582670 Algorithms for Bioinformatics

Lecture 3: Greedy Algorithms and Genomic Rearrangements

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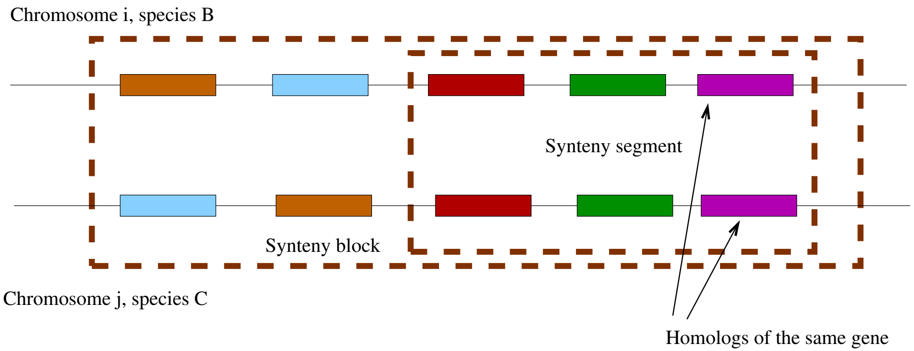
Background

- We now have genomes of several species available
- It is possible to compare genomes of two or more different species
  $\Longrightarrow$ 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

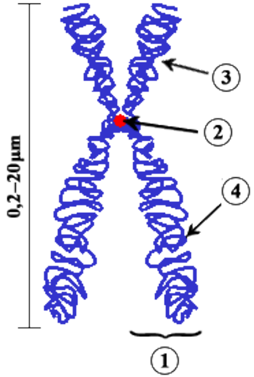
- Synteny – describes how genomic segments are located on the same chromosome or close to each other
    - Genes, markers (any sequence)
- Shared synteny between two species: genes are located close to each other in both of the species
- Synteny block (or syntenic block)
    - A set of genes or markers that co-occur together in two species
- Synteny segment (or syntenic segment)
    - Syntenic block where the *order* of genes or markers is preserved

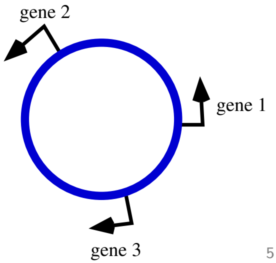
Synteny blocks and segments



Chromosomes

- Linear chromosomes
  - Eukaryotes (mostly)
- Circular chromosomes
  - Prokaryotes (mostly)
  - Mitochondria
- Chromosomes are 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

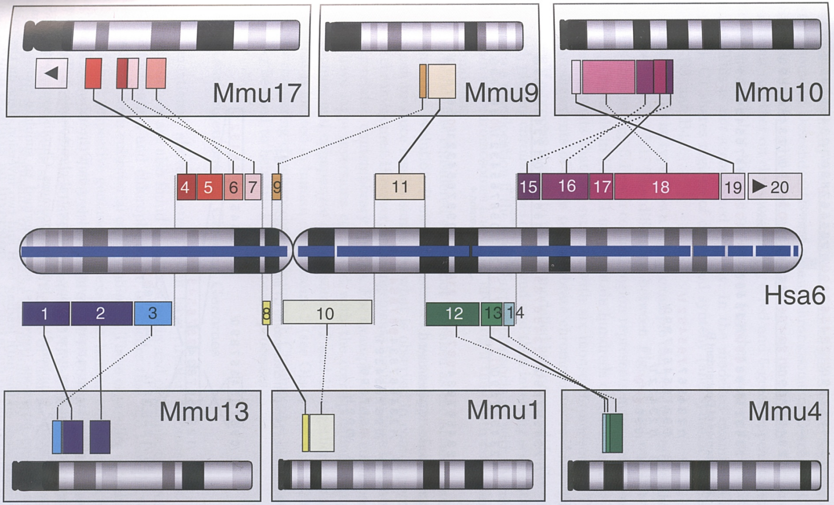


Fig. 5.1. Syntenic blocks conserved between human chromosome Hsa6 and mouse chromosomes. Broken lines indicate regions that appear in inverted orders in the two organisms. Reprinted, with permission, from Gregory SG et al. (2002) *Nature* 418:743–750. Copyright 2002 Nature Publishing Group.

Jones & Pevzner, 2004

Representing genomic rearrangements

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

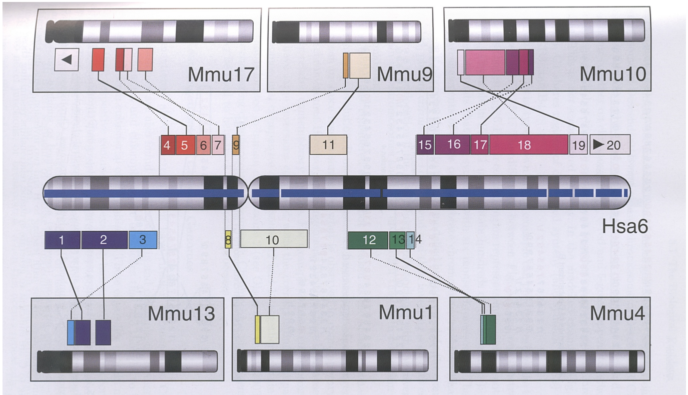


Fig. 5.1. Syntenic blocks conserved between human chromosome Hsa6 and mouse chromosomes. Broken lines indicate regions that appear in inverted orders in the two organisms. Reprinted, with permission, from Gregory SG et al. (2002) *Nature* 418:743–750. Copyright 2002 Nature Publishing Group.

Representing genomic rearrangements

- We assign numbers $1, \ldots, n$ to the found homologous sequences
- By convention, we number the sequences in the first genome by their order of appearance in the 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
  - List order corresponds to *physical order* on chromosomes!

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)		. . .
	. . .		

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

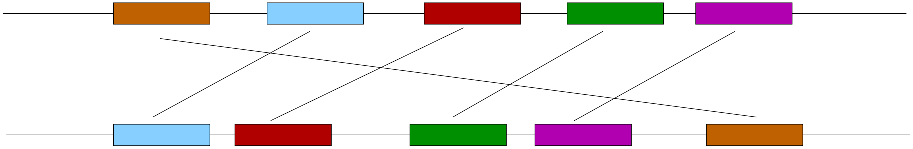
- Given two genomes (set of markers), how many
  - duplications,
  - inversions and
  - translocations

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

Minimum number of operations?
What operations? Which order?

Genome rearrangement problem

$$5\ 1\ 2\ 3\ 4 \xrightarrow{\substack{\#\text{ duplications?}\\ \#\text{ inversions?}\\ \#\text{ translocations?}}} 1\ 2\ 3\ 4\ 5$$



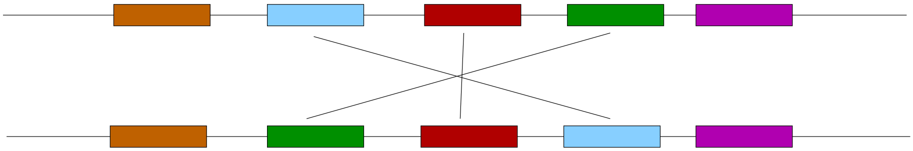
Genome rearrangement problem

$$\begin{tikzcd}
 & \pi_1\pi_2\pi_3\pi_4\pi_5 \arrow[dl] \arrow[dr] & \text{Permutation of 1,...,6} \arrow[l] \\
5\ 1\ 2\ 3\ 4 \arrow[rr, dashed] & & 1\ 2\ 3\ 4\ 5
\end{tikzcd}$$

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 $\pi_i \pi_{i+1} \dots \pi_{j-1} \pi_j$ (indexing starts from 1)
- For example, given permutation 5 1 2 3 4 and reversal $p(2, 4)$ we get permutation 5 3 2 1 4



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

Reversal distance problem

- Find the shortest **series of reversals** that, given a permutation π, transforms it to the *identity* permutation $(1, 2, \ldots, n)$.
- This reversal distance is denoted by $d(\pi)$

- Reversal distance for a pair of chromosomes:
  - Find synteny blocks in both
  - Number synteny blocks in the first chromosome to identity
  - Set π to corresponding 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 $\pi \neq i$, do a reversal such that $\pi_i = i$
- This is a *greedy* approach: we try to choose the option that looks best at the current step

Simple reversal sort: example

$\underline{5}\ 1\ 2\ 3\ 4 \implies 1\ \underline{5}\ 2\ 3\ 4 \implies 1\ 2\ \underline{5}\ 3\ 4 \implies 1\ 2\ 3\ \underline{5}\ 4 \implies 1\ 2\ 3\ 4\ \underline{5}$

- Reversal series: $p(1,2)$, $p(2,3)$, $p(3,4)$, $p(4,5)$
- Is $d(5\ 1\ 2\ 3\ 4)$ then 4?

Simple reversal sort: example

$\underline{5}\ 1\ 2\ 3\ 4 \implies 1\ \underline{5}\ 2\ 3\ 4 \implies 1\ 2\ \underline{5}\ 3\ 4 \implies 1\ 2\ 3\ \underline{5}\ 4 \implies 1\ 2\ 3\ 4\ \underline{5}$

- Reversal series: $p(1,2)$, $p(2,3)$, $p(3,4)$, $p(4,5)$
- Is $d(5\ 1\ 2\ 3\ 4)$ then 4?

$\colorbox{pink}{5 1 2 3 4} \implies \colorbox{pink}{4 3 2 1}\ 5 \implies 1\ 2\ 3\ 4\ 5$

- $d(5\ 1\ 2\ 3\ 4) = 2$

How good is simple reversal sort?

- Not so good actually
- It has to do at most $n - 1$ reversals with permutation of length n
- In our previous example, the algorithm returned a distance that is as large as $(n - 1)/2$ times the correct result $d(\pi) = 2$
  - For example, if we extend the example for $n = 1001$, the result can be as bad as $500 \times d(\pi)$

Approximation algorithms and approximation ratios

- Simple reversal sort is an *approximation algorithm*. It only produces an approximate solution.
- $\mathcal{A}(\pi)$: approximate solution returned by algorithm $\mathcal{A}$
- $OPT(\pi)$: optimal solution
- The *approximation ratio* of (minimization) algorithm $\mathcal{A}$ is the maximum approximation ratio over *all* inputs of size n:

$$\max_{|\pi|=n} \frac{\mathcal{A}(\pi)}{OPT(\pi)}$$

- The approximation ratio for simple reversal sort is thus at least $(n-1)/2$
- The approximation ratio tells how much off the solution given by the algorithm can in *worst case* be from the optimal solution

Approximation ratios for maximization problems

- Previous slide gave the approximation ration for a minimization problem like reversal distance.
- For a maximization problem (e.g. motif finding, maximizing score) the approximation ratio of an algorithm is defined as the minimum approximation ratio over *all* inputs of size n:

$$\min_{|\pi|=n} \frac{\mathcal{A}(\pi)}{OPT(\pi)}$$

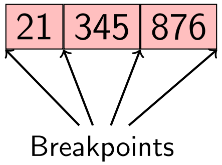
Computing reversals with breakpoints

- Let's 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 π_i and π_{i+1} are a *breakpoint* if they are not consecutive numbers
  - Adjacency: if π_i and π_{i+1} are consecutive they are an *adjacency*

Breakpoints and adjacencies

This permutation contains

- four breakpoints: begin-2, 13, 58, 6-end
- five adjacencies: 21, 34, 45, 87, 76



Breakpoints

- Each breakpoint in permutation needs to be removed to get to the identity permutation (= our target)
  - Identity permutation does not contain any breakpoints
- First and last positions special cases
- Note that each reversal can remove *at most* two breakpoints
- Denote the number of breakpoints by $b(\pi)$

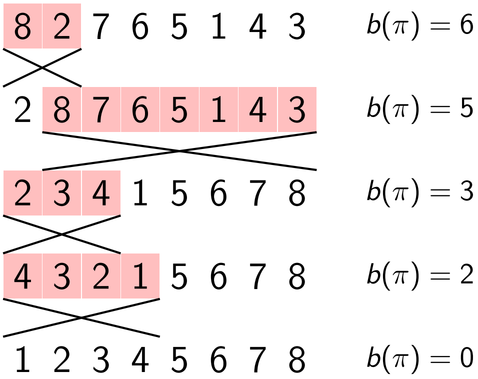
$$\boxed{21}\boxed{345}\boxed{876} \qquad b(\pi) = 4$$

Breakpoint reversal sort

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

```
1: while $b(\pi) > 0$ do
2:     Choose reversal $p$ that removes most breakpoints
3:     Perform reversal $p$ to $\pi$
4:     Output $\pi$
5: return
```

Breakpoint removal: example



Break point removal

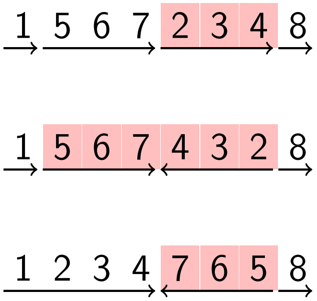
- The previous algorithm needs refinement to be correct
- Consider the following permutation

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

- 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



$\longrightarrow$ Increasing strip

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

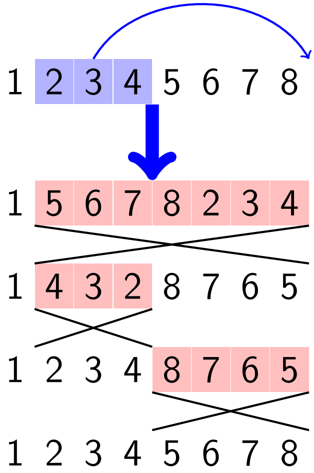
Improved breakpoint reversal sort

```
1: while $b(\pi) > 0$ do
2:     if $\pi$ has a decreasing strip then
3:         Apply reversal $p$ such that it removes most BPs
4:     else
5:         Reverse an increasing strip
6:     Output $\pi$
```

Is improved BP removal enough?

- The algorithm works pretty well:
  - A reversal removes at most two breakpoints
    $\implies$ Optimal solution cannot be better than $b(\pi)/2$
  - Improved BP removal performs at most $2 \cdot b(\pi)$ reversals
    $\implies$ The result is at most **four** times worse than the optimal
    $\implies$ The approximation ratio of improved BP removal is at most 4.
  - Is this good?
- We considered only reversals
- What about translocations?

Translocations via reversals



Translocation of 2,3,4

$p(2,8)$

$p(2,4)$

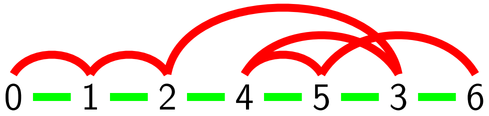
$p(5,8)$

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)

Estimating reversal distance by cycle decomposition

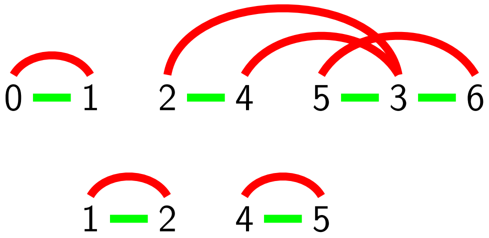
- We can estimate $d(\pi)$ by *cycle decomposition*
- Let's represent permutation $\pi = 1\ 2\ 4\ 5\ 3$ with the following graph



where edges correspond to adjacencies (identity, permutation π)

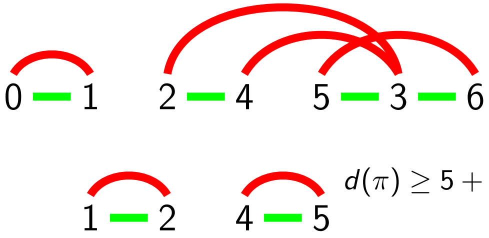
Estimating reversal distance by cycle decomposition

- 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 $c(\pi)$ be the maximum number of alternating, edge-disjoint cycles in the graph representation of π
- The following formula allows estimation of $d(\pi)$
  - $d(\pi) \geq n + 1 - c(\pi)$, where n is the permutation length



$d(\pi) \geq 5 + 1 - 4 = 2$

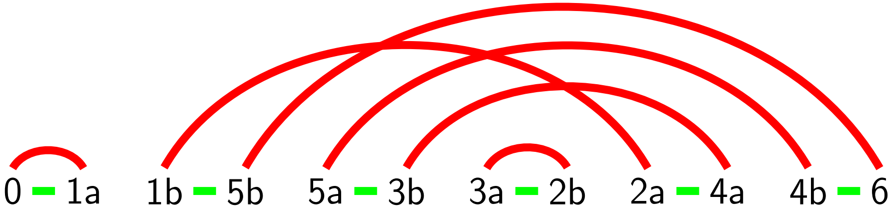
Cycle decompositions

- Cycle decomposition is NP-complete
- However, with signed data cycle decomposition becomes a trivial task (the cycles are vertex disjoint)

Cycle decomposition with signed data

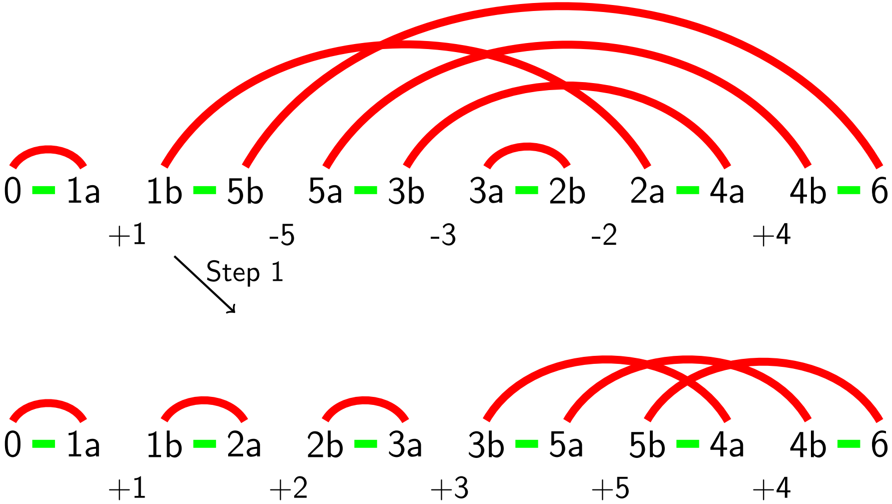
- Consider the following permutation that includes orientation of the markers
    - +1 -5 -3 -2 +4
- We modify this representation to include both endpoints of each marker:
    - 0 1a 1b 5b 5a 3b 3a 2b 2a 4a 4b 6

Graph representation of π and identity permutation

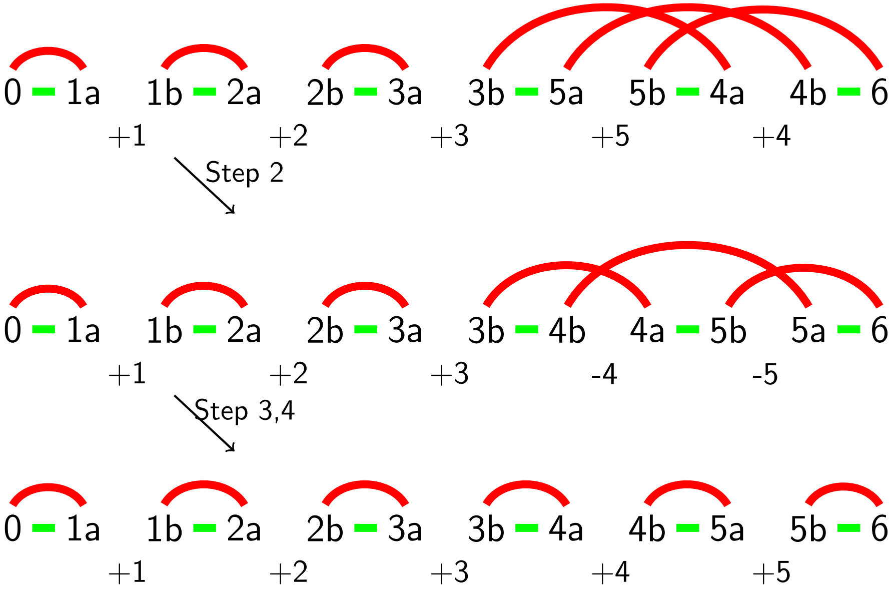


$$d(\pi) \geq n + 1 - c(\pi) = 5 + 1 - 3 = 3$$

Reversal step 1 (ad hoc greedy algorithm)


0 1a 1b 5b 5a 3b 3a 2b 2a 4a 4b 6
+1 -5 -3 -2 +4
Step 1
0 1a 1b 2a 2b 3a 3b 5a 5b 4a 4b 6
+1 +2 +3 +5 +4

Reversal steps 2,3,4



0 1a 1b 2a 2b 3a 3b 5a 5b 4a 4b 6
+1 +2 +3 +5 +4
Step 2
0 1a 1b 2a 2b 3a 3b 4b 4a 5b 5a 6
+1 +2 +3 -4 -5
Step 3,4
0 1a 1b 2a 2b 3a 3b 4a 4b 5a 5b 6
+1 +2 +3 +4 +5

$$3 \leq d(\pi) \leq 4$$

Reversal distance with signed data

However, the *exact* reversal distance in *signed data* can be computed quickly!

- It takes linear time w.r.t. the length of permutation (Bader, Moret, Yan 2001)
- The algorithm is quite involved

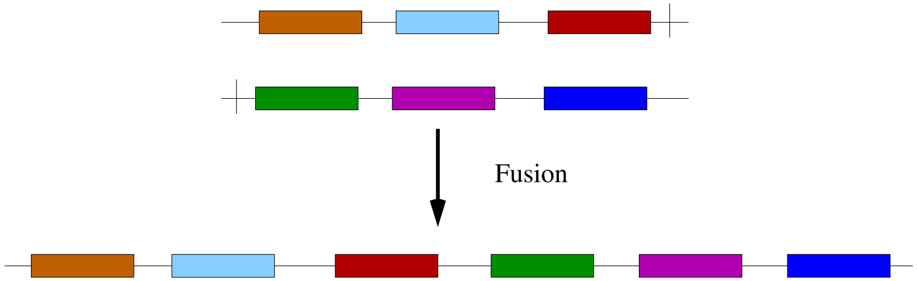
Multiple chromosomes

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

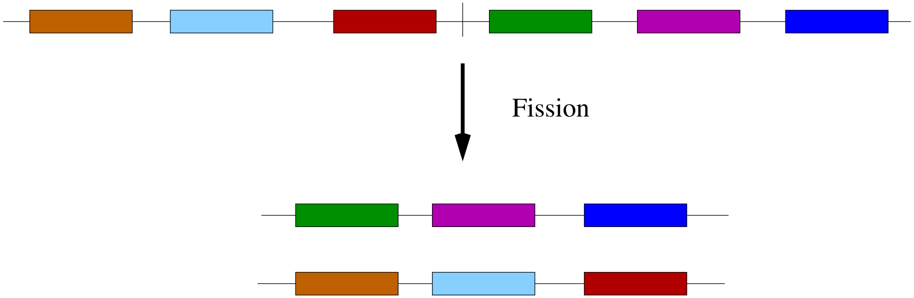
Fusions and fissions

- 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 and 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 ancestor
- Pevzner and 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 rearrangements 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

Outline

Study Group 1: (random allocation at lecture)

- Read pages 230-232 from Sung: Algorithms in Bioinformatics: A Practical Introduction, CRC Press 2010
  - 2-approximation for sorting an unsigned permutation
  - Copies distributed at the lecture.
- In the study group
  - Go through the reasoning in the proof of Lemma 9.2.
  - Simulate the 2-approximation algorithm on the permutation

    $$1\ 6\ 5\ 7\ 8\ 4\ 2\ 3\ 9$$

    How many reversals does the 2-approximation algorithm need? Is this optimal?

Study Group 2: (if you did not get material at the lecture)

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

Study Group 3: (random allocation at lecture)

- Read pages 15, 16, 19-22 (sect. 2.3) from Vazirani: Approximation algorithms, Springer 2001
    - Shortest superstring and its greedy approximation through set cover
    - Copies distributed at the lecture.
- At the study group:
    - present the reduction to set cover with some example
    - go through the proof of Lemma 2.11