CS481: Bioinformatics Algorithms

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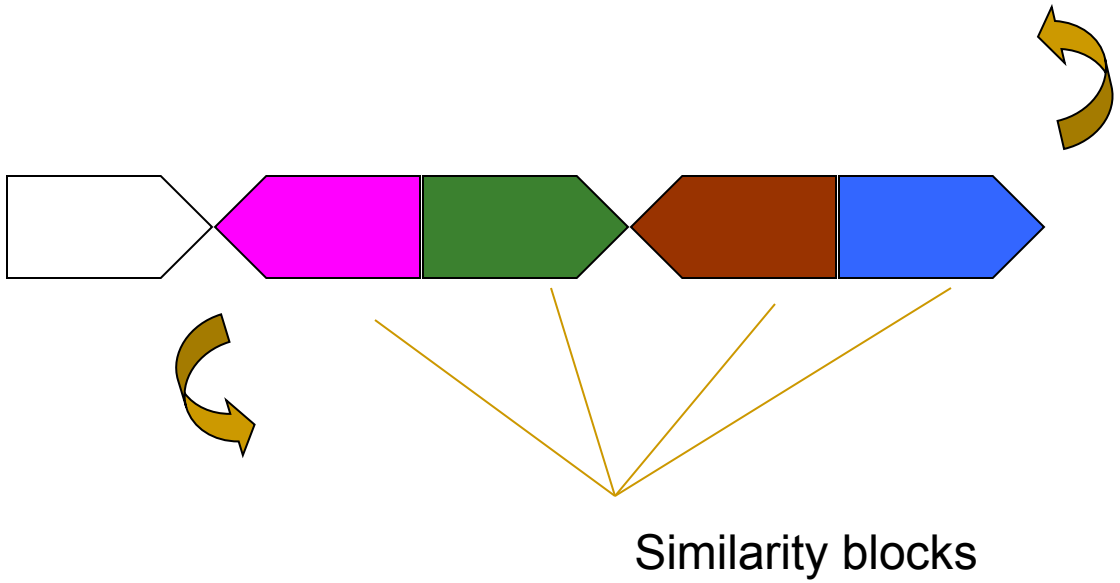
GENOME REARRANGEMENTS

Turnip vs Cabbage: Different mtDNA Gene Order

- Gene order comparison:



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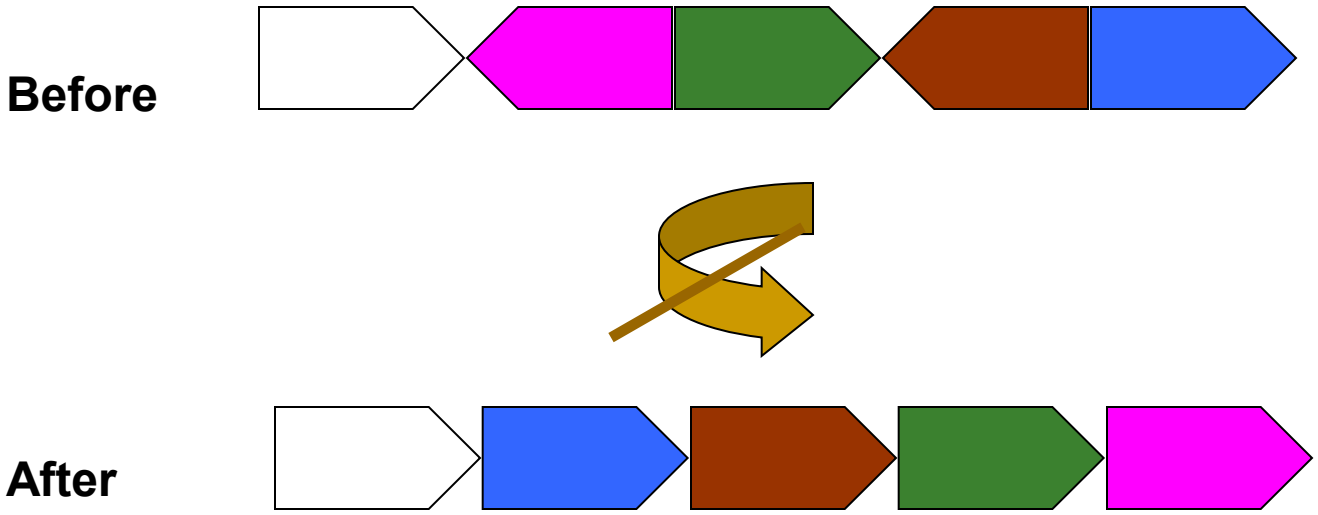
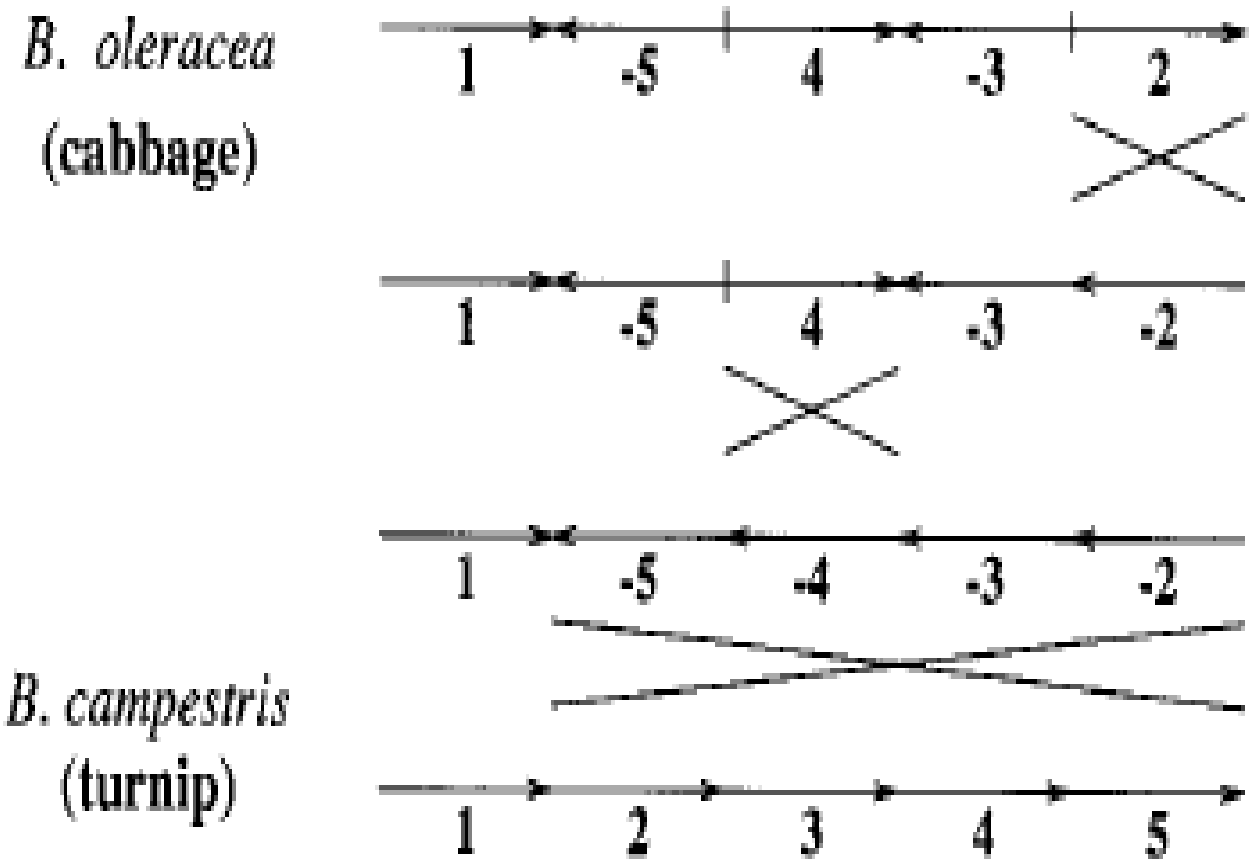


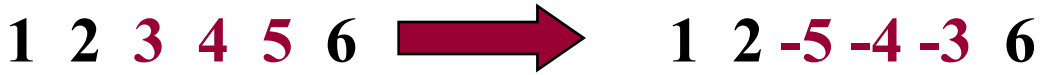
Evolution is manifested as the divergence in gene order

Transforming Cabbage into Turnip



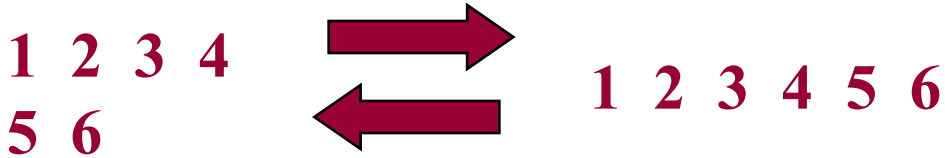
Types of Rearrangements

Reversal



Translocation

Fusion



Fission

Reversals: Example

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

$\rho(3,5)$

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

Reversals: Example

π = 1 2 3 4 5 6 7 8

$\rho(3,5)$

1 2 5 4 3 6 7 8

$\rho(5,6)$

1 2 5 4 6 3 7 8

Reversals and Gene Orders

- Gene order is represented by a permutation π:

$$\pi = \pi_1 \text{ ----- } \pi_{i-1}\ \pi_i\ \pi_{i+1} \text{ ------ } \pi_{j-1}\ \pi_j\ \pi_{j+1} \text{ ----- } \pi_n$$

$$\rho(i,j)$$

$$\pi_1 \text{ ----- } \pi_{i-1}\ \pi_j\ \pi_{j-1} \text{ ------ } \pi_{i+1}\ \pi_i\ \pi_{j+1} \text{ ----- } \pi_n$$

- Reversal $\rho(i, j)$ reverses (flips) the elements from i to j in π

Reversal Distance Problem

- Goal: Given two permutations, find the shortest series of reversals that transforms one into another
- Input: Permutations π and σ
- Output: A series of reversals $\rho_1,\ldots\rho_t$ transforming π into σ, such that t is minimum
- t - reversal distance between π and σ
- $d(\pi, \sigma)$ - smallest possible value of t, given π and σ

Sorting By Reversals Problem

- Goal: Given a permutation, find a shortest series of reversals that transforms it into the identity permutation (*1 2 … n*)
- Input: Permutation π
- Output: A series of reversals $\rho_1, \ldots \rho_t$ transforming π into the identity permutation such that *t* is minimum

Sorting By Reversals: Example

- $t = d(\pi)$ - reversal distance of π
- Example :

$$\pi = \underline{3\ 4}\ 2\ 1\ 5\ 6\ 7\ 10\ 9\ 8$$
$$4\ 3\ 2\ 1\ 5\ 6\ 7\ \underline{10\ 9\ 8}$$
$$\underline{4\ 3\ 2\ 1}\ 5\ 6\ 7\ 8\ 9\ 10$$
$$1\ 2\ 3\ 4\ 5\ 6\ 7\ 8\ 9\ 10$$

So $d(\pi) = 3$

Sorting by reversals: 5 steps

Step 0: π	2	-4	-3	5	-8	-7	-6	1
Step 1:	2	3	4	5	-8	-7	-6	1
Step 2:	2	3	4	5	6	7	8	1
Step 3:	2	3	4	5	6	7	8	-1
Step 4:	-8	-7	-6	-5	-4	-3	-2	-1
Step 5: γ	1	2	3	4	5	6	7	8

Sorting by reversals: 4 steps

Step 0: π	2	-4	-3	5	-8	-7	-6	1
Step 1:	2	3	4	5	-8	-7	-6	1
Step 2:	-5	-4	-3	-2	-8	-7	-6	1
Step 3:	-5	-4	-3	-2	-1	6	7	8
Step 4: γ	1	2	3	4	5	6	7	8

Pancake Flipping Problem

- The chef is sloppy; he prepares an unordered stack of pancakes of different sizes
- The waiter wants to rearrange them (so that the smallest winds up on top, and so on, down to the largest at the bottom)
- He does it by flipping over several from the top, repeating this as many times as necessary

Christos Papadimitrou and Bill Gates flip pancakes

Pancake Flipping Problem: Formulation

- Goal: Given a stack of *n* pancakes, what is the minimum number of flips to rearrange them into perfect stack?
- Input: Permutation π
- Output: A series of prefix reversals $\rho_1, \ldots \rho_t$ transforming π into the identity permutation such that *t* is minimum

Pancake Flipping Problem: Greedy Algorithm

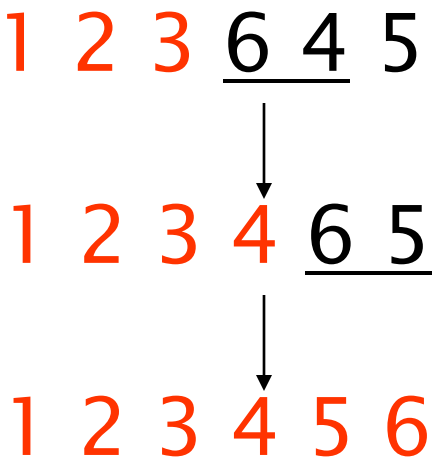
- Greedy approach: 2 prefix reversals at most to place a pancake in its right position, $2n - 2$ steps total at most
- William Gates and Christos Papadimitriou showed in the mid-1970s that this problem can be solved by at most *5/3 (n + 1) prefix reversals*

Sorting By Reversals: A Greedy Algorithm

- If sorting permutation π = 1 2 3 6 4 5, the first three elements are already in order so it does not make any sense to break them.
- The length of the already sorted prefix of π is denoted *prefix*(π)
  - *prefix*(π) = 3
- This results in an idea for a greedy algorithm: increase *prefix*(π) at every step

Greedy Algorithm: An Example

- Doing so, π can be sorted



- Number of steps to sort permutation of length *n* is at most *(n – 1)*

Greedy Algorithm: Pseudocode

SimpleReversalSort(π)

1 **for** $i \leftarrow 1$ to $n - 1$
2 $j \leftarrow$ position of element i in π (i.e., $\pi_j = i$)
3 **if** $j \neq i$
4 $\pi \leftarrow \pi * \rho(i, j)$
5 **output** π
6 **if** π is the identity permutation
7 **return**

Analyzing SimpleReversalSort

- SimpleReversalSort does not guarantee the smallest number of reversals and takes five steps on π = 6 1 2 3 4 5 :
  - Step 1: 1 6 2 3 4 5
  - Step 2: 1 2 6 3 4 5
  - Step 3: 1 2 3 6 4 5
  - Step 4: 1 2 3 4 6 5
  - Step 5: 1 2 3 4 5 6

Analyzing SimpleReversalSort (cont'd)

- But it can be sorted in two steps:

  π = 6 1 2 3 4 5

  - Step 1: 5 4 3 2 1 6
  - Step 2: 1 2 3 4 5 6

- So, SimpleReversalSort(π) is not optimal

- Optimal algorithms are unknown for many problems; approximation algorithms are used

Approximation Algorithms

- These algorithms find approximate solutions rather than optimal solutions
- The approximation ratio of an algorithm A on input π is:

$$A(\pi) / OPT(\pi)$$

where

$A(\pi)$ - solution produced by algorithm A
$OPT(\pi)$ - optimal solution of the problem

Approximation Ratio/Performance Guarantee

- Approximation ratio (performance guarantee) of algorithm A: max approximation ratio of all inputs of size *n*
  - For algorithm A that minimizes objective function (minimization algorithm):
    - $\max_{|\pi| = n} A(\pi) \ / \ OPT(\pi)$

Approximation Ratio/Performance Guarantee

- Approximation ratio (performance guarantee) of algorithm A: max approximation ratio of all inputs of size *n*
  - For algorithm A that minimizes objective function (minimization algorithm):
    - $\max_{|\pi| = n} A(\pi) / OPT(\pi)$
  - For maximization algorithm:
    - $\min_{|\pi| = n} A(\pi) / OPT(\pi)$

Adjacencies and Breakpoints

$$\pi = \pi_1 \pi_2 \pi_3 \ldots \pi_{n-1} \pi_n$$

- A pair of elements π_i and π_{i+1} are adjacent if

$$\pi_{i+1} = \pi_i \pm 1$$

- For example:

$$\pi = 1 \ \ 9 \ \ \underline{3 \ \ 4} \ \ \underline{7 \ \ 8} \ \ 2 \ \ \underline{6 \ \ 5}$$

- (3, 4) or (7, 8) and (6,5) are adjacent pairs

Breakpoints

There is a breakpoint between any adjacent element that are non-consecutive:

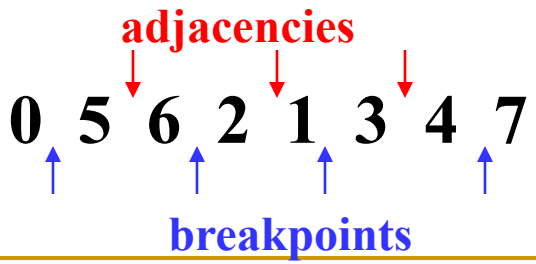
$$\pi = 1 \mid 9 \mid 3 \;\; 4 \mid 7 \;\; 8 \mid 2 \mid 6 \;\; 5$$

- Pairs (1,9), (9,3), (4,7), (8,2) and (2,6) form breakpoints of permutation π
- $b(\pi)$ - # breakpoints in permutation π

Adjacency & Breakpoints

- **An adjacency - a pair of adjacent elements that are consecutive**
- **A breakpoint - a pair of adjacent elements that are not consecutive**

$\pi = 5\ \ 6\ \ 2\ \ 1\ \ 3\ \ 4$ ⟶ **Extend π with $\pi_0 = 0$ and $\pi_7 = 7$**



Extending Permutations

- We put two elements $\pi_0 = 0$ and $\pi_{n+1} = n+1$ at the ends of π

  Example:

$\pi = 1 \mid 9 \mid 3 \;\; 4 \mid 7 \;\; 8 \mid 2 \mid 6 \;\; 5$

Extending with *0* and *10*

$\pi = 0\ 1 \mid 9 \mid 3 \;\; 4 \mid 7 \;\; 8 \mid 2 \mid 6 \;\; 5 \mid 10$

Note: A new breakpoint was created after extending

Reversal Distance and Breakpoints

- Each reversal eliminates at most 2 breakpoints.

π = 2 3 1 4 6 5

0 | 2 3 | 1 | 4 | 6 5 | *7* $b(\pi) = 5$

0 1 | 3 2 | 4 | 6 5 | *7* $b(\pi) = 4$

0 1 2 3 4 | 6 5 | *7* $b(\pi) = 2$

0 1 2 3 4 5 6 *7* $b(\pi) = 0$

Reversal Distance and Breakpoints

- Each reversal eliminates at most 2 breakpoints.
- This implies:

  reversal distance ≥ #breakpoints / 2

π = 2 3 1 4 6 5

0 | 2 3 | 1 | 4 | 6 5 | 7	$b(\pi) = 5$
0 1 | 3 2 | 4 | 6 5 | 7	$b(\pi) = 4$
0 1 2 3 4 | 6 5 | 7	$b(\pi) = 2$
0 1 2 3 4 5 6 7	$b(\pi) = 0$

Sorting By Reversals: A Better Greedy Algorithm

BreakPointReversalSort(π)

1 **while** $b(\pi) > 0$

2 Among all possible reversals, choose reversal ρ minimizing $b(\pi \cdot \rho)$

3 $\pi \leftarrow \pi \cdot \rho(i, j)$

4 **output** π

5 **return**

Sorting By Reversals: A Better Greedy Algorithm

BreakPointReversalSort(π)

1 **while** $b(\pi) > 0$

2 Among all possible reversals, choose reversal ρ minimizing $b(\pi \cdot \rho)$

3 $\pi \leftarrow \pi \cdot \rho(i, j)$

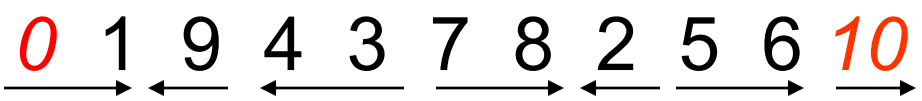
4 **output** π

5 **return**

Problem: this algorithm may work forever

Strips

- Strip: an interval between two consecutive breakpoints in a permutation
  - Decreasing strip: *strip* of elements in decreasing order (e.g. 6 5 and 3 2).
  - Increasing strip: *strip* of elements in increasing order (e.g. 7 8)



  - A single-element strip can be declared either increasing or decreasing. We will choose to declare them as decreasing with exception of the strips with *0* and *n+1*

Reducing the Number of Breakpoints

Theorem 1:

If permutation π contains at least one decreasing strip, then there exists a reversal ρ which decreases the number of breakpoints (i.e. $b(\pi \bullet \rho) < b(\pi)$)

Things To Consider

- For π = 1 4 6 5 7 8 3 2

  0 1 | 4 | 6 5 | 7 8 | 3 2 | *9* $b(\pi) = 5$

  - Choose decreasing strip with the smallest element *k* in π (*k* = 2 in this case)

Things To Consider (cont'd)

- For π = 1 4 6 5 7 8 3 2

  0 1 | 4 | 6 5 | 7 8 | 3 2 | *9* $b(\pi) = 5$

  - Choose decreasing strip with the smallest element k in π (k = 2 in this case)

Things To Consider (cont'd)

- For π = 1 4 6 5 7 8 3 2

  0 1 | 4 | 6 5 | 7 8 | 3 2 | *9* $b(\pi) = 5$

  - Choose decreasing strip with the smallest element *k* in π (*k* = 2 in this case)
  - Find *k* – *1* in the permutation

Things To Consider (cont'd)

- For π = 1 4 6 5 7 8 3 2

  0 1 | 4 | 6 5 | 7 8 | 3 2 | *9* $b(\pi) = 5$

  - Choose decreasing strip with the smallest element *k* in π (*k* = 2 in this case)
  - Find *k* – *1* in the permutation
  - Reverse the segment between *k* and *k-1*:
  - *0* 1 | 4 | 6 5 | 7 8 | 3 2 | *9* $b(\pi) = 5$

  - *0* 1 2 3 | 8 7 | 5 6 | 4 | *9* $b(\pi) = 4$

Reducing the Number of Breakpoints Again

- If there is no decreasing strip, there may be no reversal ρ that reduces the number of breakpoints (i.e. $b(\pi \bullet \rho) \geq b(\pi)$ for any reversal ρ).
- By reversing an increasing strip (# of breakpoints stay unchanged), we will create a decreasing strip at the next step. Then the number of breakpoints will be reduced in the next step (theorem 1).

Things To Consider (cont'd)

- There are no decreasing strips in π, for:

$$\pi = \underrightarrow{0\ 1\ 2} \mid \underrightarrow{5\ 6\ 7} \mid \underrightarrow{3\ 4} \mid \underrightarrow{8} \quad b(\pi) = 3$$

$$\pi \bullet \rho(6,7) = \underrightarrow{0\ 1\ 2} \mid \underrightarrow{5\ 6\ 7} \mid \underleftarrow{4\ 3} \mid \underrightarrow{8} \quad b(\pi) = 3$$

- ✓ $\rho(6,7)$ does not change the # of breakpoints
- ✓ $\rho(6,7)$ creates a decreasing strip thus guaranteeing that the next step will decrease the # of breakpoints.

ImprovedBreakpointReversalSort

ImprovedBreakpointReversalSort(π)
1 **while** $b(\pi) > 0$
2 **if** π has a decreasing strip
3 Among all possible reversals, choose reversal ρ that minimizes $b(\pi \cdot \rho)$
4 **else**
5 Choose a reversal ρ that flips an increasing strip in π
6 $\pi \leftarrow \pi \cdot \rho$
7 **output** π
8 **return**

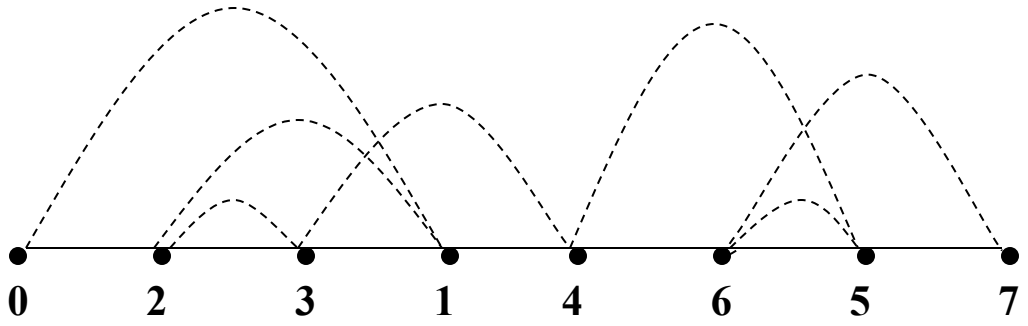
ImprovedBreakpointReversalSort: Performance Guarantee

- *ImprovedBreakPointReversalSort* is an approximation algorithm with a performance guarantee of at most 4
  - It eliminates at least one breakpoint in every two steps; at most $2b(\pi)$ steps
  - Approximation ratio: $2b(\pi) \ / \ d(\pi)$
  - Optimal algorithm eliminates at most 2 breakpoints in every step: $d(\pi) \geq b(\pi) / 2$
  - Performance guarantee:
    - $(\ 2b(\pi) \ / \ d(\pi) \ ) \geq [\ 2b(\pi) \ / \ (b(\pi) \ / \ 2) \ ] = \ 4$

GRAPHS

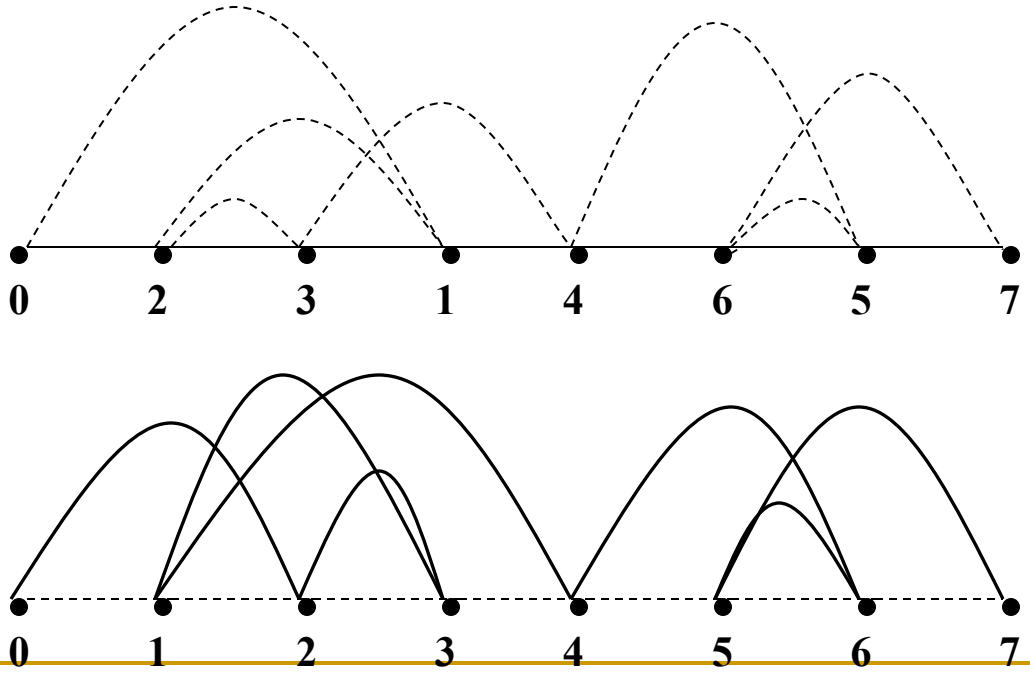
Breakpoint Graph

1) **Represent the elements of the permutation π = 2 3 1 4 6 5 as vertices in a graph (ordered along a line)**
2) **Connect vertices in order given by π with black edges (black path)**
3) **Connect vertices in order given by 1 2 3 4 5 6 with grey edges (grey path)**
4) **Superimpose black and grey paths**



Two Equivalent Representations of the Breakpoint Graph

- **Consider the following Breakpoint Graph**
- **If we line up the gray path (instead of black path) on a horizontal line, then we would get the following graph**
- **Although they may look different, these two graphs are the same**

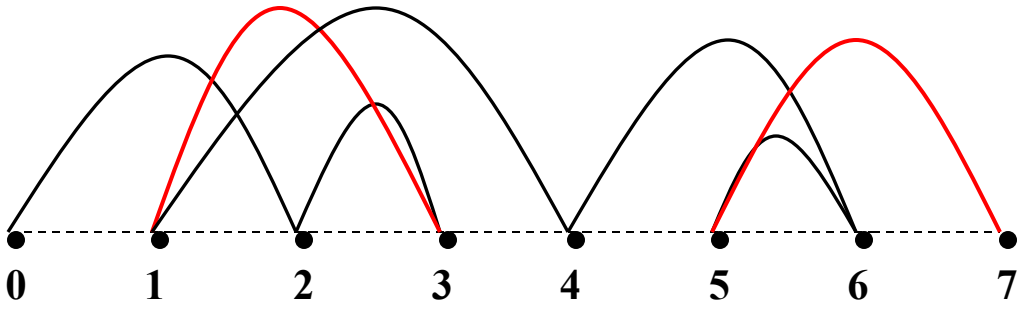


What is the Effect of the Reversal ?

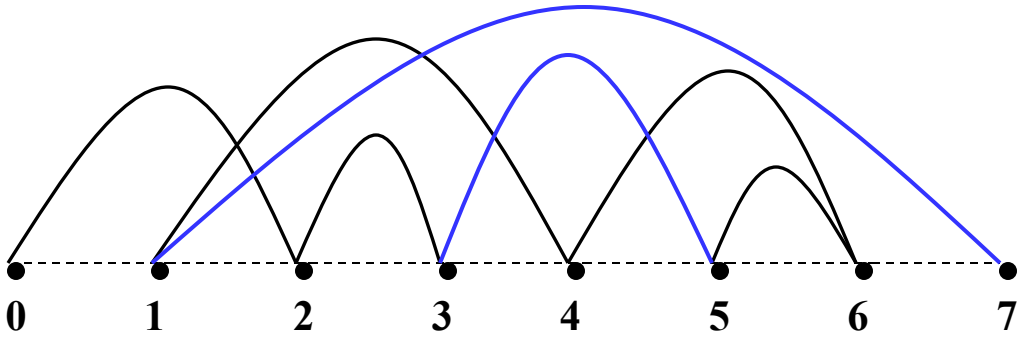
How does a reversal change the breakpoint graph?

- **The gray paths stayed the same for both graphs**
- **There is a change in the graph at this point**
- **There is another change at this point**
- **The black edges are unaffected by the reversal so they remain the same for both graphs**

Before: 0 2 3 1 4 6 5 7

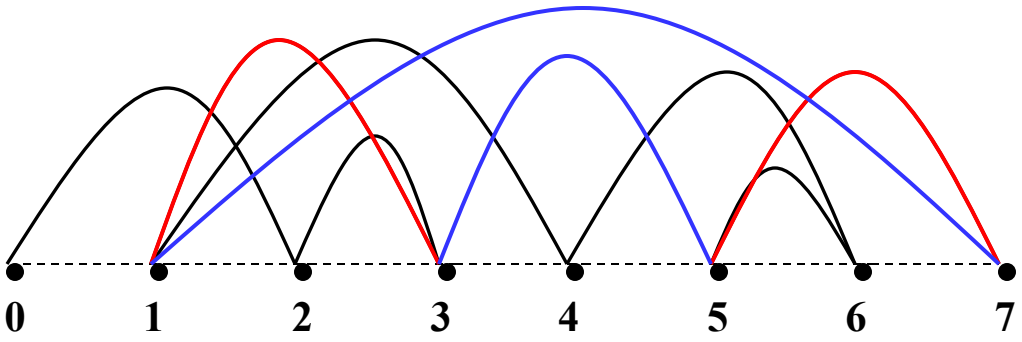


After: 0 2 3 5 6 4 1 7



A reversal affects 4 edges in the breakpoint graph

- **A reversal removes 2 edges (red) and replaces them with 2 new edges (blue)**



Effects of Reversals

Case 1:

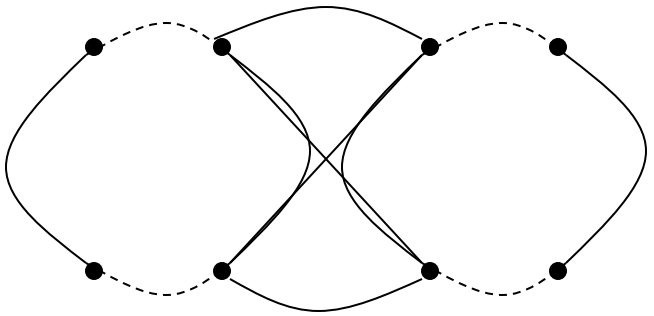
Both edges belong to the same cycle

- **Remove the center black edges and replace them with new black edges (there are two ways to replace them)**
- **(a) After this replacement, there now exists 2 cycles instead of 1 cycle**
- **(b) Or after this replacement, there still exists 1 cycle**

Therefore, after the reversal $c(\pi\rho) - c(\pi) = 1$

$c(\pi\rho) - c(\pi) = 0$ or 1

This is called a proper reversal since there's a cycle increase after the reversal.



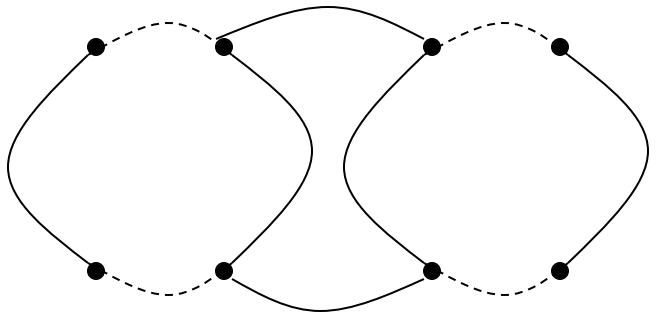
Effects of Reversals (Continued)

Case 2:

Both edges belong to different cycles

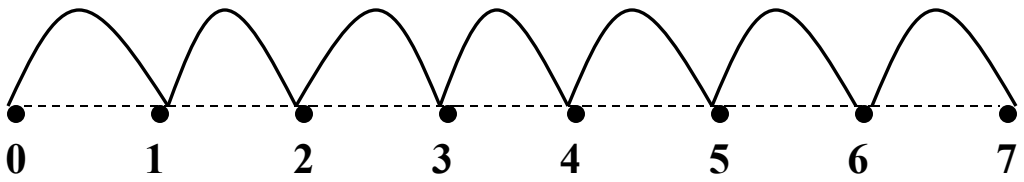
- **Remove the center black edges and replace them with new black edges**
- **After the replacement, there now exists 1 cycle instead of 2 cycles**

$$c(\pi\rho) - c(\pi) = -1$$



Therefore, for every permutation π and reversal ρ, $c(\pi\rho) - c(\pi) \leq 1$

Identity permutation (n=6)



Reversal Distance and Maximum Cycle Decomposition

- **Since the identity permutation of size n contains the maximum cycle decomposition of $n+1$, $c(identity) = n+1$**

- **$c(identity) - c(\pi)$ equals the number of cycles that need to be "added" to $c(\pi)$ while transforming π into the identity**

- **Based on the previous theorem, at best after each reversal, the cycle decomposition could be increased by one, then:**

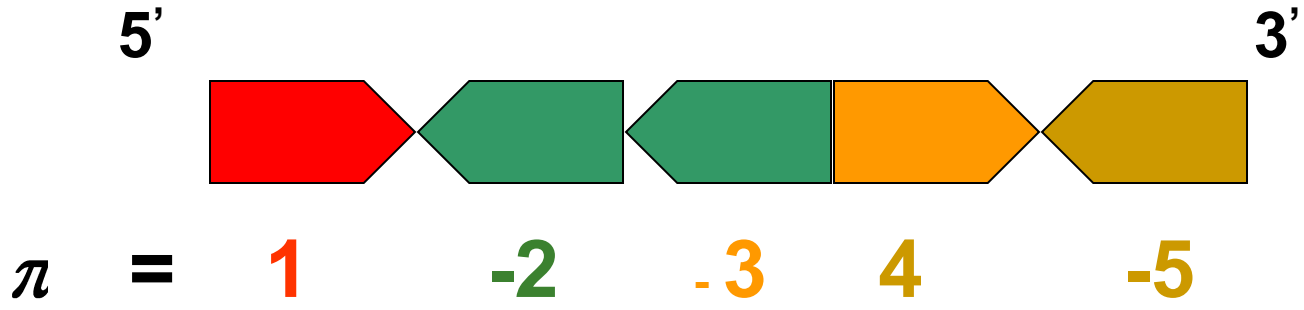
$$d(\pi) = c(identity) - c(\pi) = n+1 - c(\pi)$$

- **Yet, not every reversal can increase the cycle decomposition**

➡ ***Therefore, $d(\pi) \geq n+1 - c(\pi)$***

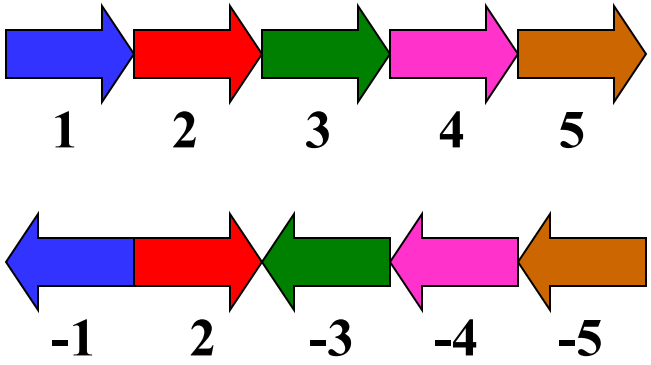
Signed Permutations

- Up to this point, all permutations to sort were unsigned
- But genes have directions… so we should consider signed permutations



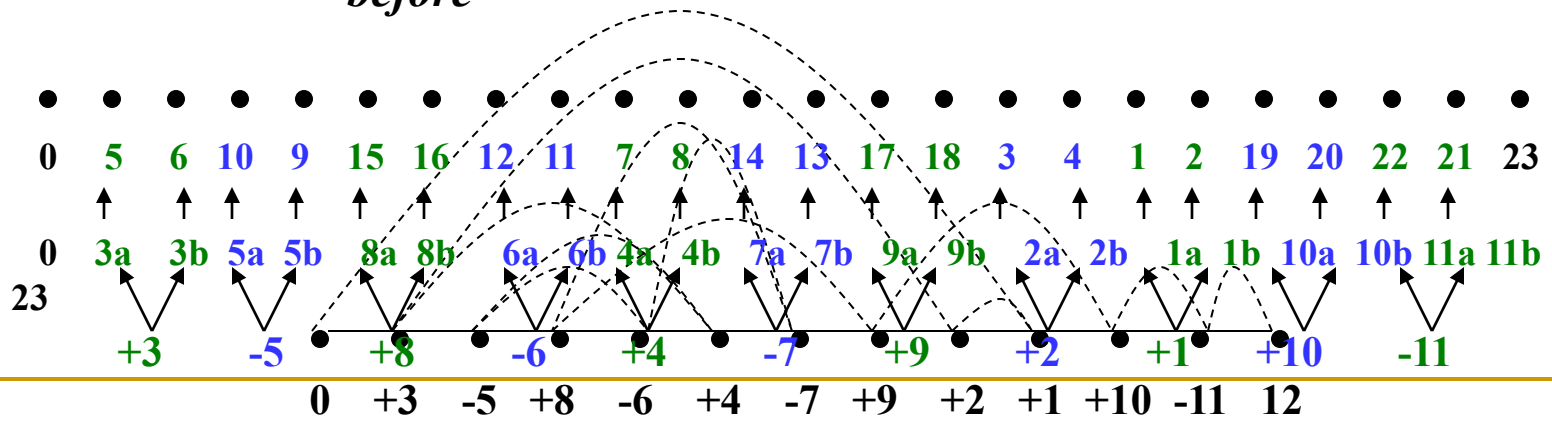
Signed Permutation

- **Genes are *directed* fragments of DNA and we represent a genome by a signed permutation**
- **If genes are in the same position but there orientations are different, they do not have the equivalent gene order**
- **For example, these two permutations have the same order, but each gene's orientation is the reverse; therefore, they are not equivalent gene sequences**



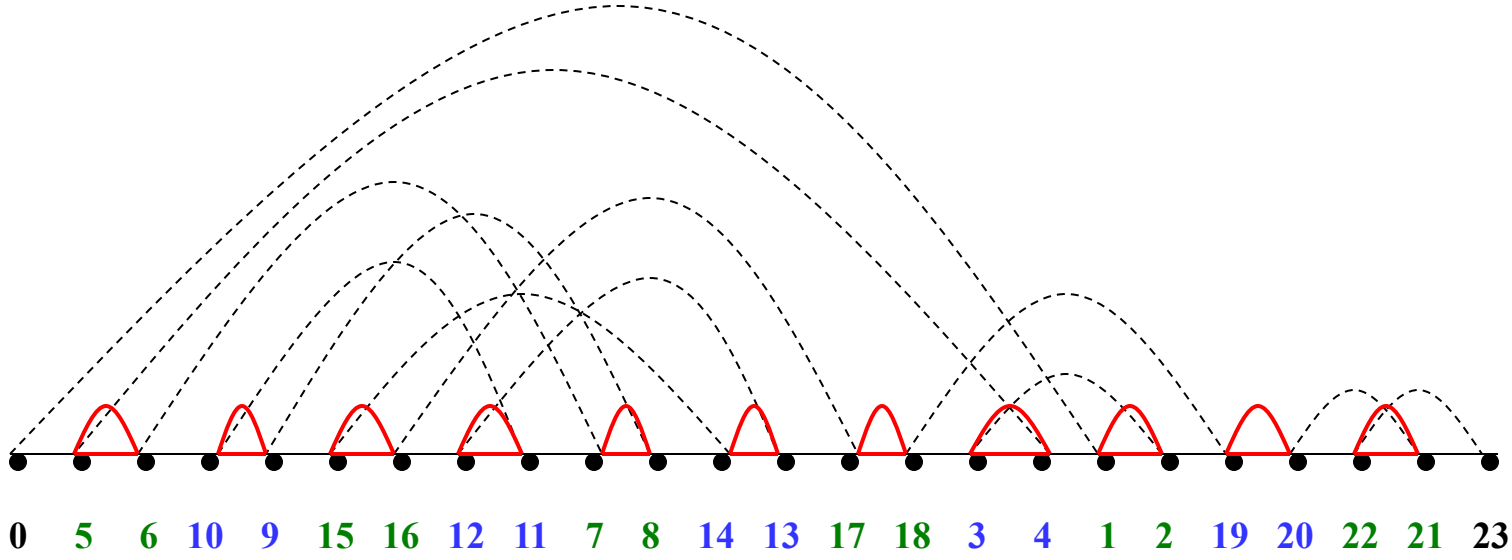
From Signed to Unsigned Permutation

- **Begin by constructing a normal signed breakpoint graph**
- **Redefine each vertex x with the following rules:**
  - ***If vertex x is positive, replace vertex x with vertex 2x-1 and vertex 2x in that order***
  - ***If vertex x is negative, replace vertex x with vertex 2x and vertex 2x-1 in that order***
  - ***The extension vertices x = 0 and x = n+1 are kept as it was before***



From Signed to Unsigned Permutation (Continued)

- **Construct the breakpoint graph as usual**
- **Notice the alternating cycles in the graph between every other vertex pair**
- **Since these cycles came from the same signed vertex, we will not be performing any reversal on both pairs at the same time; therefore, these cycles can be removed from the graph**

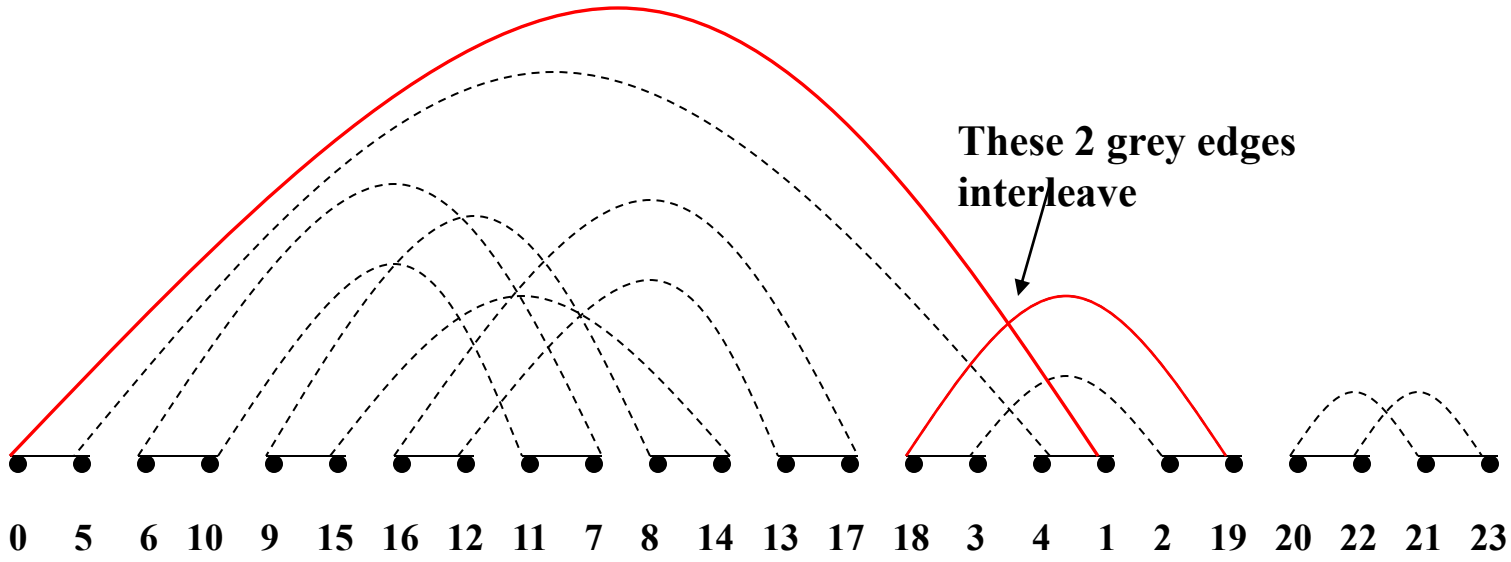


Interleaving Edges

- **Interleaving edges are grey edges that cross each other**

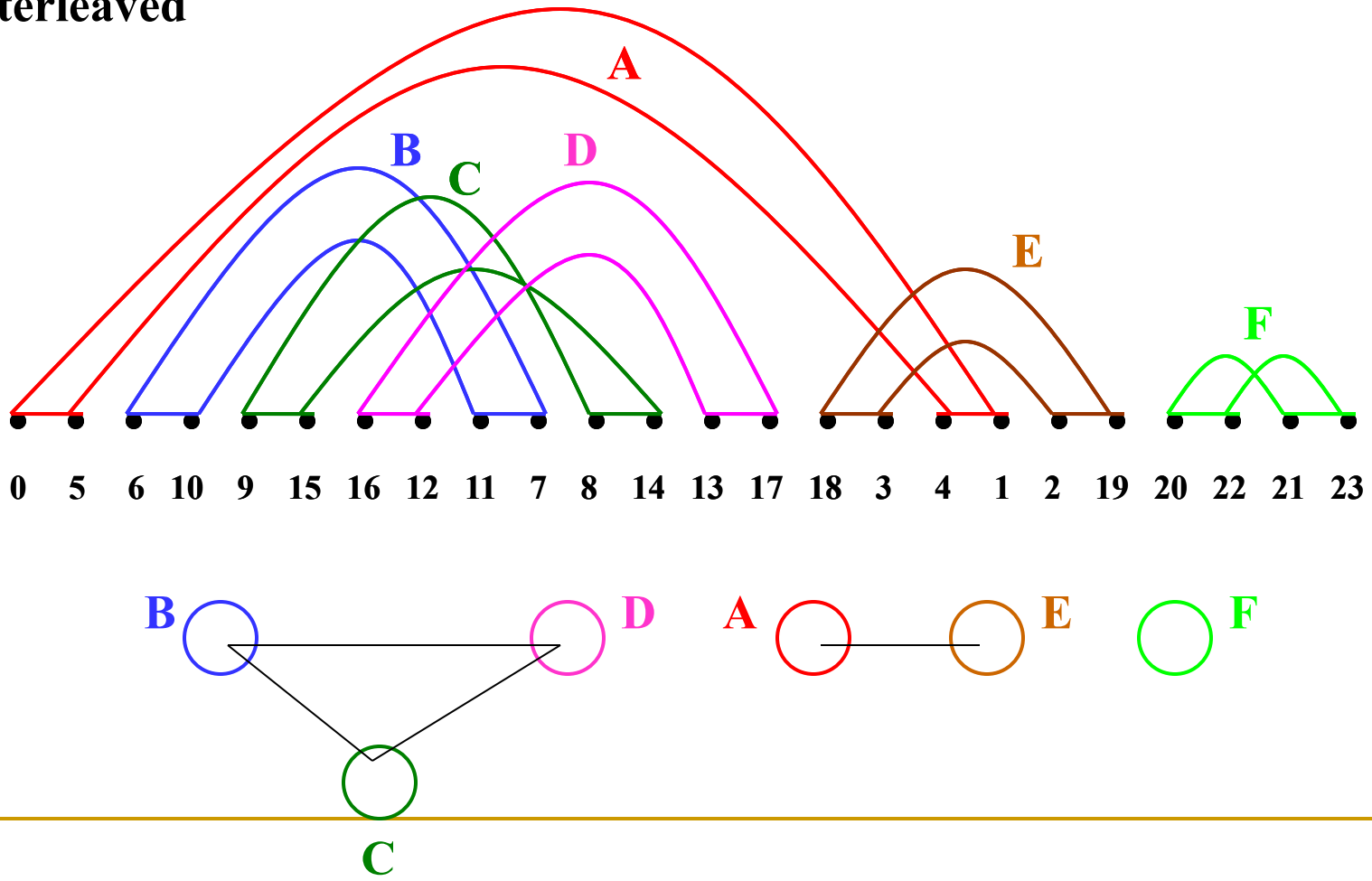
  Example: Edges (0,1) and (18, 19) are interleaving

- **Cycles are interleaving if they have an interleaving edge**



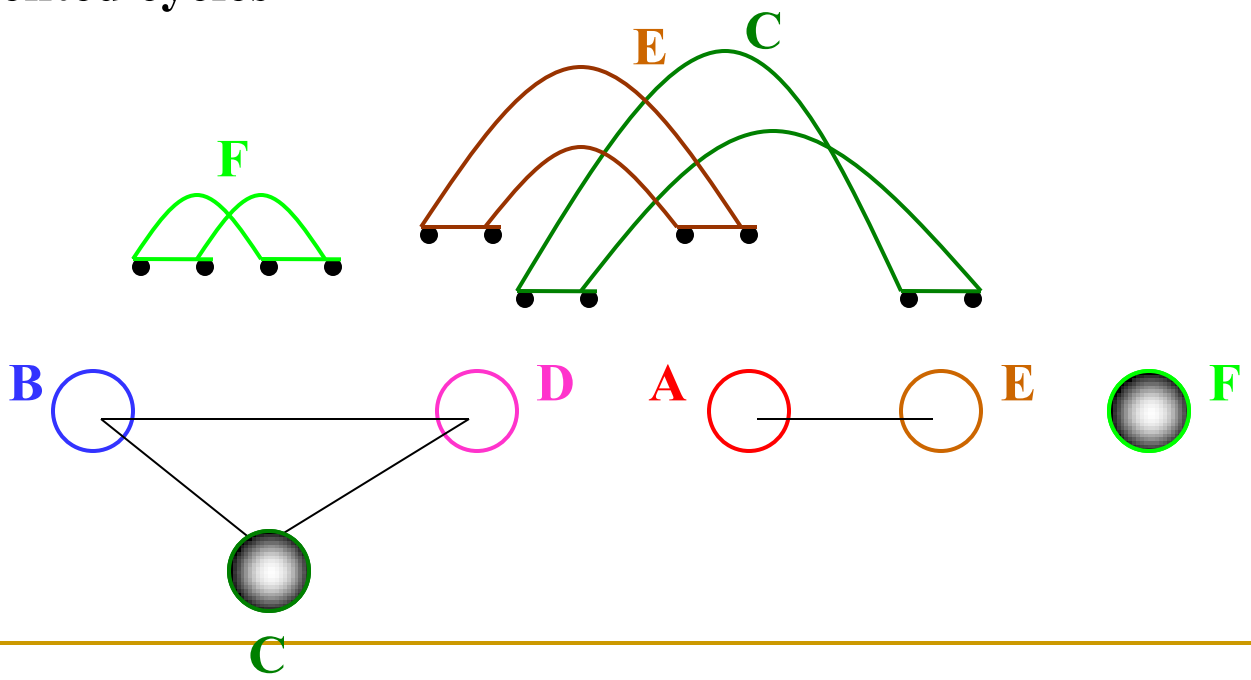
Interleaving Graphs

• **An Interleaving Graph is defined on the set of cycles in the Breakpoint graph and are connected by edges where cycles are interleaved**



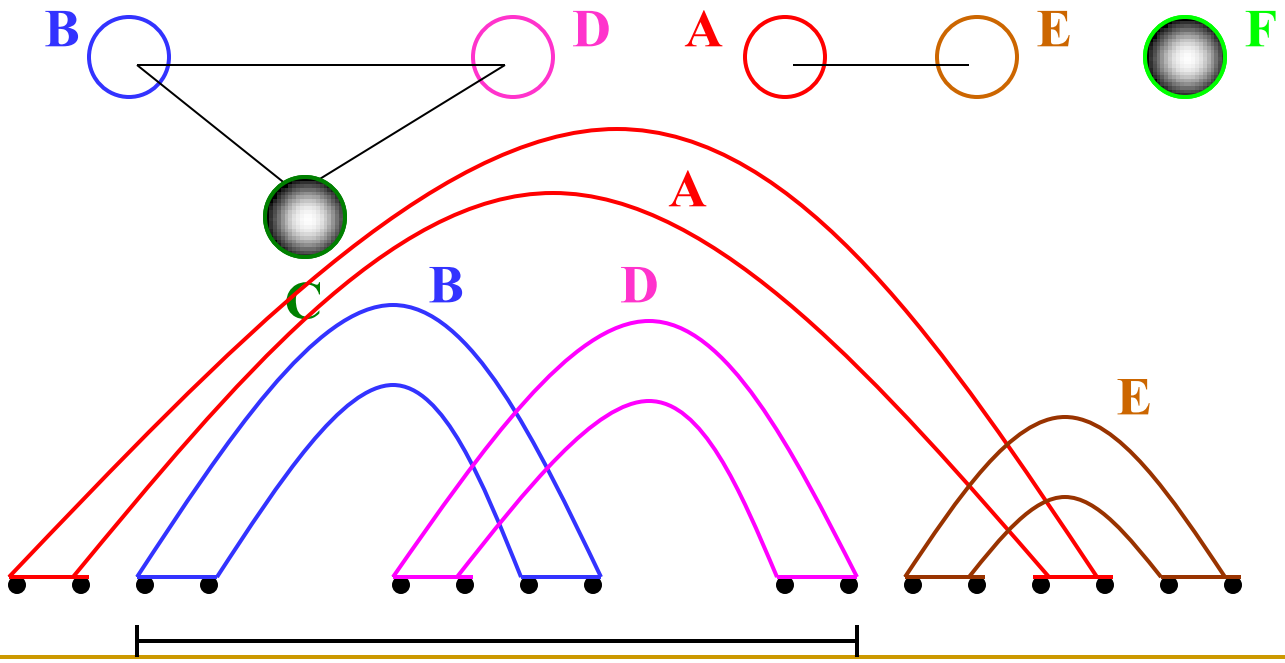
Interleaving Graphs (Continued)

- **Oriented cycles are cycles that have the following form**
- **Mark them on the interleave graph**
- **Unoriented cycles are cycles that have the following form**
- **In our example, A, B, D, E are unoriented cycles while C, F are oriented cycles**



Hurdles

- **Remove the oriented components from the interleaving graph**
- **The following is the breakpoint graph with these oriented components removed**
- **Hurdles are connected components that do not contain any other connected components within it**



Reversal Distance with Hurdles

- **Hurdles are obstacles in the genome rearrangement problem**
- **They cause a higher number of required reversals for a permutation to transform into the identity permutation**
- **Let $h(\pi)$ be the number of hurdles in permutation π**
- **Taking into account of hurdles, the following formula gives a tighter bound on reversal distance:**

$$d(\pi) \geq n+1 - c(\pi) + h(\pi)$$