Quantifying Rearrangements in Pangenomes

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Bielefeld University

May 15th, 2025

Rearrangements

INVERSIONS IN THE CHROMOSOMES OF DROSOPHILA PSEUDOOBSCURA*

TH. DOBZHANSKY AND A. H. STURTEVANT
California Institute of Technology, Pasadena, California

Received August 23, 1937

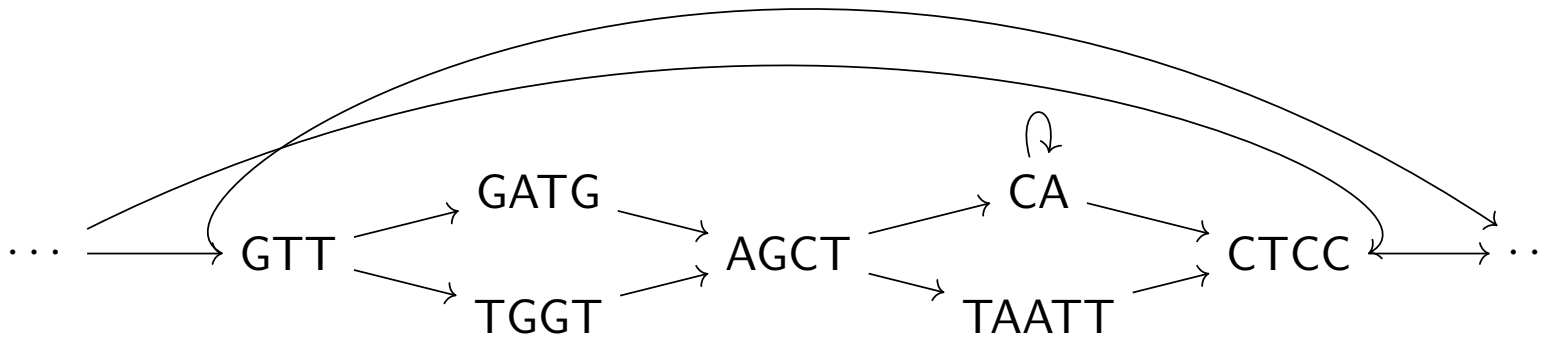
INDEPENDENT FUNCTIONS OF VIRAL PROTEIN AND NUCLEIC ACID IN GROWTH OF BACTERIOPHAGE*

BY A. D. HERSHEY AND MARTHA CHASE
(*From the Department of Genetics, Carnegie Institution of Washington, Cold Spring Harbor, Long Island*)

(Received for publication, April 9, 1952)

- ∼30,000 inversions affect more bases of the human genome than ∼5,000,000 SNVs
- Pivotal role in:
  - Evolution
  - Disease
- Rearrangement Quantification for Structural Variants ≈ Alignment for SNVs

Abstracting from Local Variations



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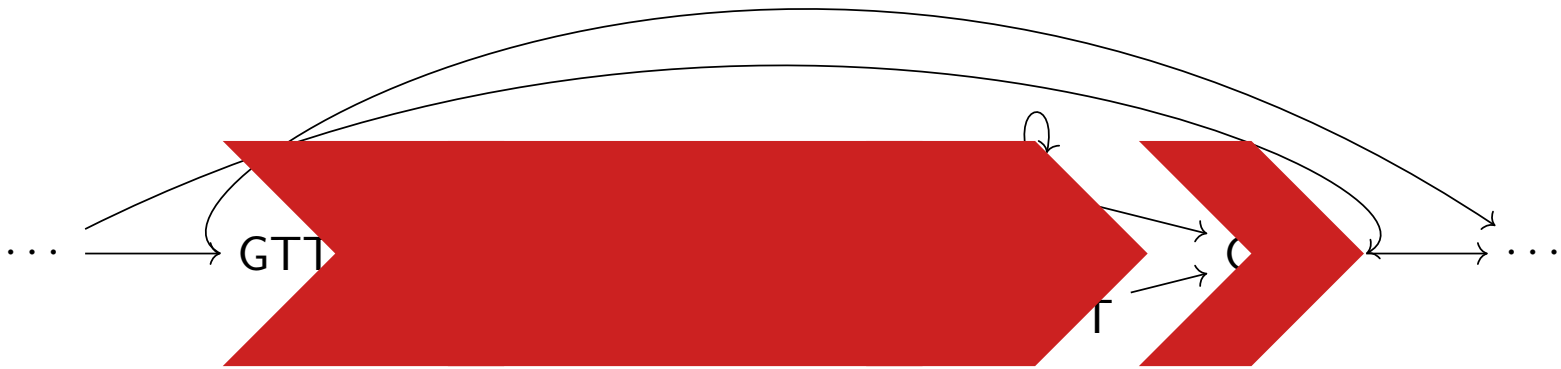

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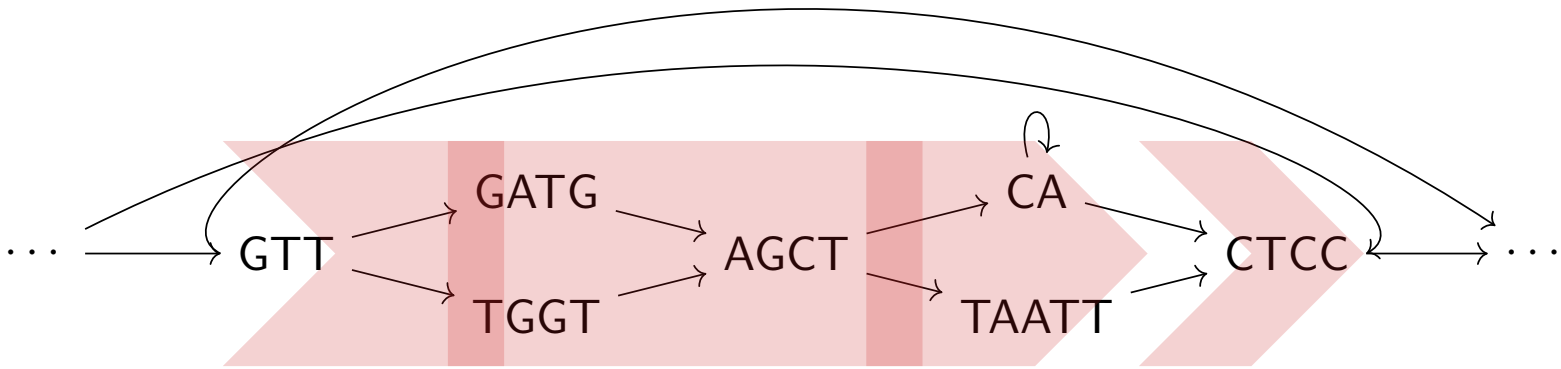

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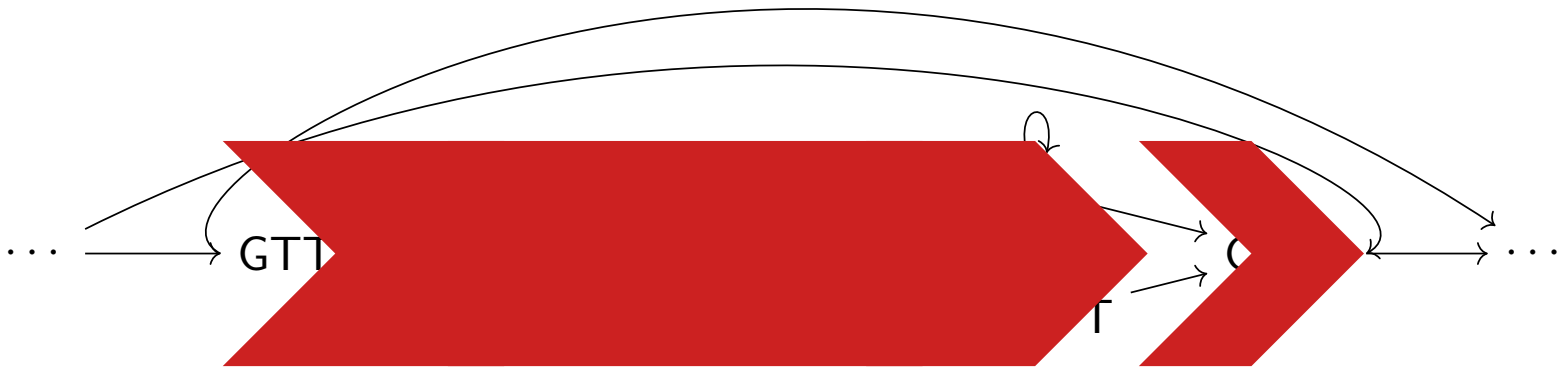

$\rightarrow$ Collinear Block Detection.

Marker, Chromosome, Genome, Pangenome

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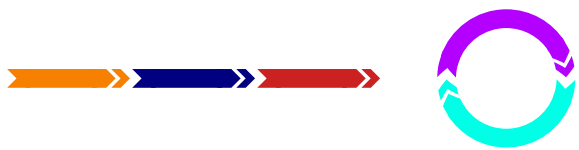

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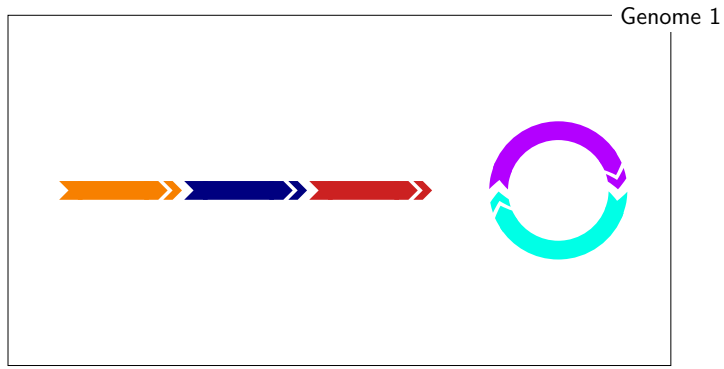
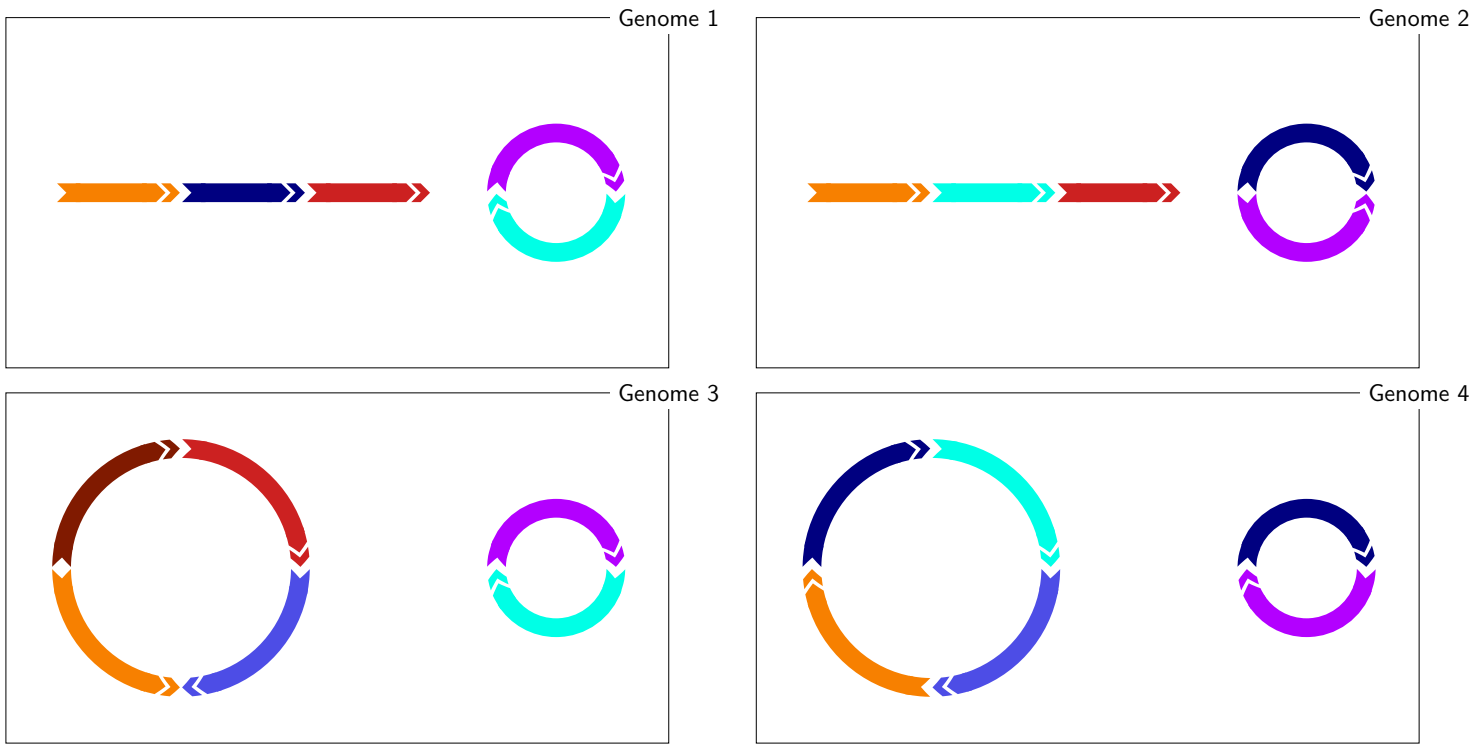
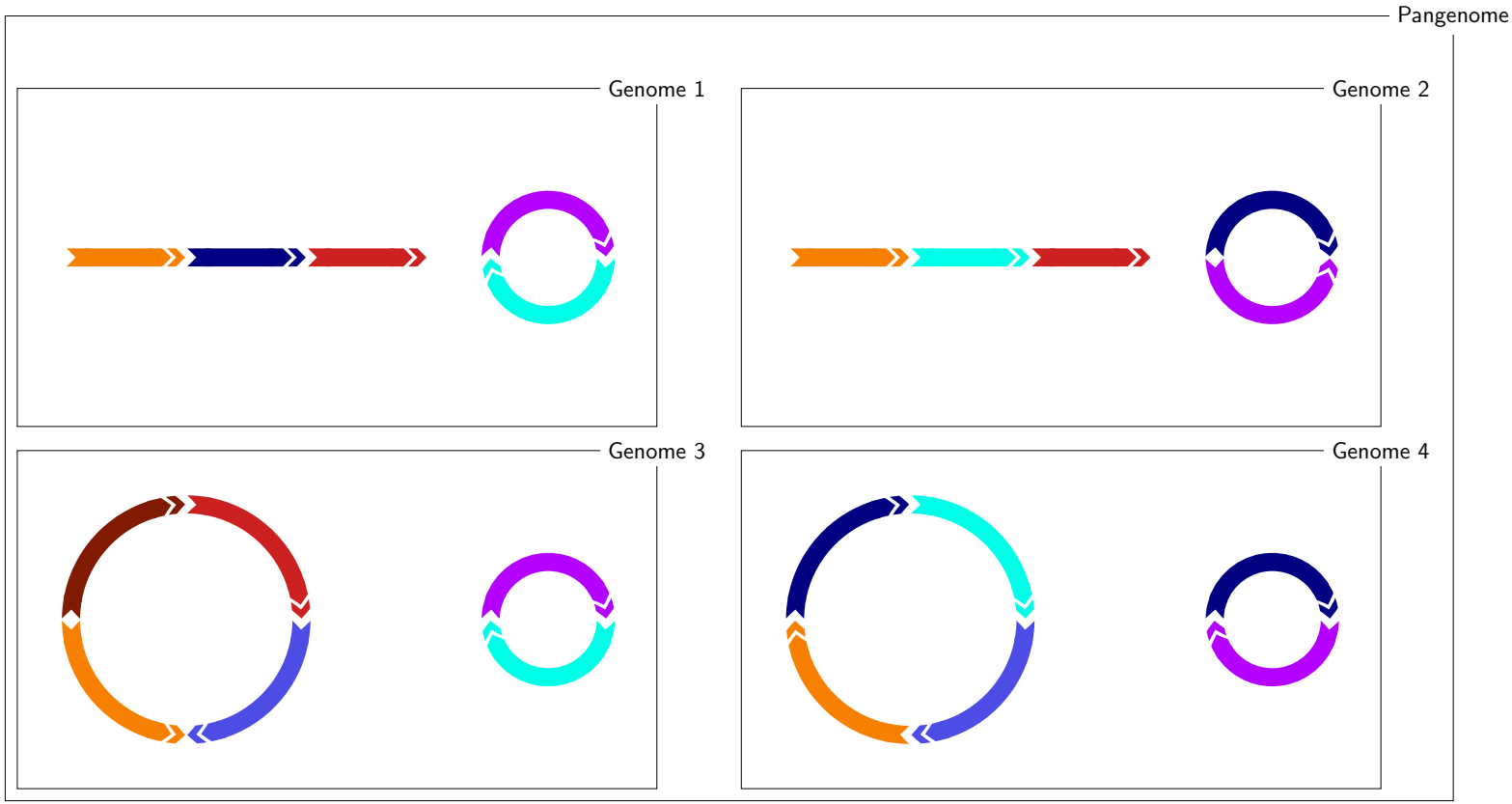


Marker, Chromosome, Genome, Pangenome



Marker, Chromosome, Genome, Pangenome

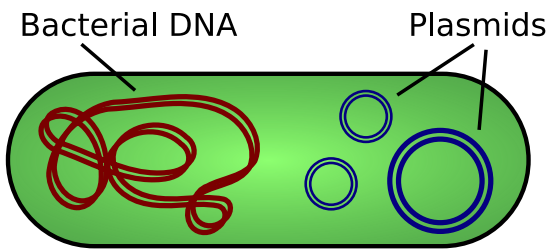


SPP - Ancestral Reconstruction with a Given Tree

Joint work with Daria Frolova (, Jens Stoye, Daniel Doerr)

Background: Plasmids

- Extrachromosomal DNA
- Common in bacteria
- Mostly circular
- Some plasmids can be transferred between hosts (even cross-species)
- Often carry resistance or virulence genes
- Frequent structural changes



Application: Plasmids

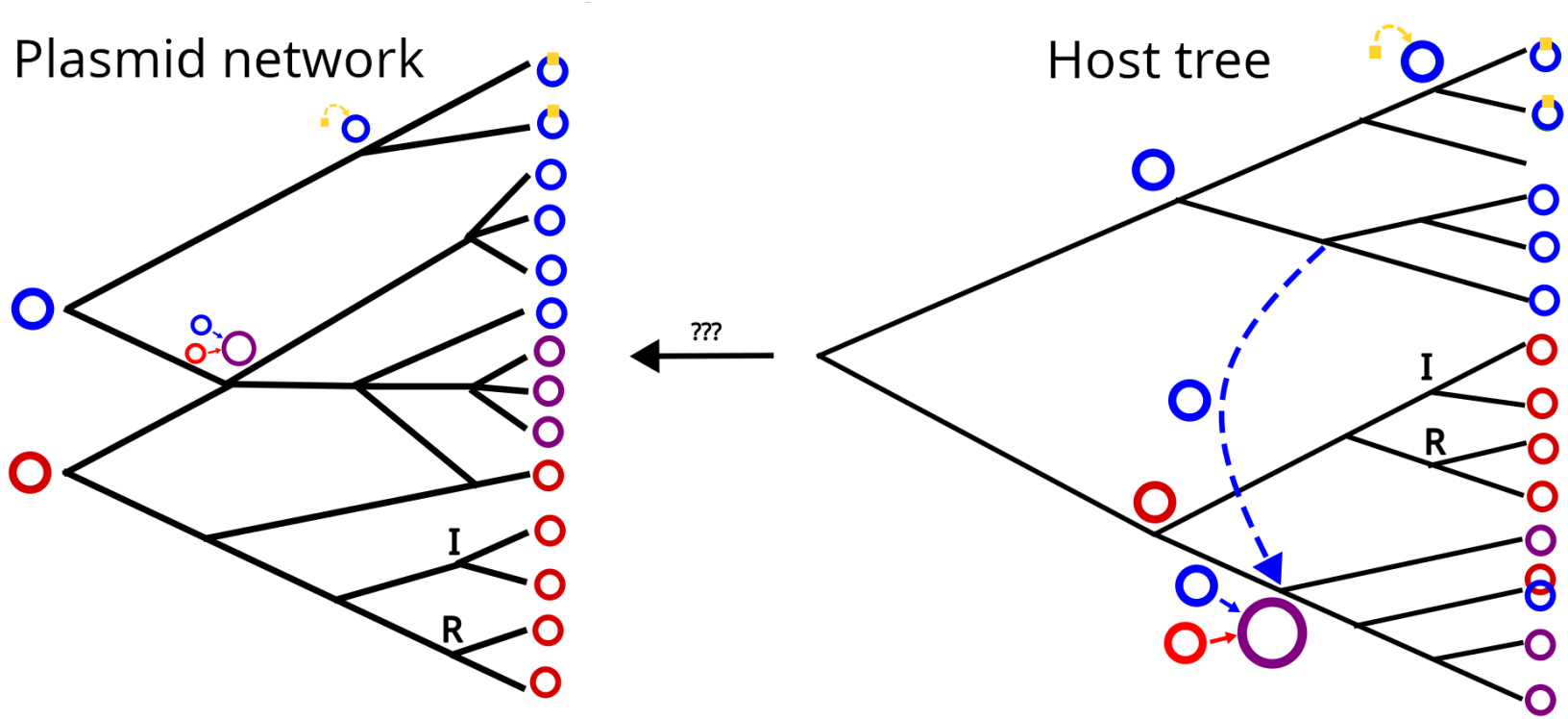


Image by courtesy of Daria Frolova

Application: Plasmids

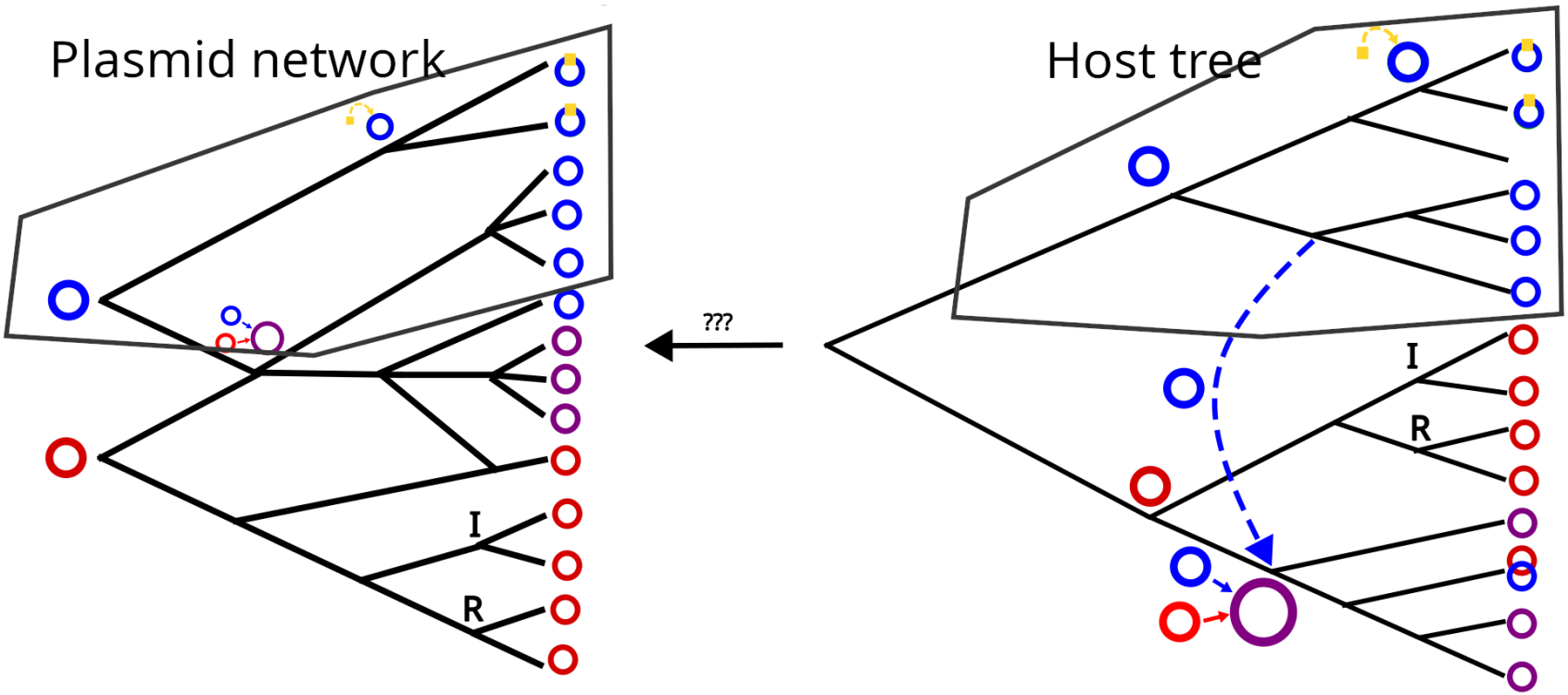
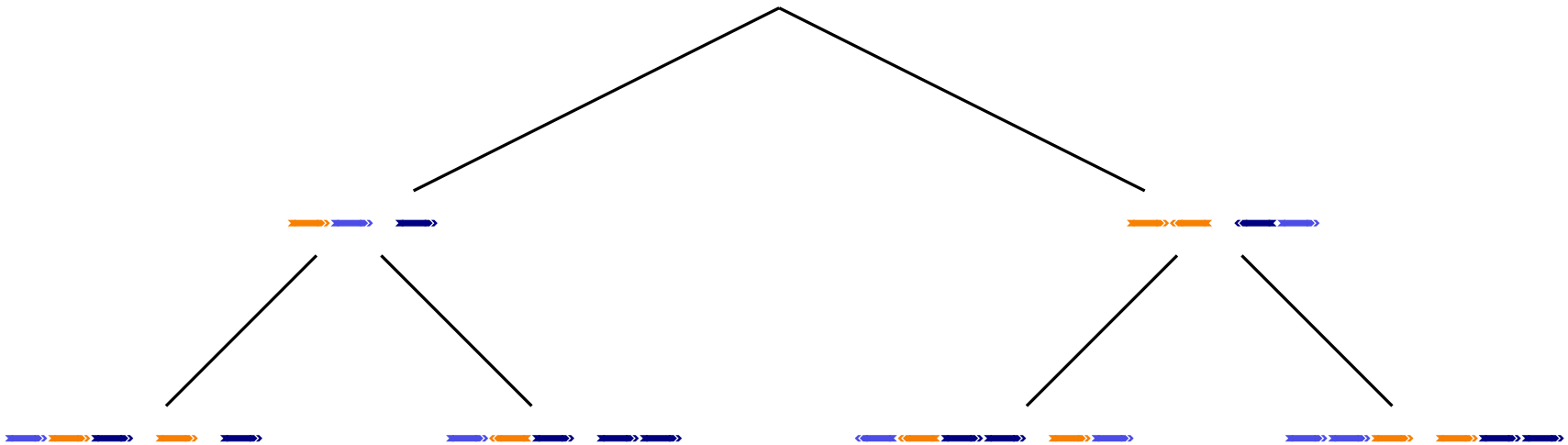


Image by courtesy of Daria Frolova

Small Parsimony for Natural Genomes



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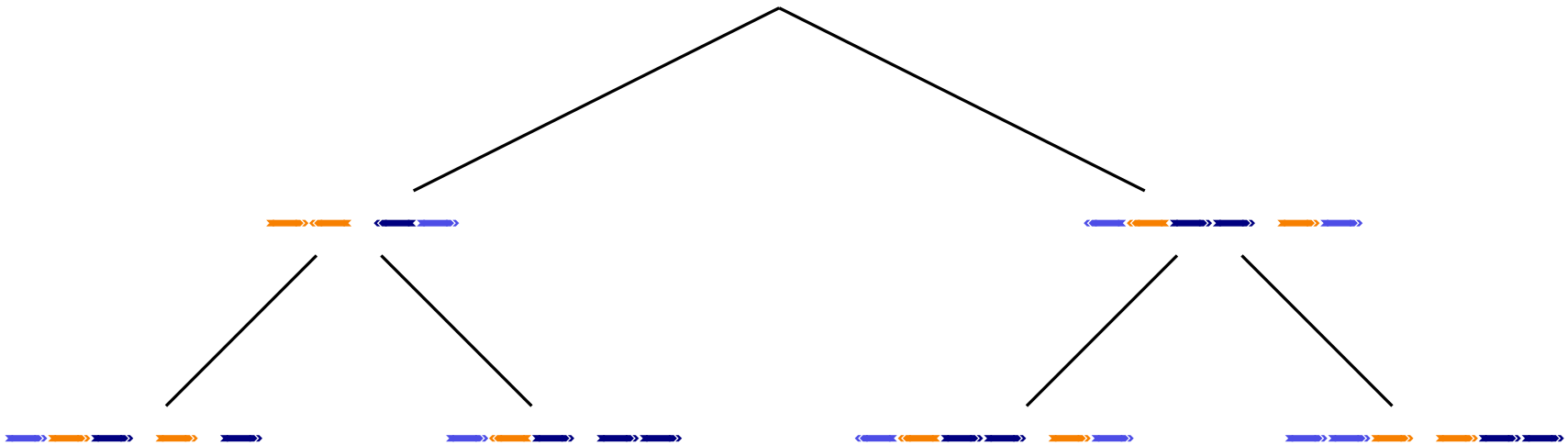

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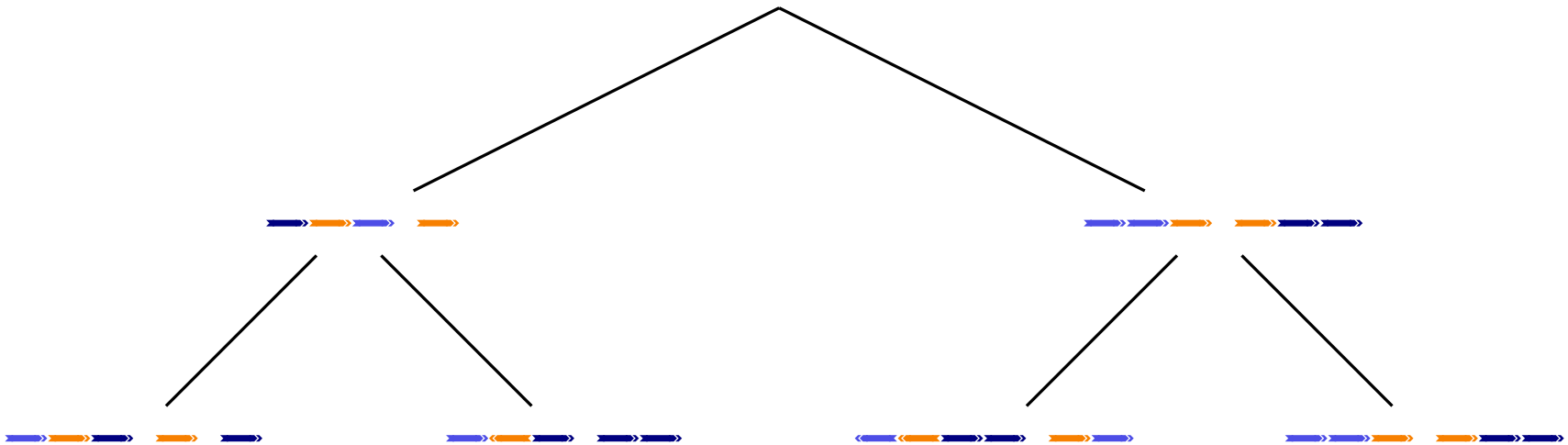

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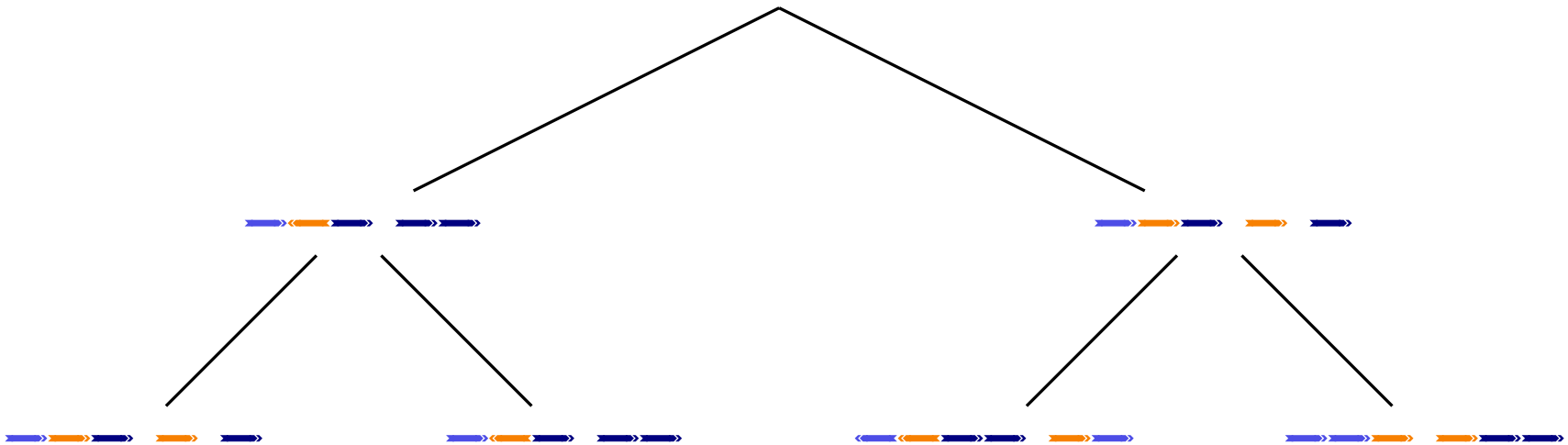

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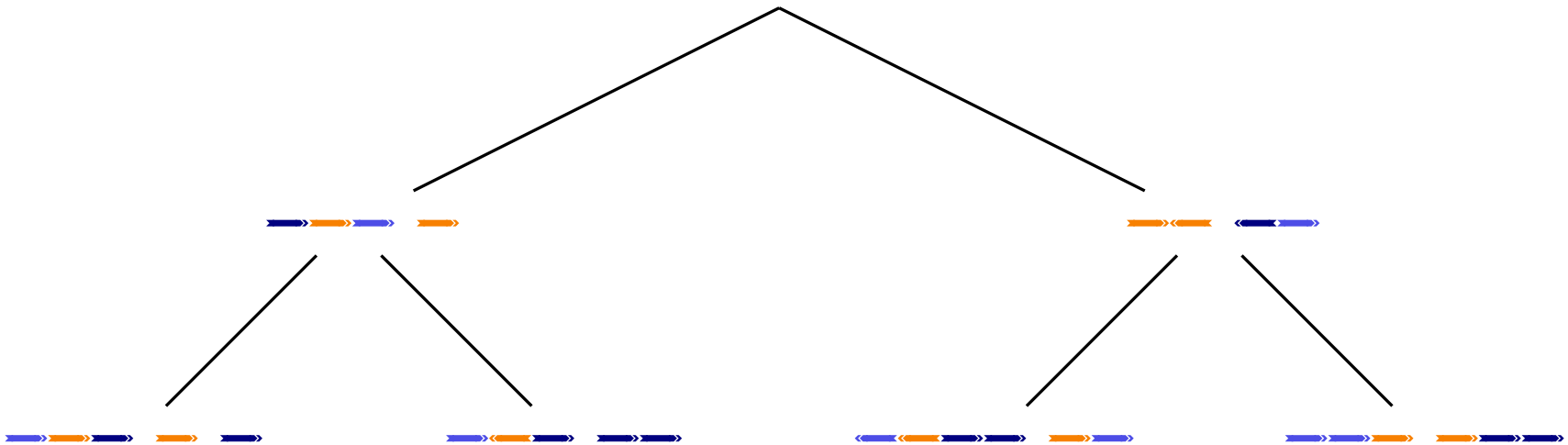

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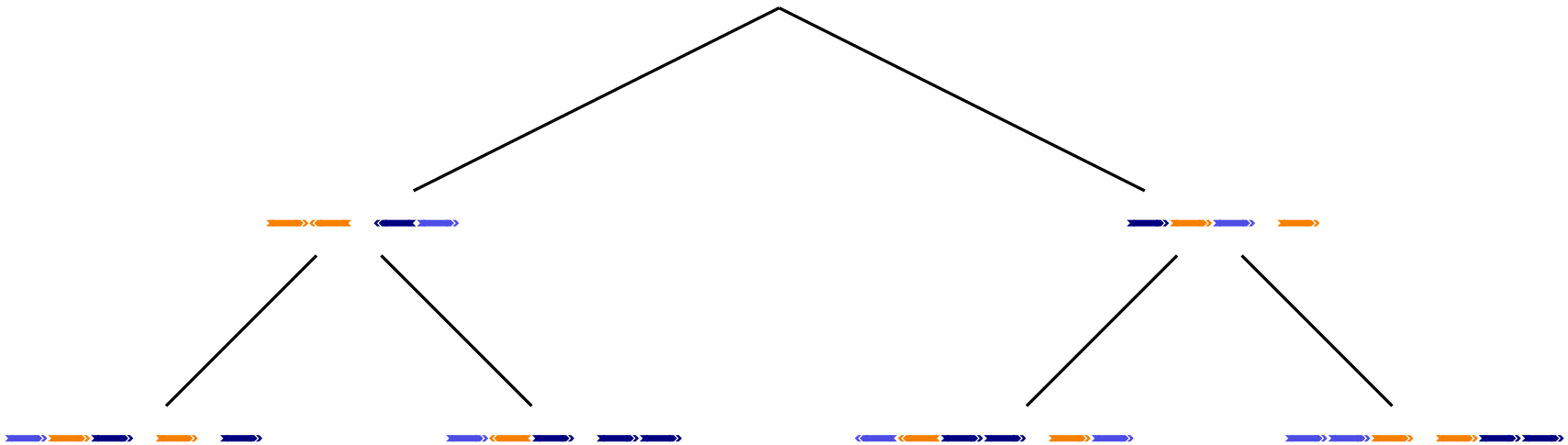

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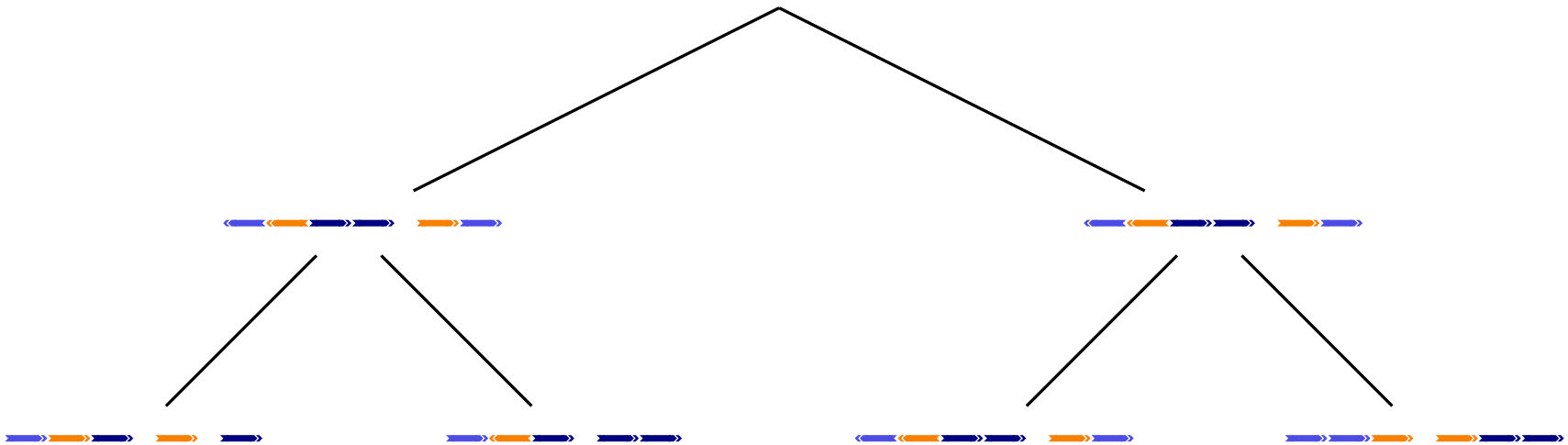

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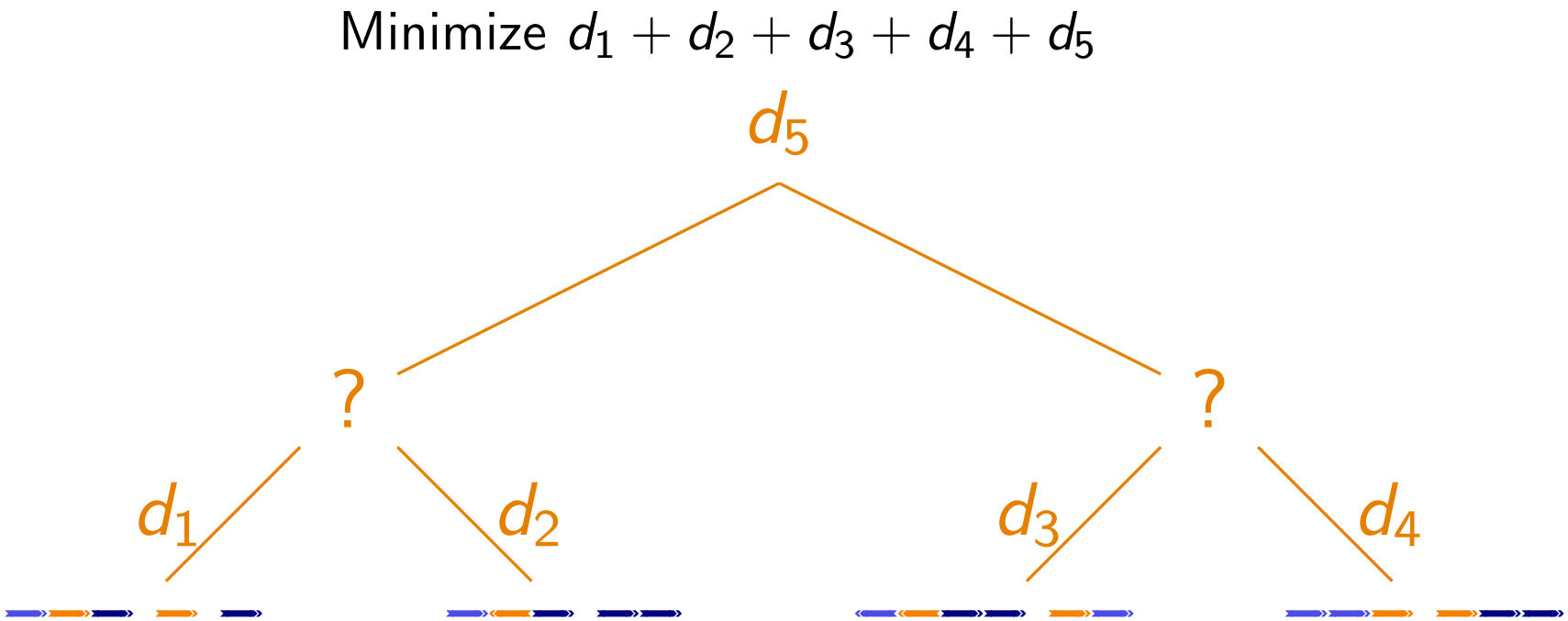
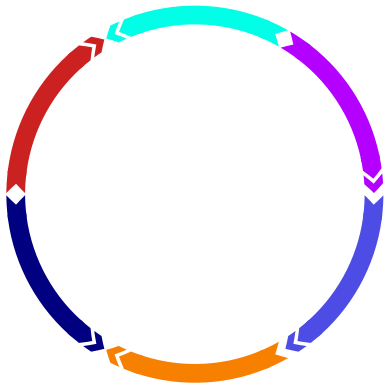


Model: Double-Cut-And-Join



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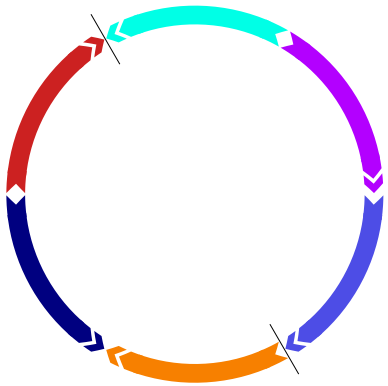

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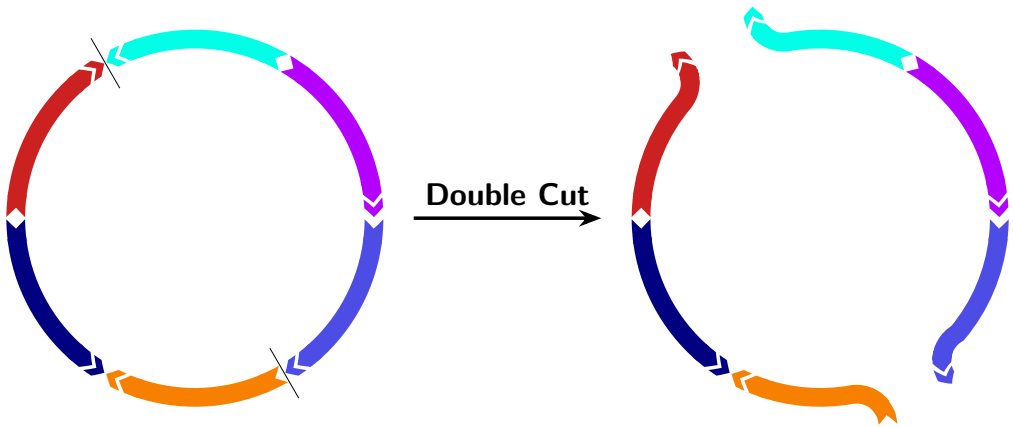

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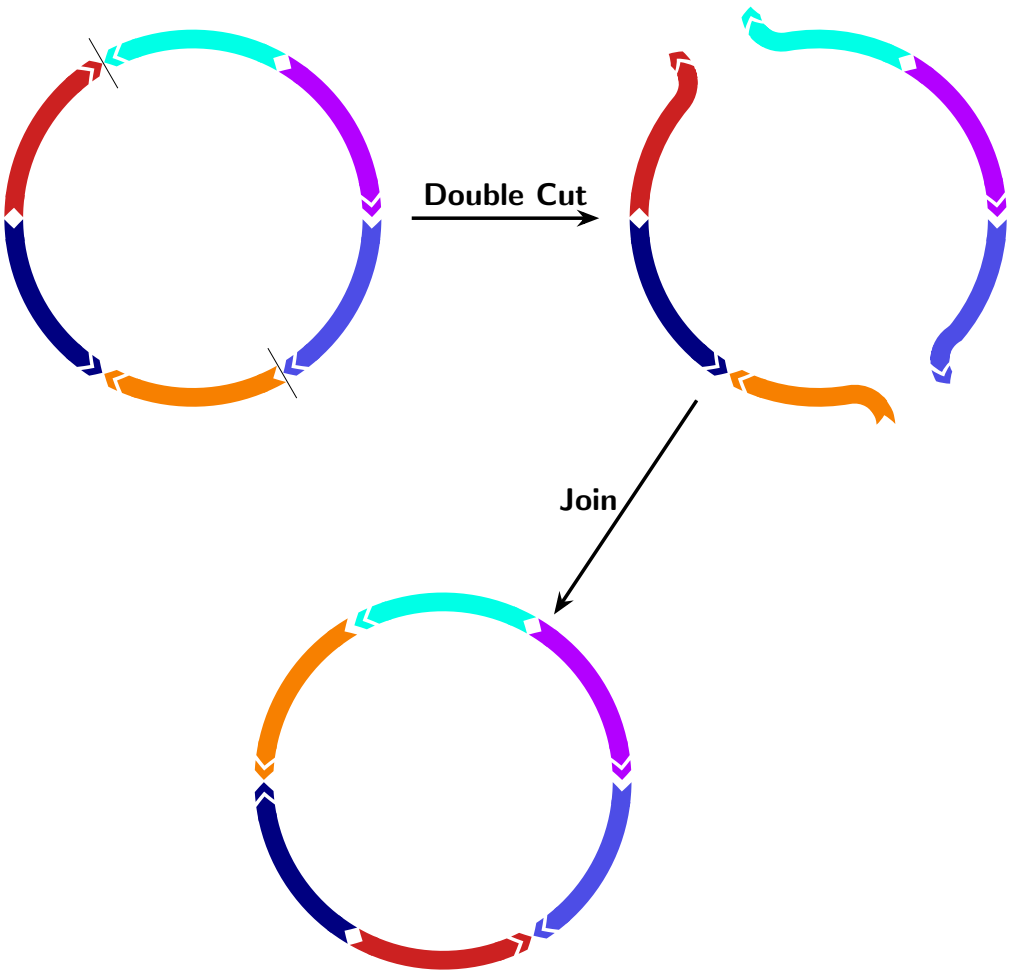

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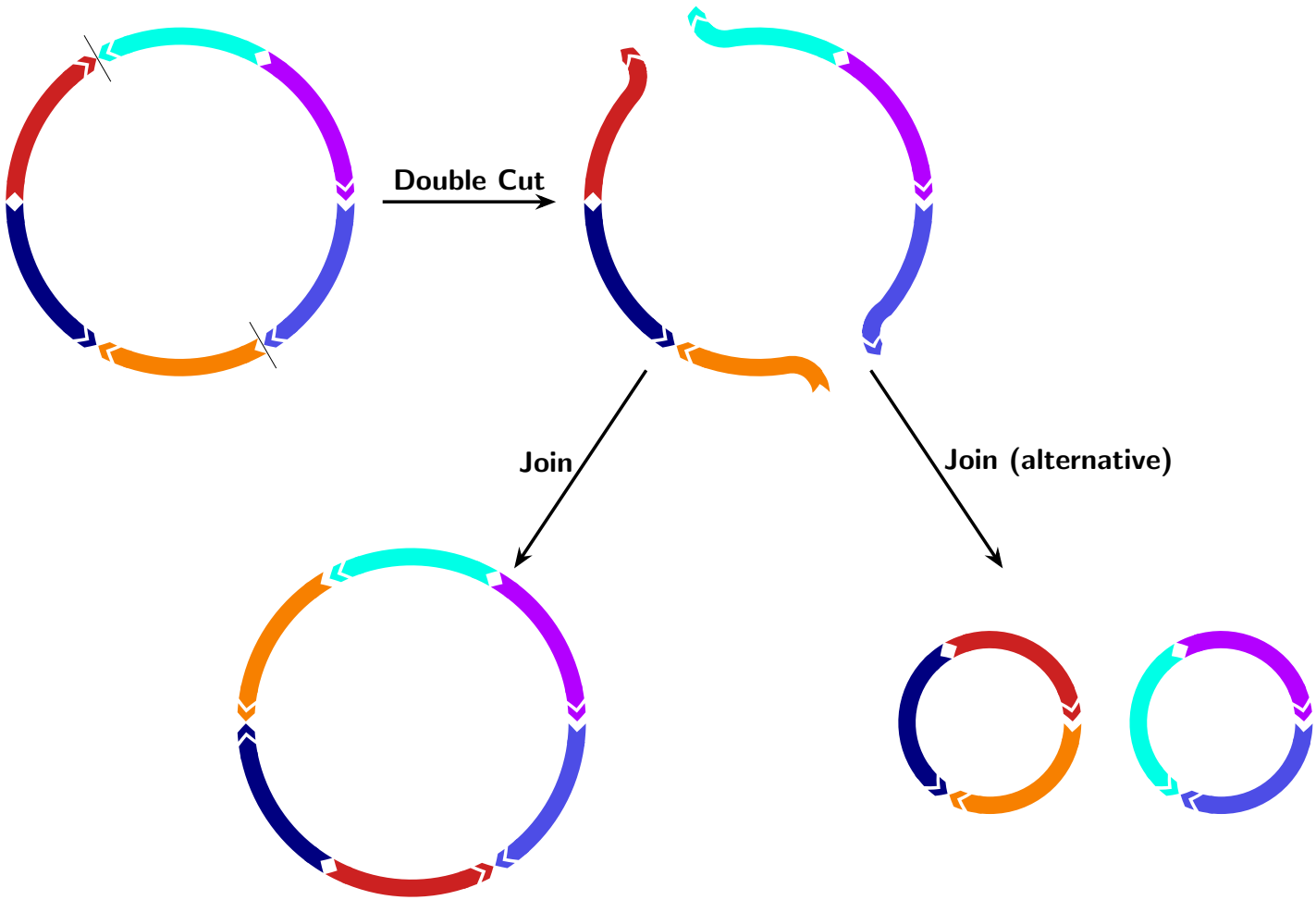
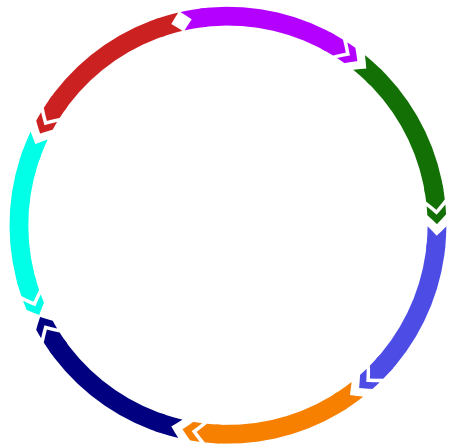


Insertions and Deletions



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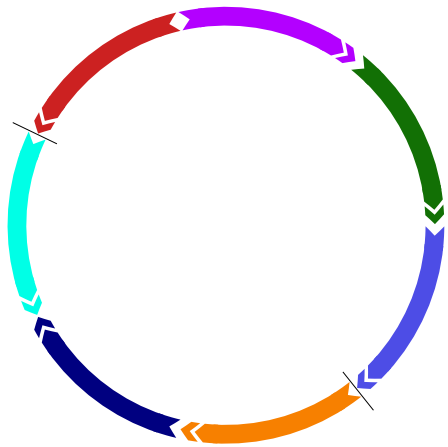

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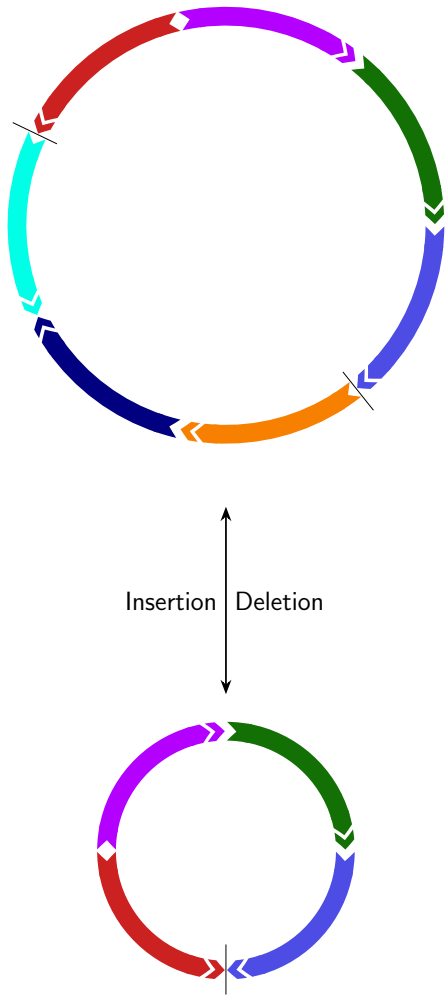
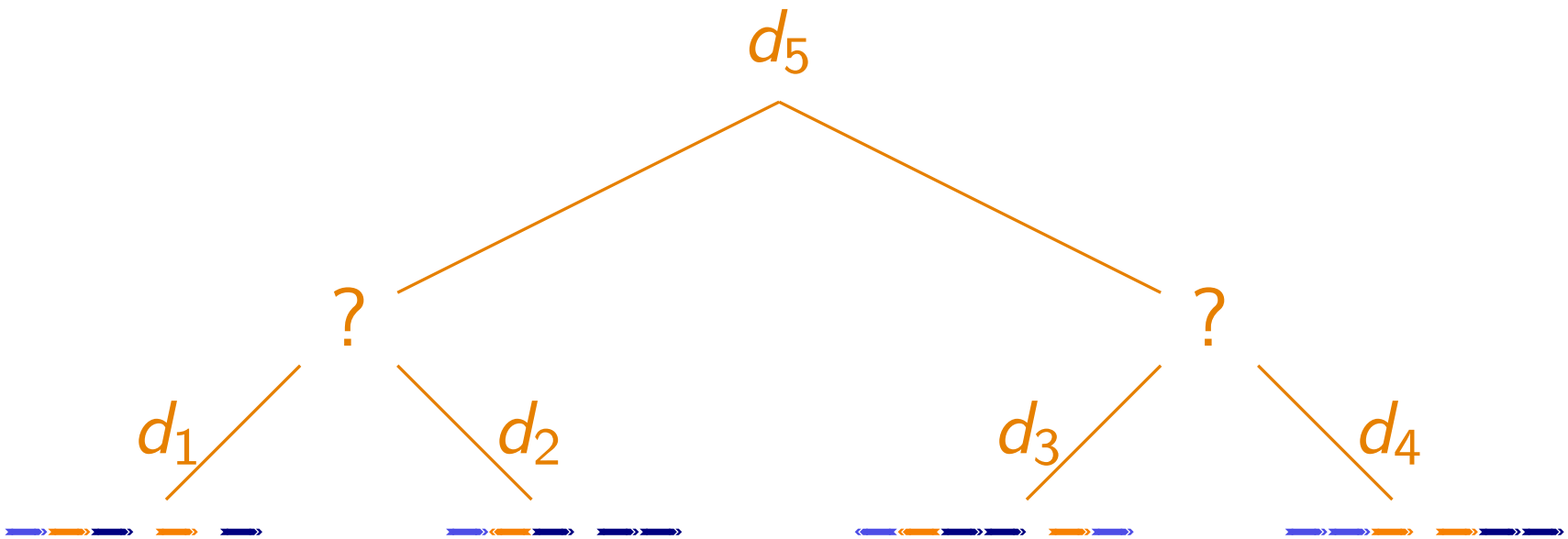


Small Parsimony for Natural Genomes

Minimize $d_1 + d_2 + d_3 + d_4 + d_5$



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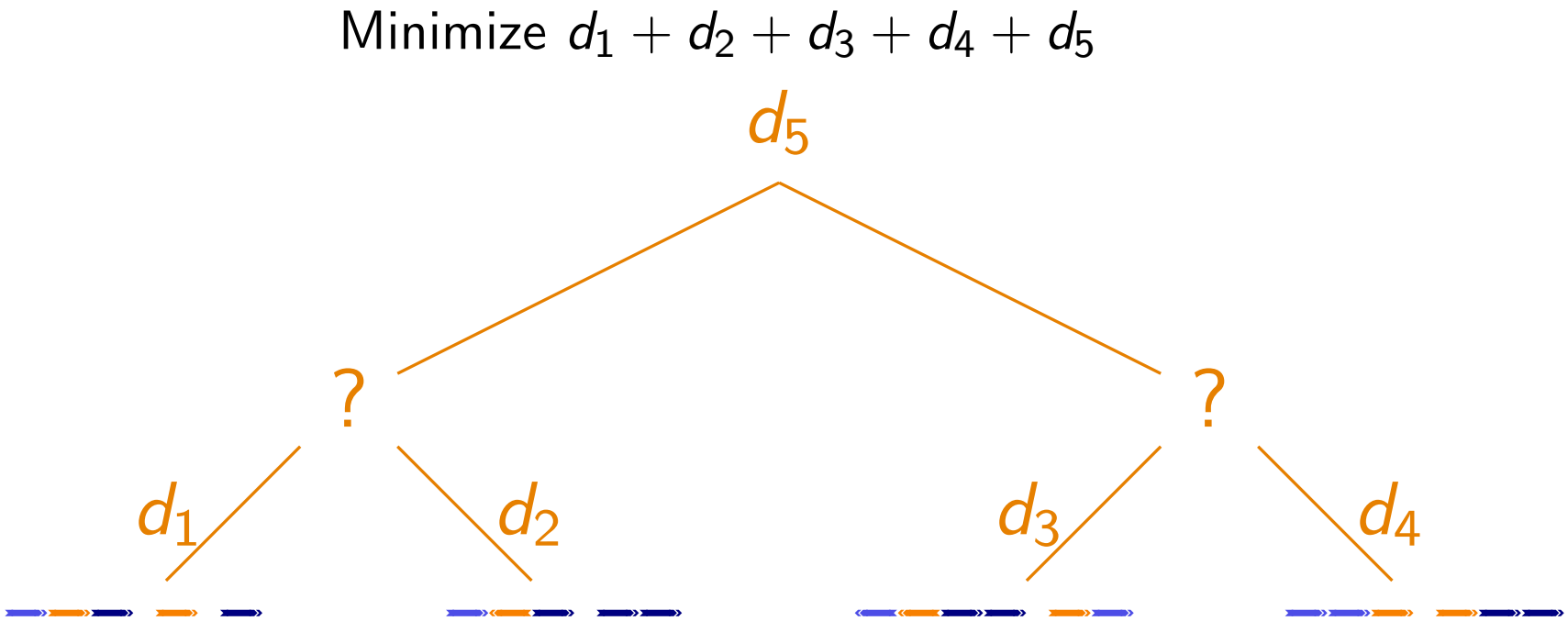
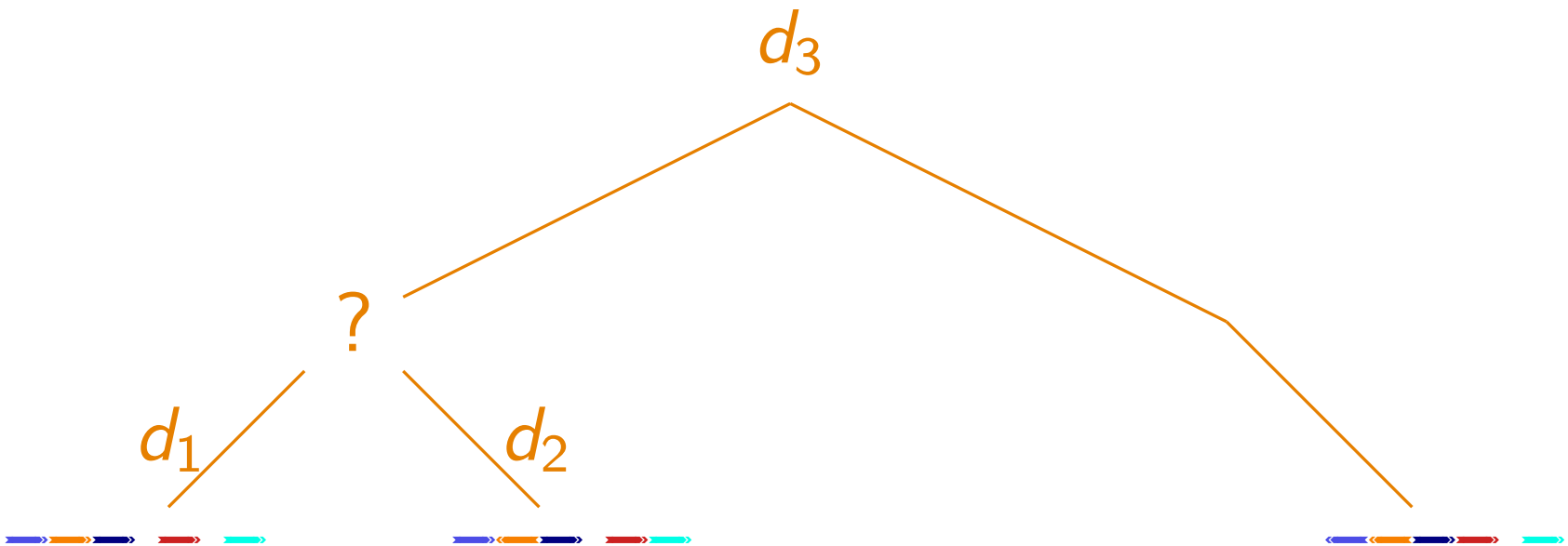


d_1, d_2, d_3, d_4, d_5: (Minimum number of) DCJ and indel operations between the genomes.

Small Parsimony for Natural Genomes



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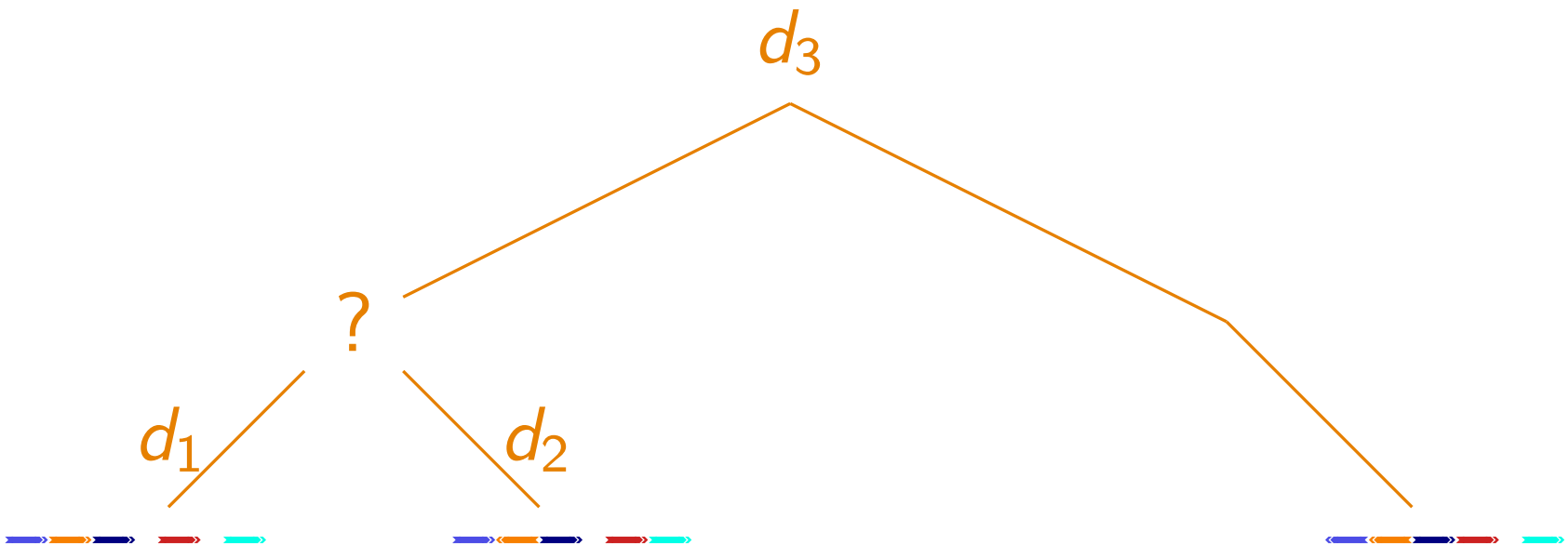

$\rightarrow$ NP Hard

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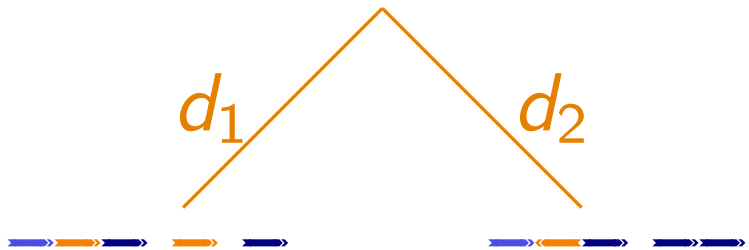

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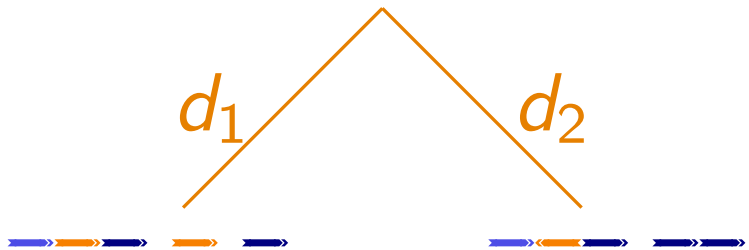

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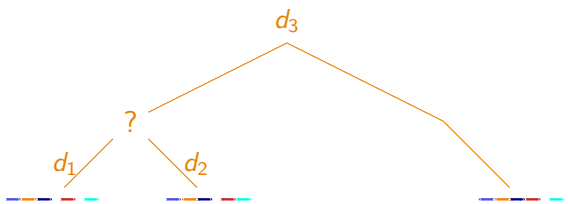
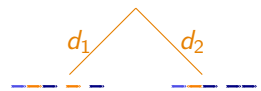


$\longrightarrow$ NP Hard



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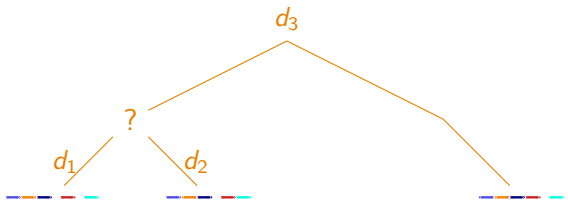

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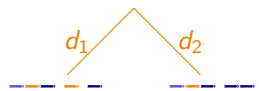

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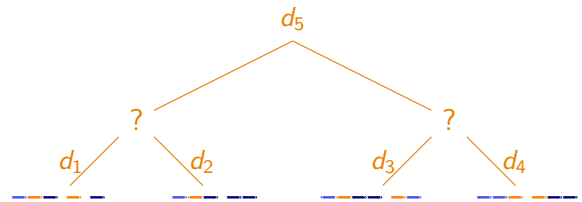

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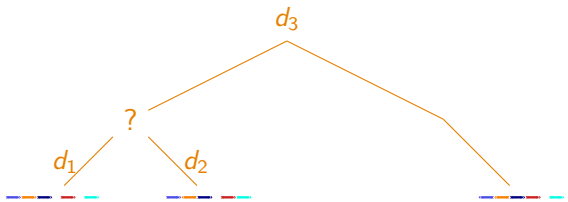

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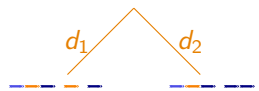

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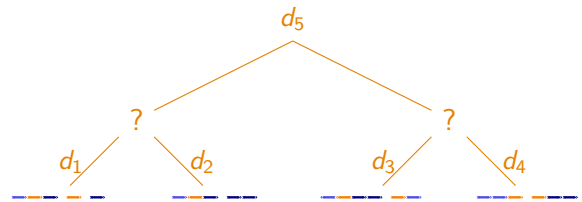

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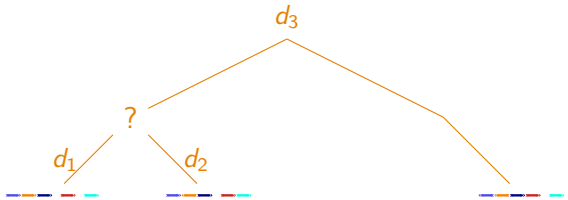

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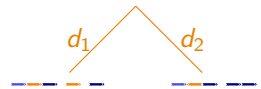

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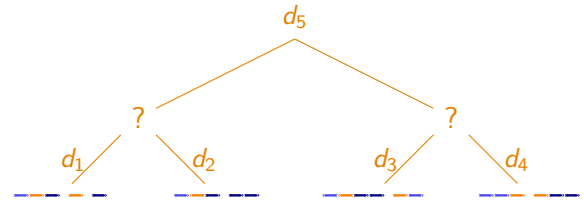


$\rightarrow$ NP Hard

$\rightarrow$ Solution via ILP

Integer Linear Programming (ILP)

Algorithm 1 Capping-free Small Parsimony

Objective

Minimize

$$\sum_{E \in E(T)} (\alpha\, \mathtt{f}_E + (\alpha - 1)\, \mathtt{w}_E)$$

Global level

For each genome $\mathbb{A} = (\mathcal{E} \cup \mathcal{T}, \mathcal{M} \cup \mathcal{A})$ of phylogeny T:

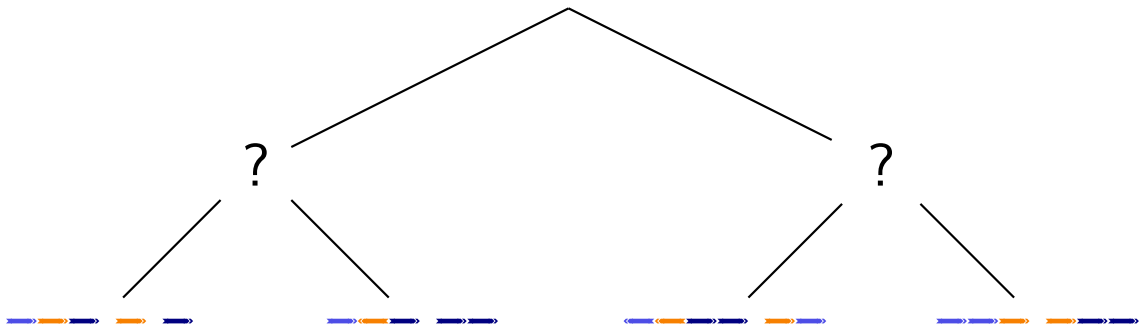
(C.01)	$\mathtt{g}_u = \mathtt{g}_v$	with $(u, v) \in \mathcal{M}$
(C.02)	$\sum_{m \in F} \mathtt{g}_{m^h} \geq L_F^{\mathbb{A}}$ $\sum_{m \in F} \mathtt{g}_{m^h} \leq H_F^{\mathbb{A}}$	for each family F
(C.03)	$\sum_{uv \in \mathcal{A}} \mathtt{a}_{uv} = \mathtt{g}_v$	$\forall v \in \mathcal{E} \cup \mathcal{T}$

Local level

For each edge $E = (\mathbb{A}, \mathbb{B}) \in E(T)$ with $\mathcal{CFMRD}(\mathbb{A}, \mathbb{B}) = (\mathcal{E} \cup \mathcal{T}, E_{\text{adj}} \; E_{\text{ext}} \cup E_{\text{self}})$:

(C.04)	$\mathtt{w}_E = \sum_{e \in E_{\text{adj}}} \mathbf{w}(e) x_e$
(C.05)	$\mathtt{f}_E = \mathtt{n}_E - \mathtt{c}_E + \mathtt{q}_E + \mathtt{s}_E$
(C.06)	$\mathtt{n}_E = \frac{1}{2} \sum_{e \in E_{\text{ext}}} \mathtt{x}_e$
(C.07)	$\mathtt{c}_E = \sum_{v \in \mathcal{E}} \mathtt{r}_v^c$
(C.08)	$2\mathtt{q}_E \geq \mathtt{p}_E^{ab} + \mathtt{p}_E^{\max a} + \mathtt{p}_E^{\max b} - \mathtt{p}_E^{AB}$

Vast Solution Space for Ancestral Adjacencies



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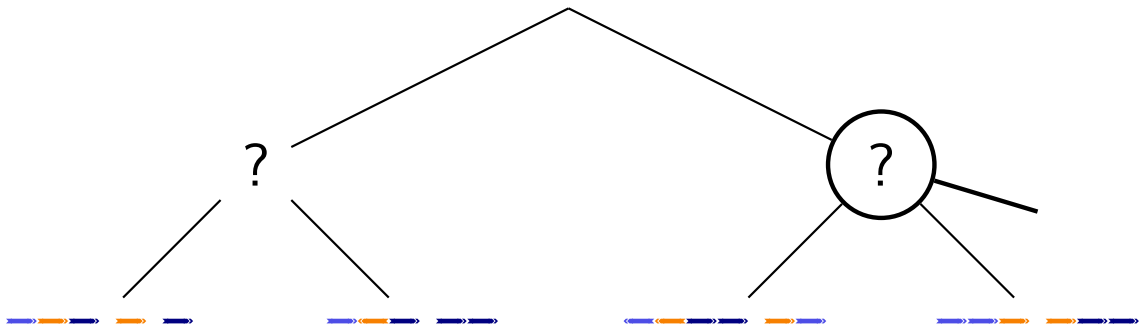
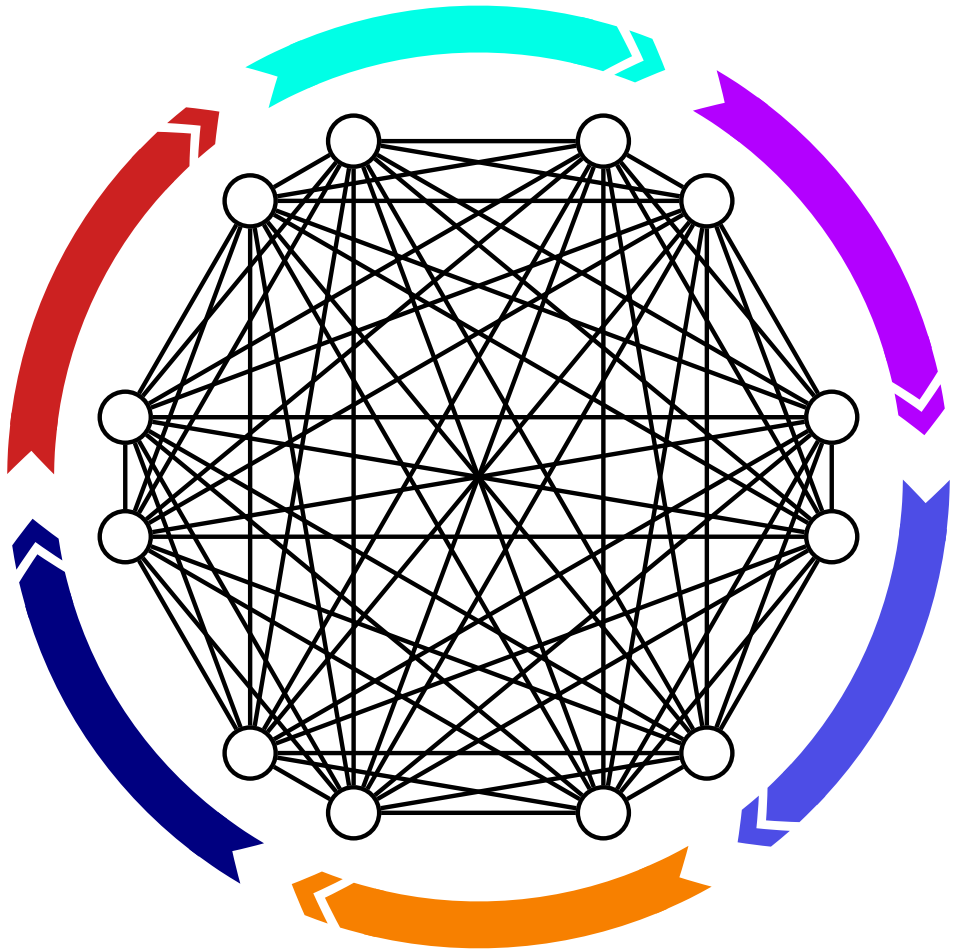


Vast Solution Space for Ancestral Adjacencies



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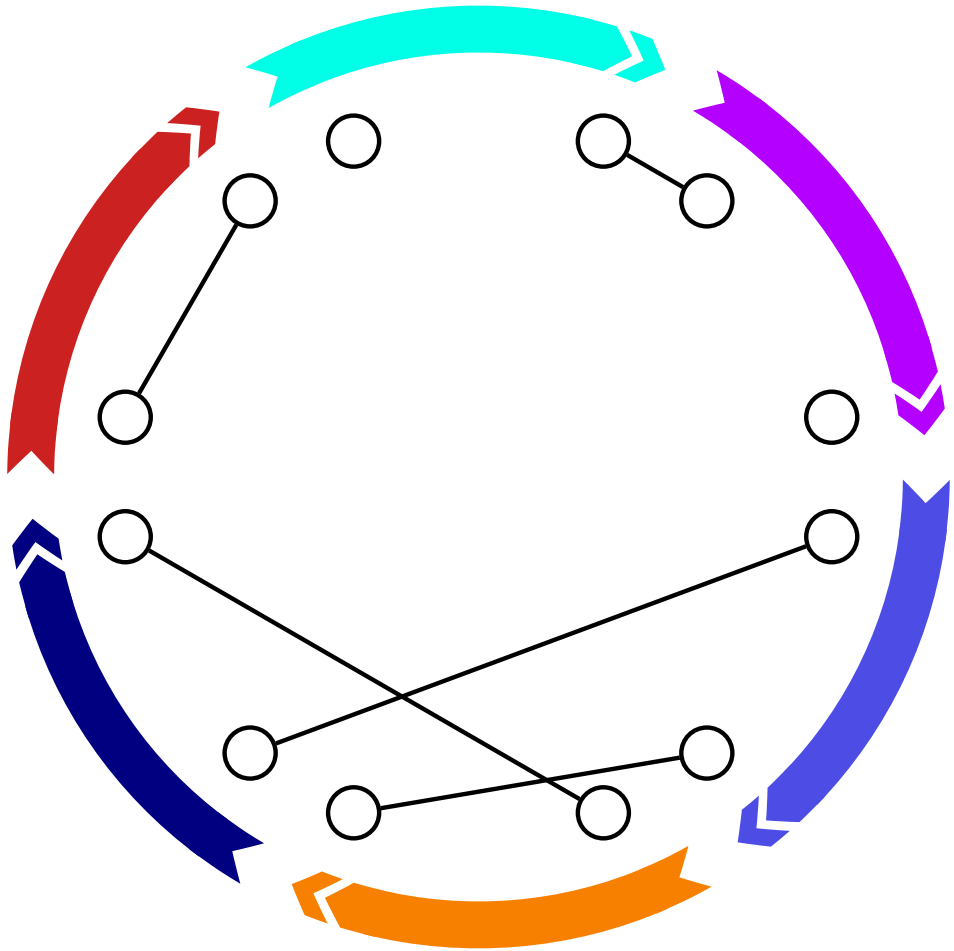

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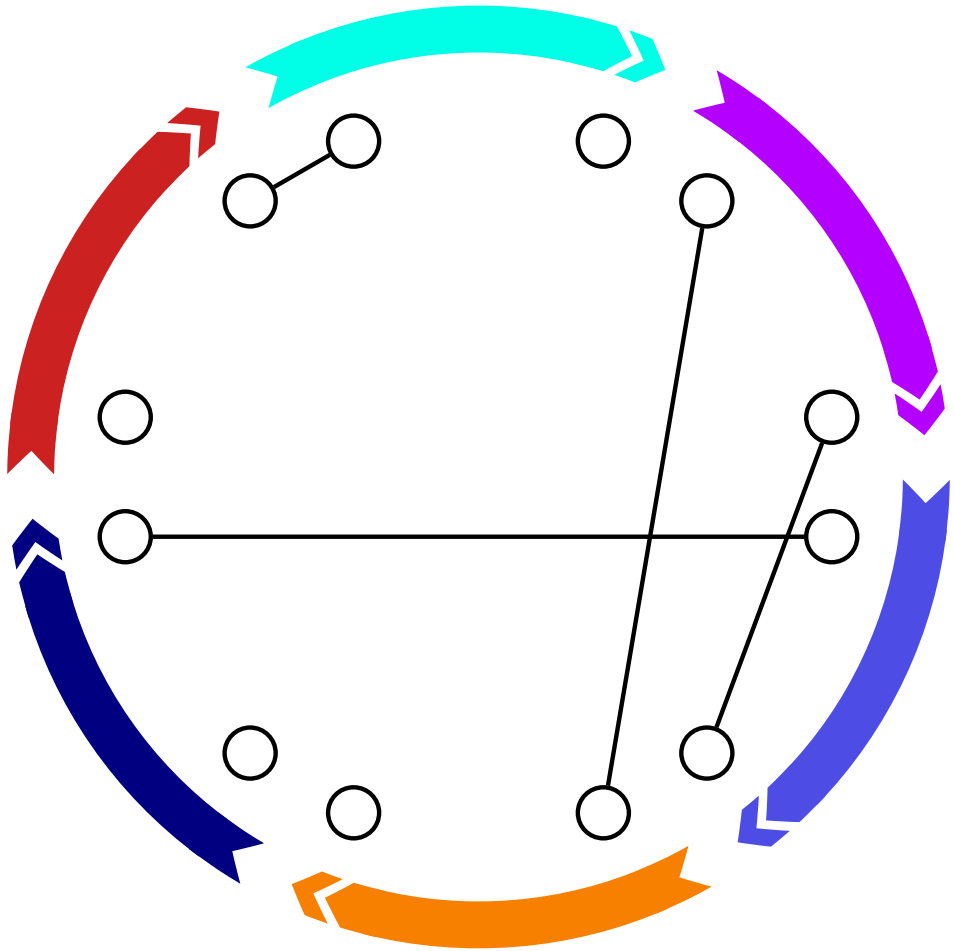

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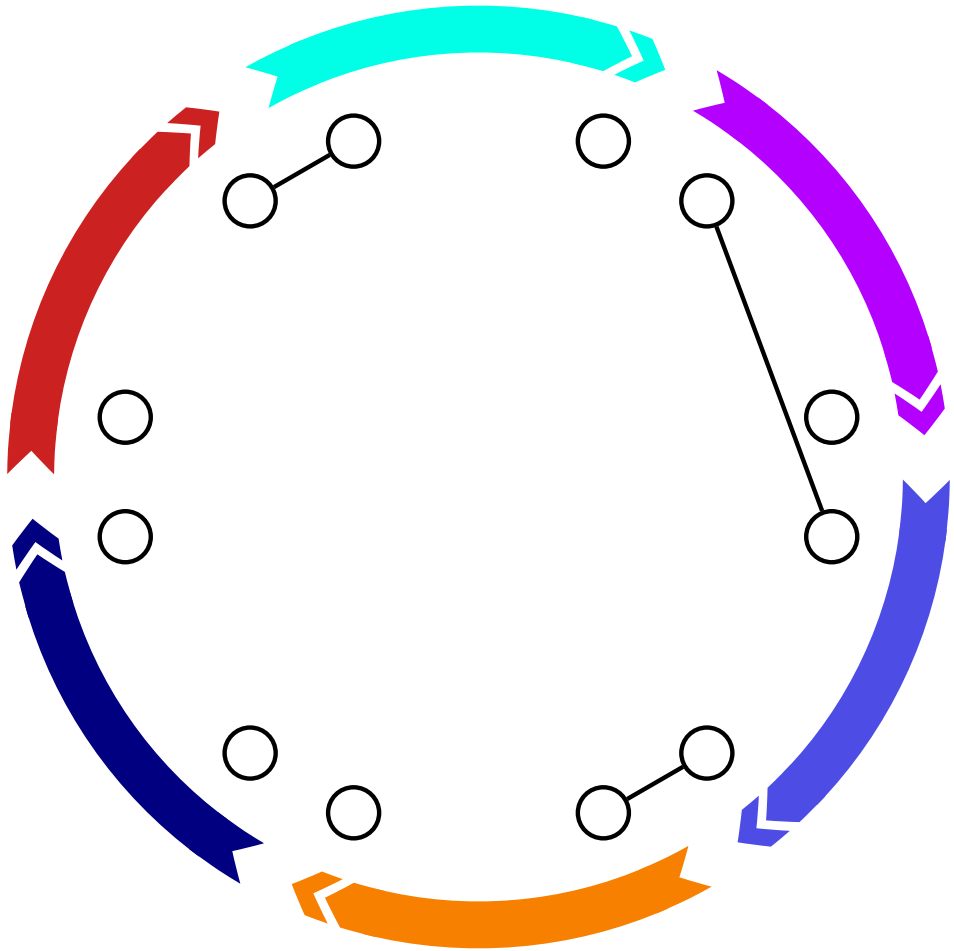

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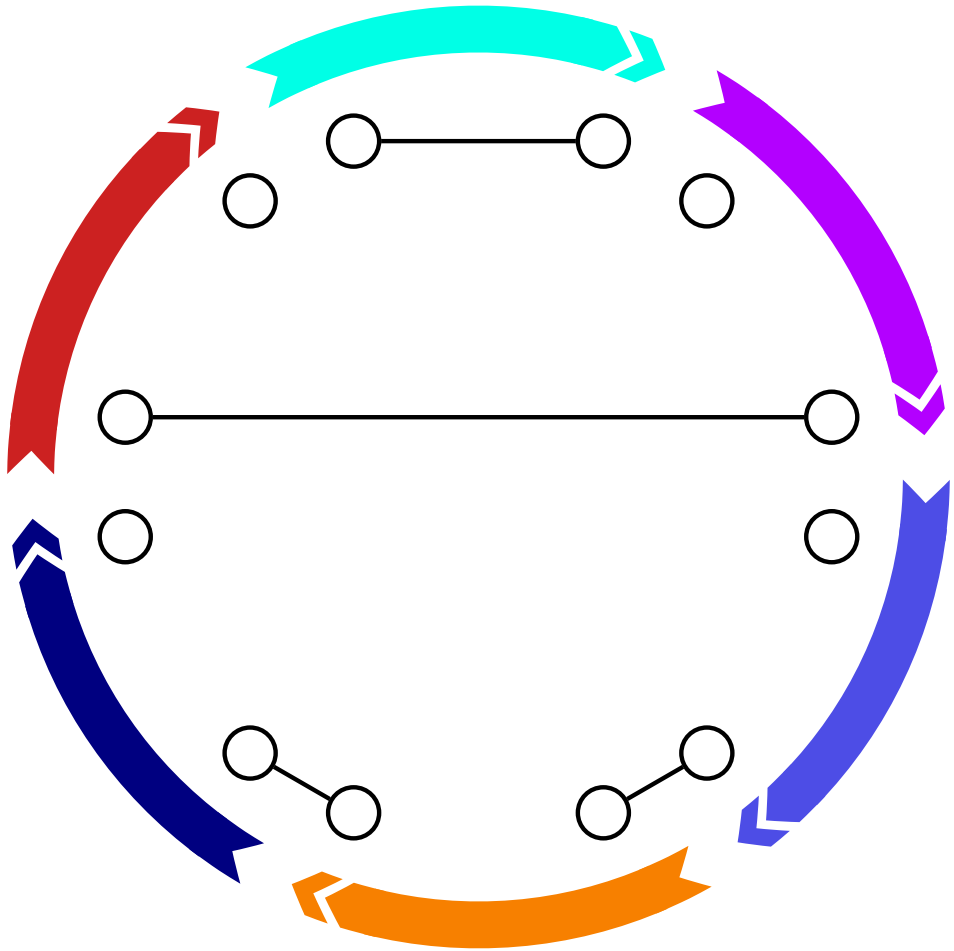
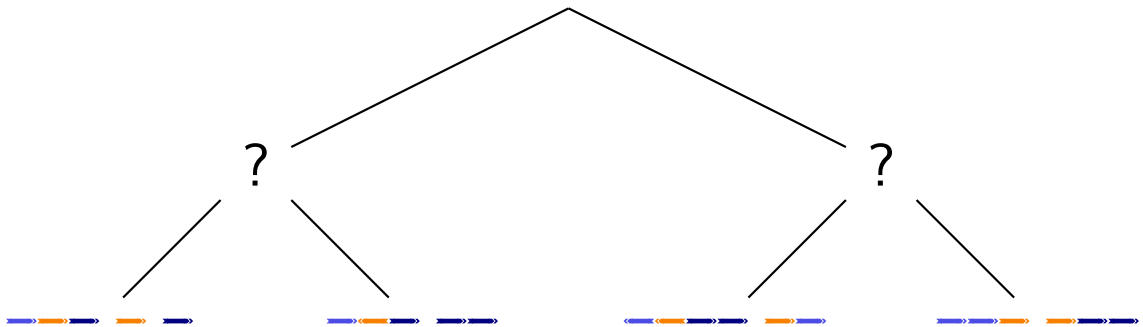


Heuristic Solution: Filter Adjacencies Based on Leafs



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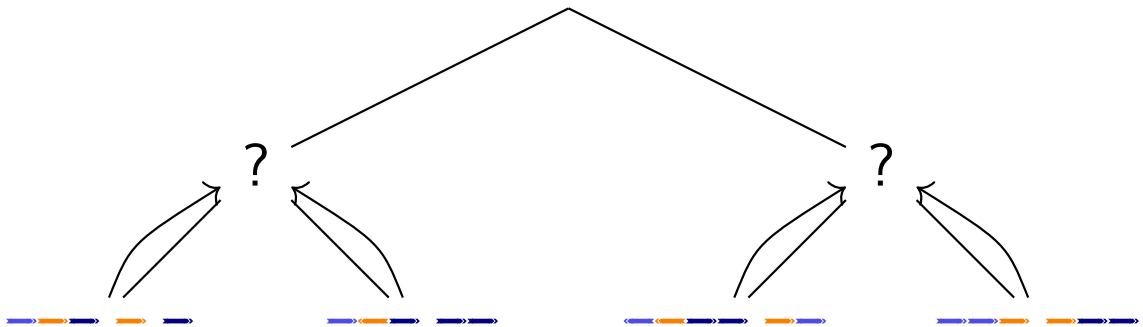
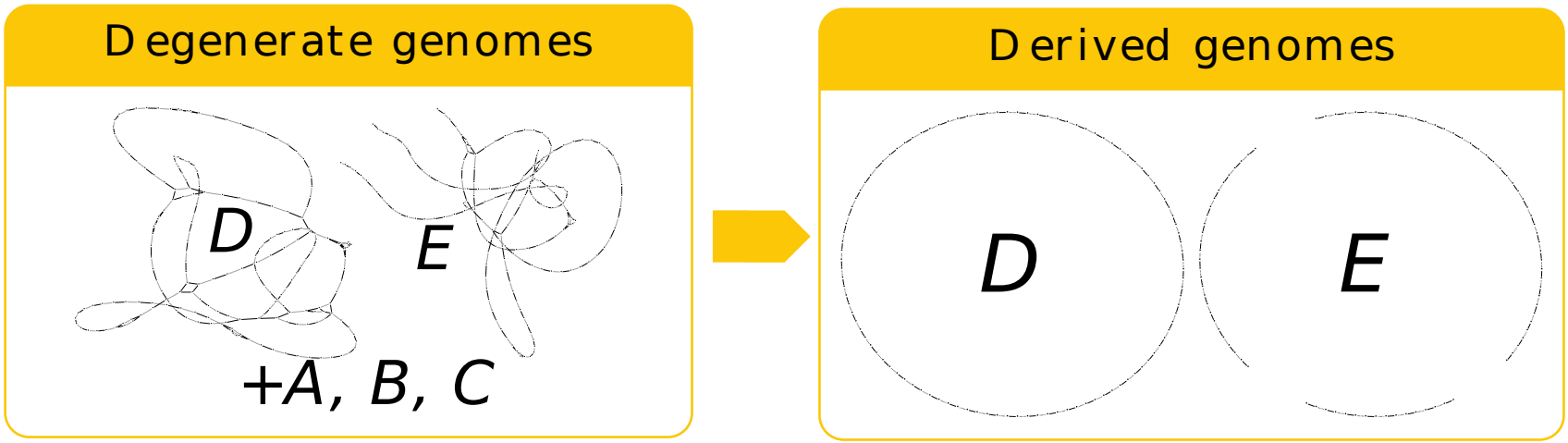


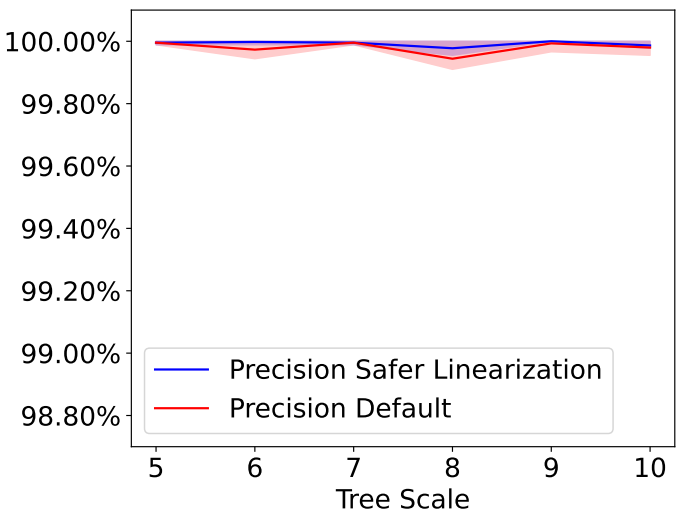
Degenerate Genomes

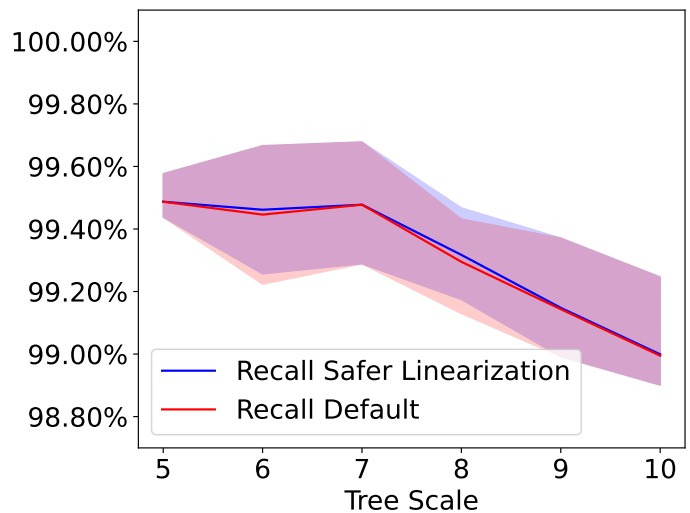


(Slightly) Adapted from (Doerr, Chauve, 2021).

Degenerate Genomes - the Good

On simulated data (ZOMBI+pre-filtering with DeCoSTAR), *if the ground truth adjacencies are represented in the degenerate genome*:





Degenerate Genomes - the Bad

- Good pre-filtering (DeCoSTAR) requires gene trees.

- Is not exact.

Our idea: Filter and Solver Tricks

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- Filter out adjacencies that are provably not needed.
  $\rightarrow$ Exploit features of the data:

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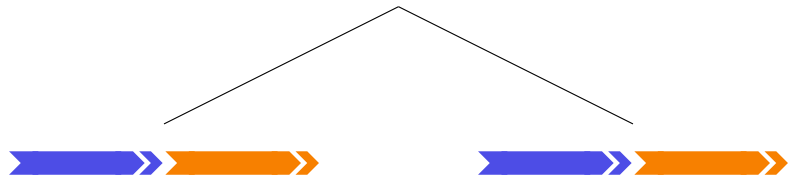

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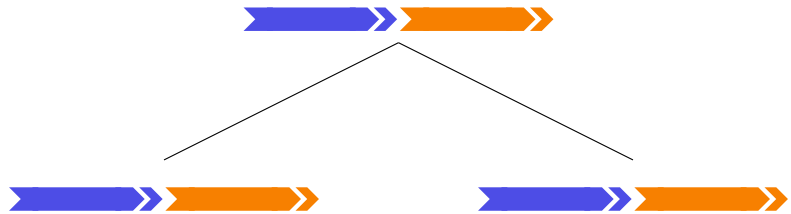

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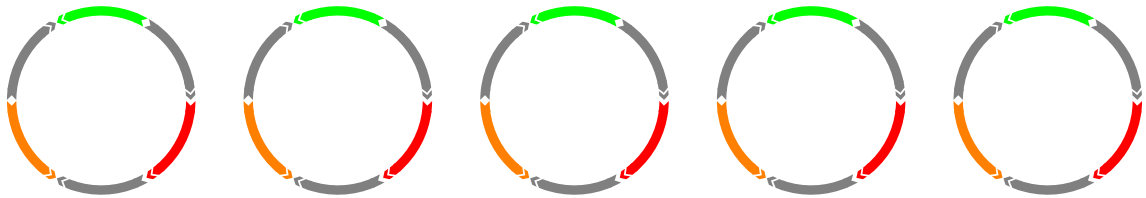

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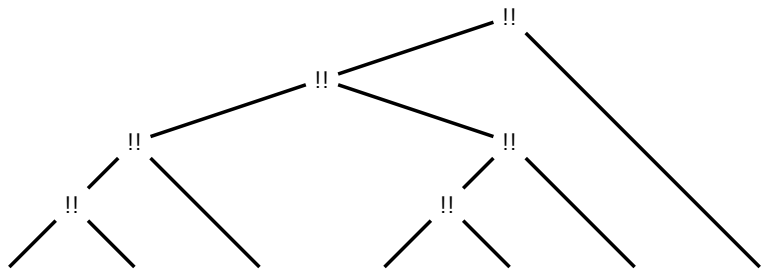

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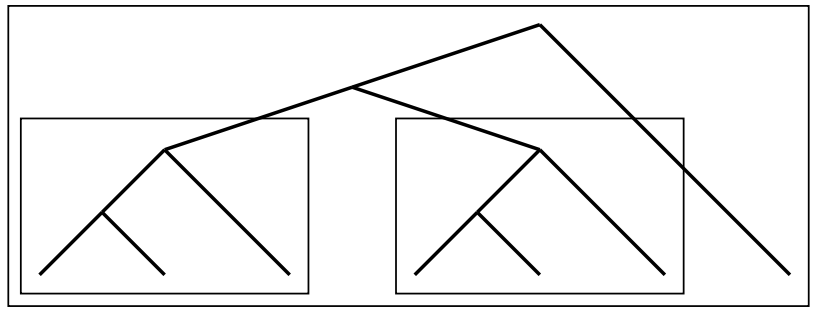

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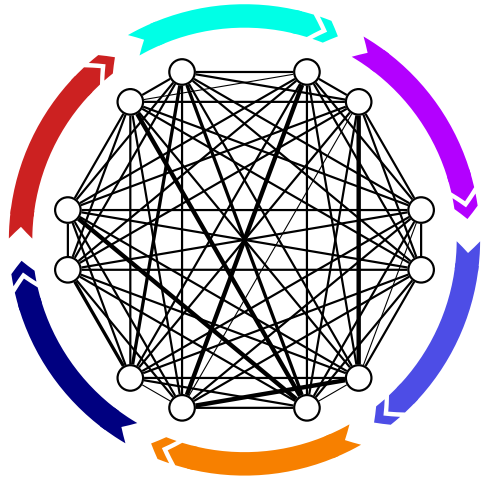

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Extremely Preliminary Results

gurobi 12 on 1 thread with 1 hour time limit on all lineages (17) with 20 leaves or fewer

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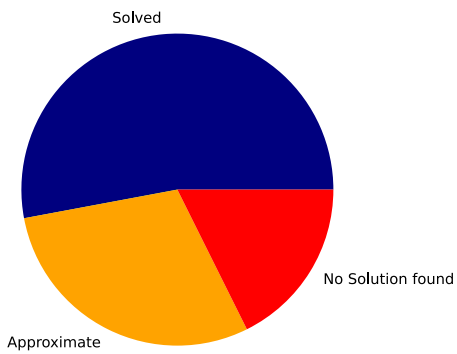
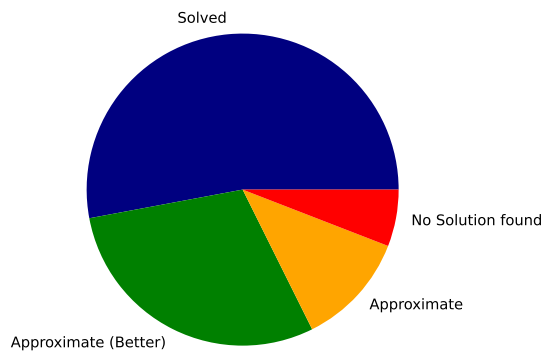
Unoptimized



Optimized



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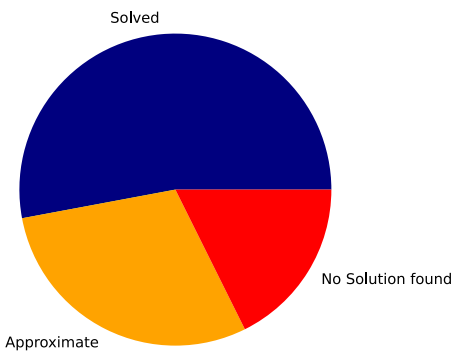
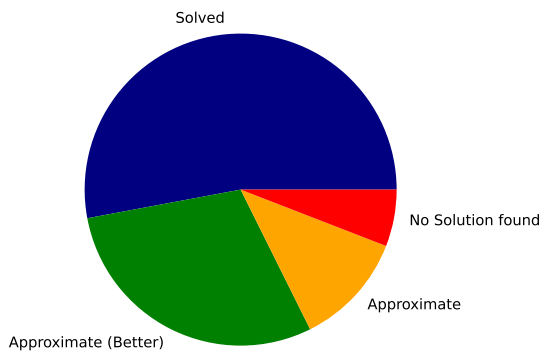


Optimized



- Main problem seems to be proving optimality.

SPP - Long Term Perspectives

- Transfer bounds from less complex (sub-) problems

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- SPP-variant that can model other types of events (horizontal transfers, chromosome duplication,...)
- Large Parsimony problem (no given tree)

CARP - A Specialized Problem for Pangenomes

Joint work with Jens Stoye

Quantifying Rearrangement Complexity in Pangenomes - Intuition

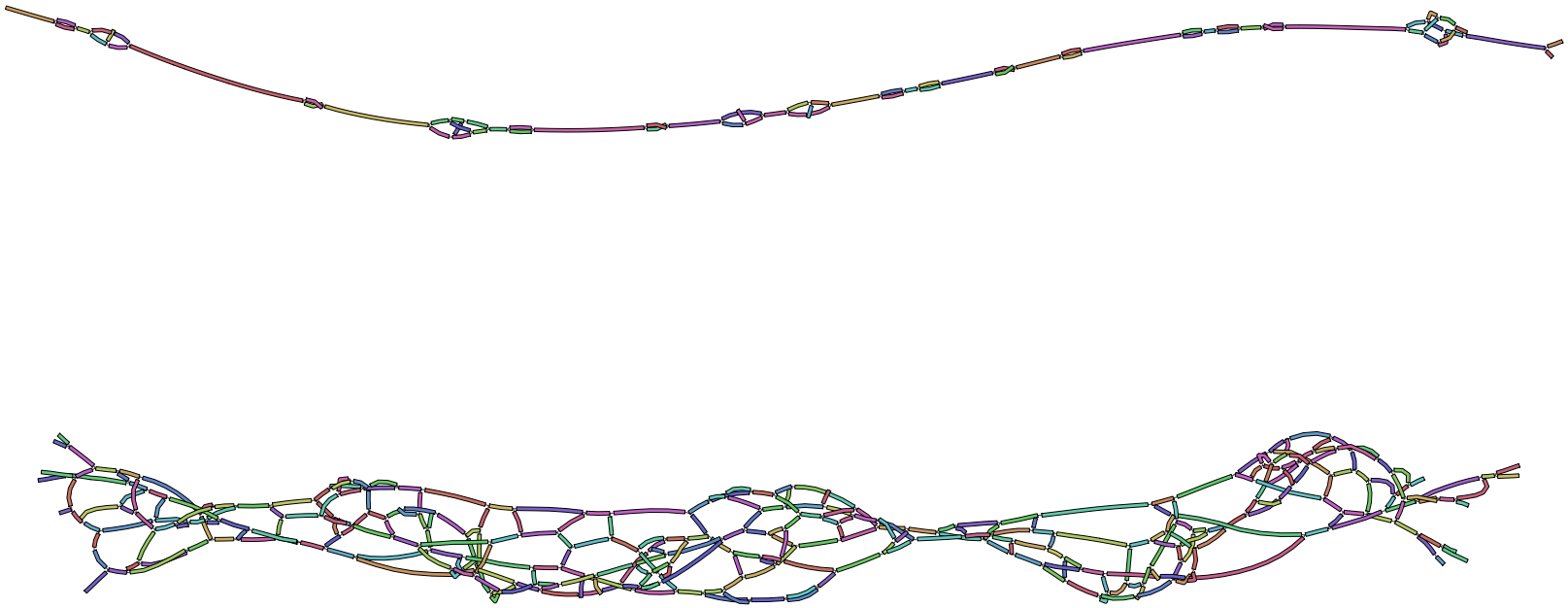

Image by courtesy of Luca Parmigiani

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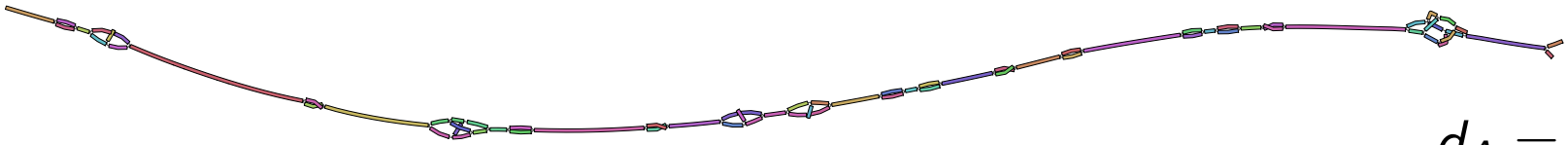
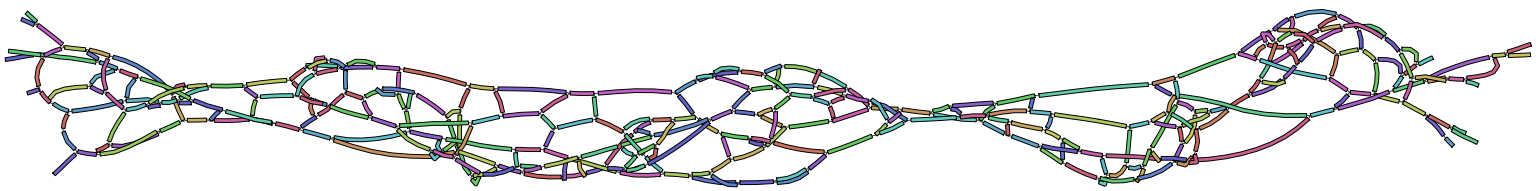


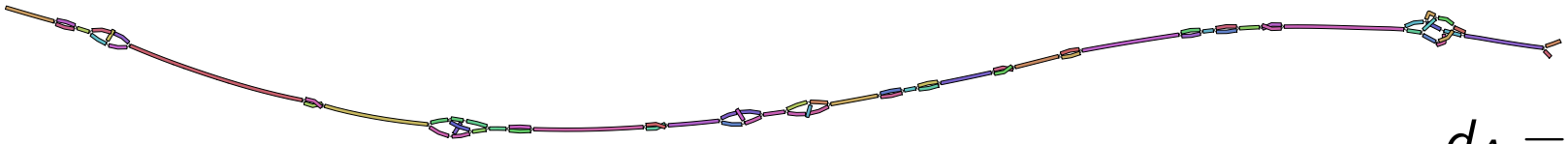
$d_A = 14$



$d_B = 107$

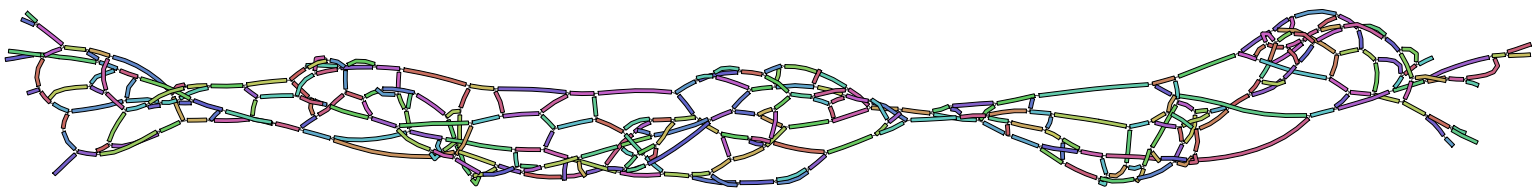
Image by courtesy of Luca Parmigiani

Quantifying Rearrangement Complexity in Pangenomes - Intuition



$d_A = ??$

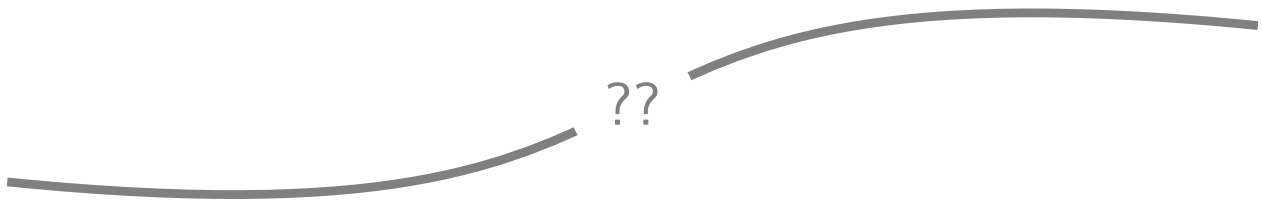
$d_A < d_B$



$d_B = ??$

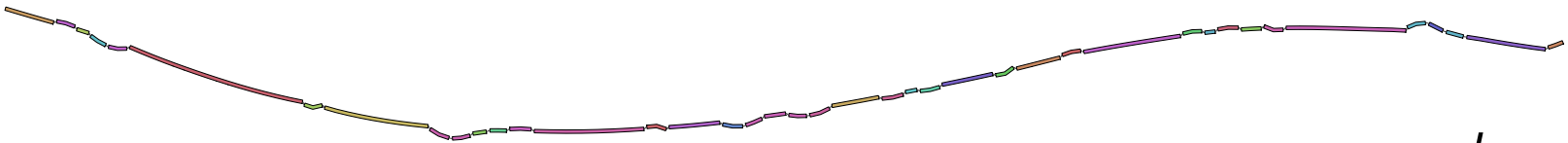
Image by courtesy of Luca Parmigiani

Quantifying Rearrangement Complexity in Pangenomes - Strategy



Quantifying Rearrangement Complexity in Pangenomes - Strategy

~~Boring~~ **Simple Pangenome**



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Quantifying Rearrangement Complexity in Pangenomes - Strategy

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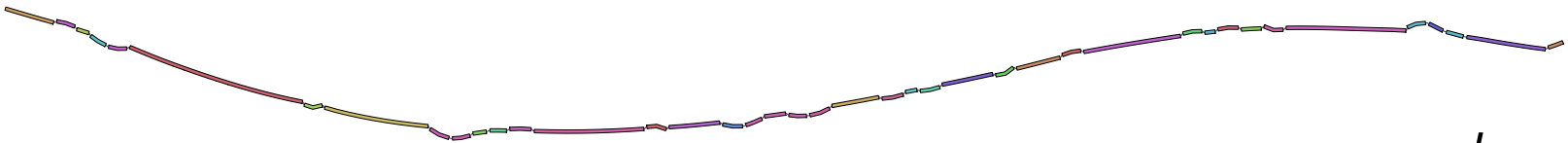

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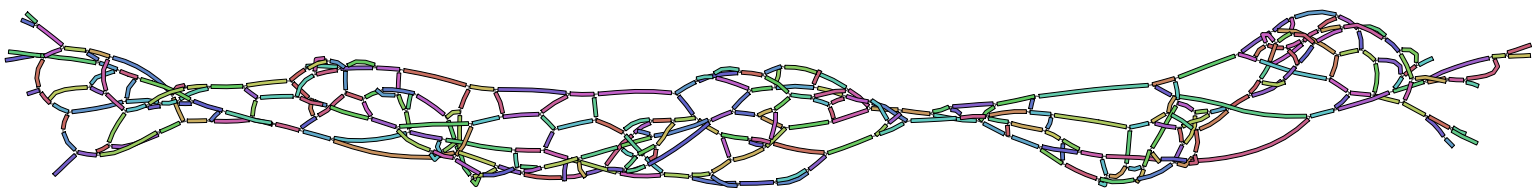

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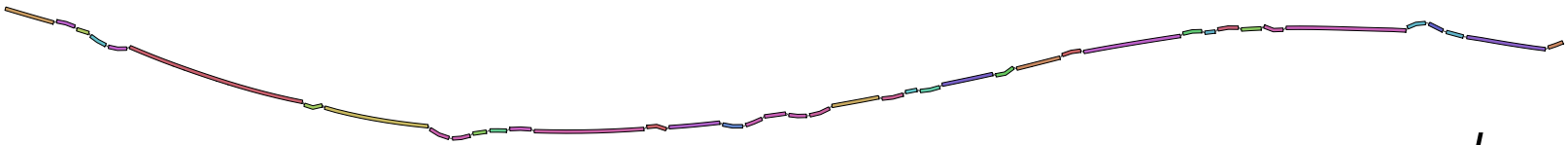
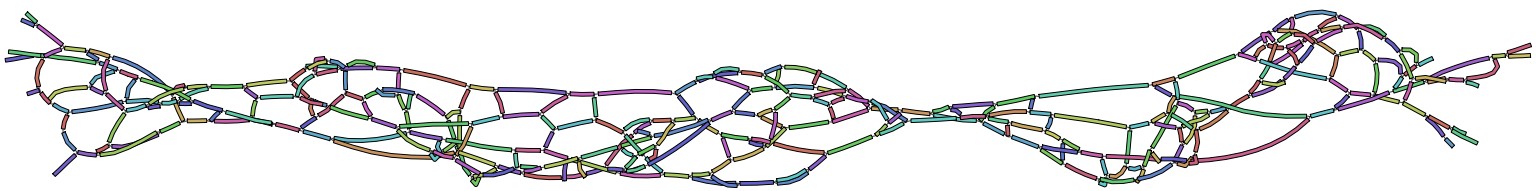


$d_X = 0$

Transform by operations T



$d_B = |T|$

Multi-Breakpoint Graph (MBPG)

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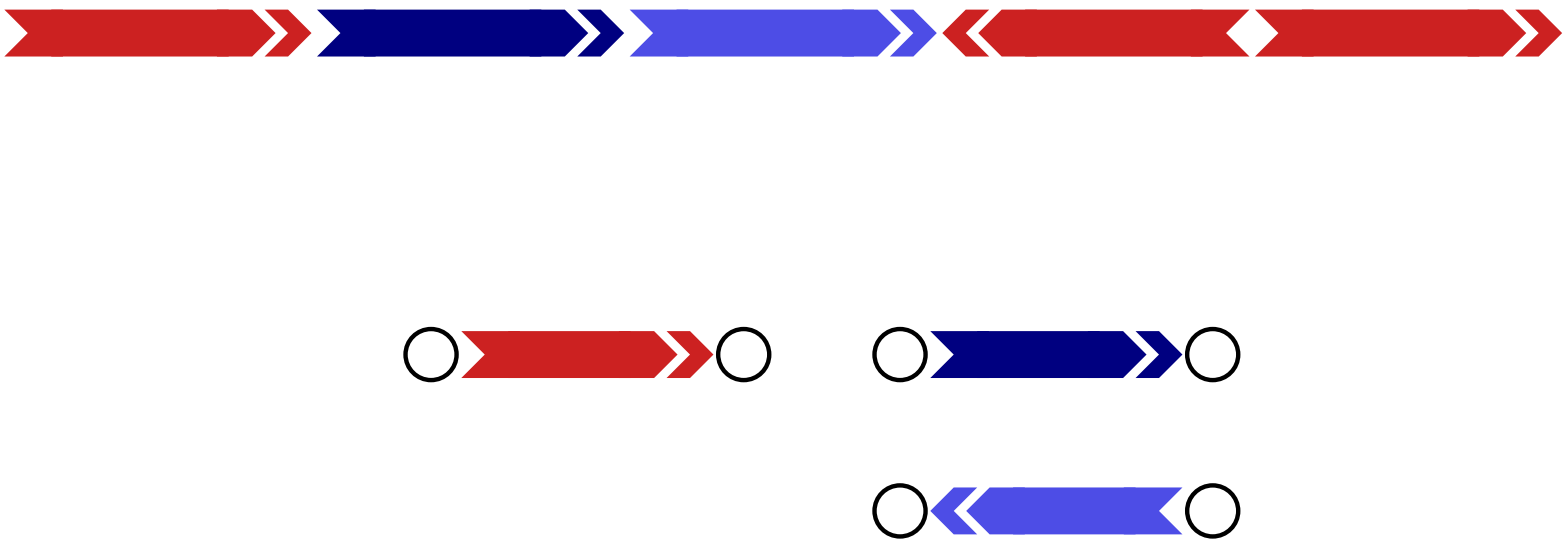

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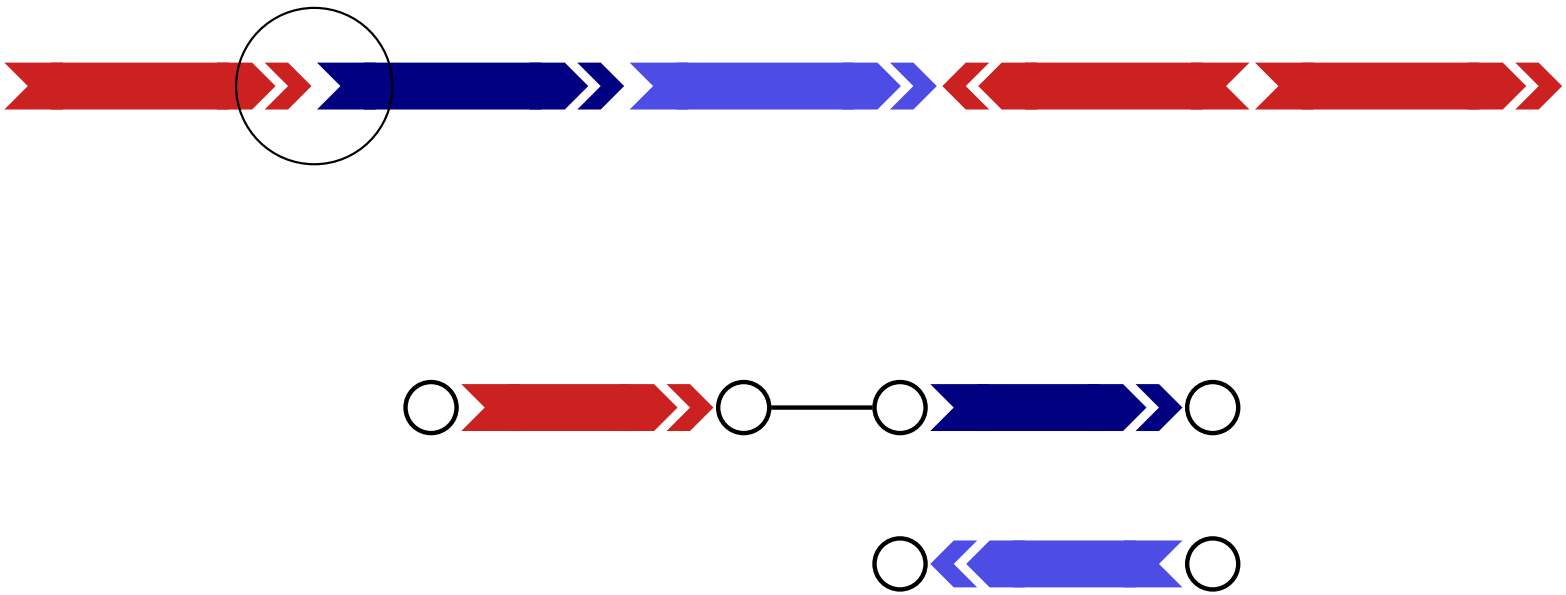

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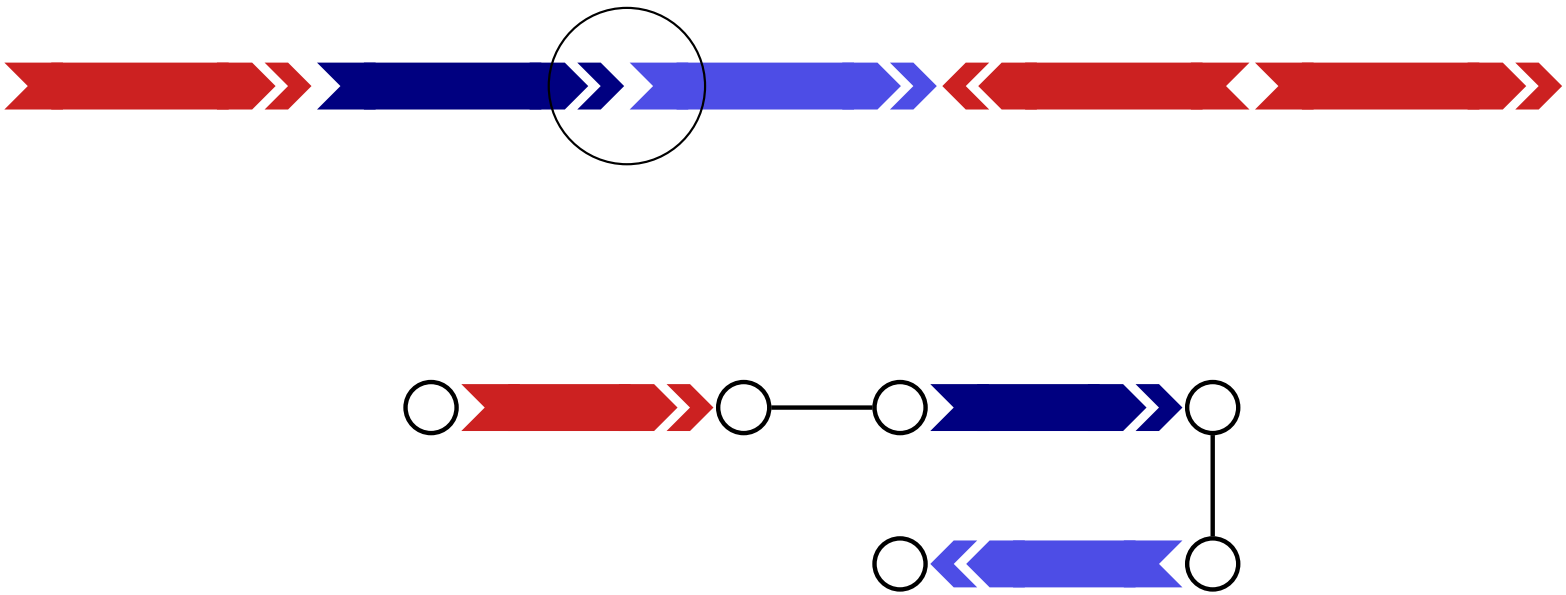

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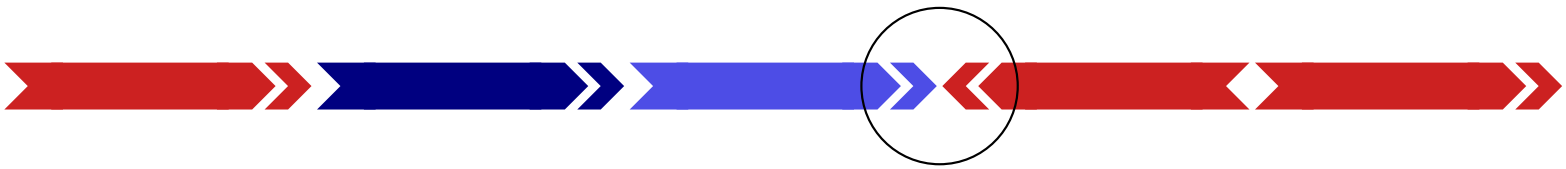

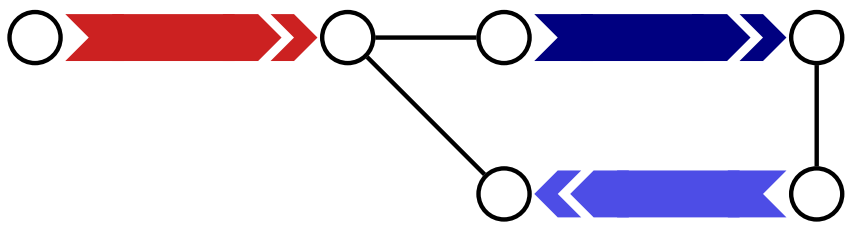

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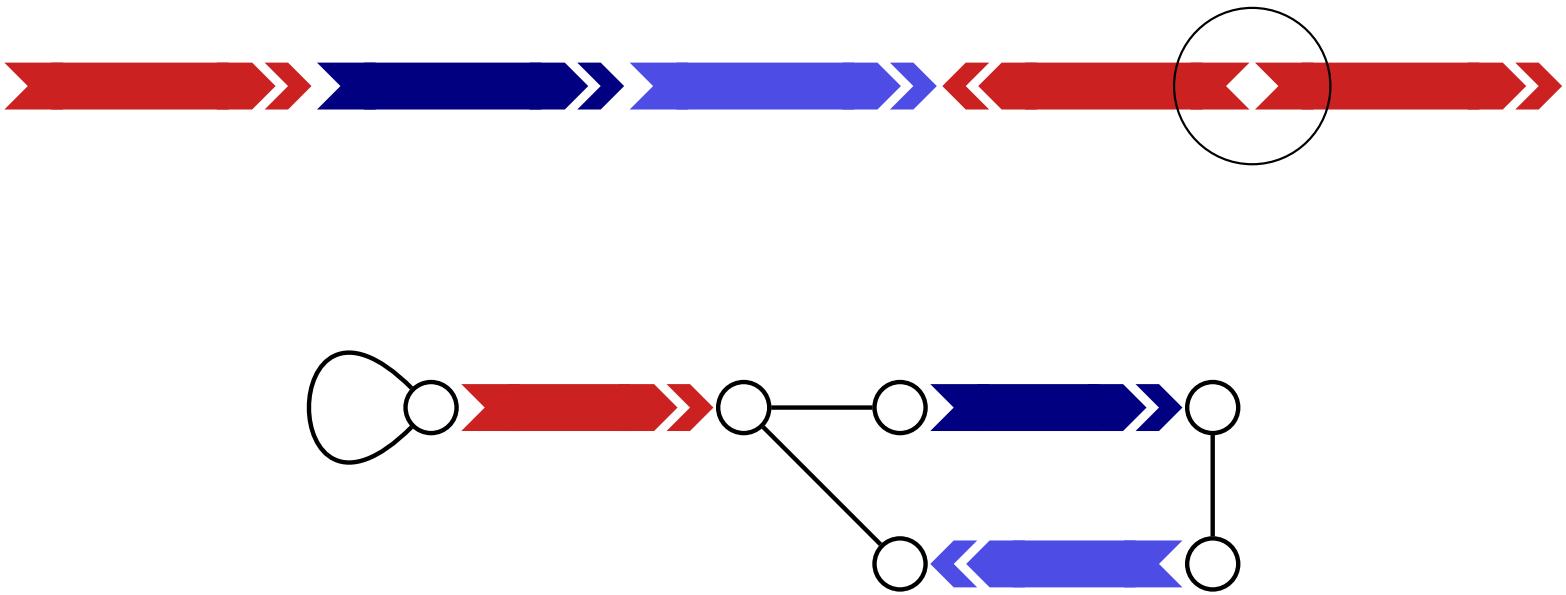

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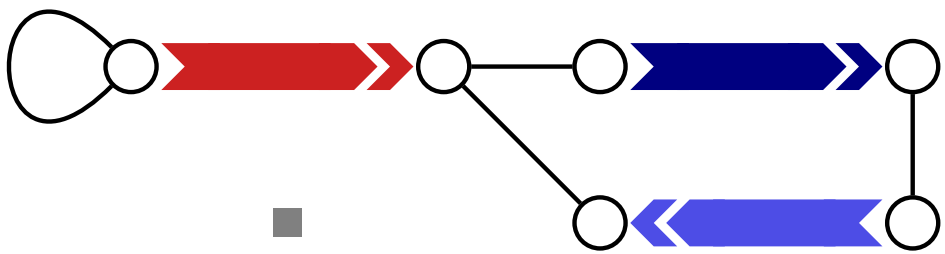

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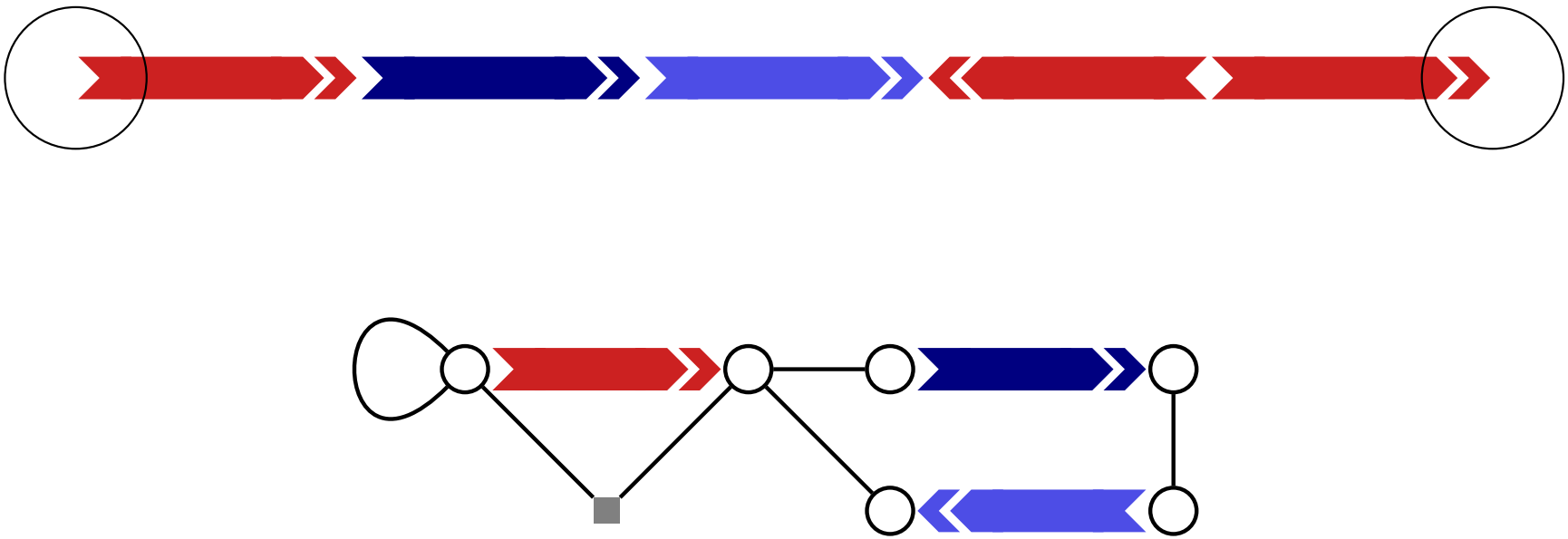

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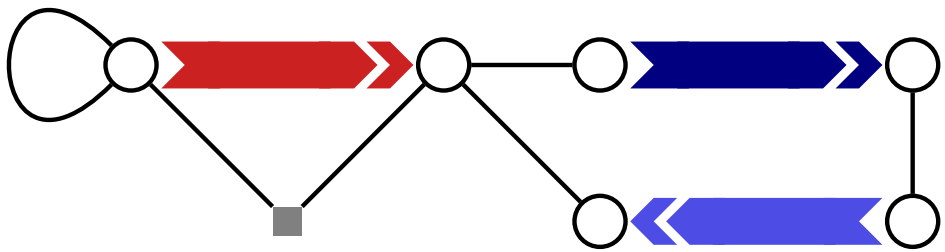
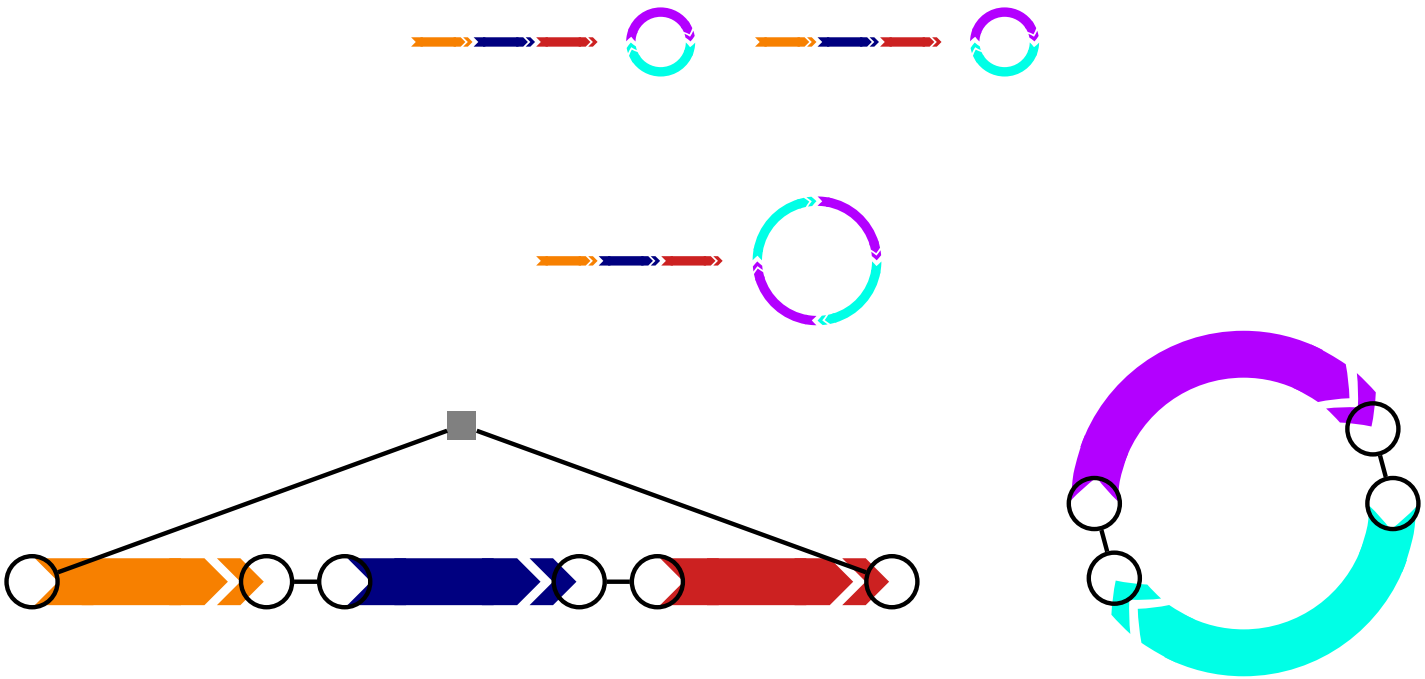


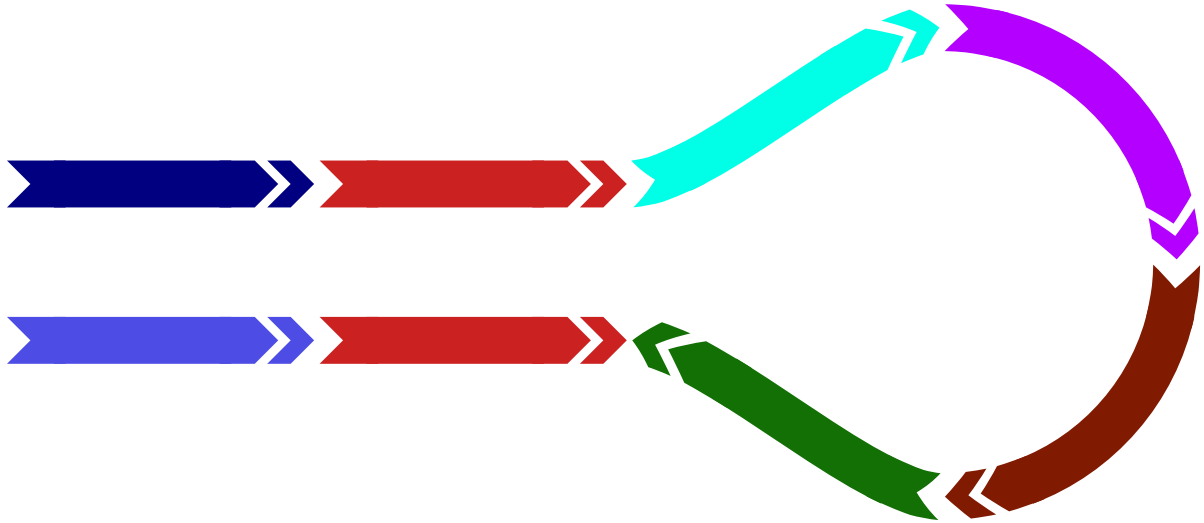
- GFA format (w/o sequence) can be represented as an MBPG
- Note: We still assume local variants have been filtered

MBPG of a Simple Pangenome

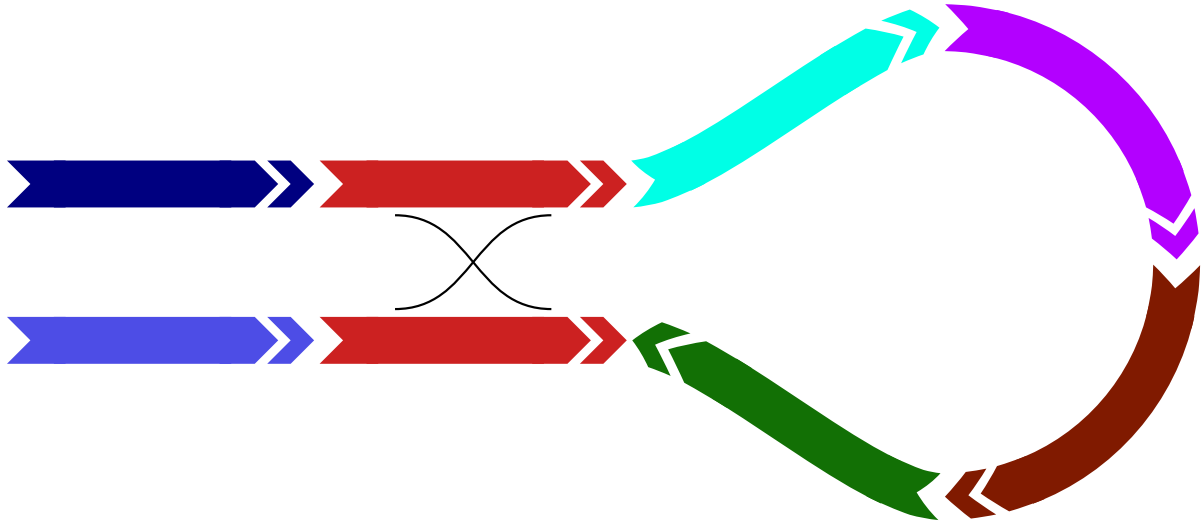


- Simple pangenome $\iff$ adjacencies are a perfect matching

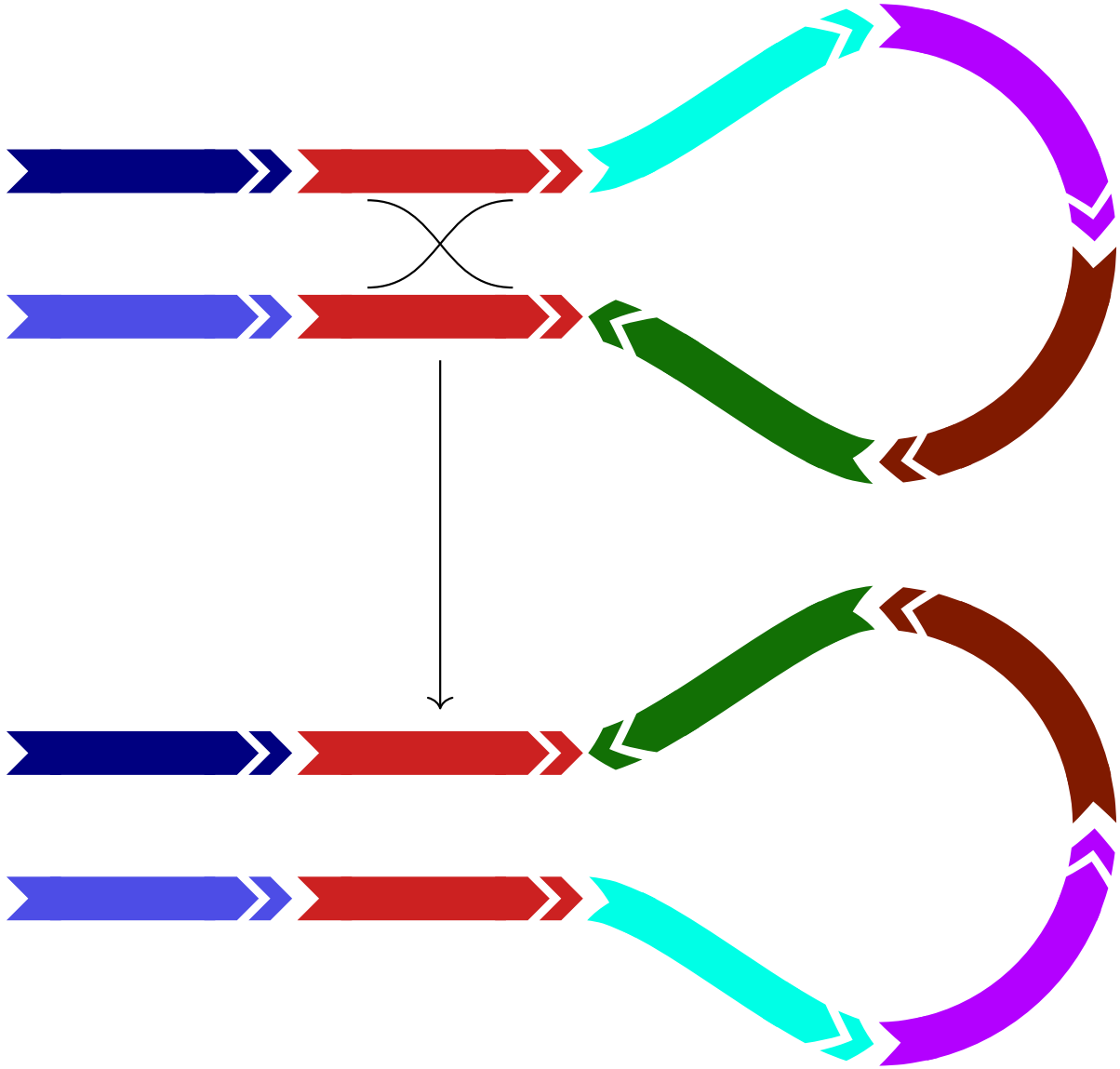
Rearrangements and Homologous Recombinations



Rearrangements and Homologous Recombinations



Rearrangements and Homologous Recombinations



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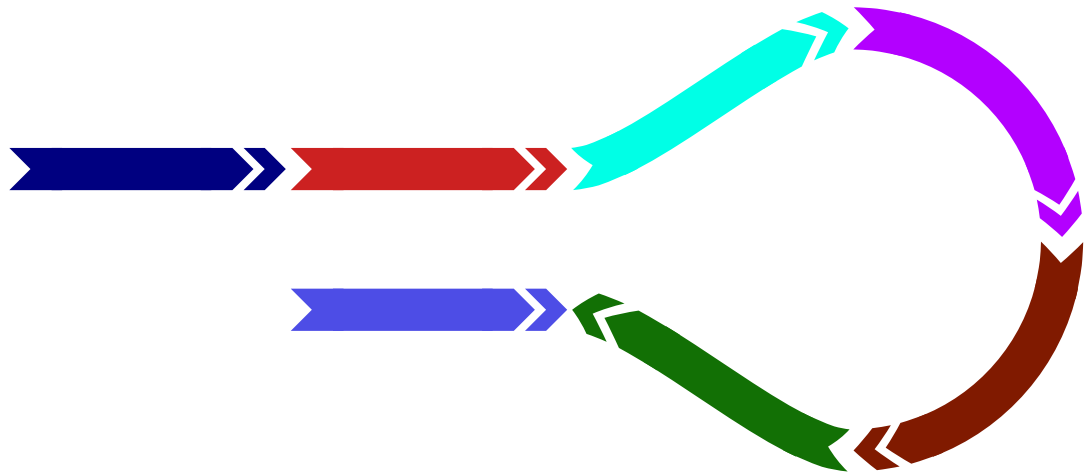

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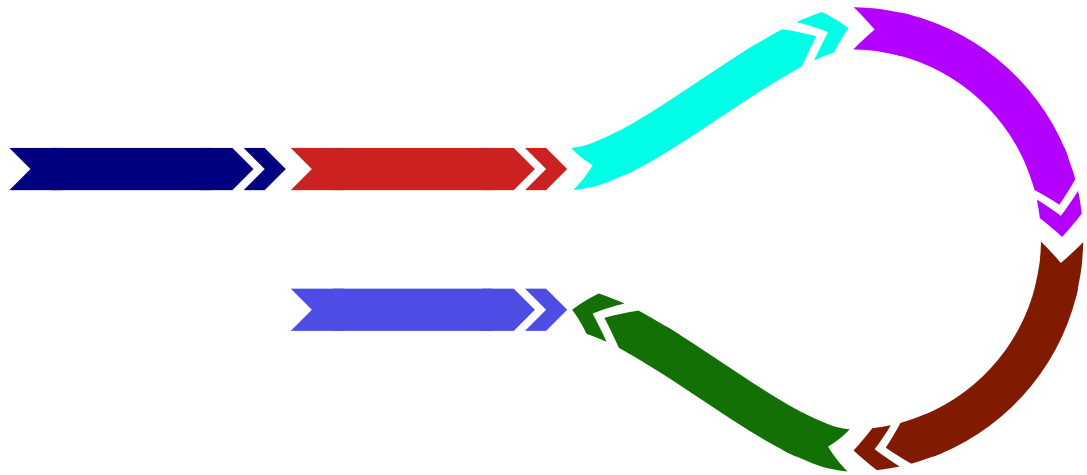
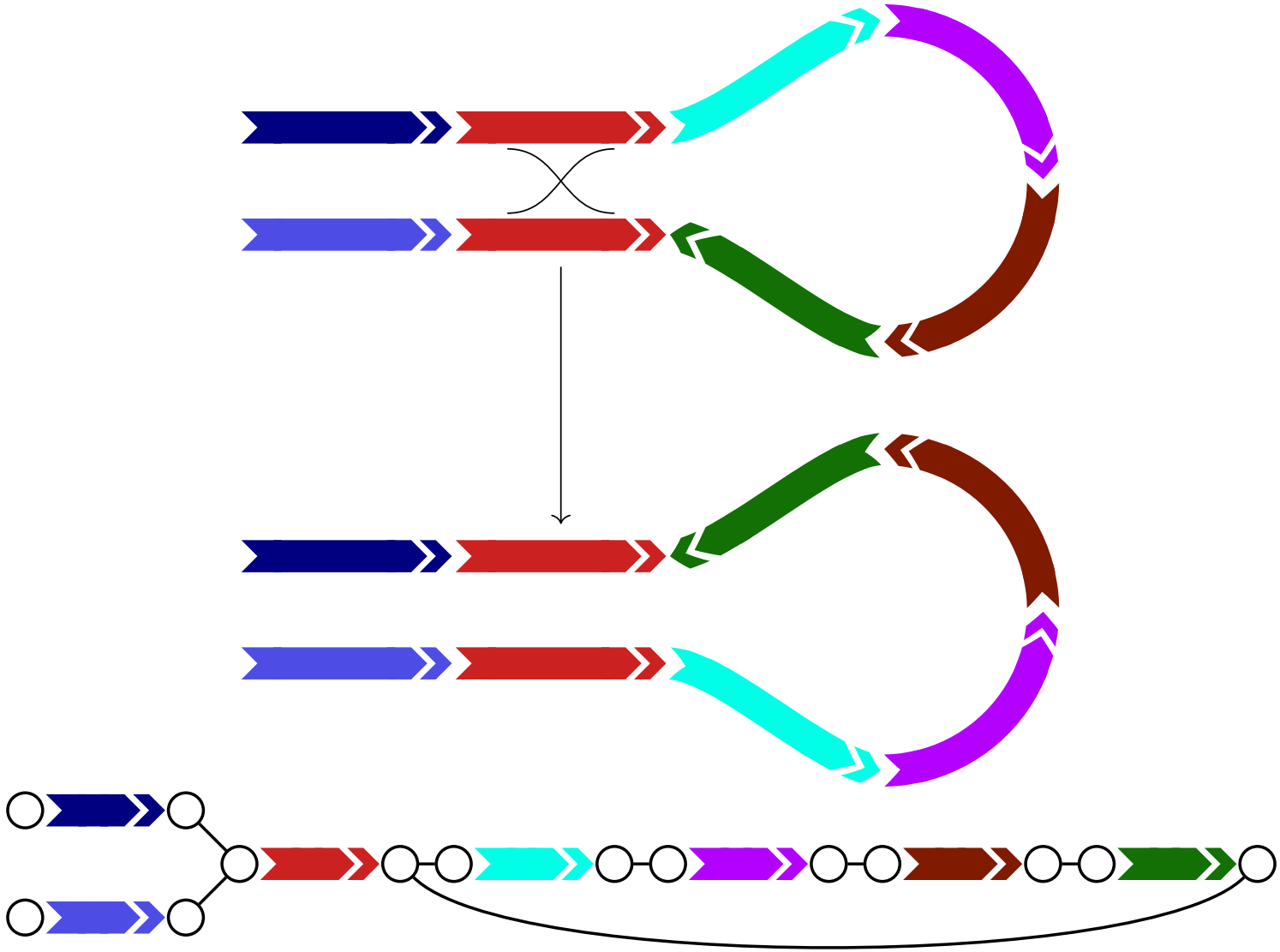


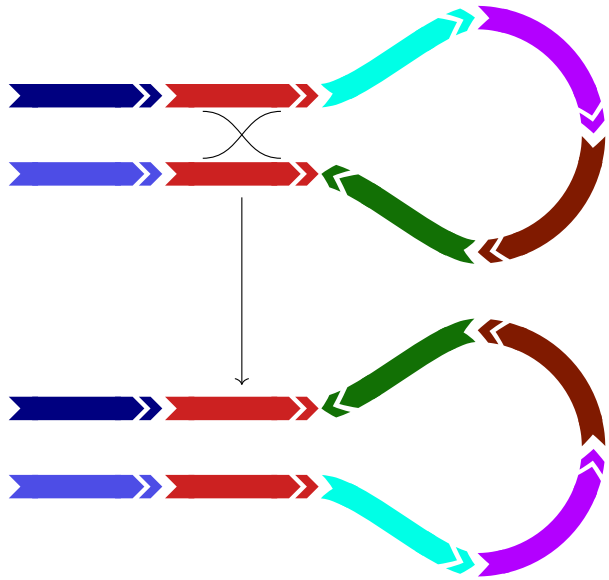
- No rearrangements via Homologous Recombination.

MBPG and Homologous Recombinations



- Homologous Recombinations don't change the graph!

(Non)-Adjacency Modifying Operations



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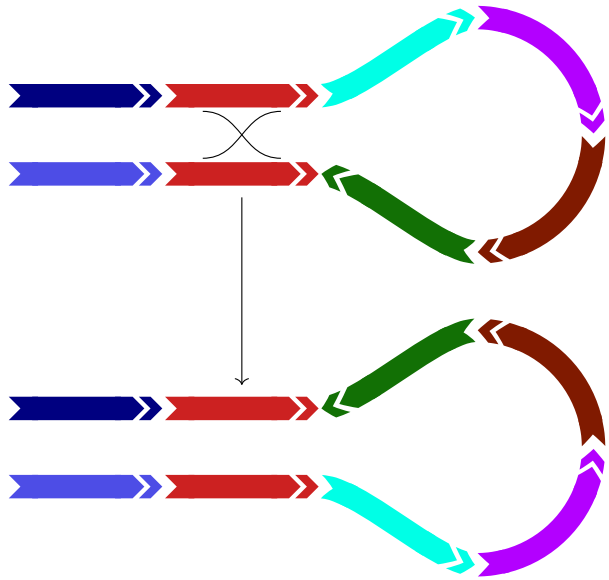

- No change in adjacencies!

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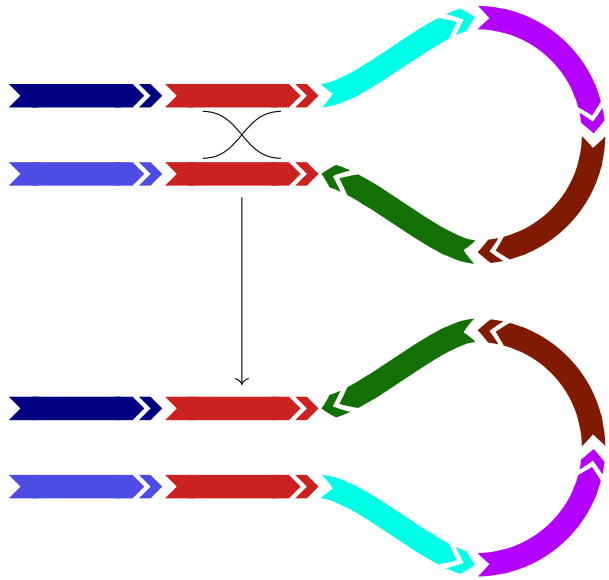

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  $\rightarrow$ Non-Adjacency Modifying Operations (Namos)

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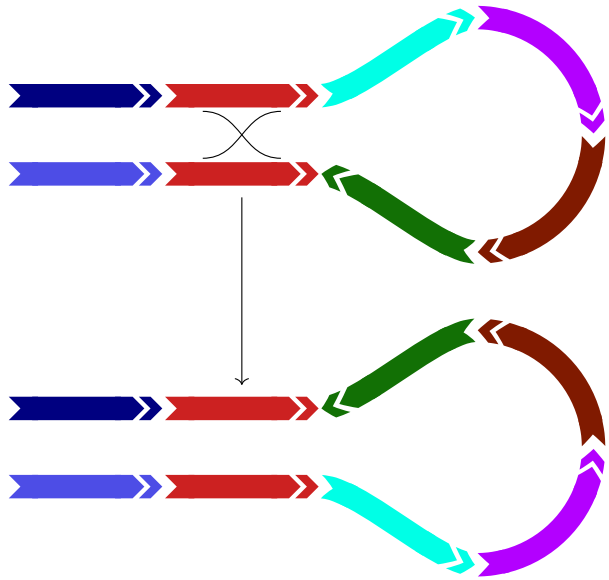

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  $\leftrightarrow$ Adjacency Modifying Operations (Amos)

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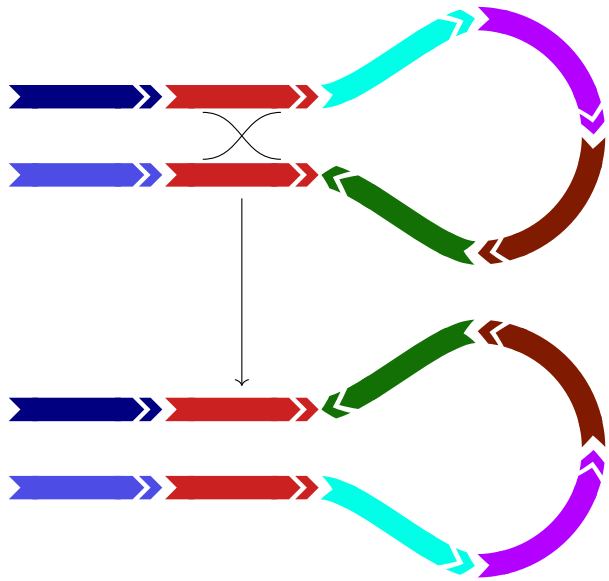

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Amos can introduce structural complexity!

Amos - Example: Segmental Duplication

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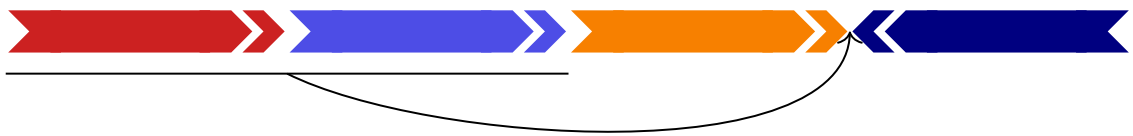

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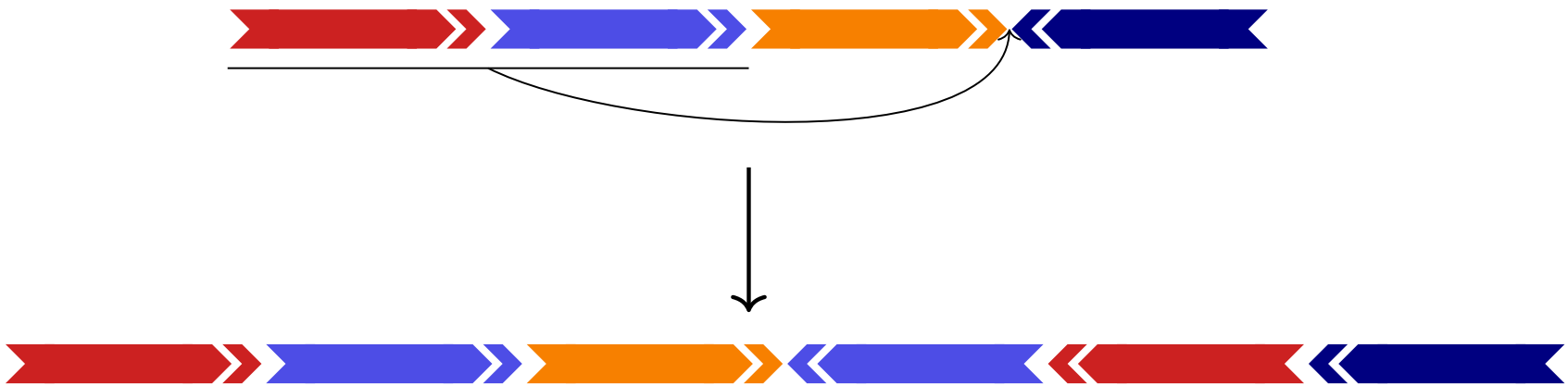
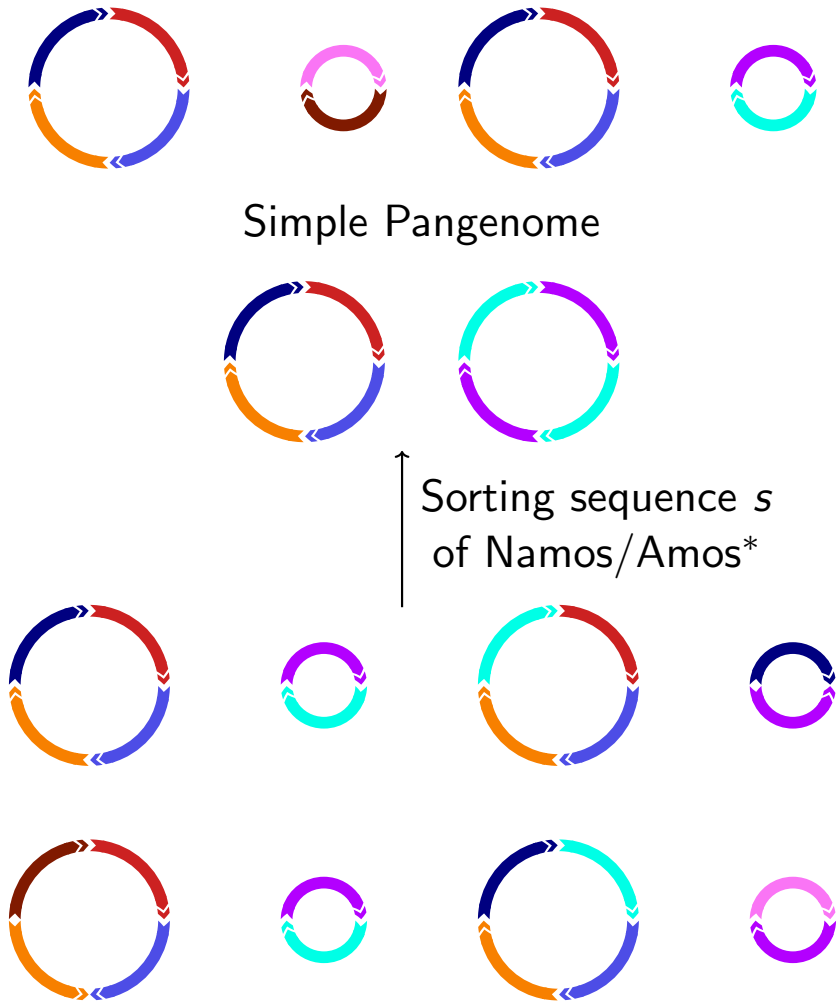


General Ancestral Reconstruction Problem (GARP)



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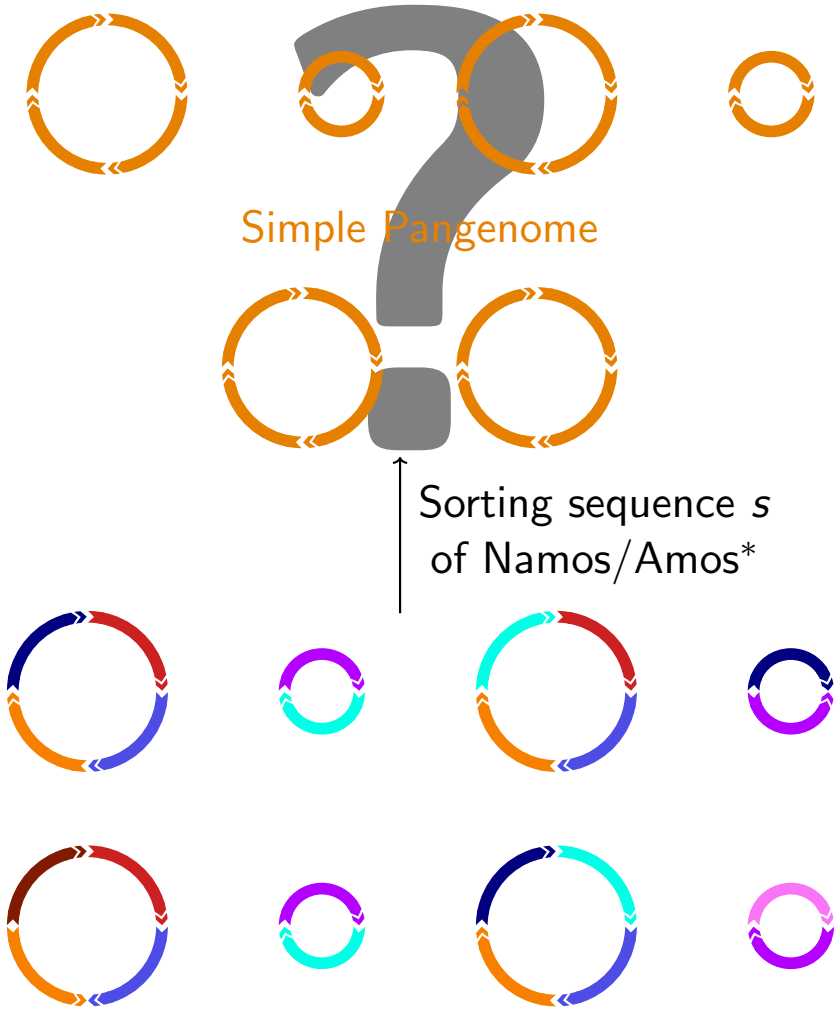

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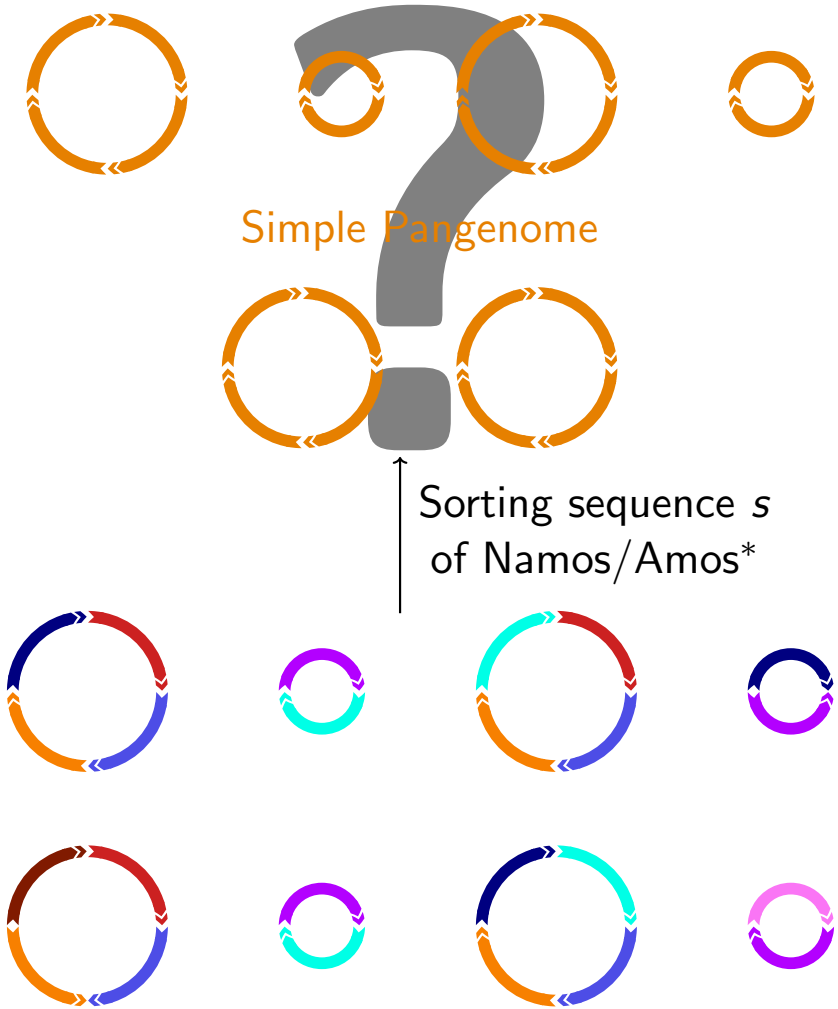

- #Amos in s: measure of the Structural Complexity.

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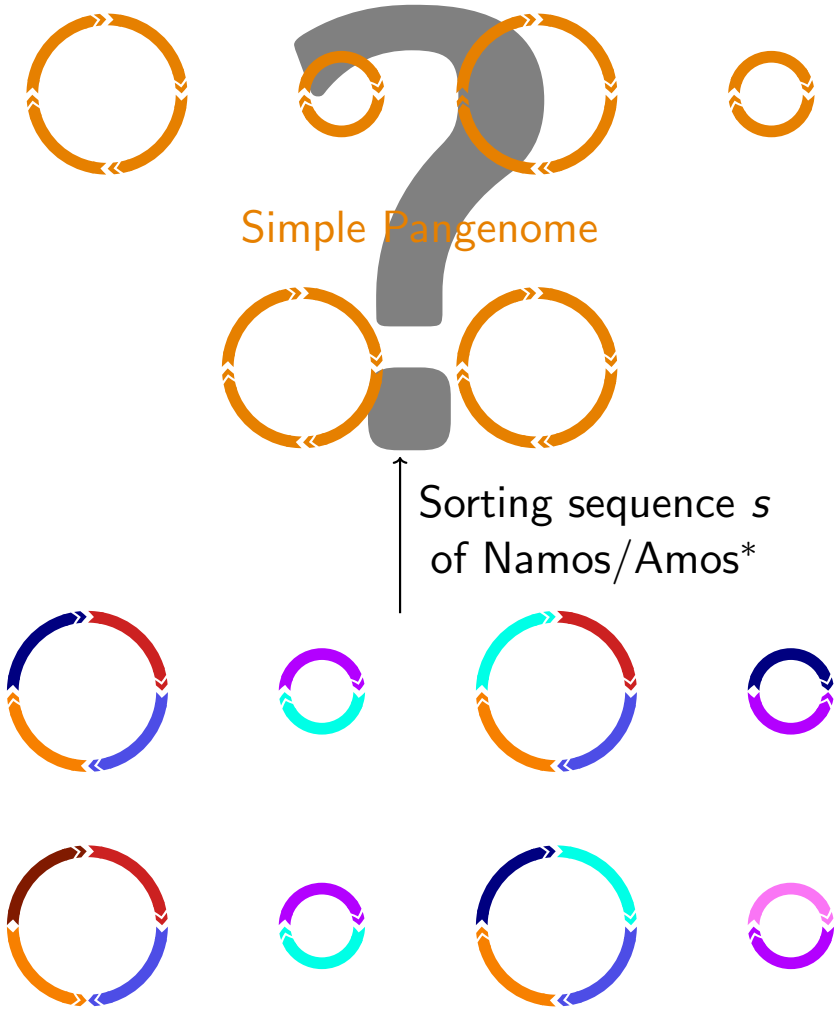
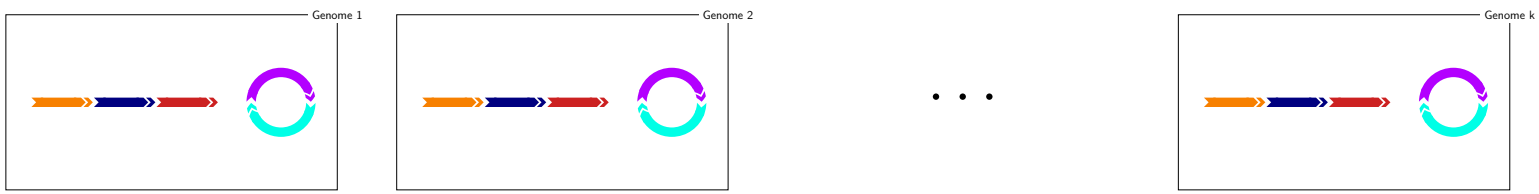


- #Amos in s: measure of the Structural Complexity.
- * with minimal #Amos

k-Coalescence – an important Namo



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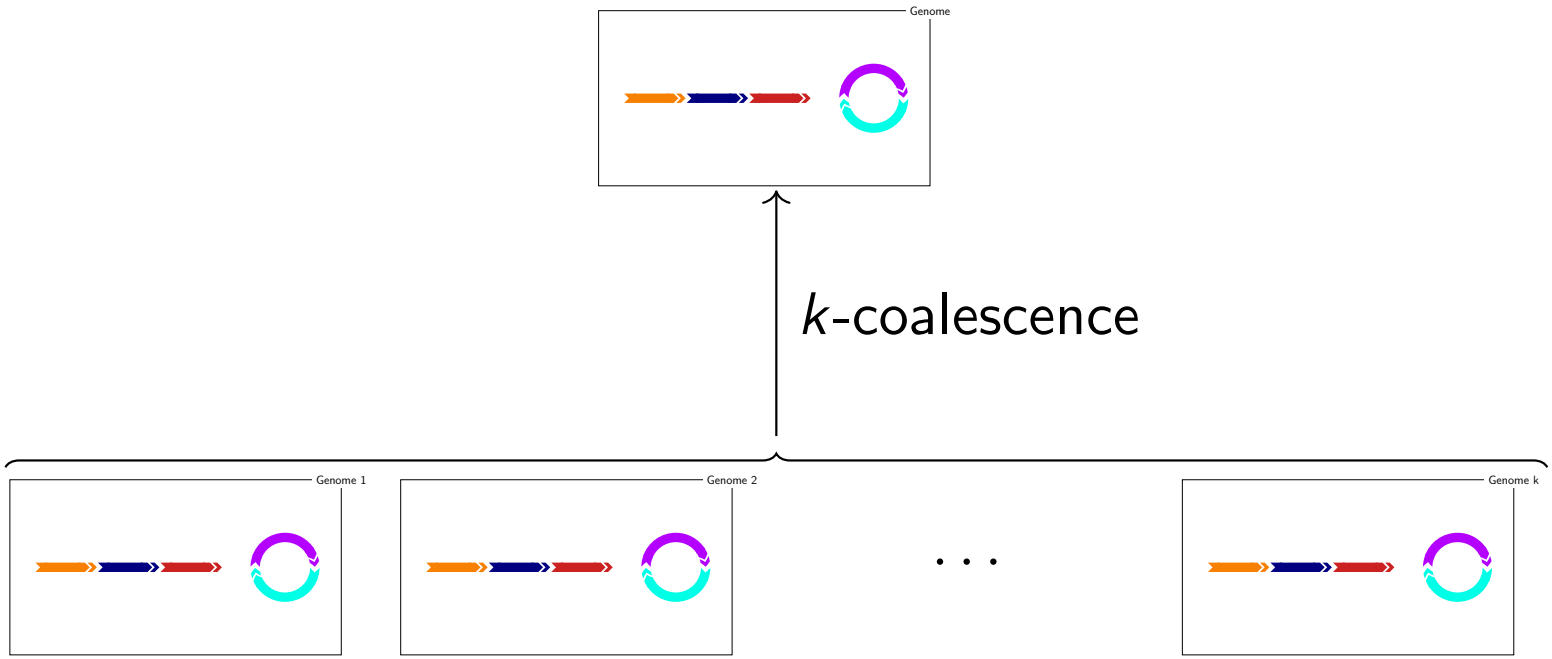
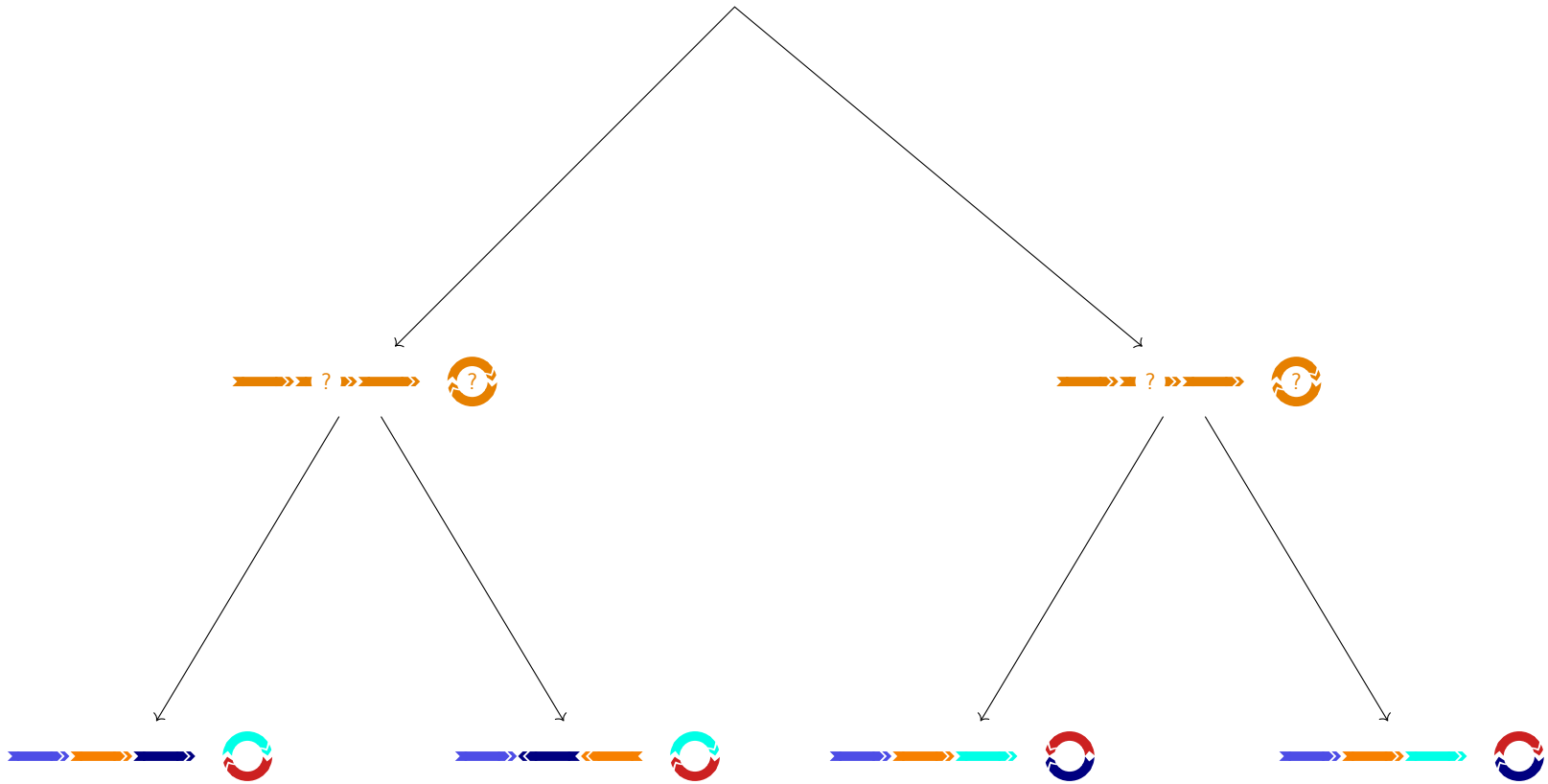


Large Parsimony Problem and GARP



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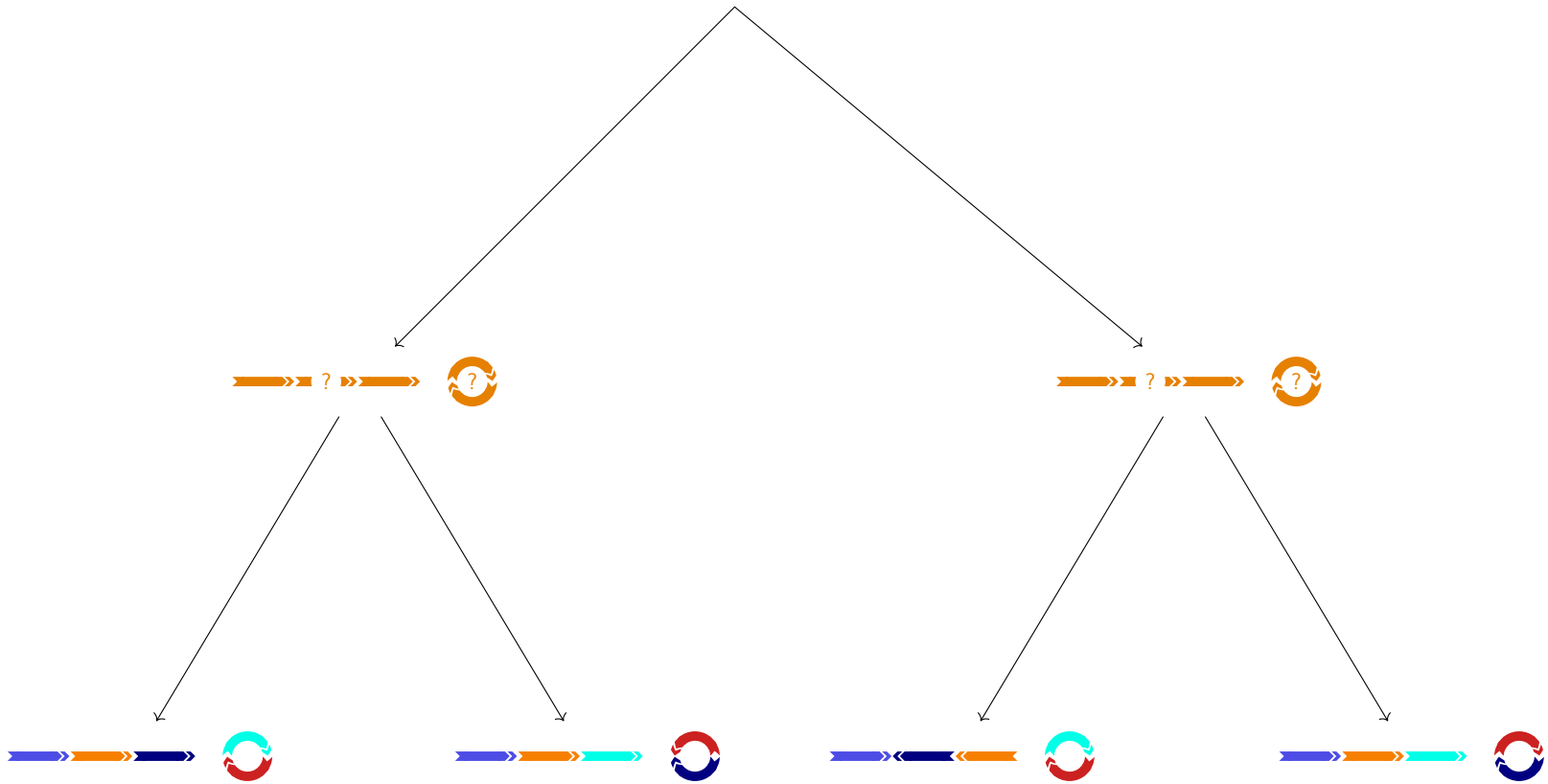

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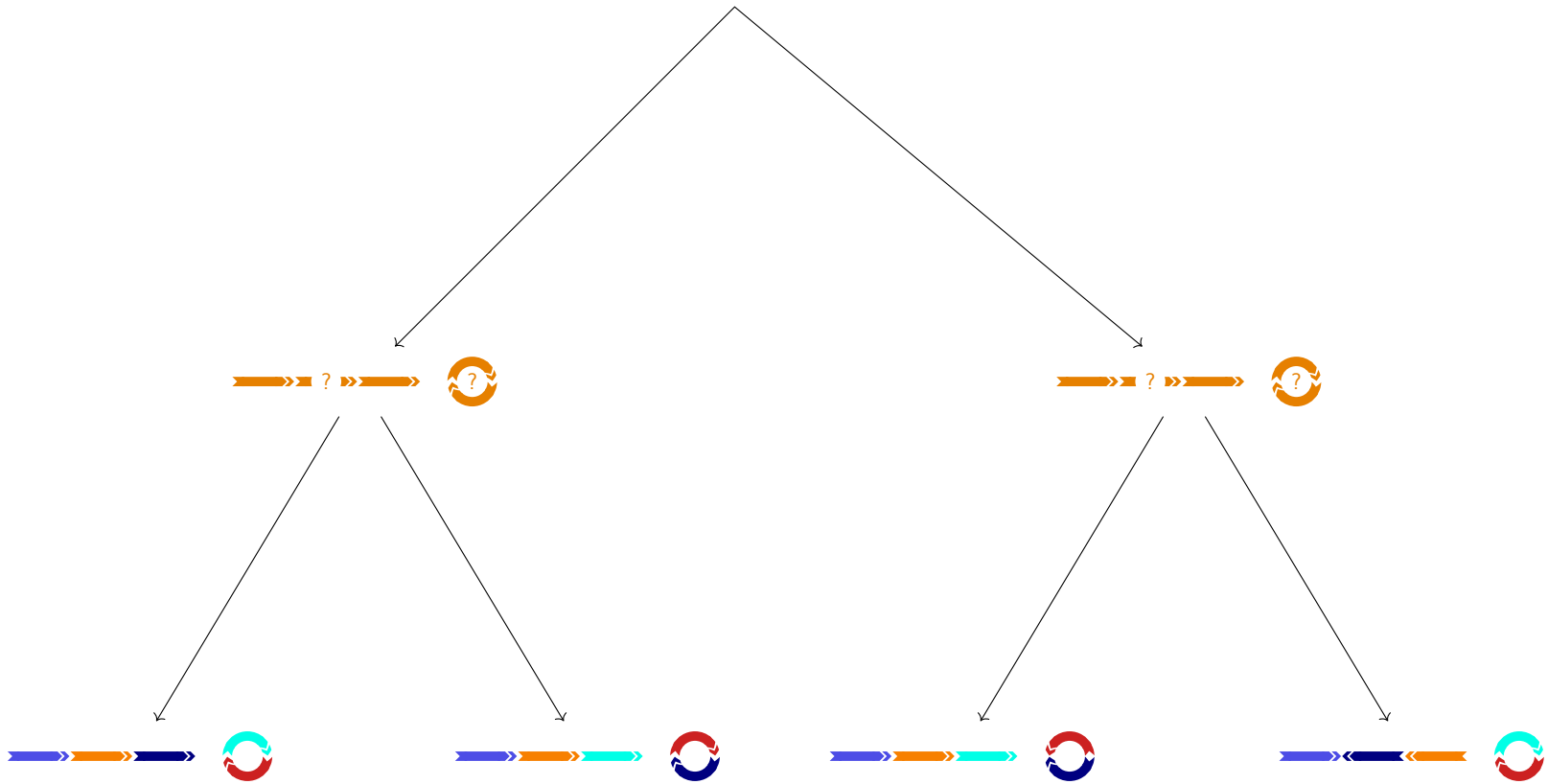

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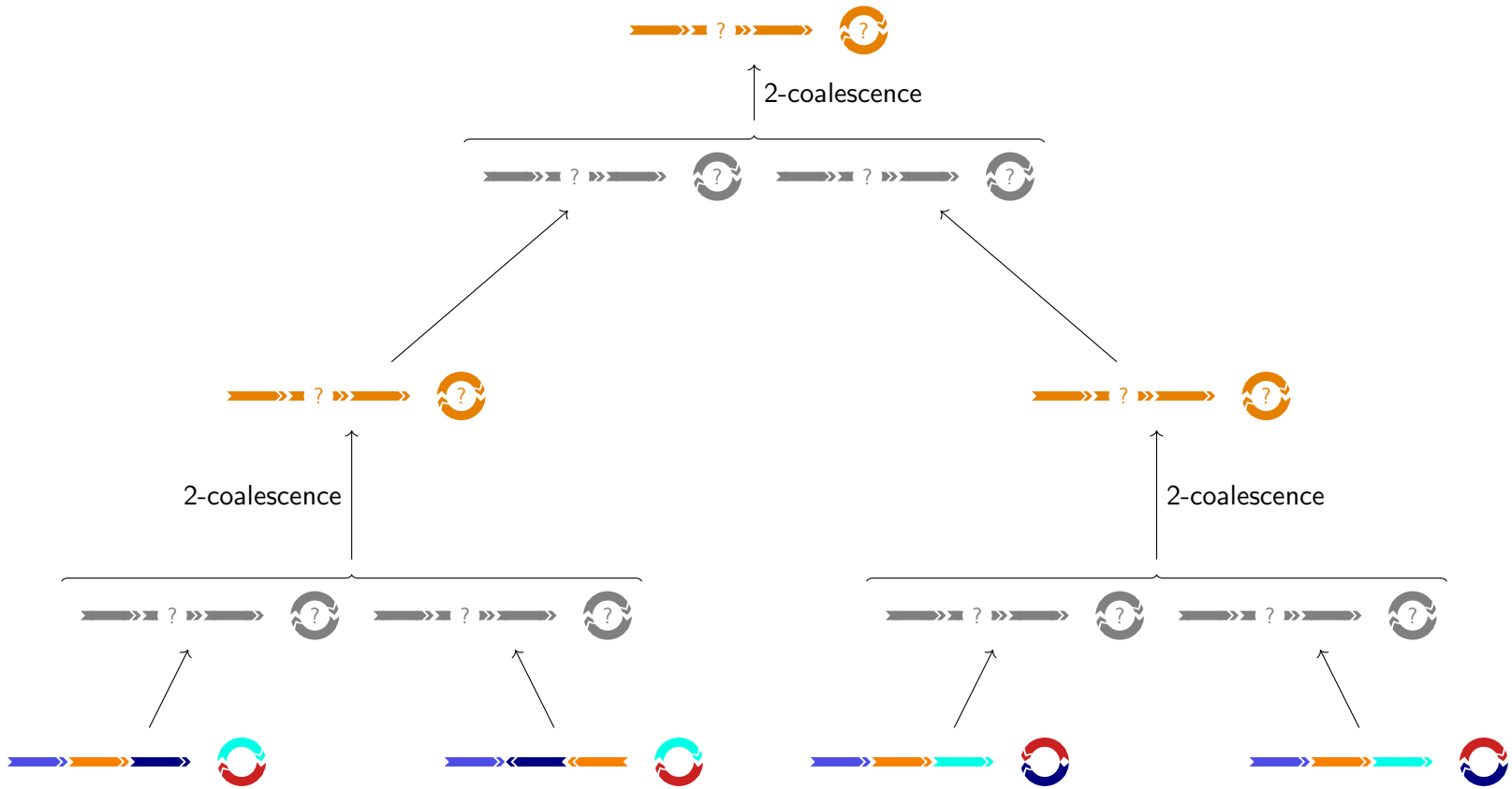

GARP and Classical Problem Formulations

Problem name	Given genomes	Classical Formulation	Namos (N)
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Median problem	Genomes $X_1, \ldots, X_k$ on the same marker set (single copy)	Find a genome Y that minimizes the total distance to $X_1, \ldots, X_k$.	– (k-coalescence)
Large parsimony	Genomes $X_1, \ldots, X_k$ on the same marker set (single copy)	Find a binary tree with leaves $X_1, \ldots, X_k$ and minimal total distance between the genomes at each edge.	2-coalescence

- Very limited interaction between genomes (mostly coalescence, sometimes chromosome (de-)duplication)

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$\rightarrow$ For a lower bound, we need a "maximally powerful" set of Namos

Obervations from the MBPG

Observation

Given a Namo o and pangenomes $\mathbb{P}, \mathbb{P}'$, where $\mathbb{P} \xrightarrow{o} \mathbb{P}'$, the MBPGs of $\mathbb{P}$ and $\mathbb{P}'$ are identical.

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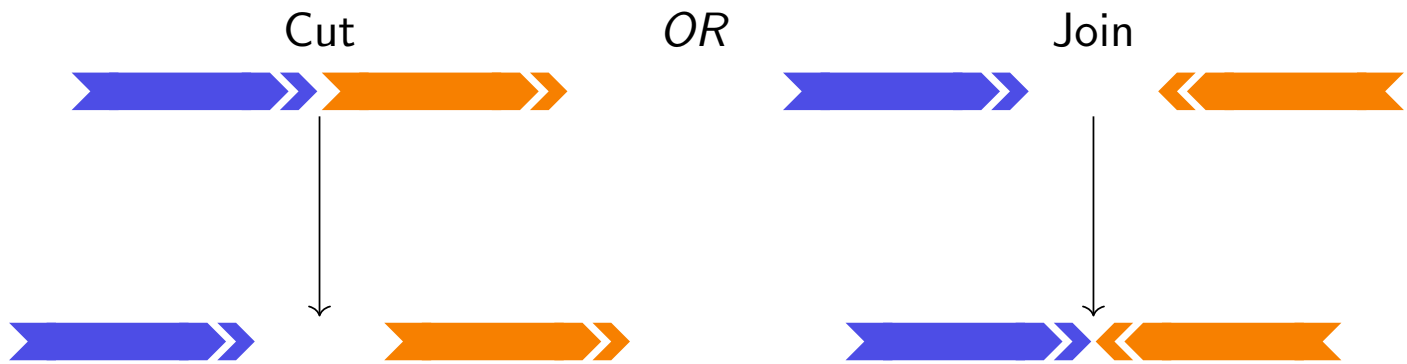
Definition

A set of Namos N is called MBPG-complete, if for all pairs of pangenomes $\mathbb{P}, \mathbb{P}'$ with the same MBPG there is a sequence of Namos $o_1 o_2 \dots o_k \in N^*$, such that $\mathbb{P} \xrightarrow{o_1} \xrightarrow{o_2} \cdots \xrightarrow{o_k} \mathbb{P}'$.

SCJ - A simple Amo



SCJ-CARP Theoretical result

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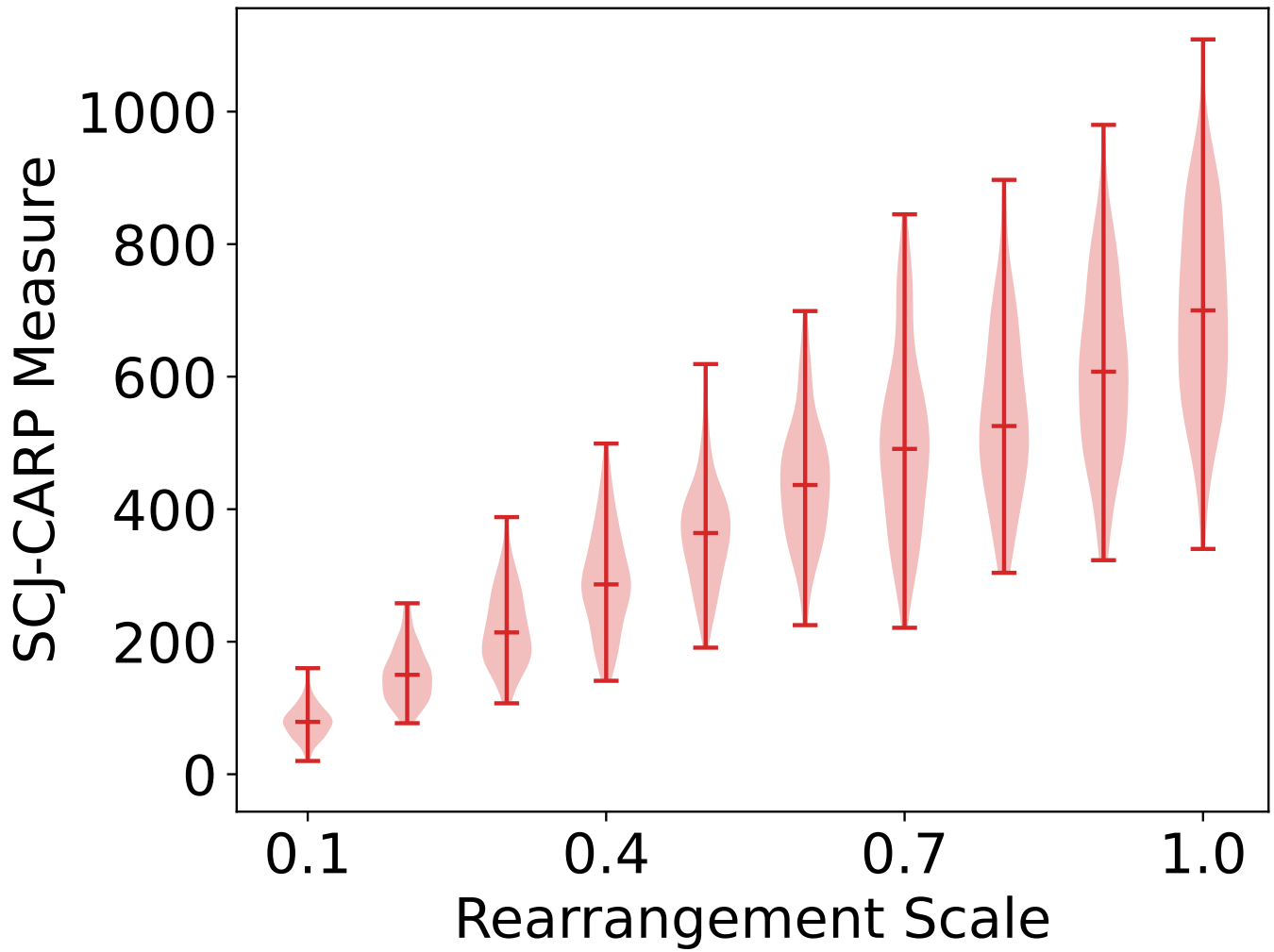
- SCJ Large Parsimony is NP-hard
- However SCJ-CARP:

Lemma

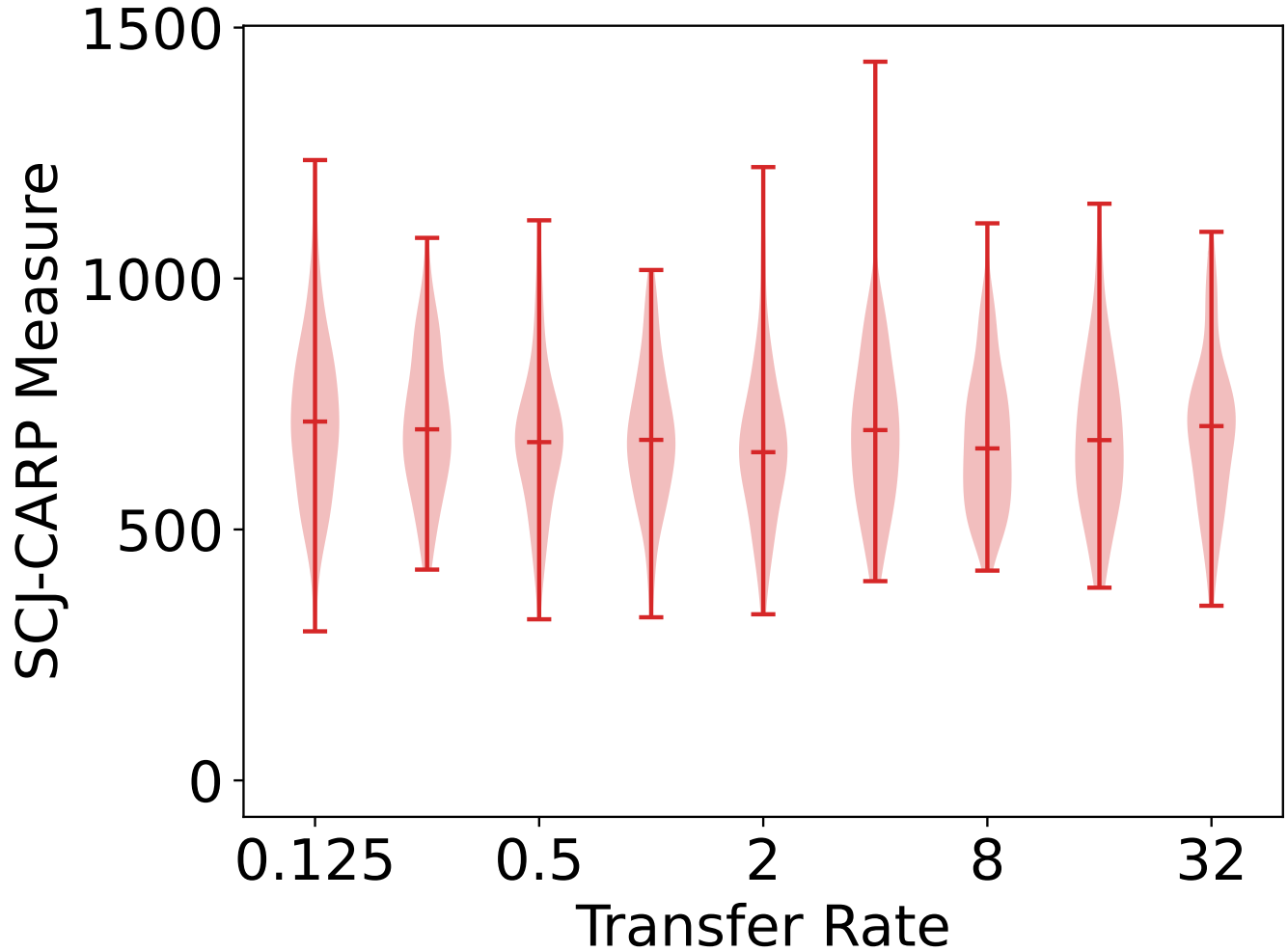
One needs exactly $|E_C|$ SCJs to transform a pangenome into a simple one where $E_C \subset E_A$ is a subset of adjacency edges that can be determined in linear time.

SCJ-CARP Tracks Rearrangements



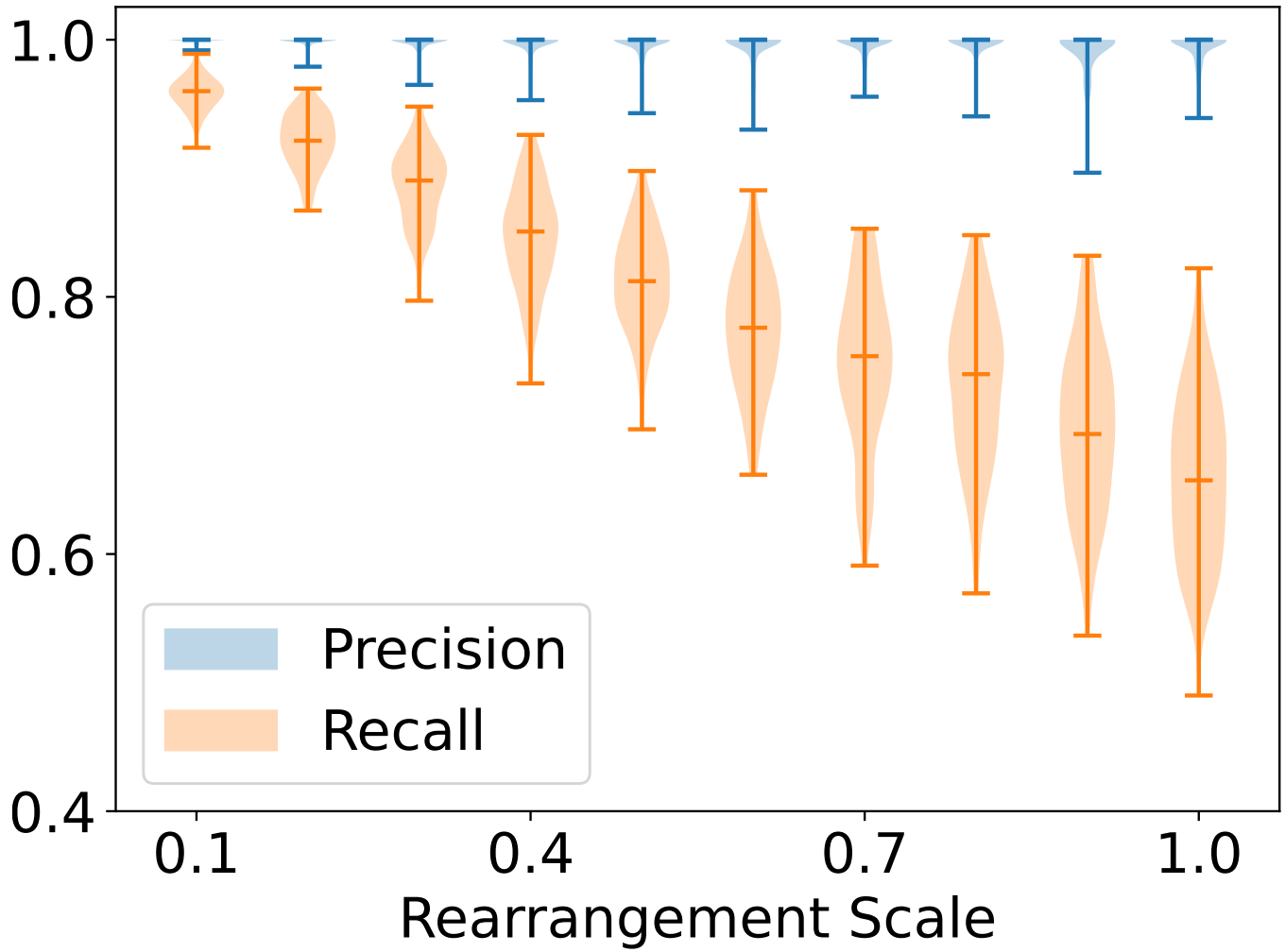
Pearson Coefficient: 0.88

SCJ-CARP Does Not Track Horizontal Effects



Pearson Coefficient: -0.01

SCJ-CARP Reconstructs Ancestral Adjacencies (to a Limited Extent)



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- Weighted Namos

Conclusion

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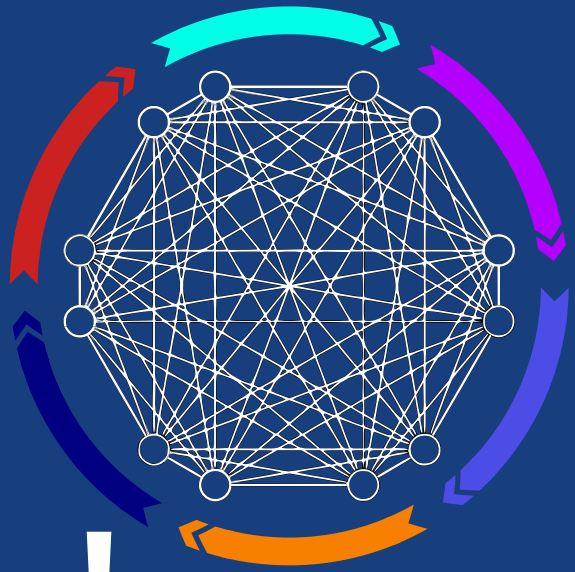
- Future work: (Formal definition for) Marker segmentation on pangenomes



Thank you!

slides