Permutations in comparative genomics

Anthony Labarre
Anthony.Labarre@cs.kuleuven.be

Katholieke Universiteit Leuven (K.U.L.)

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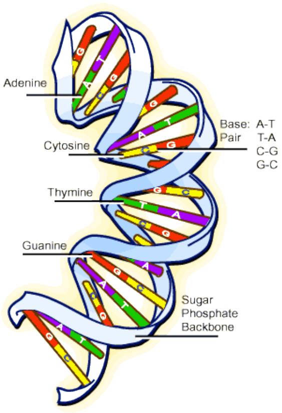
Algorithms & Permutations 2012

A few definitions

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



Comparing genomes at the nucleotide level

- Most common comparisons: at the nucleotide level;

Example (sequence alignment)

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

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

At the gene level

- Some mutations involve whole segments of nucleotides;
- Genomes = signed permutations if genomes:
  1. are totally ordered sets of genes, and
  2. only differ by gene order (no duplications, no deletions).

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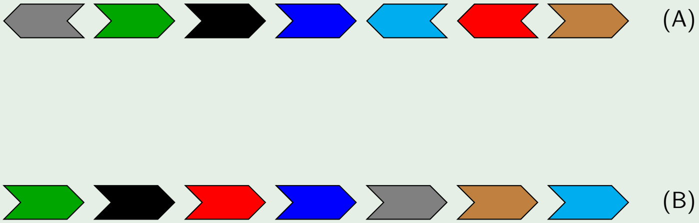

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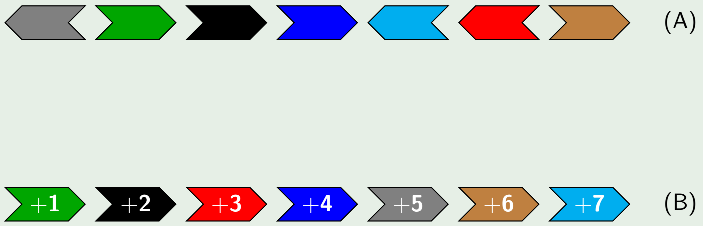

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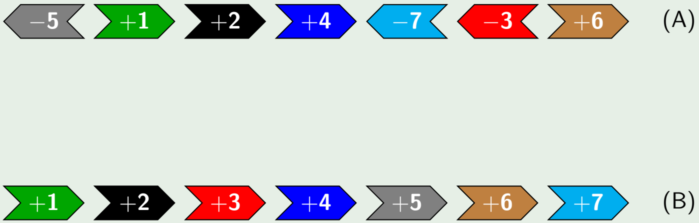

Comparing genomes

- Two main ways of comparing genomes:
  1. by identifying “common” or close content;
  2. by measuring their distance according to evolutionary events;
- Both approaches yield measures of (dis)similarity between permutations;
- (Many other measures are available, but they’re generally not biologically relevant (see e.g. [Estivill-Castro and Wood, 1992]));

What lies ahead

- I will give an overview of several representative problems:
  - comparing signed and unsigned permutations;
  - enumeration problems, with applications;
  - using comparisons to reconstruct evolution;
- Links with other interesting areas;
- Open problems and suggestions for future research;

Measuring similarity

- Search for segments that are “alike”;
- This is a form of approximate pattern matching:
  1. at the nucleotide level: look for subsequences that are “almost the same”;
     (this is how genomes are partitioned to yield permutations)
  2. at the gene level: look for subsequences that have exactly the same content BUT in a possibly different order;
- Point 2 motivates the next definition;

Common intervals

Definition

A **common interval** of permutations $\pi^1, \pi^2, \ldots, \pi^m$ in $S_n^{\pm}$ is a subset of $\{1, 2, \ldots, n\}$ whose elements form a substring of $\pi^1, \pi^2, \ldots, \pi^m$ (up to reordering and sign changes).

Biological motivation: genes that stuck together in an ancestor and in the present species are not likely to have been separated during evolution.

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Example (<u>some</u> common intervals of two given permutations)

$$\begin{array}{llllllllll} \langle 9 & -8 & 4 & -5 & -6 & 7 & 1 & 2 & 3\rangle & \{4,5,6,7,8,9\}, \{1,2,3\} \\ \langle 1 & 2 & 3 & -8 & 7 & -4 & -5 & 6 & -9\rangle & \{4,5,8\}\text{: NO} \end{array}$$

Intervals and measures

- Other variants exist (e.g. conserved intervals);
- Measures of (dis)similarity can be built and computed efficiently [Bergeron and Stoye, 2006];
  - ✓ simple to compute;
  - ✓ biologically relevant;
  - × do not correspond to evolutionary events;
- ... which is why we'll now have a look at "event-based" measures;

Genome rearrangements

- Genomes evolve by point mutations, but also by means of mutations involving whole segments;
- **Parsimony principle** in biology: a shorter scenario of mutations is more likely;
- This motivates the study of the following problem;

Genome rearrangements

Problem (pairwise genome rearrangement problem)

Given: *permutations π, σ in $S_n^{\pm}$, and a generating set S of $S_n^{\pm}$.*
Find: *a sequence of t elements of S that:*

1. *transforms π into σ (or conversely), and*
2. *such that t is as small as possible.*

- This yields a *distance* $d_S(\cdot, \cdot)$ between permutations;

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- $\Rightarrow$ find a minimum-length factorisation of π into the product of elements of S;

Example: sorting by signed reversals

$\pi = \quad -5 \quad +1 \quad +2 \quad +4 \quad -7 \quad -3 \quad +6$

$\sigma = \quad +1 \quad +2 \quad +3 \quad +4 \quad +5 \quad +6 \quad +7$

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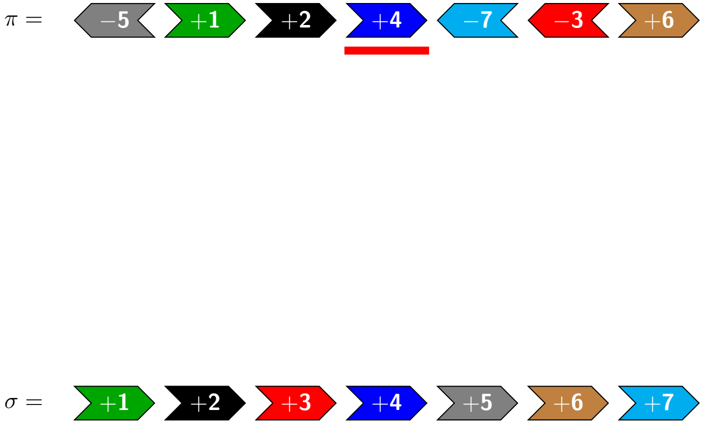

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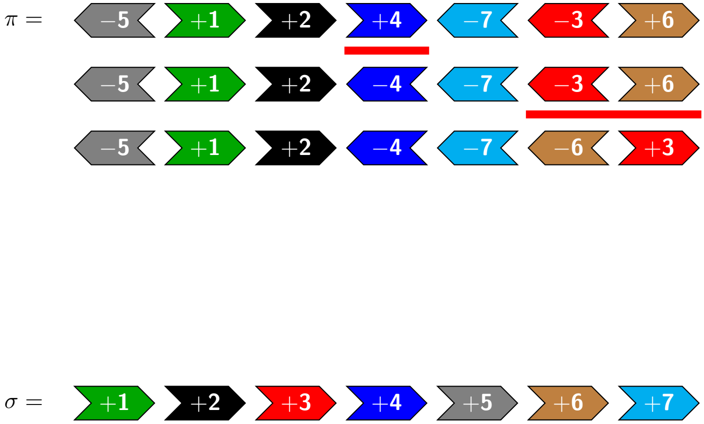

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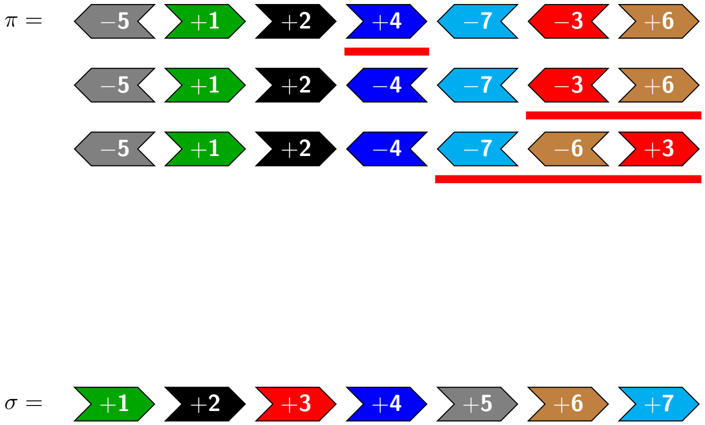

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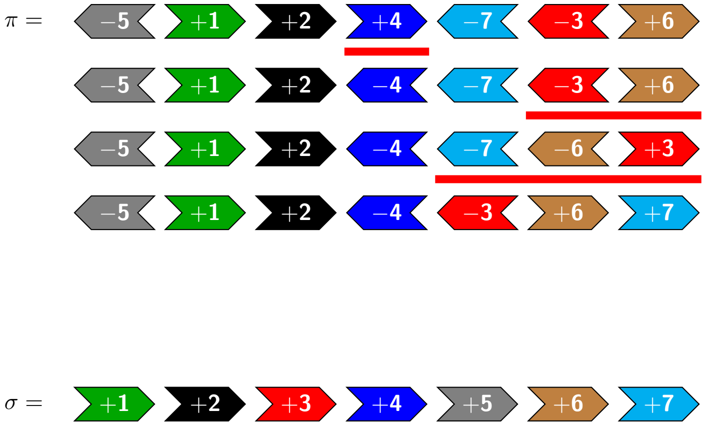

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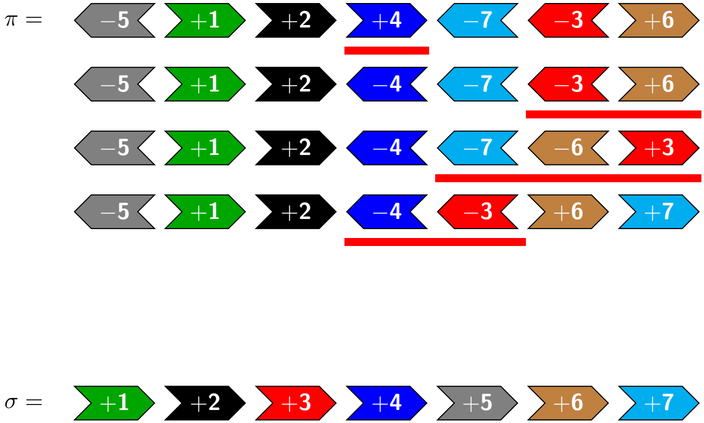

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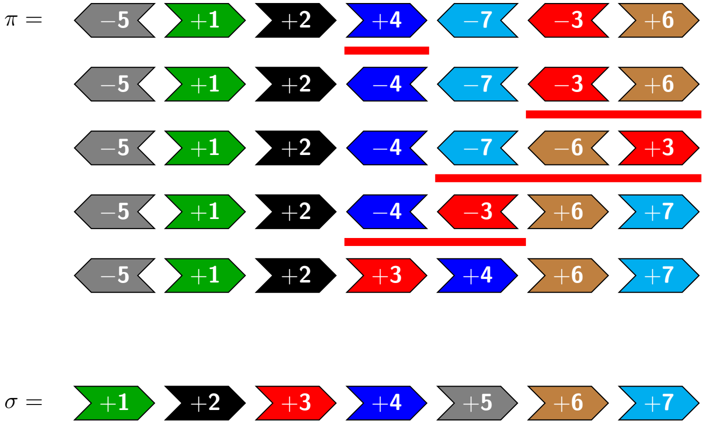

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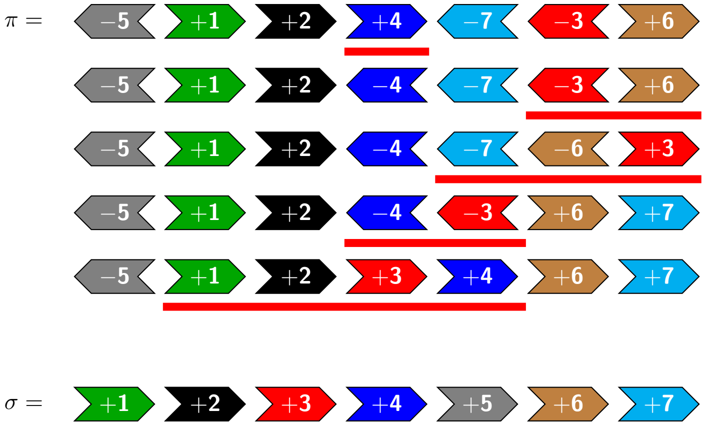

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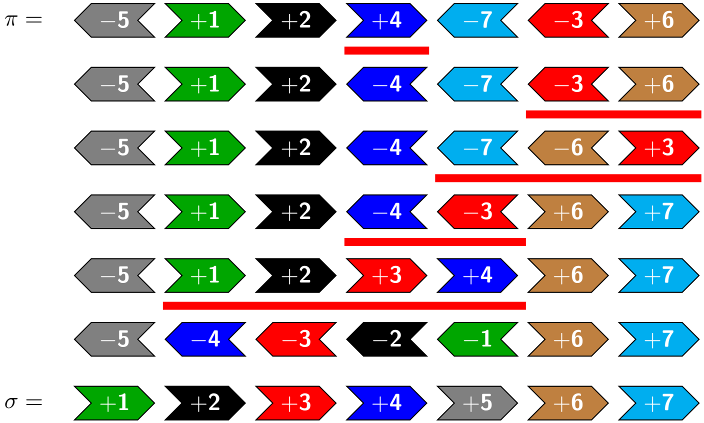

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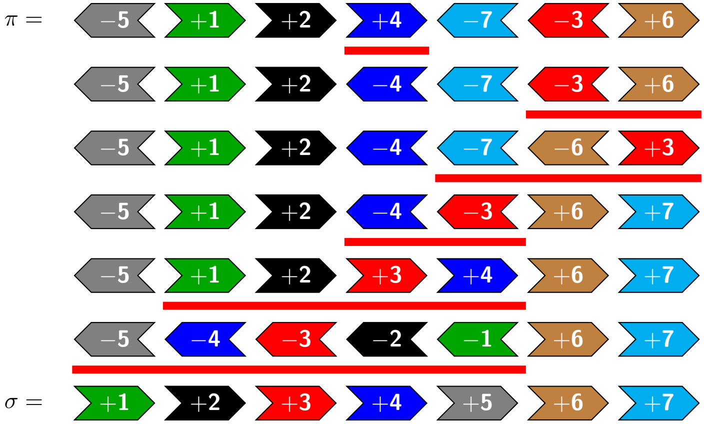


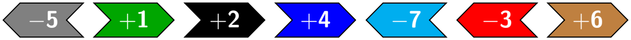
$$srd(\pi,\sigma) \leq 6$$

Computing genome rearrangement distances

- Proving upper bounds is “easy” (find a sequence that works);
- But how do we guarantee that a given sequence is optimal?
- We usually rely on variants of the *breakpoint graph*, first introduced by [Bafna and Pevzner, 1996];
- That structure proved very useful in:
  1. obtaining bounds and approximations;
  2. computing distances exactly in polynomial time;
  3. proving complexity results;

The *breakpoint graph*

- Going back to our example:

$\pi =$ 

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$$\pi = \quad -5 \quad +1 \quad +2 \quad +4 \quad -7 \quad -3 \quad +6$$
$$\pi' = 0 \quad 10 \quad 9 \quad 1 \quad 2 \quad 3 \quad 4 \quad 7 \quad 8 \quad 14 \quad 13 \quad 6 \quad 5 \quad 11 \quad 12 \quad 15$$

1. double π's elements $(i \mapsto \{2|i|-1, 2|i|\})$ and add $\mathbf{0}$ and $\mathbf{2n+1}$

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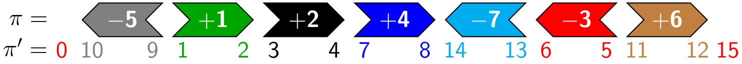

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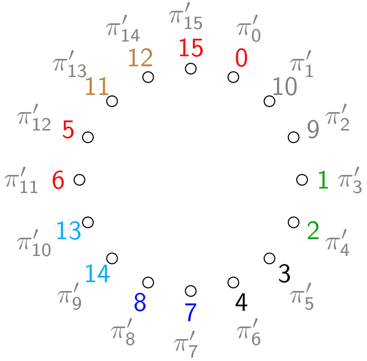
π'_{14} π'_{15} π'_0
π'_{13} 12 15 0 π'_1
11 10
π'_{12} 5 9 π'_2
π'_{11} 6 1 π'_3
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14 3
π'_9 8 7 4 π'_5
π'_8 π'_7 π'_6

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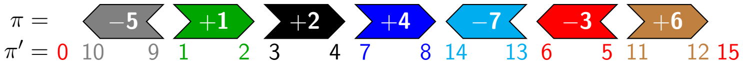

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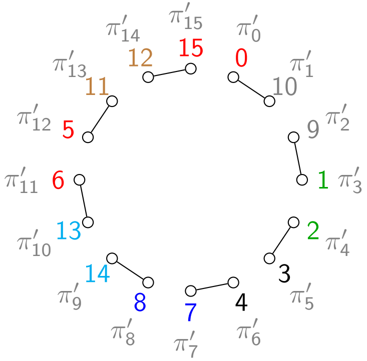

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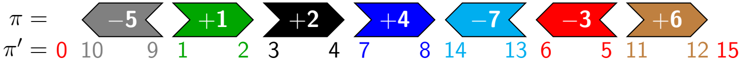

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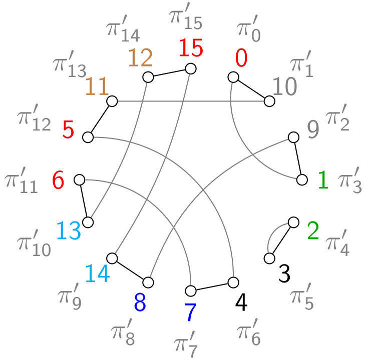
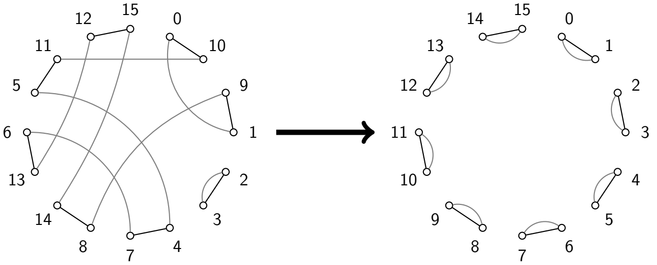
4. **grey edges** connect distinct consecutive genes



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:



- ⇒ goal: create new cycles in as few moves as possible;

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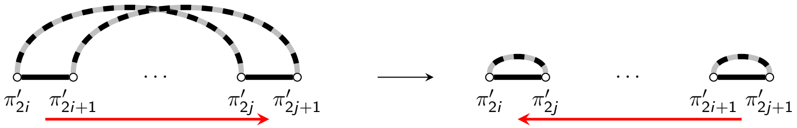

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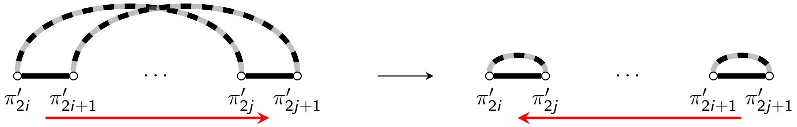

- Therefore, for all π in $S_n^{\pm}$:

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

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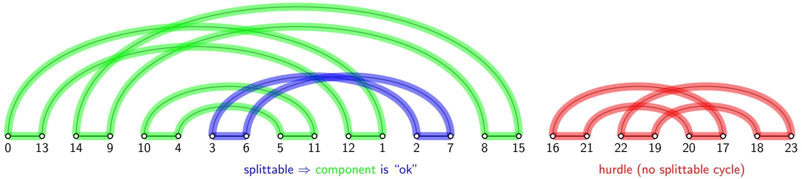

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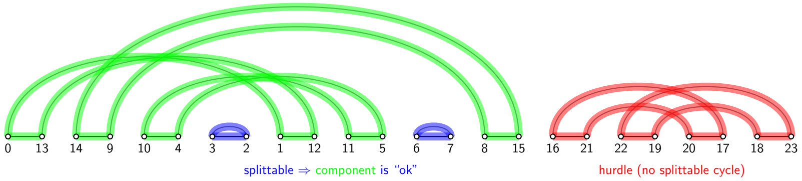

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Theorem ([Hannenhalli and Pevzner, 1999])

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- Computing $srd(\cdot)$ / sorting can be done in polynomial time;

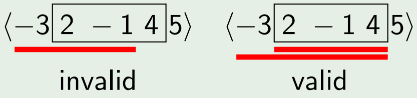
Integrating other constraints: “perfection”

- (recall Mathilde Bouvel’s talk)
- As seen before, some genes “stick together”;

Problem (perfect sorting by signed reversals)

Given: *a permutation π in $S_n^{\pm}$, and a set S of intervals of π.*
Find: *a minimum-length sequence of signed reversals that sorts π and whose elements do not overlap with intervals from S.*

Example (<u>not</u> sorting sequences)


$\langle -3\ \boxed{2\ -1\ 4}\ 5\rangle$
invalid
$\langle -3\ \boxed{2\ -1\ 4}\ 5\rangle$
valid

A more general view: double cut-and-join

- The “double-cut-and-join” (DCJ) operation is defined directly on the breakpoint graph:
- Idea: **cut** two black edges and **join** their endpoints;
    - Simulates signed reversals and block-interchanges (2 DCJs for the latter);
    - $\Rightarrow$ sorting by DCJs $\equiv$ sorting by signed reversals with weight 1 and block-interchanges with weight 2;

Theorem ([Yancopoulos et al., 2005])

For any π in $S_n^{\pm}$: $dcj(\pi) = n + 1 - c(BG(\pi))$.

Some results and some questions (non exhaustive)

- What has been done:

Operation	Sorting	Distance	Best approximation
signed reversal	$O(n^{3/2})$ [Han, 2006]	$O(n)$ [Bader et al., 2001]	1
perfect signed reversal	NP-hard [Figeac and Varré, 2004]		?
prefix signed reversal	?	?	2 [Cohen and Blum, 1995]
double cut and join	$O(n)$ [Yancopoulos et al., 2005]		1

- What could be done:
  - Prefix signed reversals:
    1. complexity of sorting / computing the distance?
    2. largest value the distance can reach?
    3. "better-than-2"-approximation?
  - Characterise "hard instances" using pattern matching/avoidance;

Unsigned permutations

- In some situations, gene orientation may be unknown or can be disregarded;
- Genomes are then modelled by the more traditional unsigned permutations;
- Of course, rearrangements in that setting do not affect orientation;

The breakpoint graph in the unsigned case

- More direct construction than in the signed case;
- Let's build the breakpoint graph of $\pi = \langle 4\ 1\ 6\ 2\ 5\ 7\ 3 \rangle$:

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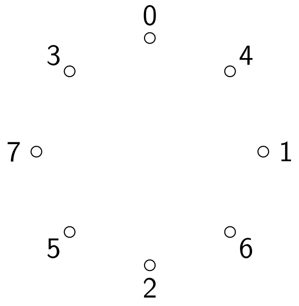

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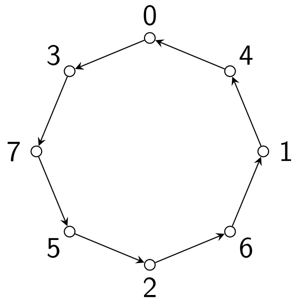

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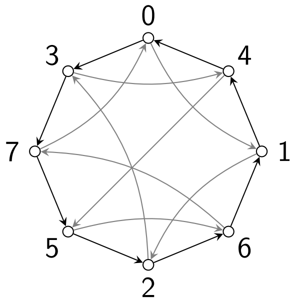

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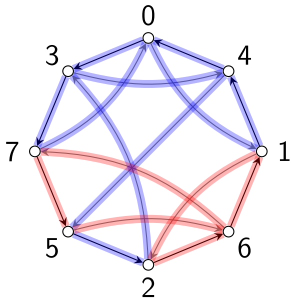

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$BG(\pi)$ decomposes in a unique way into alternating cycles

Breakpoint graphs as permutations

- Nice property of $BG(\pi)$: its alternating cycle decomposition matches the traditional disjoint cycle decomposition of

$$\overline{\pi} = (0, 1, 2, \ldots, n) \circ (0, \pi_n, \pi_{n-1}, \ldots, \pi_1);$$

- As a consequence, we can express the action of *any* rearrangement σ on π using $\overline{\pi}$:

Lemma ([Labarre, 2012])

For all π, σ in S_n, we have $\overline{\pi \circ \sigma} = \overline{\pi} \circ \overline{\sigma}^{\pi}$.

- ... and we can recycle known results in this context;

Obtaining lower bounds

- Lower bounds can be automatically obtained as follows:

Initial problem:
computing $d_S(\pi)$:

$$\pi \longrightarrow \pi \circ x_1 \longrightarrow \pi \circ x_1 \circ x_2 \longrightarrow \cdots \longrightarrow \iota$$

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New problem:
computing $d_C(\overline{\pi})$:

$$\begin{tikzcd}
\pi \arrow[r] \arrow[d, bend right] & \pi \circ x_1 \arrow[r] & \pi \circ x_1 \circ x_2 \arrow[r, dash] & \cdots \arrow[r] & \iota \arrow[d, bend left] \\
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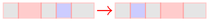
- This yields tight lower bounds on:
  1. the block-interchange distance [Christie, 1996];
  2. the transposition distance [Bafna and Pevzner, 1998];
  3. the prefix transposition distance [Labarre, 2012];

Three examples

- How one can obtain bounds on the following distances:
  1. block-interchange distance ($bid(\cdot)$):



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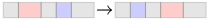
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     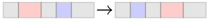
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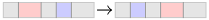
  1. block-interchange distance ($bid(\cdot)$): 
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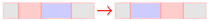
  2. transposition distance ($td(\cdot)$): 

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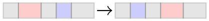
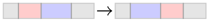

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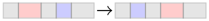

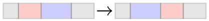

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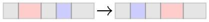
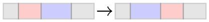
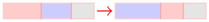

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     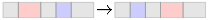
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     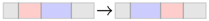
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     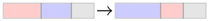
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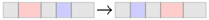
  1. block-interchange distance ($bid(\cdot)$): 
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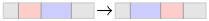
  2. transposition distance ($td(\cdot)$): 
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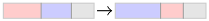
  3. prefix transposition distance ($ptd(\cdot)$): 
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        $\frac{n+1+c(BG(\pi))}{2} - 2c_1(BG(\pi)) - \begin{cases} 0 \text{ if } \pi_1 = 1, \\ 1 \text{ otherwise.} \end{cases}$;

A word of caution

- Don’t think that sorting unsigned permutations is trivial;
- $bid(\cdot)$ and $exc(\cdot)$ are indeed easy to compute, but:
  1. sorting by (prefix or arbitrary) reversals becomes NP-hard;
  2. sorting by transpositions is NP-hard;
  3. sorting by double cut-and-joins is NP-hard;
  4. sorting by prefix transpositions is open;

Results on sorting unsigned permutations

- What has been done:

	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, 1999b]		11/8 [Berman et al., 2002]
	transposition	NP-hard [Bulteau et al., 2011b]		11/8 [Elias and Hartman, 2006]
prefix	exchange	$O(n)$ [Akers et al., 1987]		1
prefix	reversal	NP-hard [Bulteau et al., 2011a]		2 [Fischer and Ginzinger, 2005]
prefix	transposition	?	?	2 [Dias and Meidanis, 2002]

- What could be done:
  - better approximations;
  - complexity of prefix transposition problems?

Counting problems

- What is the distribution of a given rearrangement distance?
- Most tight bounds on rearrangement distances are obtained using the breakpoint graph and its cycles;
- Use the distribution of cycles in the breakpoint graph to approximately answer the above;

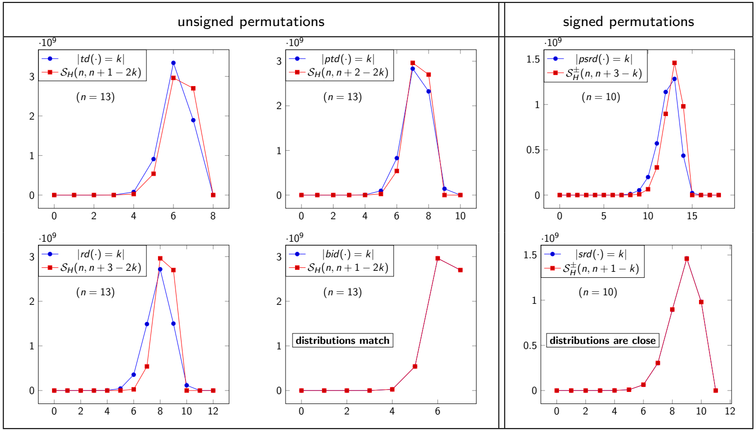
Hultman numbers

- Hultman numbers count permutations whose breakpoint graph contains k cycles:

$$\mathcal{S}_H(n,k) = |\{\pi \in S_n \mid c(BG(\pi)) = k\}| \qquad \text{unsigned case}$$
$$\mathcal{S}_H^{\pm}(n,k) = |\{\pi \in S_n^{\pm} \mid c(BG(\pi)) = k\}| \qquad \text{signed case}$$

- Similar in spirit to Stirling numbers of the first kind;
- Explicit formulas are available for computing $\mathcal{S}_H(n,k)$ and $\mathcal{S}_H^{\pm}(n,k)$ (see e.g. [Grusea and Labarre, 2011]);
- Also available: generating functions, expected value and variance;

Approximating distance distributions using Hultman numbers



(distance distributions from [Galvão and Dias, 2011])

Experiments wrap-up and perspectives

- Some distance distributions are extremely well approximated using (some function of) the Hultman numbers;
- Can bounds be tightened by trying to minimise the difference between the distributions?
- Can the proximity of distributions be used to argue that exact computation of hard distances is overrated?

Listing optimal sequences

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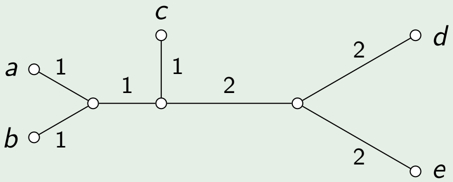
- $\Rightarrow$ can we list all optimal sequences for a given instance?
- Efficient algorithms exist for listing:
    - all optimal signed reversals [Swenson et al., 2011];
    - all optimal sequences [Badr et al., 2011];

Median problems

- Measures of similarities between genomes are useful in reconstructing phylogenies;

Example (phylogeny from distance matrix)

	a	b	c	d	e
a	0	2	3	6	6
b	2	0	3	6	6
c	3	3	0	5	5
d	6	6	5	0	4
e	6	6	5	4	0



- (The matrix must satisfy some conditions [Buneman, 1971]);

Median problems

- Parsimony again: search for a tree that minimises the total number of evolutionary events (i.e. the sum of all edge weights);
- In its simplest form, the problem we want to solve is:

Problem (median of three)

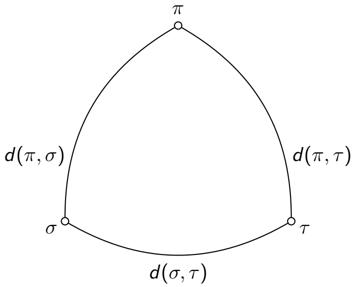
Given: π, σ, τ *in* $S_n^{\pm}$*; a distance* $d : S_n^{\pm} \times S_n^{\pm} \rightarrow \mathbb{N}$.
Find: *a permutation* μ *in* $S_n^{\pm}$ *that minimises*

$$w(\mu) = d(\pi, \mu) + d(\sigma, \mu) + d(\tau, \mu).$$

- Can be generalised to more than three input permutations;

Generic bounds [Siepel and Moret, 2001]

- Generic lower and upper bounds for any distance:



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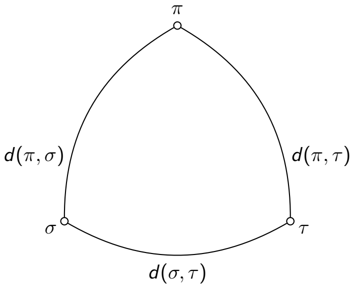

- $w(\mu) \leq \min\{\overbrace{d(\pi,\sigma)+d(\pi,\tau)}^{\text{if } \mu=\pi}, \overbrace{d(\pi,\sigma)+d(\sigma,\tau)}^{\text{if } \mu=\sigma}, \overbrace{d(\pi,\tau)+d(\sigma,\tau)}^{\text{if } \mu=\tau}\}.$

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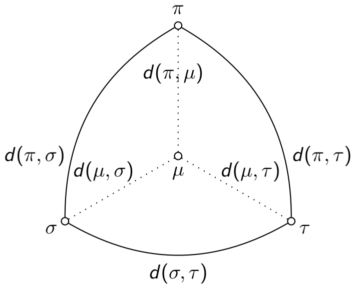

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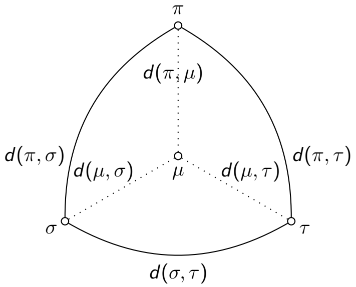

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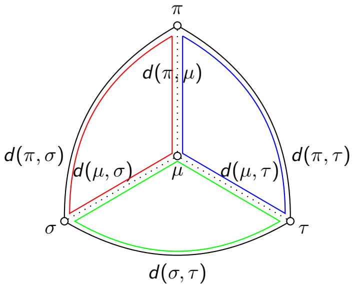

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  $\ge d(\pi,\sigma)+d(\pi,\tau)+d(\sigma,\tau)$ (triangle inequalities)

Results on median problems

- What has been done:

Operation or measure	Median of three	Best approximation
breakpoint	NP-hard [Bryant, 1998]	5/3 [Caprara, 2002]
signed breakpoint	NP-hard [Bryant, 1998]	7/6 [Pe'er and Shamir, 2000]
exchange	?	?
signed reversal	NP-hard [Caprara, 2003]	4/3 [Caprara, 1999a]
signed double-cut-and-join	NP-hard [Caprara, 2003]	4/3 [Caprara, 1999a]
transposition	NP-hard [Bader, 2011]	?

- What could be done:
  1. complexity of the exchange median problem?
     (trivial for 2 permutations, NP-hard for ≥ 4; what about 3?)
  2. better approximations;
  3. "median clouds" [Eriksen, 2009];

Possible future directions

- More realistic distances:
  - several kinds of operations, weighted differently;
  - learning *ad hoc* distances?
- Generalising the bijection $\pi \mapsto \overline{\pi}$:
  - obtain *upper* bounds;
  - extend to *signed* permutations;
- Can we build bridges to other fields (e.g. pattern matching)?
- Complexity and approximability issues;

Thanks!!!

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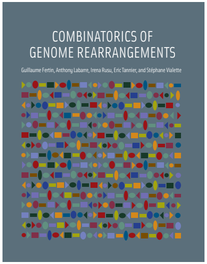
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Guillaume Fertin, Anthony Labarre, Irena Rusu, Eric Tannier, and Stéphane Vialette

with Guillaume Fertin,
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The MIT Press, 2009.

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