Algorithms for Genome Research

Pedro Feijão

Winter 2014/15

pfeijao@cebitec.uni-bielefeld.de

Preliminaries

- Wiki Page:
  `http://wiki.techfak.uni-bielefeld.de/gi/Teaching`

- Organization

Genome Rearrangements

Lecture 1 - Comparative Genomics – Genome Rearrangements

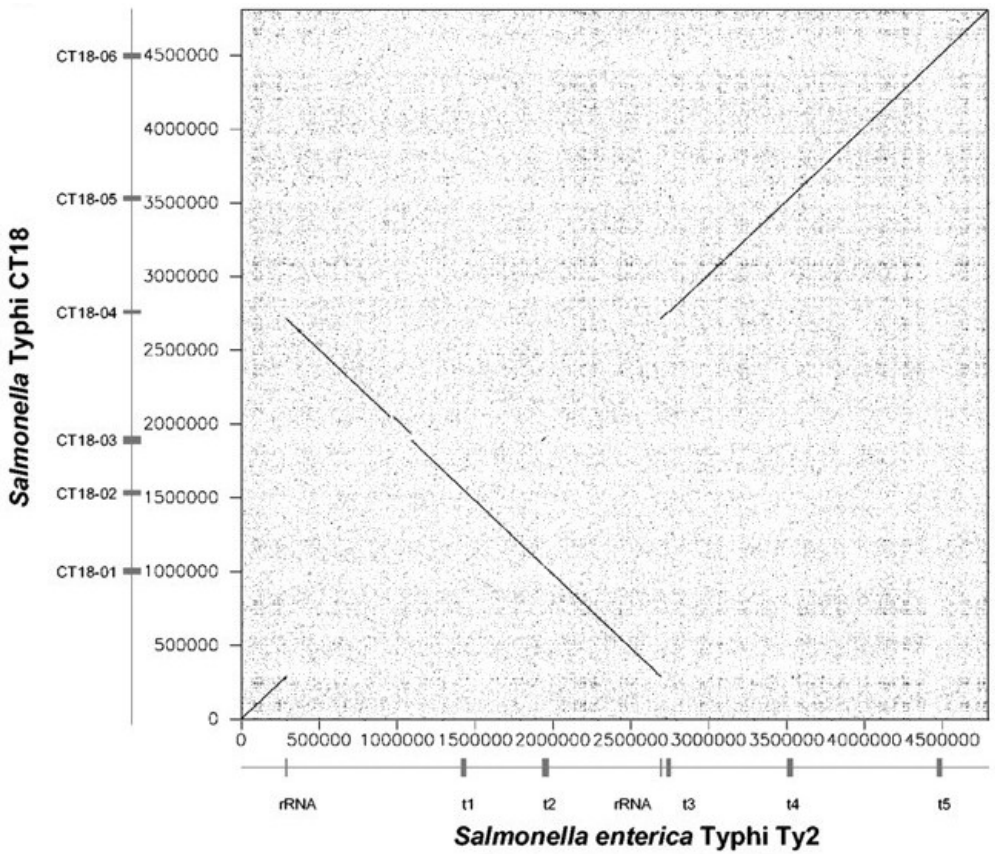
Turnip (Speiserübe) vs. Cabbage (Weißkohl)

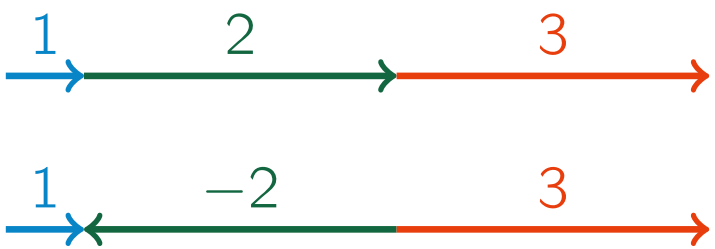
Although cabbages and turnips share a recent common ancestor, they look and taste different.

Genome Rearrangements - Background

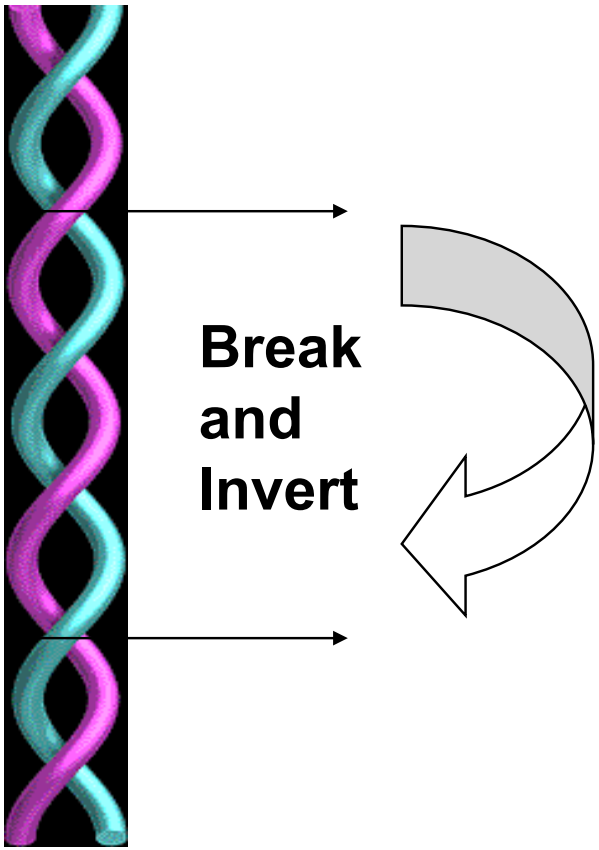
- In the 1980s Jeffrey Palmer studied evolution of plant organelles by comparing mitochondrial genomes of cabbage and turnip.
- He found 99% similarity between genes.
- These surprisingly similar gene sequences differed in gene order.
- This study helped pave the way to analyzing genome rearrangements in molecular evolution.

Genome Rearrangements - Background





Reversal Example



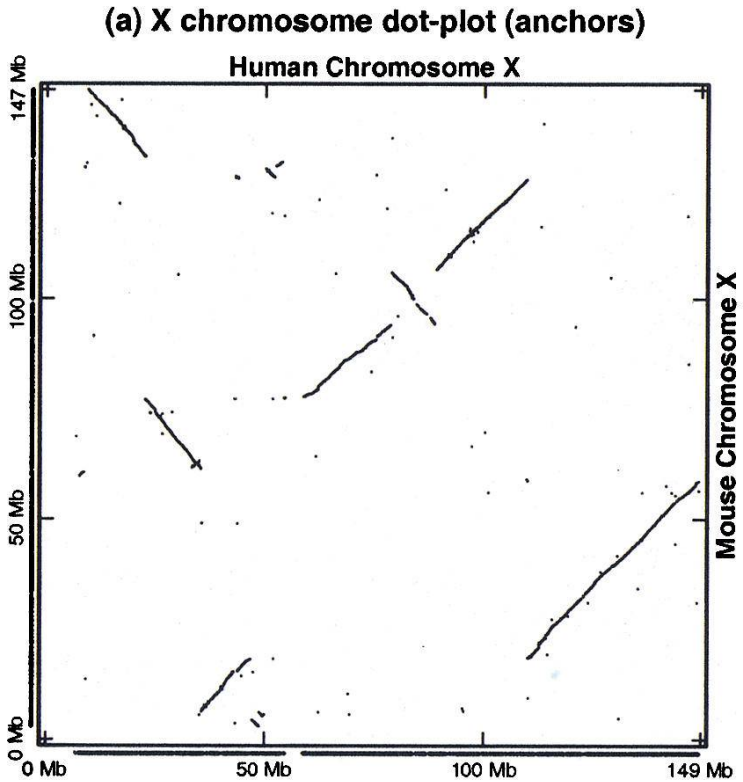
5’ ATGCCTGTACTA 3’

3’ TACGGACATGAT 5’

5’ ATGTACAGGCTA 3’

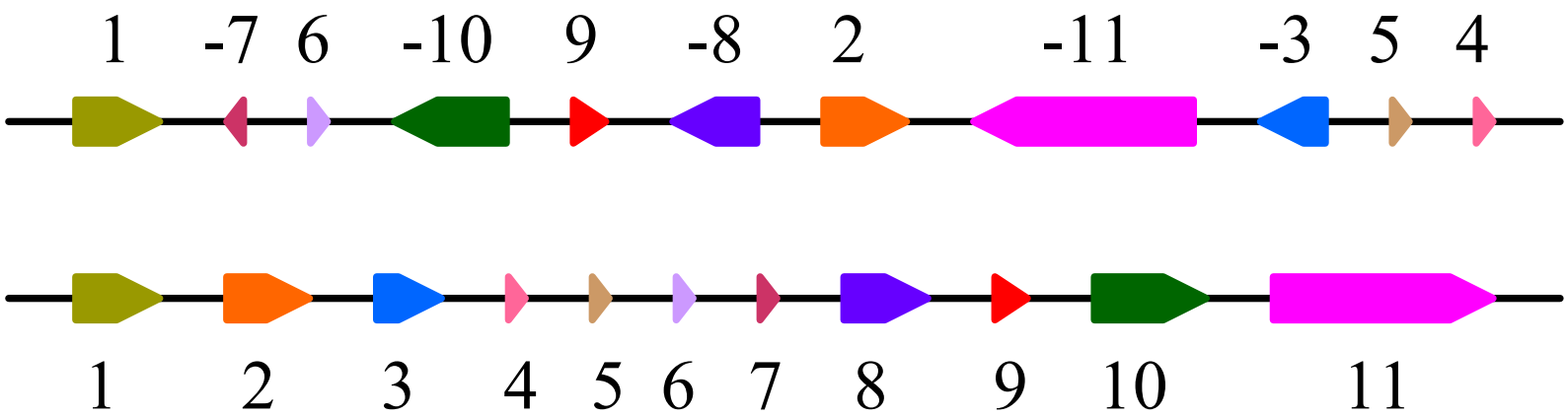
3’ TACATGTCCGAT 5’

Human vs. Mouse – X-chromosome



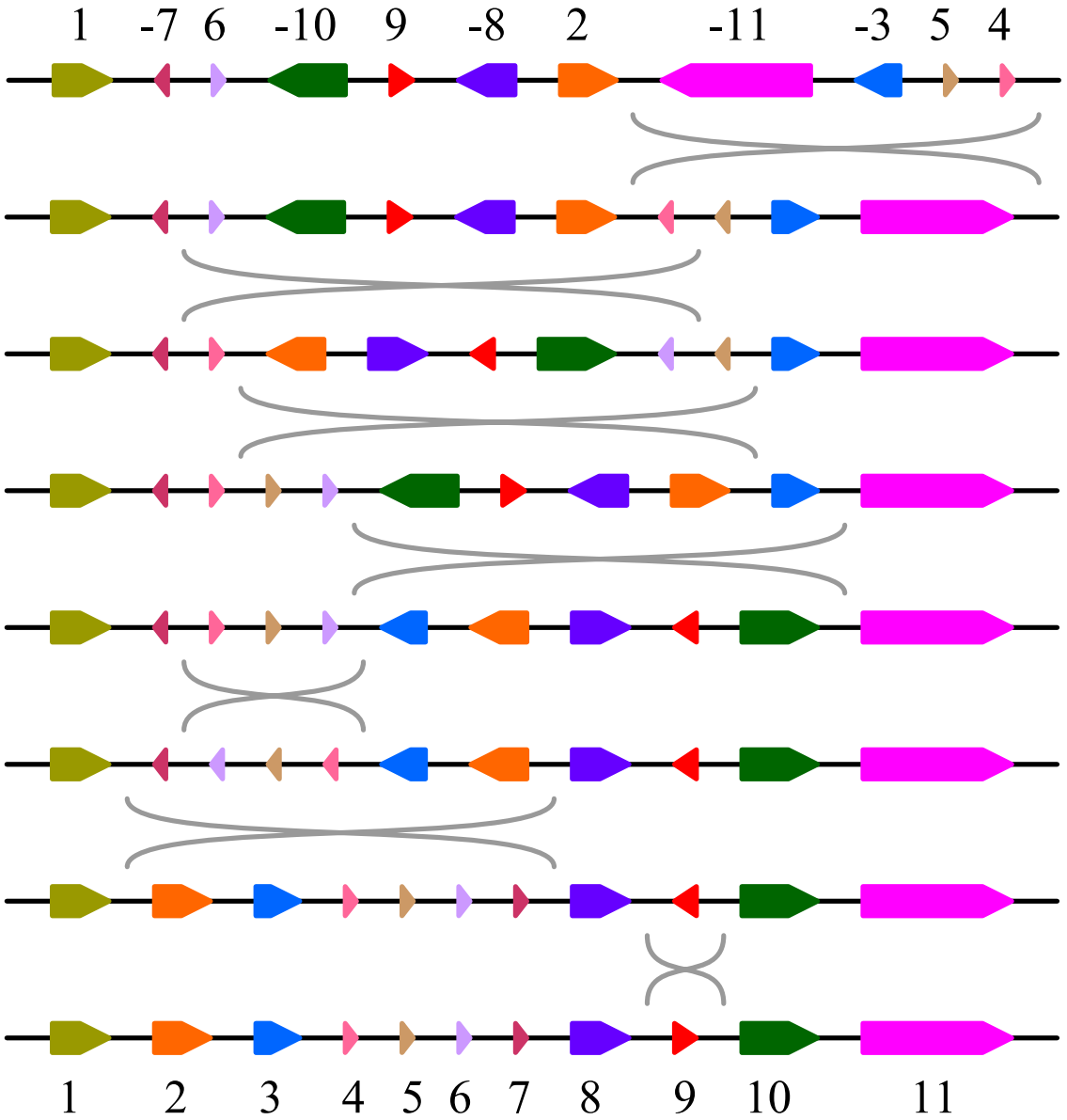
Pevzner, P.A. and Tesler, G. 2003. **Genome rearrangements in mammalian evolution: Lessons from human and mouse genomic sequences**. *Genome Res.* **13**: 13-26.

Human vs. Mouse – X-chromosome

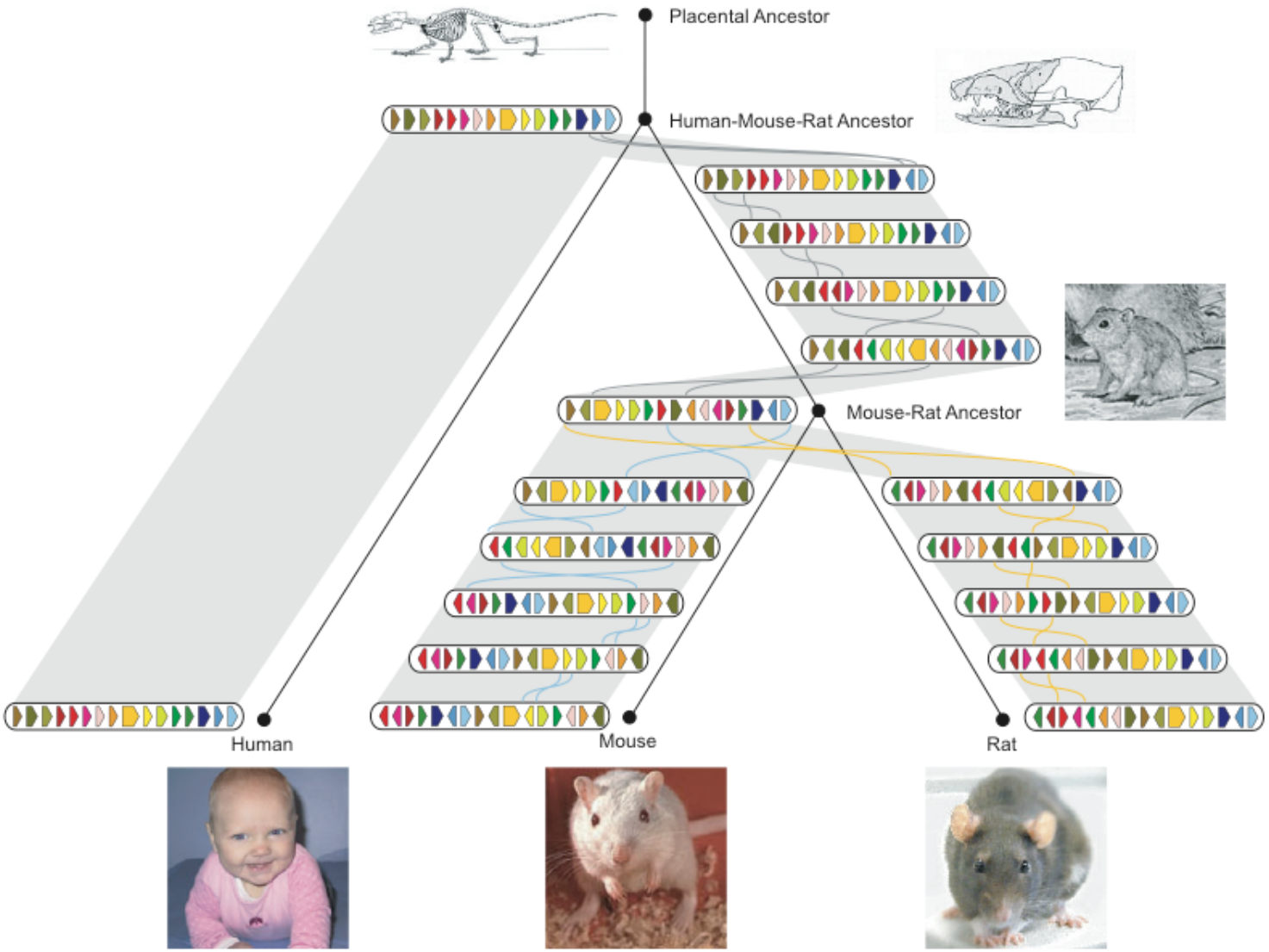


- How many rearrangements do we need to *transform* one genome into the other?

Human vs. Mouse – X-chromosome



X Chromosome history

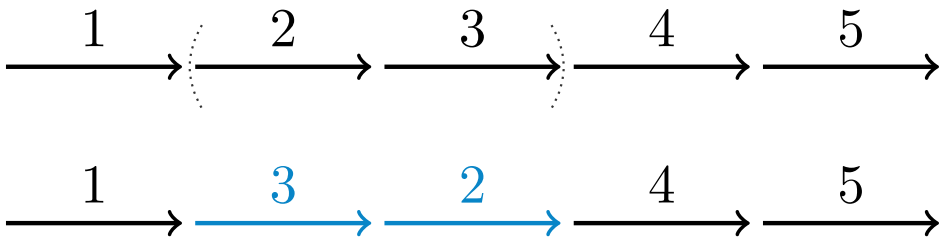


Rat Consortium, *Nature*, 2004

Genome Rearrangements

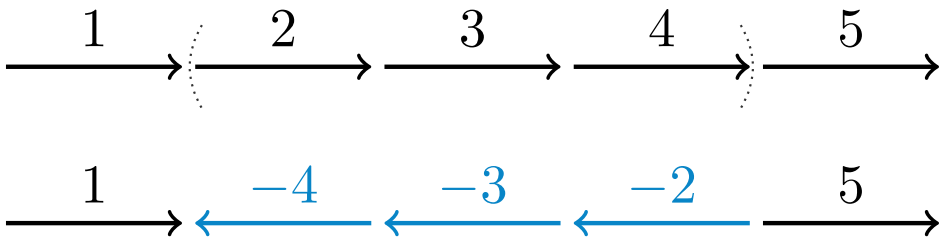
- **Genome rearrangements** are evolutionary events that *shuffle* the genome.
- Important questions:
  - What is the **minimum number** of rearrangement operations needed to transform one genome into another? (Distance)
  - Can we find a **rearrangement scenario** with this minimum number of operations? (Sorting)
- Several types of **rearrangement operations** were studied:

Common Rearrangement Operations



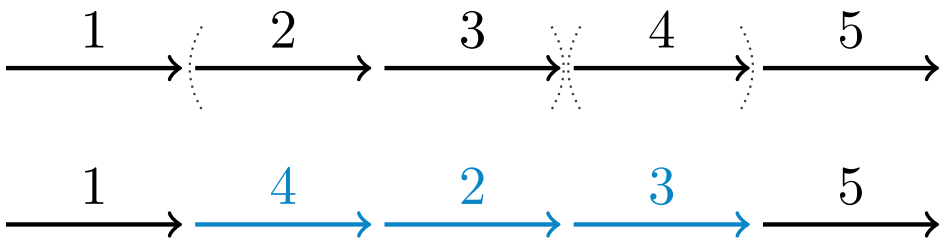
Unsigned Reversal/Inversion

Common Rearrangement Operations



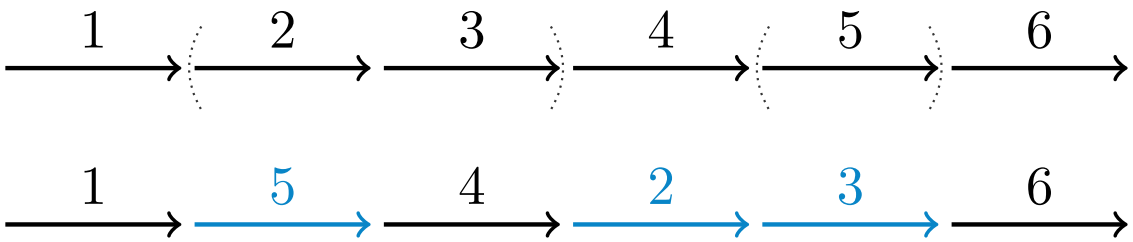
Signed Reversal/Inversion

Common Rearrangement Operations



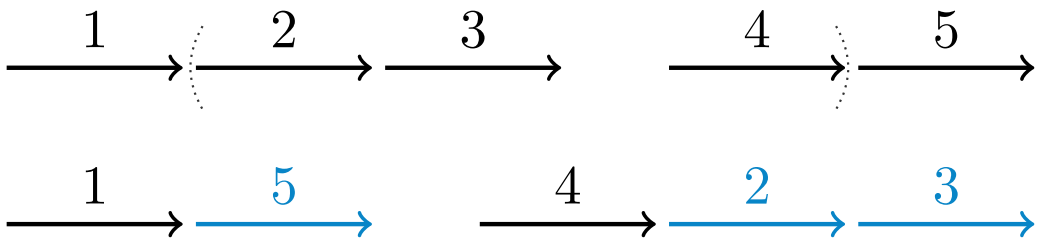
Transposition

Common Rearrangement Operations



Block Interchange

Common Rearrangement Operations



Translocation (*multichromosomal* operation)

Genome Rearrangement Models

- Several models were proposed, allowing only one operation or combining two or more.
- Each different models results in a *combinatorial problem* that must be solved.
- Usually polinomially solvable, notable exceptions: Unsigned reversal and Transposition (NP-hard)

Reversal Models

- Since 1990, beginning with Sankoff in 1992, many papers have been devoted to the subject of **reversal distance**.
- The *unsigned reversal* distance is NP-hard (Caprara 1997)
- The *signed reversal* was solved polynomially by Hannenhalli and Pevzner in 1995.

Definitions

- A **signed permutation** is a permutation on the set $\{0, 1, \ldots, n\}$ in which every element has a *sign*. To simplify, permutations will always start with 0 and end with n. *For example*:

$$\pi_1 = (0 \quad -2 \quad -1 \quad 4 \quad 3 \quad 5 \quad -8 \quad 6 \quad 7 \quad 9)$$

- A **point** $p \cdot q$ is a pair of consecutive elements in the permutation. In the above example, $0 \cdot -2$ and $-2 \cdot -1$ are the first two points of π_1.
- When a point is in the form $i \cdot (i+1)$ or $-(i+1) \cdot -i$ it is called an **(conserved) adjacency**. Otherwise, it is a **breakpoint**.

Breakpoints

$$\pi_1 = (0 \quad -2 \quad -1 \quad 4 \quad 3 \quad 5 \quad -8 \quad 6 \quad 7 \quad 9)$$

- In this permutation, there are *two* adjacencies, $-2 \cdot -1$ and $6 \cdot 7$, and *seven* breakpoints.
- The **Breakpoint Distance** is the number of breakpoints in a permutation, that is, distance from the **identity**:

$$\mathrm{Id} = (0 \quad 1 \quad 2 \quad 3 \quad 4 \quad 5 \quad 6 \quad 7 \quad 8 \quad 9)$$

- It is one the simplest measure of dissimilarity for genome rearrangements. *Notation*: $d_{\mathrm{BP}}(\pi_1) = 7$.

For instance, the permutation

$$\pi_2 = (0 \quad -4 \quad -3 \quad -2 \quad -1 \quad 5 \quad 6 \quad 7 \quad 8 \quad 9)$$

has 2 breakpoints, which means that π_2 is *closer* to the identity than π_1.

Reversals

- An **reversal** of a permutation interval reverts the *order* and *sign* of all elements of the interval.

$$\pi_1 = (0 \quad -2 \quad -1 \quad 4 \quad 3 \quad 5 \quad -8 \quad 6 \quad 7 \quad 9)$$

$$\pi_1' = (0 \quad -2 \quad -5 \quad -3 \quad -4 \quad 1 \quad -8 \quad 6 \quad 7 \quad 9)$$

- The **reversal distance** is the minimum number of reversals needed to transform one permutation into another (usually the other permutation is the identity). Notation: $d_R(\pi_1)$.
- Finding such a scenario of reversals is called **sorting by reversals**.
  - *Distance* vs. *Sorting*

BP vs. Reversals

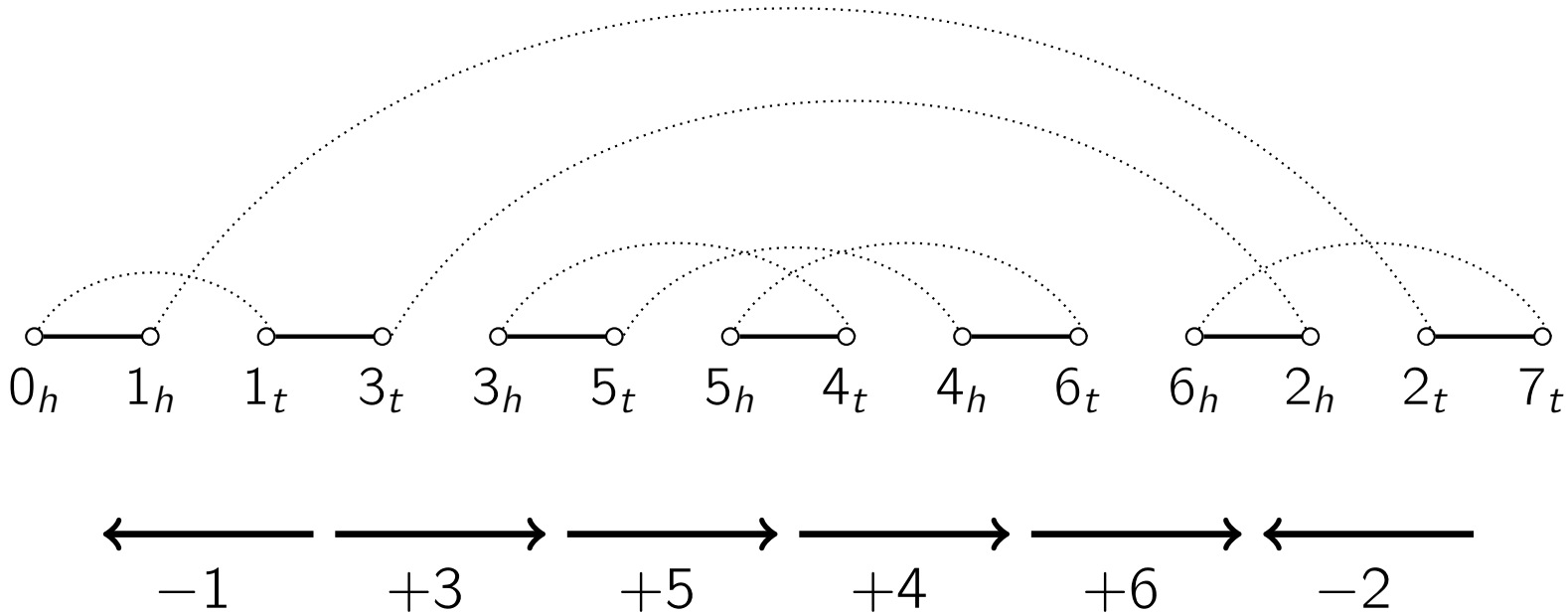
- A reversal changes the number of breakpoints by at most 2.
- This gives a simple *lower bound* for the reversal distance:

$$d_R(\pi_1) \geq \frac{d_{\text{BP}}(\pi_1)}{2}$$

- Using BP for lower bound is an useful *first approach* in many models.

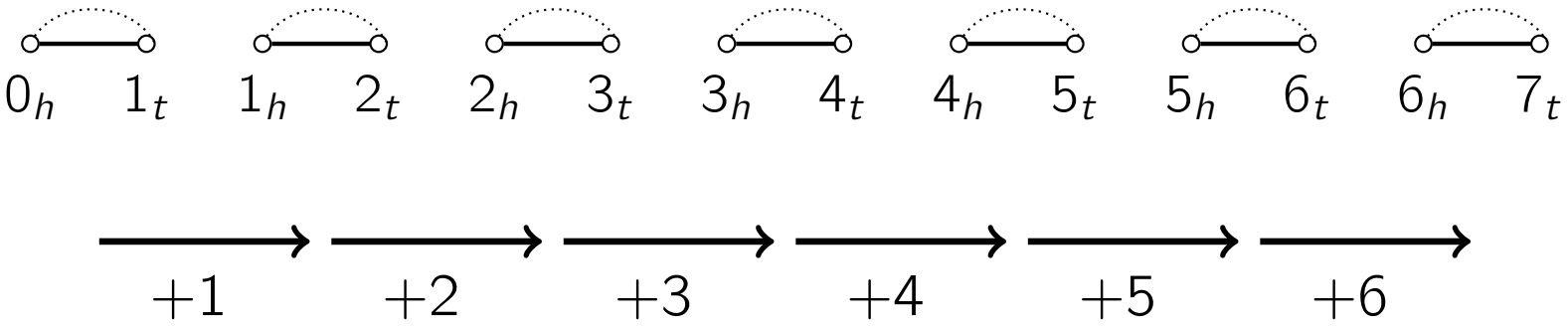
Breakpoint Graph - Genomes as Graphs

- The BP graph of a is a very useful structure for studying rearrangement problems. Notation $BP(\pi)$.
- **Vertices** are the gene extremities (tail and head).
- **Black edges** between consecutive gene extremities (reality edges).
- **Grey edges** between consecutive gene extremities of the identity (desire edges).



Breakpoint Graph

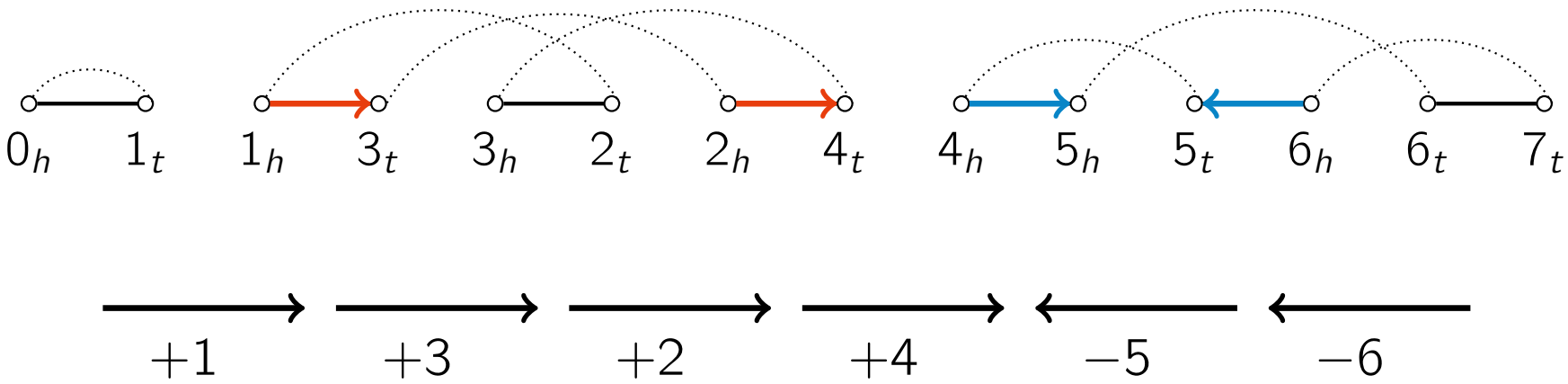
- When the input genome is the identity, the BP graph is composed of n **trivial cycles**.



- Sorting is equivalent to **increasing the cycles of the BP graph**.
- What happens in the BP graph when a reversal is applied?

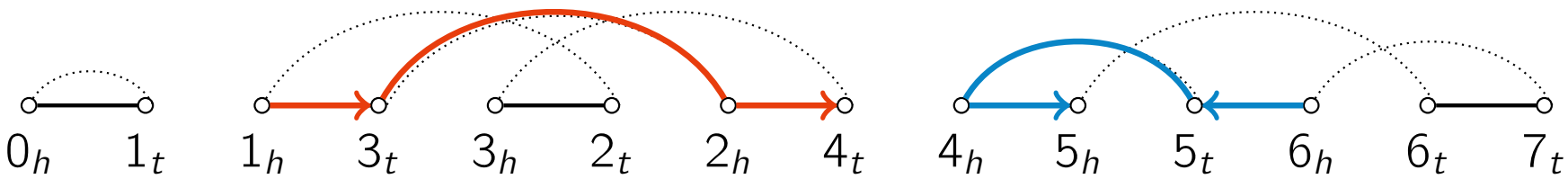
BP Graph Elements

- Two black edges in they same cycle are **convergent** if, when traversing the cycle both edges induce the *same direction*. Otherwise, they are **divergent**.



BP Graph Elements

- A grey edge is **oriented** if its two incident black edges are *divergent*, otherwise the edge is **unoriented**.



- Equivalently, a grey edge is **oriented** if it "contains" an odd number of vertices, and **unoriented** otherwise (even number of vertices).

BP Graph Elements

- A cycle is **oriented** if it contains *at least one* oriented edge. Otherwise, it is **unoriented**.

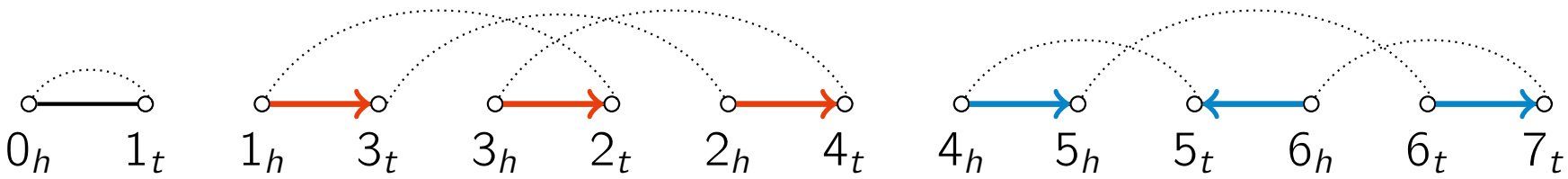
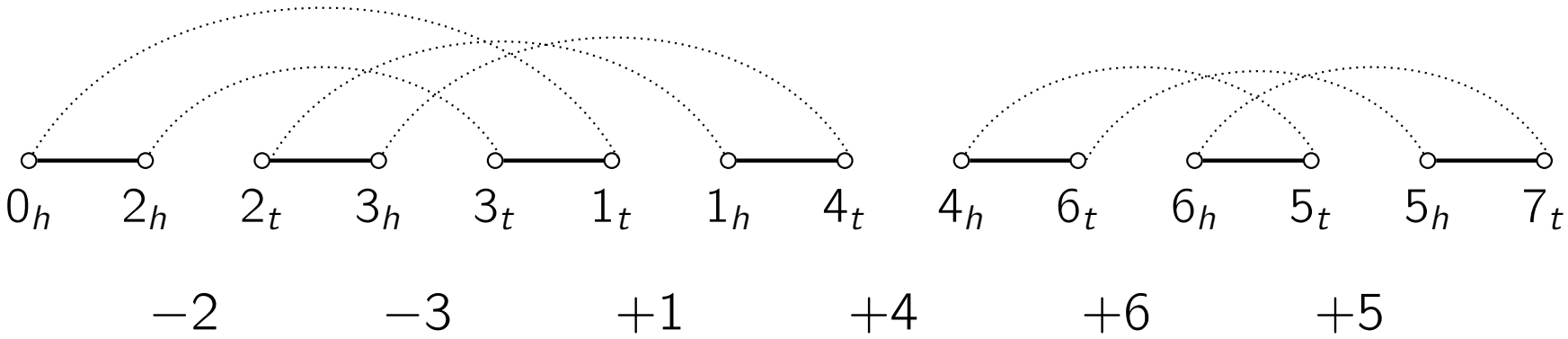


Figure : Example of unoriented and oriented cycles.

BP Graph Components

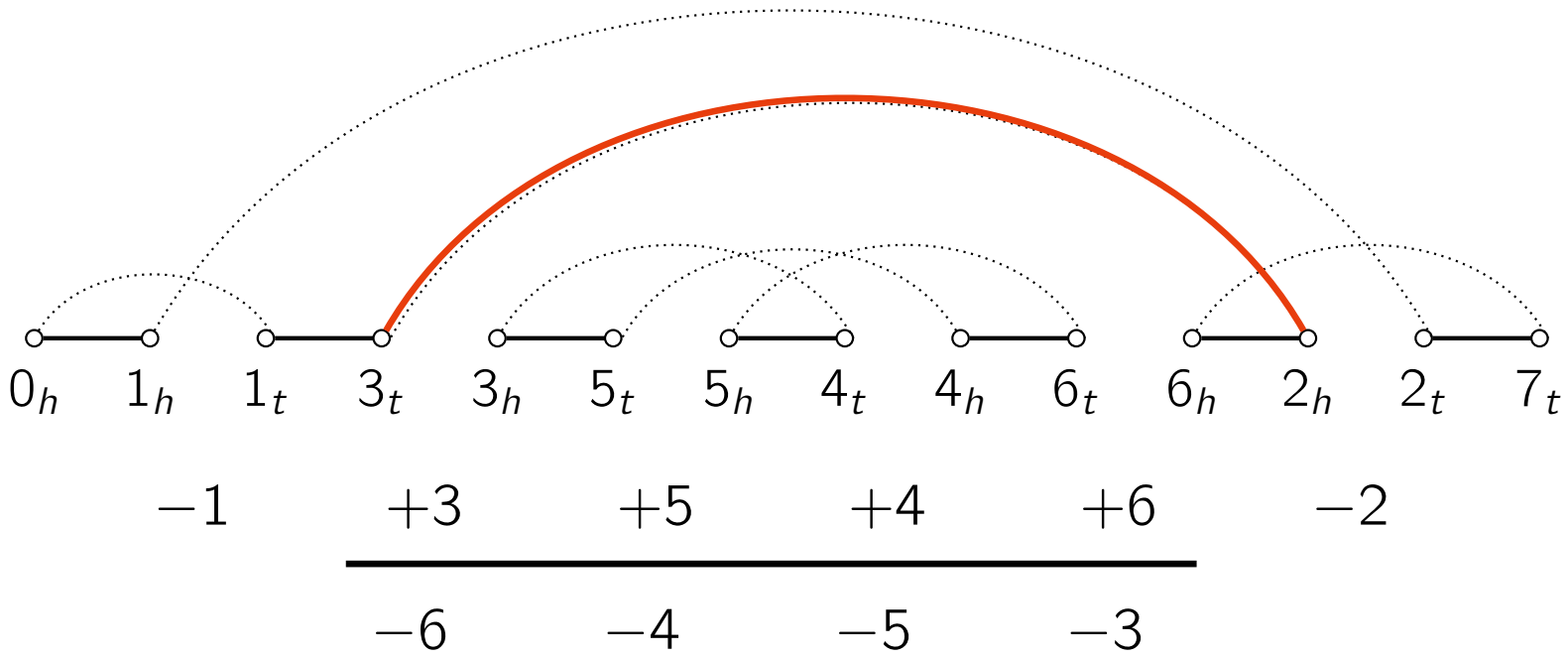
- Two cycles are **connected** if they have overlapping edges.
- A **component** is a subset of connected cycles.

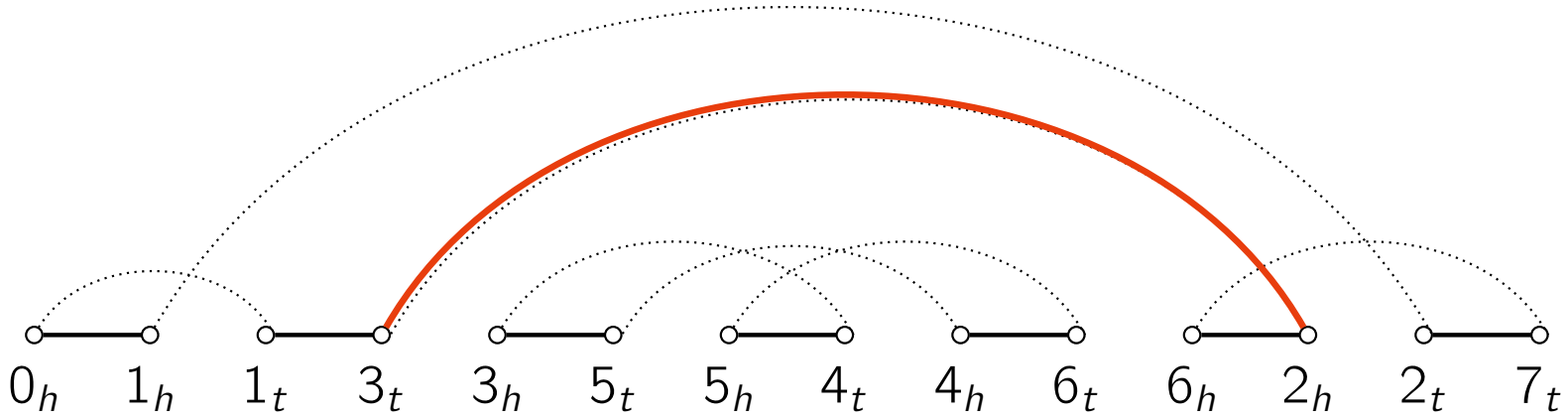


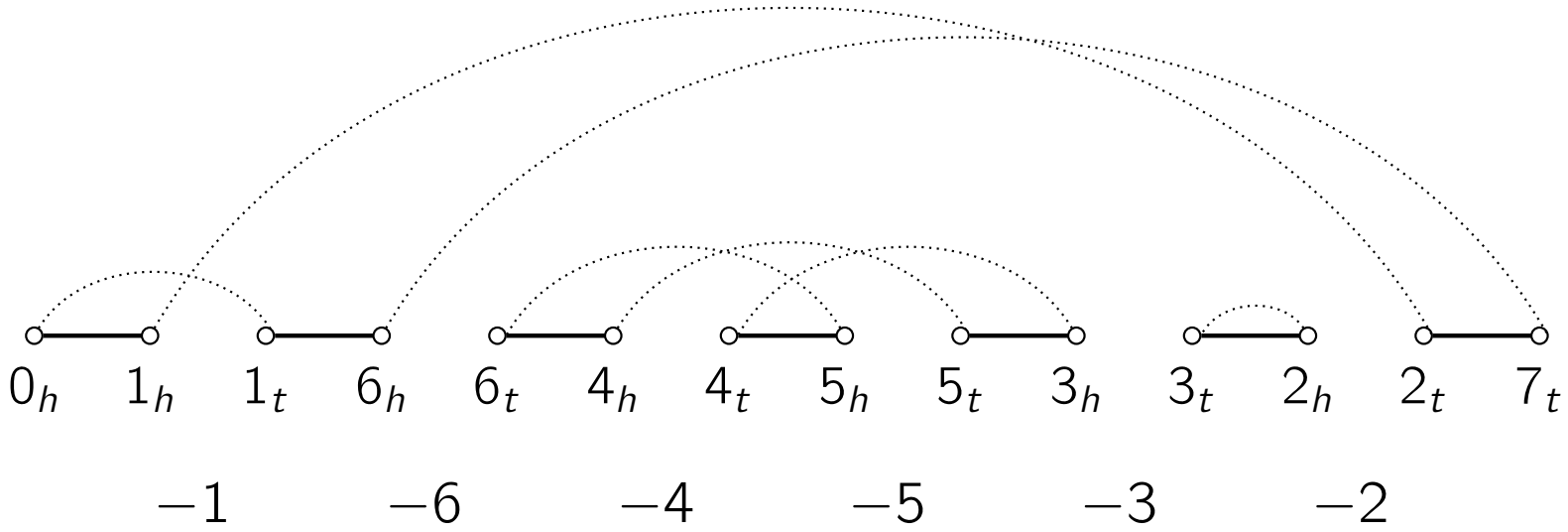
- An **oriented component** has at least one oriented cycle, otherwise it is a **unoriented component**.

Inducing Reversals

- A reversal **induced** by a grey edge (equivalenty, by two black edges) reverses the elements that are *completely* contained in the edge.




0_h 1_h 1_t 3_t 3_h 5_t 5_h 4_t 4_h 6_t 6_h 2_h 2_t 7_t
-1 $+3$ $+5$ $+4$ $+6$ -2

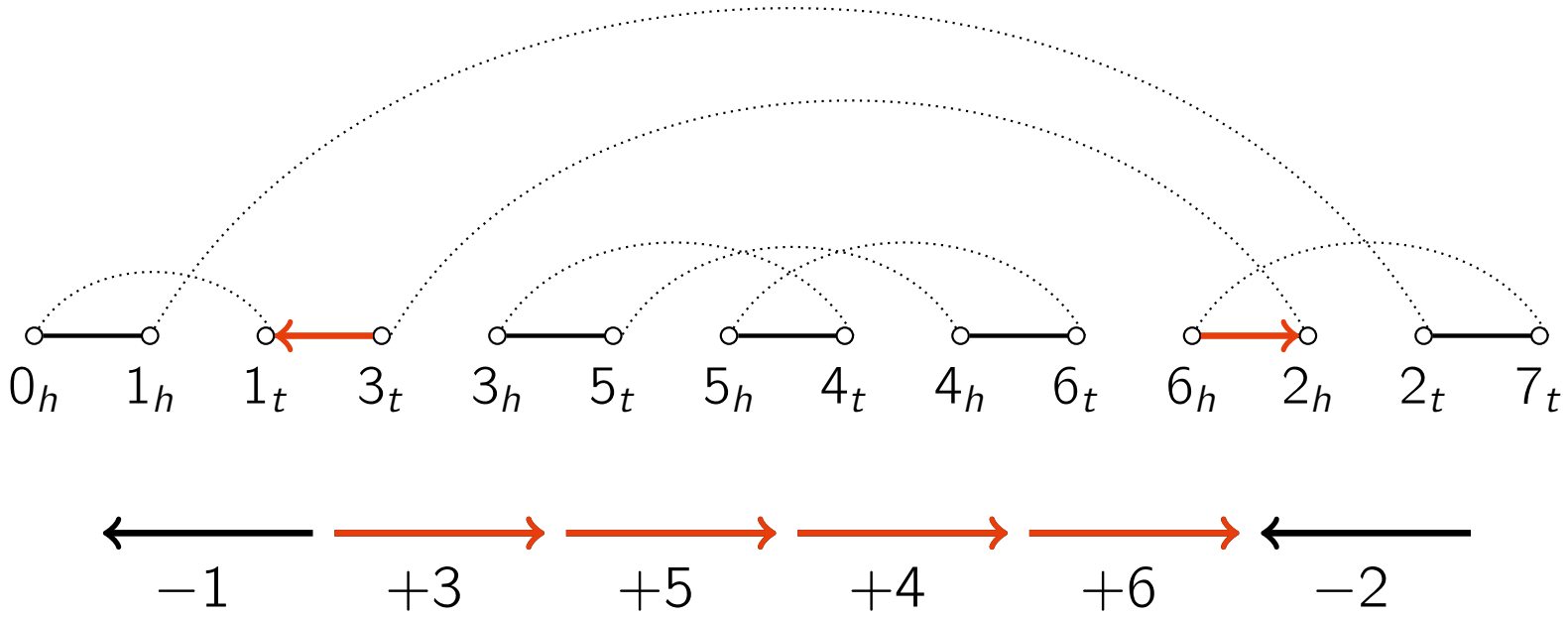

0_h 1_h 1_t 6_h 6_t 4_h 4_t 5_h 5_t 3_h 3_t 2_h 2_t 7_t
-1 -6 -4 -5 -3 -2

Reversals and effect on cycles

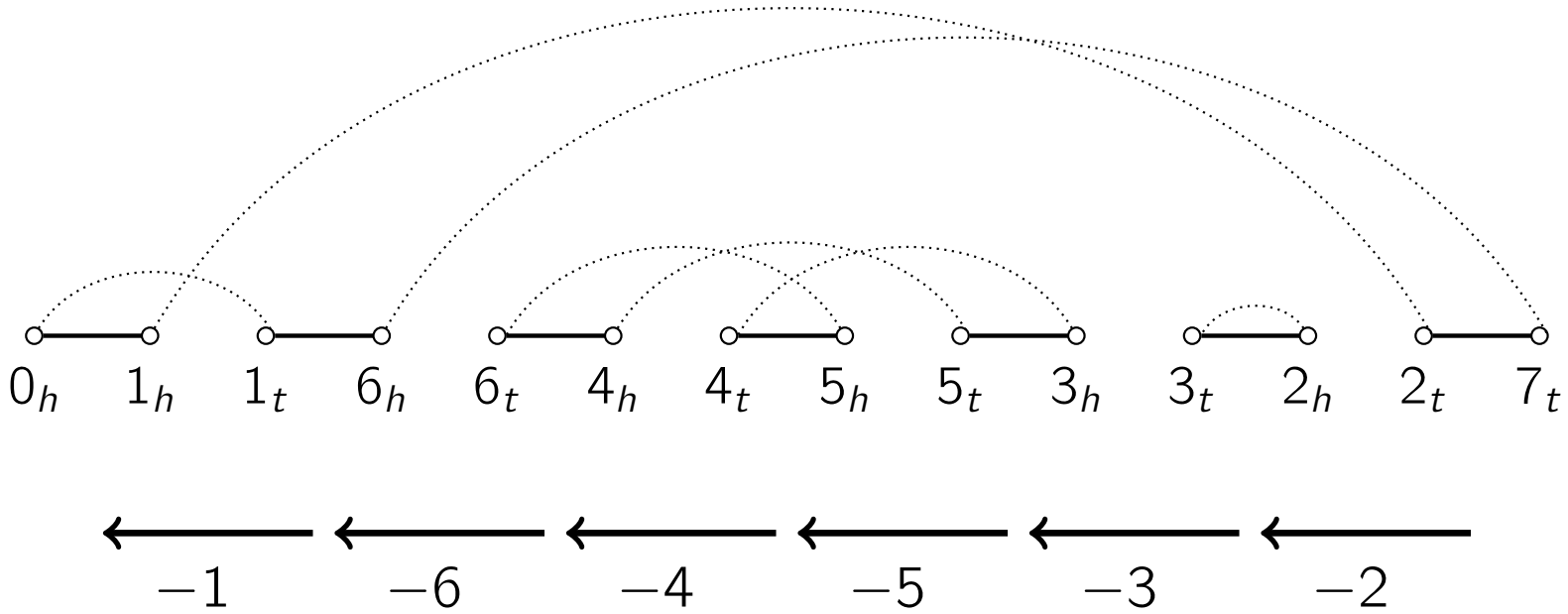
1. Black Edges are on the **same cycle**:
   - **Type I**: Divergent edges: breaks the cycle. $\Delta C = +1$.
   - **Type II**: Convergent edges: $\Delta C = 0$, may change cycle orientation.
2. Black Edges on **different cycles**:
   - **Type III**: Merges the two cycles. $\Delta C = -1$.

So far, we only used **Type I** operations, to sort oriented components.

Type I - Same Cycle, divergent

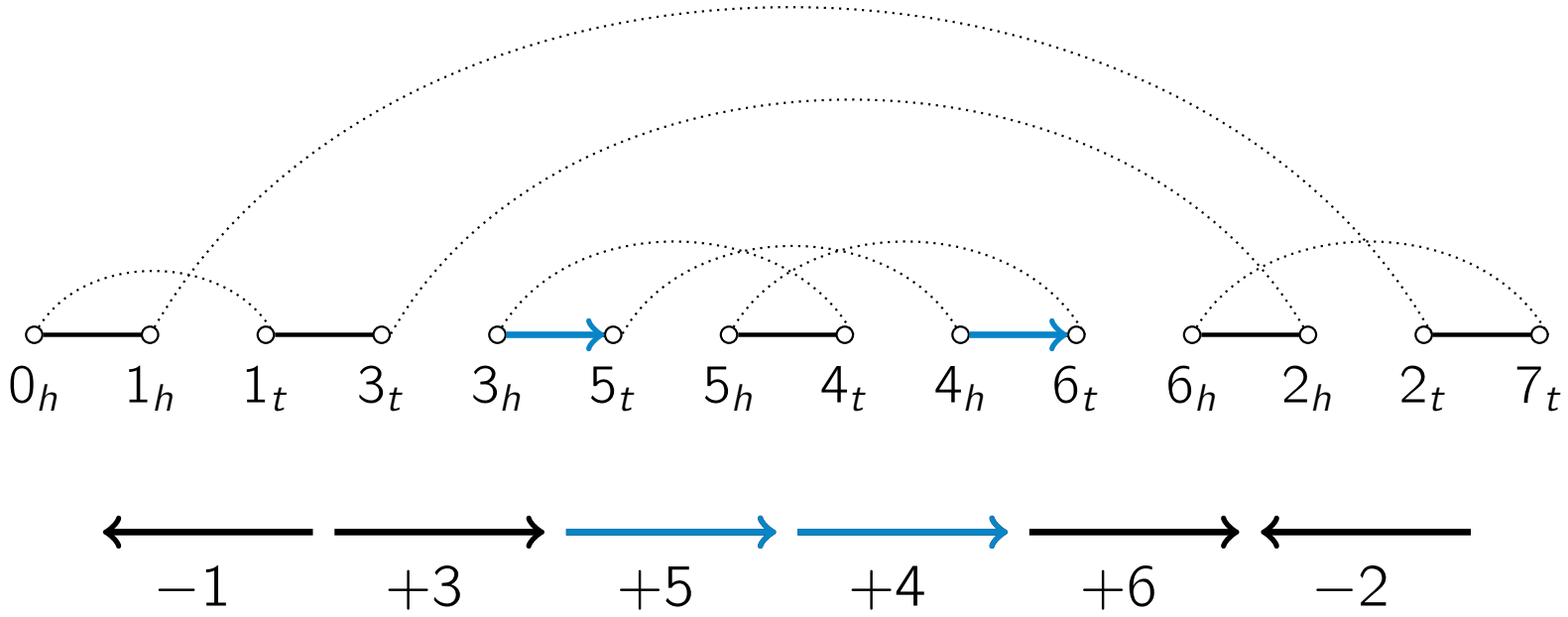


Type I - Same Cycle, divergent

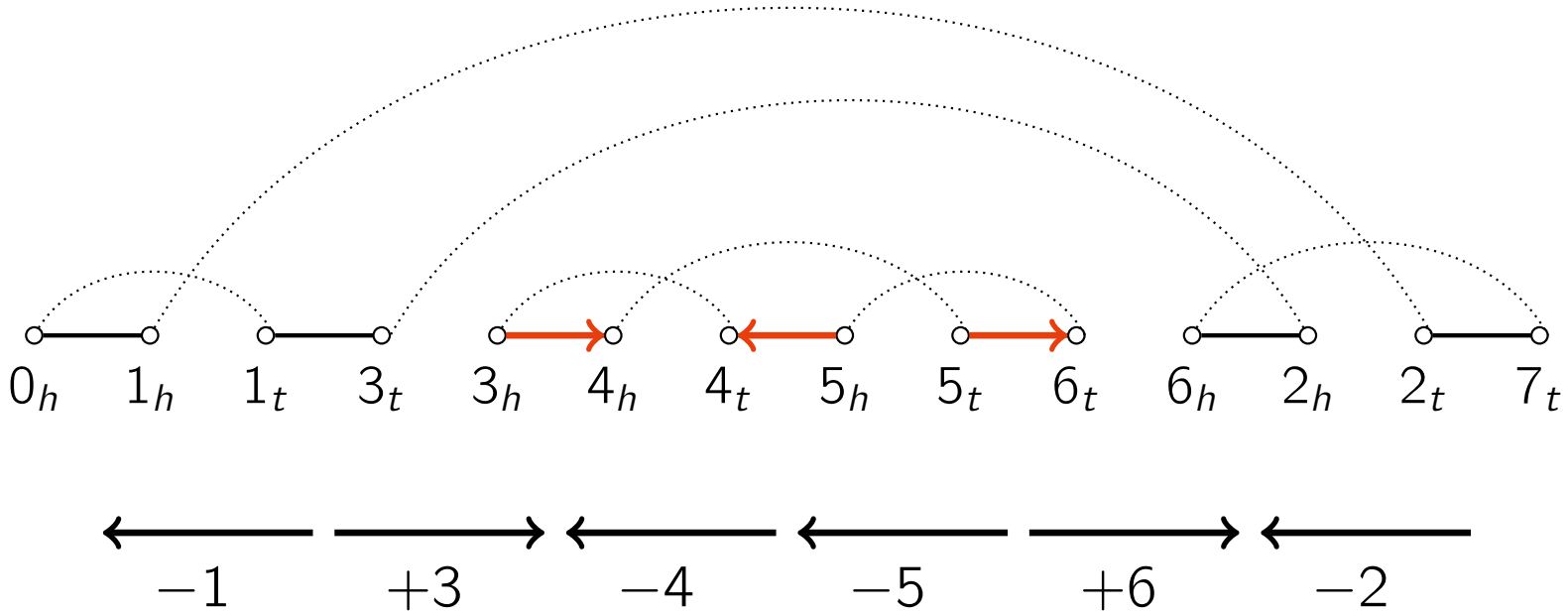


This reversal increases the number of cycles by one, $\Delta C = +1$.

Type II - Same Cycle, convergent

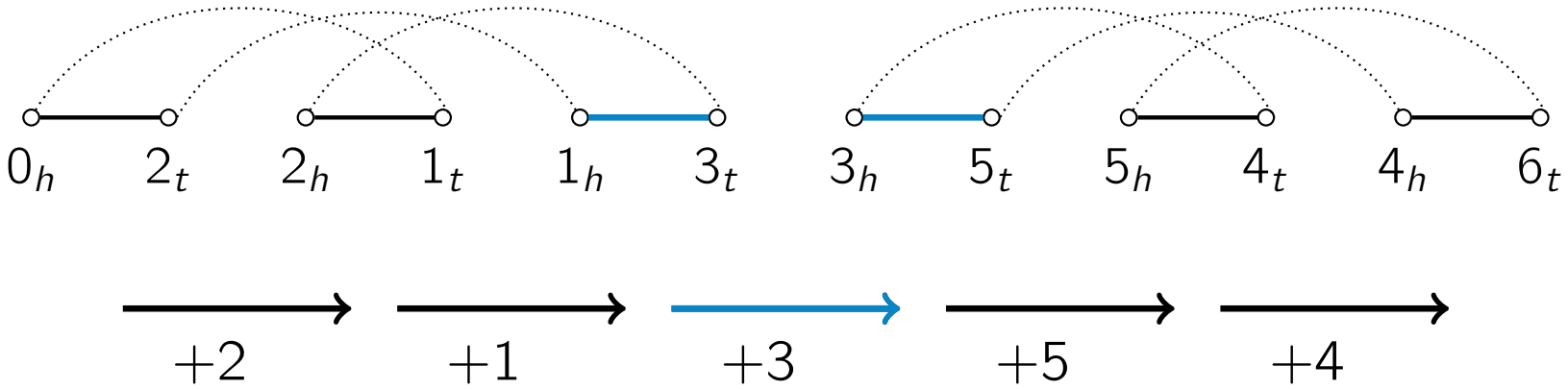


Type II - Same Cycle, convergent

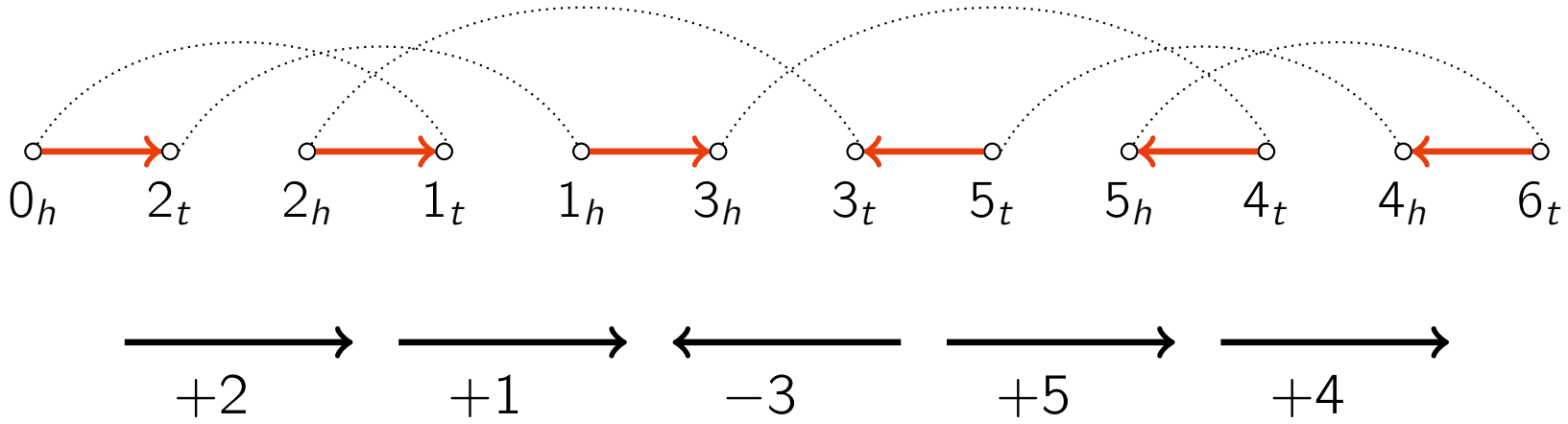


Does not change number of cycles ($\Delta C = 0$), but the cycle is **oriented**.

Type III - Different Cycles



Type III - Different Cycles



Merges the two cycles, decreasing the number of cycles by one ($\Delta C = -1$), but the new cycle is **oriented**.

Breakpoint Graph - Lower Bound

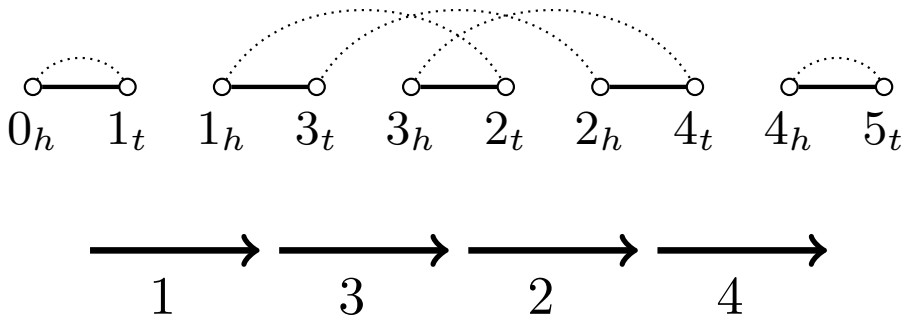
- A reversal changes the number of cycles of the BP graph at most by 1.
- Then, we have a **lower bound** for the reversal distance:

$$d_R(\pi) \geq N - C$$

  where C is the *number of cycles* in the BP graph of π.
- This bound is **very tight**, that is, usually it is exactly the reversal distance.
- When is this bound not *exactly* the distance?
  - When it is not possible to increase the cycles of BP with a reversal.
  - That occurs in the presence of **unoriented components**.

Unoriented components

- In the example below, there is no reversal that increases the number of cycles.

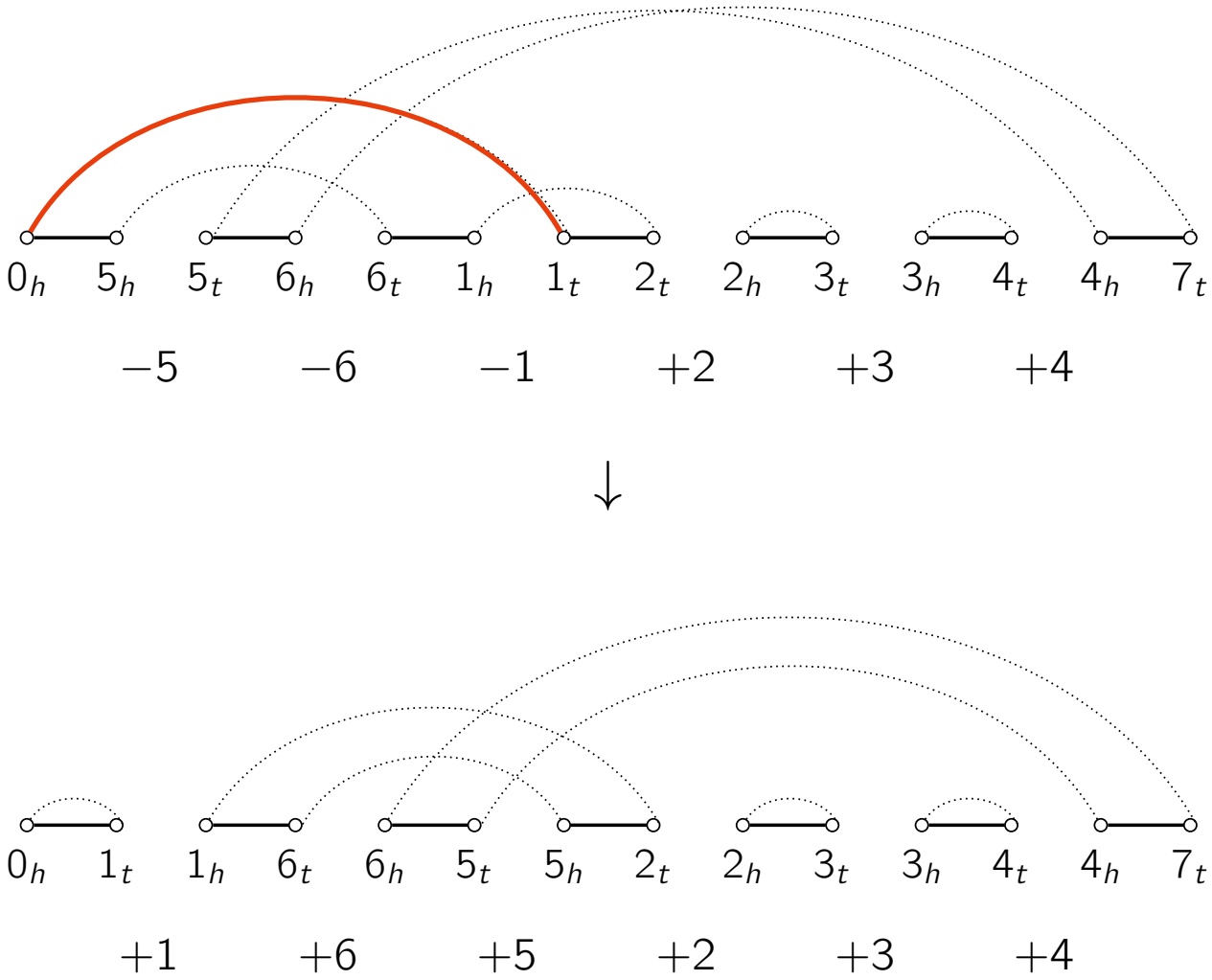


- The lower bound is $N - C = 5 - 3 = 2$, but the real distance is 3, because one extra reversal is needed to *orient* the unoriented cycle in the BP graph.
- Let's first consider the *good* cases, without unoriented components.

Sorting oriented components

- If there are only oriented components, there is always a reversal that increases the number of cycles.
- The problem is, after such a reversal, it is possible the some components become **unoriented**.

Bad reversal - Example



- Increased number of cycles but created a bad component!

Finding "good" reversals

- Is it possible to find a reversal that increases the number of cycles **AND** also does not create an unoriented component? **YES!**

Sorting oriented components

Theorem (Hannenhalli-Pevzer, 95)

If the graph $BP(\pi)$ has only **oriented components**, *then*

$$d_R(\pi) = N - C$$

where N is the number of elements of π and C is the number of cycles of $BP(\pi)$.

- This means that there is always at least one "good" reversal, that increases the number of cycles of $BP(\pi)$ and *does not create any unoriented component*.
- These are called **safe reversals**. How can we find them?