



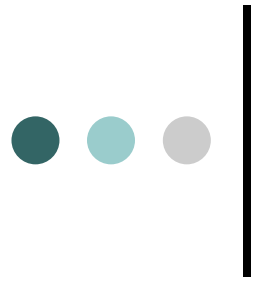
Gene and genome duplication

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Plan

1. Genome rearrangement and multigene families
2. Genome duplication
3. Duplication of chromosomal segments
4. Conclusion



Genome rearrangement

Chromosomes evolved by insertion, deletion, movement of genes

Genomic approach: Compare gene orders

Hypothesis: Homologous genes are known

Chromosome \longrightarrow sequence of signed genes (or blocks)

b -a d -e -c f



Multigene families

In the human genome ~15% protein genes duplicated
(*Li, Wang, Nekrutenko, 2001*)

~16% yeast, ~25% Arabidopsis (*Wolfe, 2001*)

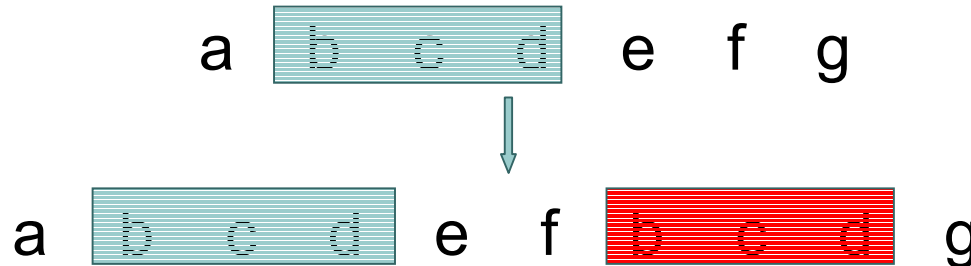
Compare sequences of signed genes allowing **many copies of each gene**

b -a d a -e -c e f d a

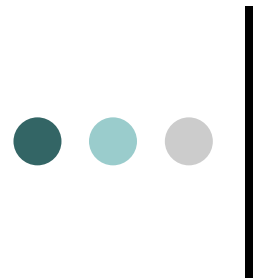


Multigene families due to:

- ❑ Single gene duplication;
- ❑ **Segment duplication**: Tandem duplication or duplication transposition



- ❑ Horizontal gene transfer;
- ❑ **Genome-wide doubling** event



Algorithms and models

- **Genome rearrangement** with multigene families

- Exemplar approach, *Sankoff 1999*

- Insertion, deletion, gene duplication,

Marron, Swensen, Moret 2003

- **Reconciliation analysis**, projecting gene tree on phylogenetic tree

Hallett, Lagergren 2000, Page, Cotton 2000;

Chen, Durand, Farach 2000, Sankoff, El-Mabrouk 2000

- **Probabilistic models** for the generation of multigene families



Find the ancestor of a genome with multiple gene copies

- **Genome duplication**

N. El-Mabrouk and D. Sankoff, SIAM, J. Comp., 2003

- **Duplication of chromosomal segments**

N. El-Mabrouk, J. Comp. Sys. Sci., 2002

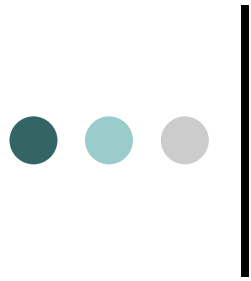
- **Genome duplication for unordered chromosomes**

N. El-Mabrouk and D. Sankoff 1998



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Genome doubling

1: a b -d ; 2: h c f -g e



1: a b -d ; 2: h c f -g e

1': a b -d ; 2': h c f -g e

Tetraploid = 4n chromosomes

Evidence across the **eukaryote spectrum**; Two duplications in early **vertebrate** evolution (*McLysaght et al. 2002*)

Particularly prevalent in **plants** (rice, oats, corn, wheat, soybeans, Arabidopsis...)



Wolfe, Shields 1997: Traces of duplication in **Saccharomyces cerevisiae**. 55 duplicated regions representing 50% of the genome



From 8 to 16 chromosomes

- I : +20 -1
- II : +40 -3 -7 +8 -5 +6
- III : +90 -10 -11
- IV : +20 +12 +12 +54 +15 +210 -3 -13 -16 +17 -24 -22 -14
-23 -19 +18 -9
- V : +280 -25 -27 -4 -26 -13
- VI : +550 -36
- VII : +36 +25 +26 +32 +6 -33 +5 -30 -34 -31 -29
- VIII : +350 -14 -37 -29 -1
- IX : +38 +39 +270
- X : +10 +40 +410 -28 -42
- XI : +42 +40 +43 +350 -41 -52 -38
- XII : +500 -53 -31 -55 -16 -18 -17 -45 -30 -15 -44
- XIII : +46 +44 +190 -43 -54 -48 -47 -46
- XIV : +49 +20 +37 +50 +390 -11
- XV : +49 +210 -22 -52 -50 -23 -45 -51 -47 -2
- XVI : +48 +32 +33 +51 +8 +240 -7 -34



Originally, duplicated genome =
2 identical copies of each chromosome

After rearrangements, duplicated segments scattered among
the genome

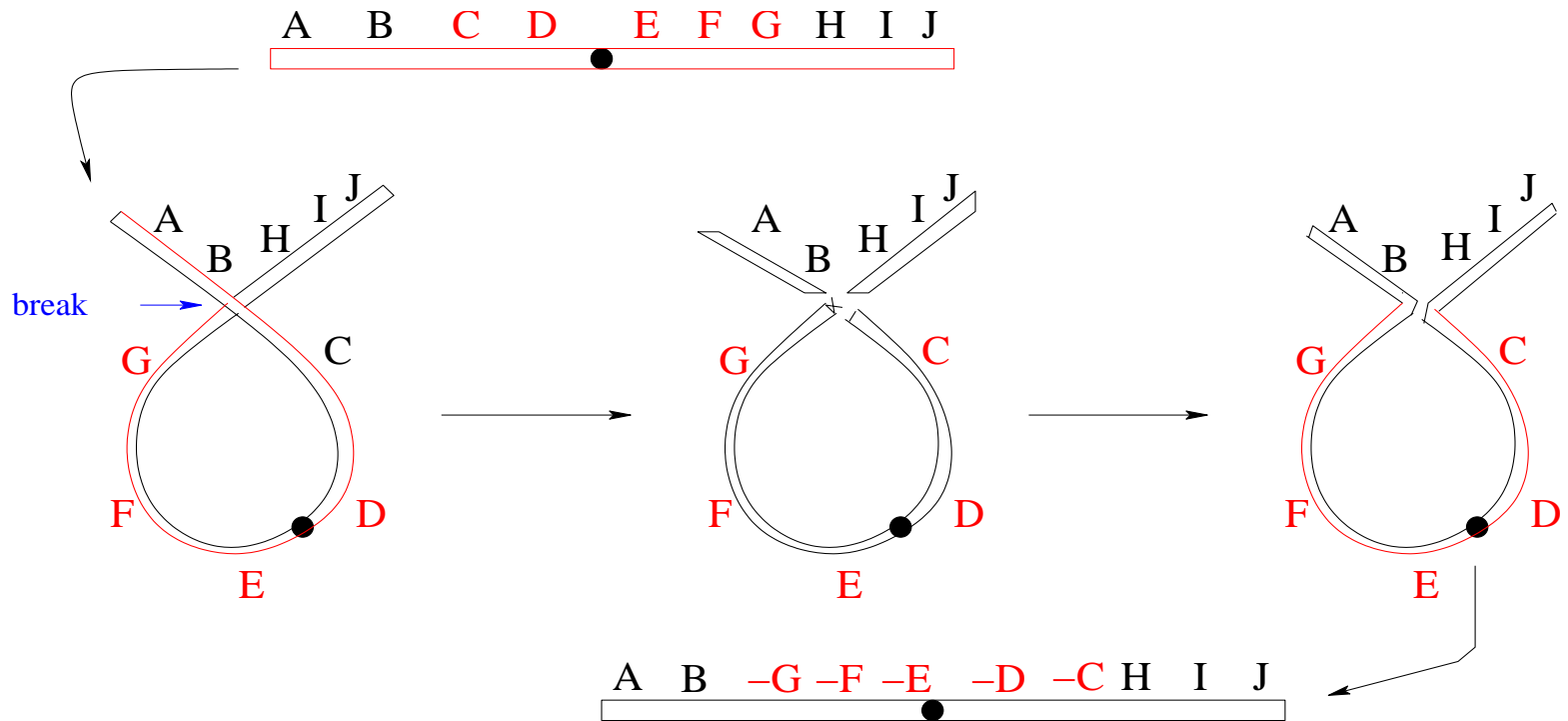
Present-day genome: Signed gene sequences, 2 copies of
each gene

Reconstruct original gene order at time of duplication

Minimum number of reversal and/or translocation



Inversion





Translocation

Reciprocal translocation:



Fusion:



Fission:





Problem:

Rearranged duplicated genome G:

1: +a +b -c +b -d 3: -e +g -f -d
2: -c -a +f 4: +h +e -g +h

Unknown duplicated genome H:

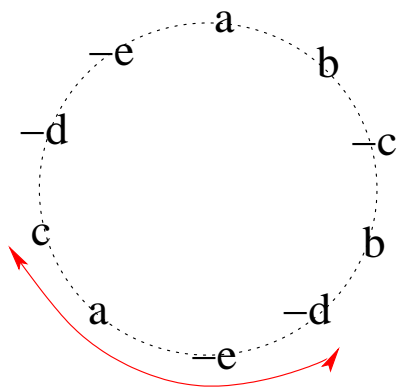
1: +a +b -d 3: +h +c +f -g +e
2: +a +b -d 4: +h +c +f -g +e

Min. num. of inversion and/or translocation transforming G into H

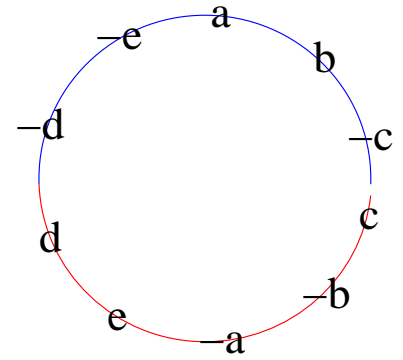
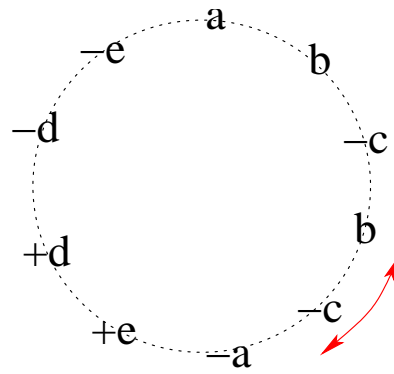
Multi-chromosomal case: H has an even number of chromosomes. Not necessarily the case for G



The circular case



Rearranged genome



Ancestral duplicated genome



Method

Genome rearrangement: Minimum number of rearrangements to transform one genome into another

First polynomial algorithm by *Hannenhalli and Pevzner* for

- Reversals only
- Translocations only
- Reversals and translocations

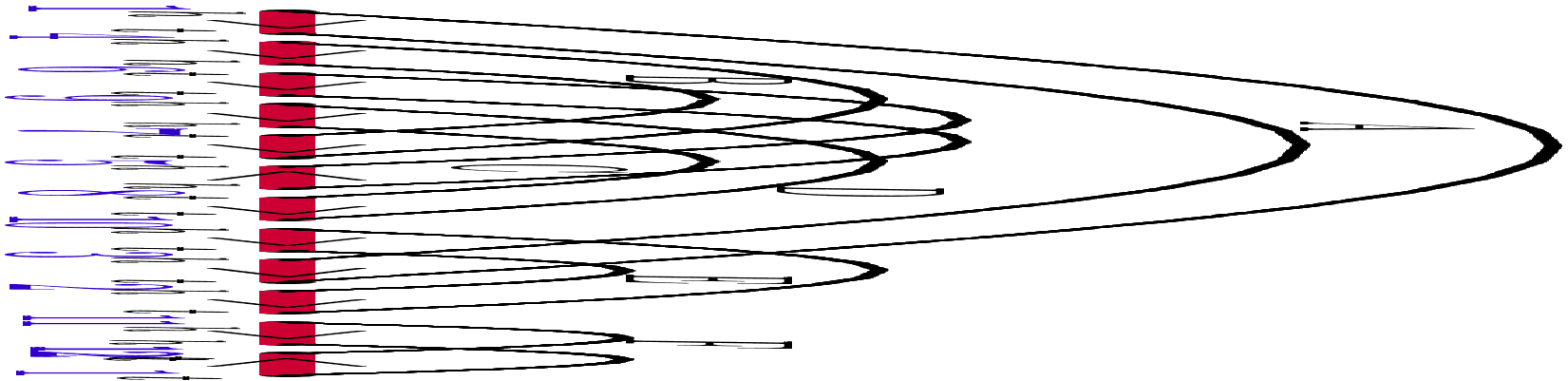
Ancestral duplicated genome of G minimizing the HP formula



The breakpoint graph

$$G_1 = +1 \ +4 \ -6 \ +9 \ -7 \ +5 \ -8 \ +10 \ +3 \ +2 \ +11 \ +12$$

$$G_2 = +1 \ +2 \ +3 \ +4 \ +5 \ +6 \ +7 \ +8 \ +9 \ +10 \ +11 \ +12$$

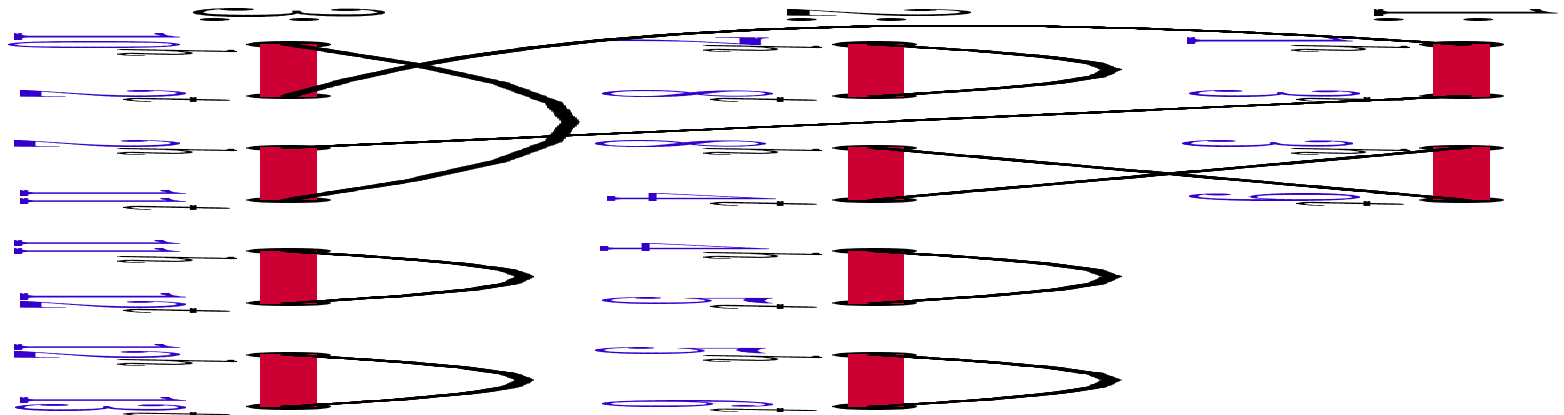




Multichromosomal case

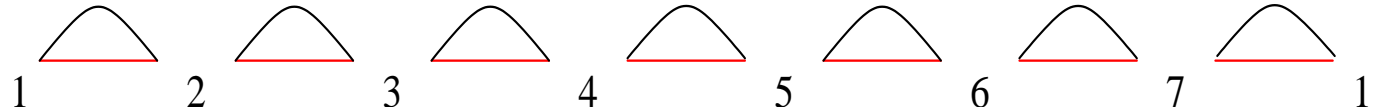
G_1 : I: 1 3 9 II: 7 8 4 5 6 III: 10 2 11 12
13

G_2 : I: 1 2 3 4 5 6 II: 7 8 9 III: 10 11 12 13





When $G_1 = G_2$, maximum number of cycles



Perform reversals increasing nb of cycles

Good component: Can be solved by good reversals

Bad component: Requires bad reversals

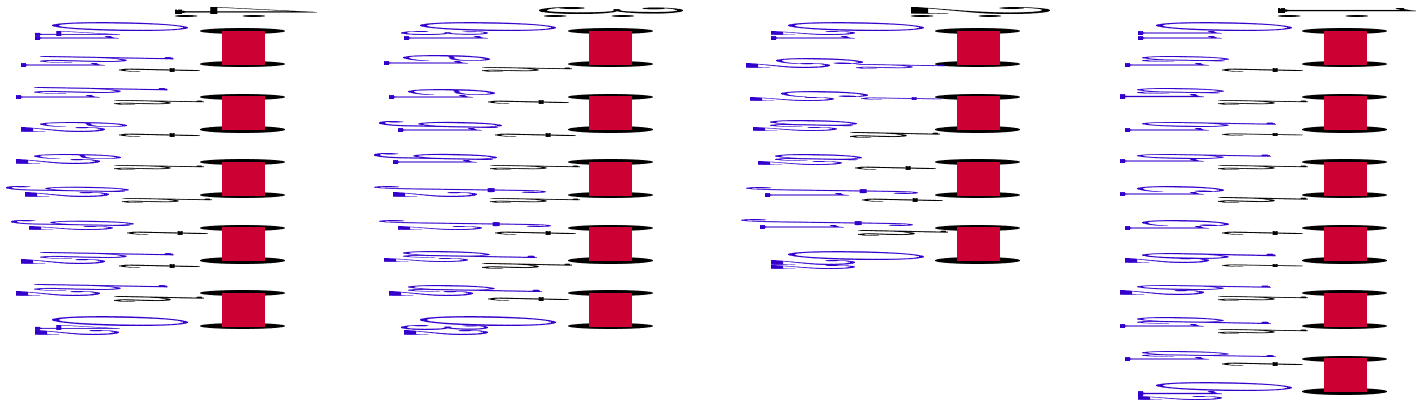
$$\text{HP: } RD(G_1, G_2) = b - c + m + f$$

b : red edges; c : cycles; m : bad components; f : Correction of 0, 1 or 2



Genome halving

Partial graph for G :

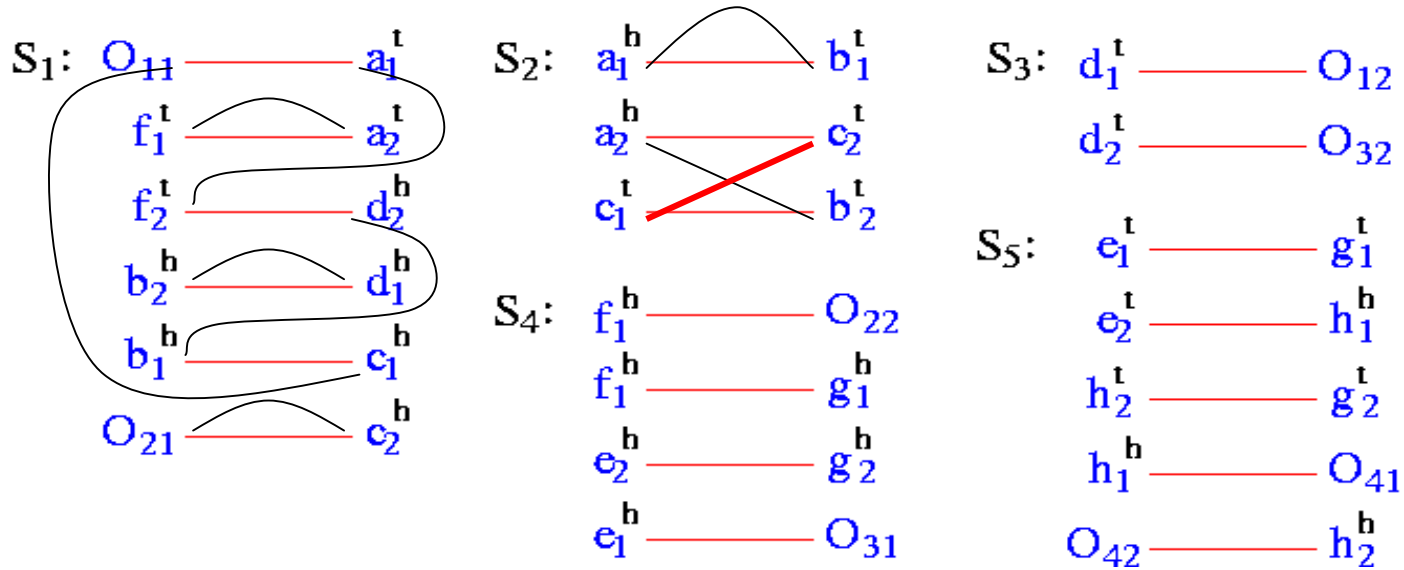


Set of **valid black edges** representing a duplicated genome

Find a set of valid black edges minimizing HP



Decomposition into natural subgraphs



Natural subgraphs of even size are completable

Amalgamate natural graphs into completable supernatural graphs

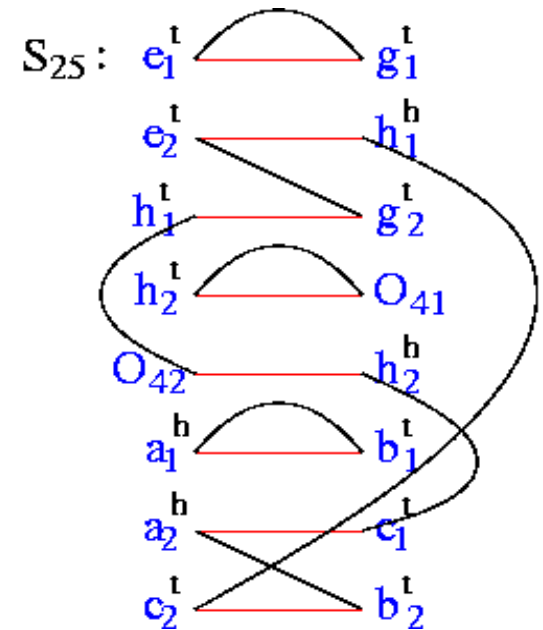
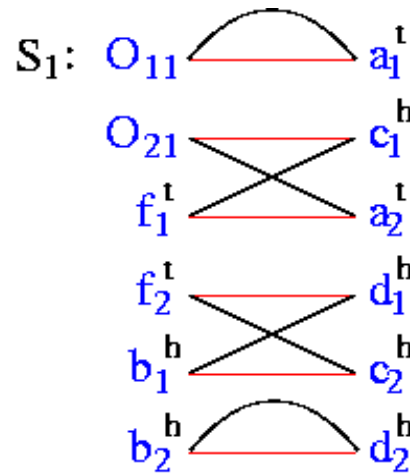
Example: Amalgamate S_2 and $S_5 \implies S_1, S_{25}, S_3, S_4$



Upper bound on the number of cycles

S_e a supernatural graph of n edges, $S_e(\Gamma_e)$ a completed graph with c_e cycles

- If S_e not amalgamated, $c_e \leq n/2 + 1$
- Otherwise, $c_e \leq n/2$



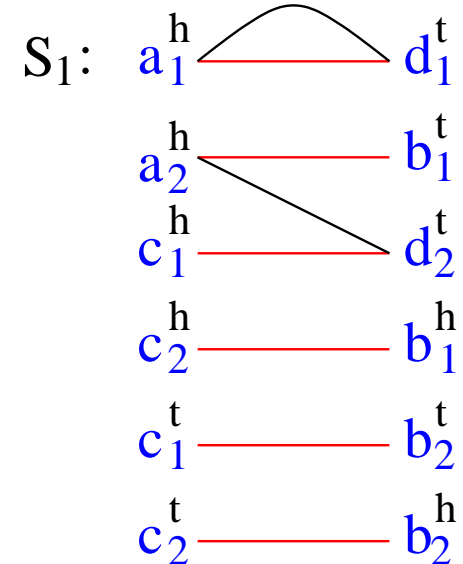
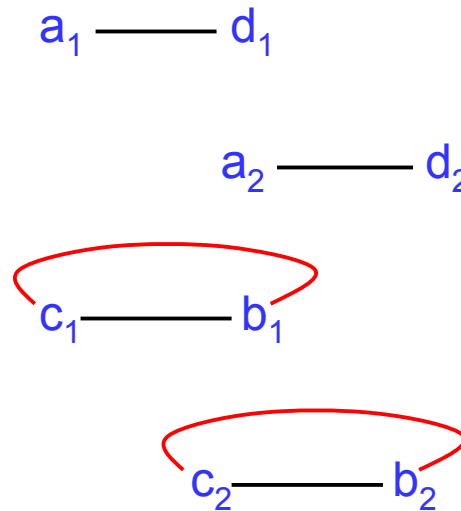
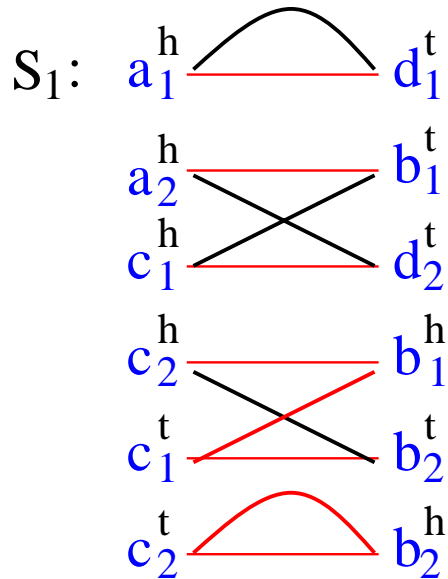


Maximizing cycles – Multichromosomal case

Complete each subgraph separately

Avoid to create **circular fragments**

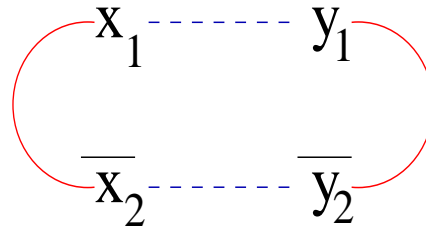
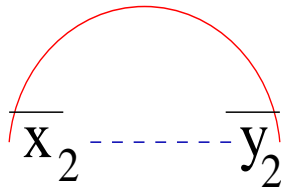
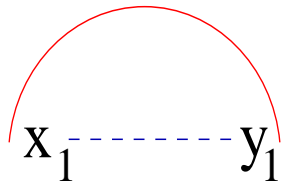
Bad graph:





Maximizing cycles 2

Avoid black edges creating **circular fragments**:

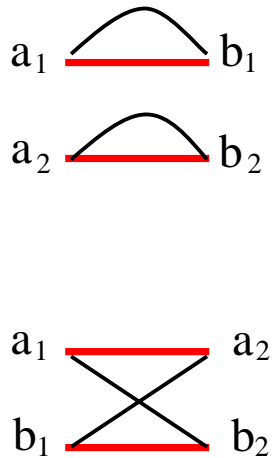


A pair of edges that does not create a **circular fragment** nor a **bad graph** is called **possible**

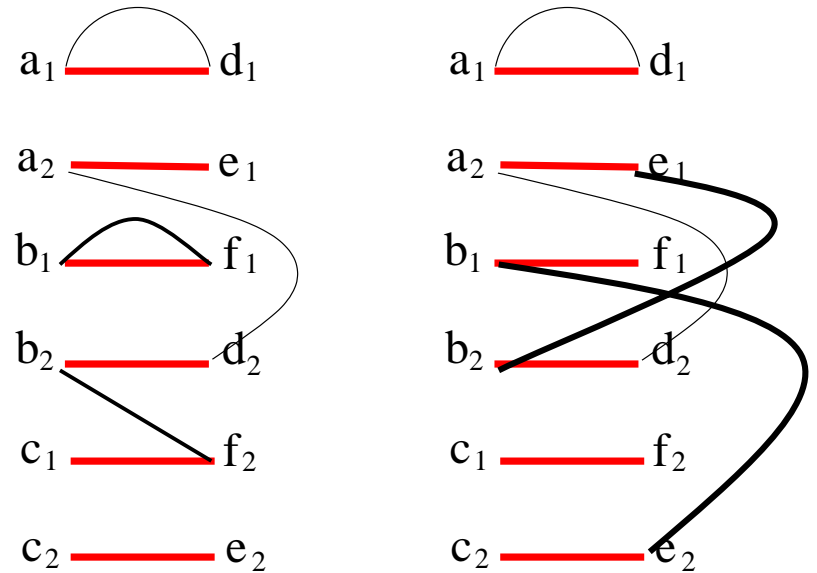


Algorithm dedouble

2-edges graph:



n-edges graph:





Algorithm dedouble 2

Linear time algorithm constructing a maximal completed graph with c cycles:

$$c = n/2 + \gamma$$

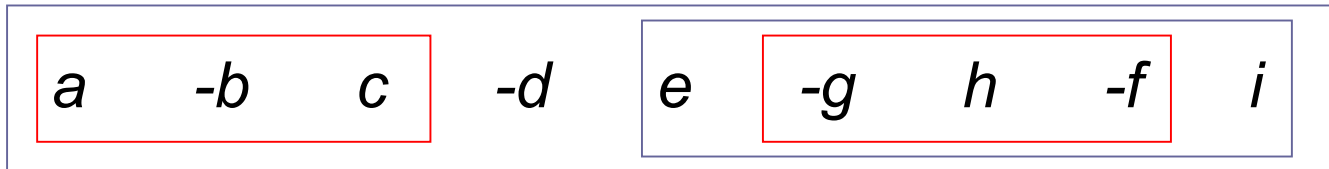
- n : number of red edges
- γ : number of natural graphs (not amalgamated)



Bad components

Related to subpermutations or conserved intervals

minSP: SP not contained in any SP



- Rearrangement by **translocations**:
Bad components = minSPs
- Rearrangement by **inversions and/or translocations**:
Bad components subset of minSPs



Bad components 2

Local SPs of G :

$$\underline{a_1 \quad b_1 \quad c_1 \quad d_1 \quad e_1} \quad \boxed{-d_2 \quad b_2 \quad c_2 \quad -a_2} \quad e_2$$

Lemma: In a max completed graph, if there is minSP not a local SP, then correction to eliminate the minSP

Corollary: If G does not contain local SPs, then duplicated genome H produced by the algorithm is such that:

$$RO(G,H) \text{ minimal}$$



Bad components 3

General case:

$$RO(G) = n/2 - \gamma(G) + m(G) + \phi(G)$$

n : nb of red edges; $\gamma(G)$: nb of natural graphs; $m(G)$: nb of bad local SPs; $\phi(G)$: correction depending on local SPs

Multichromosomal case: Exact algorithm

Circular case: Uncertainty of up to 2 reversals



Application: Yeast genome

Degenerate tetraploid, duplication 10^8

years ago (*Wolfe and Shield, 1997*). 55 duplicated regions



Sorting by translocations: 45 translocations

Sorting by inversions and/or translocations: No local SPs, thus no reversal. Still 45 translocations



A circular genome

Mitochondrial genome of *Marchantia polymorpha*: many genes in 2 or 3 copies (*Oda et al. 1992*)

Unlikely to be a tetraploid

A map with 25 pairs of genes was extracted from the Genbank entry

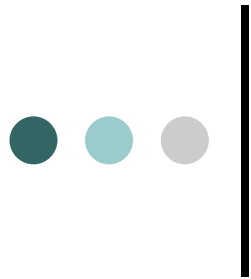
Sorting by reversals: minimum of 25 reversals

Similar to a random distribution \implies No trace of duplication



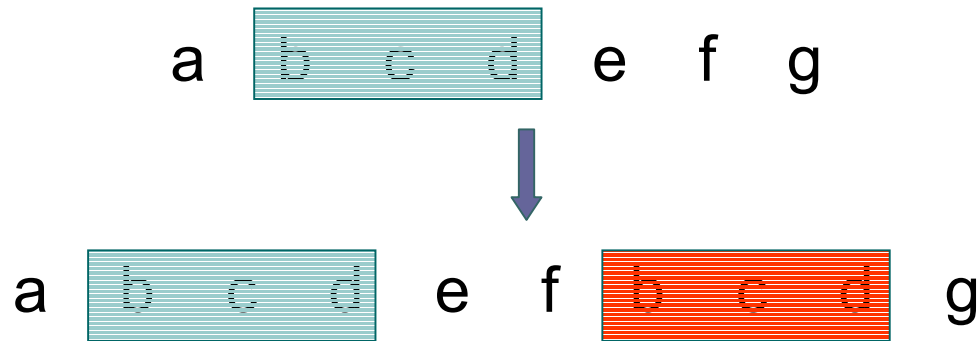
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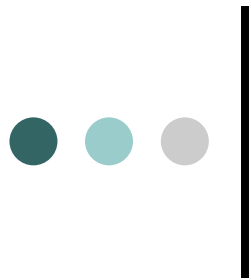


Duplication of chromosomal segments

Duplication of entire regions from one location to another in the genome



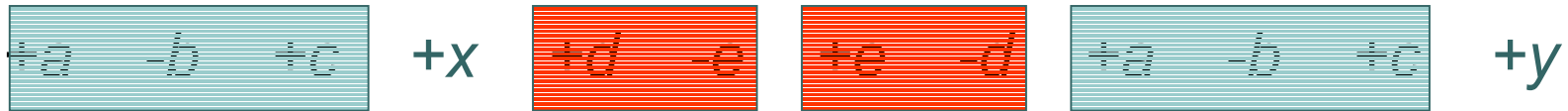
Very recent segment duplication in the human genome (*Eichler et al., 1999*)



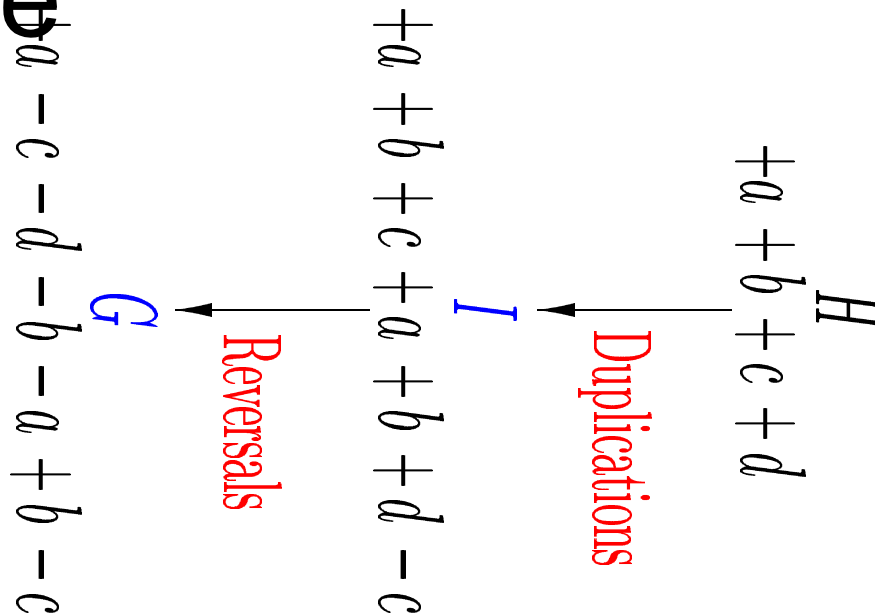
Data: A genome containing many copies of each gene

Problem: An ancestral genome containing one copy of each gene, minimizing reversals + segment duplication

$D(G)$: Number of repeats of G



At most two copies of each gene



A reversal can decrease by at most two number of repeats of G

Find I minimizing $RD(G, I) = D(I) + R(G, I)$

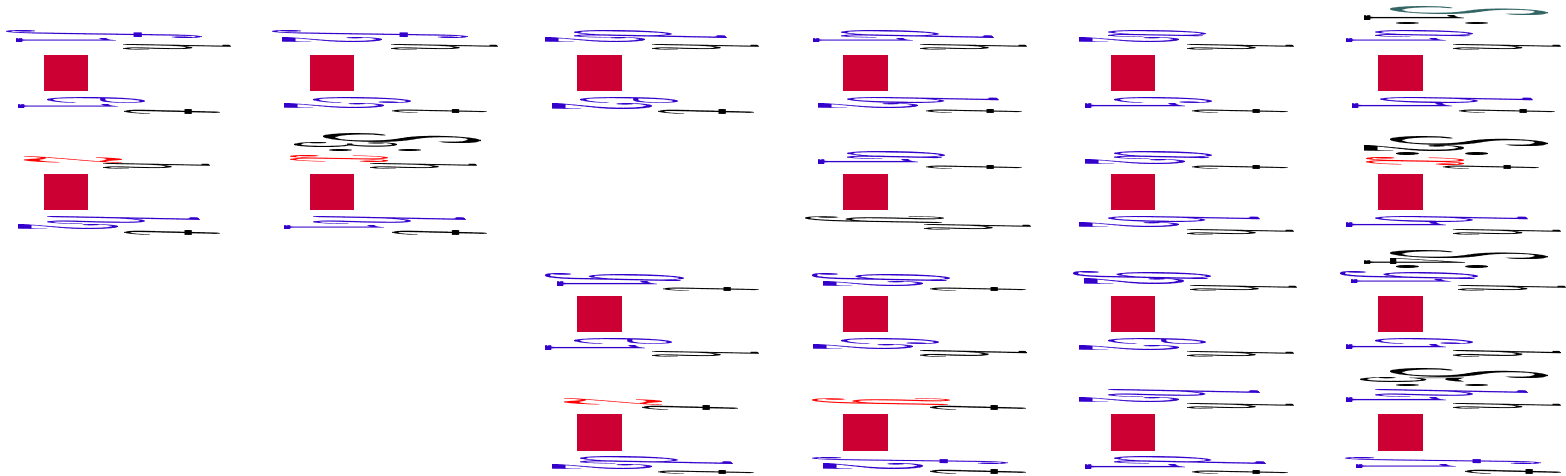
Ignoring bad components \rightarrow minimize $\Delta(G) = D(I) + n(G) - c(G, I)$



Genome:

a₁ b₁ x h₁ f₁ e₁ g₁ -c₁ -a₂ -b₂ -z d₂ e₂ -g₂ -c₂ -f₂ y

Natural graphs:

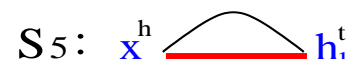
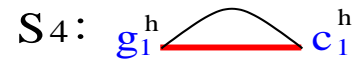
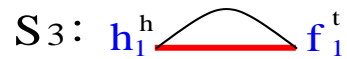
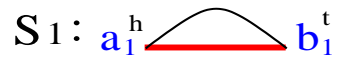


E : Graphs of even size with only duplicated genes

$$\Delta(G) \geq D(G) - |E|$$

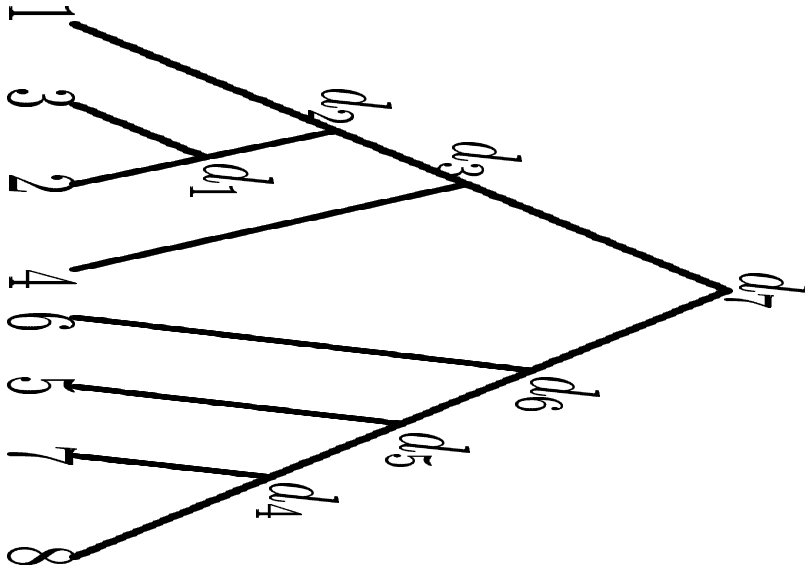
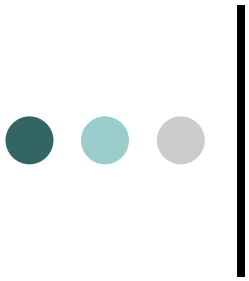
Algorithm

- For graphs not in E , red edges = black edges;
- For graphs in E , similar to genome duplication



BUT: Possibly more than one circular fragment. A correction is required

Approximation algorithm with tight bounds in $O(|E| n)$



1, 2, 3, 4, 5, 6, 7, 8
↓ Paralog pairings

1, {2, 3}, 4, 5, 6, {7, 8}

Remove one ↓ copy of each duplicate

1, 2, 4, 5, 6, 7

↓ Paralog pairings

{1, 2}, 4, 6, {5, 7}

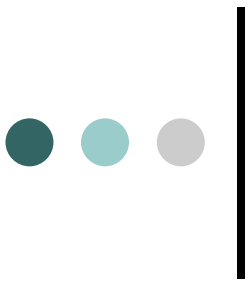
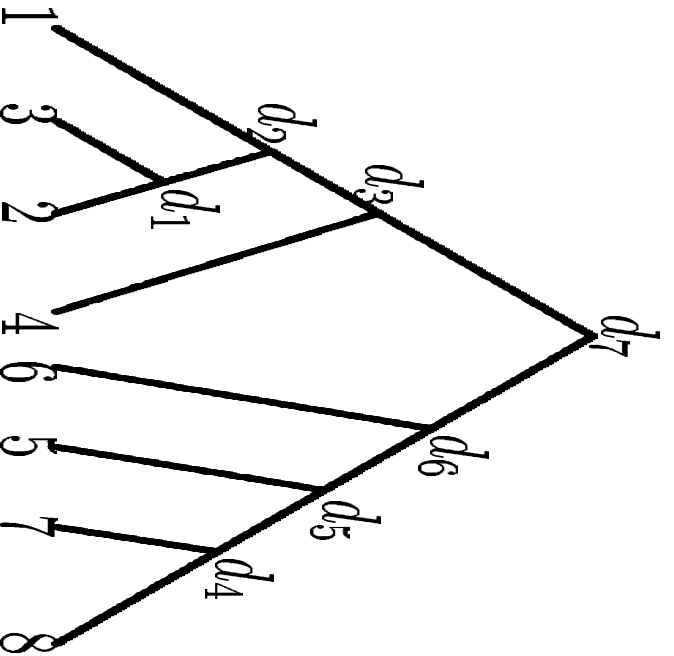
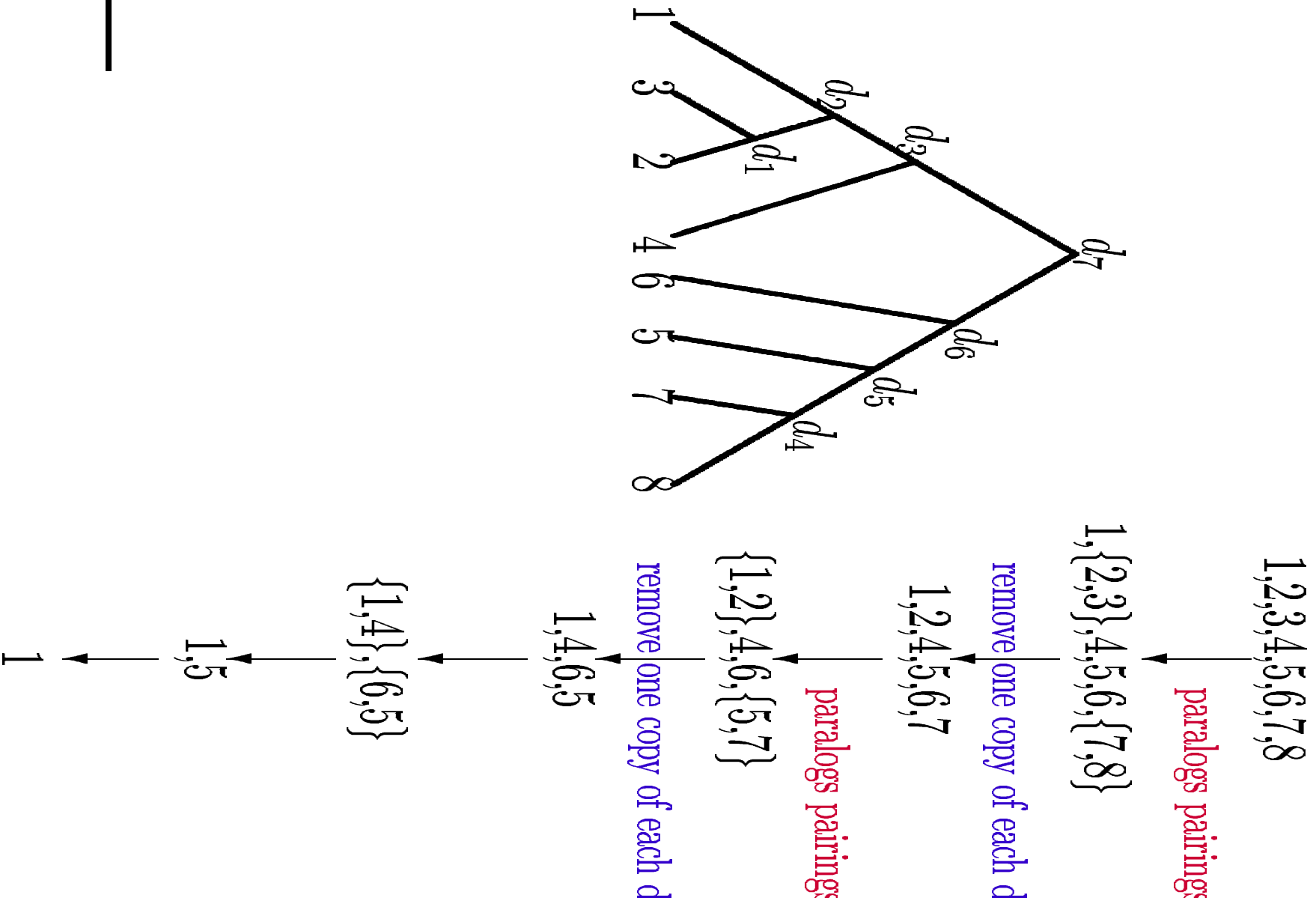
Remove one ↓ copy of each duplicate

1, 4, 6, 5

{1, 4}, {6, 5}

↓
1, 6

↓
1





Conclusion

- First bioinformatics tools to reconstruct the evolutionary history of a single genome
- Genome duplication: A linear-time exact algorithm for reversals and/or translocations
- Segment duplication: A polynomial approximation algorithm with bounds for reversals
- Extension: Consider the centromere. Some translocations not allowed