CSE 566 Spring 2023

Whole-Genome Comparison

Instructor: Mingfu Shao

Sequence Comparison

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  Seq2: **T C C T A G A T C C G T T C G**

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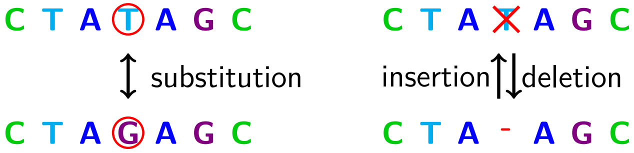
- Point mutations
  - Nucleotide substitutions
  - Nucleotide indels



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$$\downarrow$$

$$
\begin{array}{lccccccccccccccccc}
\text{Seq1:} & \textcircled{A} & C & \textcircled{G} & T & A & G & A & - & C & C & G & \textcircled{C} & T & \cancel{A} & C & \cancel{A} & G \\
 & | & | & | & | & | & | & | & & | & | & | & | & | & & | & & | \\
\text{Seq2:} & \textcircled{T} & C & \textcircled{C} & T & A & G & A & \cancel{T} & C & C & G & \textcircled{T} & T & - & C & - & G
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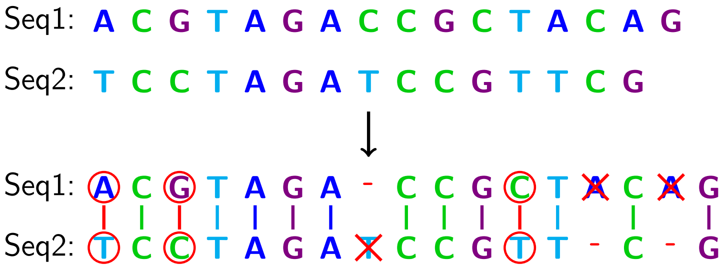

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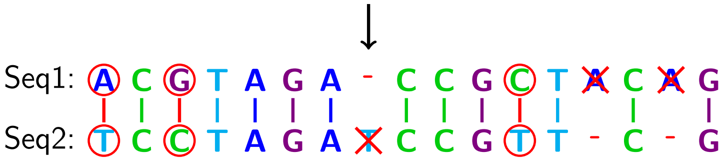

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- Determines the **distance/similarity** and the **one-to-one correspondence** between the nucleotides.

- **Efficient algorithm:** dynamic programming

Multiple Sequence Comparison

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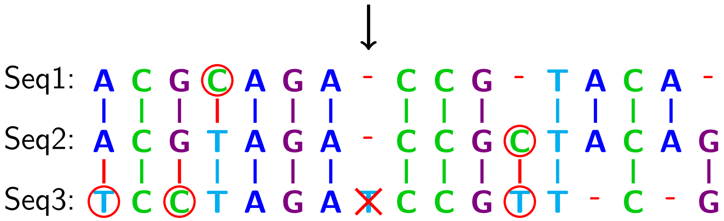

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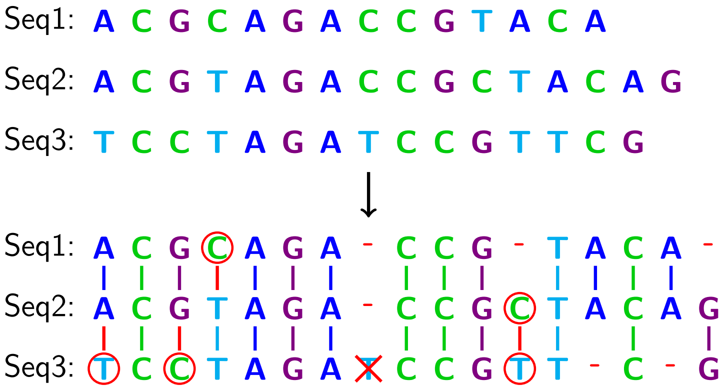
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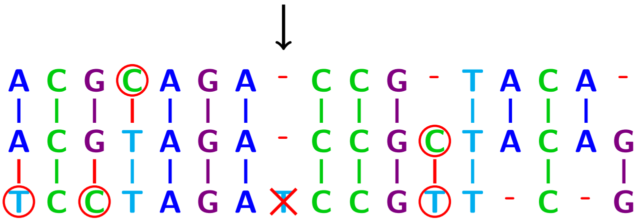

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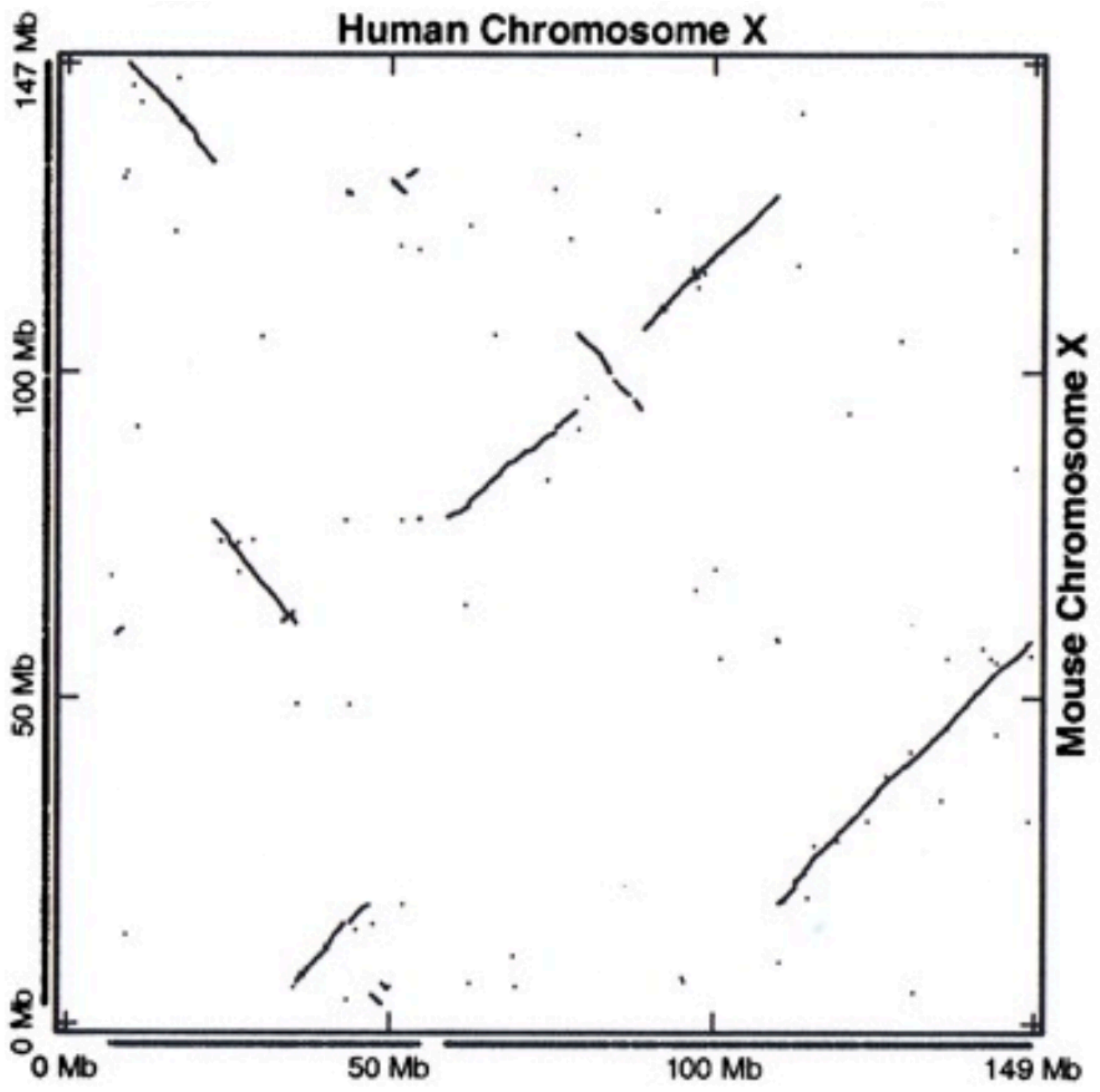
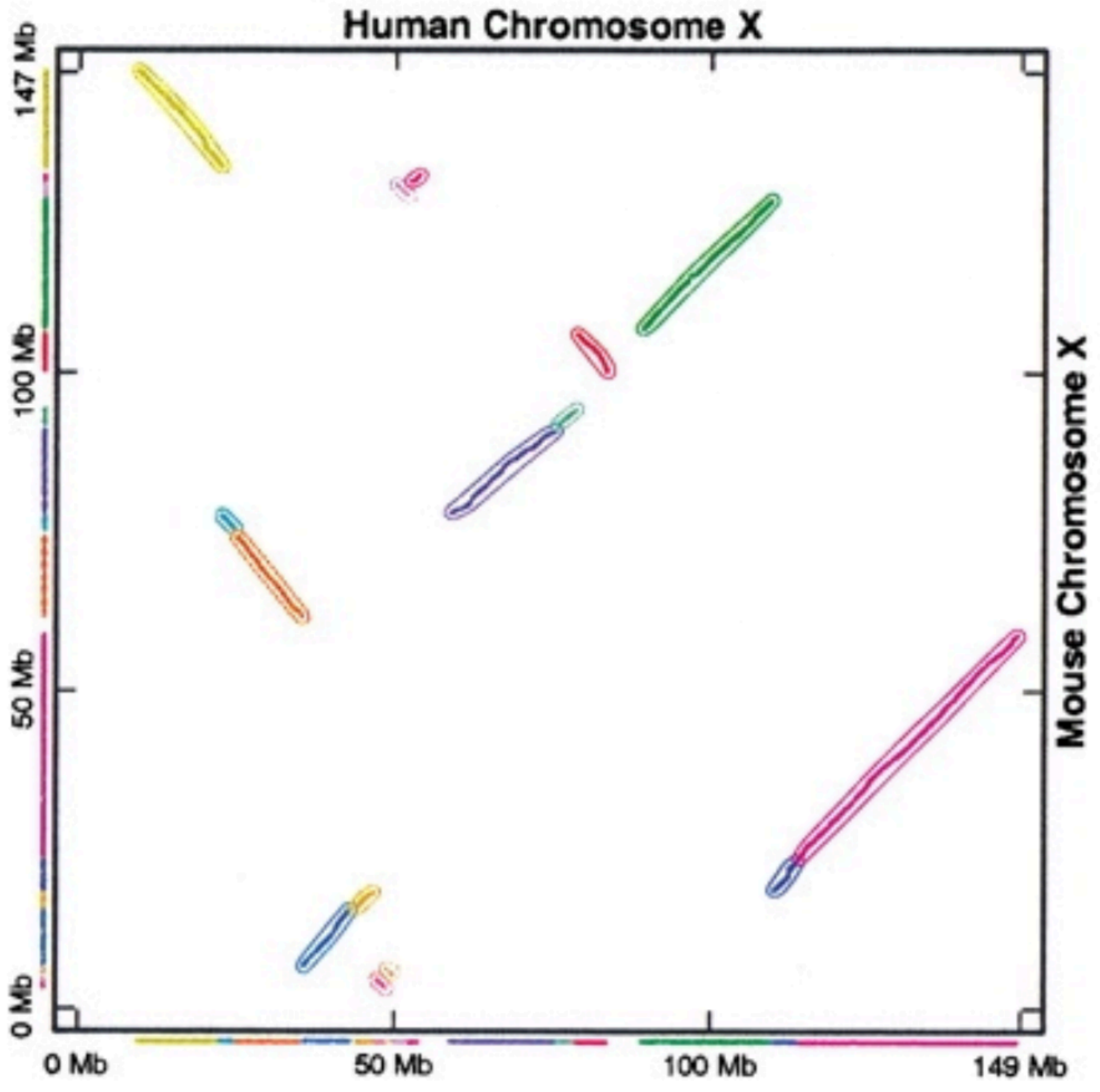
- **NP-hard** for almost all formulations.
- **Heuristics:** progressive methods, iterative algorithms.

Comparing Whole-Genome





Model of Whole-genomes

- **Genome:** a set of chromosomes.
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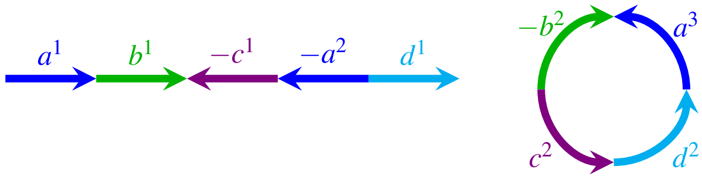

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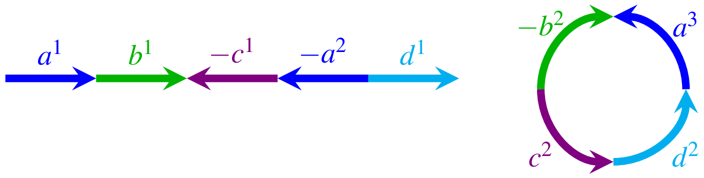

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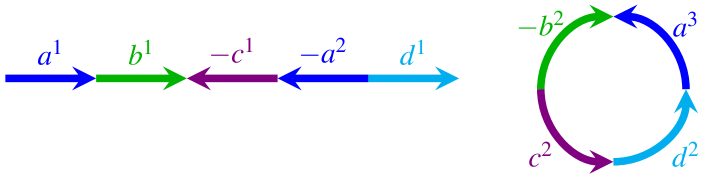

- Each gene has a **sign**, indicating its transcriptional direction.
- All genes are grouped into **gene families**.

Whole-genome Comparison

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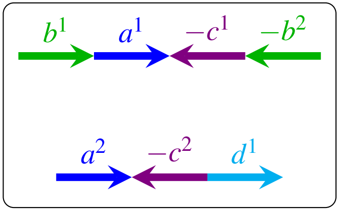
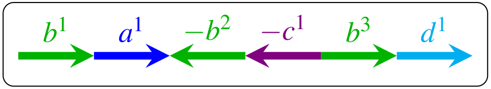


(G_1)



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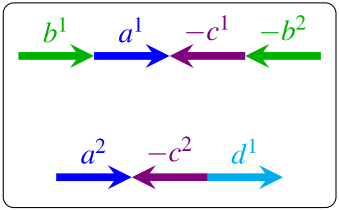

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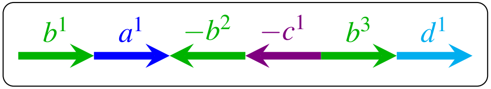

(G_2)

- Different copy numbers for some gene families.
- Different number of chromosomes.
- Different gene orders and orientations.

Large-scale Events

- **Content-modifying** events: change copy numbers
  - Segmental duplication
  - Tandem duplication
  - Lateral gene transfer
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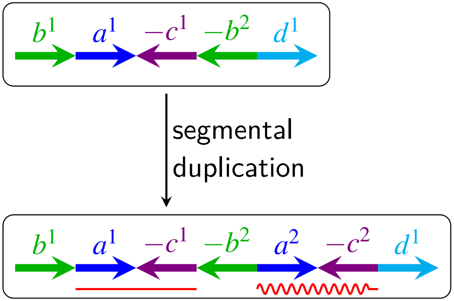
b^1 a^1 $-c^1$ $-b^2$ d^1
segmental duplication
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- **Rearrangements**: change number of chromosomes, gene orders and orientations.
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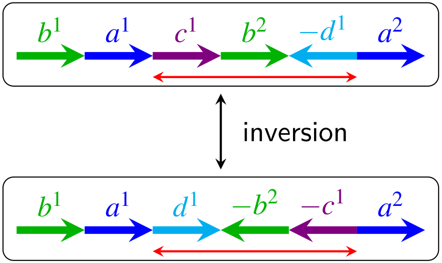

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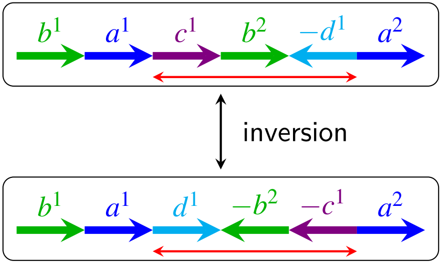
b^1 a^1 c^1 b^2 $-d^1$ a^2
inversion
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- Almost all rearrangements can be represented by the universal **DCJ** (double-cut-and-join) operation.

DCJ (double-cut-and-join) Operation

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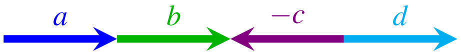
- Some definitions



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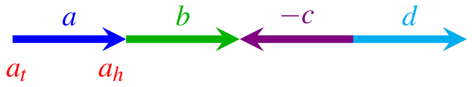

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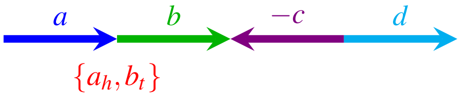

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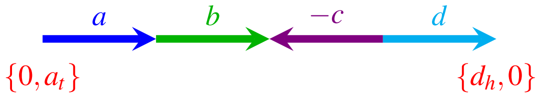

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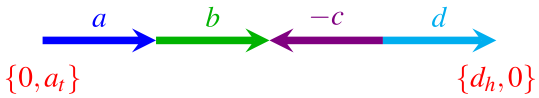

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Various Cases of DCJ Operation

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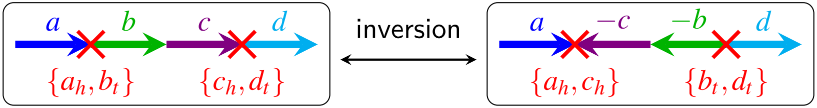

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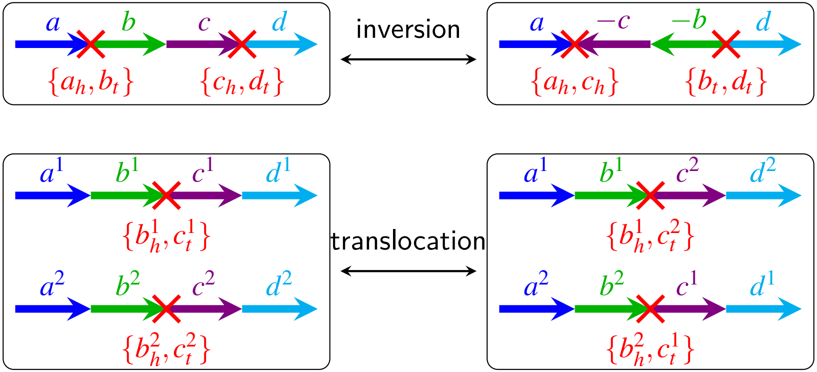

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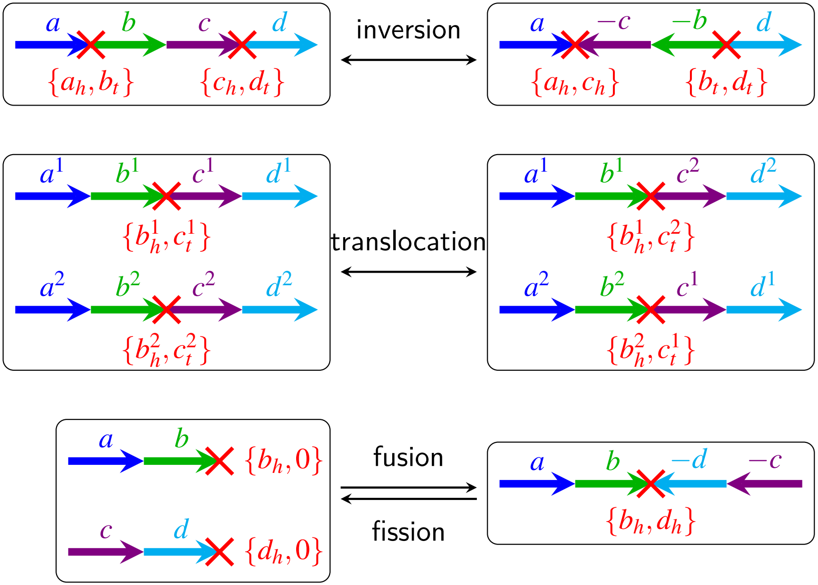

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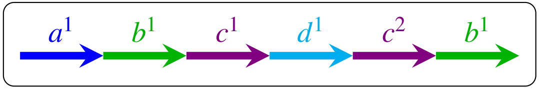

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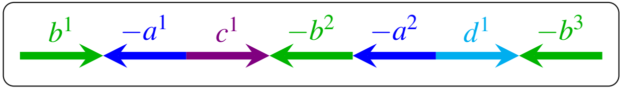

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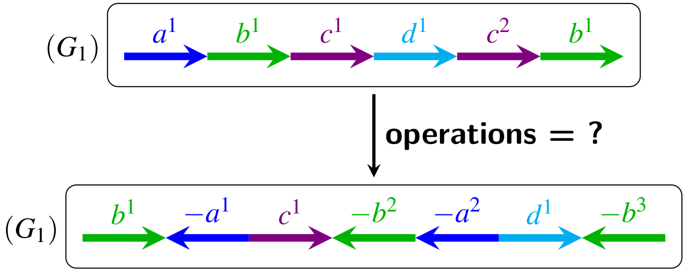

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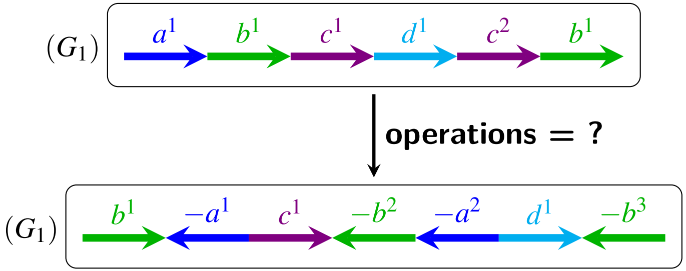

- Diversity of the edit distance problems
  - Assumptions on the given genomes.
  - Which types of events are in the evolutionary model.

Edit Distance (without Duplicate Genes)

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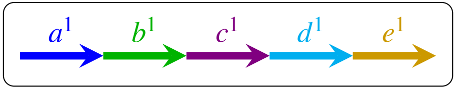
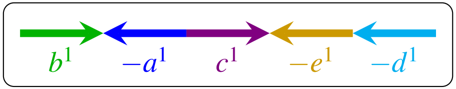


(G_2)



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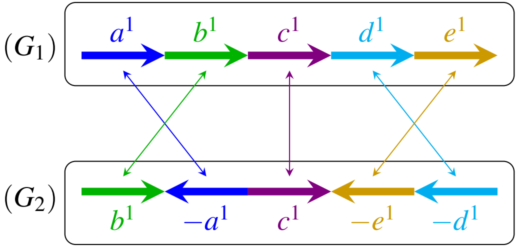

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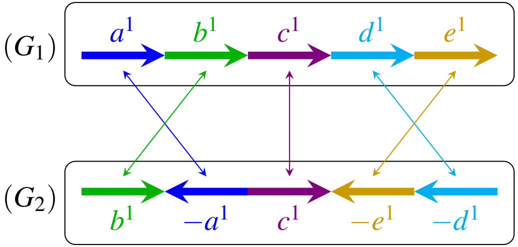

- Edit distances that can be computed in **linear time**:
  - **Inversion distance** (*Hannenhalli and Pevzner, 1995; Bader et al., 2001*)
  - **DCJ distance** (*Bergeron et al., 2006*)
  - **DCJ + Insertion + Deletion** (*Braga et al., 2010; Compeau et al., 2013*)

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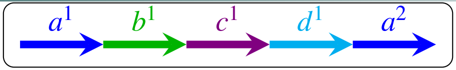

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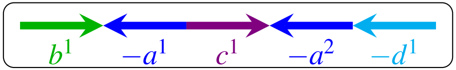

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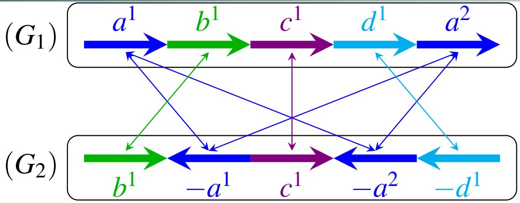

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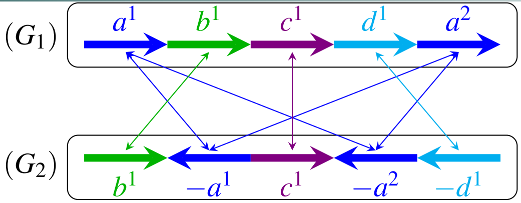

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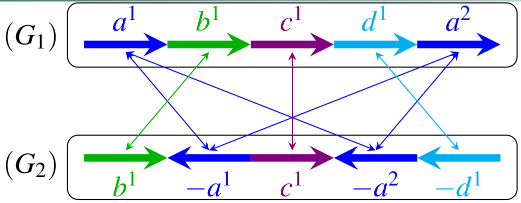

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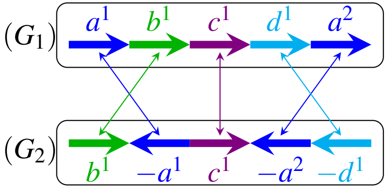

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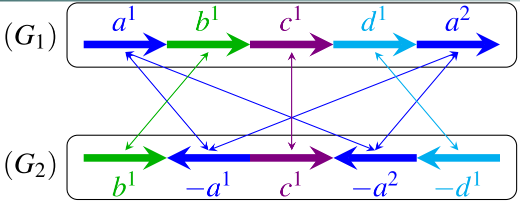

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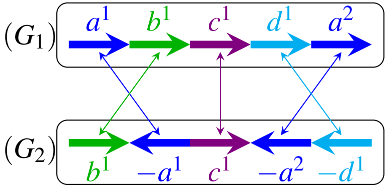

- **Exemplar (*Sankoff, 1999*):** To select one gene in each family, such that a certain distance is minimized.

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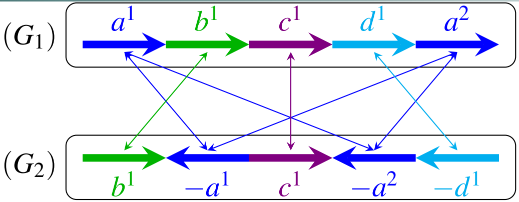

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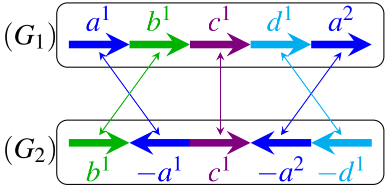

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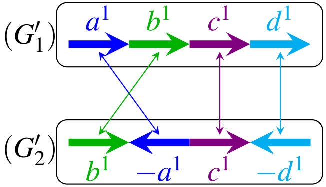

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- Under the **exemplar** strategy:
  - **Inversion distance:** Branch-and-Bound (*Sankoff et al., 1999*)
  - **Breakpoint distance:** Divide-and-Conquer (*Nguyen et al., 2005*)

Multiple Whole-genome Comparison

- **Median distance problem:** Given k genomes $G_1, G_2, \cdots, G_k$, to compute a *median* genome G_0 such that $\sum_{i=1}^{k} d(G_0, G_i)$ is minimized.

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- **DCJ median distance:** Branch-and-Bound (*Zhang et al, 2009*), Decomposition scheme (*Xu and Sankoff, 2008*)

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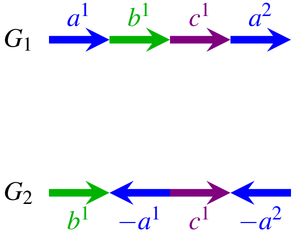
4. These problems are interesting for computer scientists, since they usually have very special structures.

DCJ Distance (without Duplicate Genes)



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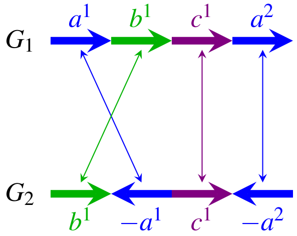

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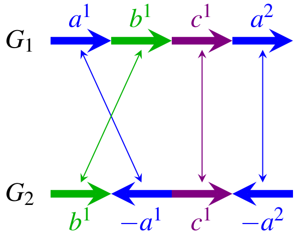

- Adjacency Graph

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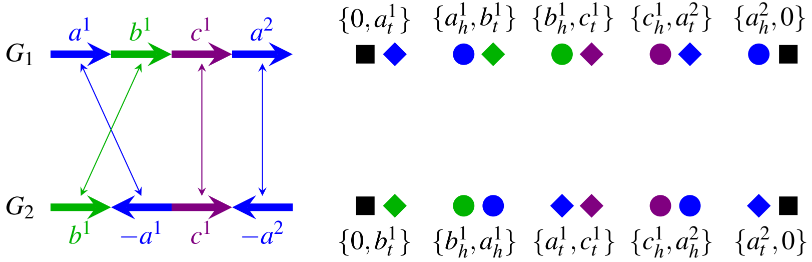

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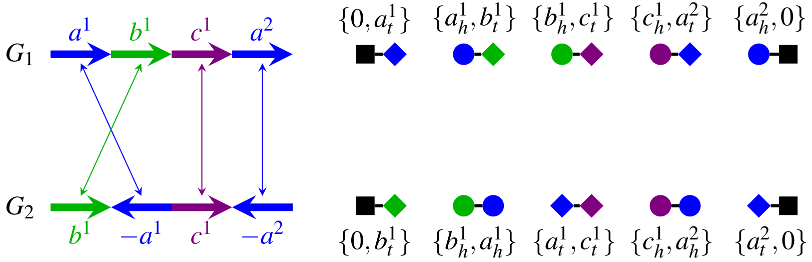

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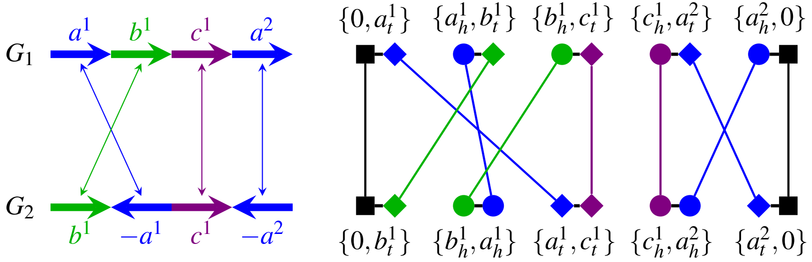

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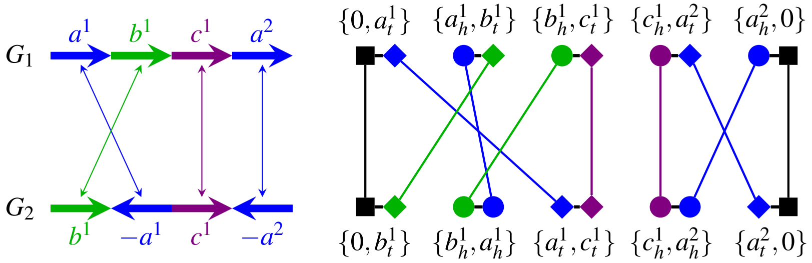

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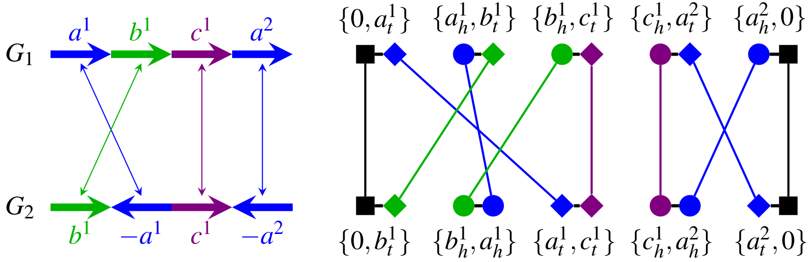

- Adjacency Graph
- The adjacency graph consists of vertex-disjoint cycles.
- DCJ distance: $d(B) = \#$(adjacencies) - $\#$(cycles).

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- A fast and exact algorithm.
  - An ILP formulation that gives the optimal solution.
  - Efficient Algorithms to identify optimal substructures.

Integer Linear Program (ILP)

- Mathematical Formulation

$$\begin{aligned} \max \quad & c^T x && (\textbf{Objective function}) \\ s.t. \quad & Ax \leq b && (\textbf{Constraints}) \\ & x \in \mathbb{Z}^n && (\textbf{Variables}) \end{aligned}$$

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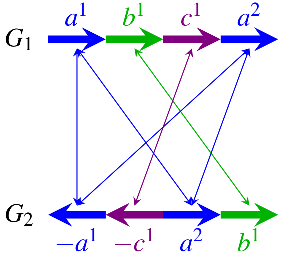
ILP Formulation



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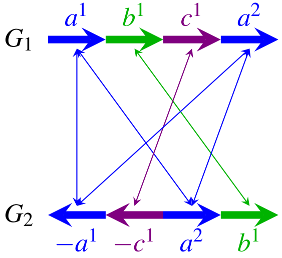

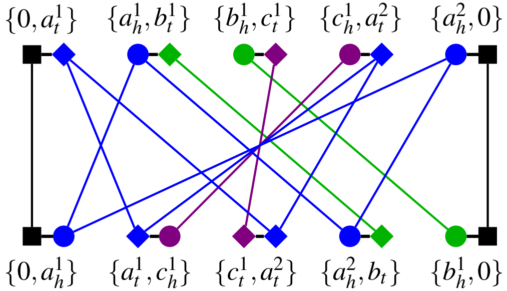

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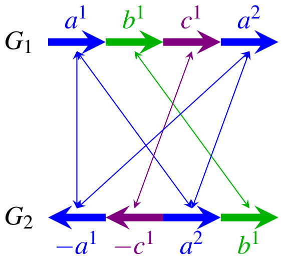

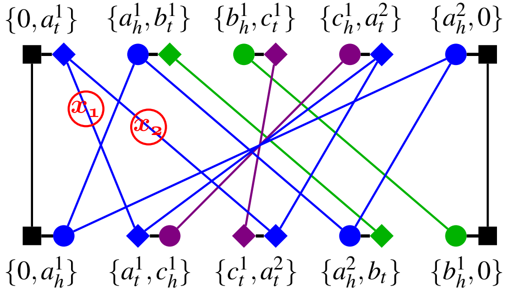

- Variables: $x_e \in \{0, 1\}$, indicating choosing e or not.

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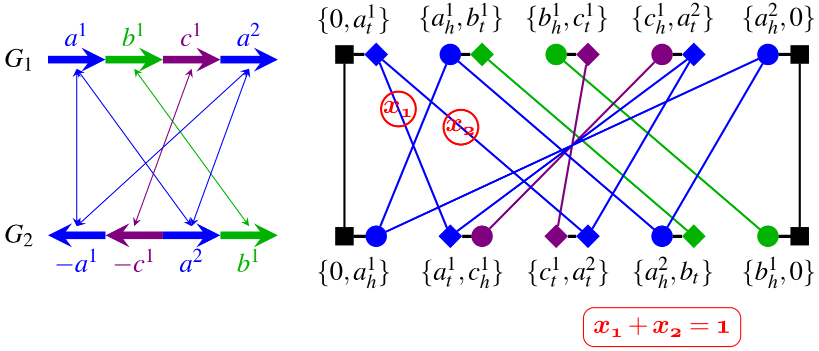

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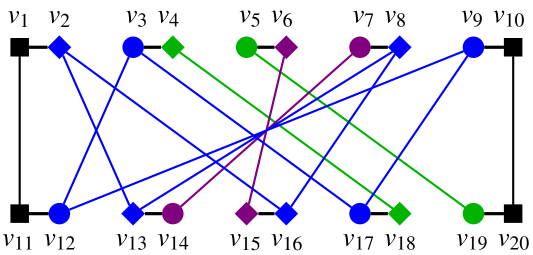

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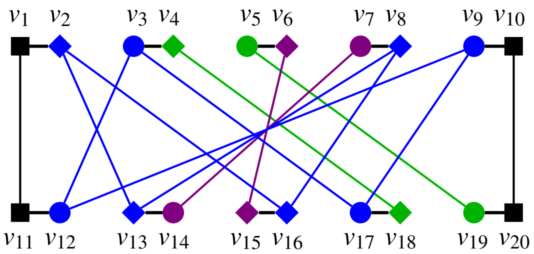

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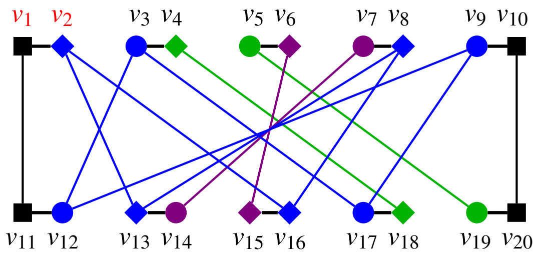
$y_1 = y_2$



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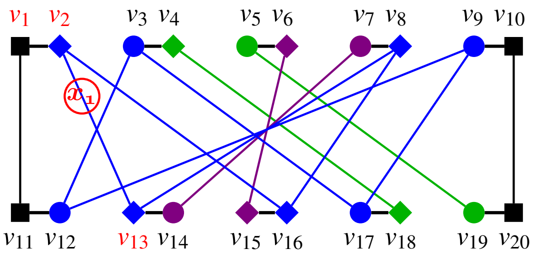

v_1 v_2 v_3 v_4 v_5 v_6 v_7 v_8 v_9 v_{10}
x_1
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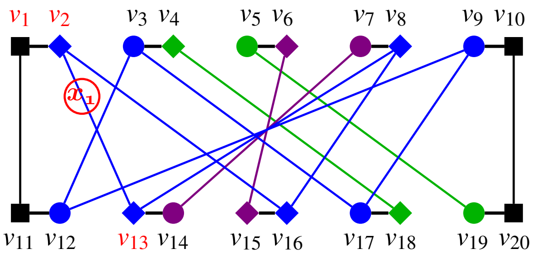

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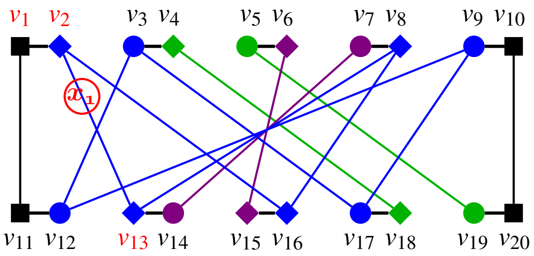

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