# Algorithms for Bioinformatics Autumn 2011

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# Lecture 3

## GREEDY ALGORITHMS AND GENOME REARRANGEMENTS

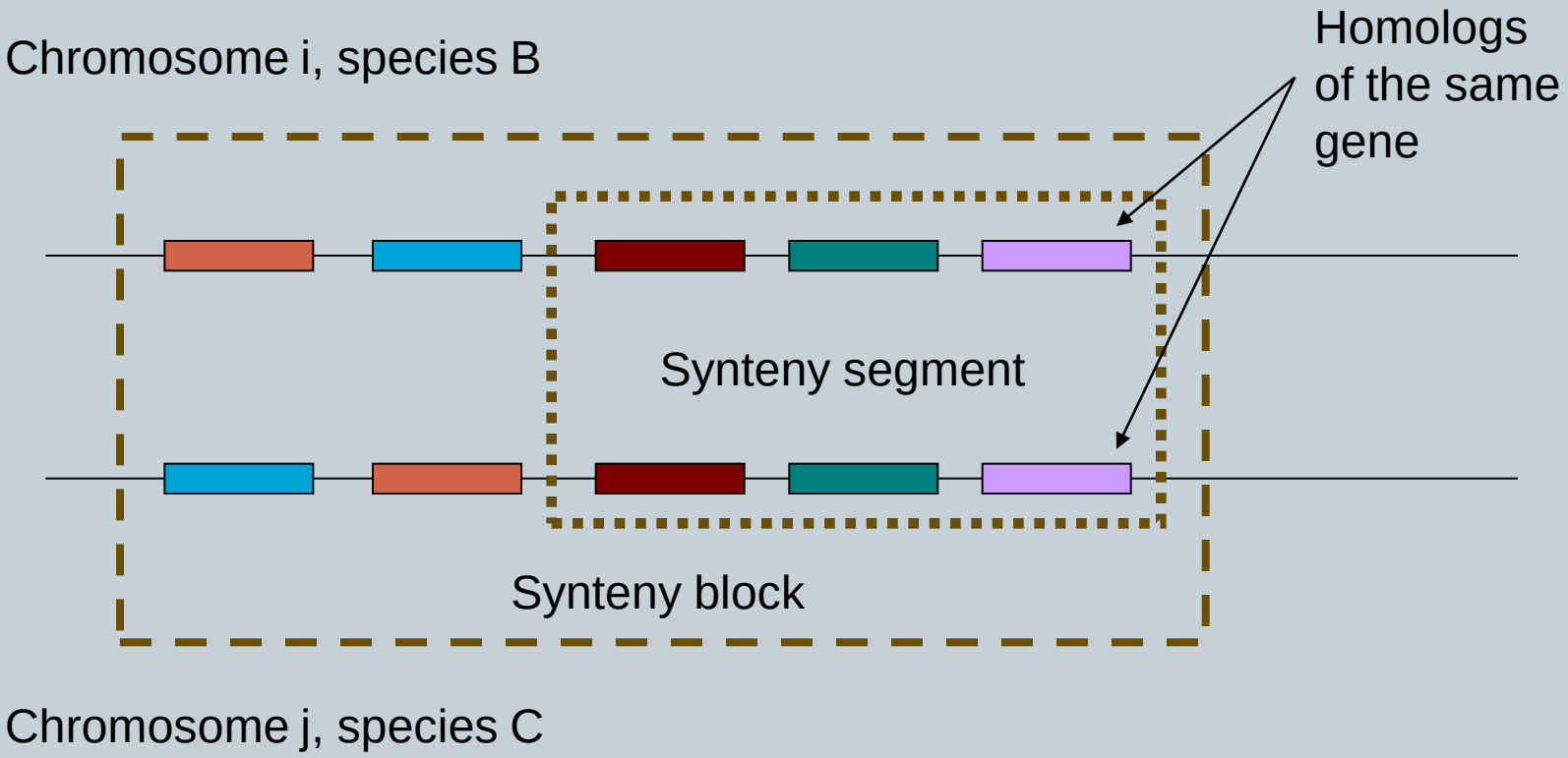
# Background

- Genome sequencing enables us to compare genomes of two or more different species
  - -> Comparative genomics
- Basic observation:
  - Closely related species (such as human and mouse) can be almost identical in terms of genome contents…
  - …but the order of genomic segments can be very different between species

# Synteny blocks and segments

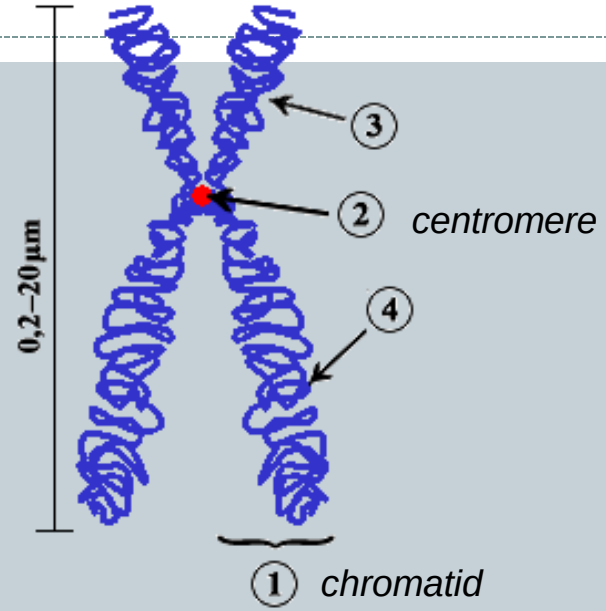
- Synteny – means genomic segments located on the same chromosome
  - Genes, markers (any sequence)
- Synteny block (or syntenic block)
  - A set of genes or markers that co-occur together in two species
- Synteny segment (or syntenic segment)
  - Syntenic block where the *order* of genes or markers is preserved

# Synteny blocks and segments

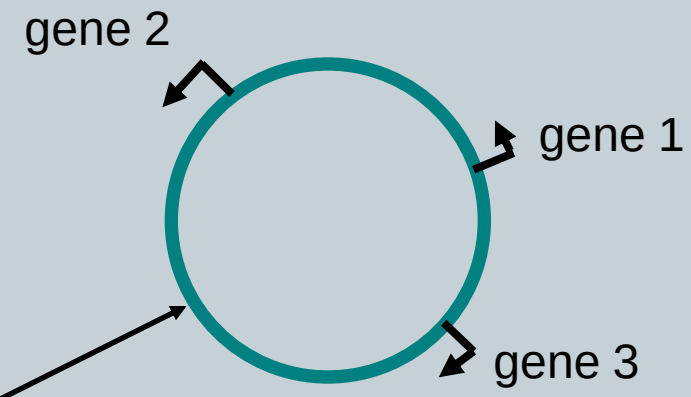


# Chromosomes

- Linear chromosomes
  - Eukaryotes (mostly)




- Circular chromosomes
  - Prokaryotes (mostly)
  - Mitochondria




Also double-stranded: genes can be found on both strands (*orientations*)

# Example: human vs mouse genome

- Human and mouse genomes share thousands of homologous genes, but they are
  - Arranged in different order
  - Located in different chromosomes
- Examples
  - Human chromosome 6 contains elements from six different mouse chromosomes
  - Analysis of X chromosome indicates that rearrangements have happened primarily *within* chromosome

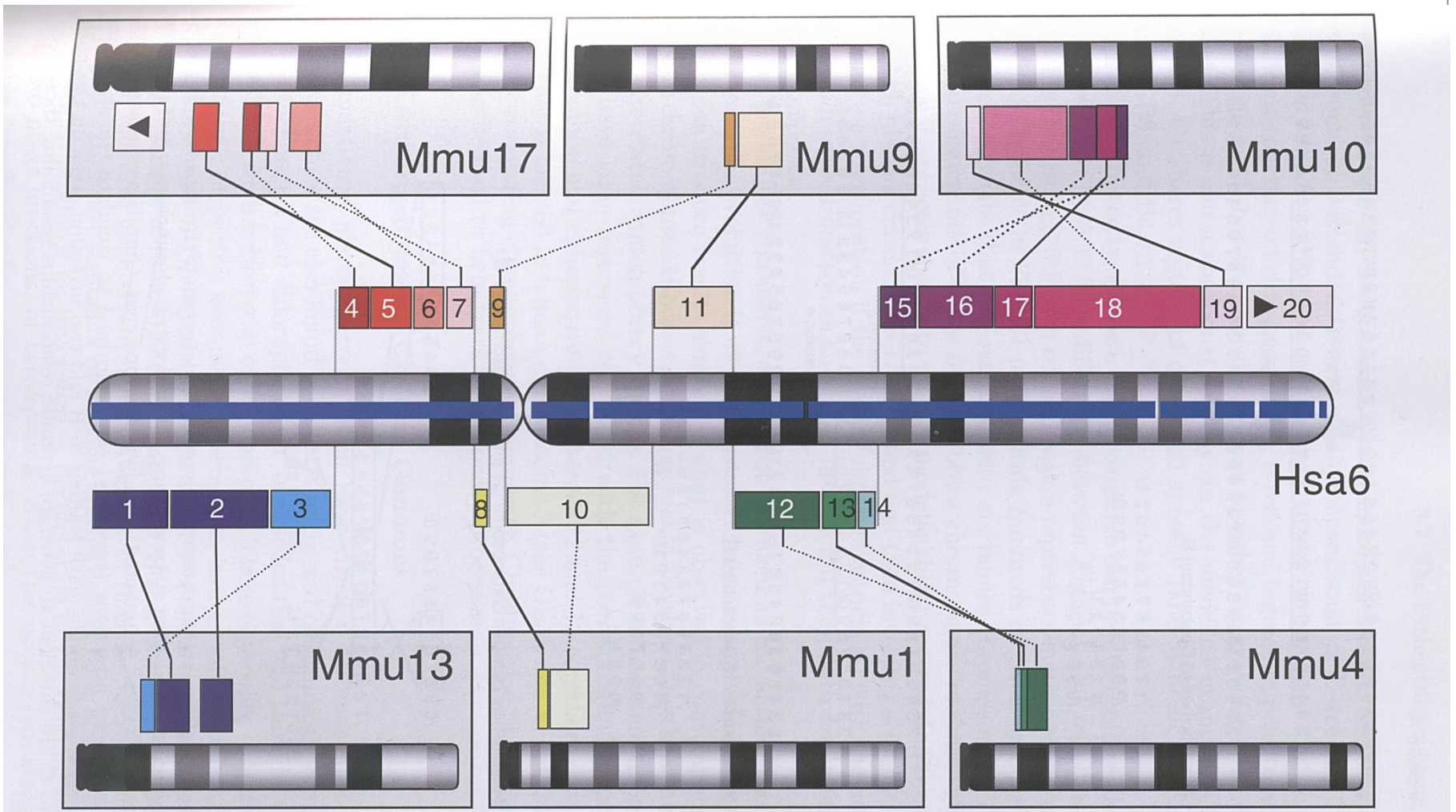



**Fig. 5.1.** Syntenic blocks conserved between human chromosome Hsa6 and mouse chromosomes. Broken lines indicate regions that appear in inverted orders in the two organisms. Reprinted, with permission, from Gregory SG et al. (2002) *Nature* 418:743–750. Copyright 2002 Nature Publishing Group.

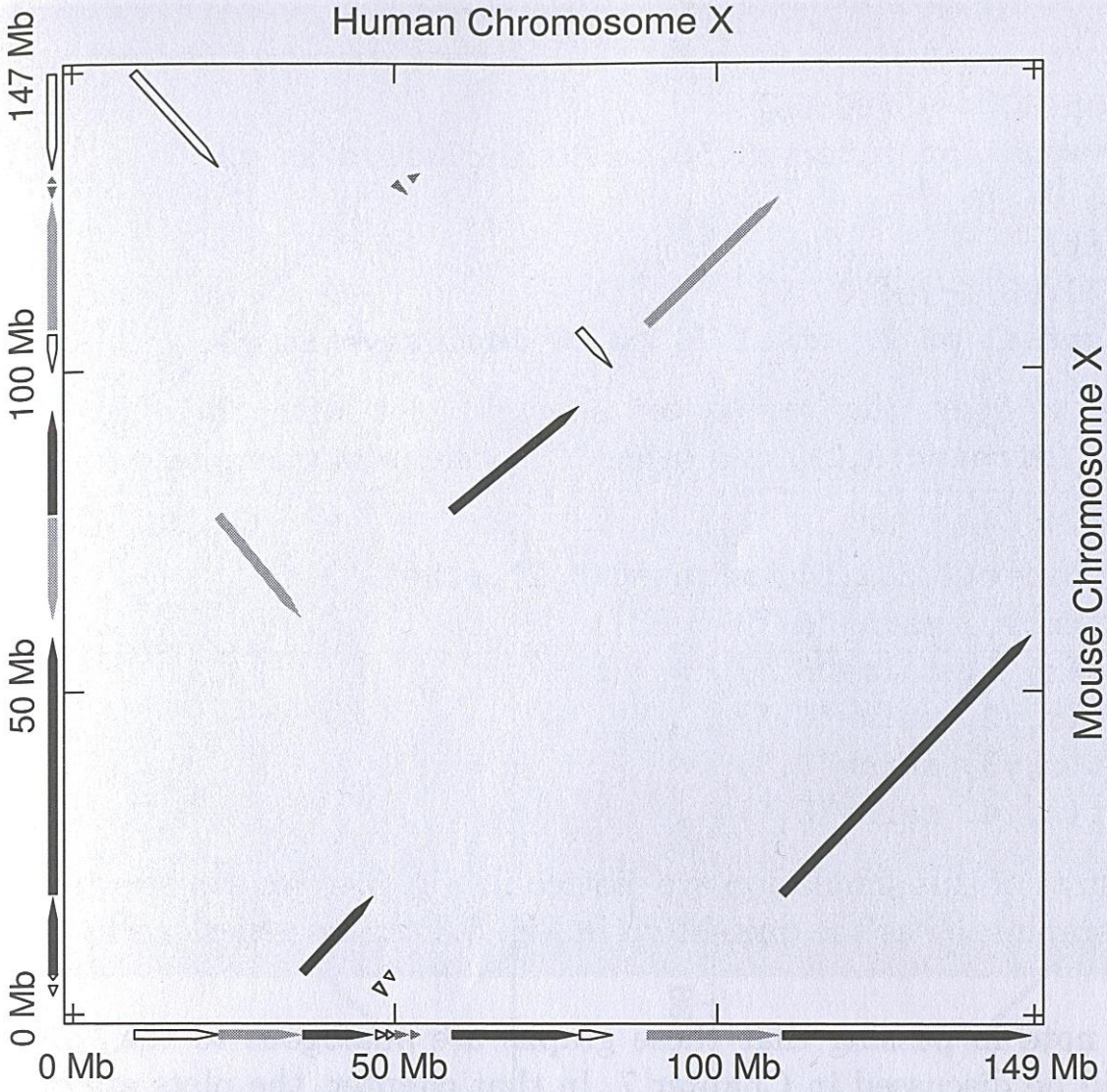



**Fig. 5.3.** Synteny blocks shared by human and mouse X chromosomes. The arrowhead for each block indicates the direction of increasing coordinate values for the human X chromosome. Reprinted, with permission, from Pevzner P and Tesler G (2003) *Genome Research* 13:37–45. Copyright 2003 Cold Spring Harbor Laboratory Press.

# Representing genome rearrangments

- When comparing two genomes, we can find homologous sequences in both using sequence comparison algorithms (next lecture).
- This gives us a map between sequences in both genomes

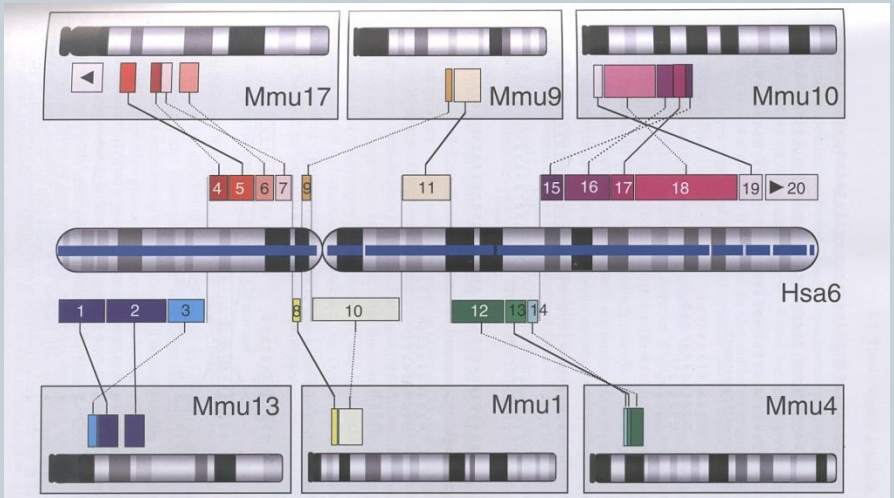



**Fig. 5.1.** Syntenic blocks conserved between human chromosome Hsa6 and mouse chromosomes. Broken lines indicate regions that appear in inverted orders in the two organisms. Reprinted, with permission, from Gregory SG et al. (2002) *Nature* 418:743–750. Copyright 2002 Nature Publishing Group.

# Representing genome rearrangments

- We assign numbers 1,…,n to the found homologous sequences
- By convention, we number the sequences in the first genome by their order of appearance in chromosomes
- If the homolog of *i* is in reverse orientation, it receives number *–i* (*signed data*)
- For example, consider human vs mouse gene numbering on the right

| **Human** | | **Mouse** | |
|---|---|---|---|
| 1 | (gnat2) | 12 | (inpp1) |
| 2 | (nras) | 13 | (cd28) |
| 3 | (ngfb) | 14 | (fn1) |
| 4 | (gba) | 15 | (pax3) |
| 5 | (pklr) | -9 | (il10) |
| 6 | (at3) | -8 | (pdc) |
| 7 | (lamc1) | -7 | (lamc1) |
| 8 | (pdc) | -6 | (at3) |
| 9 | (il10) | … | |
| … | | | |

List order corresponds to *physical order* on chromosomes!

# Permutations

- The basic data structure in the study of genome rearrangements is *permutation*
- A permutation of a sequence of *n* numbers is a reordering of the sequence
- For example, 4 1 3 2 5 is a permutation of 1 2 3 4 5

# Genome rearrangement problem

- Given two genomes (set of markers), how many
  - duplications,
  - inversions and
  - translocations

  do we need to do to transform the first genome to the second?

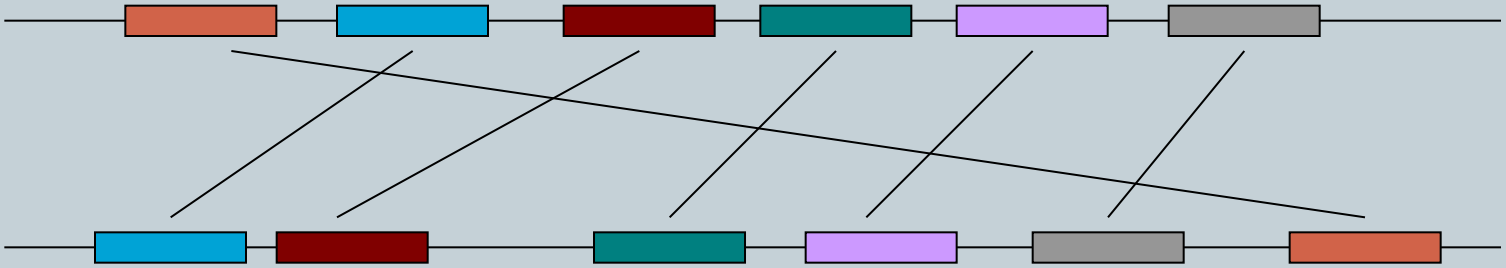
*Minimum number of operations?*

*What operations? Which order?*

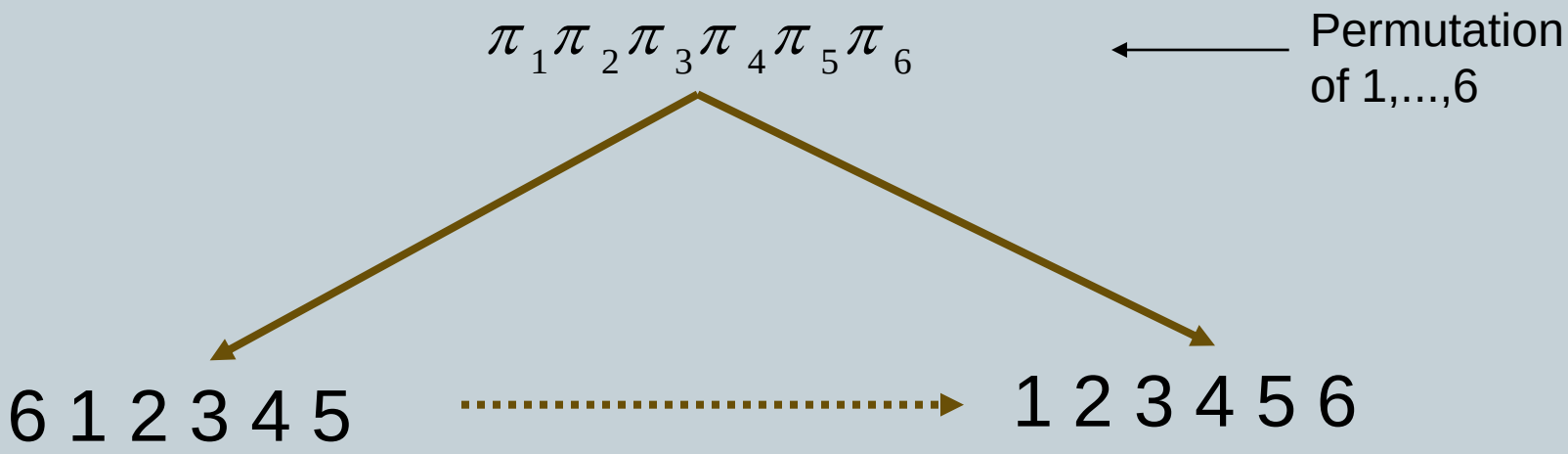
# Genome rearrangement problem

#duplications?
#inversions?
#translocations?

6 1 2 3 4 5 → 1 2 3 4 5 6



# Genome rearrangement problem



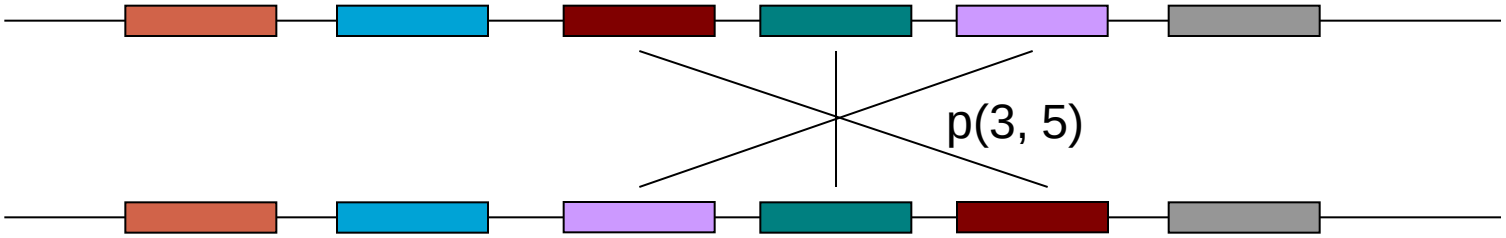

Keep in mind, that the two genomes have been evolved from a common ancestor genome!

# Genome rearrangements using reversals (=inversions) only

- Let's consider a "simpler" problem where we just study **reversals** with *unsigned data*
- A reversal p(i, j) reverses the order of the segment $\prod_i \prod_{i+1} \ldots \prod_{j-1} \prod_j$ (indexing starts from 1)
- For example, given permutation

  6 1 2 3 4 5 and reversal p(3, 5) we get permutation

  6 1 4 3 2 5




...note that we do not care about exact *positions* on the genome

# Reversal distance problem

- Find the shortest **series of reversals** that, given a permutation ∏, transforms it to the *identity* permutation (1, 2, …, n)
- This quantity is denoted by d(∏)

- Reversal distance for a pair of chromosomes:
  - Find synteny blocks in both
  - Number blocks in the first chromosome to identity
  - Set ∏ to correspond matching of second chromosome's blocks against the first
  - Find reversal distance

# Solving the problem by sorting

- Our first approach to solve the reversal distance problem:
  - Examine each position i of the permutation from left to right
  - At each position, if $\prod_i \neq i$, do a reversal such that $\prod_i = i$
- This is a *greedy* approach: we try to choose the best option at each step

# Simple reversal sort: example

6 1 2 3 4 5 -> 1 6 2 3 4 5 -> 1 2 6 3 4 5 -> 1 2 3 6 4 5

-> 1 2 3 4 6 5 -> 1 2 3 4 6 5

Reversal series: p(1,2), p(2,3), p(3,4), p(4,5), p(5,6)

Is d(6 1 2 3 4 5) then 5?

6 1 2 3 4 5 -> 5 4 3 2 1 6 -> 1 2 3 4 5 6

D(6 1 2 3 4 5) = 2

# How good is simple reversal sort?

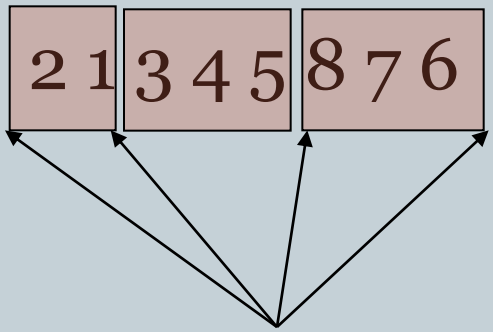
- Not so good actually
- It has to do at most n-1 reversals with permutation of length n
- The algorithm can return a distance that is as large as (n – 1)/2 times the correct result d(∏)
  - For example, if n = 1001, result can be as bad as 500 x d(∏)

# Computing reversals with breakpoints

- Lets investigate a better way to compute reversal distance
- First, some concepts related to permutation $\Pi_1\Pi_2,\ldots,\Pi_{n-1}\Pi_n$
  - Breakpoint: two elements $\Pi_i$ and $\Pi_{i+1}$ are a *breakpoint*, if they are not consecutive numbers
  - Adjacency: if $\Pi_i$ and $\Pi_{i+1}$ are consecutive, they are called *adjacency*

# Breakpoints and adjacencies

This permutation contains
four breakpoints *begin*-2, 13, 58, 6-*end* and
five adjacencies 21, 34, 45, 87, 76




Breakpoints

# Breakpoints

- Each breakpoint in permutation needs to be removed to get to the identity permutation (=our target)
  - Identity permutation does not contain any breakpoints


b(∏) = 4

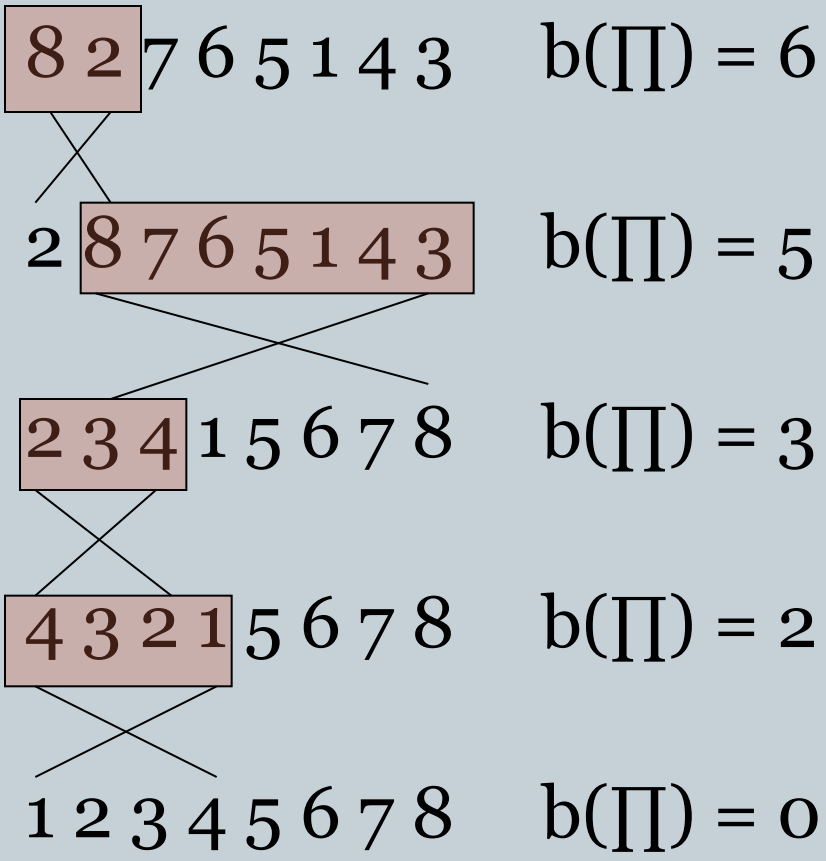
- First and last positions special cases
- Note that each reversal can remove *at most* two breakpoints
- Denote the number of breakpoints by b(∏)

# Breakpoint reversal sort

- Idea: try to remove as many breakpoints as possible (max 2) in every step

1. While b(∏) > 0
2. Choose reversal p that removes most breakpoints
3. Perform reversal p to ∏
4. Output ∏
5. return

# Breakpoint removal: example



# Breakpoint removal

- The previous algorithm needs refinement to be correct
- Consider the following permutation:

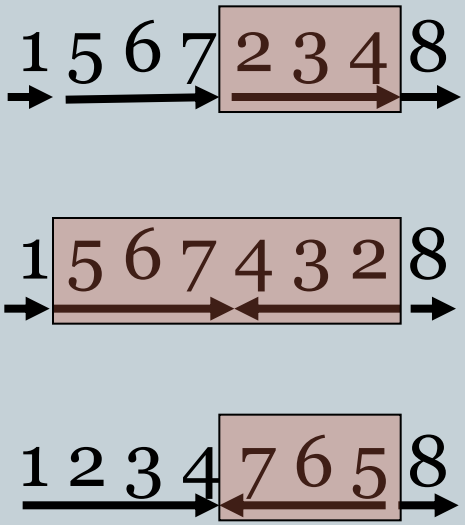
1 5 6 7 2 3 4 8

- There is no reversal that decreases the number of breakpoints!

# Breakpoint removal

- Reversal can always decrease breakpoint count if permutation contains *decreasing strips*

Strip: maximal segment without breakpoints




Increasing strip

Decreasing strip (including segments of length 1, except 1 and n if they are located at their correct locations)

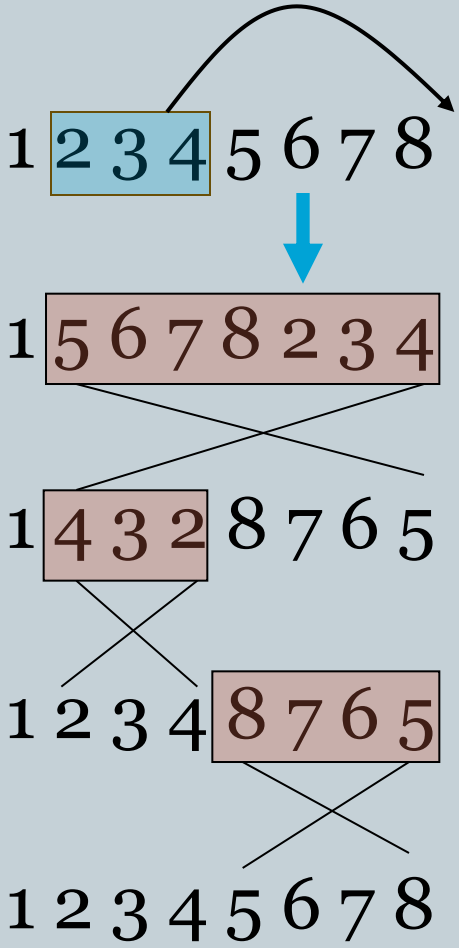
# Improved breakpoint reversal sort

1. While b(∏) > 0
2. If ∏ has a decreasing strip
3. Do reversal p that removes most BPs
4. Else
5. Reverse an increasing strip
6. Output ∏
7. return

# Is Improved BP removal enough?

- The algorithm works pretty well:
  - It produces a result that is at most **four** times worse than the optimal result
  - …is this good?
- We considered only reversals
- What about translocations & duplications?

# Translocations via reversals




Translocation of 2,3,4

p(2,8)

p(2,4)

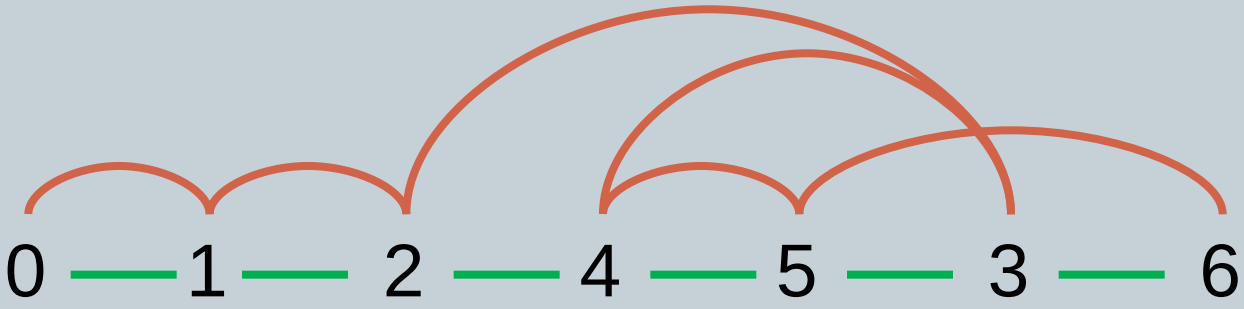
p(5,8)

# Genome rearrangements with reversals

- With *unsigned* data, the problem of finding minimum reversal distances is *NP-complete*
- An algorithm has been developed that achieves 1.375-approximation (Berman et al. ESA 2002)
- However, reversal distance in *signed data* can be computed quickly!
  - It takes linear time w.r.t. the length of permutation (Bader, Moret, Yan, 2001)
  - We will not cover that algorithm here, but give some insight into central concepts leading to it.

# Estimating reversal distance by cycle decomposition

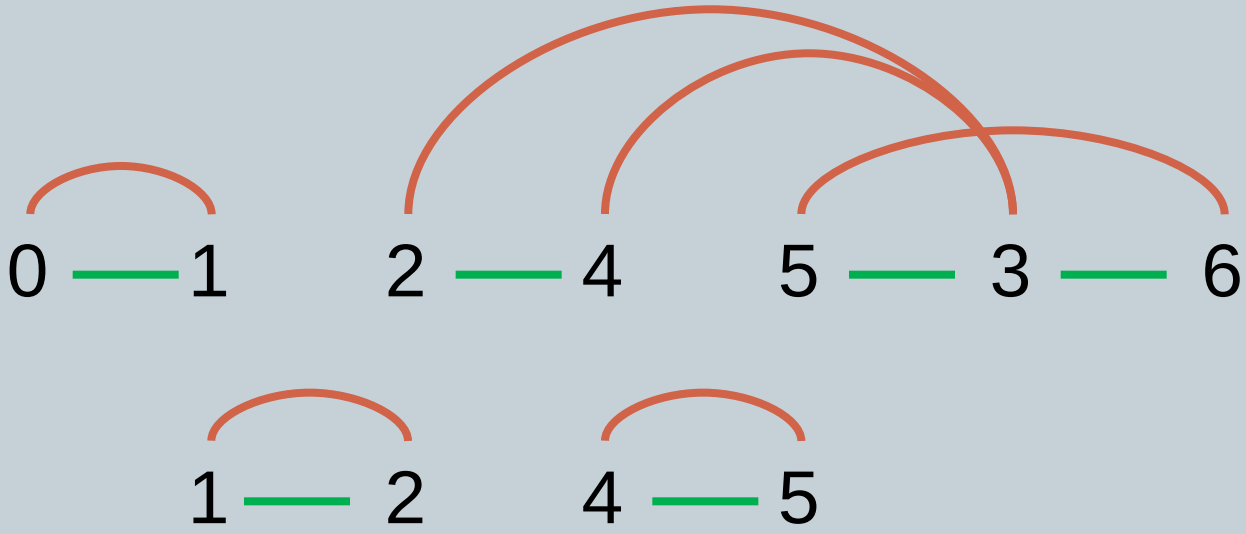
- We can estimate d(∏) by *cycle decomposition*
- Lets represent permutation ∏ = 1 2 4 5 3 with the following graph




where edges correspond to adjacencies (identity, permutation F)

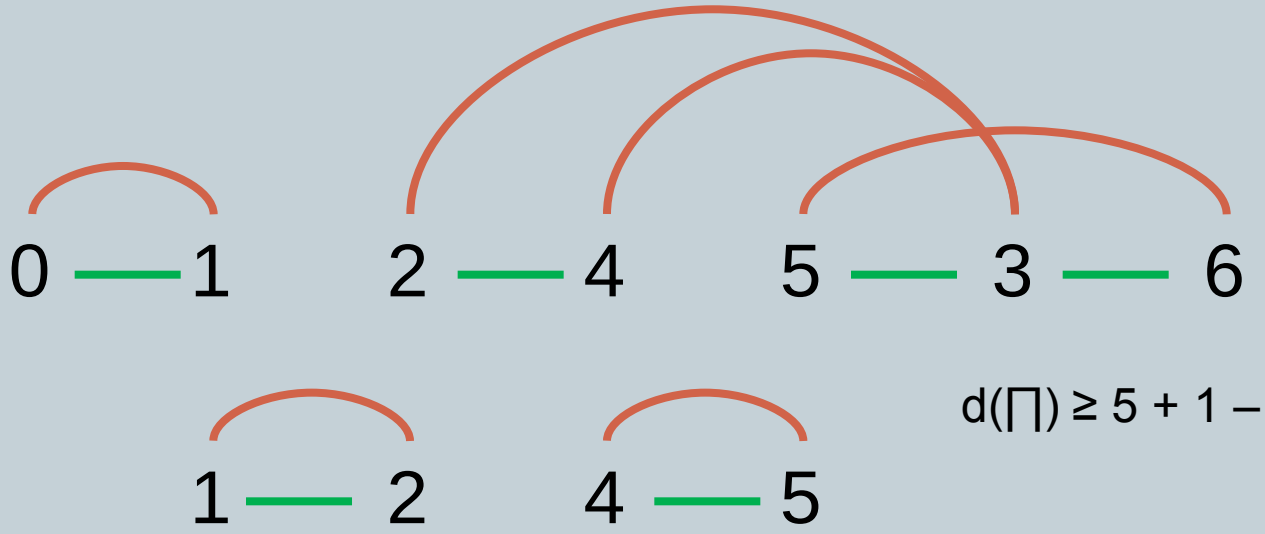
# Estimating reversal distance by cycle decomposition

- Cycle decomposition: a set of cycles that
  - have edges with alternating colors
  - do not share edges with other cycles (=cycles are edge disjoint)



# Cycle decompositions

- Let c(∏) the maximum number of alternating, edge-disjoint cycles in the graph representation of ∏
- The following formula allows estimation of d(∏)
  - d(∏) ≥ n + 1 – c(∏), where n is the permutation length



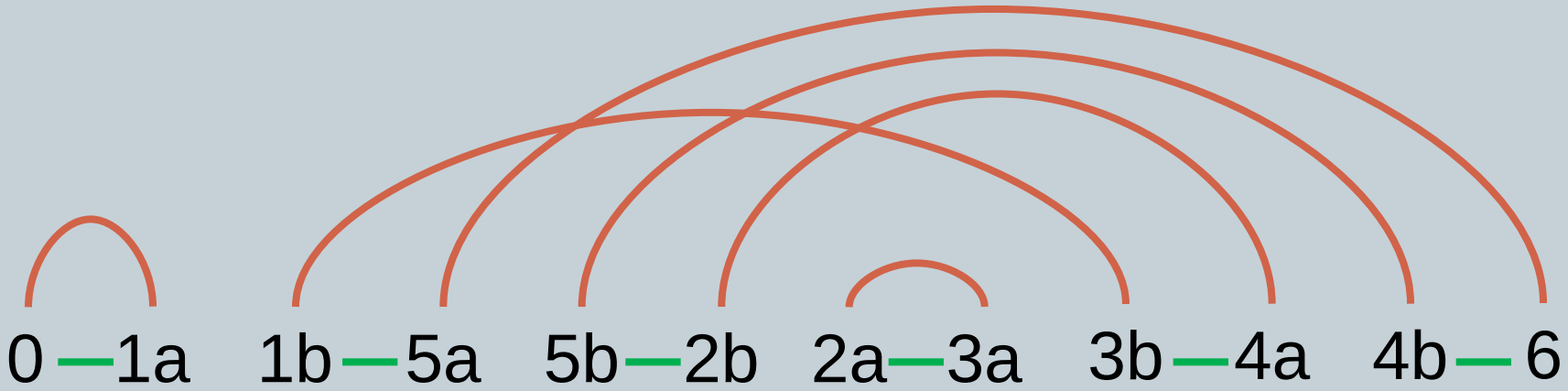
# Cycle decompositions

- Cycle decomposition is NP-complete
- However, with signed data cycle decomposition becomes a trivial task
  - Lead also to efficient (but rather involved) reversal distance algorithms on signed data.

# Cycle decomposition with signed data

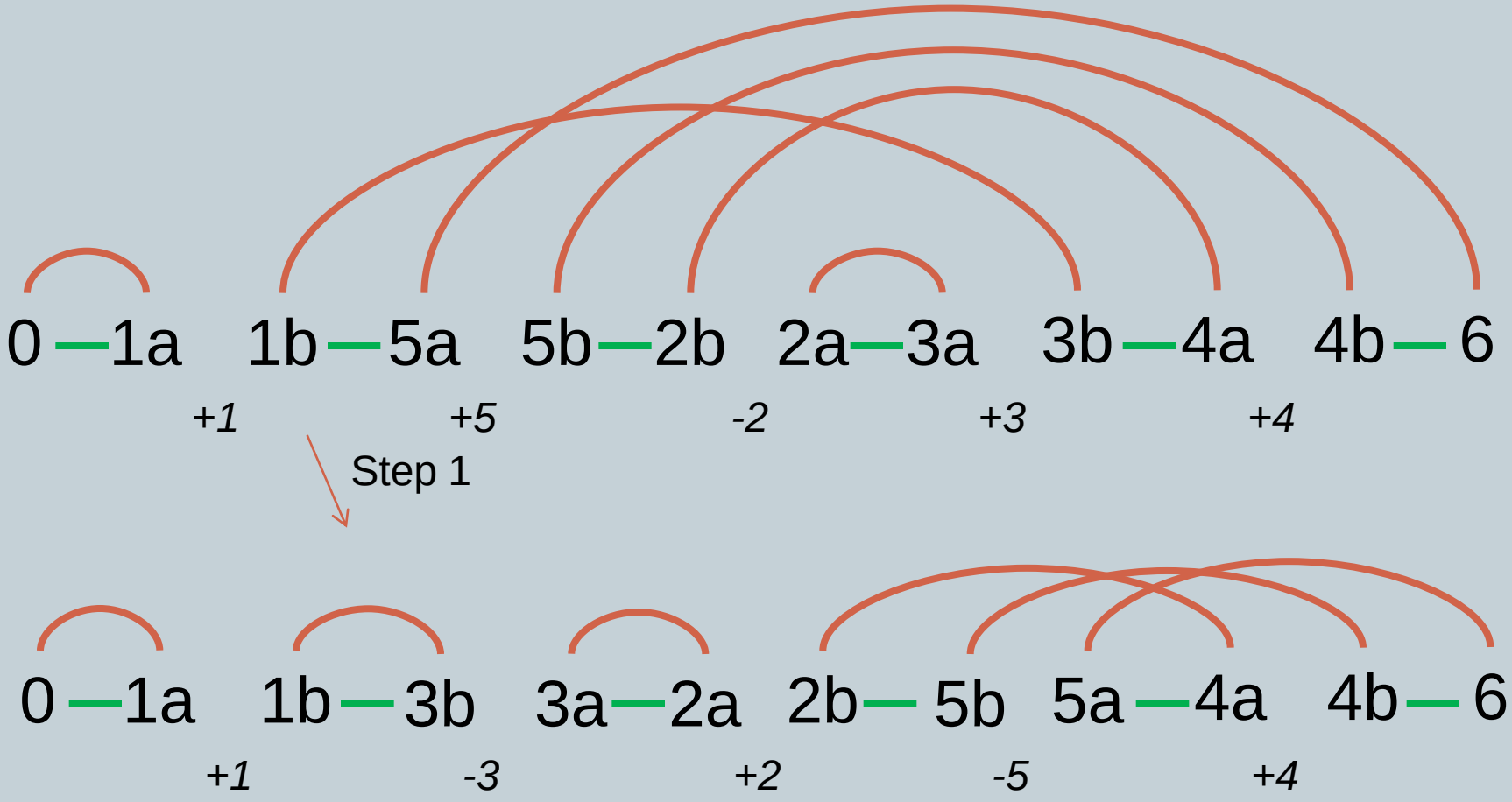
- Consider the following two permutations that include *orientation* of markers
  - *J: +1 +5 -2 +3 +4*
  - *K: +1 -3 +2 +4 -5*
- We modify this representation a bit to include both endpoints of each marker:
  - J': 0 1a 1b 5a 5b 2b 2a 3a 3b 4a 4b 6
  - K': 0 1a 1b 3b 3a 2a 2b 4a 4b 5b 5a 6

# Graph representation of J’ and K’

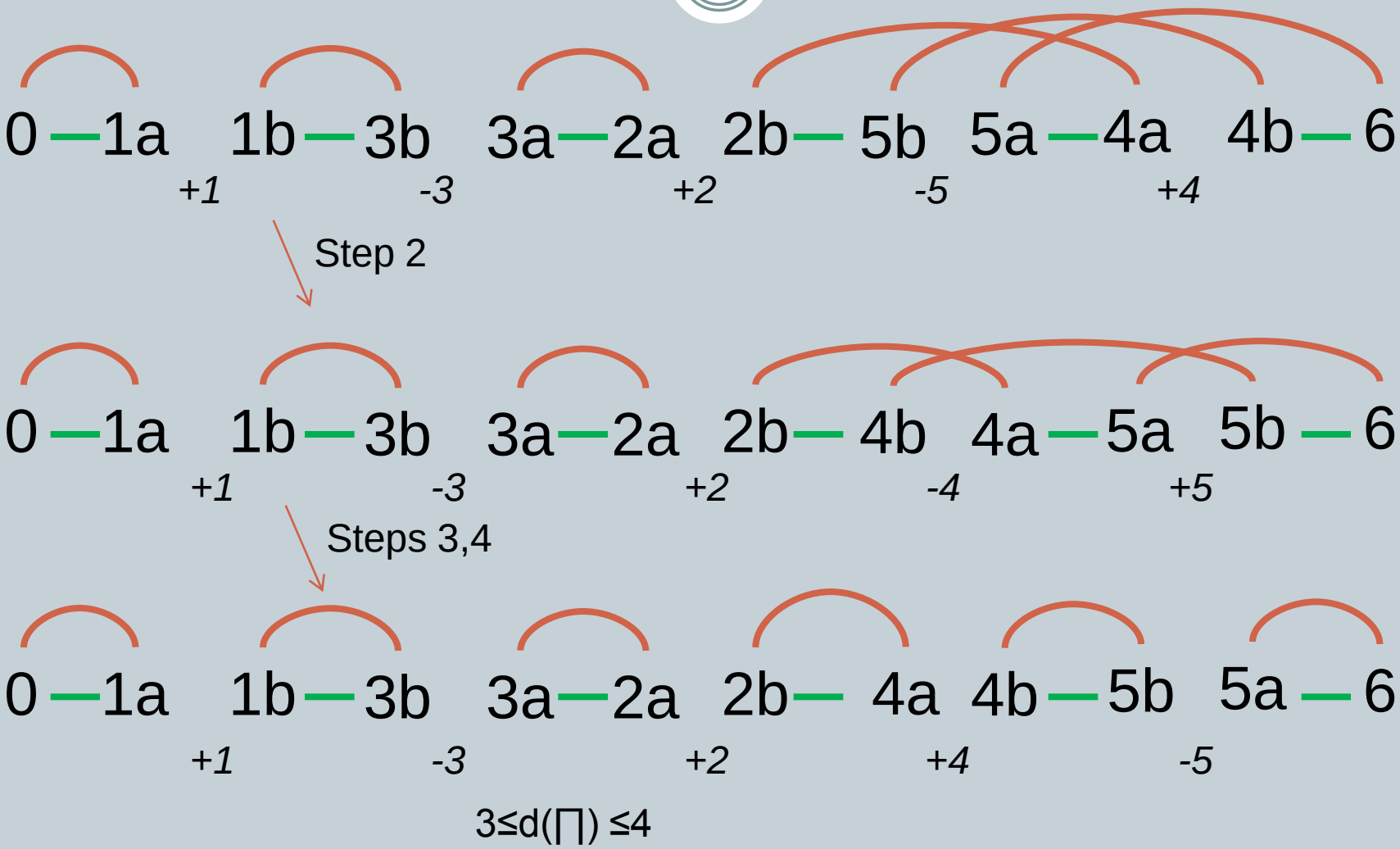



$d(\prod) \geq n + 1 - c(\prod) = 5+1-3=3$

# Reversal step 1 (ad hoc greedy algorithm)



# Reversal steps 2,3,4



# Multiple chromosomes

- In unichromosomal genomes, inversion (reversal) is the most common operation
- In multichromosomal genomes, inversions, translocations, *fissions* and *fusions* are most common

# Multiple chromosomes

- Let's represent multichromosomal genome as a set of permutations, with **$** denoting the boundary of a chromosome:

5 9 $ Chr 1

1 3 2 8 $ Chr 2

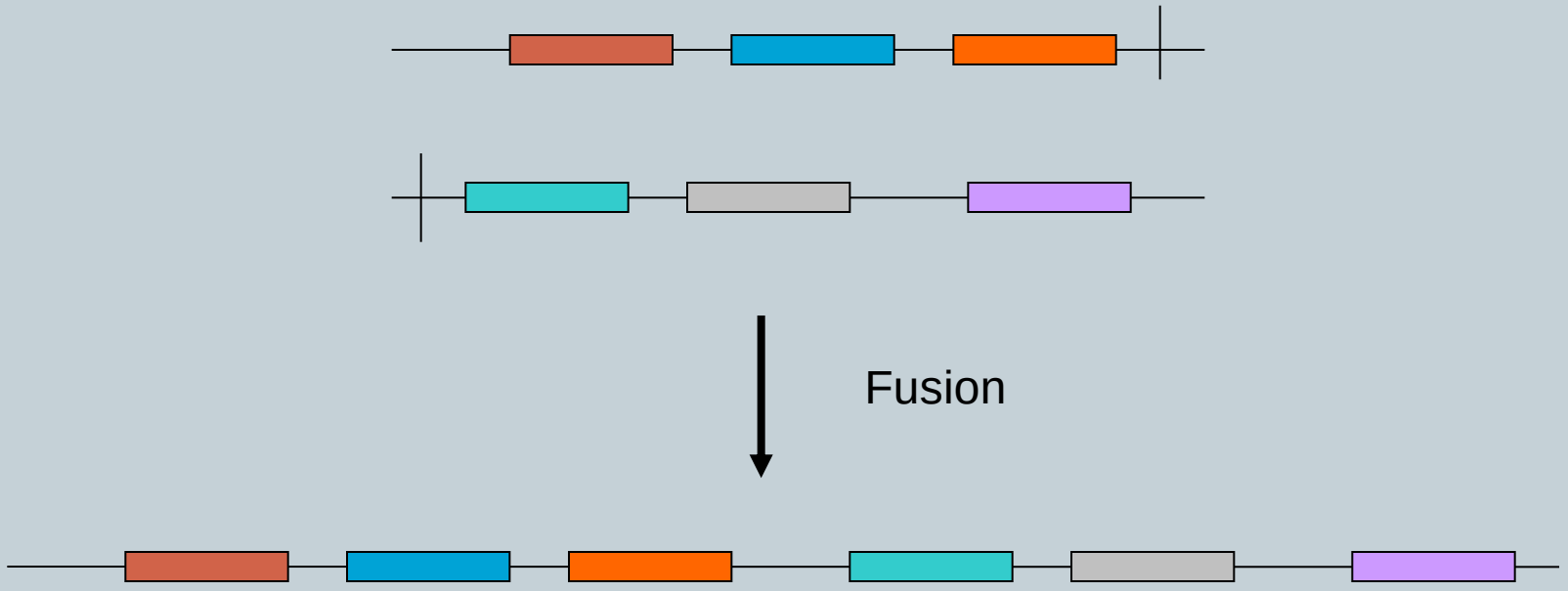
7 6 4 $ Chr 3

This notation is frequently used in software used to analyse genome rearrangements.

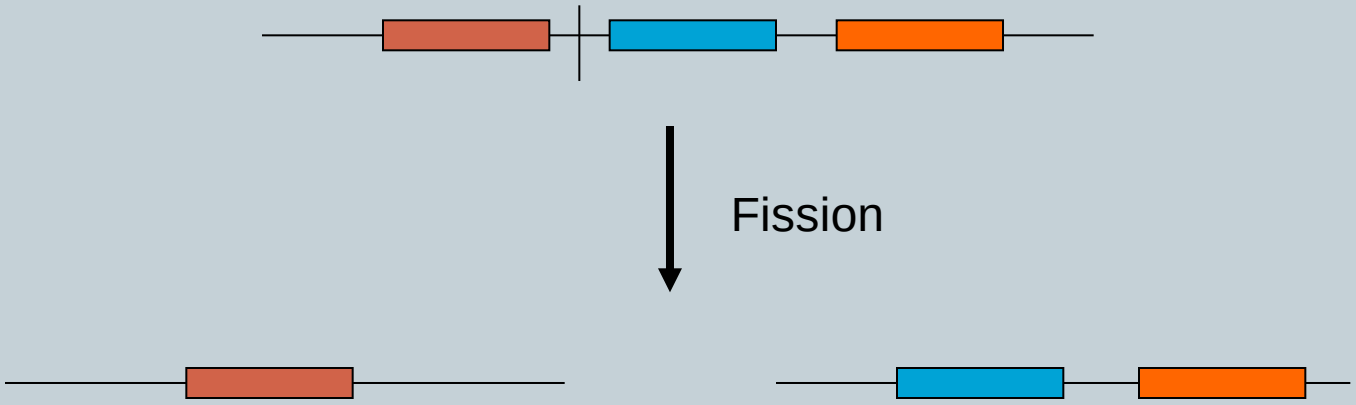
# Fusions & fissions

- Fusion: merging of two chromosomes
- Fission: chromosome is split into two chromosomes
- Both events can be represented with a translocation

# Fusion



# Fission



# Algorithms for general genomic distance problem

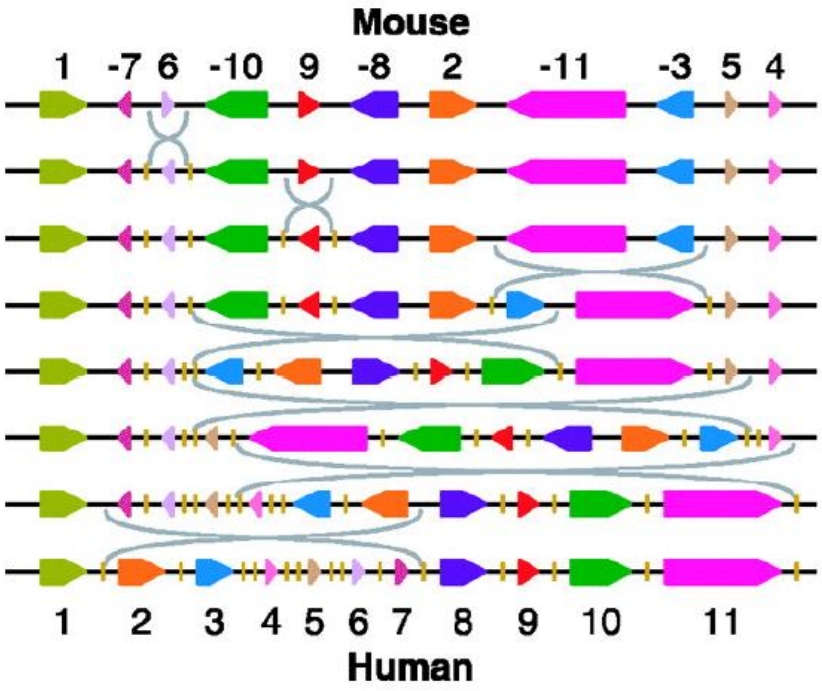
- Hannenhalli, Pevzner: Transforming Men into Mice (polynomial algorithm for genomic distance problem), *36th Annual IEEE Symposium on Foundations of Computer Science*, 1995

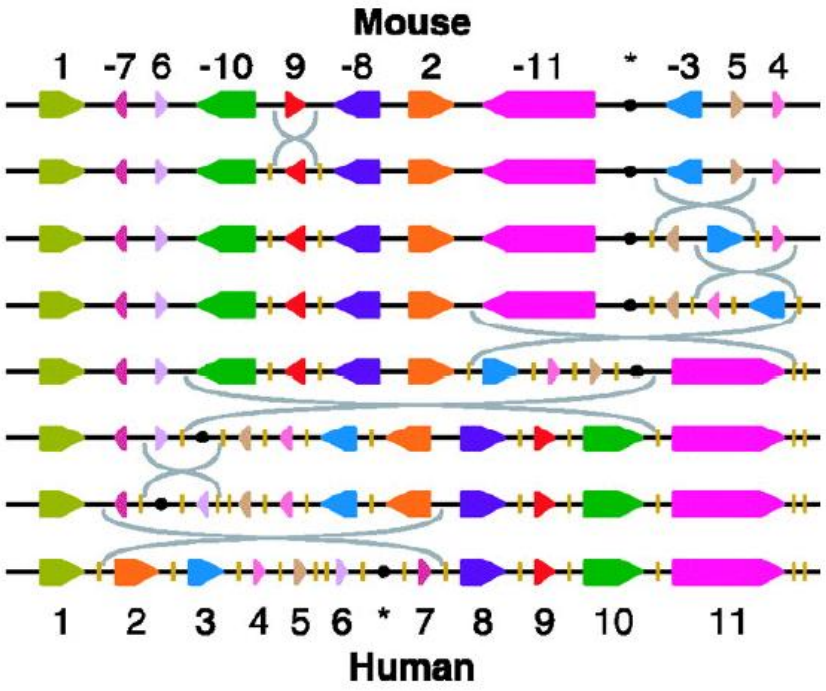
# Human & mouse revisited

- Human and mouse are separated by about 75-83 million years of evolutionary history
- Only a few hundred rearrangements have happened after speciation from the common ancestory
- Pevzner & Tesler identified in 2003 for 281 synteny blocks a rearrangement from mouse to human with
  - 149 inversions
  - 93 translocations
  - 9 fissions

# Discussion

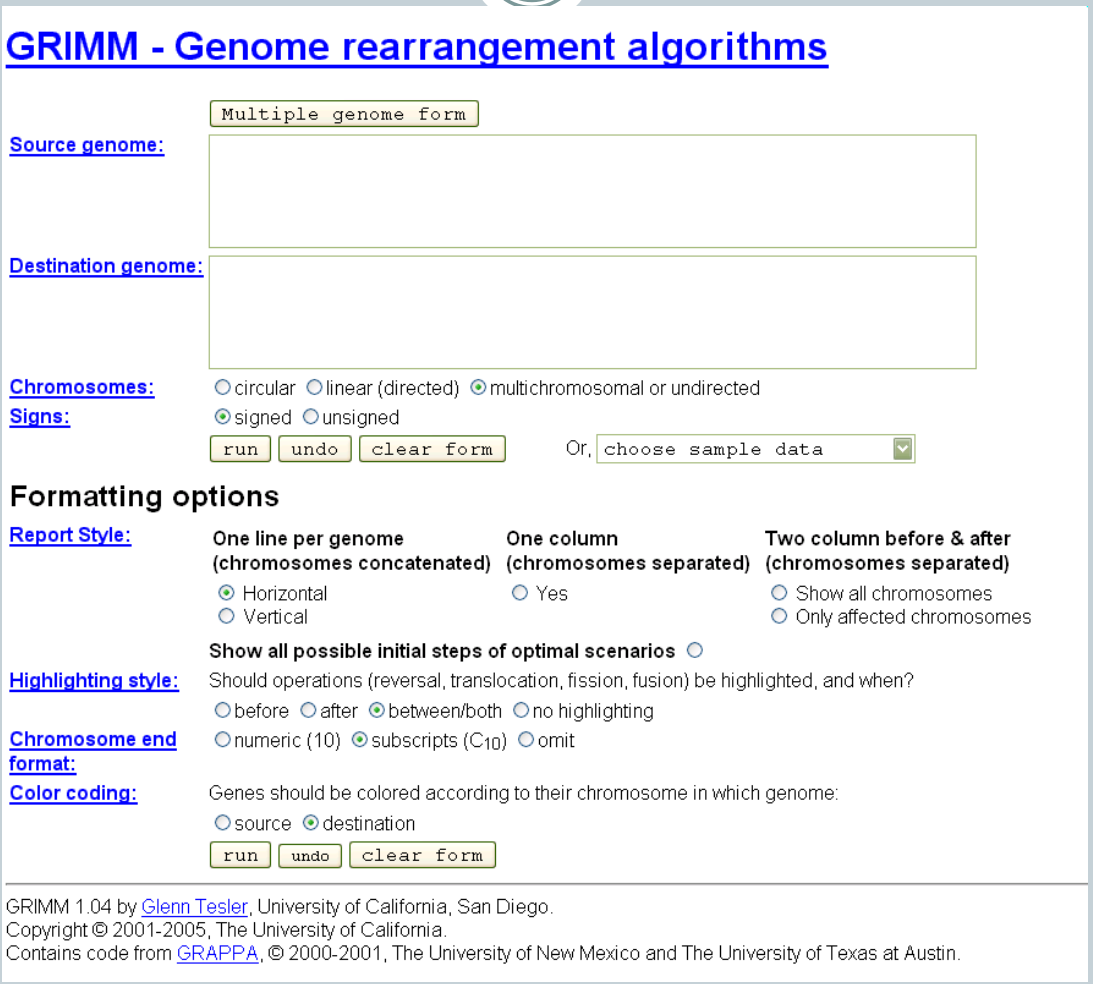
- Genome rearrangement events are very rare compared to, e.g., point mutations
  - We can study rearrangement events further back in the evolutionary history
- Rearrangements are easier to detect in comparison to many other genomic events
- We cannot detect homologs 100% correctly so the input permutation can contain errors




Two different genome rearrangement scenarios giving the same result.

# GRIMM demonstration




Glenn Tesler, GRIMM: genome rearrangements web server. Bioinformatics, 2002

# GRIMM file format

```
# useful comment about first genome
# another useful comment about it
>name of first genome
1 -4 2 $ # chromosome  1
-3 5 6 $ # chromosome 2
>name of second genome
5 -3  $
6 $
2 -4 1 $
```

GRIMM supports analysis of one, two or more genomes

# Study group assignments

MONDAY 26.9. 12-14 B222

# Group 1: firstnames A - H

- Read pages 136 and 137 from Jones & Pevzner
  - Greedy approach to motif finding
- At study group, solve Problem 5.18
  - Design an input for the GreedyMotifSearch algorithm that causes the algorithm to output an incorrect result.

# Group 2: firstnames I-N

- Read pages 15, 16, 19-22 (sect. 2.3) from Vazirani: Approximation algorithms, Springer 2001
  - Shortest superstring and its greedy approximations through set cover
  - (copies shared at the lecture, ask lecturer for pdf)
- At study group, present the reduction to set cover with some example

# Group 3: firstnames O-Z

- Read 4 first pages of Heber & Stoye: Finding All Common Intervals of k Permutations, CPM 2001
  - An alternative way to define and compute genomic distances
  - http://www.springerlink.com/content/ucc65djy0ft2bmq8/
- At study group, simulate Algorithm 1 with some example.