Algorithms and Bioinformatics

Part II — Comparative Genomics

Laurent Bulteau

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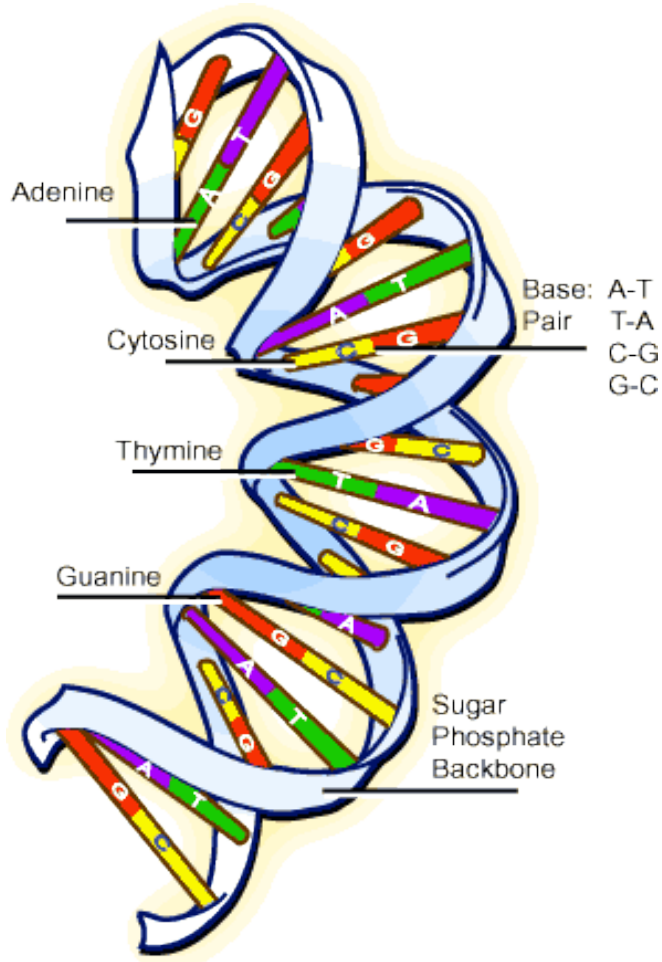
II.1 — Models and Distances

Laurent Bulteau
Slides from Anthony Labarre

Context and motivations

- **D**eoxyribo**n**ucleic **a**cid: double helix of *nucleotides* (A, C, G, T);
- Complementarity (A-T, C-G): one strip is enough;
- *Gene* = sequence of nucleotides (that codes for a specific protein);
- *Chromosome* = ordered set of genes;
- *Genome* = set of chromosomes;
- **Goal:** compare genomes;



Context and motivations

- Biologists are interested in comparing species, for example:
  - in order to classify them;
  - in order to explain evolution by reconstructing scenarios;
- (Dis)similarity measures are needed;
- Usually based on the sequenced genomes;

At the nucleotide level

- Most comparisons take place at the nucleotide level;

Example (sequence alignment)

$$\begin{array}{lccccccccccccc} S_1: & \cdots & T & C & C & G & C & C & A & - & - & C & T & A & \cdots \\ & & | & | & & | & & | & & & & | & & | & \\ S_2: & \cdots & T & C & G & G & A & C & T & G & G & C & - & A & \cdots \end{array}$$

- Matches, substitutions, insertions and deletions;
- Correspond to mutations;

At the "gene" level

- Some mutations act on *segments* of nucleotides;
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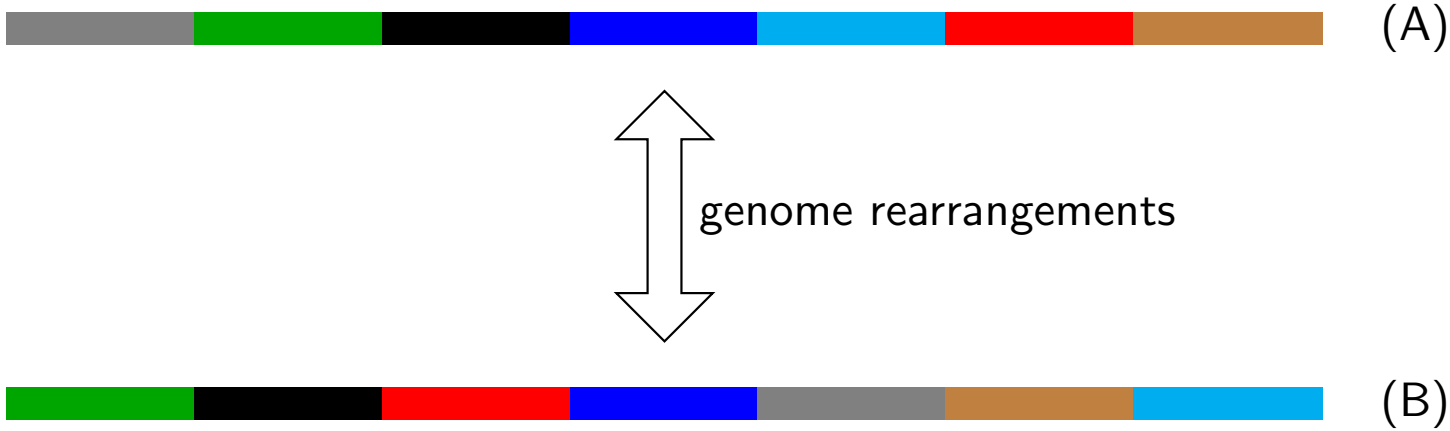

Genome rearrangements

- Our problem:

Problem (PAIRWISE GENOME REARRANGEMENT)

Input: *genomes G_1, G_2, a set S of mutations;*
Goal: *find a shortest sequence of elements of S that transforms G_1 into G_2.*

- Related, simpler problem: compute the **evolutionary distance** $d_S(G_1, G_2)$ (i.e. just the **length** of a shortest sequence);
- Many variants, depending on how genomes are modelled, what (and how) mutations are taken into account, etc.;

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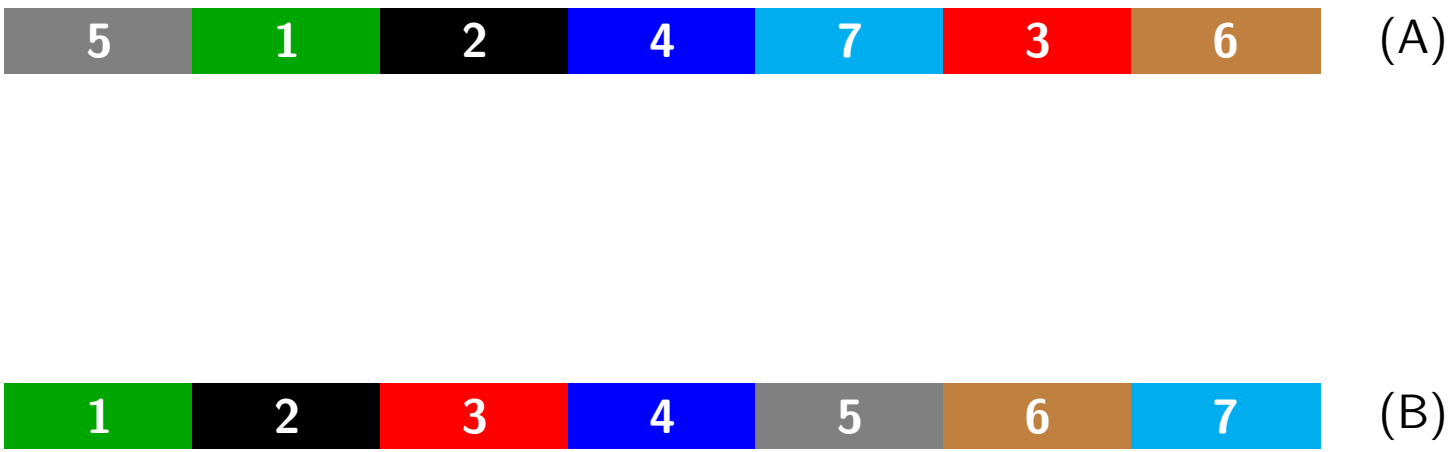

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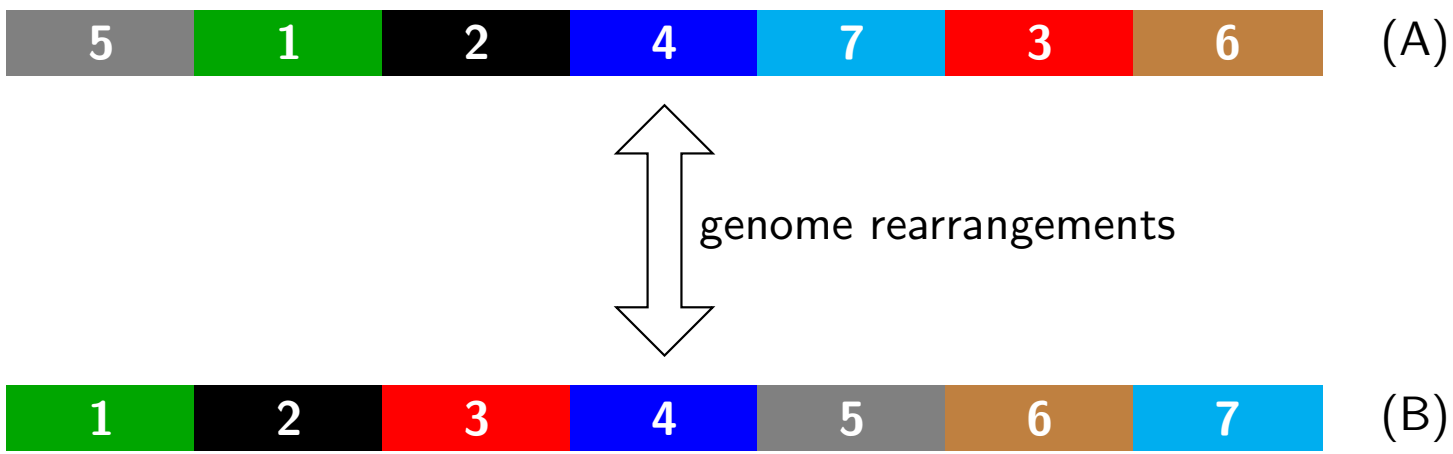

Genome rearrangements for permutations

- Segments can be numbered as we wish, so we assume either genome is the **identity permutation** $\iota = \langle 1\ 2\ \cdots\ n \rangle$ and we wish to **sort** the other genome:

Problem (GENOME REARRANGEMENT (PERMUTATIONS))

Input: *a permutation π in S_n, a set $S \subseteq S_n$ of (per)mutations;*
Goal: *find a shortest sorting sequence of elements of S for π.*

- Again, we can also focus on merely computing $d_S(\pi)$ – the length of an optimal sorting sequence;
- S must generate S_n for any pair of permutations to be a finite distance apart;

Notation and definitions pertaining to permutations

- Permutations can be written in one- or two-row notation:

$$\pi = \left\langle \begin{array}{cccccc} 1 & 2 & 3 & 4 & 5 & 6 \\ 4 & 1 & 6 & 2 & 5 & 3 \end{array} \right\rangle = \langle 4\ 1\ 6\ 2\ 5\ 3 \rangle.$$

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- We deal exclusively with $[n] = \{1, 2, \ldots, n\}$;
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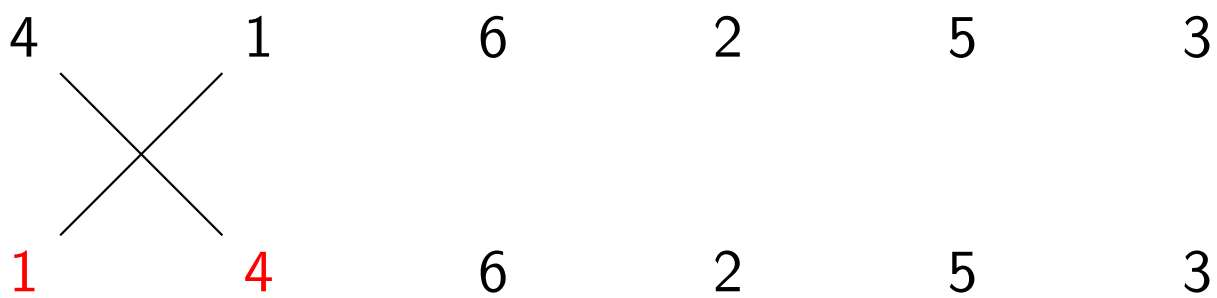
- Composition: the usual $\circ$, which means that in $\pi \circ \sigma$, σ is applied first;

Sorting permutations by adjacent exchanges

- Simple operation : exchange any two adjacent elements:

Example



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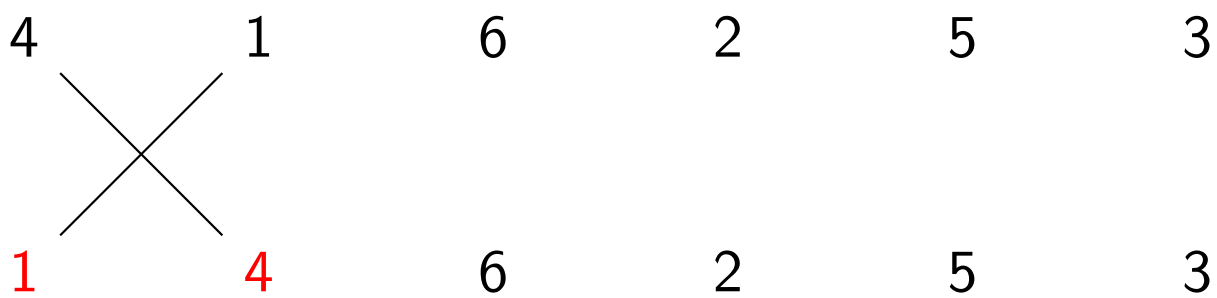

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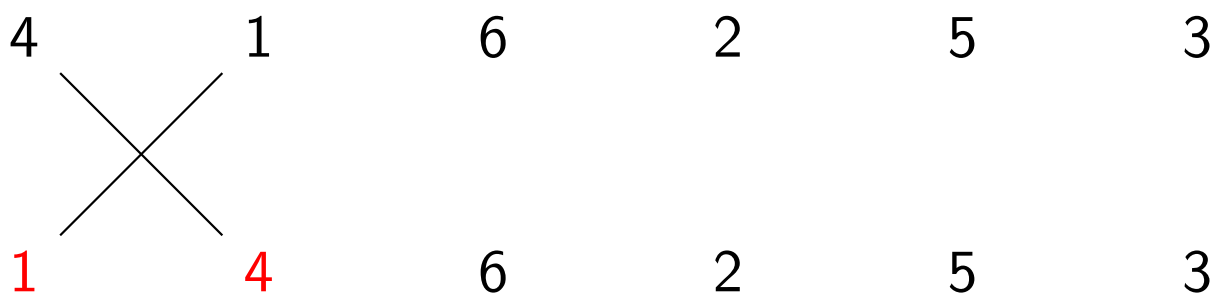

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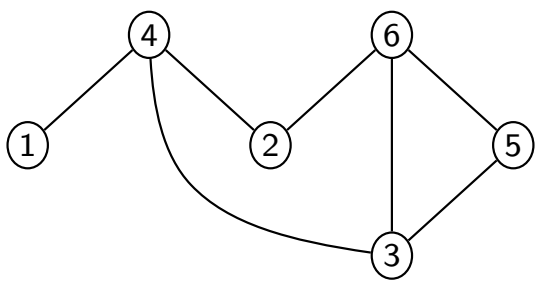
- Solution:
  - sorting: use Bubble Sort;
  - distance: the number of swaps used by Bubble Sort;

A closed formula for the adjacent exchange distance

- An **inversion** in a permutation is a pair of misplaced elements: (π_i, π_j) with $i < j$ and $\pi_i > \pi_j$;
- The **permutation graph** of π has $[n]$ as vertex set and the inversions of π as edges;

Example (the permutation graph of $\langle 4\ 1\ 6\ 2\ 5\ 3 \rangle$)



A closed formula for the adjacent exchange distance

Theorem

The adjacent exchange distance of π is $|Inv(\pi)| = |E(PG(\pi))|$.

Proof sketch.

Each adjacent swap "fixes" at most one inversion, which is equivalent to removing an edge from PG, and we can always find such a move at every step if $\pi \neq \iota$. □

Sorting permutations by exchanges

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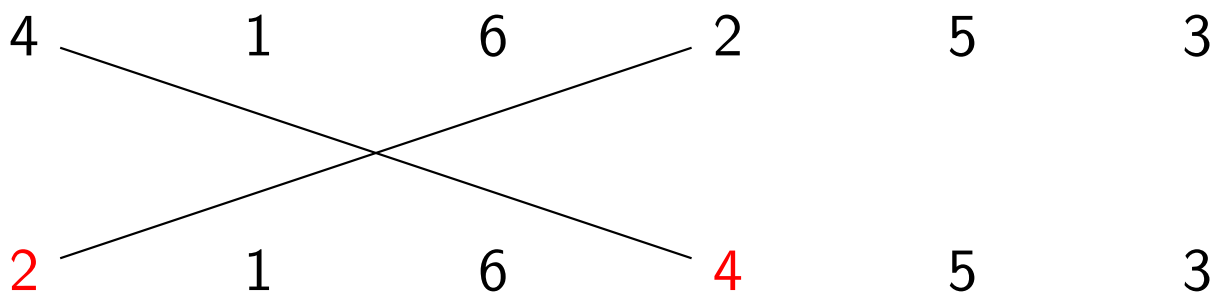

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- Here's a more complete example:

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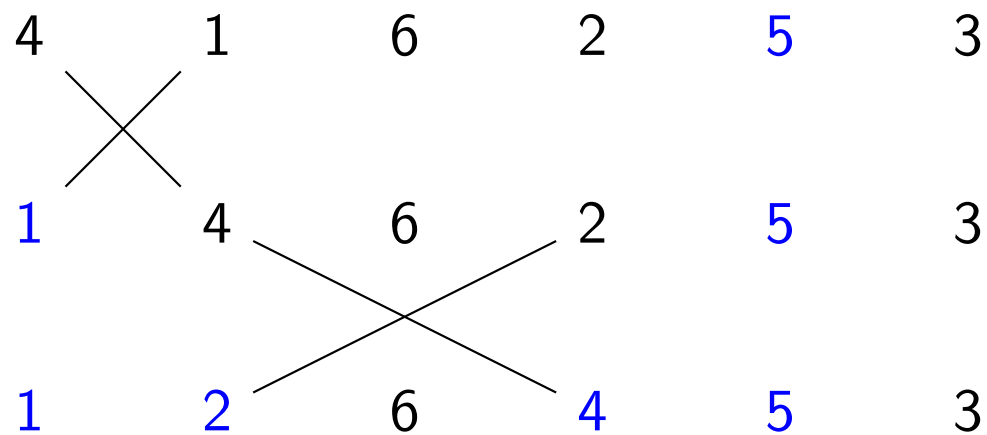

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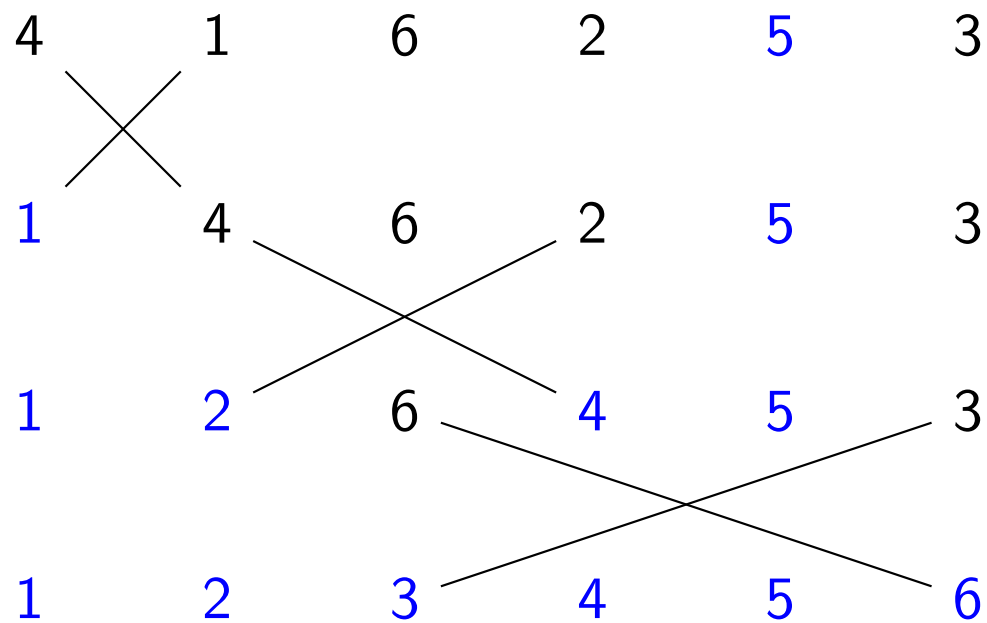

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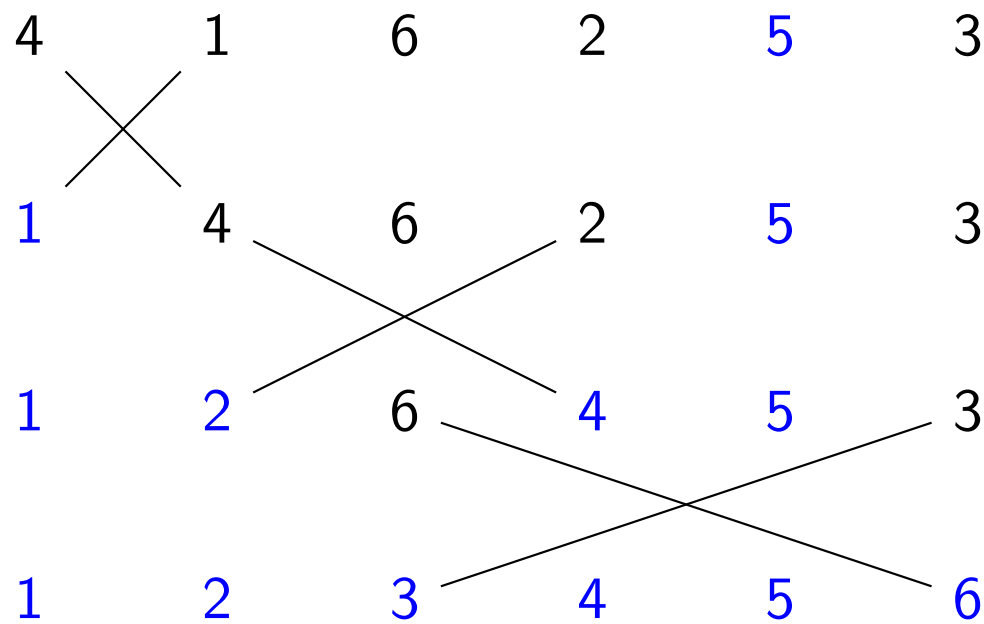

- It works... but can we do better?

Sorting permutations by exchanges

- Our goal: each element should be "at the right place";
- Some elements are already where they should be, so they won't move;
- Strategy: read permutation from left to right, and:
  - if $\pi_i = i$, pass;
  - otherwise, exchange π_i with i;

Sorting permutations by exchanges

- The algorithm obviously terminates;
- At every step, we "fix" one or two positions;
- We use the minimum number of exchanges;
- On the other hand, we'd like to be able to compute the distance without sorting;

Cycles

- Computing the distance requires using the **cycles** of the permutation;
- Those cycles are obtained by iterating the permutation's action on $\{1, 2, \ldots, n\}$, stopping when all elements have been visited;

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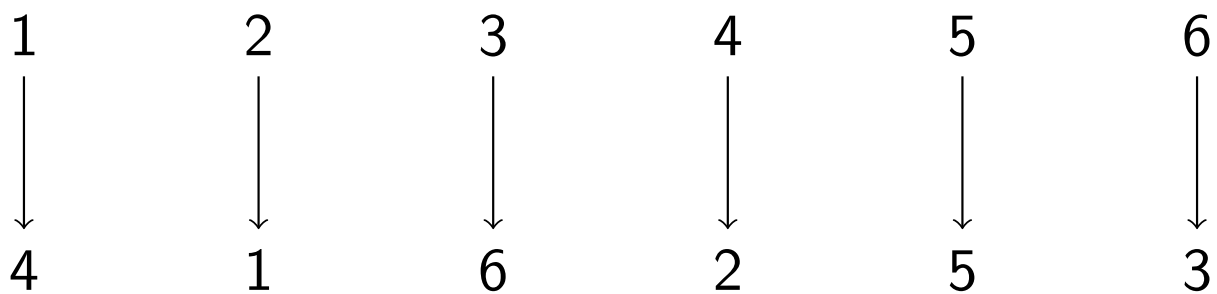

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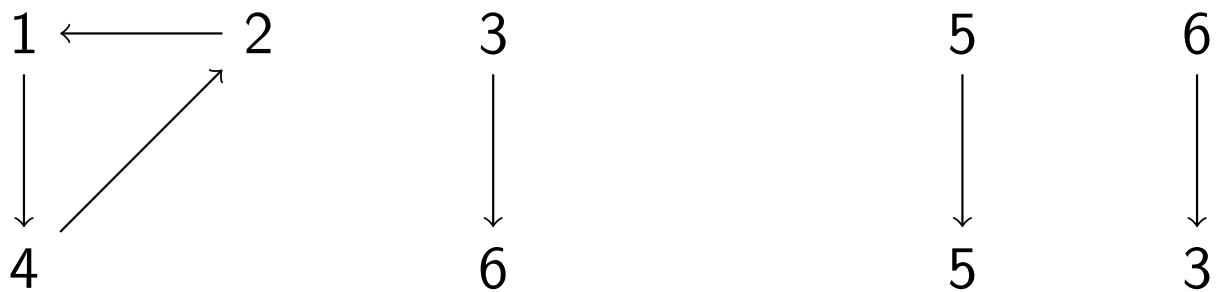

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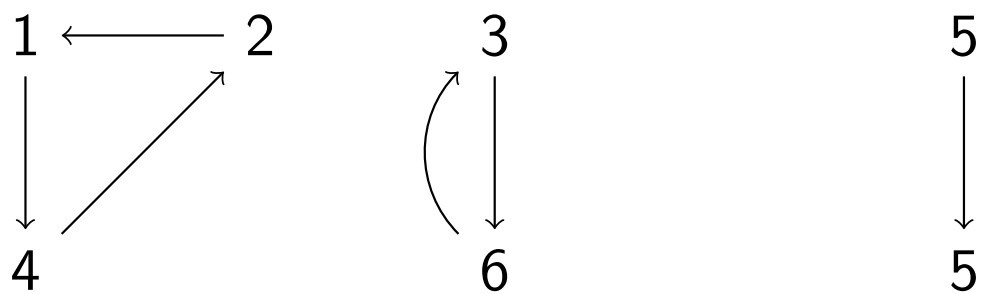

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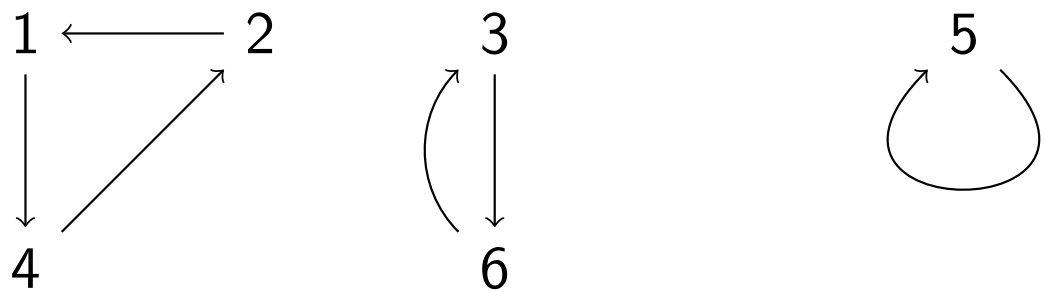

Disjoint cycle decomposition of permutations

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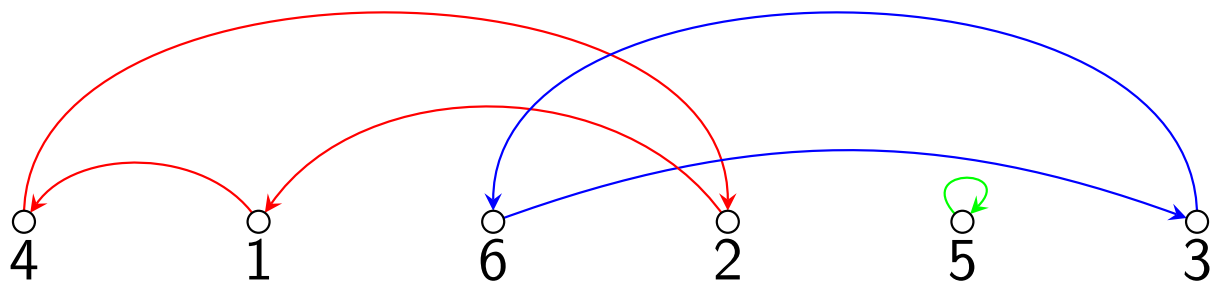

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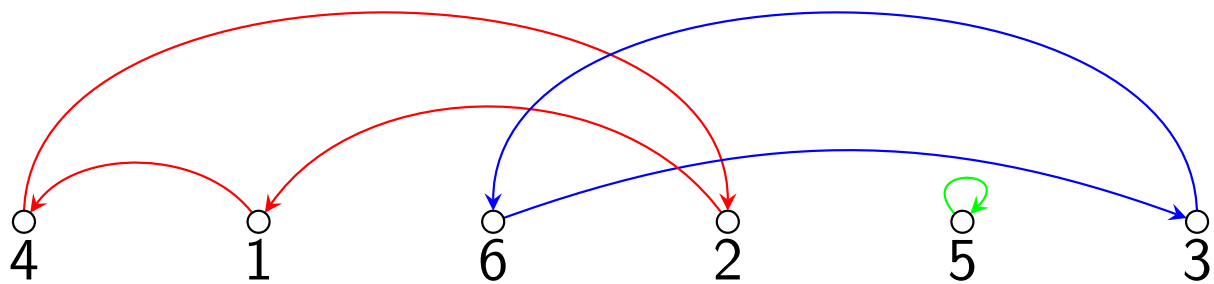

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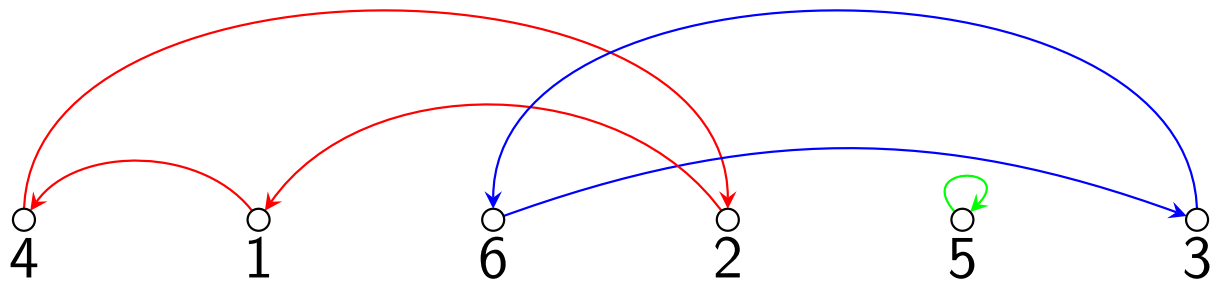
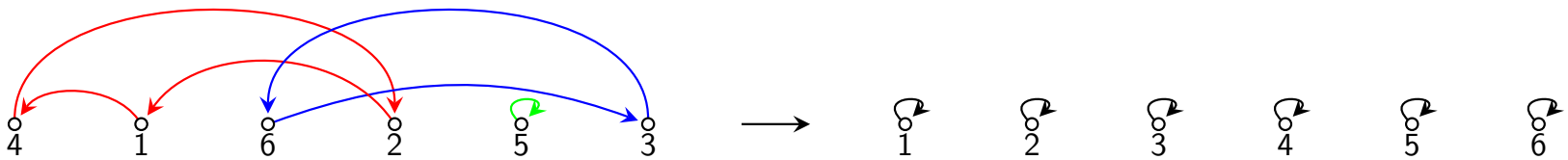


- The number of cycles of π is written $c(\pi)$;
- 1-cycles are sometimes omitted;

Cycles and sorting

- Cycles of length 1 correspond to sorted elements; all other cycles consist of elements that are misplaced;



- Sorting comes down to splitting cycles until we only have cycles of length 1;
- Our algorithm repeatedly splits k-cycles into a 1-cycle and a $(k-1)$-cycle;

Computing the "exchange distance" $exc(\cdot)$

- At each step, we can always create a new cycle if $\pi \neq \iota$, so:

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Theorem ([Cayley, 1849])

The exchange distance of π in S_n is $n - c(\pi)$.

Lessons from sorting by exchanges

- Note that ι is the only permutation with n cycles;
- The formula $exc(\pi) = n - c(\pi)$ expresses:
  - the difference between the number of cycles we have and the number of cycles we want;
  - and the fact that at each step, we can obtain exactly one new cycle.
- This point of view will be *crucial* to sorting problems;

Practice

For the algorithms below, a permutation is represented as a size-n array with values and indices ranging from 1 to n.

1. Give a linear-time algorithm computing the inverse of a permutation.
2. Give a linear-time algorithm computing an optimal sequence of swaps sorting a permutation.
3. Give a linear-time algorithm computing the decomposition of a permutation into disjoint cycles
4. Let S be a set of permutations defining distance d_S over $\mathcal{S}_n$, such that S is stable by inversion ($\pi \in S \Rightarrow \pi^{-1} \in S$).
   - Prove that $d_S(\pi) = d_S(\pi^{-1})$ for every permutation π.
   - The stability by inversion is a sufficient condition to have the above property, but is it necessary?

Block-interchanges and transpositions

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- We'll now look at two generalisations of exchanges:
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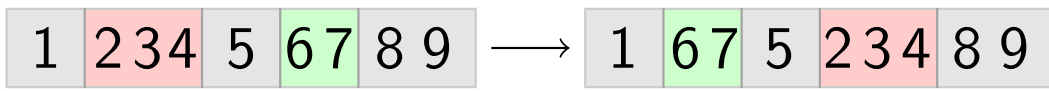

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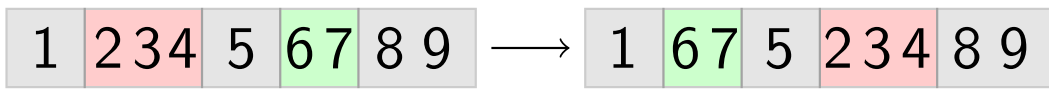
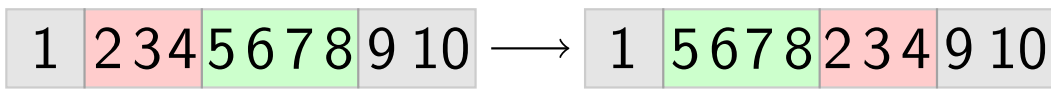


- **Transpositions** displace an interval of the permutation;



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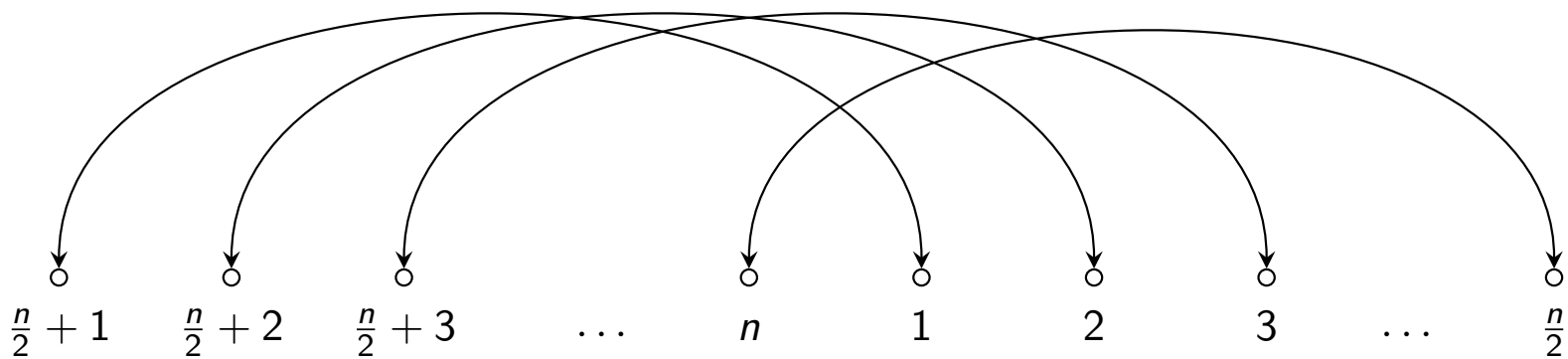

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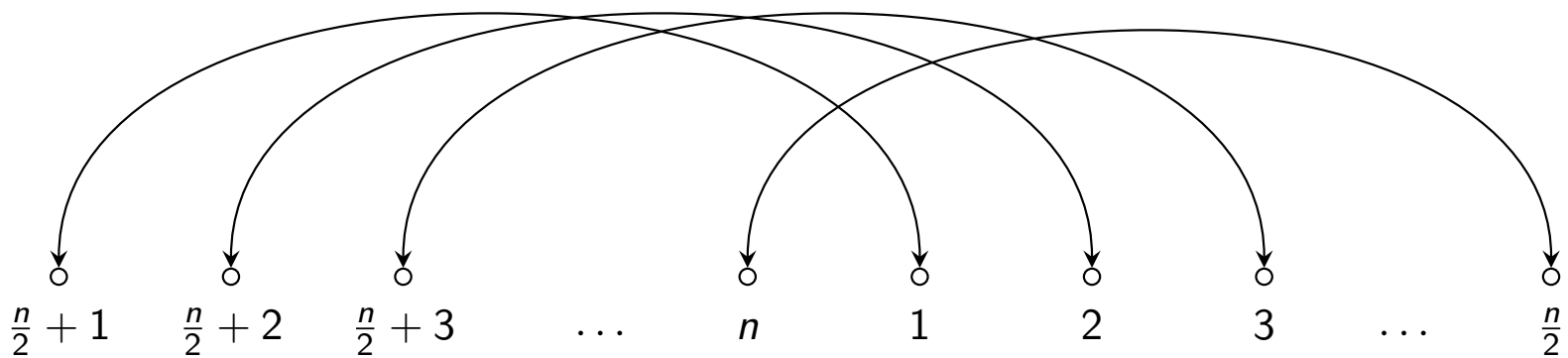

- We'll need something else since we cannot bound the effect of an operation in that setting;

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- (the term "breakpoint" will be explained later);
- Let's build the directed breakpoint graph of $\pi = \langle 4\ 1\ 6\ 2\ 5\ 7\ 3 \rangle$:

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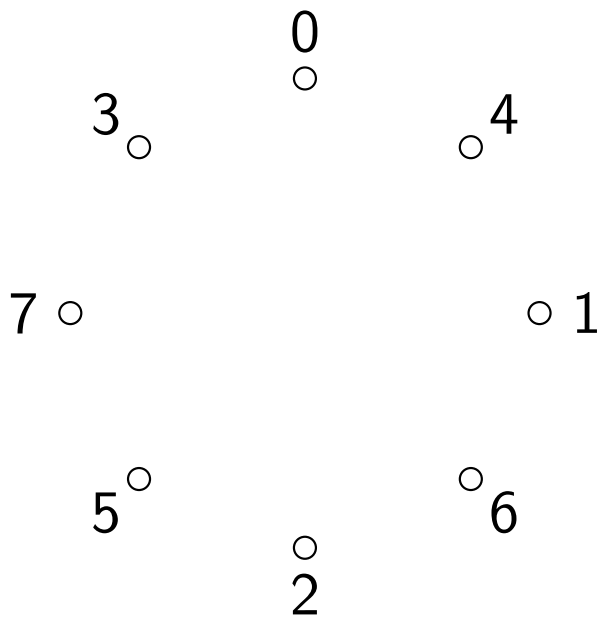

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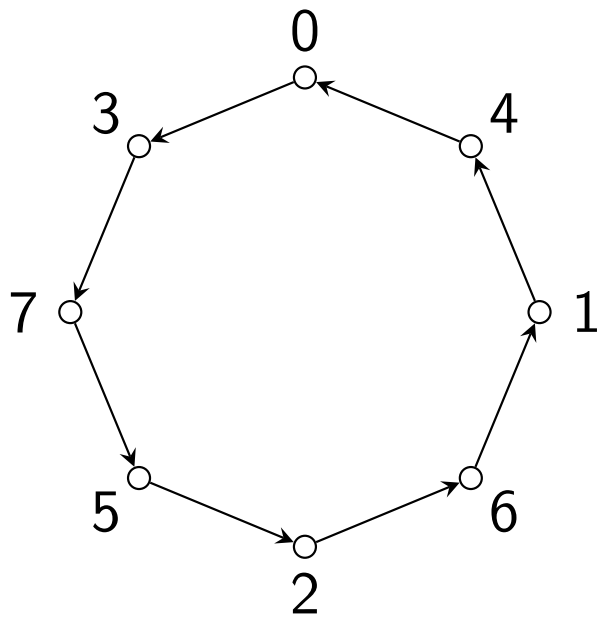

1. build the ordered vertex set $(\pi_0 = 0, \pi_1, \pi_2, \ldots, \pi_n)$;
2. add **black arcs** for every ordered pair $(\pi_i, \pi_{i-1 \pmod{n+1}})$;

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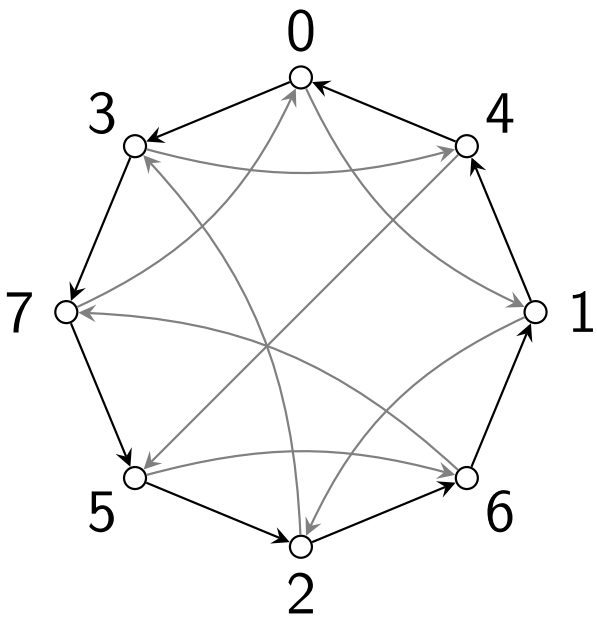

1. build the ordered vertex set $(\pi_0 = 0, \pi_1, \pi_2, \ldots, \pi_n)$;
2. add **black arcs** for every ordered pair $(\pi_i, \pi_{i-1 \pmod{n+1}})$;
3. add **grey arcs** for every ordered pair $(i, i+1 \pmod{n+1})$;

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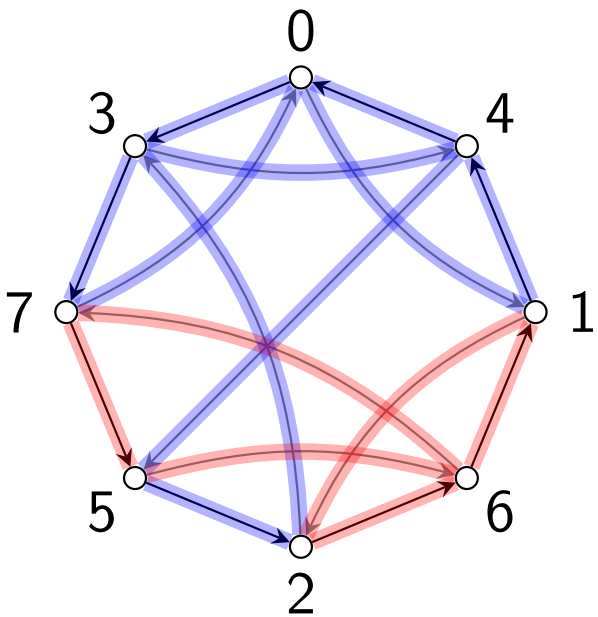

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$DBG(\pi)$ decomposes in a unique way into **alternating cycles**

Formal definition of the directed breakpoint graph

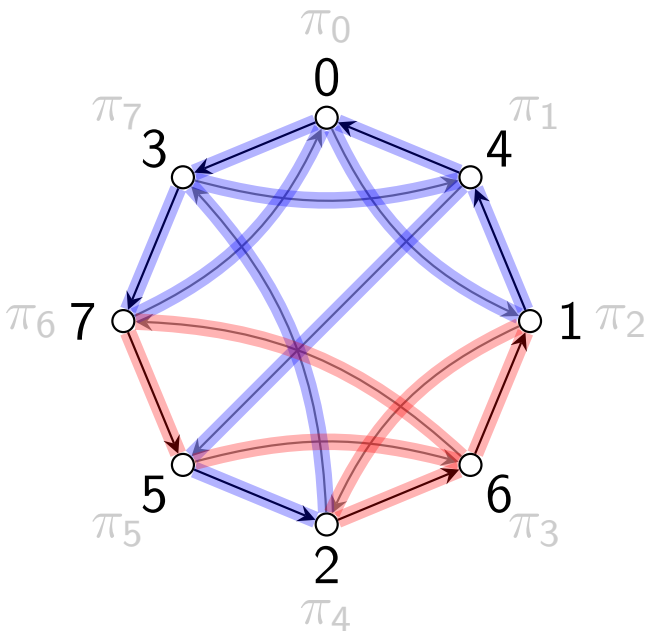
Definition ([Bafna and Pevzner, 1998])

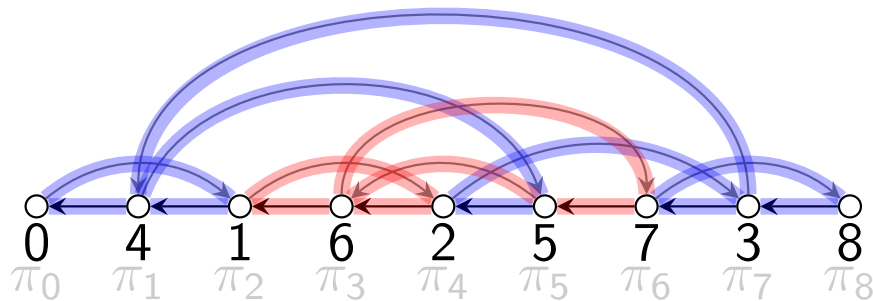
The **directed breakpoint graph** of $\langle \pi_1\ \pi_2\ \cdots\ \pi_n \rangle$ is defined by:

1. an ordered vertex set $V = (\pi_0 = 0, \pi_1, \pi_2, \ldots, \pi_n)$;
2. a bicoloured arc set $A = A_B \cup A_G$, where:
   - 2.1 $A_B = \{(\pi_i, \pi_{i-1 \pmod{n+1}}) : 0 \leq i \leq n\}$;
   - 2.2 $A_G = \{(i, i+1 \pmod{n+1}) : 0 \leq i \leq n\}$;

Circular vs. linear layout

- One can also represent the directed breakpoint graph using a linear layout without affecting the cycle structure:

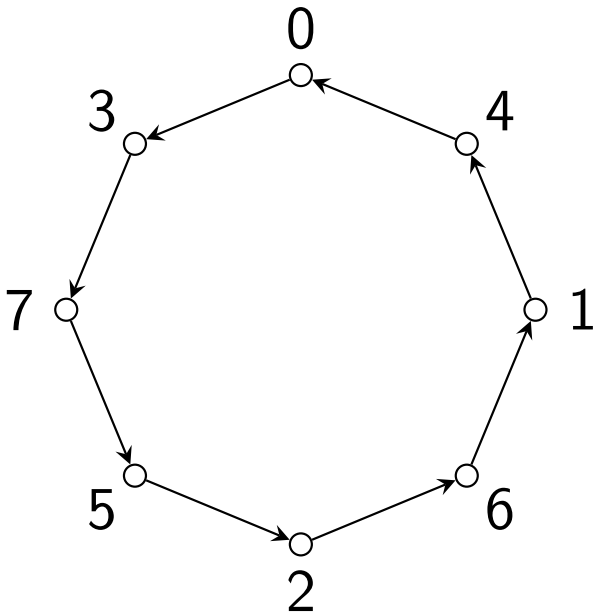


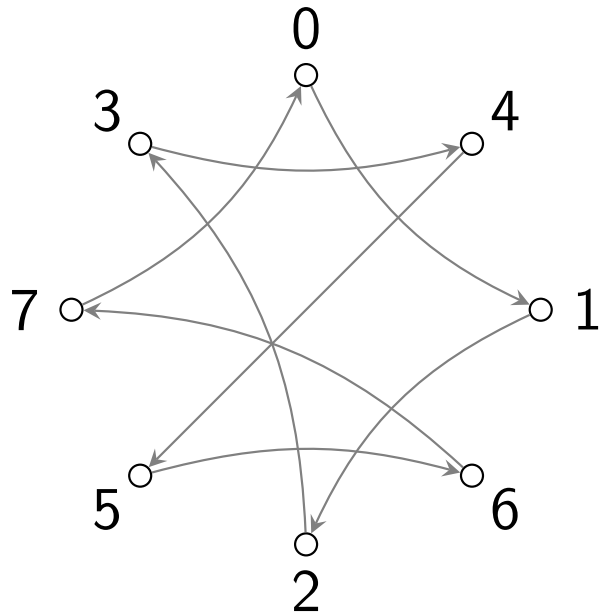


- Circular $\rightarrow$ linear: split 0 into 0 and $n+1$;
- Linear $\rightarrow$ circular: merge 0 and $n+1$ into 0;
- (in both cases: adapt arcs accordingly);

Intuitions behind $DBG(\pi) - 1$

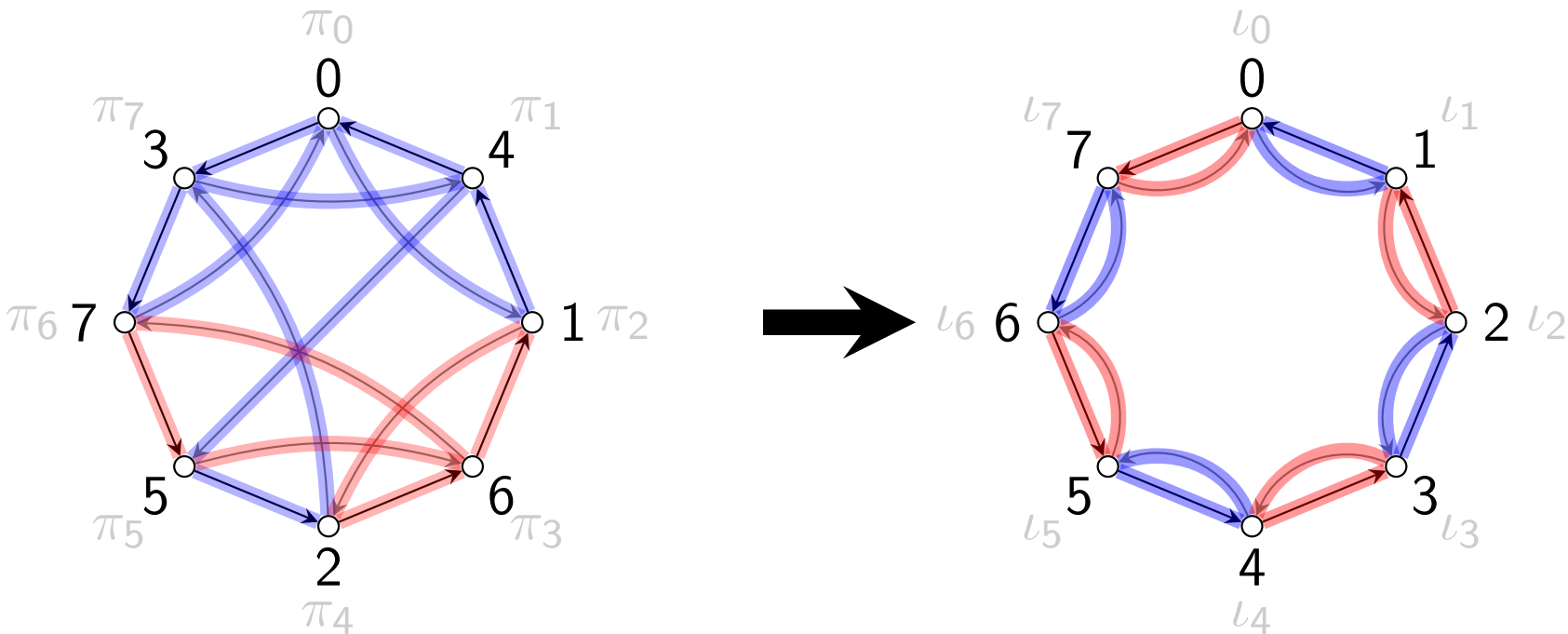
- Both "monochromatic" cycles represent an ordering:
  1. the black one represents the one we have ("reality");
  2. the grey one represents the one we want to obtain ("desire");





Intuitions behind $DBG(\pi)$ – 2

- The alternating cycles are a blend of "reality" and "desire", and we must act on those cycles to turn "reality" into "desire";
- When we are done, we have the largest number of cycles;

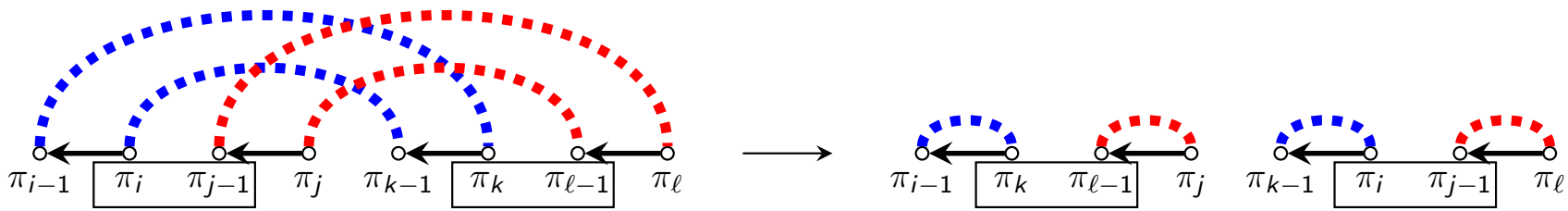


Proving lower bounds

- One way of proving lower bounds on distances: be optimistic:
  1. find out the "best case";
  2. pretend we're always in that case;
- Techniques based on breakpoint graphs follow the same spirit as those based on the disjoint cycle decomposition, but less freedom is allowed (details later);
- Usually: case analysis to determine by how much a parameter of the graph can change with one operation;

Lower bounding the block-interchange distance

A block-interchange $\beta(i, j, k, \ell)$ increases the number of cycles in *DBG* by at most 2:

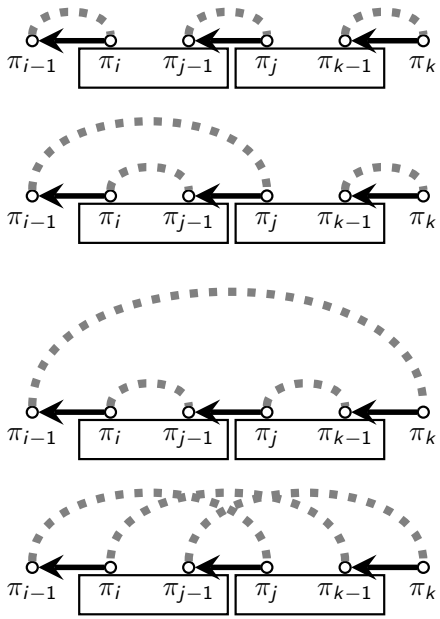


Theorem ([Christie, 1996])

For all π *in* S_n*:* $bid(\pi) \geq \frac{n+1-c(DBG(\pi))}{2}$.

Lower bounding the transposition distance

A transposition $\tau(i, j, k)$ increases the number of **odd** cycles in DBG by at most 2:



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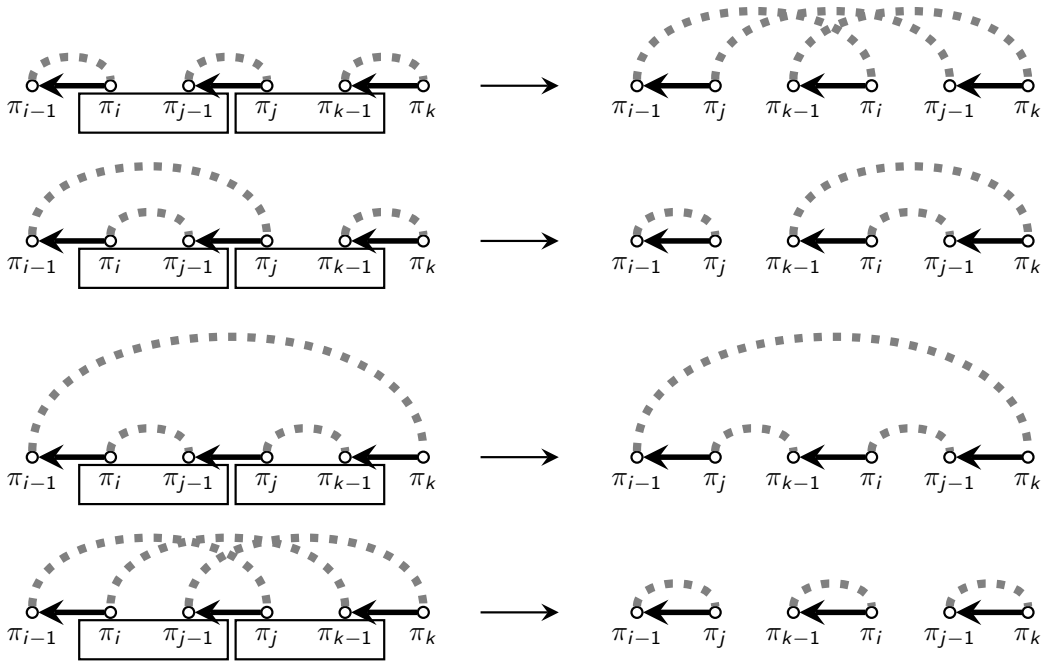

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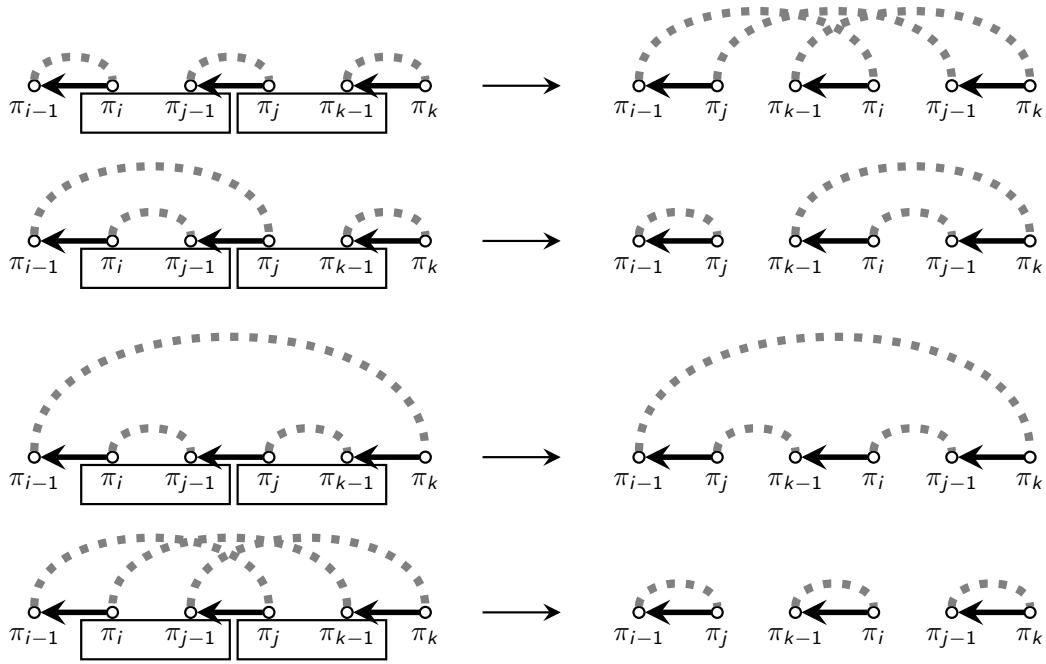

Theorem ([Bafna and Pevzner, 1998])

For all π in S_n: $td(\pi) \geq \frac{n+1-c_{odd}(DBG(\pi))}{2}$.

Practice

5. Give sorting sequences for the following permutations, and prove they are optimal

   - $\langle 654321 \rangle$, using block-interchanges
   - $\langle 3254761 \rangle$, using transpositions

Proving upper bounds

- One way of proving upper bounds on distances: be pessimistic:
  1. find out the "worst case";
  2. pretend we're always in that case;
- For better upper bounds: be less pessimistic:
  - case analyses of varying difficulty;
  - look at *sequences* of moves;

Upper bounds

- For block-interchanges, we have:

Theorem ([Christie, 1996])

For all π in S_n: $bid(\pi) \leq \frac{n+1-c(DBG(\pi))}{2}$.

- Which equals the lower bound and therefore the exact distance;

Upper bounds

- For transpositions:

  Theorem ([Bafna and Pevzner, 1998])

  For all π in S_n: $td(\pi) \leq \frac{3}{4}(n + 1 - c_{odd}(DBG(\pi))) = \frac{3}{2}OPT$.

- Current best approximation: 11/8 [Elias and Hartman, 2006]

Practice

6. Show that $td(\pi) \leq n - LIS(\pi)$, where LIS denotes the length of the longest increasing subsequence.

7. Give a polynomial-time 2-approximation algorithm for the Transposition Distance problem.

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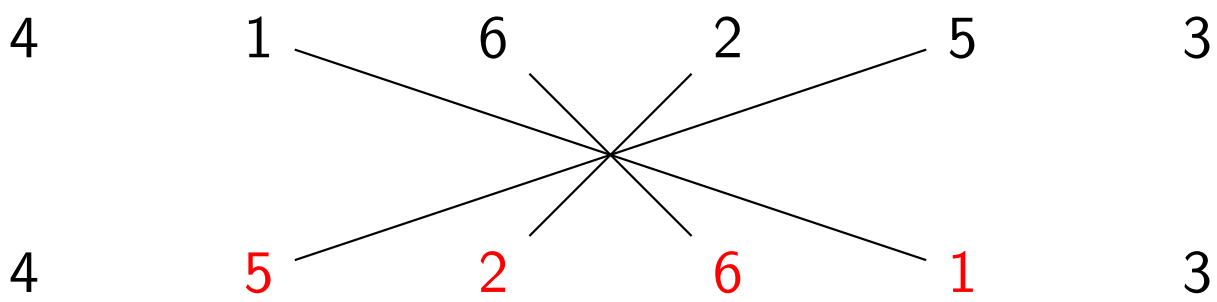
Hint 1: Use the lower bound based on the number of cycles: $td(\pi) \geq \frac{n+1-c(DBG(\pi))}{2}$

Hint 2: If π displays a cycle of the *right* form, give a transposition creating two cycles. Otherwise, turn a cycle into the right form with one transposition.

Reversals

- Another type of mutation occurs frequently: **reversals**, which reverse the order of elements on an interval of the permutation;

Example



Reversals

- Here's an optimal sorting sequence[1]:

Example (optimal sorting sequence of reversals)

6 genes 6 singletons, 0 2-strips Unsigned Reversal Distance: 4

One optimal reversal scenario

Step	Description	
0	(Source)	4 1 6 2 5 3
1	Reversal	4 1 2 6 5 3
2	Reversal	4 5 6 2 1 3
3	Reversal	1 2 6 5 4 3
4	Reversal (Destination)	1 2 3 4 5 6

- Bad news: stuff seen so far doesn't work;

[1] Obtained using GRIMM: `http://grimm.ucsd.edu/cgi-bin/grimm.cgi`

Breakpoints

Definition ([Watterson et al., 1982])

A **breakpoint** in a permutation π is an ordered pair (π_i, π_{i+1}) with $|\pi_{i+1} - \pi_i| \neq 1$ (otherwise it's an **adjacency**).

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Example (breakpoints of $\langle 3\ 1\ 5\ 4\ 2\ 8\ 6\ 7 \rangle$)

$$3 \bullet 1 \bullet 5 \quad 4 \bullet 2 \bullet 8 \bullet 6 \quad 7$$

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- This notion characterises elements that are "relatively misplaced": they're not consecutive in ι, nor in $\langle n\ n-1\ \cdots\ 2\ 1 \rangle$

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$$\langle \pi_1\ \pi_2\ \cdots\ \pi_n \rangle \mapsto \langle \mathbf{0}\ \pi_1\ \pi_2\ \cdots\ \pi_n\ \mathbf{n+1} \rangle$$

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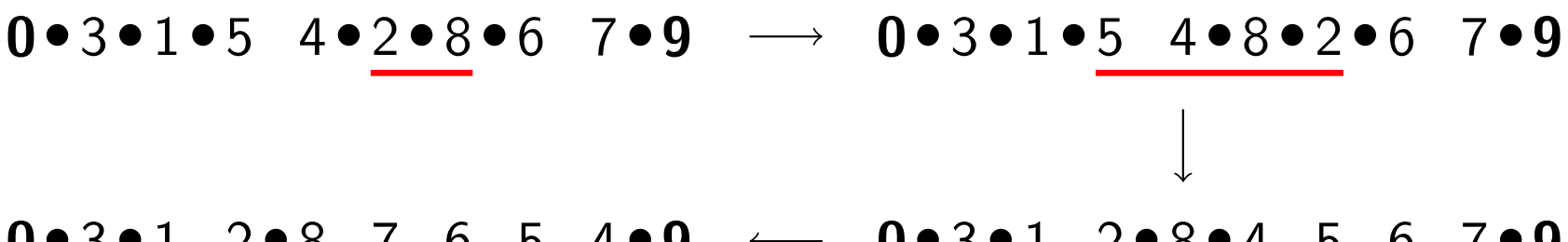
- Example: $\langle \mathbf{0} \bullet 3 \bullet 1 \bullet 5\ 4 \bullet 2 \bullet 8 \bullet 6\ 7 \bullet \mathbf{9} \rangle \Rightarrow b(\pi) = 7$;

Usefulness of breakpoints

- Observation: reversals can "fix" breakpoints:

Example



Lower bound

- A reversal can fix at most two breakpoints;
- If we're lucky, we are always in that case;
- This yields the following lower bound:

Theorem ([Kececioglu and Sankoff, 1995])

For every permutation π:

$$rd(\pi) \geq b(\pi)/2.$$

Upper bound

- On the other hand we can always fix at least one breakpoint (details: [Kececioglu and Sankoff, 1995])
- So the algorithm is a 2-approximation:

$$b(\pi)/2 \leq rd(\pi) \leq b(\pi)$$

- Can we do better?

The *undirected breakpoint graph*

- Yes, but we need a more appropriate structure:

Definition ([Bafna and Pevzner, 1996])

The **undirected breakpoint graph** of the permutation π in S_n, written $UBG(\pi) = (V, E)$, is defined by:

- $V = (\pi_0 = 0, \pi_1, \pi_2, \ldots, \pi_n, \pi_{n+1} = n + 1)$;
- $E = \underbrace{\{\{\pi_i, \pi_{i+1}\} \mid 0 \leq i \leq n\}}_{\text{black edges}} \cup \underbrace{\{\{i, i+1\} \mid 0 \leq i \leq n\}}_{\text{grey edges}}$.

The *undirected breakpoint graph*: example

- Let us build the undirected breakpoint graph $\pi = \langle 3\ 1\ 5\ 4\ 2\ 8\ 6\ 7 \rangle$:

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1. frame the permutation;

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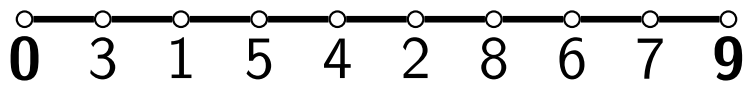

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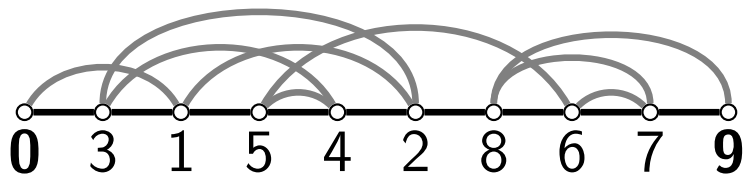

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Decomposition

- That graph decomposes into cycles:

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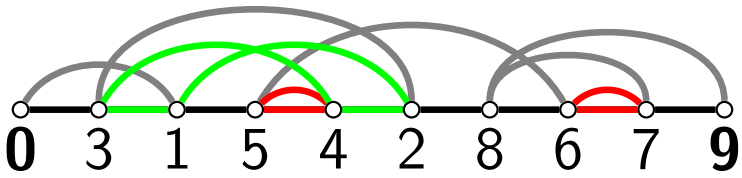

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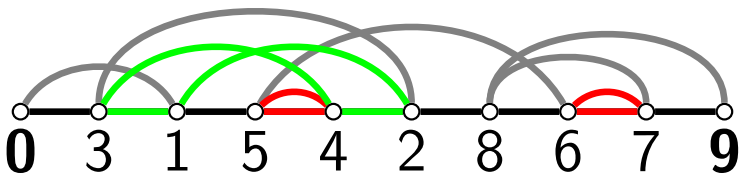

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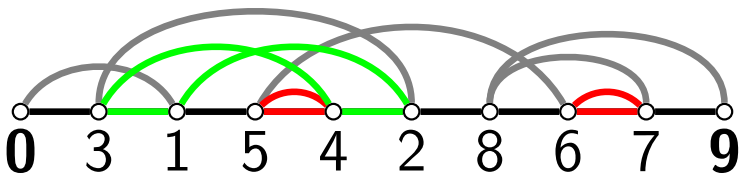

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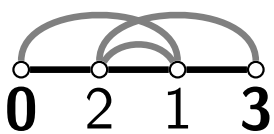

has either one 3-cycle or a 1-cycle and a 2-cycle.

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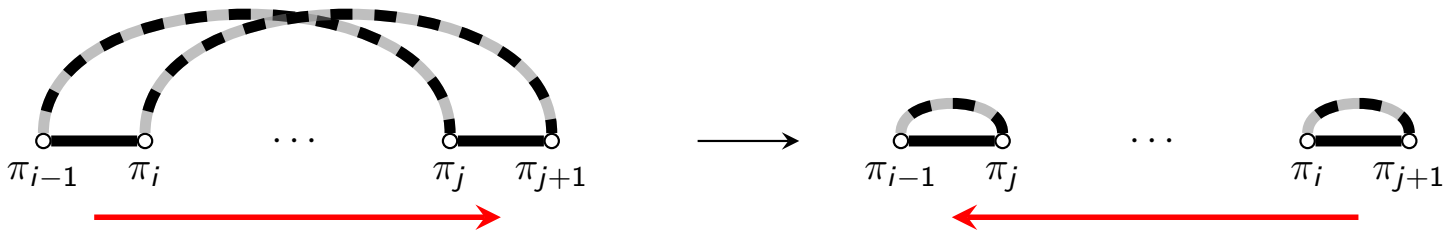
- A reversal acts on one or two cycles and can split / merge cycles;



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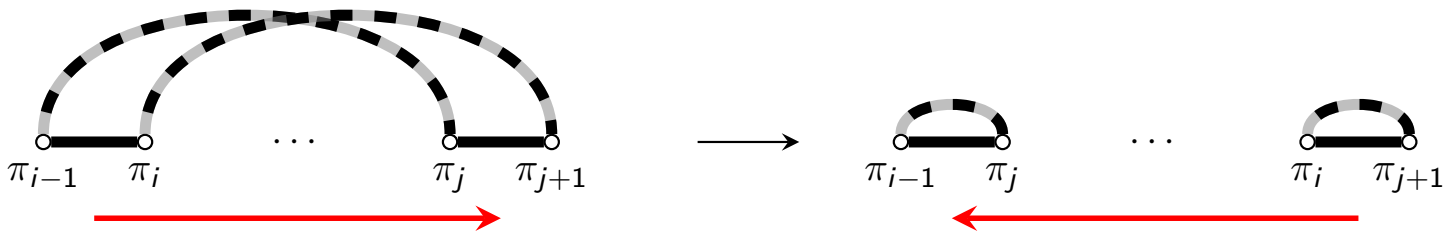

- So we're tempted to say:

$$rd(\pi) \geq n + 1 - c(UBG(\pi))$$

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Theorem ([Bafna and Pevzner, 1996])

For all π in S_n:

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where $c^*(UBG(\pi))$ is the number of cycles in a maximum cardinality decomposition.

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- Unfortunately, finding a maximum cardinality decomposition is NP-hard [Caprara, 1999];

Results on sorting permutations

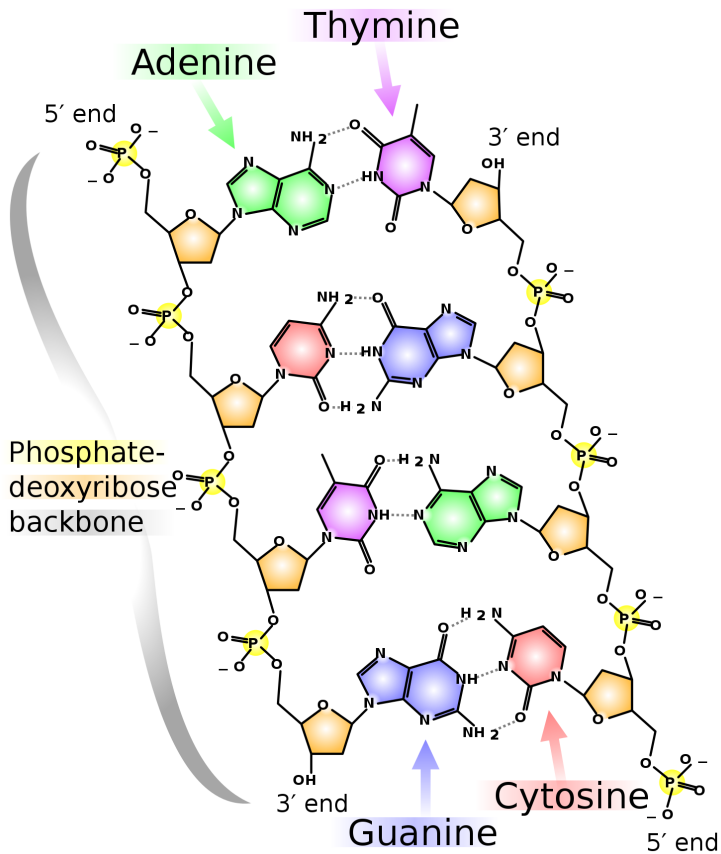
- Here's a nonexhaustive summary on sorting permutations using various operations:

	Operation	Sorting	Distance	Best approximation
	exchange	$O(n)$ [Knuth, 1995]		1
	block-interchange	$O(n)$ [Christie, 1996]		1
	double cut-and-joins	NP-hard [Chen, 2010]		?
	reversal	NP-hard [Caprara, 1999]		11/8 [Berman et al., 2002]
	transposition	NP-hard [Bulteau et al., 2012]		11/8 [Elias and Hartman, 2006]
prefix	exchange	$O(n)$ [Akers et al., 1987]		1
prefix	reversal	NP-hard [Bulteau et al., 2015]		2 [Fischer and Ginzinger, 2005]
prefix	transposition	?	?	2 [Dias and Meidanis, 2002]

- Let us move on to our next model: **signed** permutations;

Motivation

- Permutations lack realism: DNA segments are oriented;
- We need to take orientation into account;
- Therefore, two DNA segments match if:
  - they are the same, or
  - one is the **reverse complement** of the other.

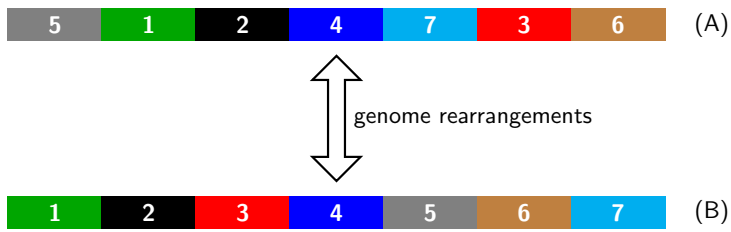


(picture by Madeleine Price Ball, taken from Wikimedia)

Motivation

- So instead of permutations:

Example (genomes → permutations)



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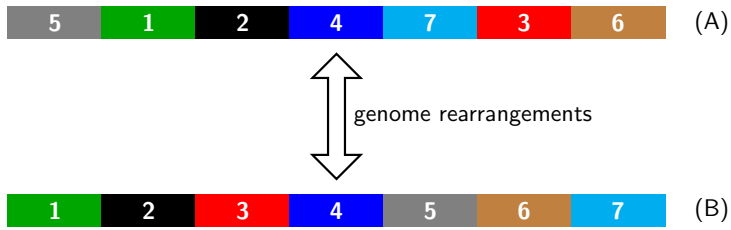

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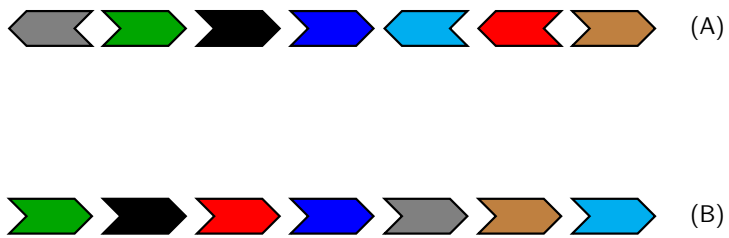

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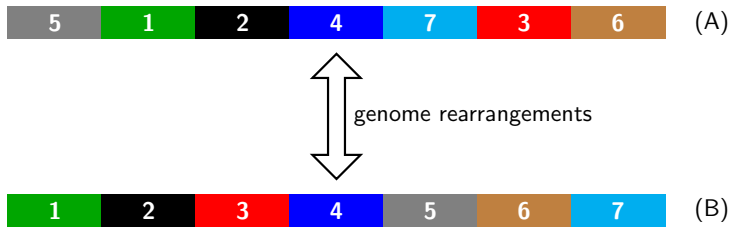

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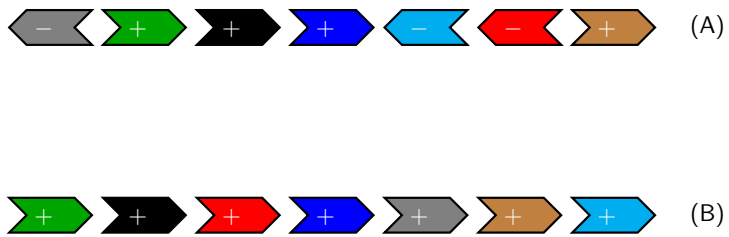

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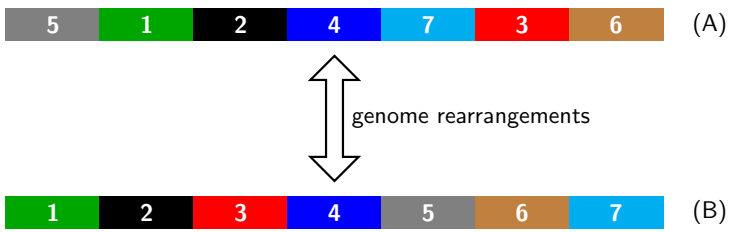

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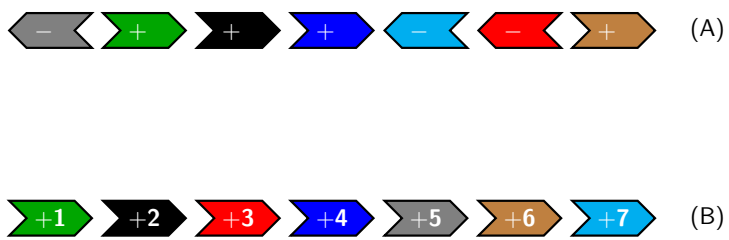

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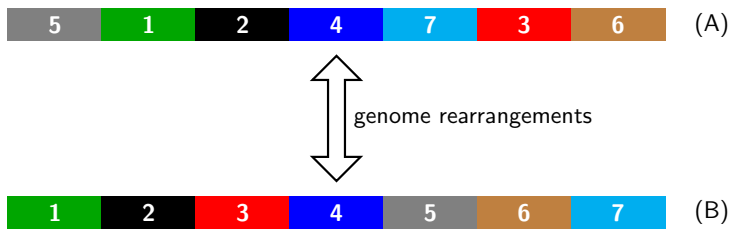

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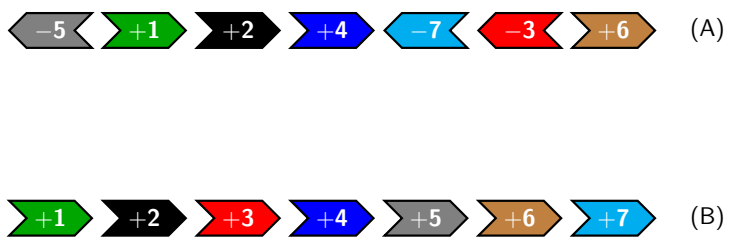

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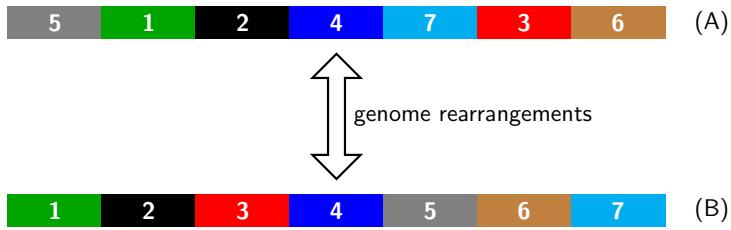

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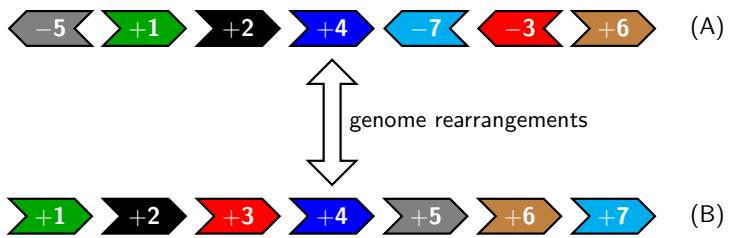

Signed (per)mutations

- Note: this does not mean that everything you know about unsigned comparisons is useless:
  1. orientation information is not always available;
  2. ideas from unsigned comparisons lead to ideas for signed comparisons;
- Mutations may now act on a segment's place **and** orientation;

Tools

- As expected, tools we've seen previously cannot be used here because they do not take signs into account;
- Then again, some ideas can be adapted;

Notation and definitions pertaining to signed permutations

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- The corresponding group is the **hyperoctahedral group** $S_n^{\pm}$;

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- As before, we're interested in sorting a given signed permutation using as few signed reversals as possible (or merely computing the length of a shortest sequence);

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$\sigma =$ 

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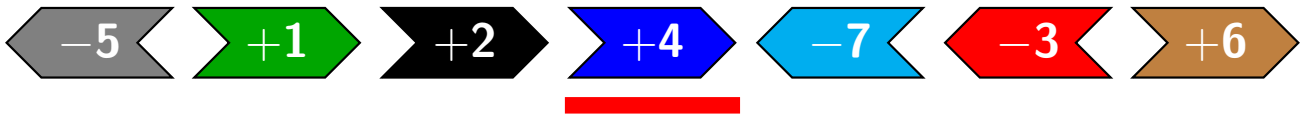
$\pi =$ 

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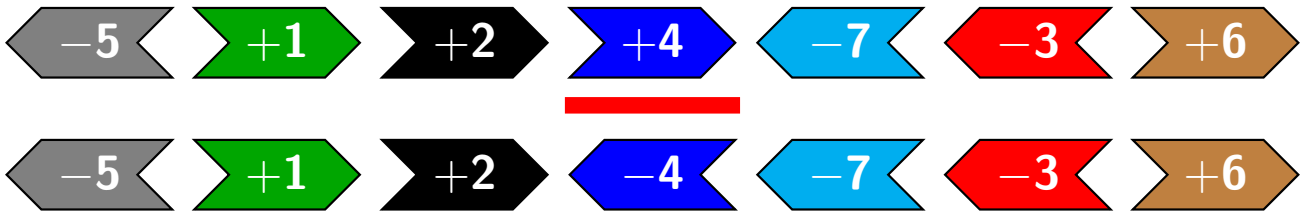
$\pi =$ 

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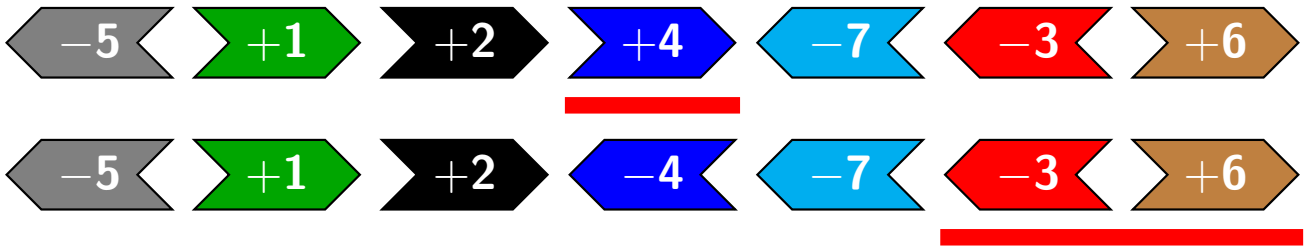
$\pi =$ 

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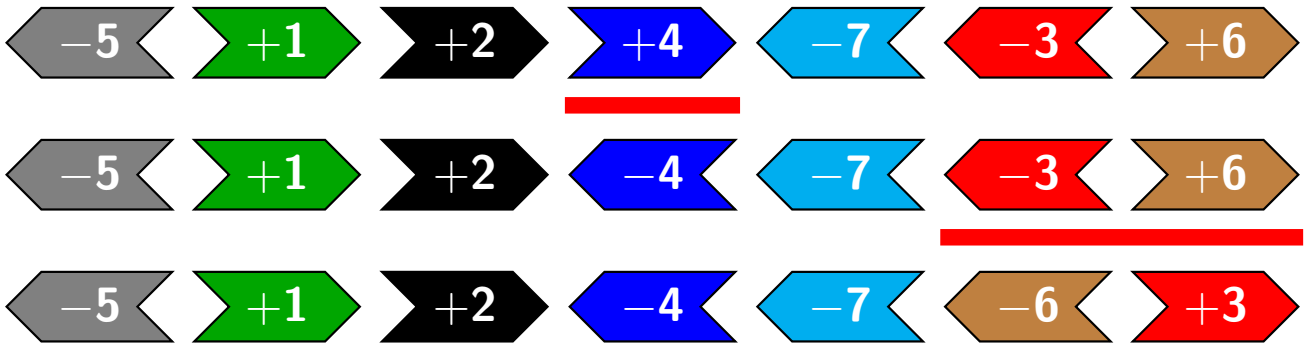
$\pi =$ 

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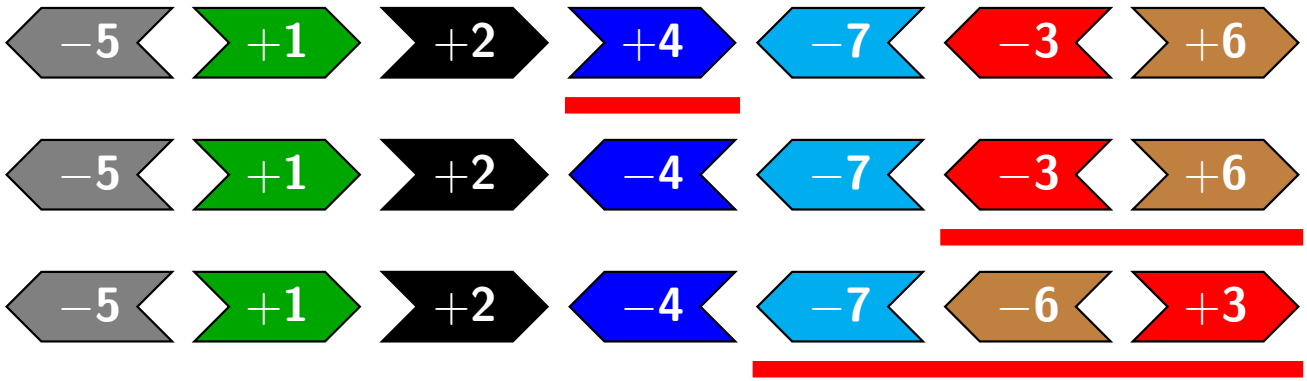
$\pi =$ 

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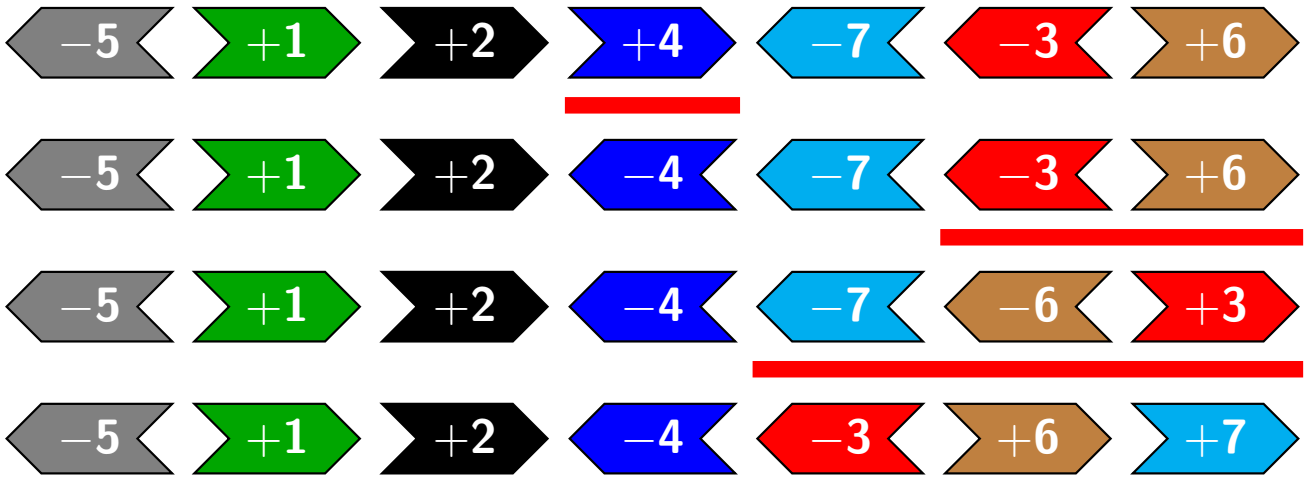
$\pi =$ 

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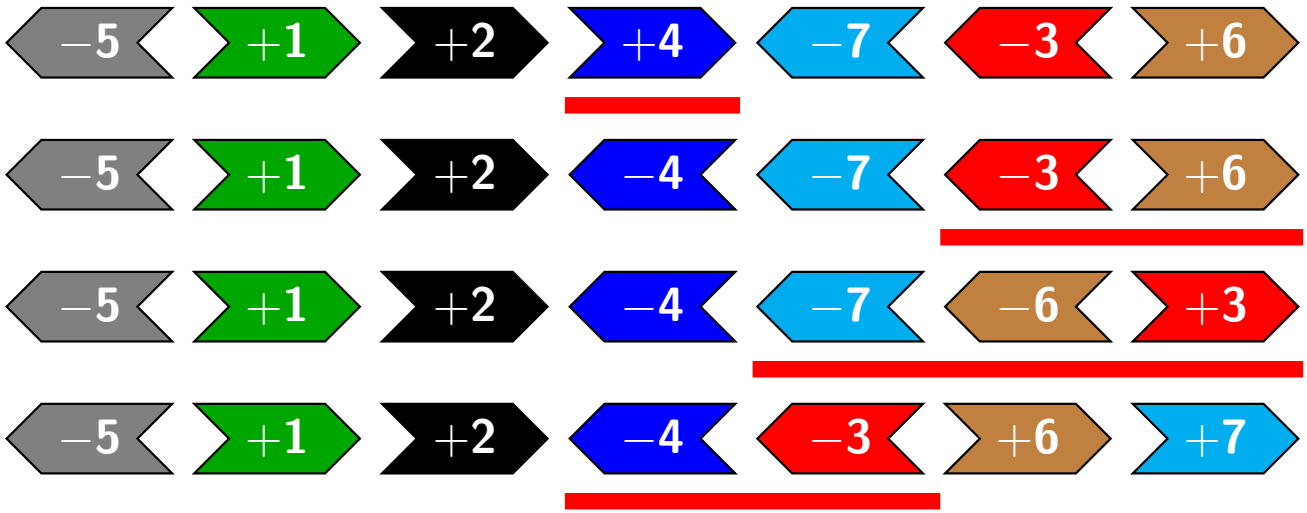
$\pi =$ 

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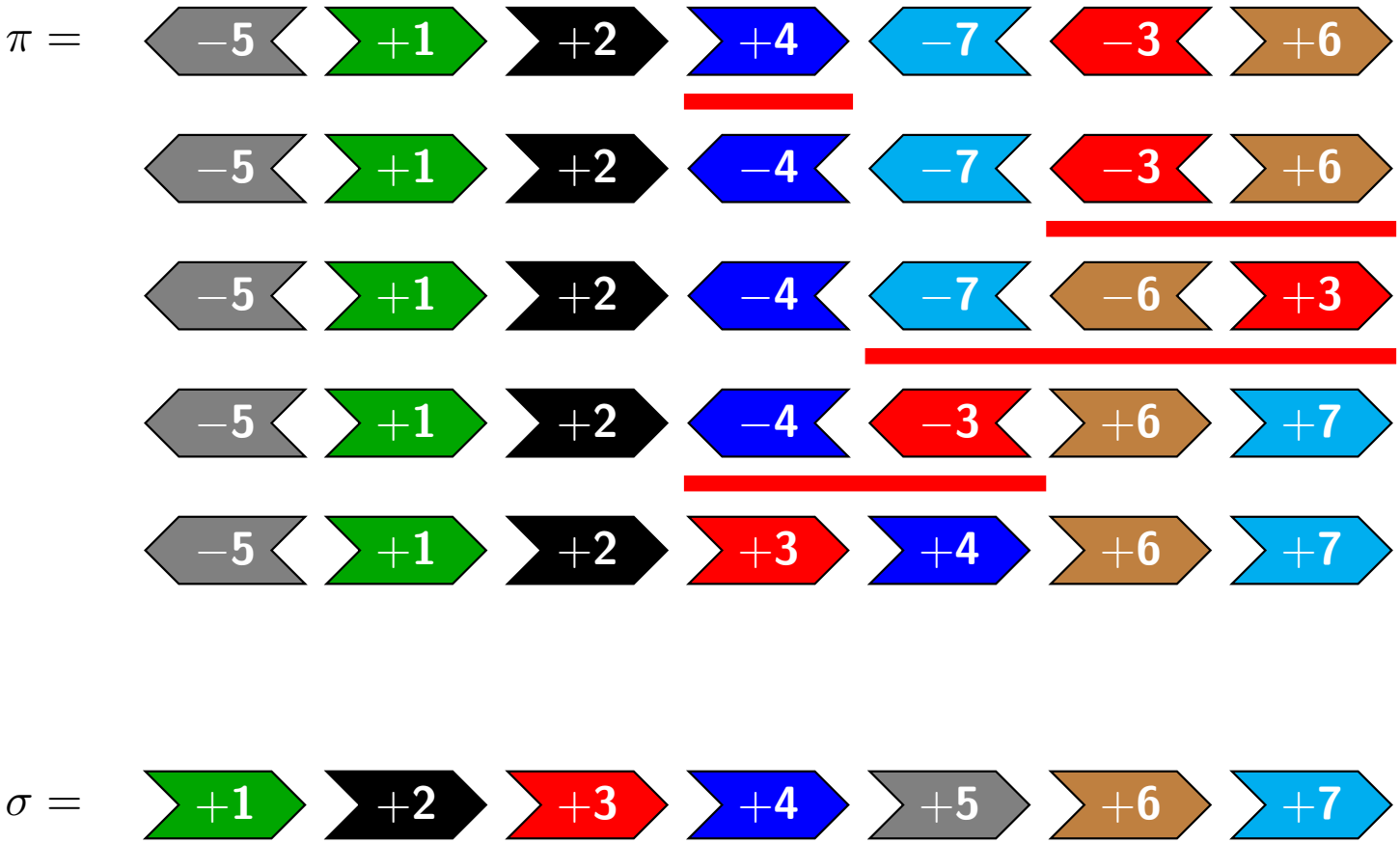

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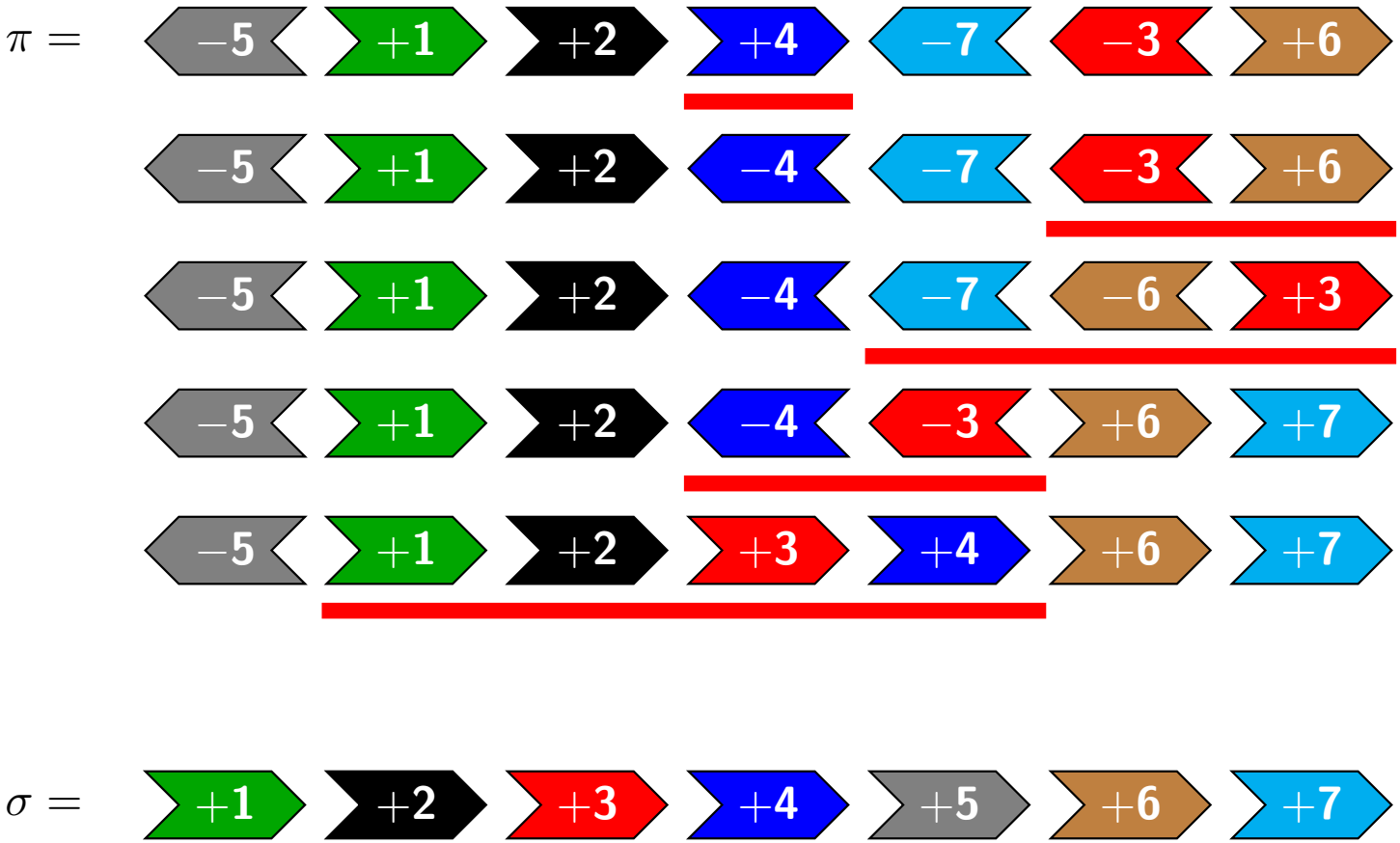

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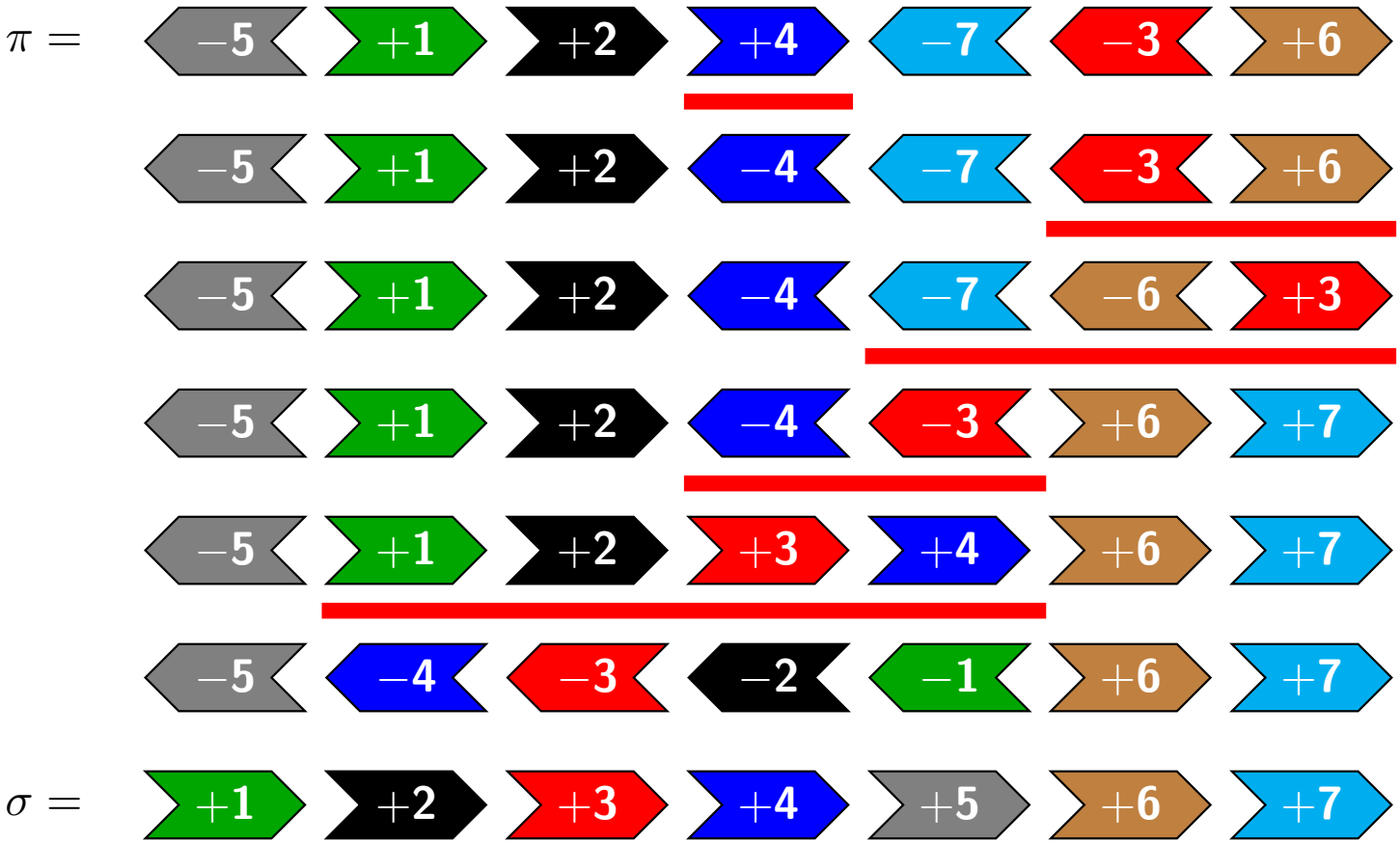

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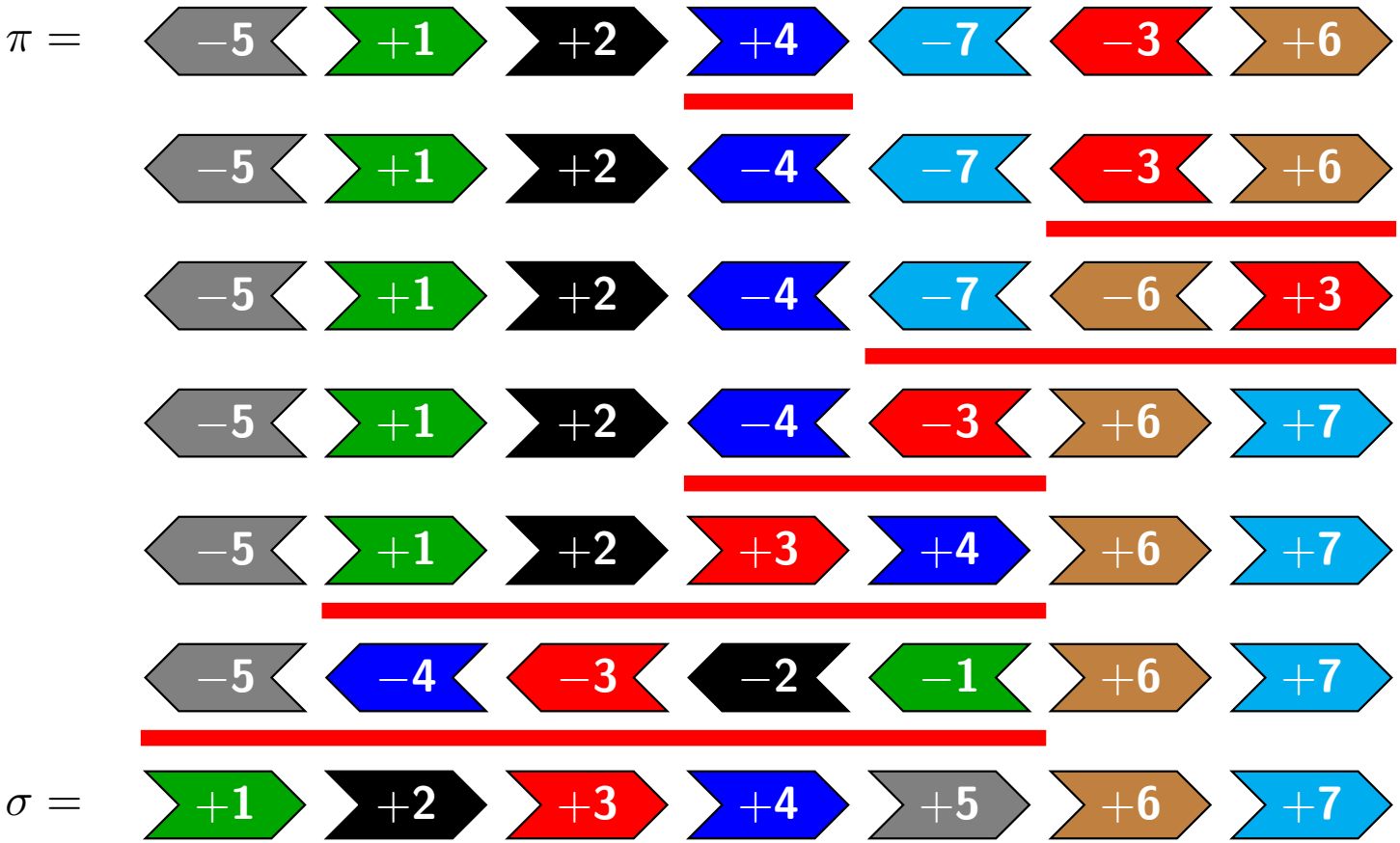

$$srd(\pi, \sigma) \leq 6$$

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- How do we attack this problem?
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- Instead, we're going to adapt the breakpoint graph to the signed setting;

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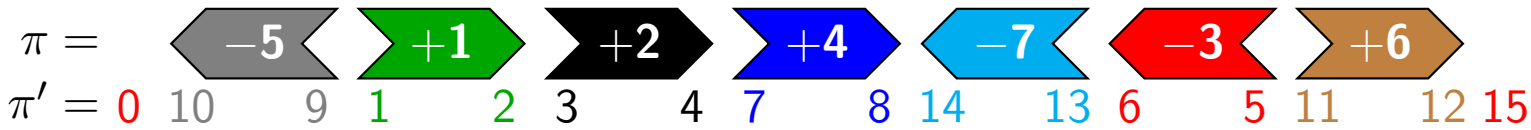

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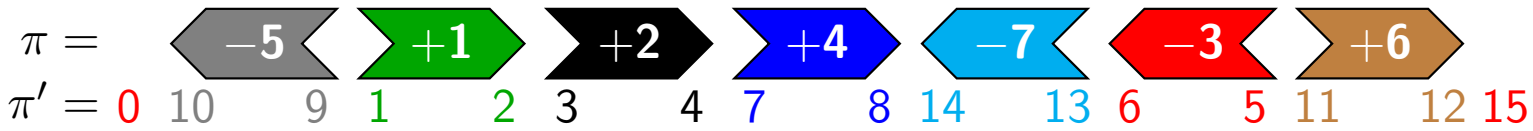

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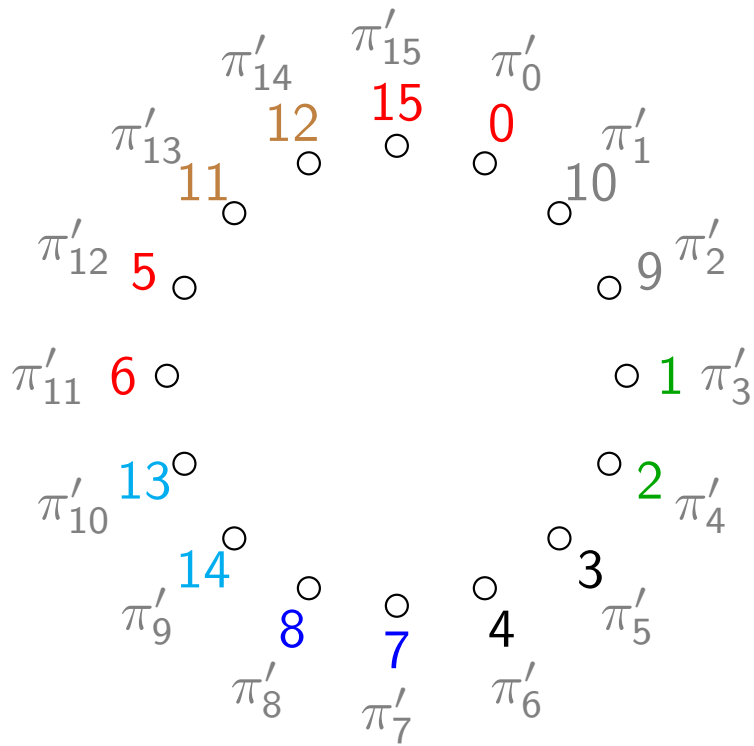

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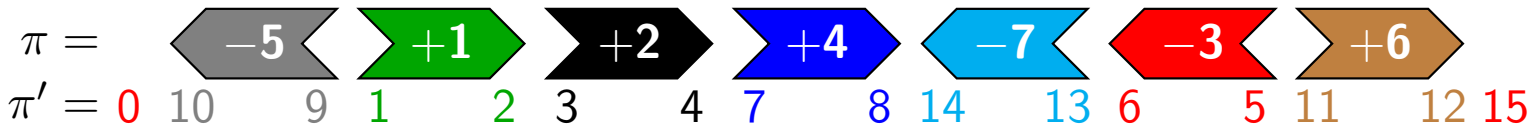

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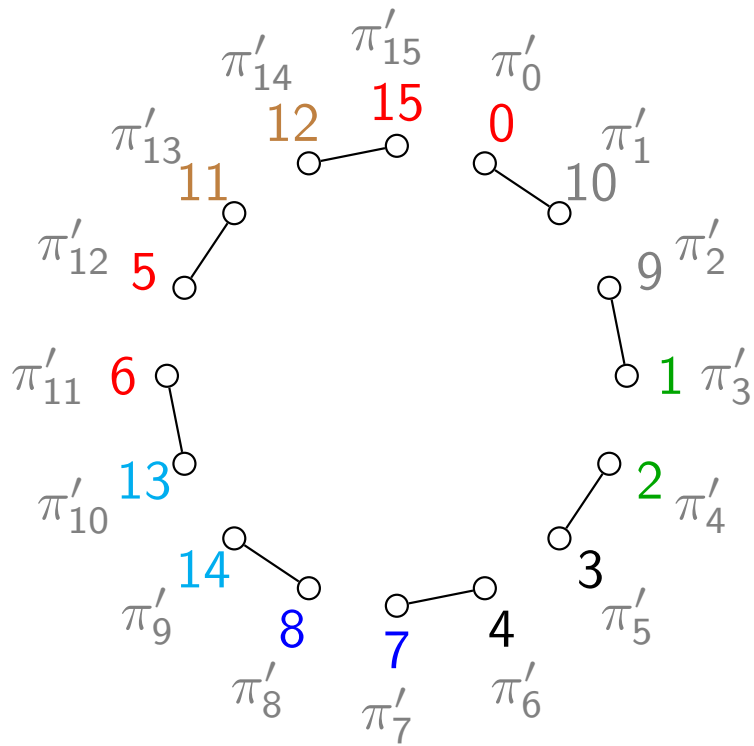

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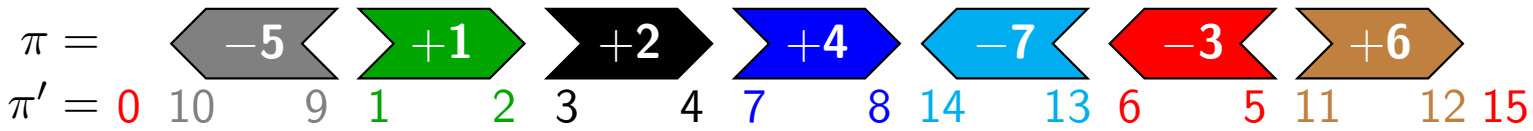

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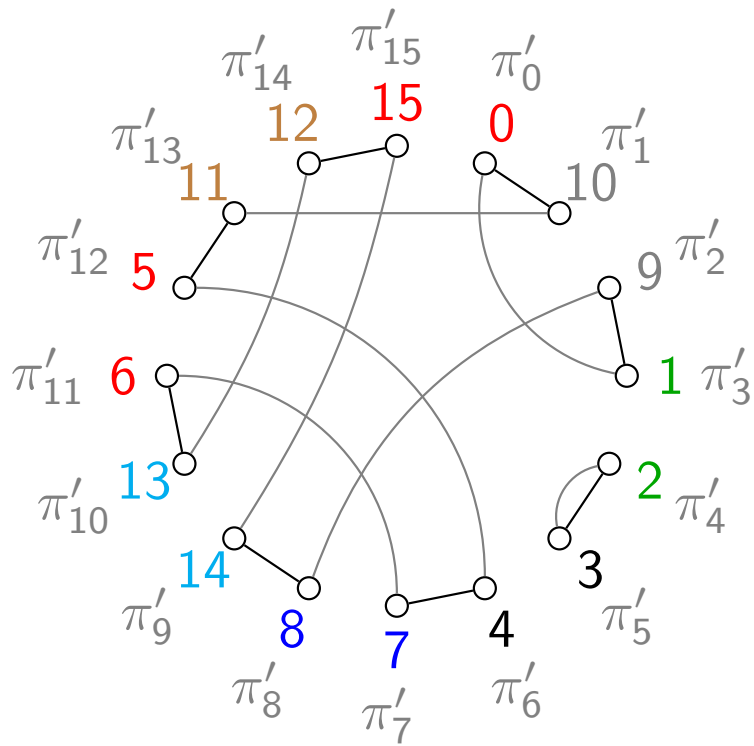
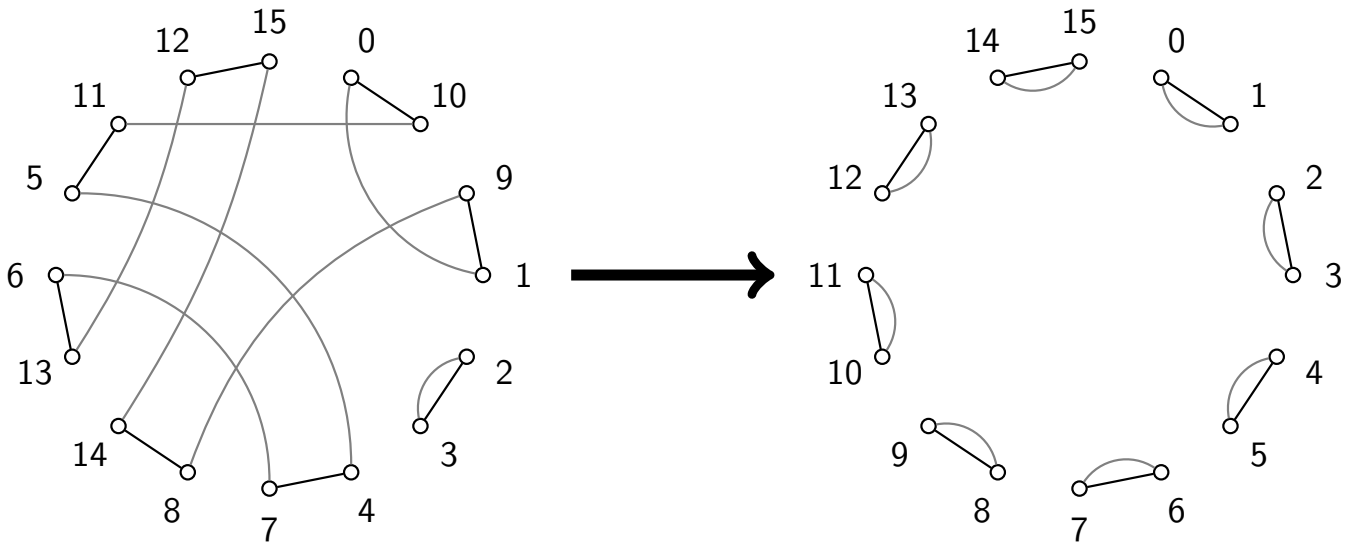


Using the breakpoint graph

- The breakpoint graph is 2-regular and decomposes as such into **alternating cycles** in a unique way;
- The breakpoint graph of $\langle 1\ 2\ \cdots\ n \rangle$ contains the largest number of cycles:



- $\Rightarrow$ goal: create new cycles in as few moves as possible;

Practice

8. Draw the breakpoint graph for the signed permutation

$$\langle -4, 3, -2, -5, 1 \rangle$$

Overview of Hannenhalli and Pevzner's solution

- [Hannenhalli and Pevzner, 1999] came up with the first polynomial-time algorithm for this problem:
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- [Gog and Bader, 2008] give fast algorithms to achieve the conversions;

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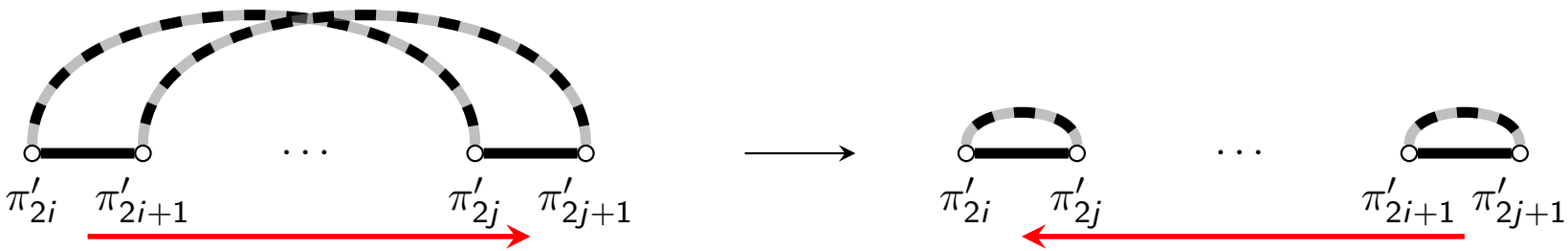

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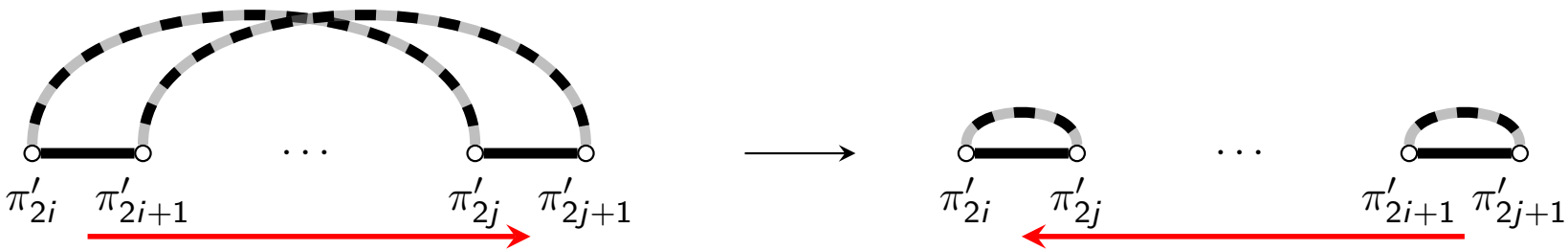

- Therefore, for all π in $S_n^{\pm}$:

$$srd(\pi) \geq n + 1 - c(BG(\pi)).$$

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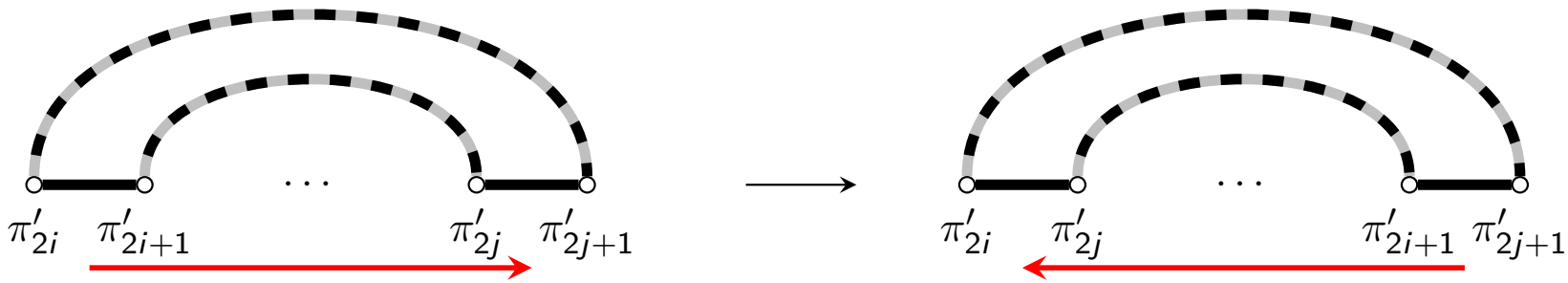

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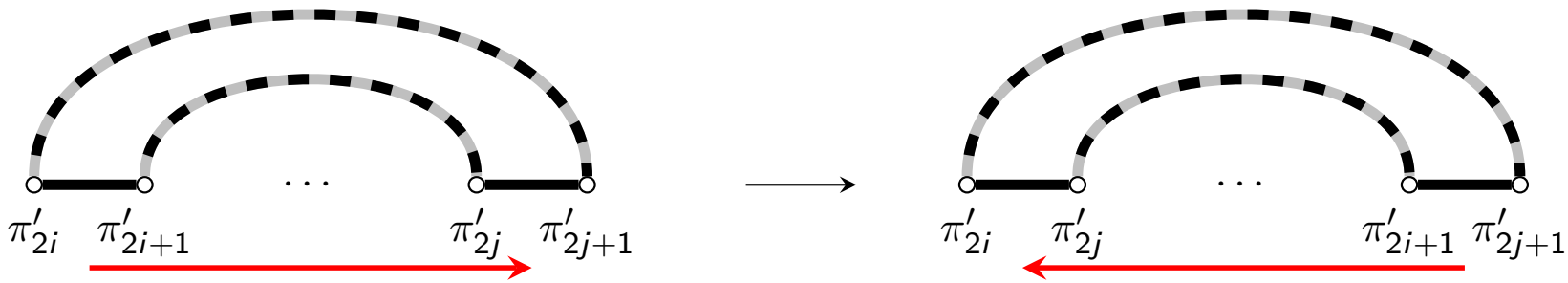

- Hence the inequality: we can split "good" cycles, and we cannot split "bad" cycles;
  - standard terminology: "good" = **oriented**, "bad" = **unoriented**;

Handling good cycles

- Things are actually more complicated than that;
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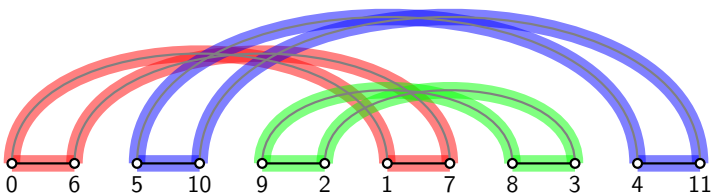
Example (careless and careful cycle splitting)



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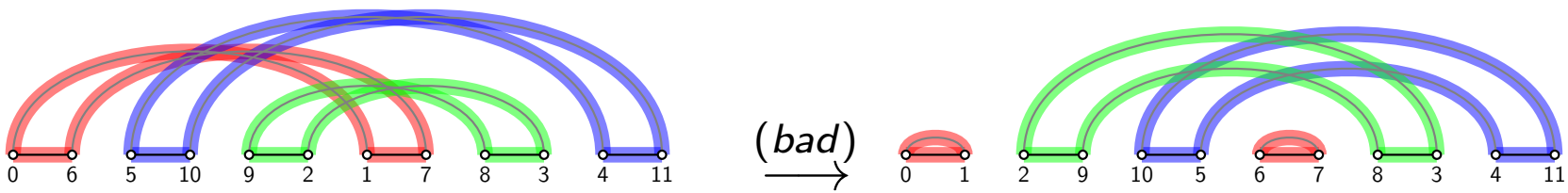

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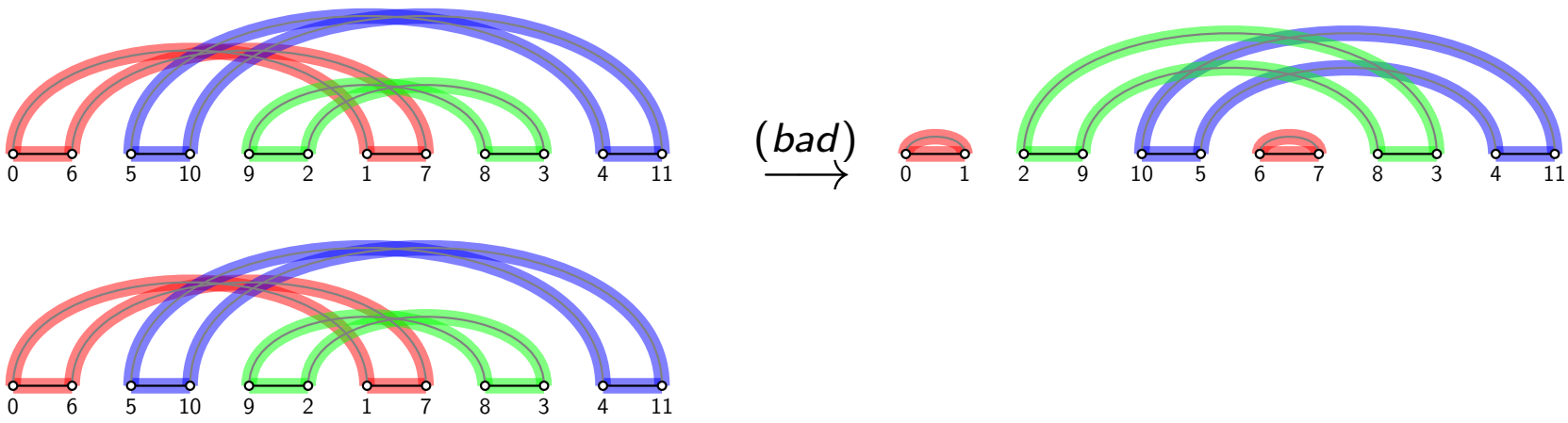

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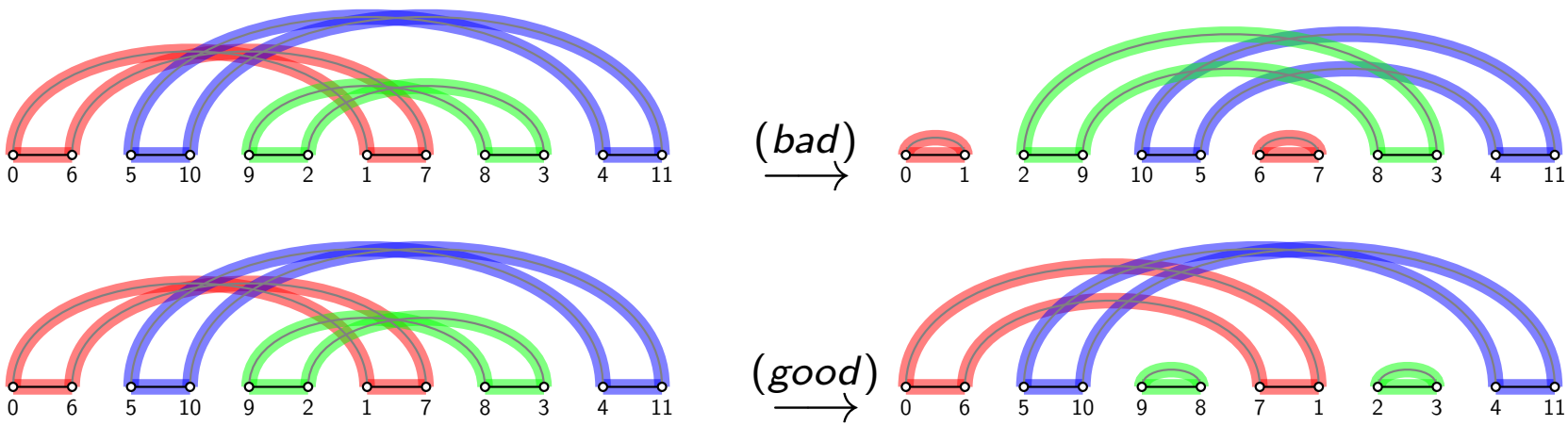
- Even when we don't have bad cycles, the order in which we do things matters!

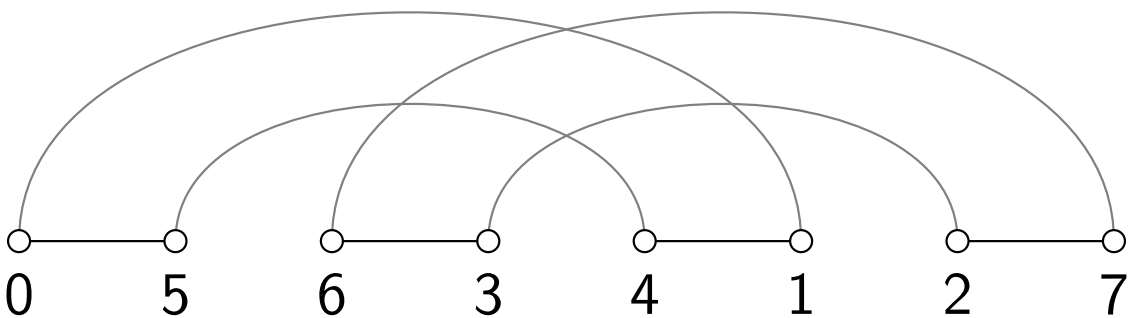
Example (careless and careful cycle splitting)



Handling bad cycles

- "Bad" cycles are not so bad if we can make them "good" (see previous example);
- But sometimes we can't:

Example (a minimal permutation with only bad cycles)



Components

- Although reversals only modify the "contents" of a single cycle, they may also modify the configuration of some other cycles;
- This suggests that cycles are not the right "unit" to deal with;
- We need to consider collections of cycles, or **components** instead;

Interleaving cycles

- Grey edge $\{\pi'_i, \pi'_j\}$ **spans** the interval $[i, j]$ in π';
- Two grey edges **interleave** if their spans intersect properly;
- Two cycles **interleave** if they contain interleaving edges;
- The **interleaving graph** I_π is defined by:
  - $V(I_\pi) =$ cycles of $BG(\pi)$;
  - $E(I_\pi) =$ pairs of interleaving cycles in $BG(\pi)$;
- A **component** of the breakpoint graph is a connected component of the interleaving graph;

The interleaving graph I_π

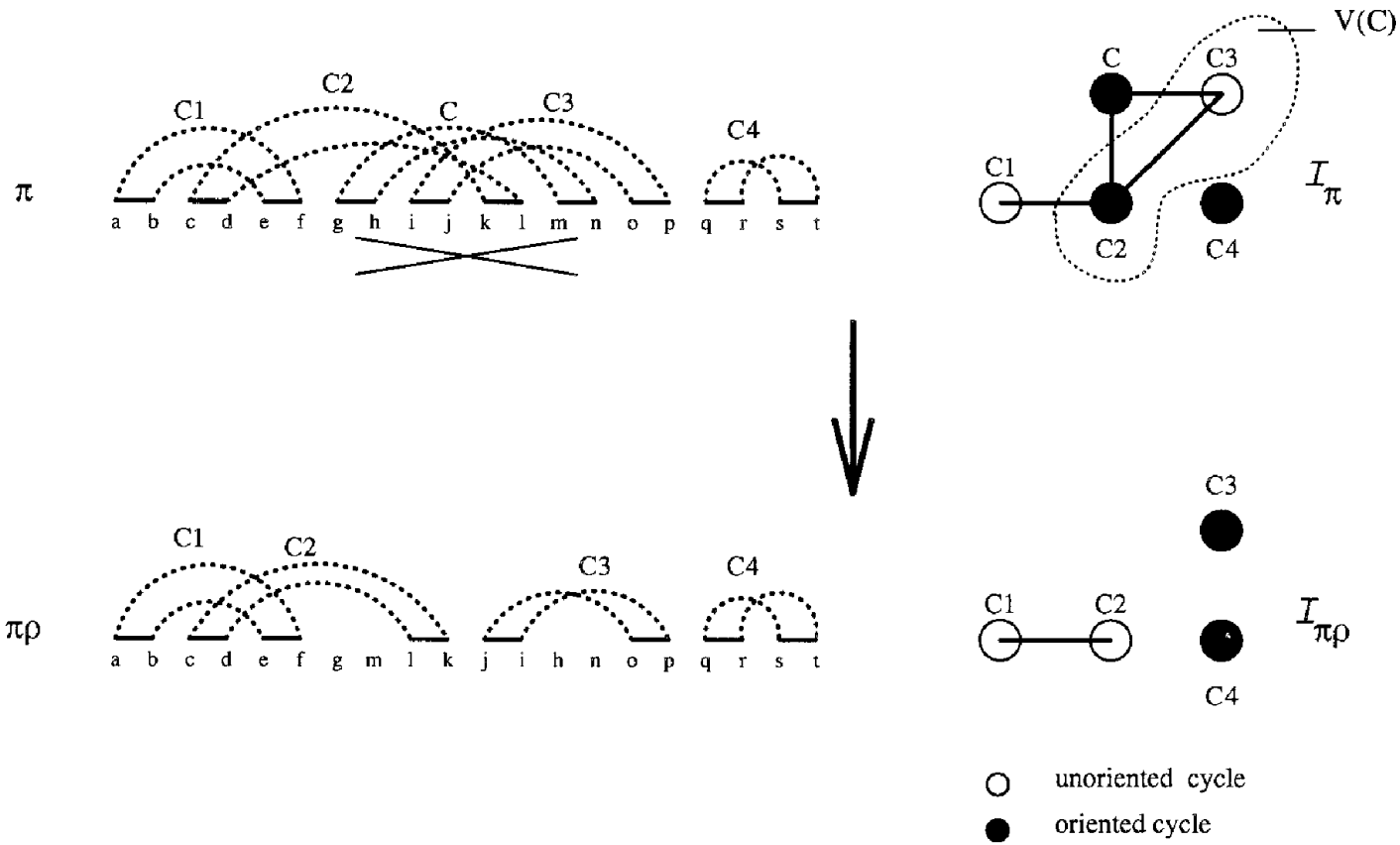


FIG. 8. Reversal on a cycle C (i) deletes vertex C from the interleaving graph; (ii) changes the orientation of vertices in $V(C)$; (iii) complements the subgraph induced by $V(C)$.

(source: [Hannenhalli and Pevzner, 1999])

Good and bad components

- A component is **bad** if it contains only bad cycles, and **good** otherwise;
- Although we must be careful (as seen before), good components are not a problem:
  - they contain good cycles, which can be split;
  - applying a signed reversal on a 2-cycle C reverses the orientation of the cycles interleaving with C (and also changes their interleaving relationships);
  - so we just need to make sure at each step that we can keep splitting cycles afterwards;

Hurdles

- "Bad" (unoriented) components are called **hurdles** and are a problem;
- There are two ways of getting rid of them:
  1. "cutting" them;
  2. "merging" them;
- Either way, one move must be wasted for each hurdle to turn them into "good" components;
- Therefore, for all π in $S_n^{\pm}$:

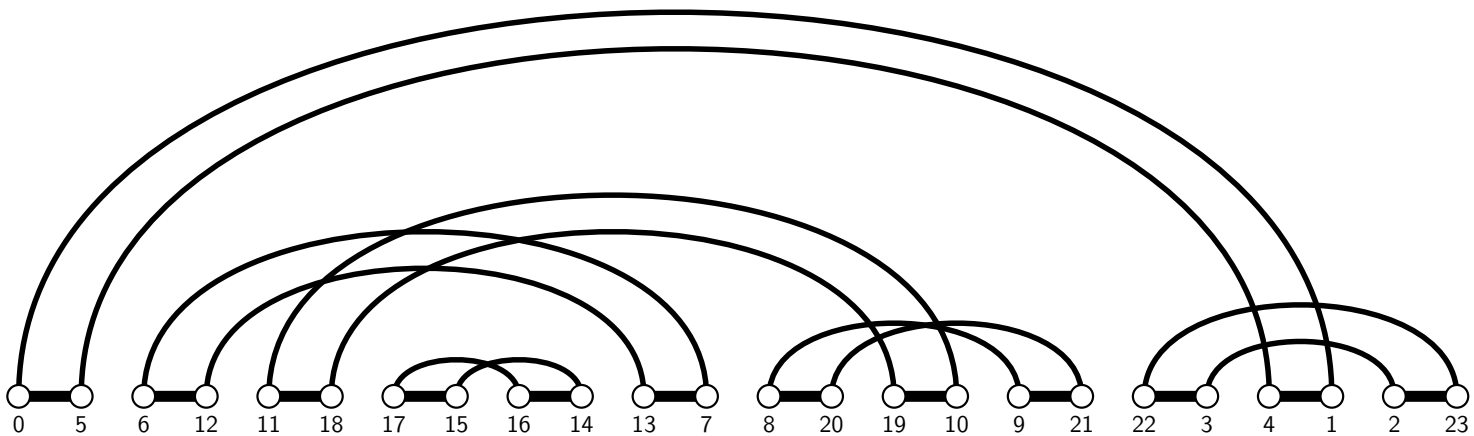
$$srd(\pi) \geq n + 1 - c(BG(\pi)) + h(\pi).$$

Practice

9. In the breakpoint graph of

$$\langle 3, -6, -9, 8, -7, 4, -10, -5, 11, 2, 1 \rangle :$$

- Identify good and bad cycles, components and hurdles
- Give a lower-bound for its signed reversal distance and an optimal sorting scenario



An actual formula

- All this (and many concealed details) leads to a formula for the signed reversal distance:

Theorem ([Hannenhalli and Pevzner, 1999])

For all π in $S_n^{\pm}$:

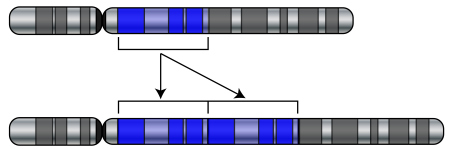
$$srd(\pi) = n + 1 - c(BG(\pi)) + \underbrace{h(\pi)}_{\text{number of hurdles}} + \underbrace{f(\pi)}_{\text{special ``fortress'' case}} .$$

Motivation

- We saw a model for representing genomes without directionality;
- We saw another model for taking directionality into account;
- Both of them lack realism in a crucial way: they don't allow duplications;
- And duplications / insertions / deletions account for a very large part of what happens in evolution [Ohno, 1970];

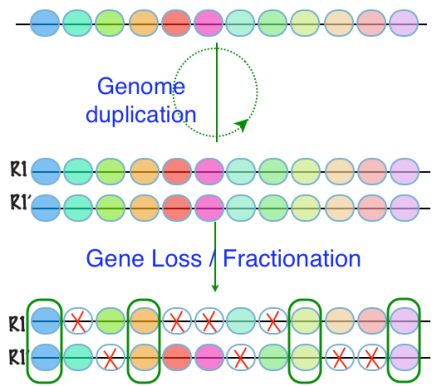
Two examples of duplications

Example (tandem duplications)



(source: K. Aainsqatsi on Wikimedia)

Example (whole genome duplication)



(source: Eric Lyons on CoGePedia)

Strings

- Since duplications pervade genomes, we should take them into account;
- We now see genomes as **strings** on an alphabet Σ;
- Be careful: similar segments have been identified, so $\Sigma = \{\text{segments}\}$ and not $\{A, C, G, T\}$;
- Our goal is still to explain evolution using most parsimonious scenarios made of fixed transformations;

Strings

- Note: the restriction to sorting problems does not work anymore;
  - if you have two A's, which one should be "number one"?
- So we really are interested in transforming one string into another, which is **not** equivalent to sorting another string;
- Sorting problems have been considered in that model, but they're just a special case of a more general problem;

Strings

- We can distinguish between several approaches based on gene contents;
- Either we have exactly the same contents in both genomes (and duplications are of course allowed);
- Or we have duplications but with different amounts of repetitions (e.g. three 1's in genome A but only two in genome B);
- This time the breakpoint graph cannot save us anymore, since we would not know how to connect elements or decompose the graph;

Balanced strings

- The number of occurrences of a character c in a string S is denoted by $occ(c, S)$;

Definition (balanced strings)

Two strings S and T on an alphabet Σ are **balanced** if:

$$\forall\ c \in \Sigma : occ(c, S) = occ(c, T).$$

- Basically, S and T are anagrams;
- Straightforward generalisation of permutations: we have duplications, but we actually still have the same content in both genomes;

Comparing balanced strings

- One way of relating genomes' contents is to identify common segments;
- In other words, we want to partition genomes into the same set of segments;
  - this is how we obtained (signed) permutations;
  - but now we want to partition the resulting sequences;

Generalising breakpoints

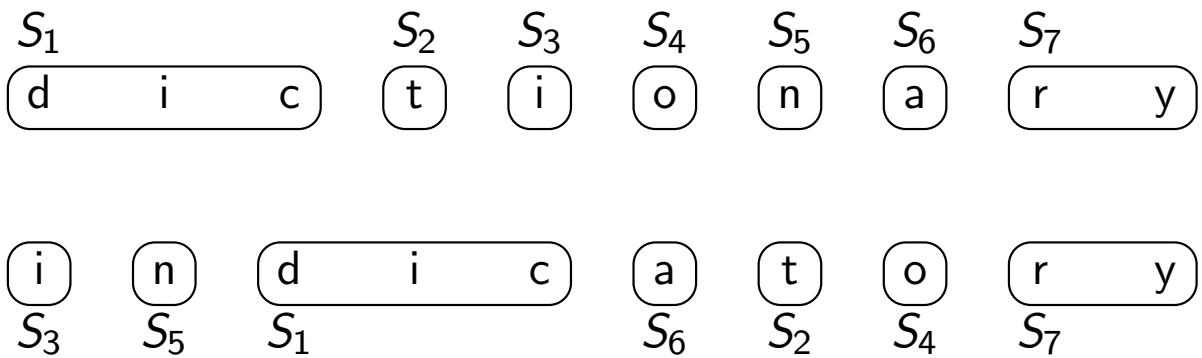
- Recall that, for permutations:
  - **adjacencies** are pairs of adjacent elements in π that are also adjacent in $\iota = \langle 1\ 2\ \cdots\ n \rangle$ (or $\chi = \langle n\ n-1\ \cdots\ 1 \rangle$ for reversals);
  - **breakpoints** are pairs that are not adjacencies;
- Recall that, for signed permutations:
  - **adjacencies** are pairs of adjacent elements in π that are also adjacent in $\iota = \langle 1\ 2\ \cdots\ n \rangle$ (or $\chi = \langle -n\ -(n-1)\ \cdots\ -1 \rangle$ for signed reversals);
  - **breakpoints** are pairs that are not adjacencies;
- Those can be generalised to any pair of permutations;
- And we can do the same thing for strings;

Minimum common string partition

- A **partition** of a string S is a set of strings that can be concatenated to obtain S;
- A **common partition** of two strings S and T is a set of strings that can be concatenated to obtain both S and T;

Example (common string partitions)

Here's a common partition of "dictionary" and "indicatory":



Minimum common string partition

- A common string partition is **minimum** if there is no smaller common string partition for the two strings under consideration;
- This leads to the following decision problem:

Problem (MINIMUM COMMON STRING PARTITION (MCSP))

Instance: *balanced strings S and T, a bound $k \in \mathbb{N}$;*
Question: *is there a common partition of S and T with at most k blocks?*

Relation(s) to rearrangement problems

- Recall that breakpoints were pairs of elements adjacent in one genome but not in the other;
- Common string partitions generalise that point of view to an arbitrary number of elements in each part;
- So if we have a minimum common string partition for S and T, we get the number of breakpoints between strings S and T;

About MCSP

- Bad news about MCSP:
  - NP-hard, even if only one gene family is nontrivial [Blin et al., 2004];
  - APX-hard, even if no character appears more than twice [Goldstein et al., 2005];
- Good news about MCSP:
  - fixed parameter tractable: a solution of size k can be found in time $f(k) \cdot \text{poly}(n)$ ($n = |S| = |T|$) [Bulteau and Komusiewicz, 2014];
- Greedy approach [Goldstein and Lewenstein, 2011]: repeatedly select an LCS without any marked letter;
  - ✓ simple and fast (runs in $O(n)$ time);
  - × approximation ratio between $\Omega(n^{0.43})$ and $O(n^{0.69})$ [Kaplan and Shafrir, 2006];

Practice

10. Give pairwise MCSP distances between the following strings (ignore capitals and whitespaces)
    - `Arrange A String`
    - `A Staring Ranger`
    - `A Garnering Tsar`
11. Find a pair of strings for which Greedy behaves as badly as possible (i.e. maximizing the approximation ratio)

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Algorithms and Bioinformatics

Part II — Comparative Genomics

II.2 — Focus on MCSP and FPT

Laurent Bulteau

Presented at WABI 2013

Workshop on Algorithms in Bioinformatics

Fixed-Parameter Algorithm for Minimum Common String Partition with Few Duplications

Laurent Bulteau, Christian Komusiewicz,
Guillaume Fertin, Irena Rusu

WABI 2013
Full version available at arxiv.org/abs/1307.7842

Outline

1 MCSP Problem

2 $O(d^{2k}n)$ FPT algorithm

3 Implementation

4 Conclusion

MCSP Problem

Minimum Common String Partition

Input: two strings of length n
Output: min. set of blocks partitioning both sequences

d e e a b c d a b c d d e b d e a b

e a b a b c d d e e a b c d d e b d

Minimum Common String Partition

Input: two strings of length n

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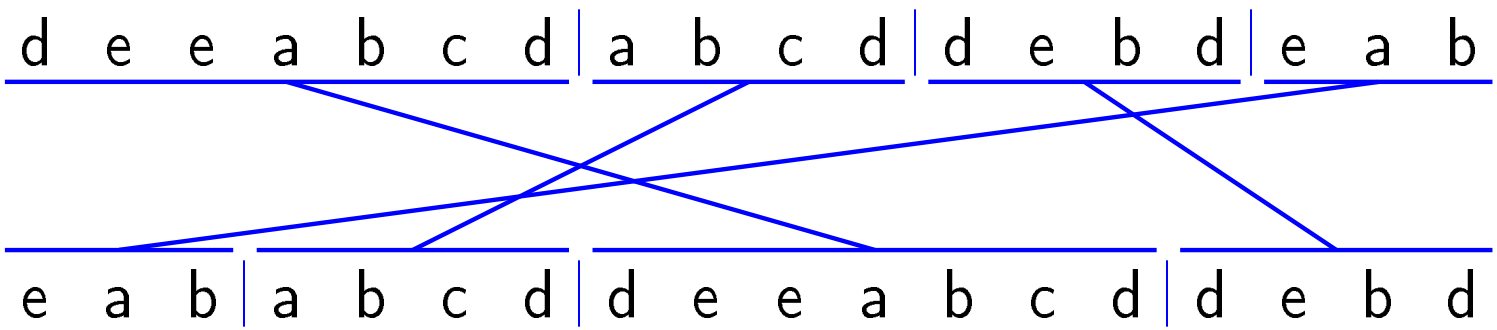


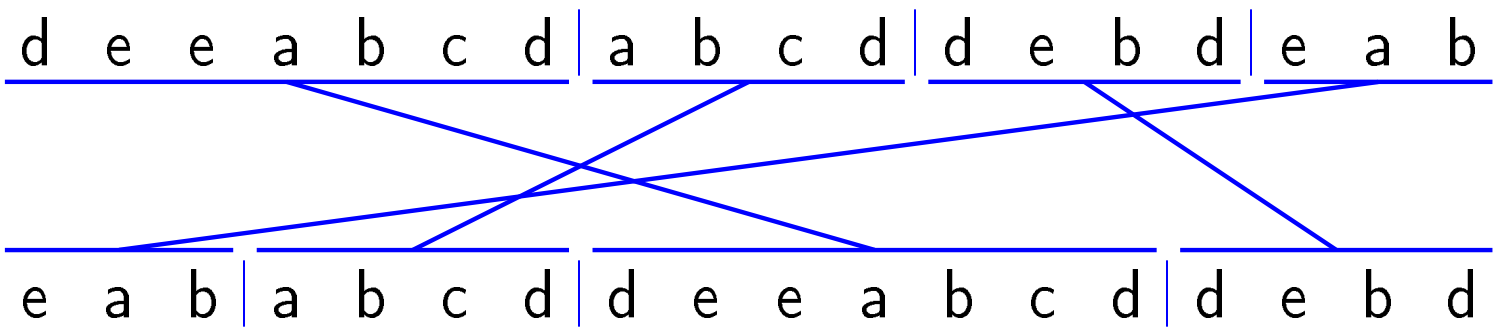
Minimum Common String Partition

Input: two strings of length n

Output: min. set of blocks partitioning both sequences

Parameters:

- d = max. number of occurences of each letter
- k = number of blocks in an optimal solution



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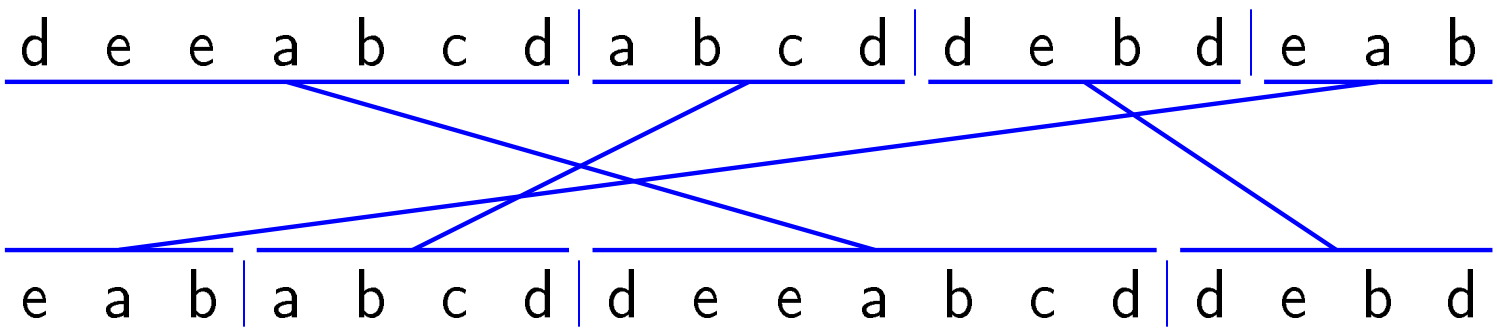

$n = 18$ elements, $d = 5$, $k = 4$

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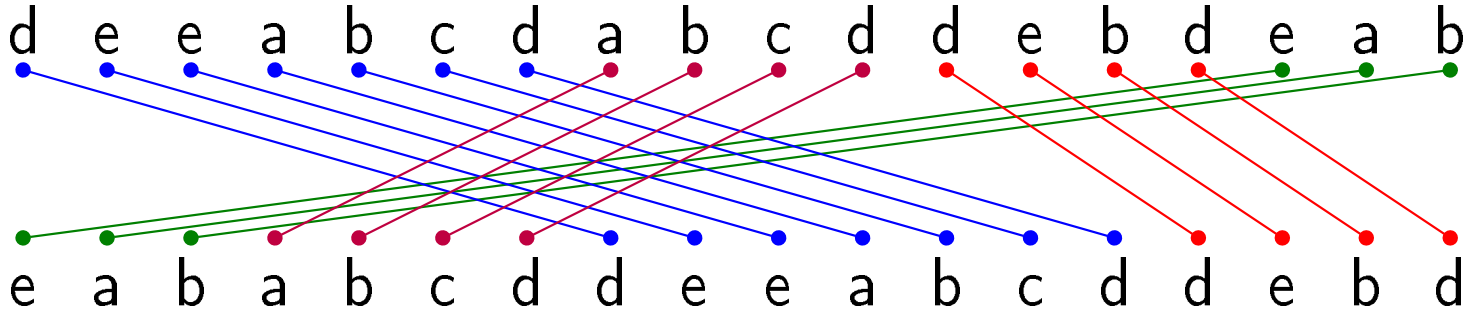

Can be seen as a matching problem

Minimum Common String Partition

Input: two strings of length n
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Parameters:

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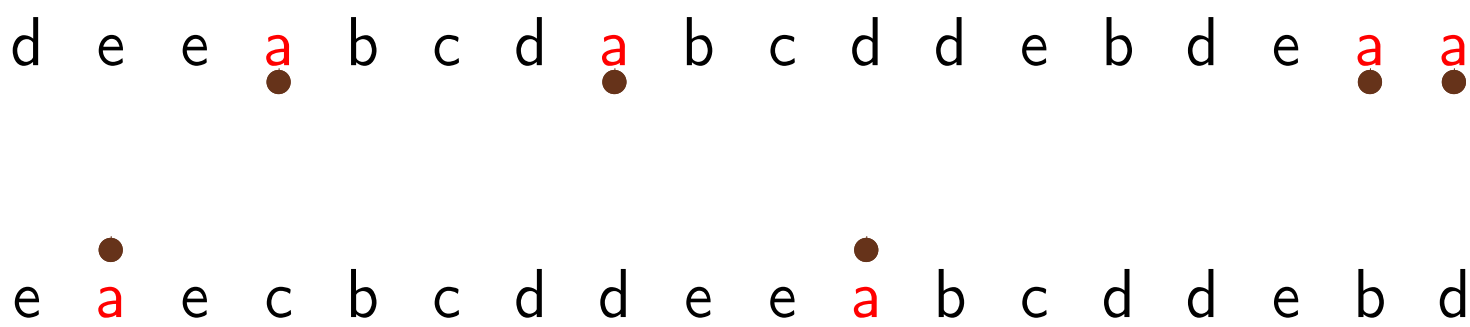

Unbalanced strings: allow deletion of abundant elements between blocks (all rare elements are kept)

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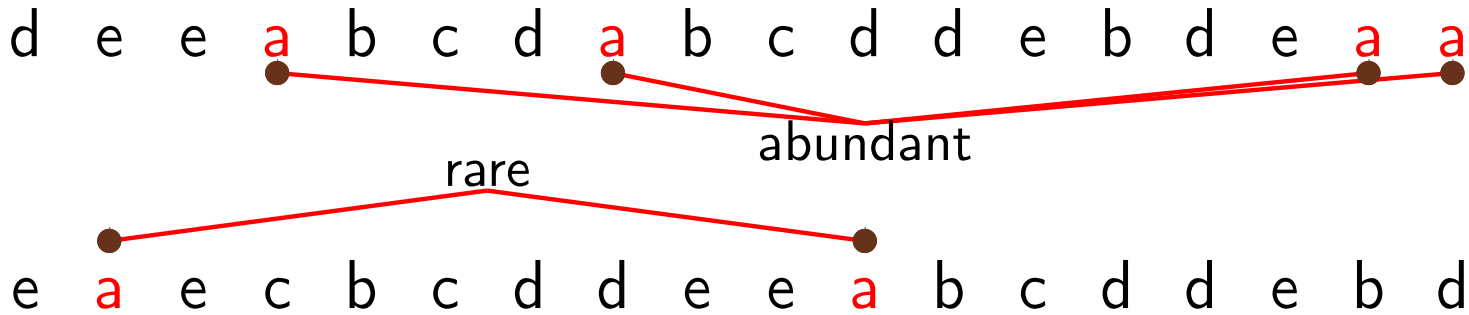

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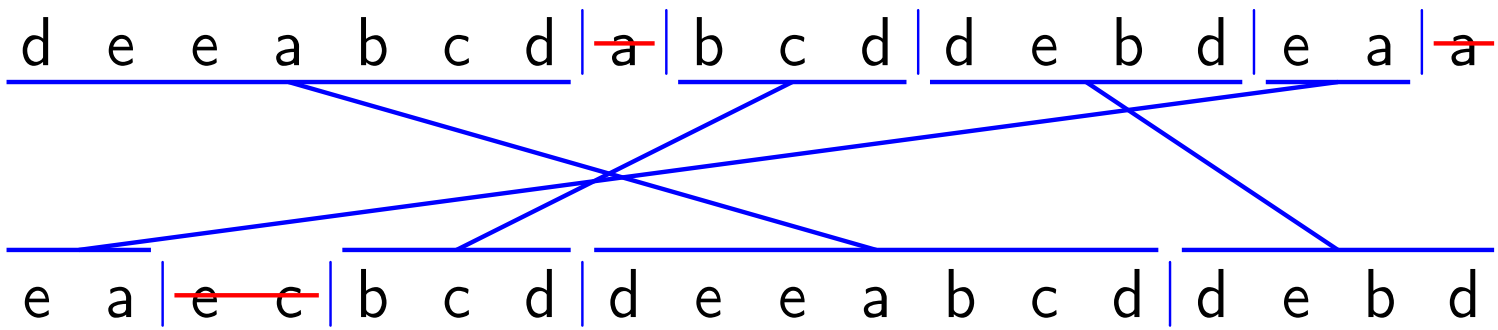

Minimum Common String Partition

- NP-hard
- FPT algorithms $d!^k \text{poly}(n)$
  k = number of blocks; d = number of duplications
- FPT algorithm with parameter k only $k^{21k^2}\text{poly}(n)$
- Improved FPT algorithm with k and d $d^{2k}\text{poly}(n)$
  + Allows for unbalanced strings
  + Implemented

Assignment of orthologous genes via genome rearrangement

X. Chen, J. Zheng, Z. Fu, P. Nan, Y. Zhong, S. Lonardi and T. Jiang 2005

Minimum Common String Partition

- **NP**-hard
- FPT algorithms $d!^k \text{poly}(n)$
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  + Implemented

Minimum common string partition problem: Hardness and approximations

A. Goldstein, P. Kolman and J. Zheng 2005

Minimum Common String Partition

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Minimum common string partition parameterized	
P. Damaschke	2008

Minimum common string partition revisited	
H. Jiang, B. Zhu, D. Zhu and H. Zhu	2012

Minimum Common String Partition

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Minimum Common String Partition Parameterized by Partition Size is Fixed-Parameter Tractable

L. Bulteau, C. Komusiewicz — Arxiv 2013

Minimum Common String Partition

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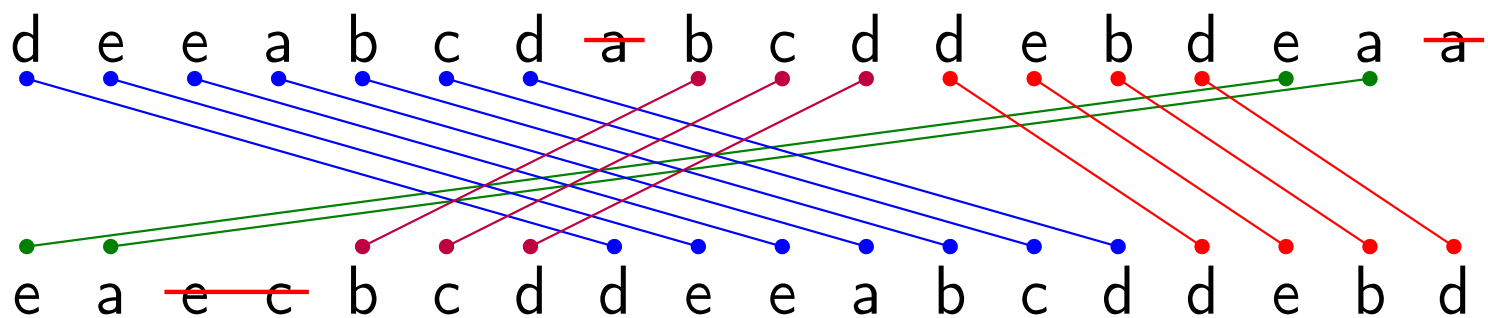
This talk

$O(d^{2k}n)$ FPT algorithm

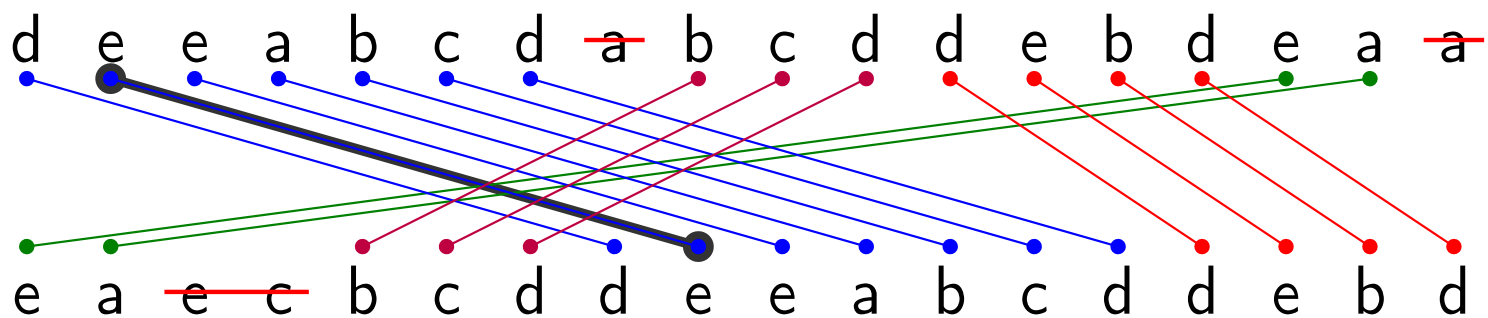
Seeds

- Optimal solution OPT, seen as a matching



Seeds

- Optimal solution OPT, seen as a matching
- One block $\leftrightarrow$ one seed



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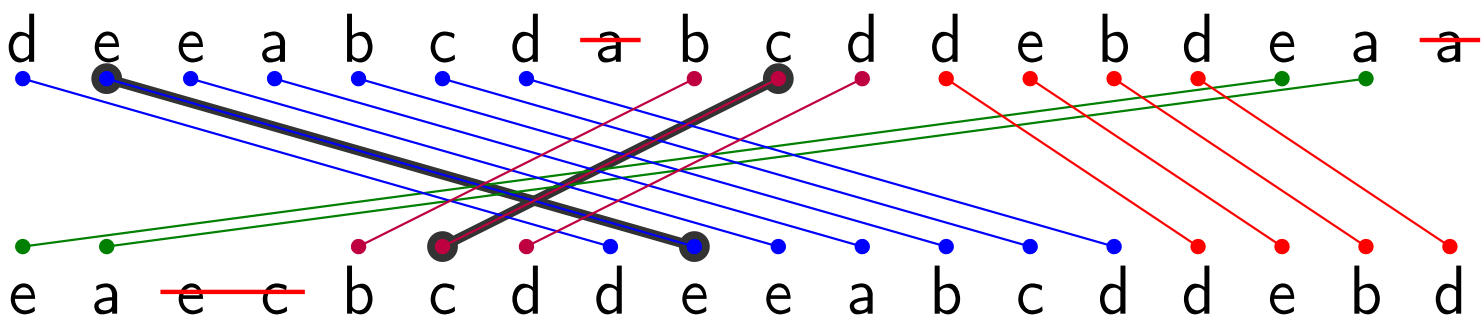

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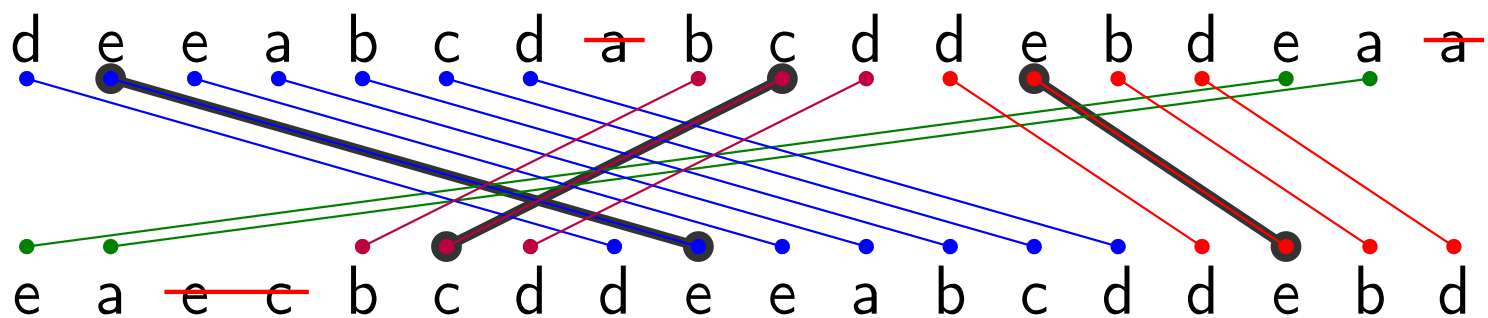

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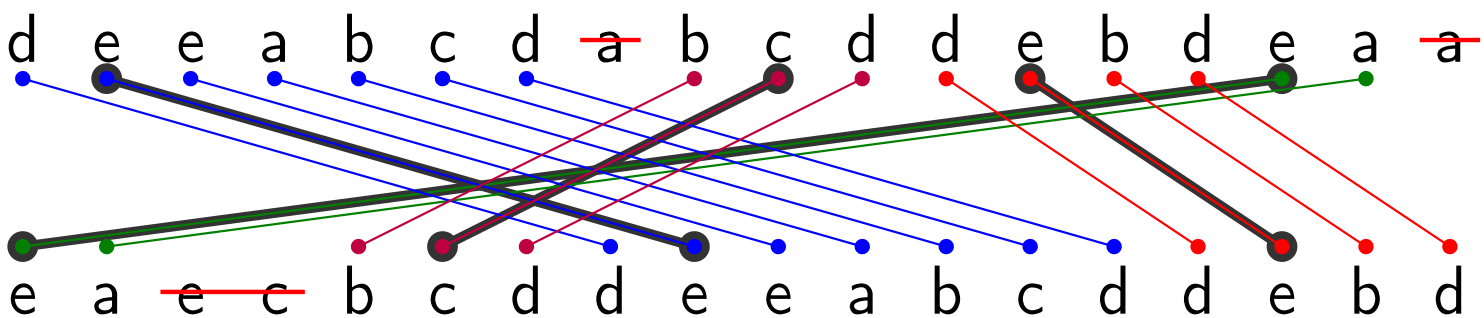
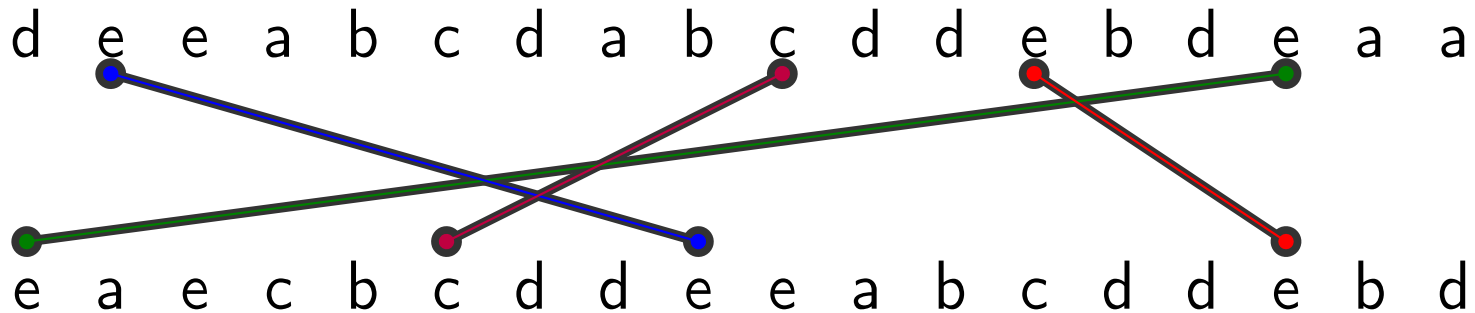


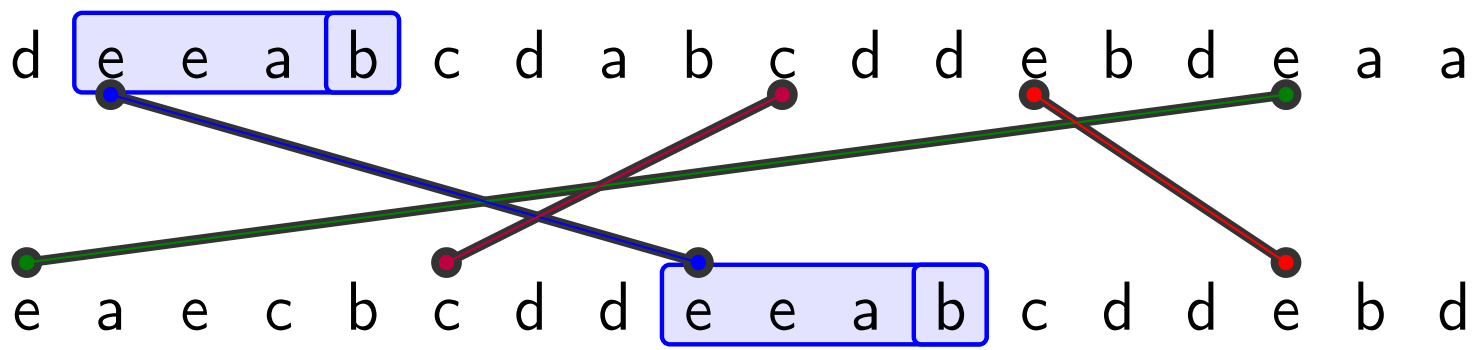
Seeds

- Optimal solution OPT, seen as a matching
- One block $\leftrightarrow$ one seed
- Goal: find a good set of seeds



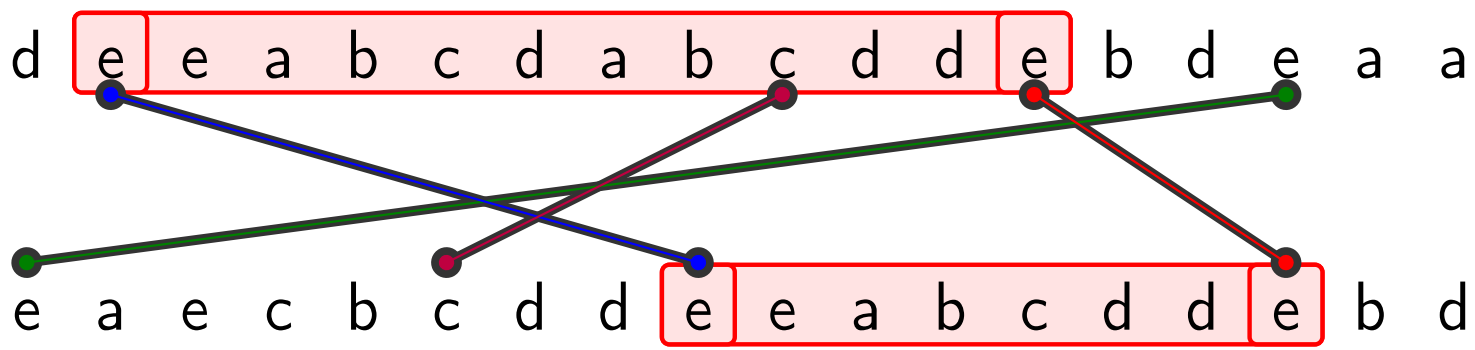
Seeds

- Optimal solution OPT, seen as a matching
- One block $\leftrightarrow$ one seed
- Goal: find a good set of seeds
  - Every rare element must be in the same block as a seed: the set is complete



Seeds

- Optimal solution OPT, seen as a matching
- One block $\leftrightarrow$ one seed
- Goal: find a good set of seeds
  - Every rare element must be in the same block as a seed:
    the set is complete
  - Two seeds cannot be in the same block:
    the set is non-redundant



Algorithm Outline

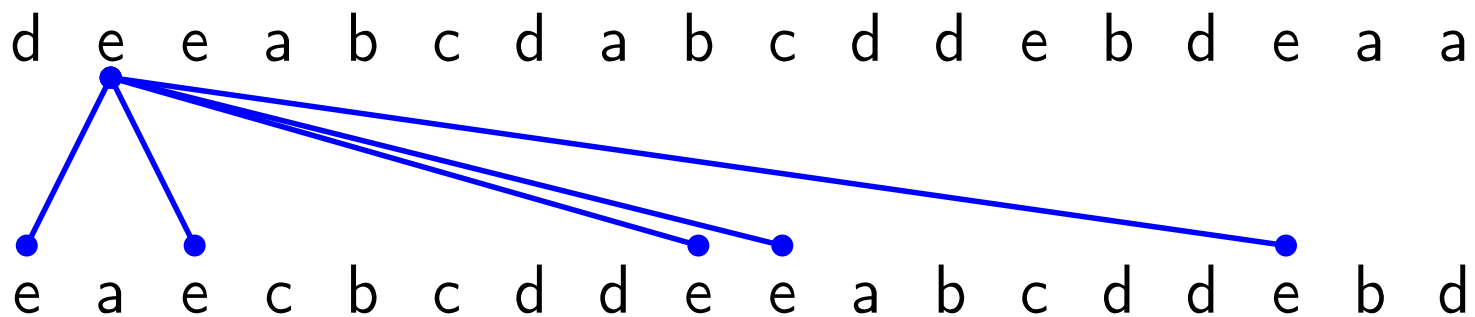
- Start with set of seeds $T = \emptyset$

d e e a b c d a b c d d e b d e a a

e a e c b c d d e e a b c d d e b d

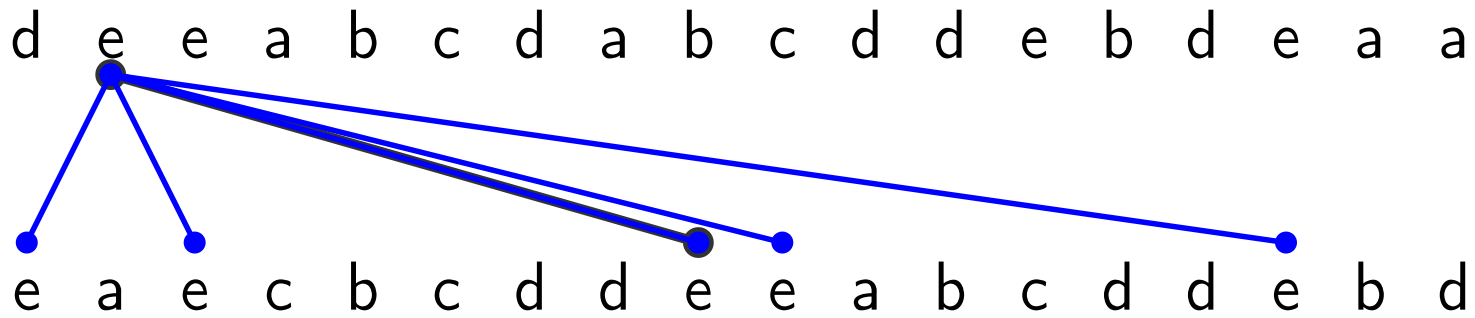
Algorithm Outline

- Start with set of seeds $T = \emptyset$
- Identify set of pairs containing 1 correct seed



Algorithm Outline

- Start with set of seeds $T = \emptyset$
- Identify set of pairs containing 1 correct seed
- Try each candidate in the set as a new seed, start again



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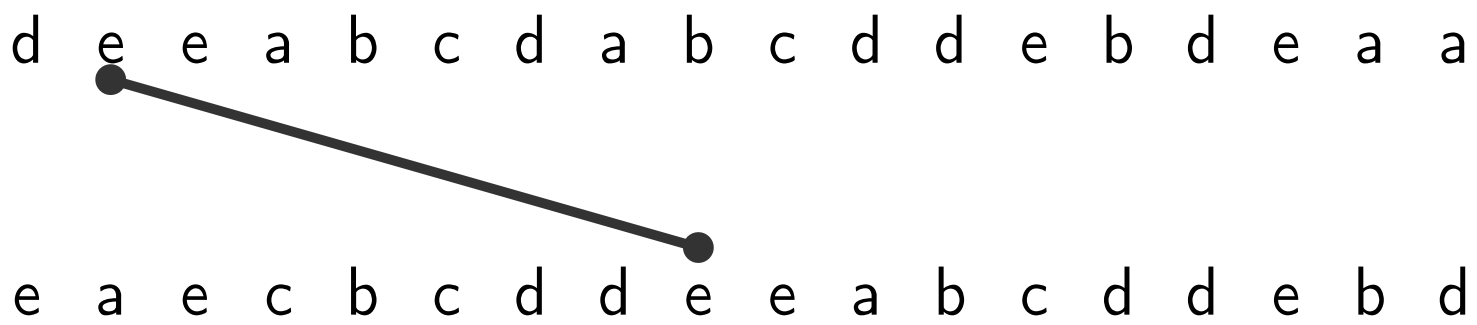

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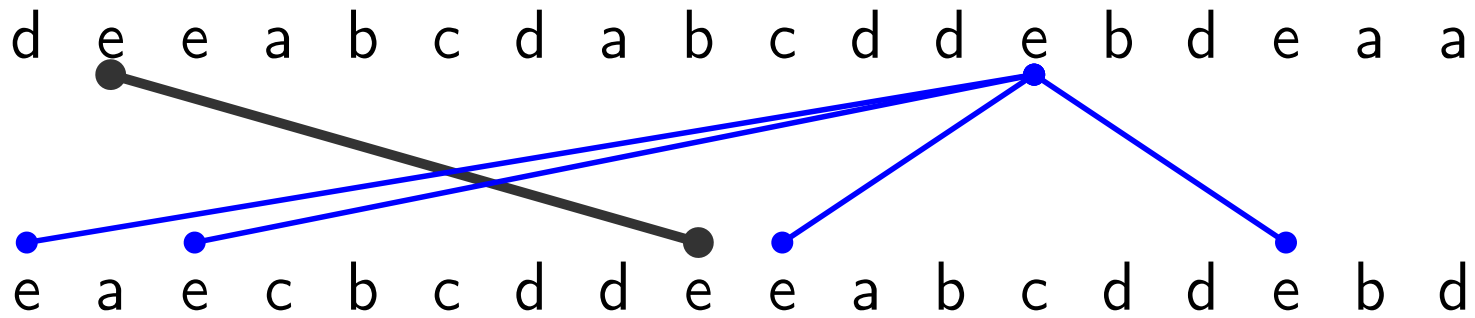

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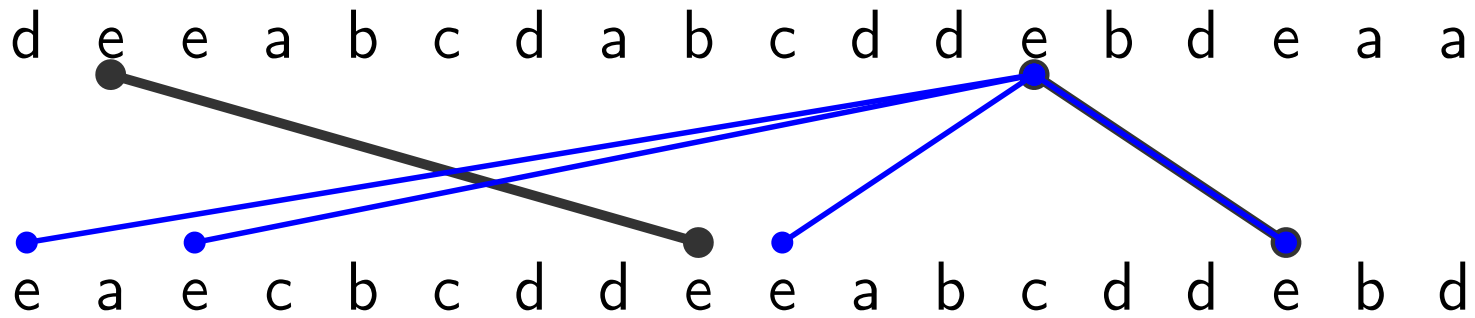

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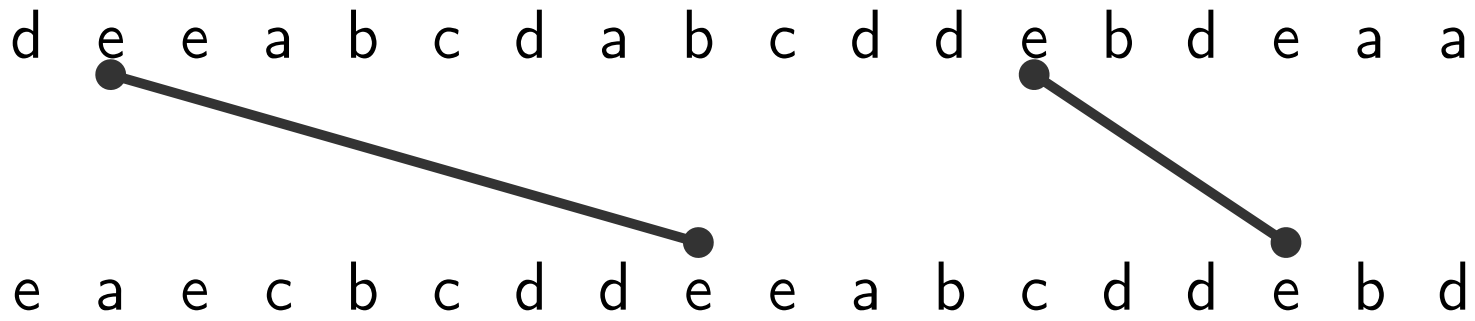

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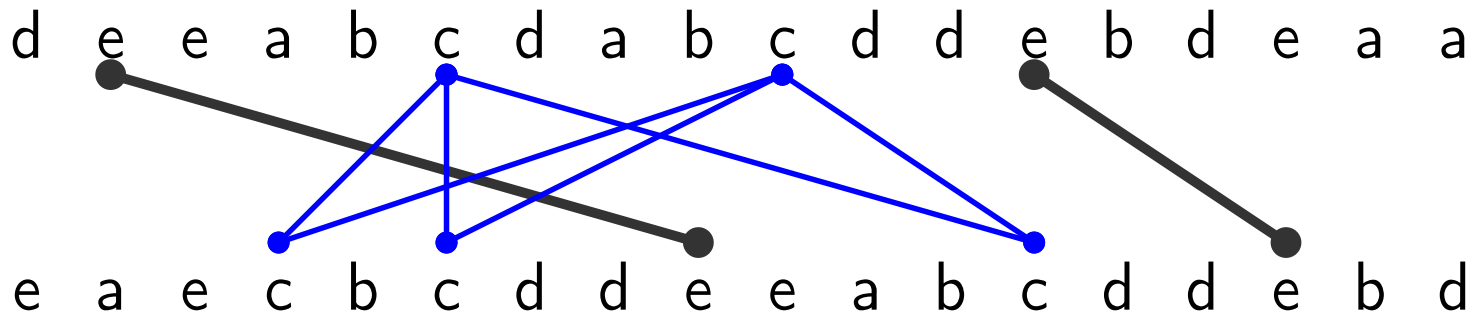

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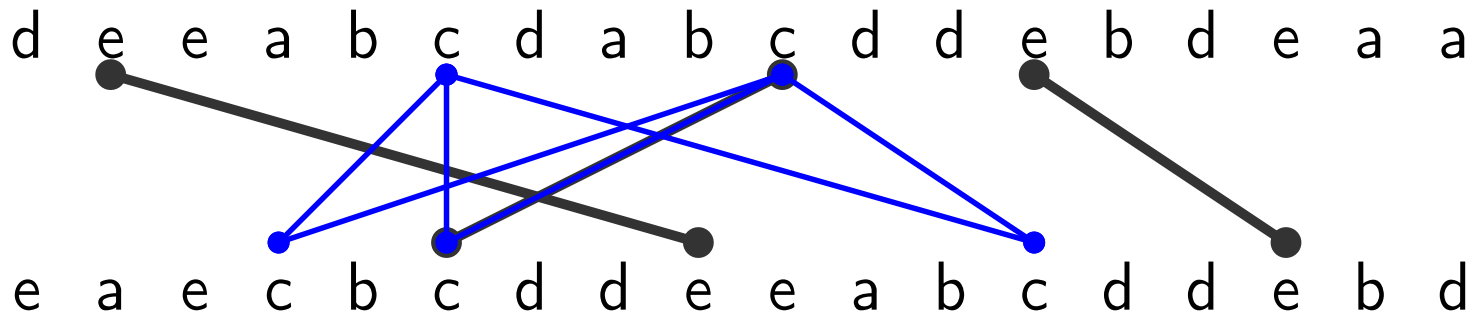

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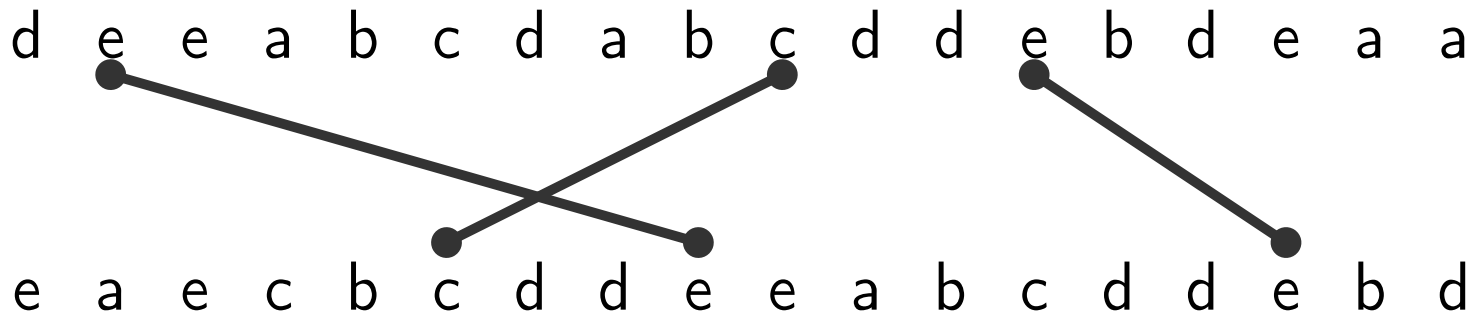

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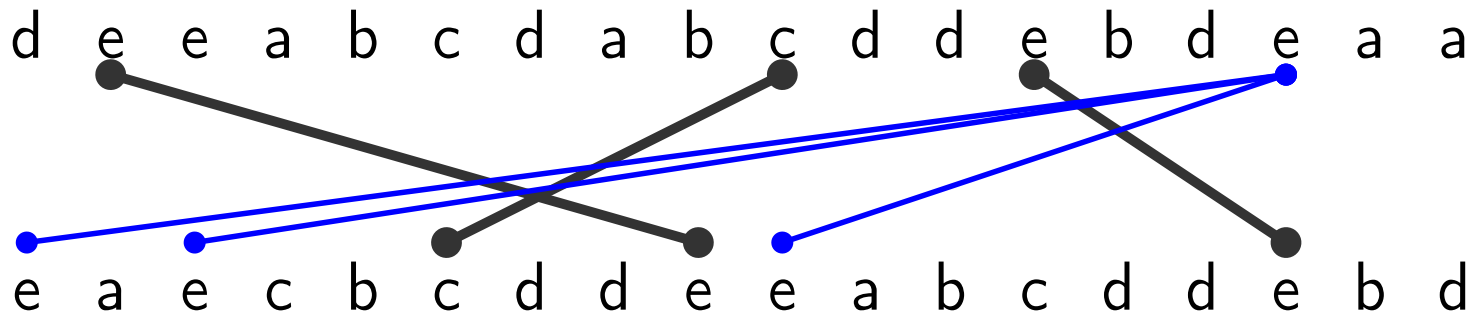

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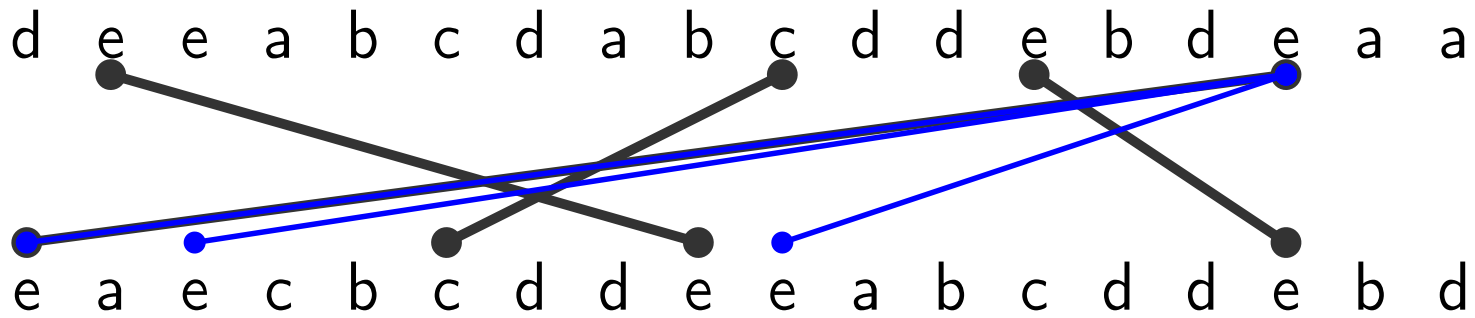

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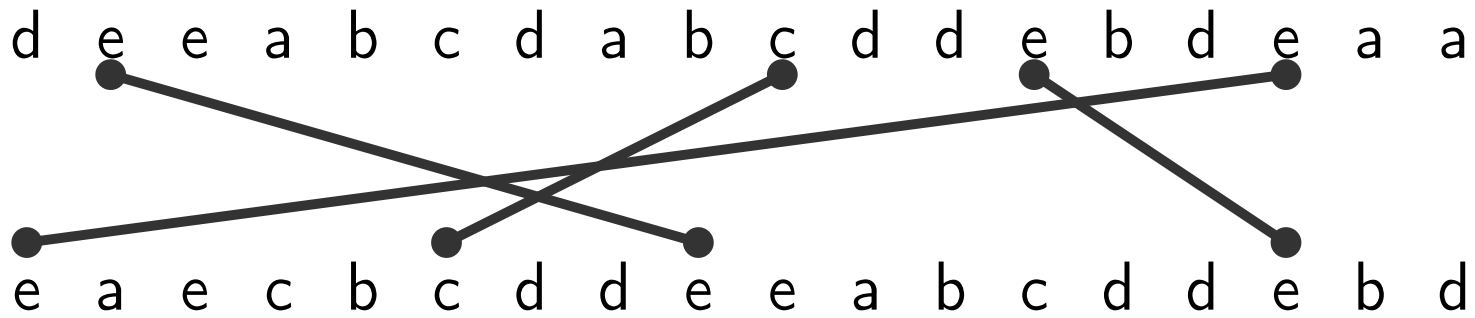

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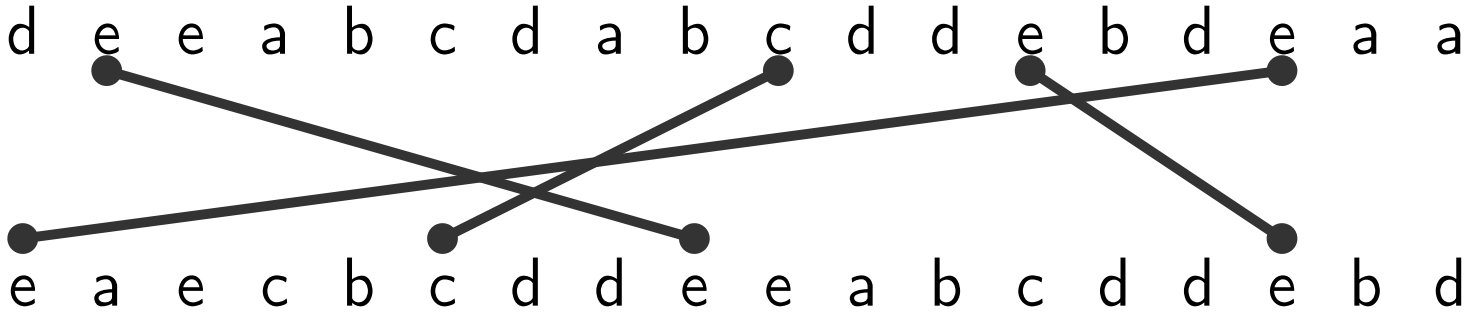

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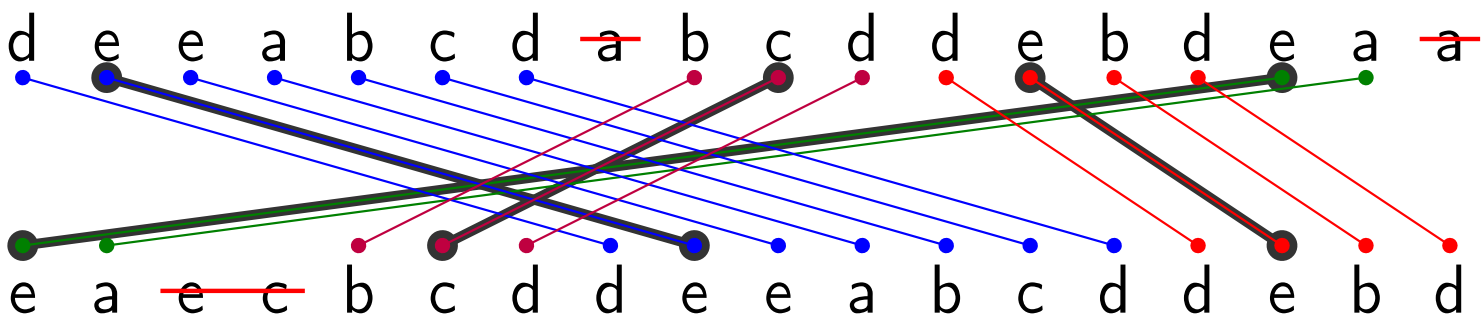

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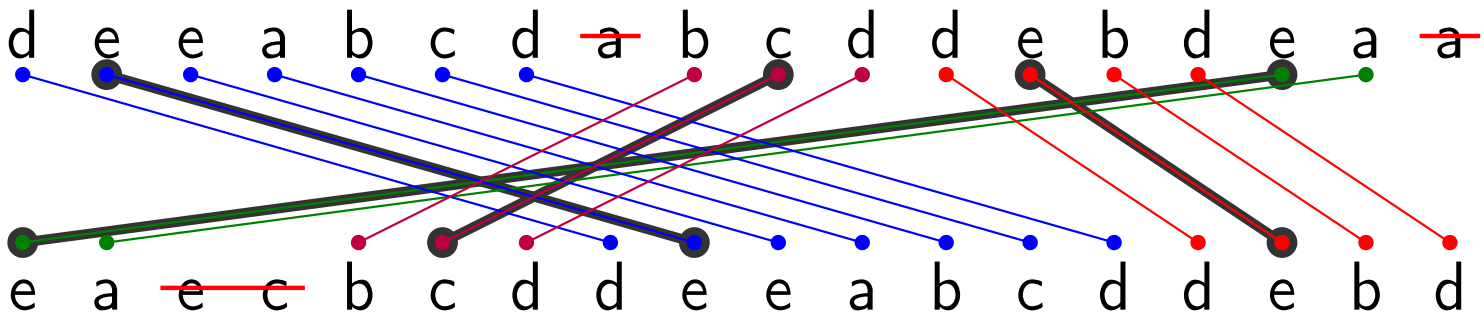
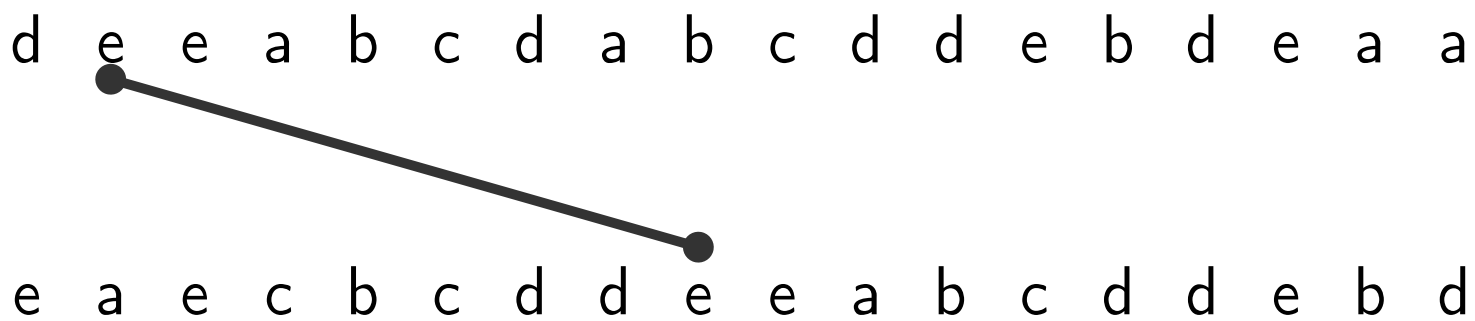


Finding new seeds (1)

Non-redundancy

In OPT, every (x, y) which is not in the same block as an already present seed can be a new seed...

- Every x which cannot be in the same block as any seed can be part of a new seed.



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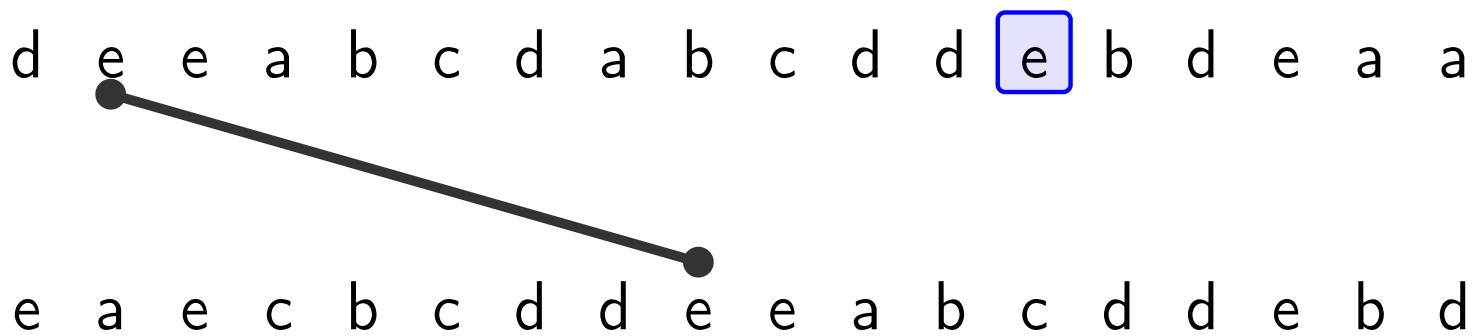

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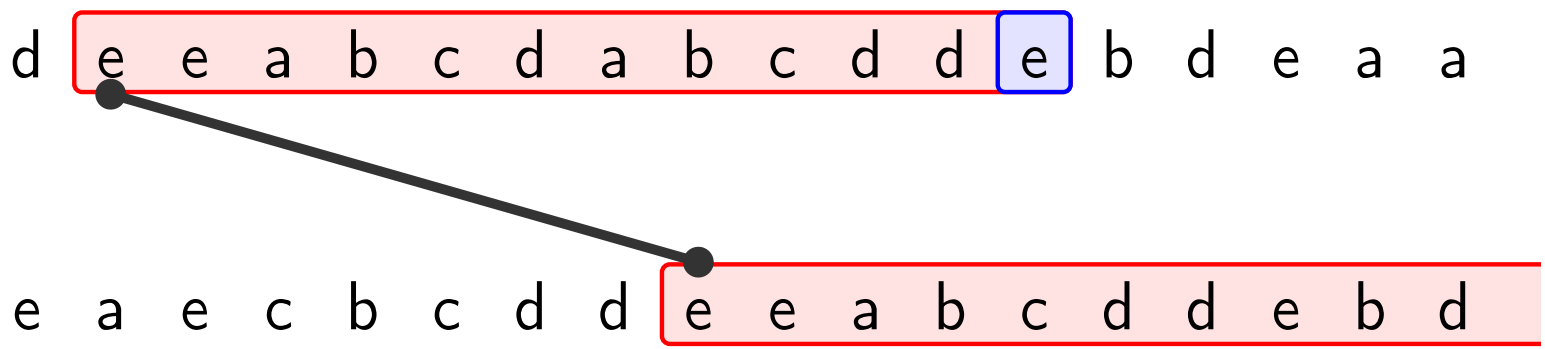

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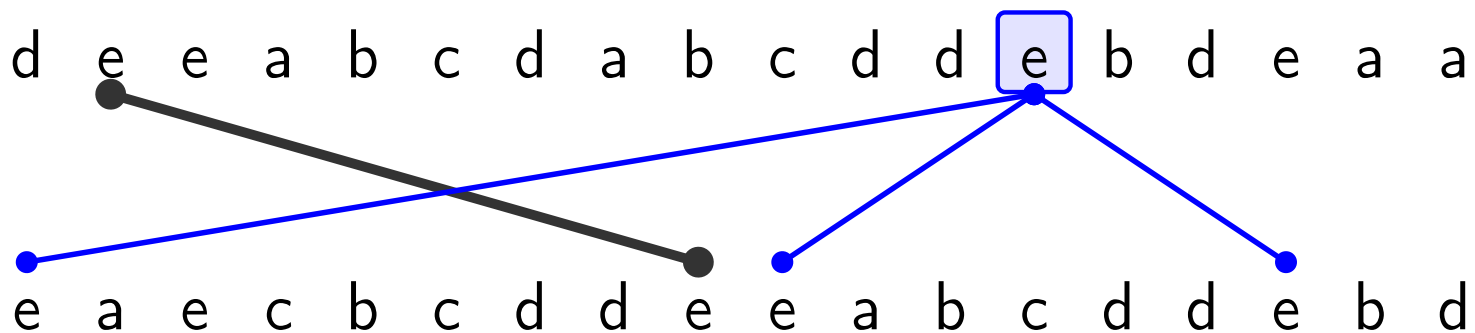
- y is one of the d copies of x in the other sequence: each such pair is a candidate



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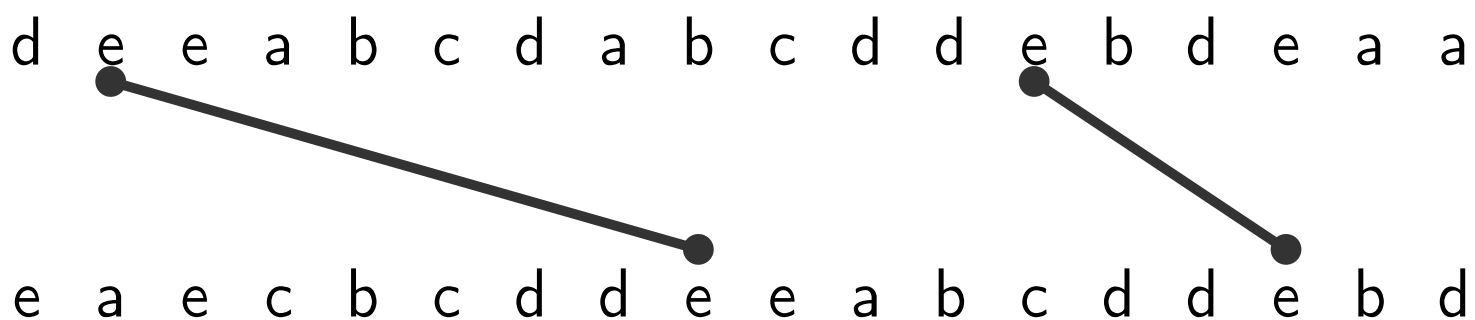
Association graph

Link together pairs (x, y) that can be in the same block as a seed



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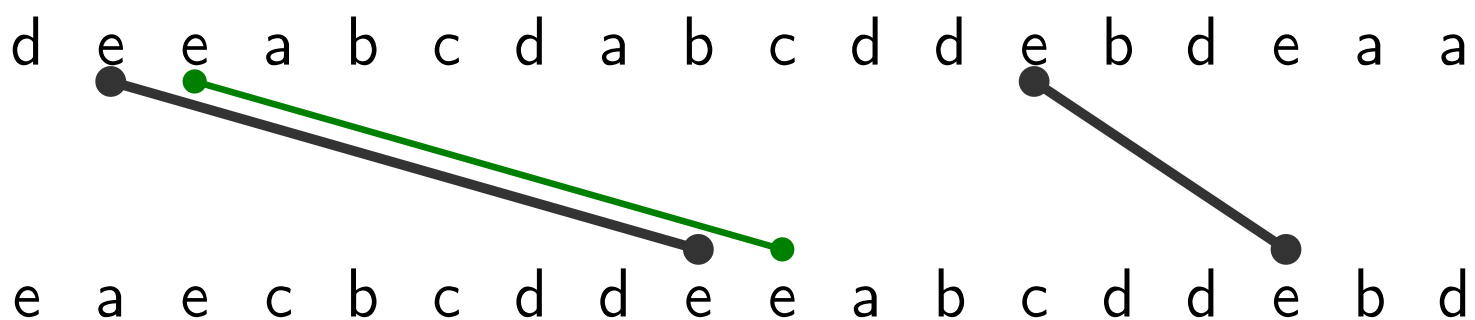

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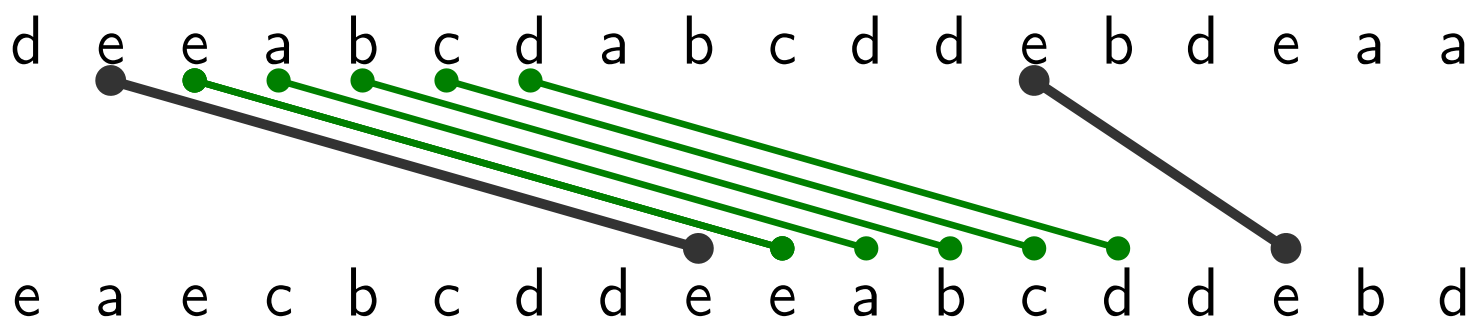

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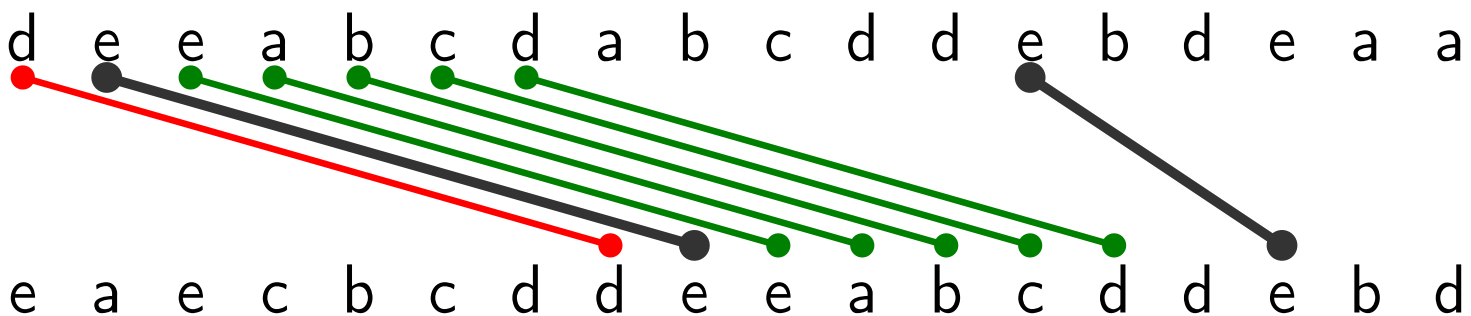

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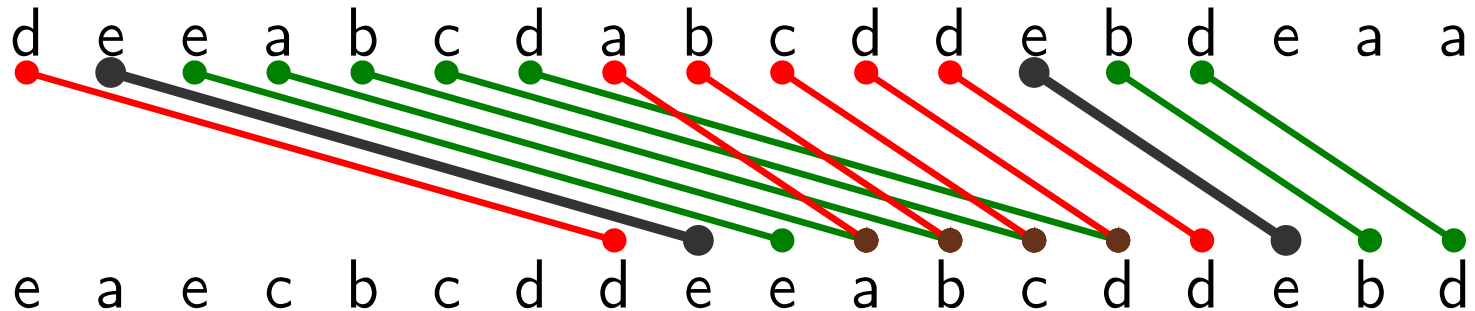

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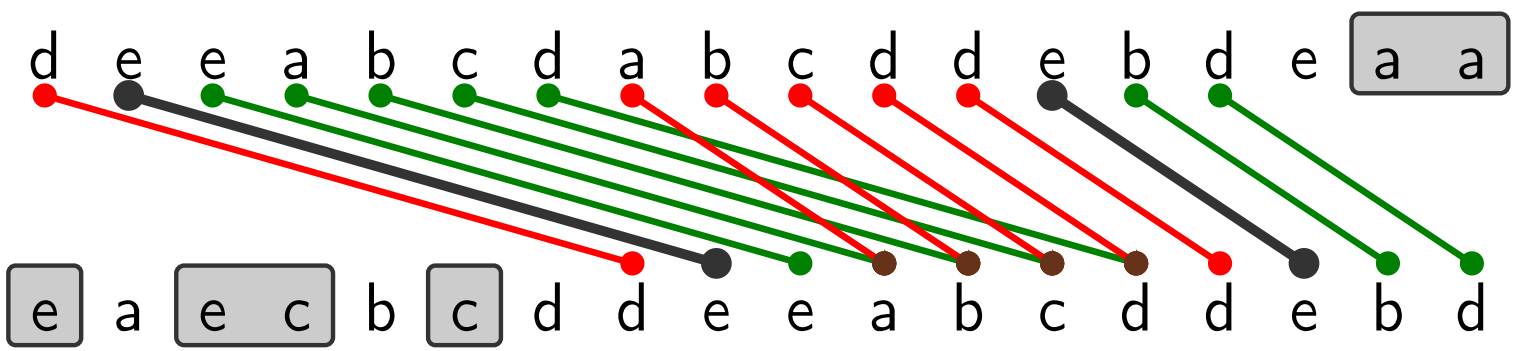

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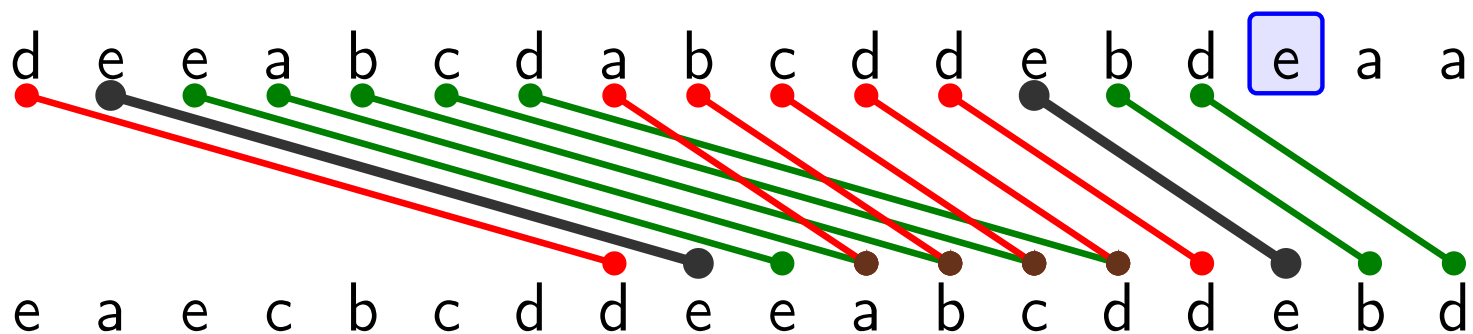

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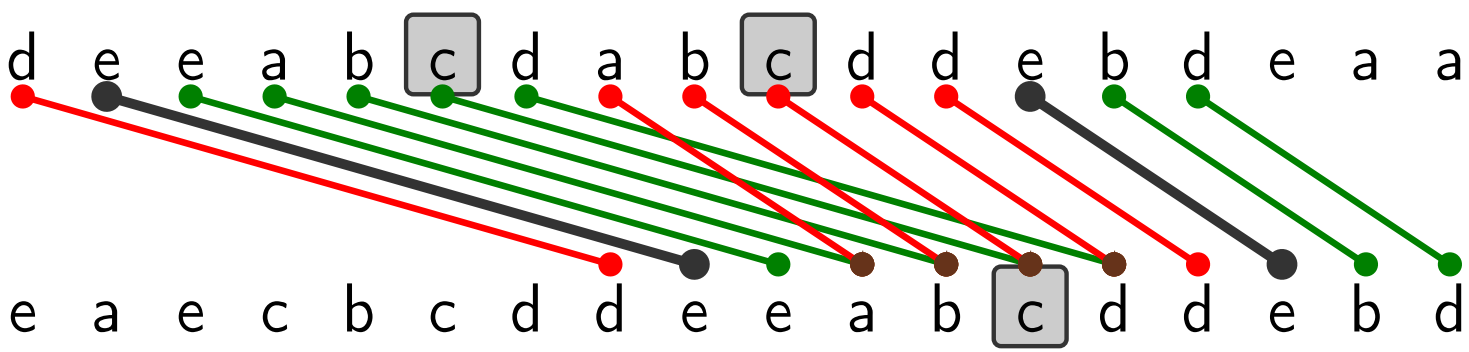
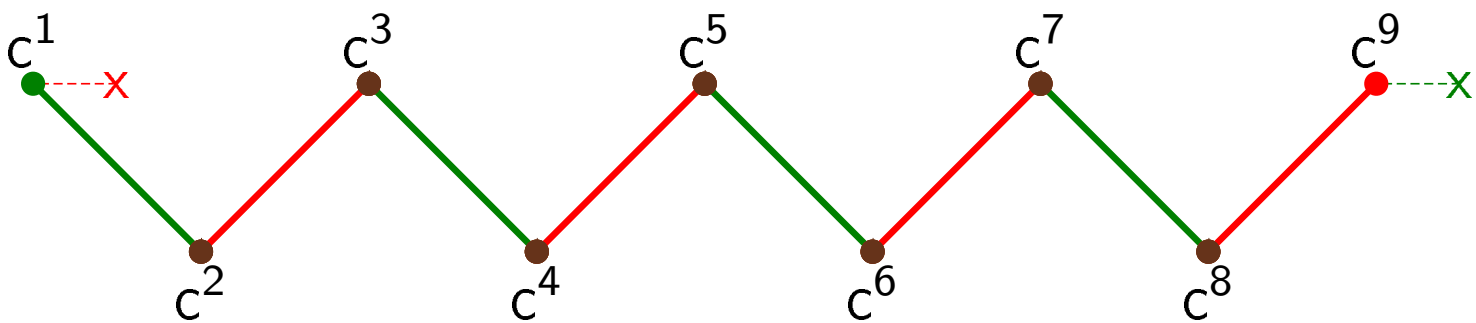
- What about degree-1 and degree-2 vertices?



Odd Paths

Path of odd length

If $(c^1, c^2, c^3, \ldots, c^{2p+1})$ is an odd path with c^1 being rare



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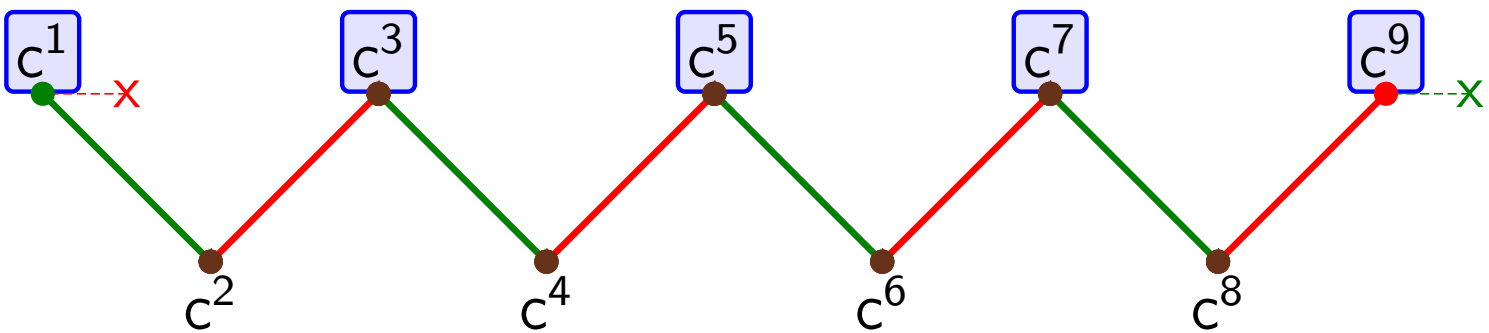

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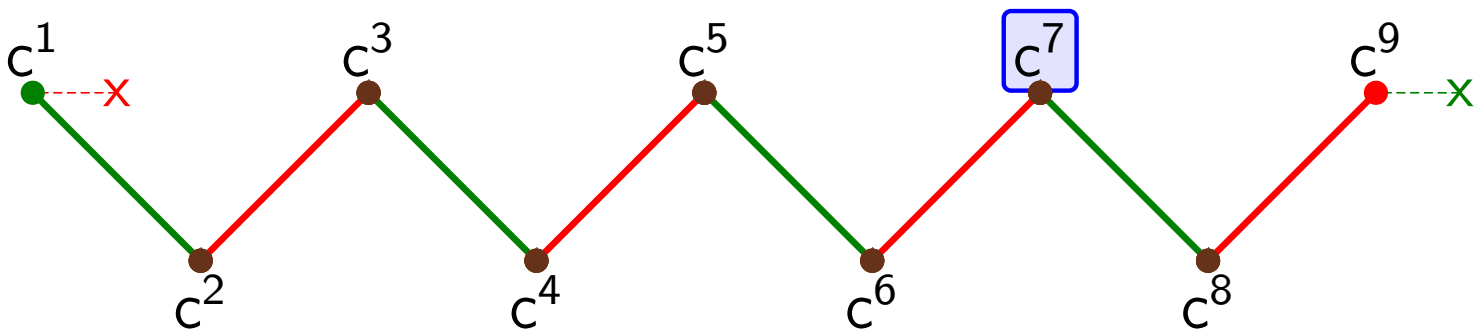

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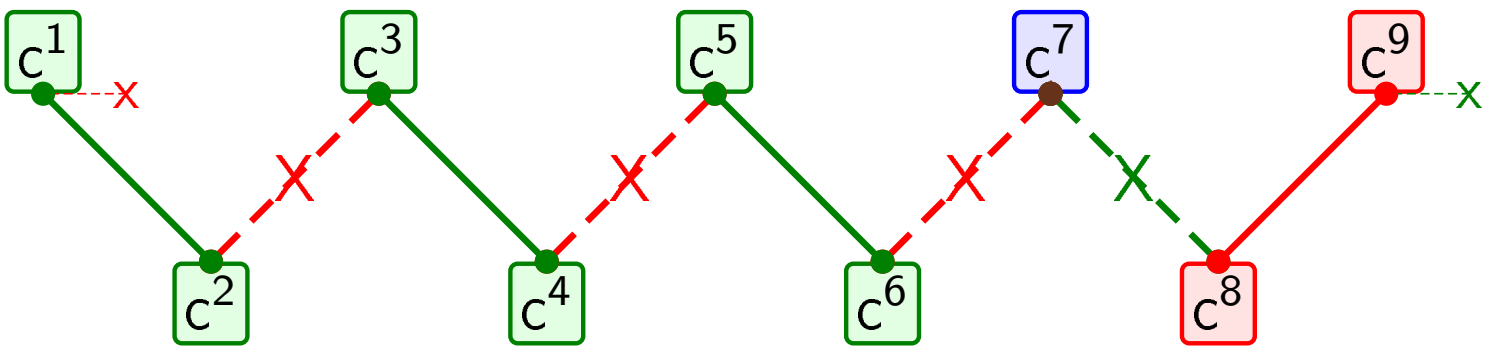

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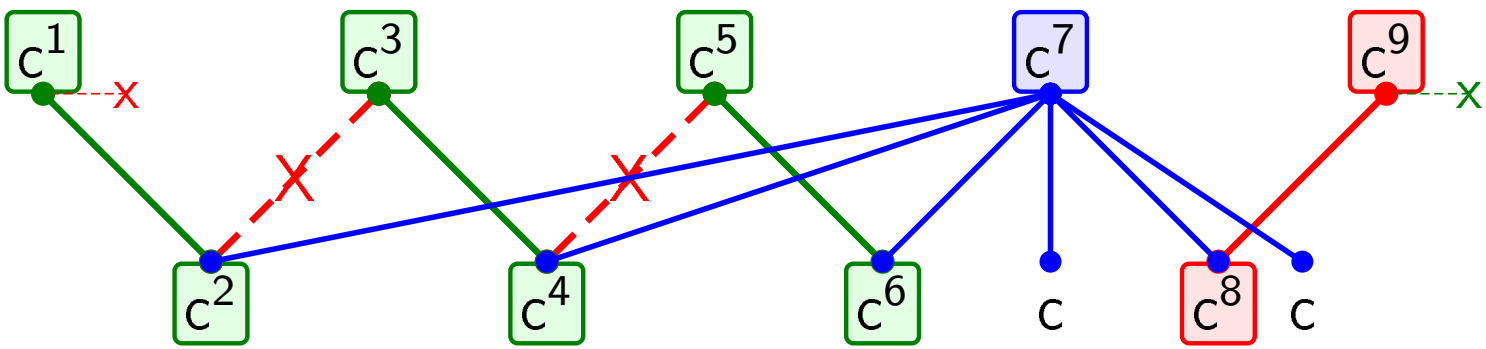

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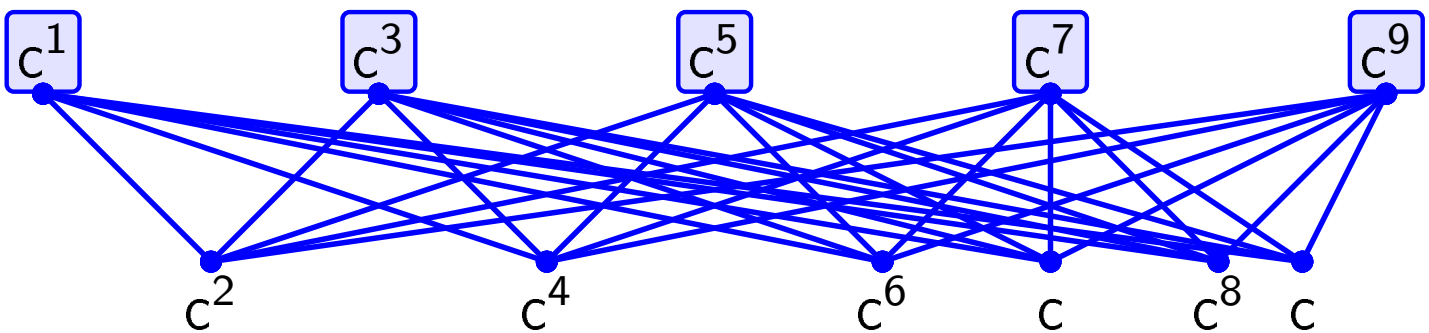
Total number of seeds to try: at most d^2.



So far...

We know how to deal with single elements and rare odd paths.

What if our association graph has only even paths, cycles, and abundant odd paths?

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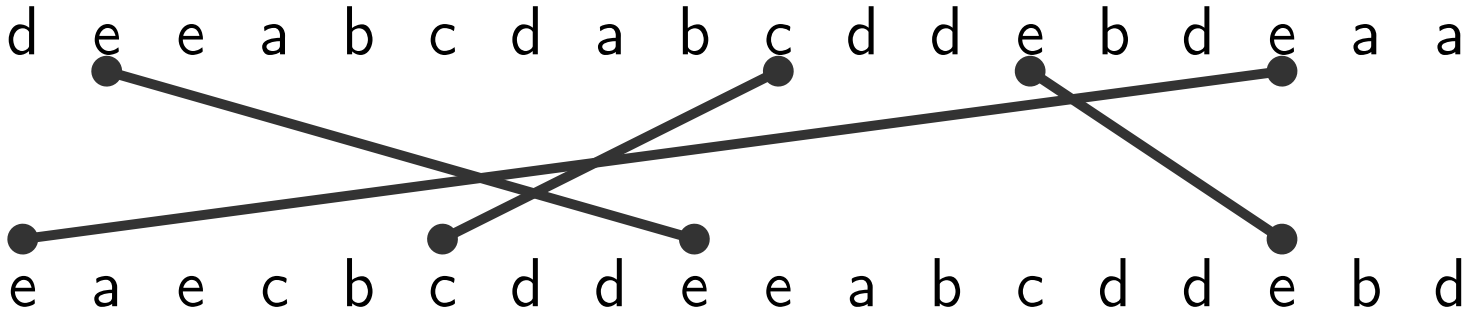
What if our association graph has only even paths, cycles, and abundant odd paths?

Then we can create a CSP based on our seeds!

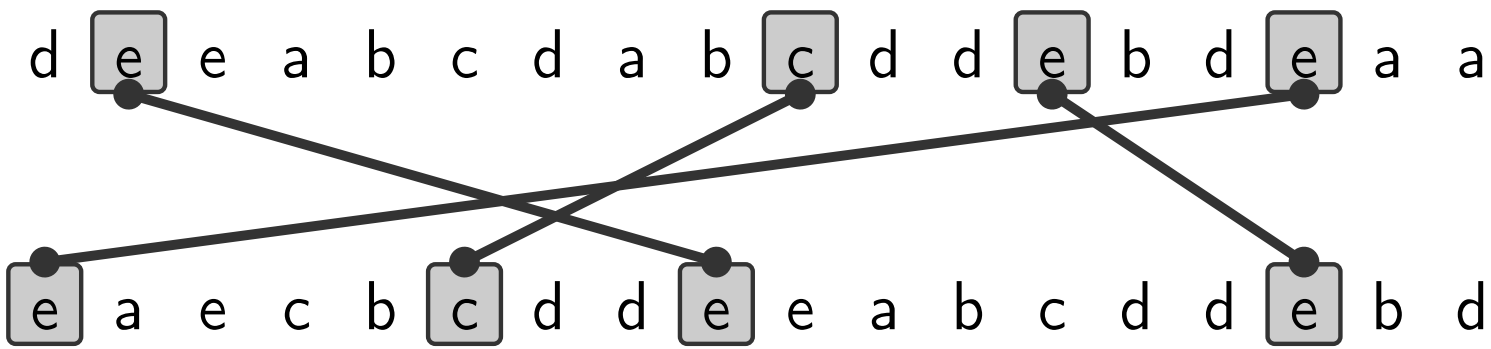
Constructing the solution

- No more seeds can be found...



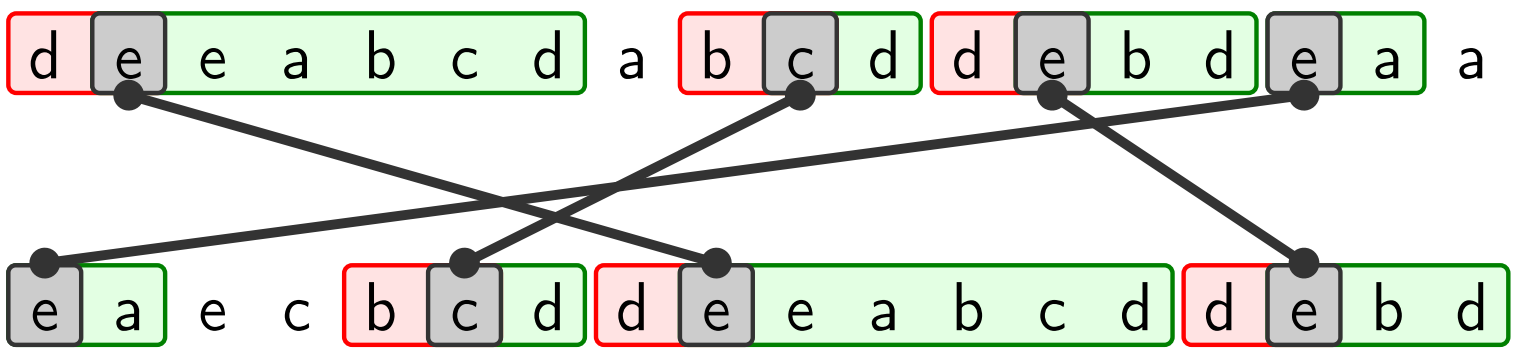
Constructing the solution

- No more seeds can be found...
- Create one block per seed



Constructing the solution

- No more seeds can be found...
- Create one block per seed
- Extend the blocks to the left and right (details omitted)



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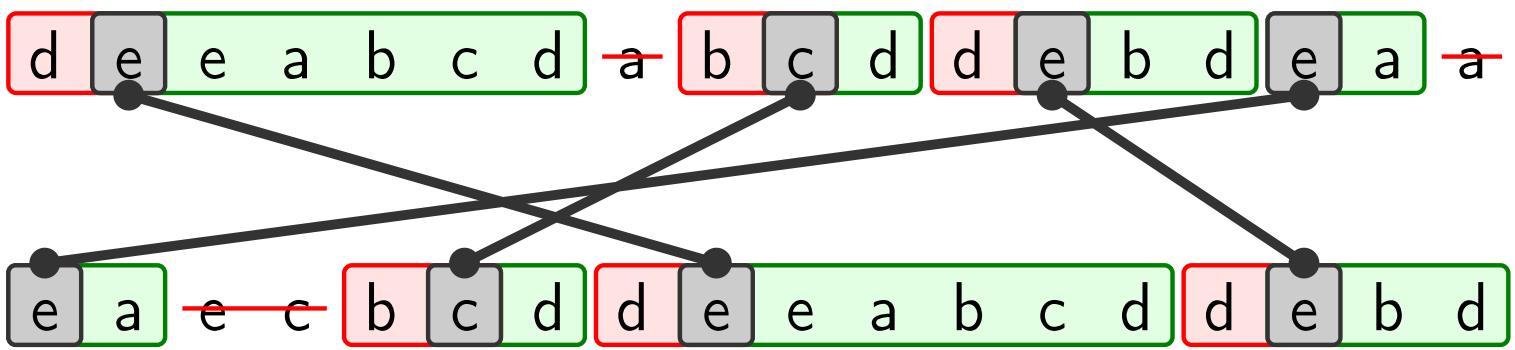

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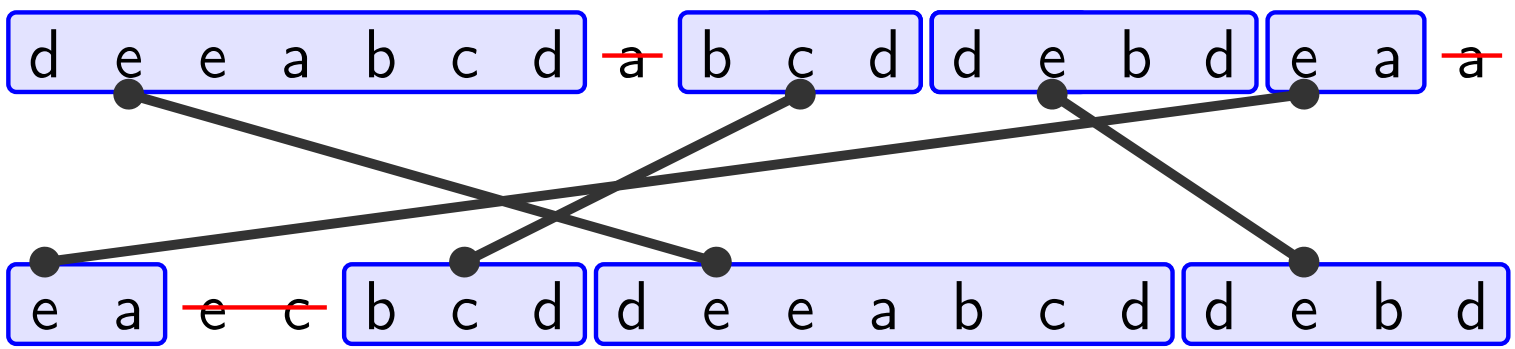
- Output the solution!



Theoretical Time Complexity

- Time complexity:
  - d or d^2 choices for each of the k seeds: d^{2k-1} branches
  - Computing the graph, looking for paths, etc.: $O(kn)$
  - Overall: $O(d^{2k}n)$
- The algorithm may try to optimize a second objective value.
- Many duplicates, few blocks: from d^2 to $3dk$
  If an odd path visits many times the same intervals, keep only $\leq 3k$ candidate seeds.

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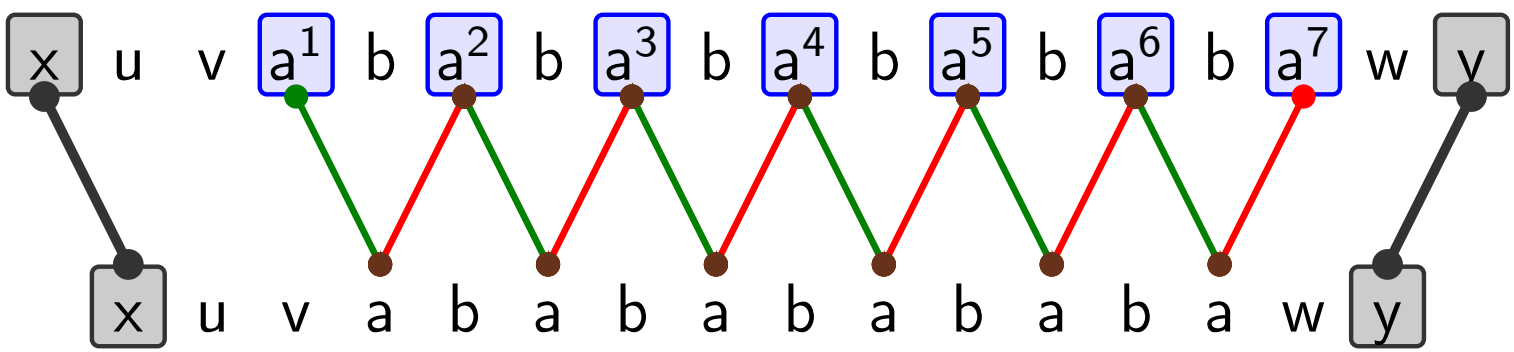

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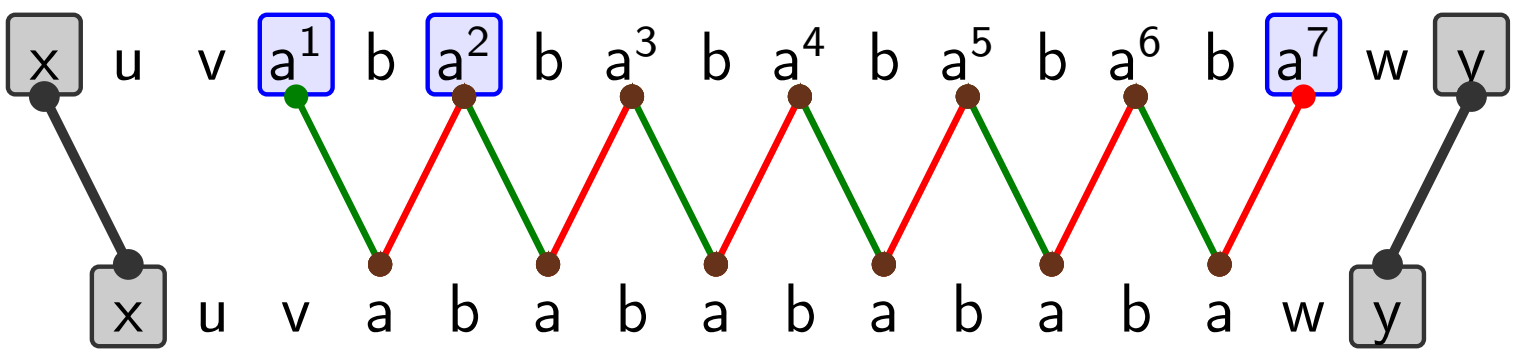
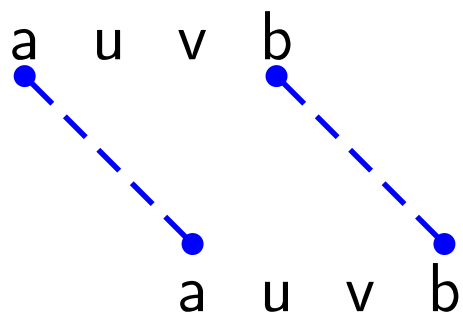


Implementation

Reduction rules

Reduction Rule 1

Merge strings with unique letters



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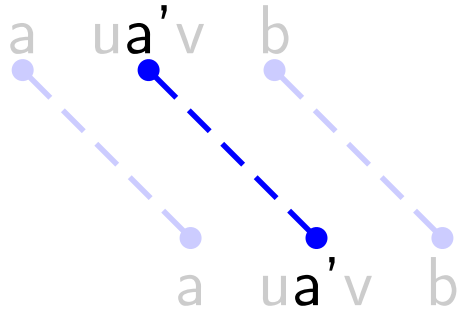

Reduction rules

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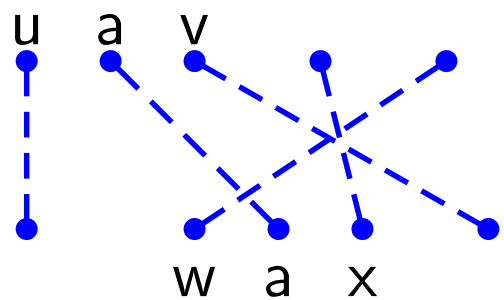
Reduction Rule 2

Remove obvious size-1 blocks



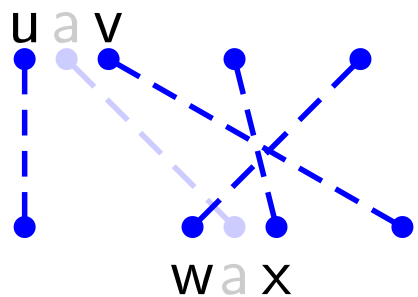
Reduction rules

Reduction Rule 1

Merge strings with unique letters

Reduction Rule 2

Remove obvious size-1 blocks



Decrease k by 1

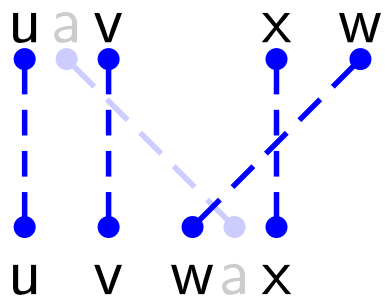
Reduction rules

Reduction Rule 1

Merge strings with unique letters

Reduction Rule 2

Remove obvious size-1 blocks



Decrease k by 2

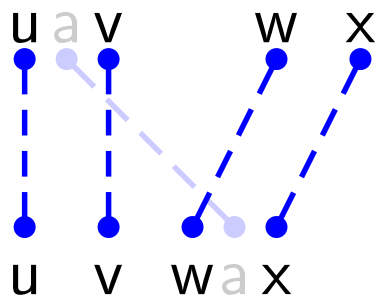
Reduction rules

Reduction Rule 1

Merge strings with unique letters

Reduction Rule 2

Remove obvious size-1 blocks



Decrease k by 3

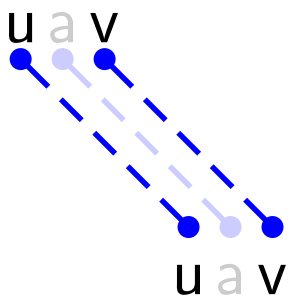
Reduction rules

Reduction Rule 1

Merge strings with unique letters

Reduction Rule 2

Remove obvious size-1 blocks



Leave k unchanged

Reduction rules

Reduction Rule 1

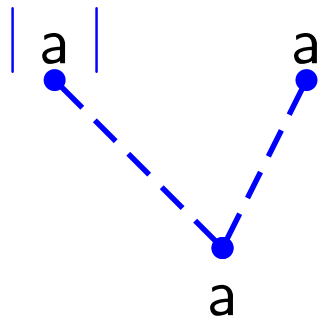
Merge strings with unique letters

Reduction Rule 2

Remove obvious size-1 blocks

Reduction Rule 3

Keep best match (one unique letter)



Reduction rules

Reduction Rule 1

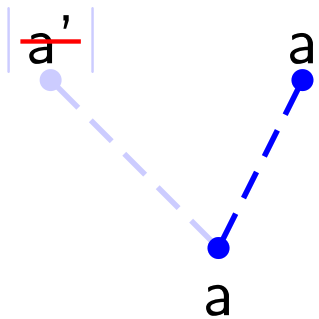
Merge strings with unique letters

Reduction Rule 2

Remove obvious size-1 blocks

Reduction Rule 3

Keep best match (one unique letter)



Reduction rules

Reduction Rule 1

Merge strings with unique letters

Reduction Rule 2

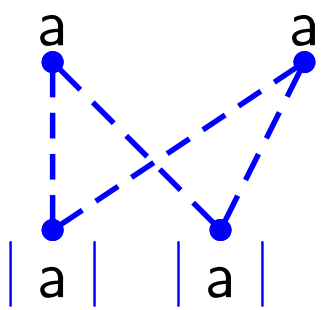
Remove obvious size-1 blocks

Reduction Rule 3

Keep best match (one unique letter)

Reduction Rule 4

Keep best match (≤ 2 occurences)



Reduction rules

Reduction Rule 1

Merge strings with unique letters

Reduction Rule 2

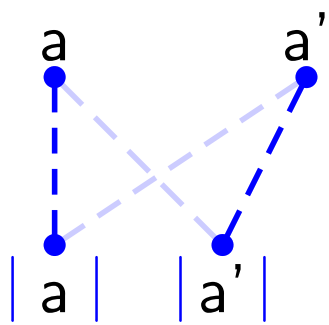
Remove obvious size-1 blocks

Reduction Rule 3

Keep best match (one unique letter)

Reduction Rule 4

Keep best match (≤ 2 occurences)



Reduction rules

Reduction Rule 1

Merge strings with unique letters

Reduction Rule 2

Remove obvious size-1 blocks

Reduction Rule 3

Keep best match (one unique letter)

Reduction Rule 4

Keep best match (≤ 2 occurences)

Reduction of genome size: from 40% to 85%

Running time on biological data

Genomic sequences from: *Borrelia burgdorferi*, *Treponema pallidum*, *Escherichia coli*, *Bacillus subtilis*, and *Bacillus thuringiensis*

Species 1	Species 2	n	k	d	t (s)
B. burg.	*T. pall.*	93	68	3	0.06
B. burg.	*E. coli*	72	59	6	0.22
B. burg.	*B. sub.*	91	63	6	0.15
B. burg.	*B. thur.*	71	51	5	0.09
T. pall.	*E coli*	93	78	5	0.35
T. pall.	*B. sub.*	144	82	7	0.18
T. pall.	*B. thur.*	128	76	6	0.15
E. coli	*B. sub.*	287	234	7	41.06
E. coli	*B. thur.*	282	221	10	18.64
B. sub.	*B. thur.*	693	340	8	249.71

EnsemblBacteria database

Running time on biological data

Genomic sequences from: *Borrelia burgdorferi*, *Treponema pallidum*, *Escherichia coli*, *Bacillus subtilis*, and *Bacillus thuringiensis*

Average letter occurences: from 1.02 to 1.24

Species 1	Species 2	n	k	d	t (s)
B. burg.	*T. pall.*	93	68	3	0.06
B. burg.	*E. coli*	72	59	6	0.22
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EnsemblBacteria database

Running time on synthetic data

Generated sequences of size $n = 1000$
Average letter occurences: from 2 to 4

k	t (s)	
	$d = 6$	$d = 8$
50	0.06	0.07
60	0.06	0.06
70	0.07	0.08
80	0.09	0.09
90	0.10	0.12
100	0.12	0.16
110	0.13	0.26
120	0.18	1.62
130	0.21	30.42

Conclusion

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Practical FPT algorithms for MCSP with association graph:

- $O\left(d^{2k}n\right)$
- $O\left((3dk)^{k}n\right)$

Conclusion

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- $O\left(d^{2k}n\right)$
- $O\left((3dk)^{k}n\right)$

Open questions:

- Extend algorithm to signed strings?
- Practical running time with high number of duplications?
- Constant-ratio approximation?