

## Introduction to computational and systems biology

- Lecture 7: Genome rearrangements
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TURKU CENTRE for COMPUTER SCIENCE

## In this lecture

- Move from a sequence-centered approach to a genome-centered approach
  - Instead of comparing gene sequences, focus on gene orders
- From sequence point-modifications to large genome rearrangements

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## Genetic rearrangements

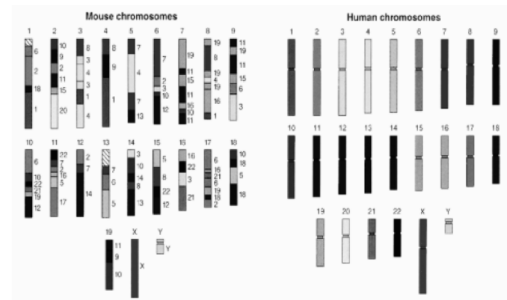
- In the evolution, the genome undergoes slight changes
  - There may be changes in the nucleotide sequence of some coding regions: insertion, deletions, changes of one nucleotide into another
  - There may be changes of big pieces of chromosomes – reversals, permutations, insertions, deletions. These are called genome rearrangements – much more rare than point mutations
    - Human and mouse separated by 80 million years of evolution, yet just around 178 rearrangements between the two genomes
  - Possible to follow the evolutionary history of a species or to compare the evolution of different species based on these rearrangements

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## Mouse chromosome vs. human chromosome



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## Rearrangements as evolution

- Research in the last decade brought evidence that rearrangements represent a “common” mode of molecular evolution
- Genome rearrangements studied since 1930s – original study on rearrangement scenarios for 17 species of *Drosophila* fruit fly
- The principle of parsimony: always look for the simplest/minimal explanation
- Gene comparison vs. genome comparison:
  - The former one analyzes at the gene level, ignoring the gene order
  - The latter one takes a global picture, ignoring the gene sequence

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## Phylogenies and genome rearrangements

- Hunting for human genes may be a slow, laborious, and expensive process
  - Study similar genetic disorders in animals to get insight into the problem
  - Example
    - Waardenburg's syndrome is an inherited genetic disorder (hearing loss and pigmentary dysplasia) – studied in mice (through breeding) and isolated on mouse Chromosome 2
    - Down syndrome is also caused by abnormal genetic rearrangements

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### Motivation

- High interest in comparing the genes of different species
- **One approach:** analyze the point mutations of one single gene (or a small number of genes) and establish *phylogenetic trees* – trees representing evolutionary distances among species
  - Sometimes this approach does not work
  - Example: the gene sequences of *Brassica oleracea* (cabbage) and *Brassica campestris* (turnip) are 99% identical, however the gene order differs dramatically
- **Another approach** – genome comparison
  - Combinatorial "puzzle": find a series of rearrangements that transform one genome into another
    - Cabbage to turnip: 3 rearrangements are enough
    - Another example: mouse X chromosome transformed into human X chromosome by 6 rearrangements (typical for X chromosome in mammals)

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### Operations on chromosomes

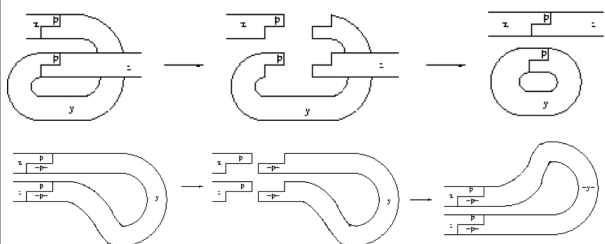
- On a single chromosome
  - Deletions
  - Insertions
  - Duplications
  - Reversals
  - Transpositions( two adjacent parts change places)
- On two chromosomes
  - Translocations (two chromosomes change their "tails")
  - Fusion (two chromosomes merge)
  - Fissions (one chromosome splits in two chromosomes)
- How do they happen?
  - Two similar regions hybridize
  - Insertions of foreign DNA
  - Duplication during erroneous cell mitosis

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### Genome rearrangements



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### Genome rearrangements

- In some cases (chloroplast in various plants, mitochondrial genomes), a single type of rearrangement event appears to have been used: *the reversal*

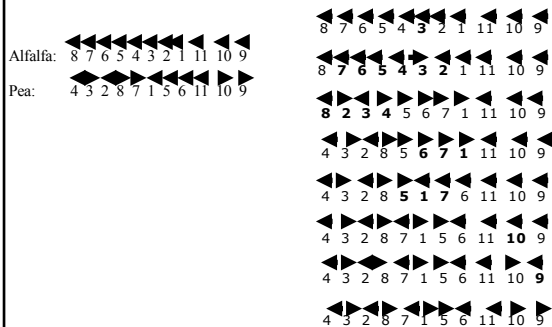
- Example:
  - Chloroplast genome in alfalfa (a plant)
    - 8 7 6 5 4 3 2 1 11 10 9
  - Chloroplast genome in pea
    - 4 3 2 8 7 1 5 6 11 10 9

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### Example: transforming alfalfa into pea



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### Modeling genome rearrangements

- Operations: exchanging various pieces of chromosomes – moving, copying, cutting and pasting of large sequences of DNA
- **Problem:** analyze the evolutionary distance between two species through the number of rearrangements needed to transform one into the other
  - This also gives insight when inferring predictions on one species based on experiments on another species
- **Model:** the combinatorial problem of sorting by reversals
  - Also known in Computer Science: sorting by prefix reversals (pancake flipping problem)

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## Sorting by reversals

- Two permutations
  - $(p_1, p_2, \dots, p_n), (q_1, q_2, \dots, q_n)$  of the set  $\{1, 2, \dots, n\}$  are given.
- A reversal  $r(i, j)$  is the permutation  $(1, 2, \dots, i-1, j, j-1, \dots, i+1, i, j+1, \dots, n)$
- The composition  $p \cdot r(i, j)$  is the permutation  $(p_1, p_2, \dots, p_{i-1}, p_j, p_{j-1}, \dots, p_{i+1}, p_i, p_{j+1}, \dots, p_n)$
- The reversal distance between the permutations  $p$  and  $q$  is the minimal number of reversals needed to transform  $p$  into  $q$
- Sorting  $p$  by reversals:** find the reversal distance between  $p$  and the identity permutation  $(1, 2, \dots, n)$  – denoted by  $d(p)$

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## The genomic data

- The data for studying genome rearrangements comes usually from two sources:
  - Physical maps
    - This leads to unsigned (usual) permutations: the direction of the genes in the two species is not specified
  - DNA sequencing
    - This leads to signed permutations: the direction of genes is specified
    - Each number in the permutation has a sign (+ or -) associated (or an arrow to the left or to the right)
    - Applying a reversal  $r(i, j)$  changes all signs (or direction of arrows) from position  $i$  to position  $j$  in the permutation

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## Unsigned permutations

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## Unsigned permutations

- Model: (unsigned) permutations
- Sorting unsigned permutations is easy
  - Trivial algorithm where each number is placed on its correct position works in linear time
- Problem: find the *minimal* number of reversals needed to sort the permutation
- Result: NP-hard (Caprara, 1997)
- Good approximations exist
  - 2-approximation (1995)
  - 1.75-approximation (1996)
  - 1.5-approximation (1998)
  - 1.375-approximation (1998)

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## Sorting unsigned permutations: a 2-approximation

- Breakpoint of a permutation: any place in the sequence where the two adjacent numbers are not consecutive; for convenience, consider the extended version of the permutation: starts with L and ends with R
  - Example: 123654 has a breaking point between 3 and 6 – denote L.123.654.R
- Clearly, a reversal can remove at most 2 breakpoints
  - Let  $b(p)$  be the number of breaking points in  $p$  and  $d(p)$  the number of reversals needed to sort  $p$
  - Result:  $b(p)/2 \leq d(p) \leq n-1$
- Strip:** a maximal subsequence without breakpoints (contains only consecutive numbers, in decreasing or increasing order)
  - Example: L.7 6.4.1.9 8.2 3.5.10 – 7 6, 2 3, 9 8, 10, 1, 4, L, R are strips
  - Strips: increasing or decreasing: L, R are considered increasing strips, all the other singleton strips are both increasing and decreasing

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## Sorting unsigned permutations

- Idea: Try to reduce the number of breakpoints in each step – the identity permutation has no breakpoints: L 1234...n R
  - If the permutation has a decreasing strip, take a reversal that reduces the number of breakpoints AND leaves a decreasing strip. If no such reversal exists, there is a reversal that removes two breakpoints
  - When the permutation has no decreasing strip, simply cut on the first two breakpoints – this will leave the number of breakpoints unchanged but will create decreasing strips
- Algorithm: Sorting Unsigned Permutations**
  - Input: permutation  $p$
  - Output: sequence of reversals sorting  $p$
  - List of reversals = empty
  - While  $p \neq$  identity permutation do
    - if  $p$  has a decreasing strip then
      - $k$  = the smallest label in a decreasing strip
      - $r$  = the reversal that cuts after  $k$  and after  $k-1$
      - if  $p \cdot r$  has no decreasing strip then
        - $l$  = the largest label in a decreasing strip
        - $r$  = the reversal that cuts before  $l$  and before  $l+1$
      - else  $r$  = the reversal that cuts between the first two breakpoints
    - $p = p \cdot r$
    - list = list +  $r$
  - Endwhile
  - Return list

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## Sorting unsigned permutation

- Observations:
  - If label  $k$  belongs to a decreasing strip and  $k-1$  belongs to an increasing strip, then there is a reversal that removes at least one breakpoint (take the reversal that cuts on the two breakpoints below)
    - $\dots(k-1)\underline{k}$  (flipping the underlined part will give a longer increasing strip)
    - $\dots k \underline{(k-1)}$  (flipping the underlined part will give a longer decreasing strip)
  - If label  $k$  belongs to a decreasing strip and  $k+1$  belongs to an increasing strip, then there is a reversal that removes at least one breakpoint (take the reversal that cuts on the two breakpoints below)
    - $\underline{k} \dots (k+1) \dots$  (flipping the underlined part will give a longer increasing strip)
    - $\underline{(k+1)} \dots k \dots$  (flipping the underlined part will give a longer decreasing strip)
- Conclusions: as long as we still preserve some decreasing strips, we can choose reversals as above

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## Sorting unsigned permutation

- If all reversals that remove breakpoints from the permutation leave no decreasing strips, then there is a reversal that removes two breakpoints
  - Let  $k$  be the smallest label involved in a decreasing strip, thus  $k-1$  is involved in an increasing strip:  $\dots(k-1)\dots k$  - let  $r$  be the reversal that cuts on the two breakpoints shown here:  $\dots(k-1)\underline{k}$
  - Let  $l$  be the largest label involved in a decreasing strip, thus  $l+1$  is involved in an increasing strip:  $\dots(l+1)\dots$  - let  $s$  be the reversal that cuts on the two breakpoints shown here:  $\underline{l} \dots (l+1) \dots$
  - The strip containing  $k$  must be inside the interval reversed by  $s$ , otherwise  $s$  leaves the permutation with a decreasing strip. Similarly,  $l$  must be inside the interval reversed by  $r$ :  $\dots(k-1)\dots$   $\dots k$   $\dots(l+1)\dots$
  - Easy to see now that  $l$  is adjacent to  $k-1$  and  $k$  is adjacent to  $l+1$ :  $\dots(k-1)\dots \dots k \dots (l+1) \dots$ . If this was not true, then there was a strip between  $(k-1)$  and  $l$  (or between  $k$  and  $l+1$ ) - that strip is made decreasing either by  $r$ , or by  $s$
  - The reversal inverting the interval between the two breakpoints above removes two breakpoints from the permutation:  $\dots(k-1)\underline{k} \dots (l+1)\dots$   
 $\rightarrow \dots(k-1)k \dots \dots(l+1)\dots$

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## Sorting unsigned permutations: examples

- Example 1  
 $L: 8\ 7\ 6\ 5\ 4\ 3\ 2\ 1\ 11\ 10\ 9$ ,  $R: -1$  is the smallest label in a decreasing strip. Apply the inversion  $L: 8\ 7\ 6\ 5\ 4\ 3\ 2\ 1\ 11\ 10\ 9$ ,  $R$   
 $L: 1\ 2\ 3\ 4\ 5\ 6\ 7\ 8\ 11\ 10\ 9$ ,  $R: -9$  is the smallest label in a decreasing strip. Apply the inversion  $L: 1\ 2\ 3\ 4\ 5\ 6\ 7\ 8\ 11\ 10\ 9$ ,  $R$   
 $L: 1\ 2\ 3\ 4\ 5\ 6\ 7\ 8\ 9\ 10\ 11$ ,  $R$
- Example 2  
 $L: 4\ 3\ 2\ 8\ 7\ 1\ 5\ 6\ 11\ 10\ 9$ ,  $R: -1$  is the smallest label in a decreasing strip. Apply the inversion  $L: 4\ 3\ 2\ 8\ 7\ 1\ 5\ 6\ 11\ 10\ 9$ ,  $R$   
 $L: 1\ 7\ 8\ 2\ 3\ 4\ 5\ 6\ 11\ 10\ 9$ ,  $R: -9$  is the smallest label in a decreasing strip. Apply the inversion  $L: 1\ 7\ 8\ 2\ 3\ 4\ 5\ 6\ 11\ 10\ 9$ ,  $R$   
 $L: 1\ 7\ 8\ 9\ 10\ 11\ 6\ 5\ 4\ 3\ 2$ ,  $R: -2$  is the smallest label in a decreasing strip. Apply the inversion  $L: 1\ 7\ 8\ 9\ 10\ 11\ 6\ 5\ 4\ 3\ 2$ ,  $R$   
 $L: 1\ 2\ 3\ 4\ 5\ 6\ 11\ 10\ 9\ 8\ 7$ ,  $R: -7$  is the smallest label in a decreasing strip. Apply the inversion  $L: 1\ 2\ 3\ 4\ 5\ 6\ 11\ 10\ 9\ 8\ 7$ ,  $R$   
 $L: 1\ 2\ 3\ 4\ 5\ 6\ 7\ 8\ 9\ 10\ 11$ ,  $R$
- Example 3  
 $L: 1\ 2\ 8\ 7\ 3\ 5\ 6\ 4$ ,  $R: -3$  is th  
 $L: 1\ 2\ 8\ 7\ 3\ 5\ 6\ 4$ ,  $R$   
 $L: 1\ 2\ 3\ 7\ 8\ 5\ 6\ 4$ ,  $R: -4$  is th  
 $L: 1\ 2\ 3\ 7\ 8\ 5\ 6\ 4$ ,  $R$   
 $L: 1\ 2\ 3\ 4\ 6\ 5\ 8\ 7$ ,  $R$   
 $L: 1\ 2\ 3\ 4\ 5\ 6\ 8\ 7$ ,  $R$   
 $L: 1\ 2\ 3\ 4\ 5\ 6\ 7\ 8$ ,  $R$

```

Algorithm: Sorting Unsigned Permutations
List of reversals=empty
While p ≠ identity do
  if p has a decreasing strip then
    k=the smallest label in a decreasing strip
    r=the reversal that cuts after k and after k-1
    if p.r has no decreasing strip then
      l=the largest label in a decreasing strip
      r=the reversal that cuts before l and before l+1
    else r=the reversal that cuts between the first two breakpoints
    p=p.r
  list=list+r
Return list
    
```

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## Sorting unsigned permutations

- The number of iterations in the algorithm is less than or equal to the number of breakpoints in the initial permutation
  - We must prove that in average each iteration removes at least one breakpoint
  - The only difficulty is caused by the reversals chosen when there are no decreasing strips - no breakpoints are removed there. Still, in the previous iteration we have removed two breakpoints
  - The argument above does not work for the first iteration, still the last iteration removes two breakpoints

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## Signed permutations

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## Signed permutations

- Model: signed permutations

- Example:



- Problem: find the minimal number of reversals sorting the permutation

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## Signed permutations

- Possible to reduce the problem to unsigned permutations
  - Each positive element  $+x$  is replaced by  $2x-1$ ,  $2x$
  - Each negative element  $-x$  is replaced by  $2x$ ,  $2x-1$
  - Instead of a signed permutation of  $1\dots n$ , we get an unsigned permutation of  $1\dots 2n$
  - Example: the signed permutation on the previous slide translates to  $1\ 2\ 4\ 3\ 5\ 8\ 7\ 9\ 10$
- Quick algorithms for the optimal sort exist.
- **Result:** there exist polynomial (quadratic) algorithms to sort a signed permutation
- Give in this lecture an intuitive algorithm in  $O(n^3)$  (Bergeron, 2001)

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## Sorting signed permutations

- The permutation is from 1 to  $n$ , add 0 in front and  $n+1$  in the end  $p=(0\ p_1\ p_2\ \dots\ p_n\ n+1)$
- An oriented pair  $(p_i, p_j)$  is a pair of consecutive integers with opposite signs ( $p_i+p_j$  is 1 or -1)
  - Example:  $(0\ 3\ 1\ 6\ 5\ -2\ 4\ 7)$  has two oriented pairs:  $(1,-2)$  and  $(-2,3)$
- An oriented pair is useful because it indicates reversals (called oriented reversals) that create consecutive elements of the permutation.
  - If  $p_i+p_j=1$ , the reversal is  $(i,j-1)$  (invert the substring from position  $i$  to position  $j-1$ )
  - If  $p_i+p_j=-1$ , the reversal is  $(i+1,j)$
  - $(1,-2)$  indicates the reversal  $(0\ 3\ 1\ 6\ 5\ -2\ 4\ 7) \rightarrow (0\ 3\ 1\ 2\ -5\ -6\ 4\ 7)$
  - $(-2,3)$  indicates the reversal  $(0\ 3\ 1\ 6\ 5\ -2\ 4\ 7) \rightarrow (0\ -5\ -6\ -1\ -3\ -2\ 4\ 7)$
- The score of an oriented reversal  $\rho$  is the number of oriented pairs in  $\rho(p)$ 
  - The score of the reversal  $(0\ 3\ 1\ 6\ 5\ -2\ 4\ 7)$  is 2:  $(0\ 3\ 1\ 2\ -5\ -6\ 4\ 7)$
  - The score of the reversal  $(0\ 3\ 1\ 6\ 5\ -2\ 4\ 7)$  is 4:  $(0\ -5\ -6\ -1\ -3\ -2\ 4\ 7)$

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## Sorting signed permutations

- **Algorithm to optimally sort a permutation with oriented pairs**
- **As long as the permutation has an oriented pair, choose an oriented reversal with maximum score**

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## Sorting signed permutations

- Example:
  - $(0\ 3\ 1\ 6\ 5\ -2\ 4\ 7)$  has two oriented pairs:  $(1,-2)$  and  $(3,-2)$  with scores 2 and 4 – choose the reversal induced by  $(3,-2)$ :  
 $(0\ 3\ 1\ 6\ 5\ -2\ 4\ 7) \rightarrow (0\ -5\ -6\ -1\ -3\ -2\ 4\ 7)$
  - $(0\ -5\ -6\ -1\ -3\ -2\ 4\ 7)$  has the following oriented pairs:
    - $(0,-1)$  with score 2:  $(0\ -5\ -6\ -1\ -3\ -2\ 4\ 7) \rightarrow (0\ 1\ 6\ 5\ -3\ -2\ 4\ 7)$
    - $(-3,4)$  with score 4:  $(0\ -5\ -6\ -1\ -3\ -2\ 4\ 7) \rightarrow (0\ -5\ -6\ -1\ 2\ 3\ 4\ 7)$
    - $(4,-5)$  with score 2:  $(0\ -5\ -6\ -1\ -3\ -2\ 4\ 7) \rightarrow (0\ -5\ -4\ 2\ 3\ 1\ 6\ 7)$
    - $(-6,7)$  with score 2:  $(0\ -5\ -6\ -1\ -3\ -2\ 4\ 7) \rightarrow (0\ -5\ -4\ 2\ 3\ 1\ 6\ 7)$
    - Choose  $(-3,4)$
  - $(0\ -5\ -6\ -1\ 2\ 3\ 4\ 7)$  has the following oriented pairs:

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## Sorting signed permutations

- $(0\ -5\ -6\ -1\ 2\ 3\ 4\ 7)$  has the following oriented pairs:
  - $(0,-1)$  with score 0:  $(0\ -5\ -6\ -1\ 2\ 3\ 4\ 7) \rightarrow (0\ 1\ 6\ 5\ 2\ 3\ 4\ 7)$
  - $(-1,2)$  with score 2:  $(0\ -5\ -6\ -1\ 2\ 3\ 4\ 7) \rightarrow (0\ -5\ -6\ 1\ 2\ 3\ 4\ 7)$
  - $(4,-5)$  with score 2:  $(0\ -5\ -6\ -1\ 2\ 3\ 4\ 7) \rightarrow (0\ -5\ -4\ -3\ -2\ 1\ 6\ 7)$
  - $(-6,7)$  with score 2:  $(0\ -5\ -6\ -1\ 2\ 3\ 4\ 7) \rightarrow (0\ -5\ -4\ -3\ -2\ -1\ 6\ 7)$
  - Choose  $(-1,2)$
- $(0\ -5\ -6\ 1\ 2\ 3\ 4\ 7)$  has the following oriented pairs:
  - $(4,-5)$  with score 2:  $(0\ -5\ -6\ 1\ 2\ 3\ 4\ 7) \rightarrow (0\ -5\ -4\ -3\ -2\ -1\ 6\ 7)$
  - $(-6,7)$  with score 2:  $(0\ -5\ -6\ 1\ 2\ 3\ 4\ 7) \rightarrow (0\ -5\ -4\ -3\ -2\ -1\ 6\ 7)$
  - Choose  $(4,-5)$
- $(0\ -5\ -4\ -3\ -2\ -1\ 6\ 7)$  has the following oriented pairs:
  - $(0,-1)$  with score 0:  $(0\ -5\ -4\ -3\ -2\ -1\ 6\ 7) \rightarrow (0\ 1\ 2\ 3\ 4\ 5\ 6\ 7)$
  - $(-5,6)$  with score 0:  $(0\ -5\ -4\ -3\ -2\ -1\ 6\ 7) \rightarrow (0\ 1\ 2\ 3\ 4\ 5\ 6\ 7)$
- The original permutation  $(0\ 3\ 1\ 6\ 5\ -2\ 4\ 7)$  can be sorted optimally in 5 steps

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## Sorting signed permutation

- Example:
  - $(0\ 3\ 4\ -2\ -5\ 1\ 6)$  has the following oriented pairs:  $(-2,3)$  with score 2,  $(1,-2)$  with score 2, and  $(4,-5)$  with score 0- choose  $(-2,3)$ :  $(0\ 3\ 4\ -2\ -5\ 1\ 6) \rightarrow (0\ -4\ -3\ -2\ -5\ 1\ 6)$
  - $(0\ -4\ -3\ -2\ -5\ 1\ 6)$  has the following oriented pairs:  $(1,-2)$  with score 2 and  $(-5,6)$  with score 2 – choose any of them (in fact, they are the same):  $(0\ -4\ -3\ -2\ -5\ 1\ 6) \rightarrow (0\ -4\ -3\ -2\ -1\ 5\ 6)$
  - $(0\ -4\ -3\ -2\ -1\ 5\ 6)$  has the following oriented pairs:  $(0,-1)$  with score 0 and  $(-4,5)$  with score 0 – choose any of them (they are the same):  $(0\ -4\ -3\ -2\ -1\ 5\ 6) \rightarrow (0\ 1\ 2\ 3\ 4\ 5\ 6)$

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