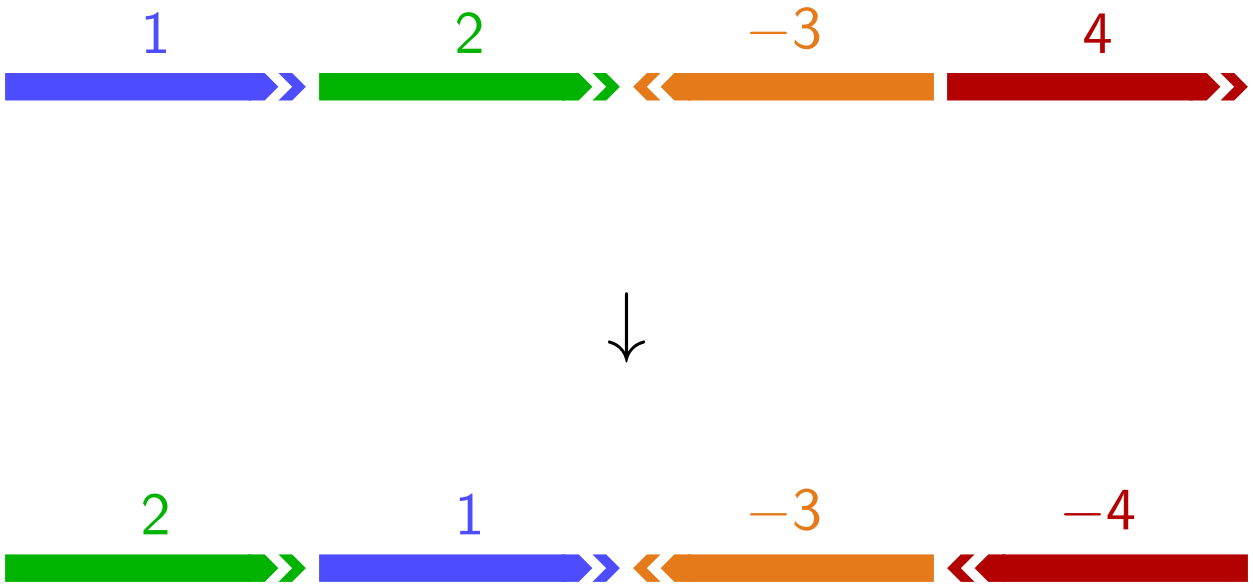
Genome rearrangements

- A central question in comparative genomics is the elucidation of similarities and differences between genomes
- Large-scale rearrangements change the number of chromosomes and/or the positions and orientations of genes (fusions, inversions, ...)
- Genomes are represented as sequences of oriented DNA fragments (genes)

- $A = (\circ\ 3\ -1\ 4\ 2\ -6\ 5\ \circ)$

Genome rearrangements

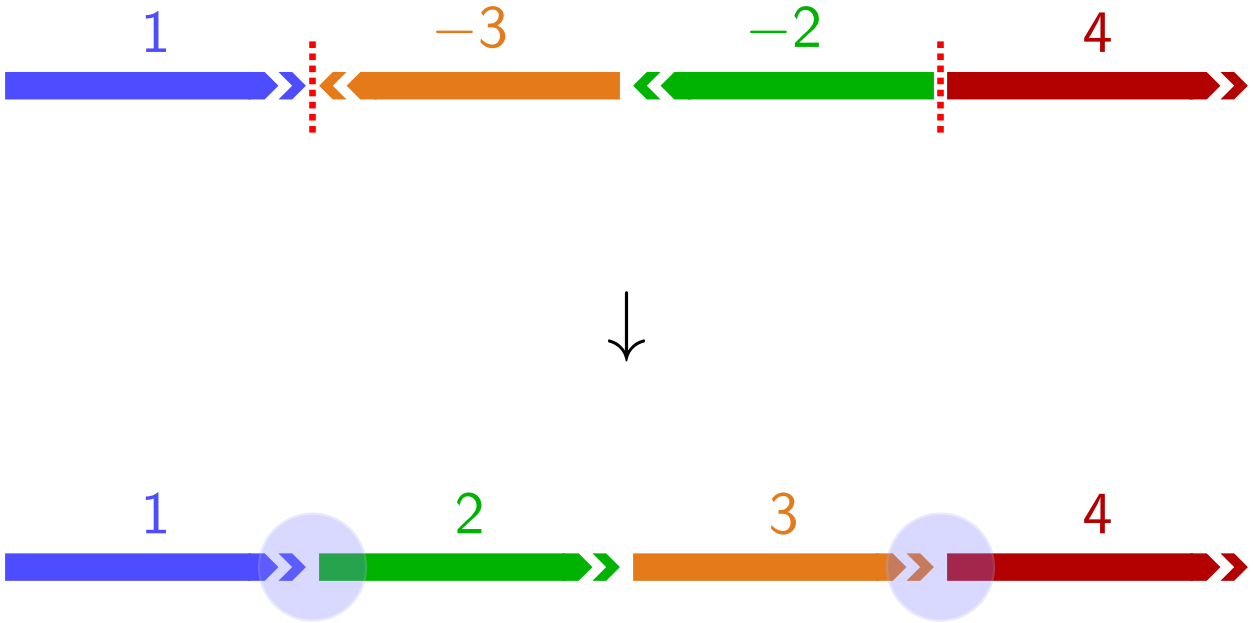
Classical problem: compute the rearrangement distance between two given genomes



The family-based setting

- Genes are grouped into *families*
- Without duplicate genes, several polynomial time algorithms are known to compute genomic distances and similarities
- With duplicate genes, problems become more intricate and many presented approaches are NP-hard

The double-cut-and-join (DCJ) operation



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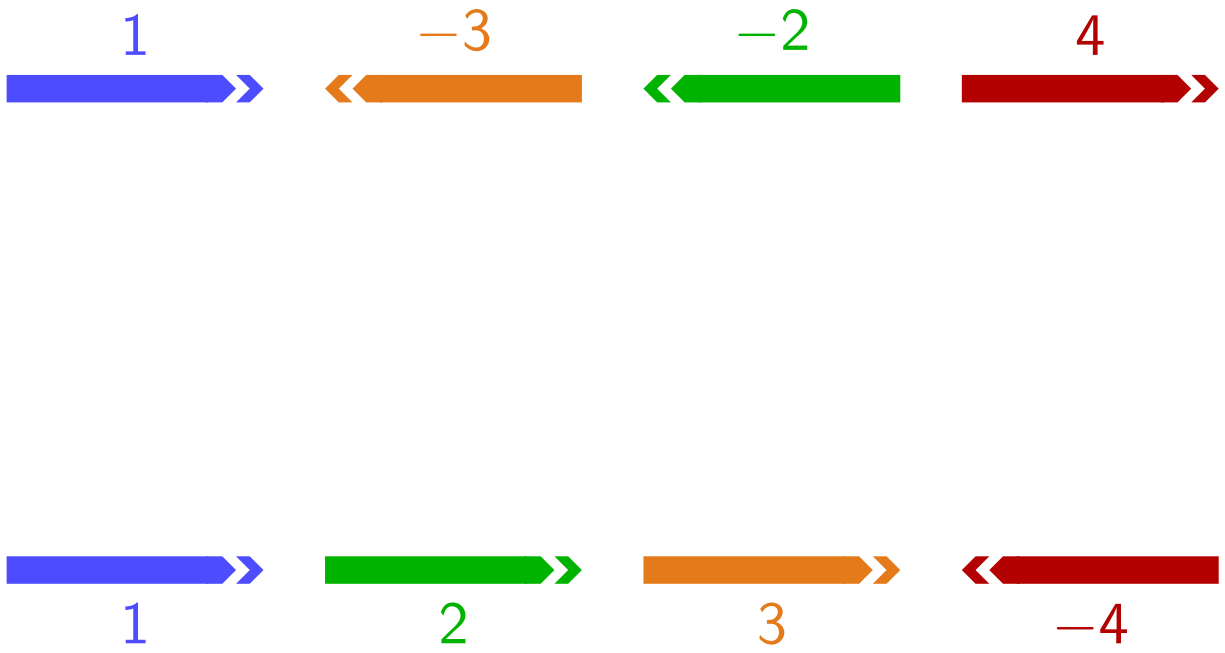

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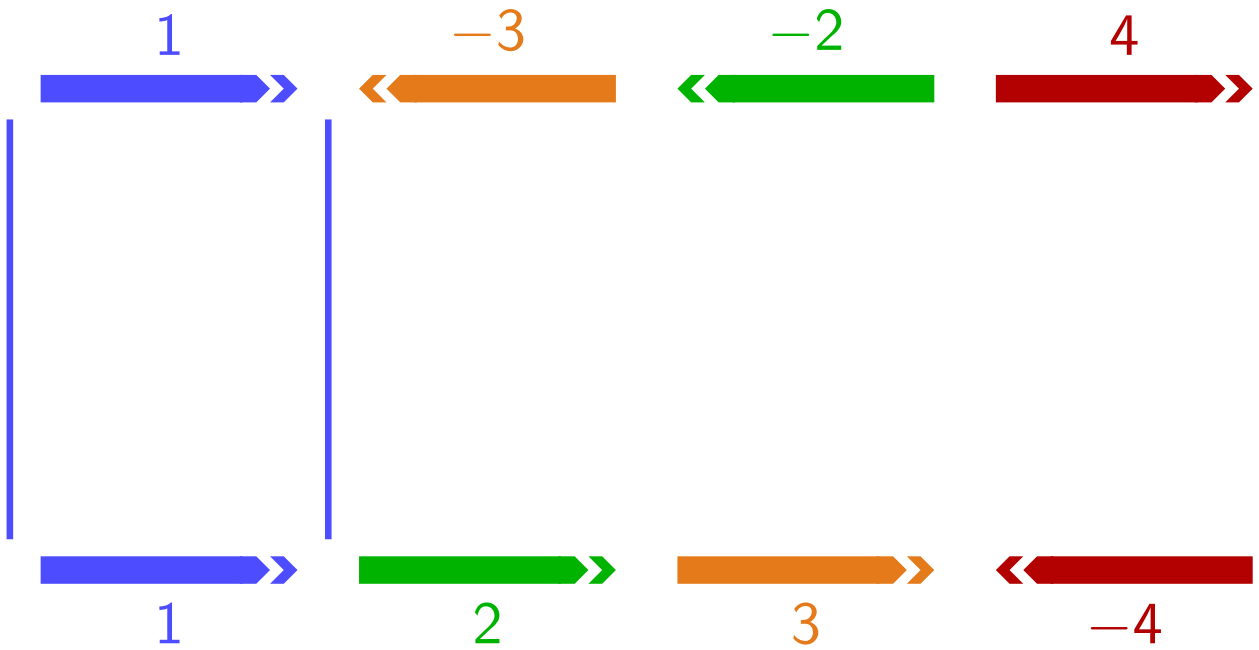

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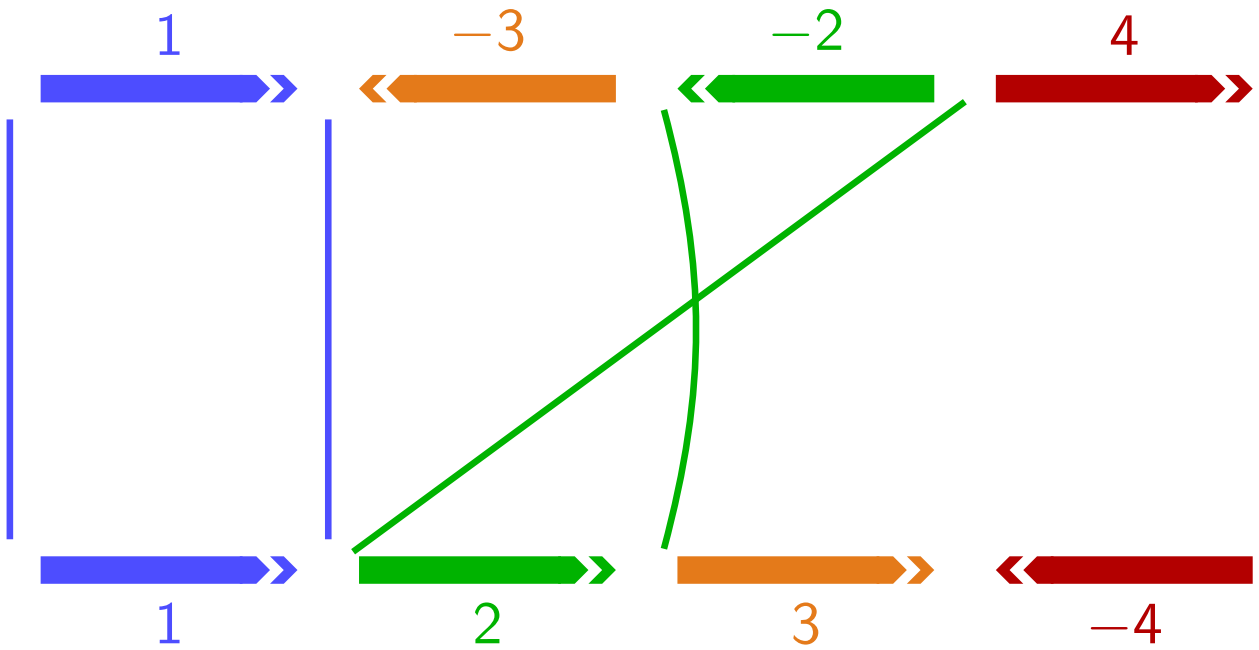

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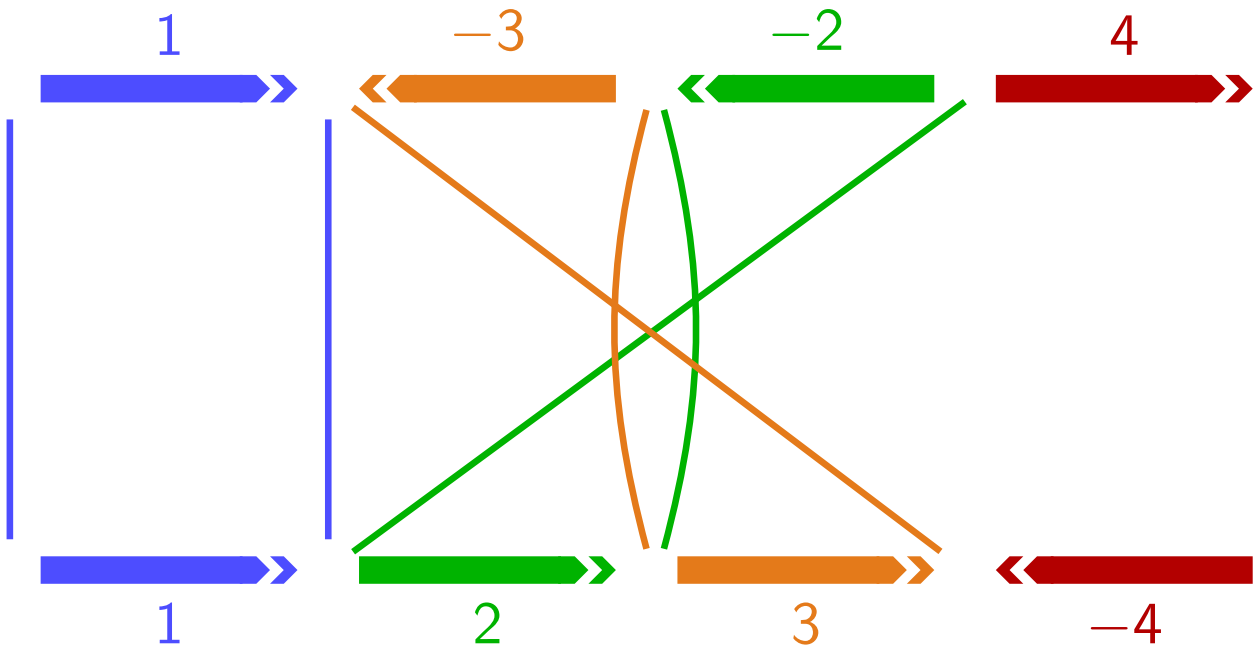

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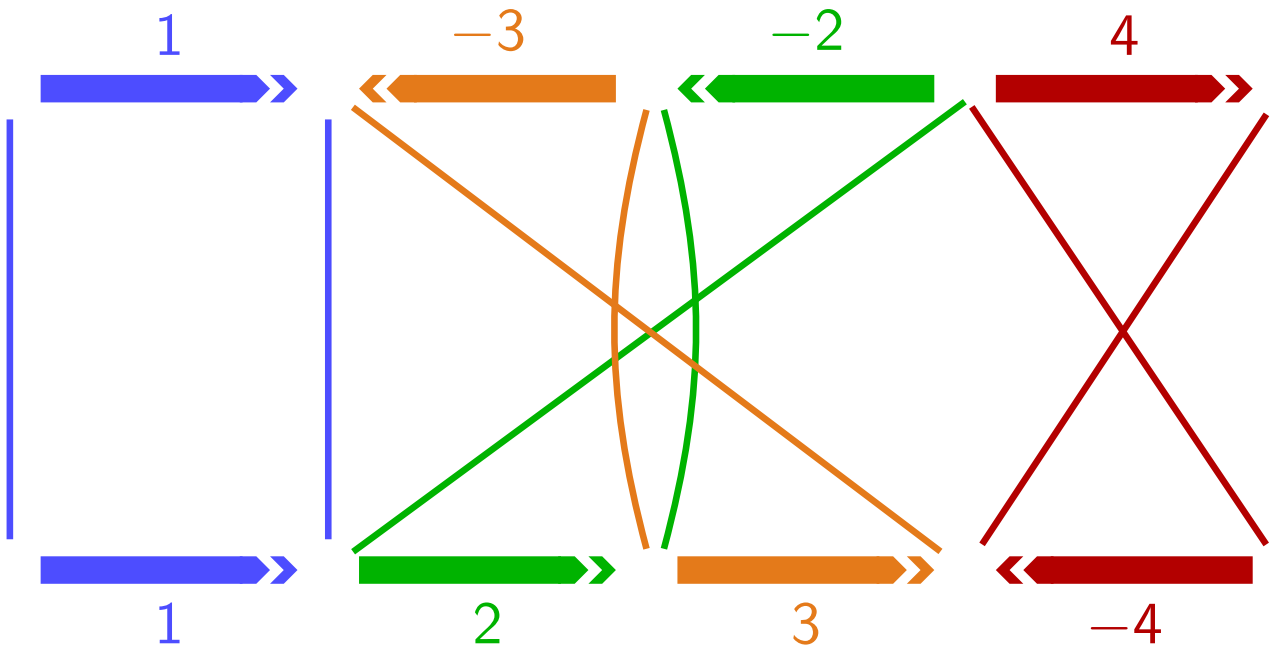

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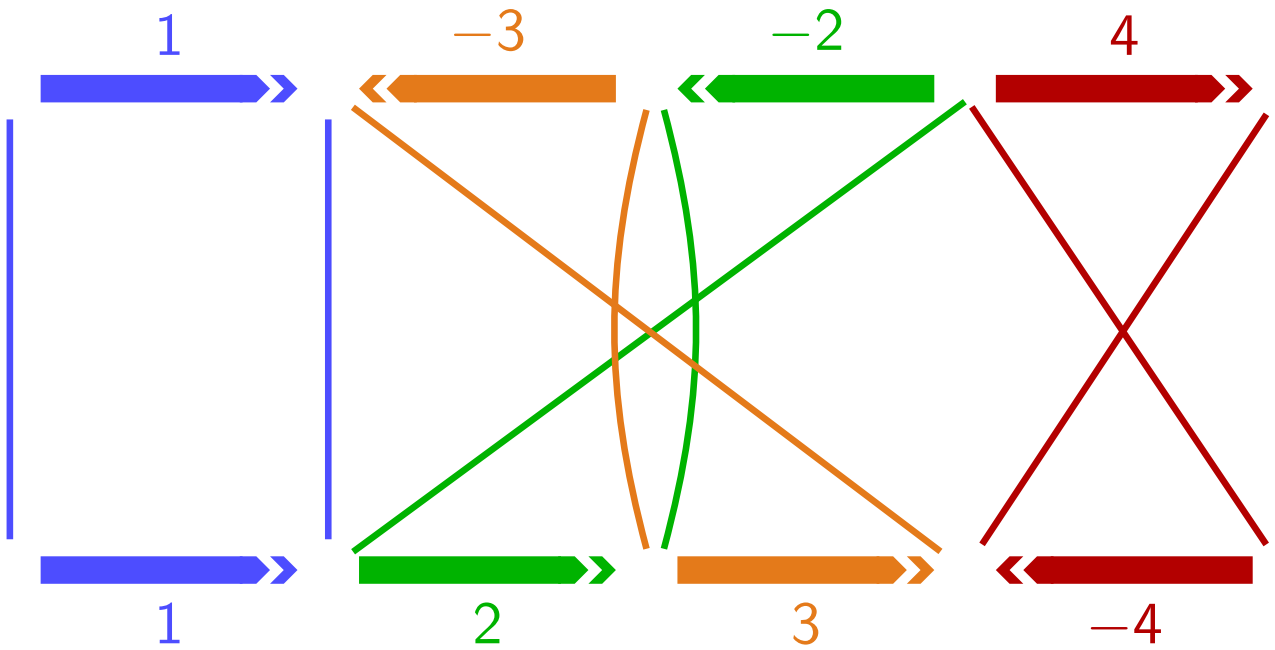


- Family-based DCJ distance: $\mathrm{d}_{\mathrm{DCJ}}(A, B) = n - c - \frac{i}{2}$

Family-based similarity

- In some contexts, similarity measures are more flexible
- Family-based DCJ similarity (Martinez *et al.*, AMB 2015):

$$\begin{aligned} s_{\mathrm{DCJ}}(A,B) &= \sum_{C\in\mathcal{P}}\left(\frac{|C|}{|C|+2}\right)+\sum_{C\in\mathcal{I}}\left(\frac{|C|}{|C|+1}\right)+\sum_{C\in\mathcal{C}}\left(\frac{|C|}{|C|}\right) \\ &= \sum_{C\in\mathcal{P}}\left(\frac{|C|}{|C|+2}\right)+\sum_{C\in\mathcal{I}}\left(\frac{|C|}{|C|+1}\right)+c \end{aligned}$$

  where $\mathcal{P}$, $\mathcal{I}$, $\mathcal{C}$ are the even paths, odd paths, cycles in $AG(A,B)$

- Can be computed as efficiently as the DCJ distance

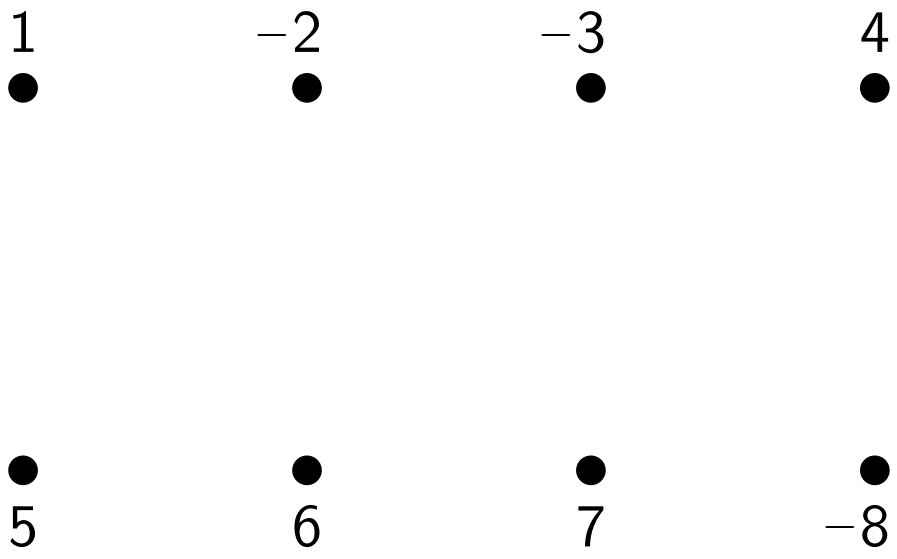
The family-based setting

However,

- Family assignments are most of the time made automatically
- Even in the absence of errors, there may be ambiguities

The family-free setting

- Each gene in each genome is represented by a unique (signed) symbol
- *Normalized gene similarities* with respect to some function σ are represented in the *gene similarity graph* $GS_\sigma(A, B)$



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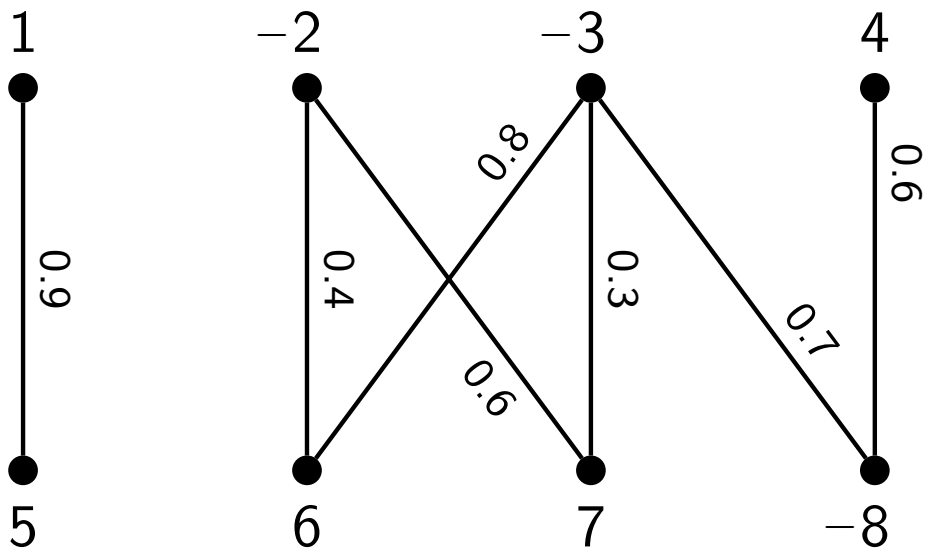


The family-free similarity

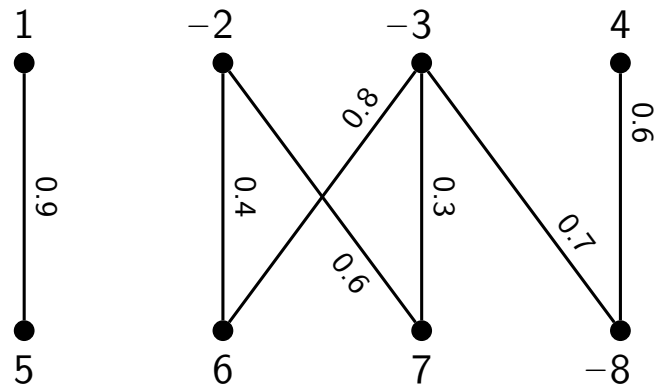
- Given a maximal matching M of the genes in A and the genes in B, inducing *reduced genomes* A^M and B^M, the family-free DCJ similarity is defined by:

$$s_\sigma(A^M, B^M) = \sum_{C \in \mathcal{P}} \left(\frac{w(C)}{|C| + 2} \right) + \sum_{C \in \mathcal{I}} \left(\frac{w(C)}{|C| + 1} \right) + \sum_{C \in \mathcal{C}} \left(\frac{w(C)}{|C|} \right)$$

  where $\mathcal{P}$, $\mathcal{I}$, $\mathcal{C}$ are the even paths, odd paths, cycles in $AG(A^M, B^M)$

- The *family-free DCJ similarity* is the highest score $s_\sigma(A^M, B^M)$ possible for any maximal matching M in $GS_\sigma(A, B)$.

The family-free similarity



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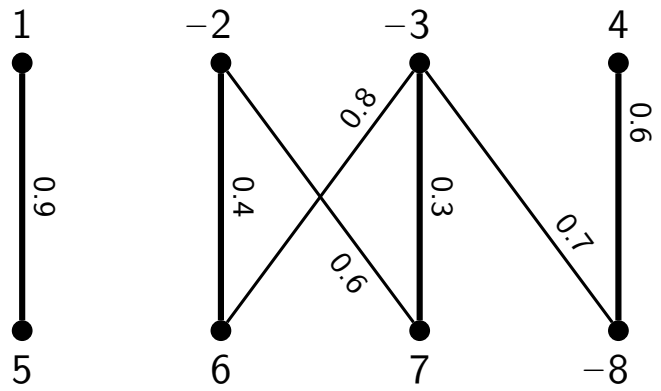

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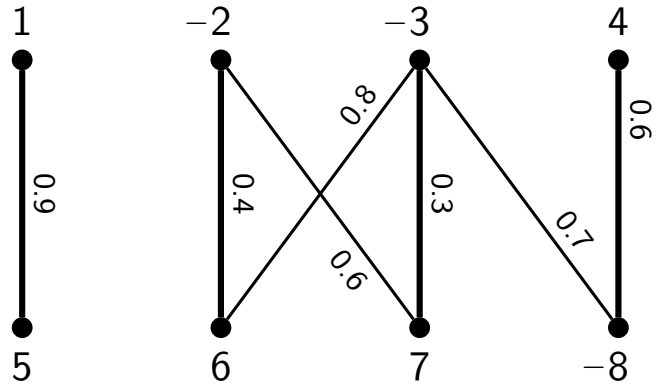

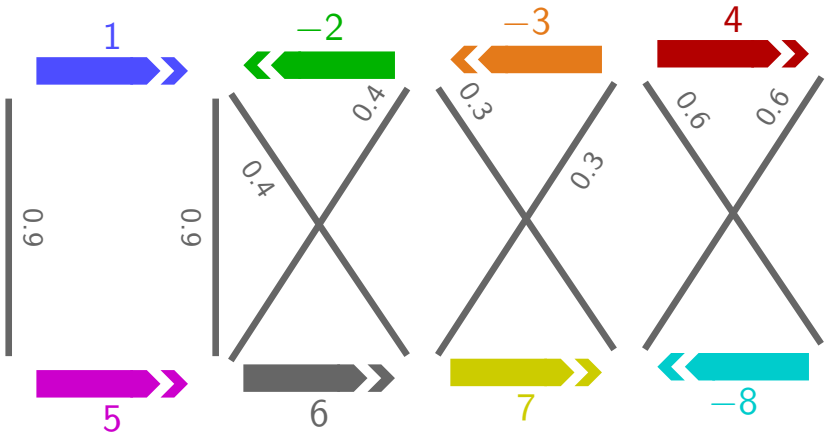

Score: $\frac{0.9}{1+1} + \frac{3.5}{7+1} = 0.8875$

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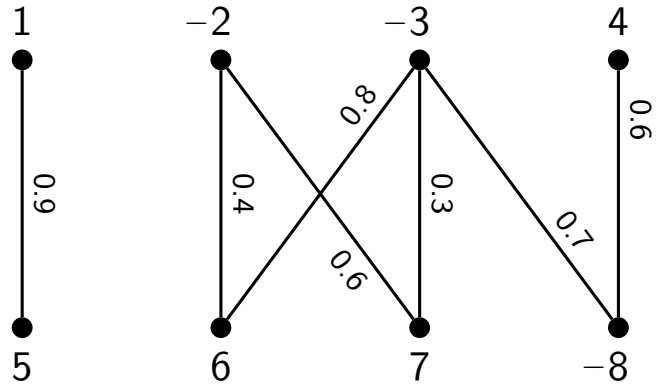

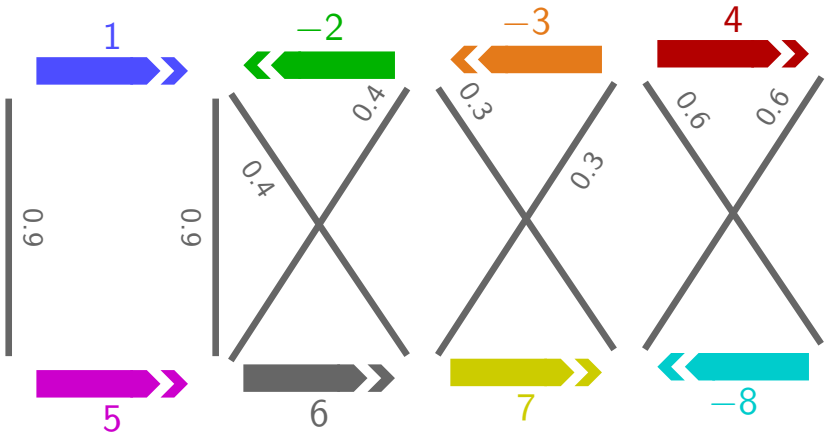

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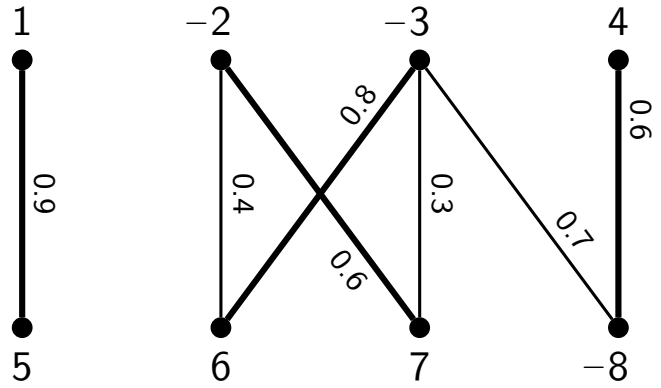

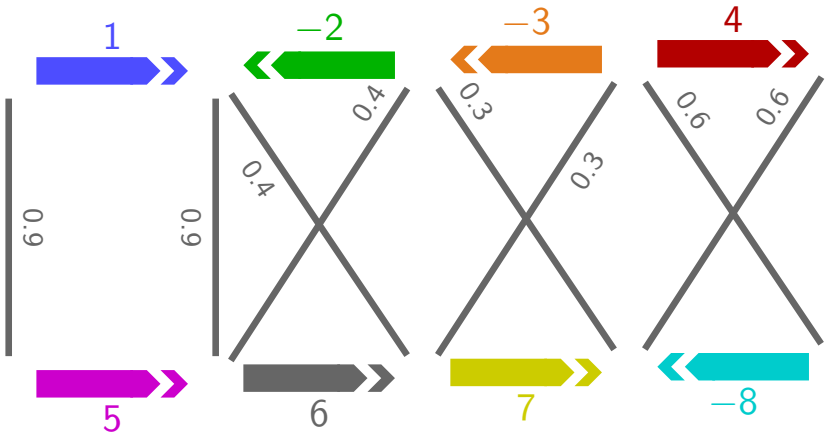

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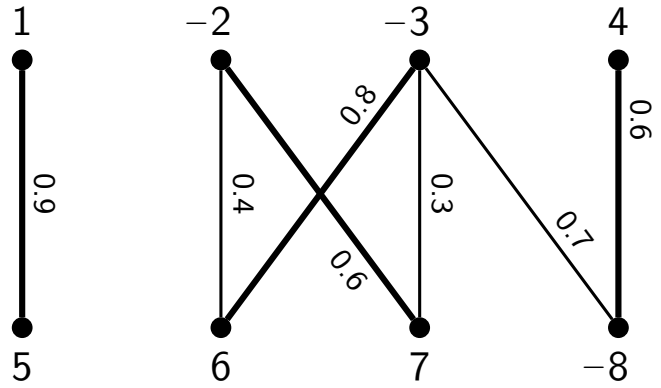

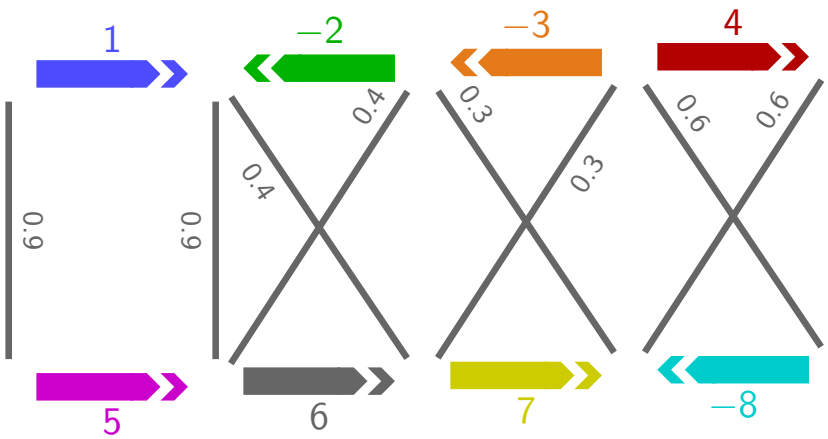

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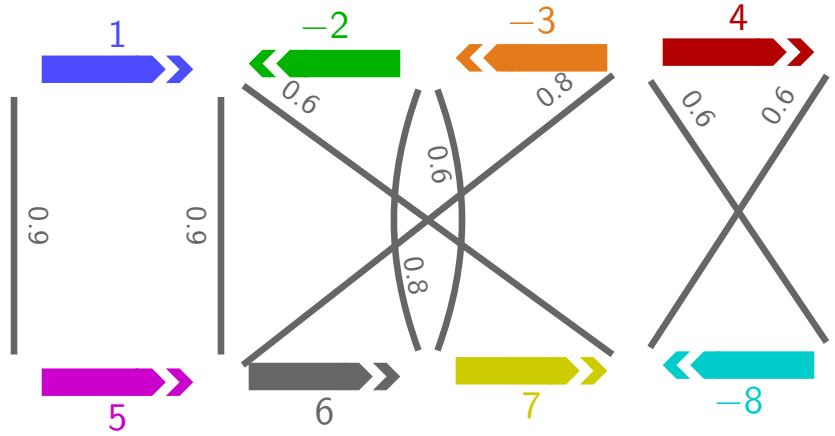


Score: $\frac{0.9}{1+1} + \frac{3.5}{5+1} + \frac{1.4}{2} = 1.733$

Inapproximability of FFDCJ-SIMILARITY

- Previously shown: FFDCJ-SIMILARITY is NP-complete (Martinez *et al.*, AMB 2015)

Theorem

FFDCJ-SIMILARITY *is APX-hard and cannot be approximated with approximation ratio better than* $22/21 = 1.0476\ldots$, *unless* $P = NP$.

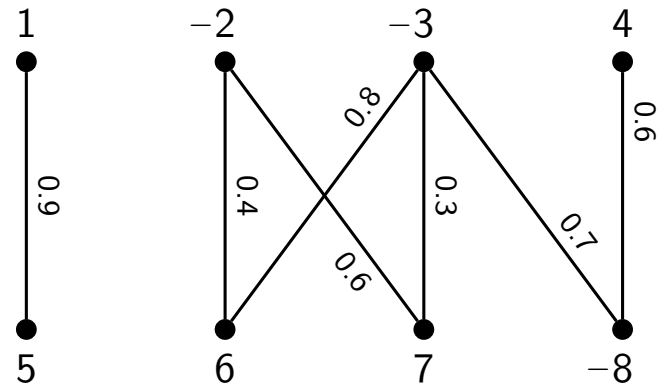
- Reduction from MAX-2SAT3 and MAX-2SAT.

Exact algorithm

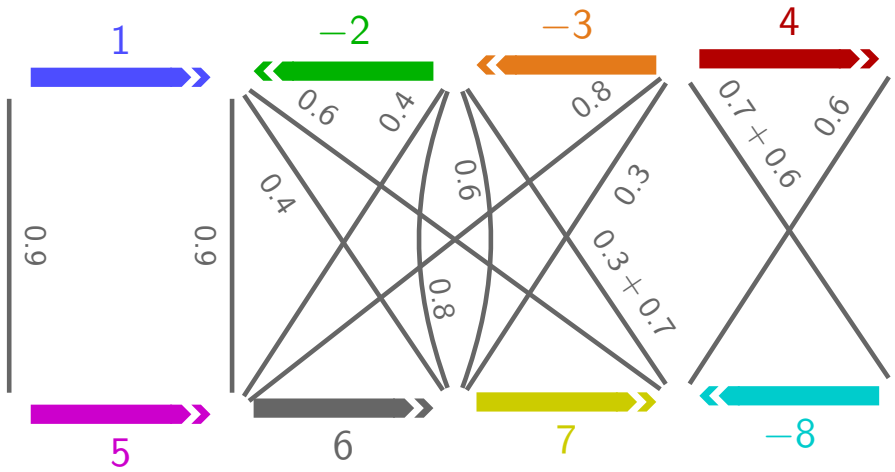
- We propose an integer linear program (ILP) formulation
- Similar to the one for the family-free DCJ distance (Martinez *et al.*, AMB 2015), based on an approach by Shao *et al.* (JCB 2015) to compute the family-based DCJ distance with gene duplications
- Has $O(N^4)$ variables and $O(N^3)$ constraints, where $N = |A| + |B|$

Heuristics

- Gene similarity graph $GS_\sigma(A, B)$:



- Weighted adjacency graph $AG_\sigma(A, B)$:



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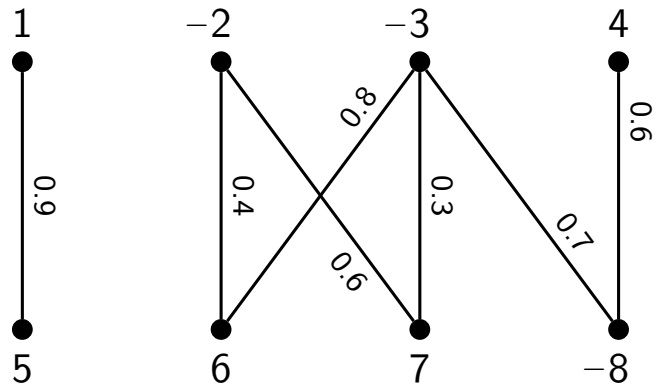

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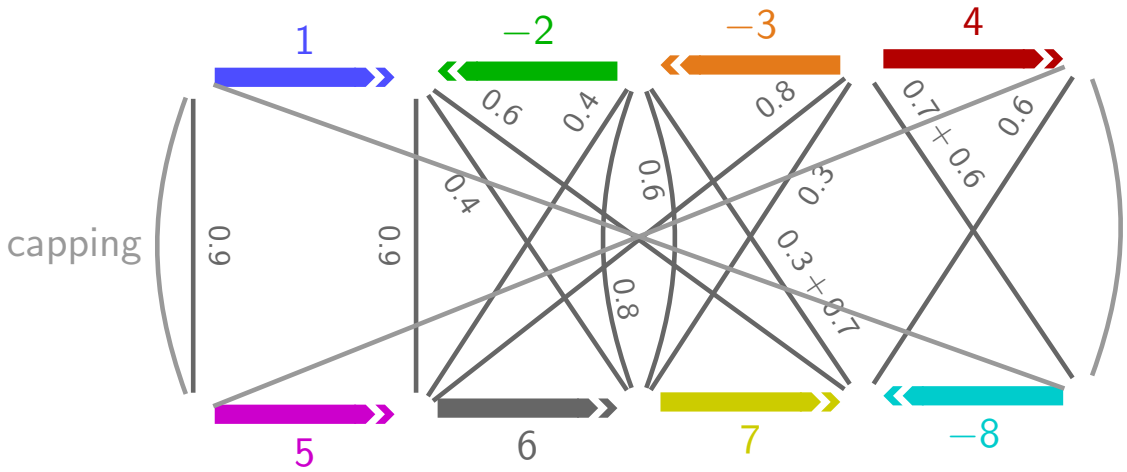

Heuristics

Goal: Pick set of consistent cycles maximizing the DCJ similarity score.

We have three heuristics:

GREEDY-DENSITY: prioritizes cycles in $AG_\sigma(A, B)$ with higher densities, where the *density* of some cycle C is given by $w(C)/|C|^2$

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GREEDY-LENGTH: prioritizes 2-cycles in $AG_\sigma(A, B)$ with higher weights, then 4-cycles with higher weights, then 6-cycles...

GREEDY-WMIS: tries to select a set of 2-cycles in $AG_\sigma(A, B)$ with the highest sum of weights by an WMIS algorithm, then a set of 4-cycles...

Experimental results

- Simulated data generated by the *Artificial Life Simulator* (ALF)
- *Gurobi* solver for the ILPs, 4 threads, time limit of 1800 s
- Heuristics implemented in C++
- Genomes of sizes around 25, 50, and 1000 (heuristics only)
- 1-, 2-, and 5-fold increase in rearrangement rates (r)

Experimental results

	ILP			Greedy-Density	Greedy-Length	Greedy-wmis
	Time (s)	Not finished	Gap (%)	Δ (%)	Δ (%)	Δ (%)
25 genes, $r = 1$	19.50	0	–	5.03	5.84	5.97
25 genes, $r = 2$	84.60	2	69.21	30.77	43.57	43.00
25 genes, $r = 5$	49.72	0	–	43.83	55.38	55.38
50 genes, $r = 1$	445.91	7	19.56	18.74	19.36	18.90
50 genes, $r = 2$	463.50	29	38.12	65.41	66.52	64.78
50 genes, $r = 5$	330.88	29	259.72	177.58	206.60	206.31

- Running time for heuristics was negligible
- Average relative delta of heuristics increases proportionally to the rate of reversals and translocations $\Rightarrow$ higher normalized weights on longer cycles

Experimental results

Observations:

- For some larger instances the relative delta for heuristics is very close to the values obtained by the ILP solver, suggesting the use of heuristics:
  - may be a good alternative for some classes of instances
  - could help the solver finding lower bounds quickly.
- Greedy-Density found solutions with delta $< 1\%$ for 38% of the instances with 25 genes
- For heuristics and genomes of size 1000, avg. running time is 9 s for $r = 1$ and 68 s $r = 5$, Greedy-Density was the best most of times

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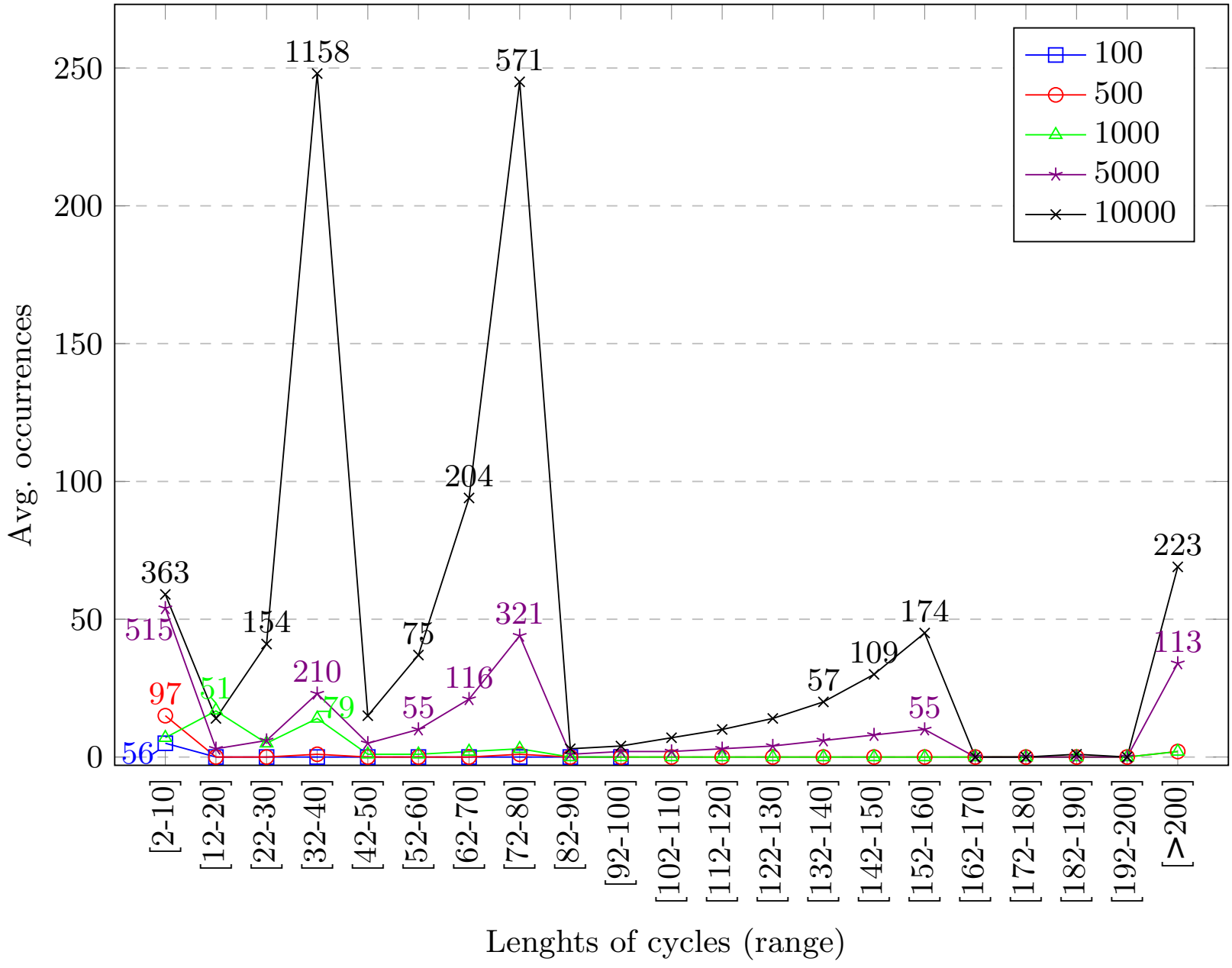
- Results (next figure) show that most of the cycles found are of short lengths compared to the genome sizes
- Even the maximum number of longer cycles found for any instance is reasonably small



(on top of some marks is shown the maximum number of cycles)

Thank you!