



Gene and genome duplication



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  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*)

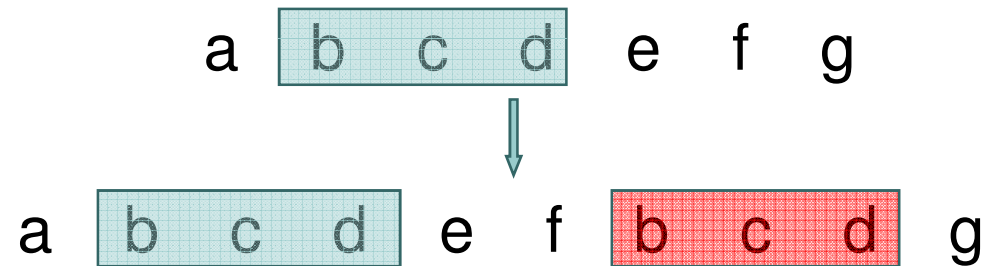
Compare sequences of signed genes allowing **many copies of each gene**

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



Multigene families due to:

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

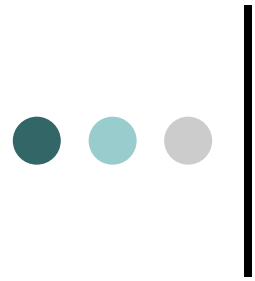


- ❑ Horizontal gene transfer;
- ❑ **Genome-wide doubling** event



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

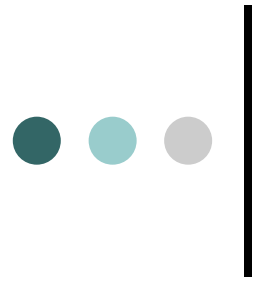
- **Genome duplication for unordered chromosomes**

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	:	+2 ● - 1
II	:	+4 ● - 3 - 7 +8 - 5 + 6
III	:	+9 ● - 10 - 11
IV	:	+20 + 12 + 12 + 54 + 15 + 21 ● - 3 - 13 - 16 + 17 - 24 - 22 - 14 -23 - 19 + 18 - 9
V	:	+28 ● - 25 - 27 - 4 - 26 - 13
VI	:	+55 ● - 36
VII	:	+36 + 25 + 26 + 32 +6 - 33 + 5 ● - 30 - 34 - 31 - 29
VIII	:	+35 ● - 14 - 37 - 29 - 1
IX	:	+38 + 39 + 27 ●
X	:	+10 + 40 + 41 ● - 28 - 42
XI	:	+42 + 40 + 43 + 35 ● - 41 - 52 - 38
XII	:	+53 ● - 53 - 31 - 55 - 16 -18 - 17 - 45 - 30 - 15 - 44
XIII	:	+46 + 44 + 19● - 43 - 54 - 48 - 47 - 46
XIV	:	+49 + 20 + 37 + 50 + 39 ● - 11
XV	:	+49 + 21 ● - 22 - 52 - 50 - 23 - 45 - 51 - 47 - 2
XVI	:	+48 + 32 + 33 + 51 + 8 + 24 ● - 7 - 34



Originally, duplicated genome =
2 identical copies of each chromosome

After rearrangements, duplicated segments scattered among
the genome

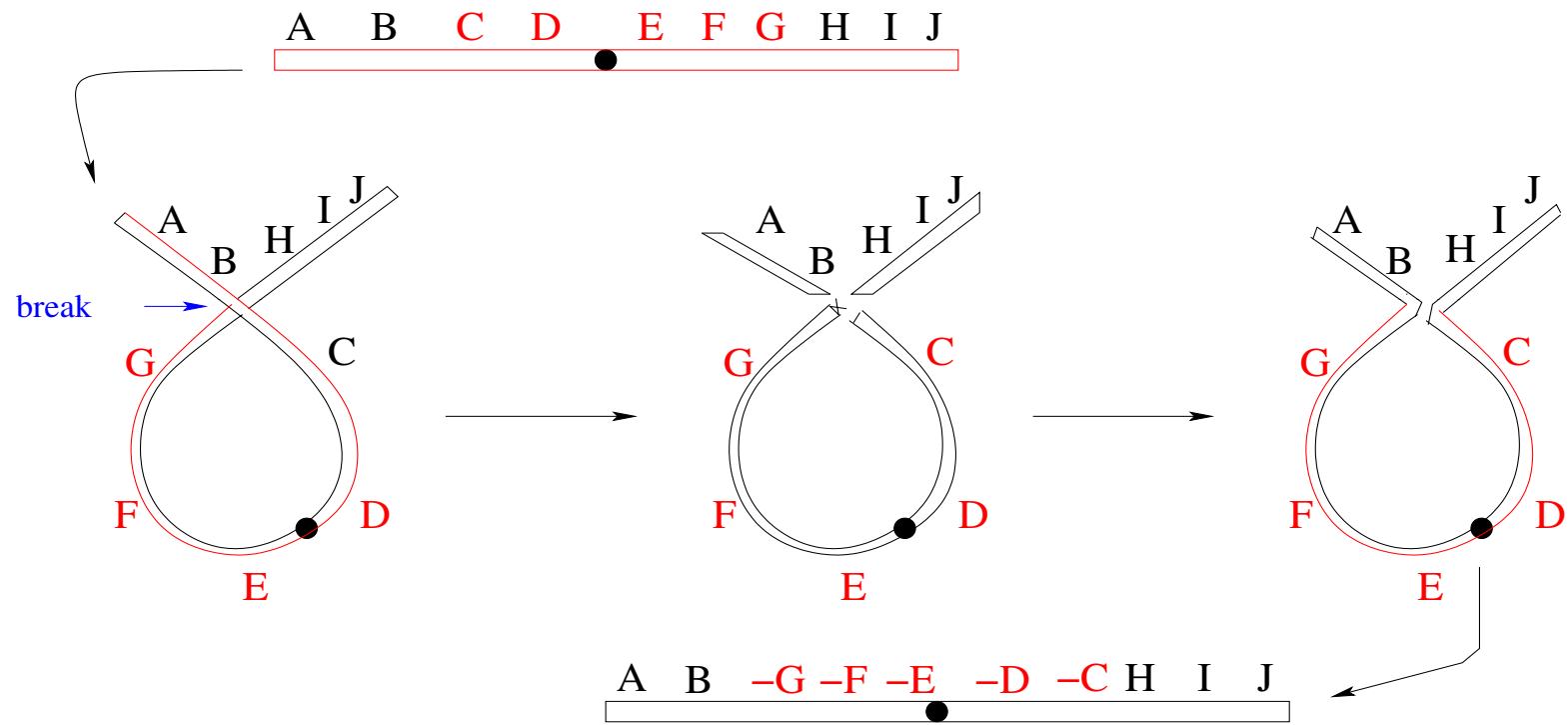
Present-day genome: Signed gene sequences, 2 copies of
each gene

Reconstruct original gene order at time of duplication

Minimum number of reversal and/or translocation



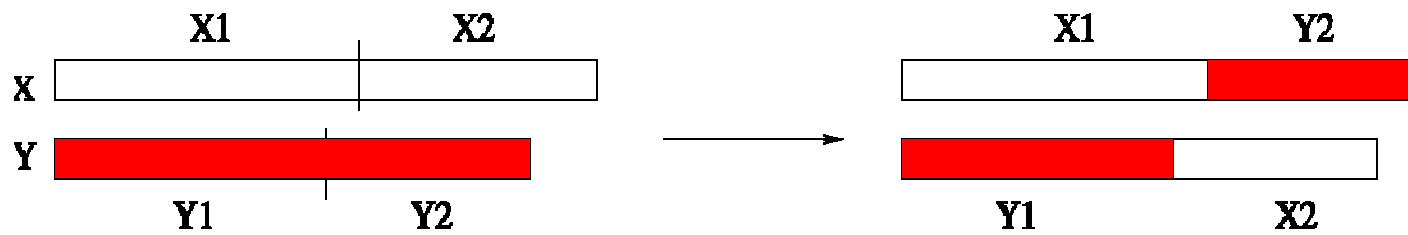
Inversion



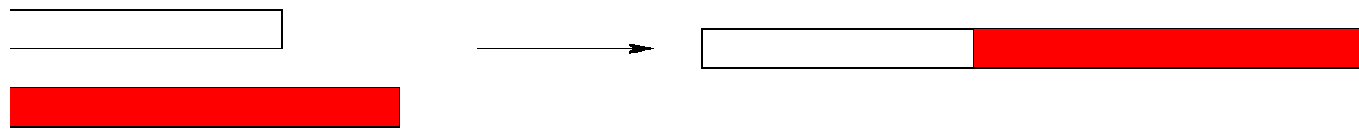


Translocation

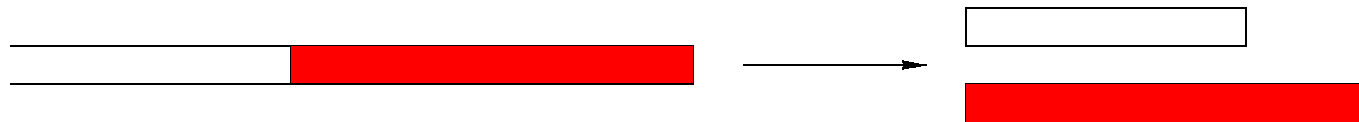
Reciprocal translocation:



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

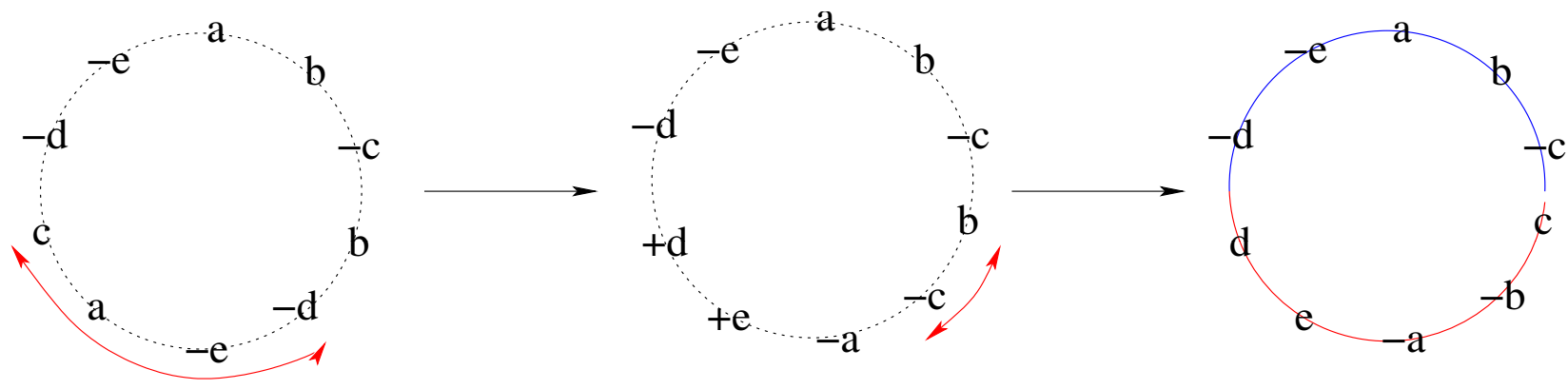
2: +a +b -d 4: +h +c +f -g +e

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

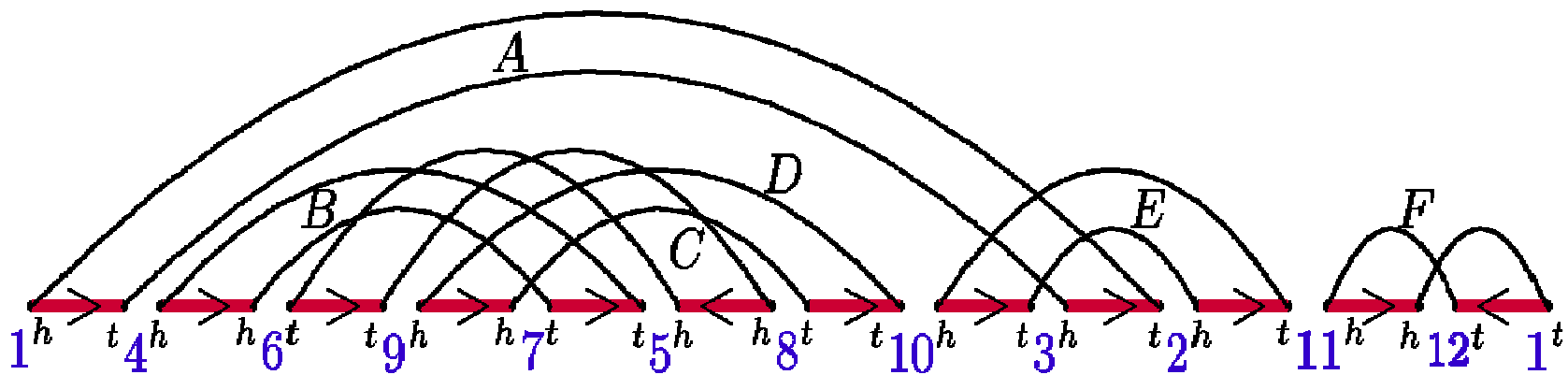
Ancestral duplicated genome of G minimizing the HP formula



The breakpoint graph

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

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

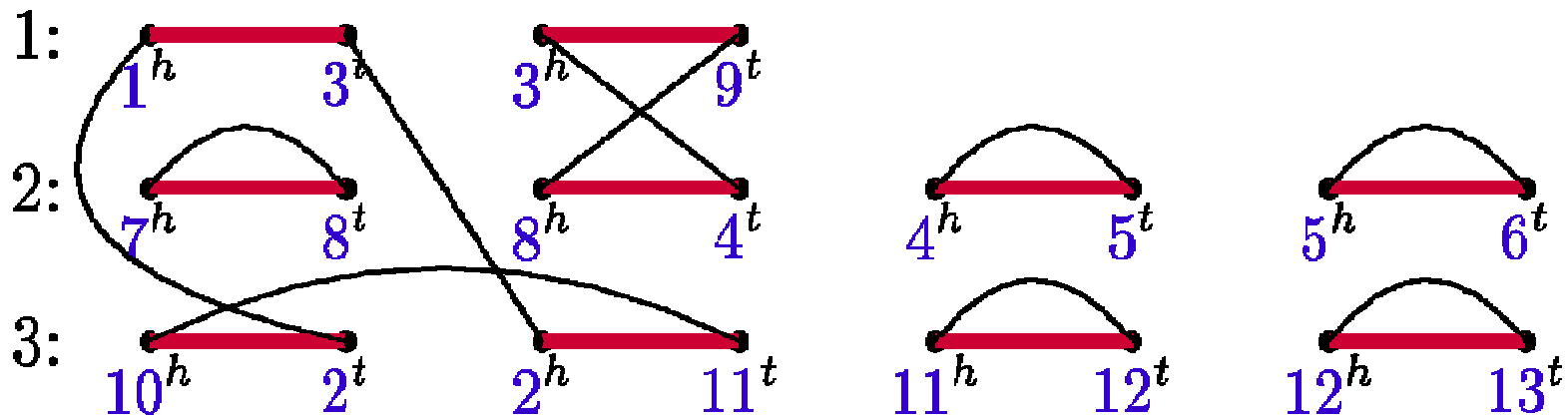




Multichromosomal case

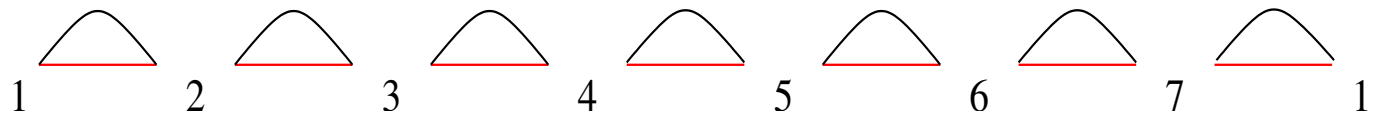
G_1 : I: 1 3 9 II: 7 8 4 5 6 III: 10 2 11 12 13

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

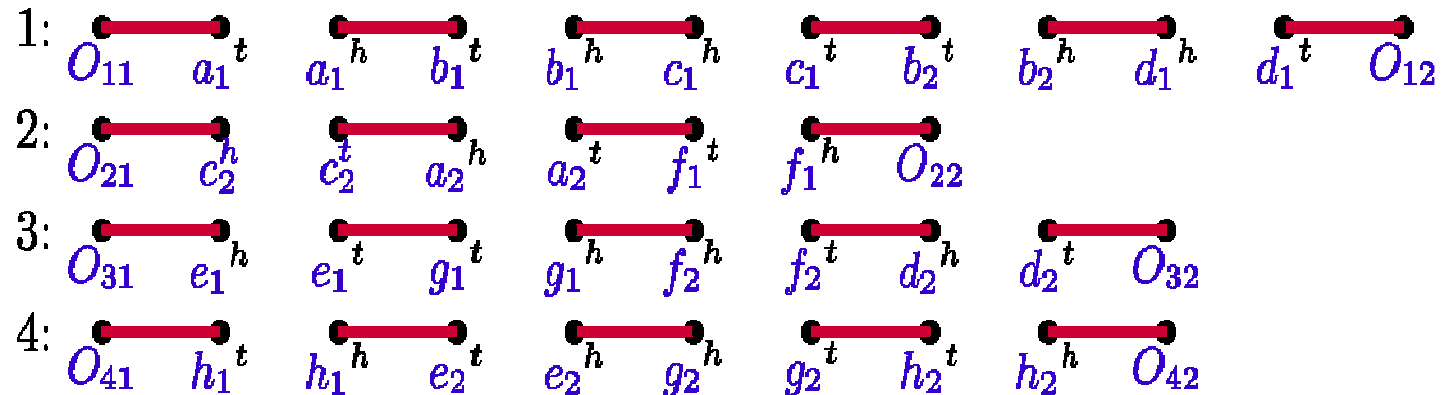
$$\text{HP: } RD(G_1, G_2) = b - c + m + f$$

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



Genome halving

Partial graph for G :

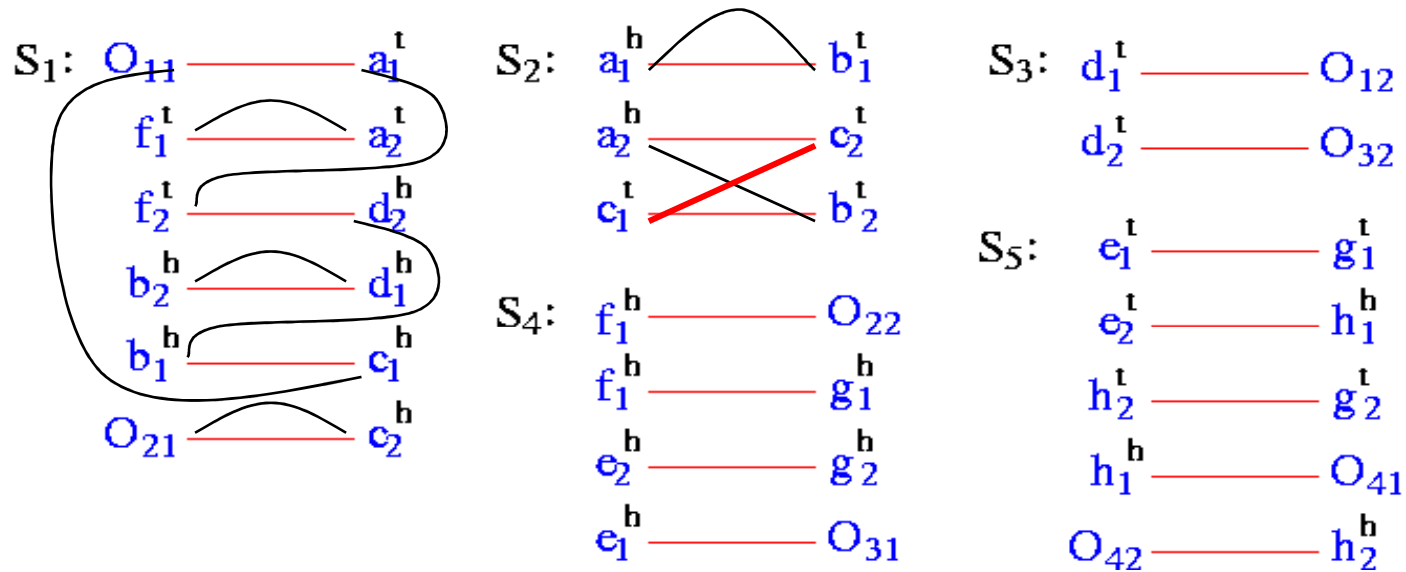


Set of valid black edges representing a duplicated genome

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

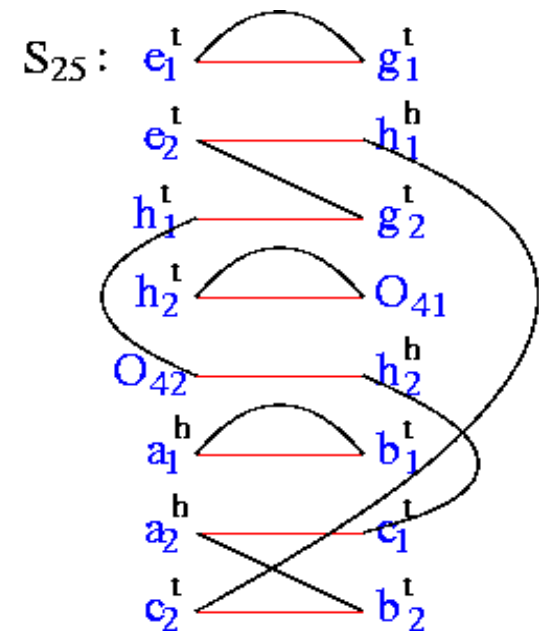
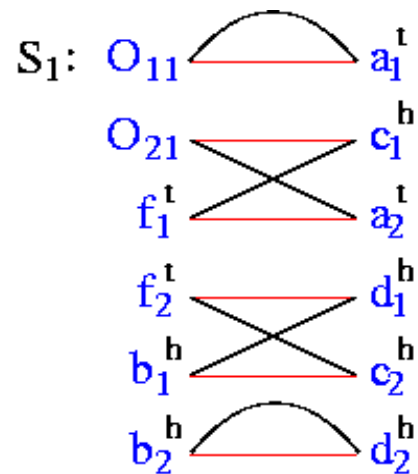
Example: Amalgamate S_2 and S_5 \longrightarrow S_1, S_{25}, S_3, S_4



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, $c_e \leq n/2$



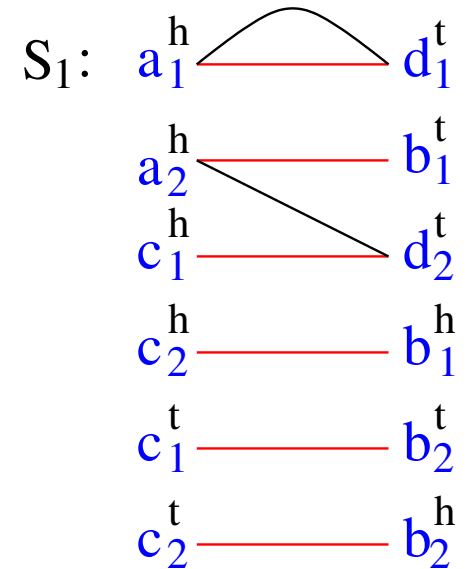
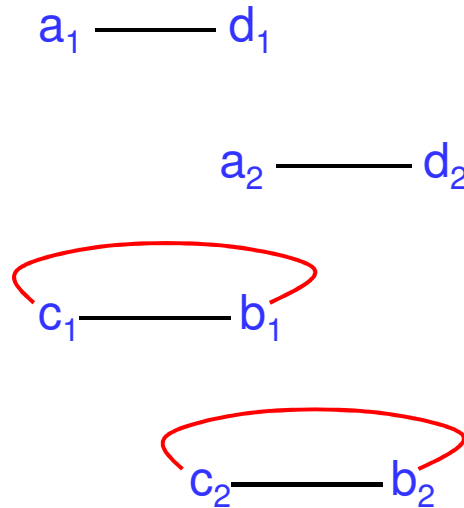
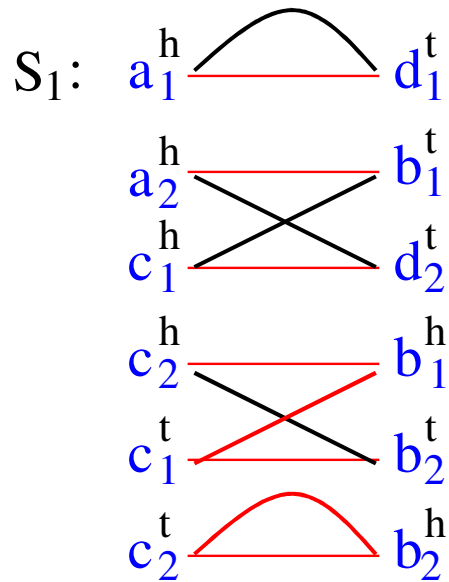


Maximizing cycles – Multichromosomal case

Complete each subgraph separately

Avoid to create **circular fragments**

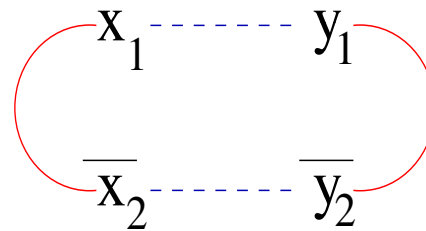
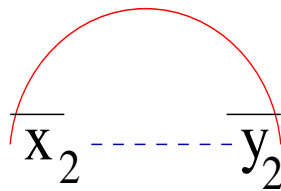
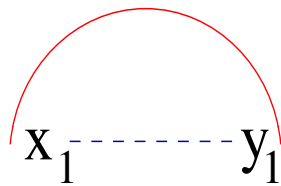
Bad graph:





Maximizing cycles 2

Avoid black edges creating **circular fragments**:

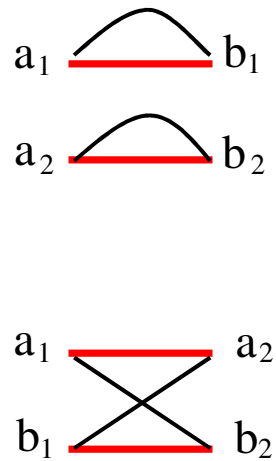


A pair of edges that does not create a **circular fragment** nor a **bad graph** is called **possible**

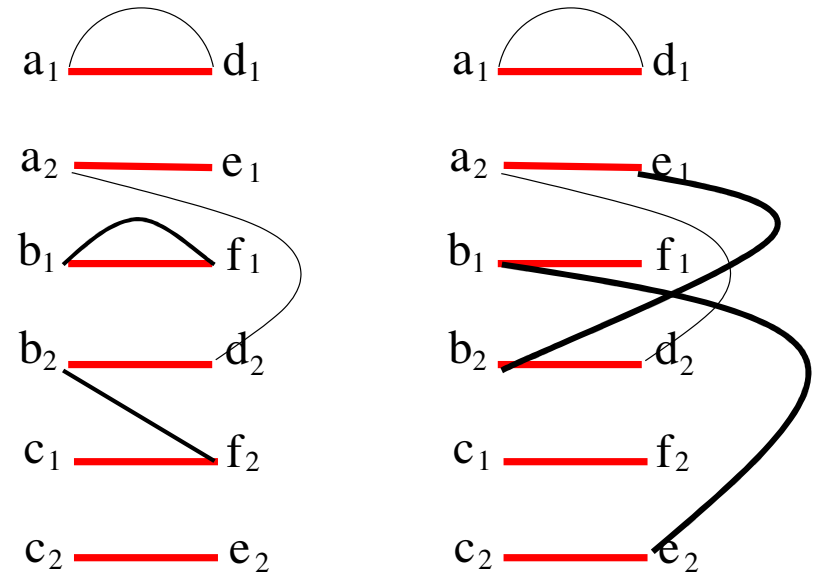


Algorithm dedouble

2-edges graph:



n-edges graph:





Algorithm dedouble 2

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

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

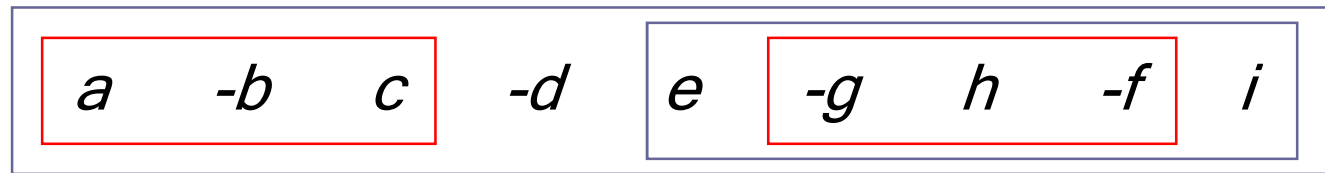
- n : number of red edges
- γ : number of natural graphs (not amalgamated)



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 :

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

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

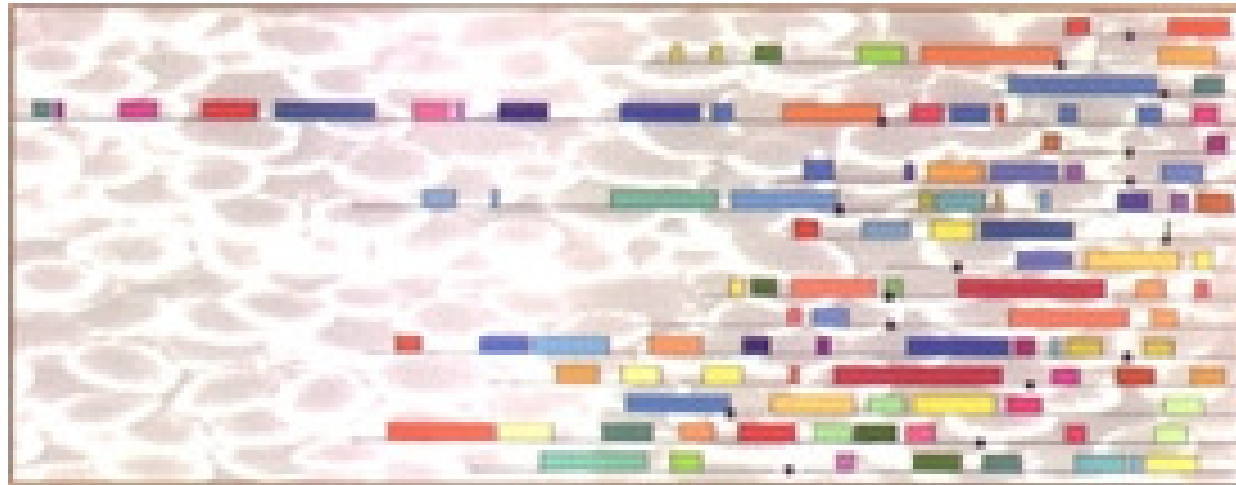
Multichromosomal case: Exact algorithm

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

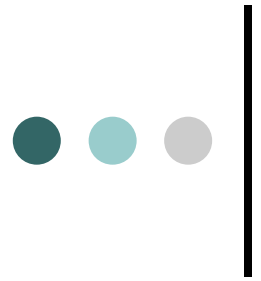
Sorting by reversals: minimum of 25 reversals

Similar to a random distribution \implies No trace of duplication



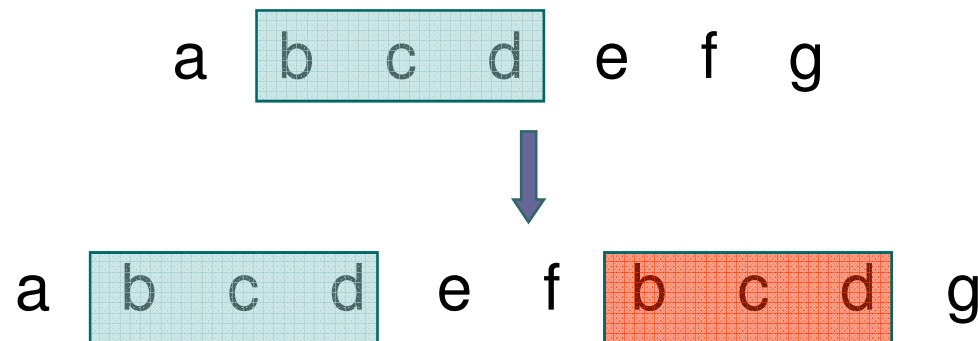
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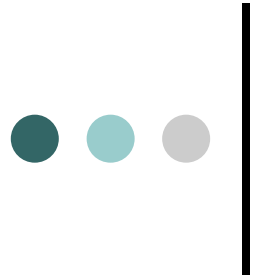


Duplication of chromosomal segments

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



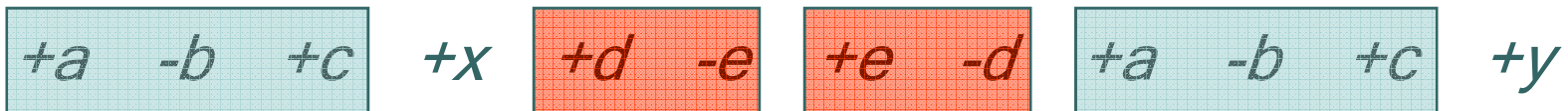
Very recent segment duplication in the human genome (*Eichler et al., 1999*)



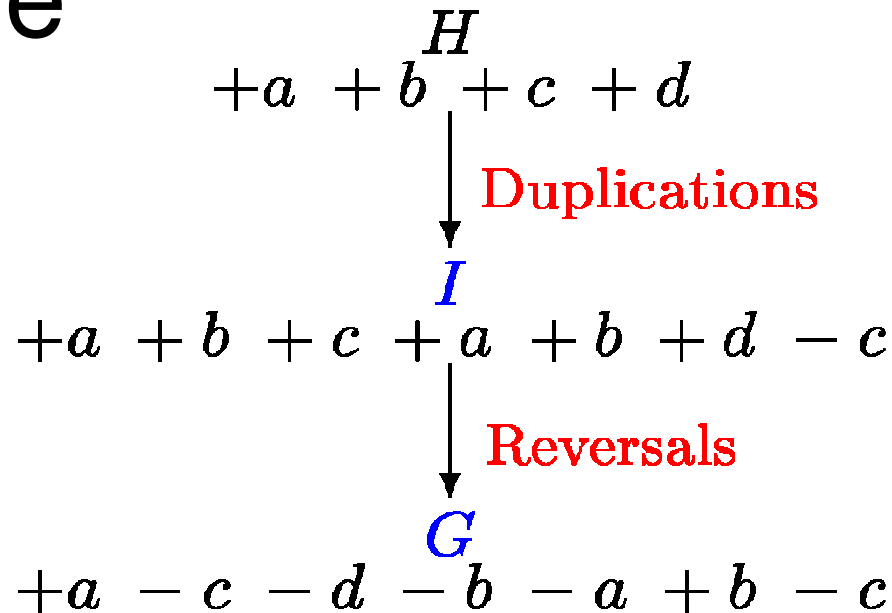
Data: A genome containing many copies of each gene

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

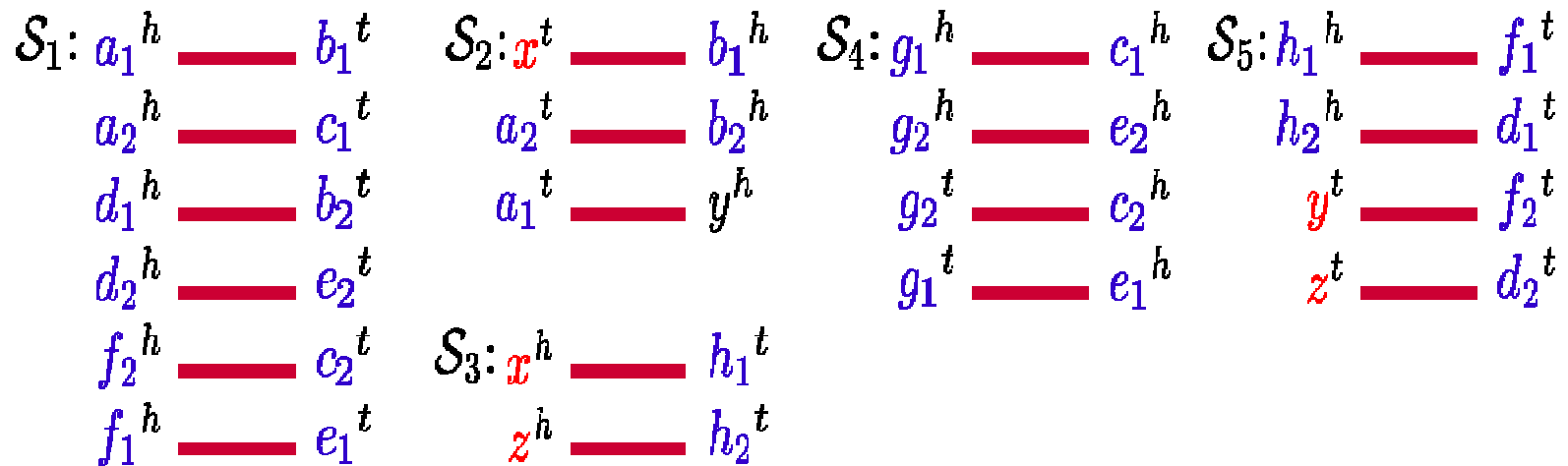
Ignoring bad components \longrightarrow minimize $\Delta(G) = D(I) + n(G) - c(G, I)$



Genome:

$a_1 \ b_1 \ x \ h_1 \ f_1 \ e_1 \ g_1 \ -c_1 \ -a_2 \ -b_2 \ -z \ d_2 \ e_2 \ -g_2 \ -c_2 \ -f_2 \ y$

Natural graphs:

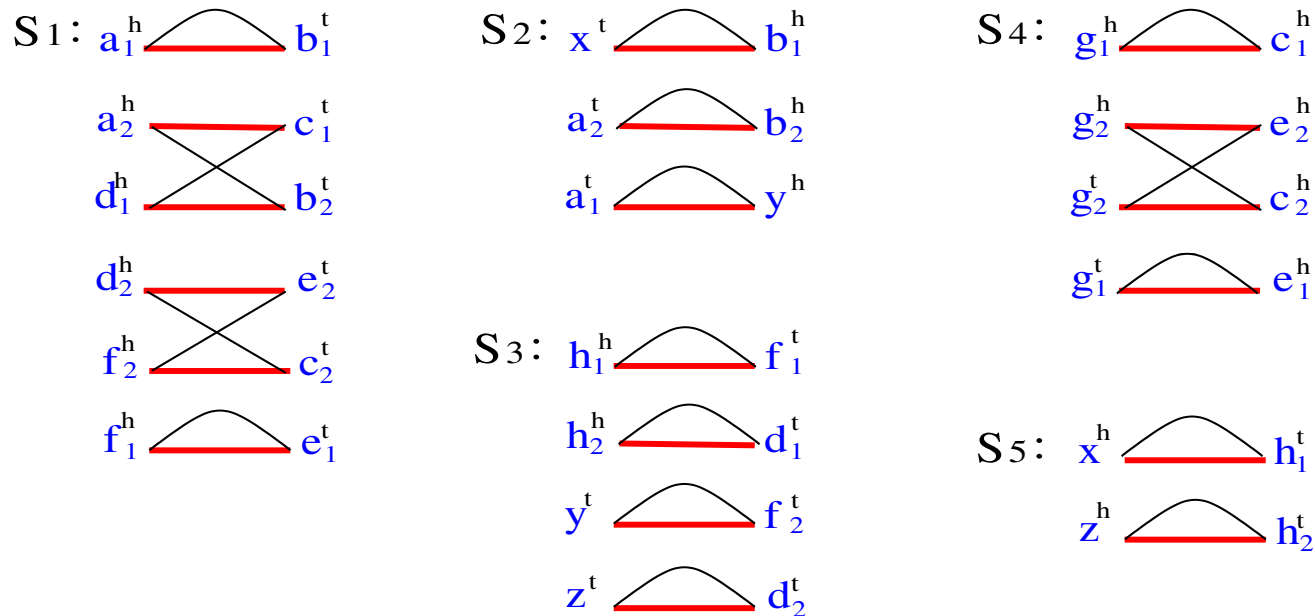


E : Graphs of even size with only duplicated genes

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

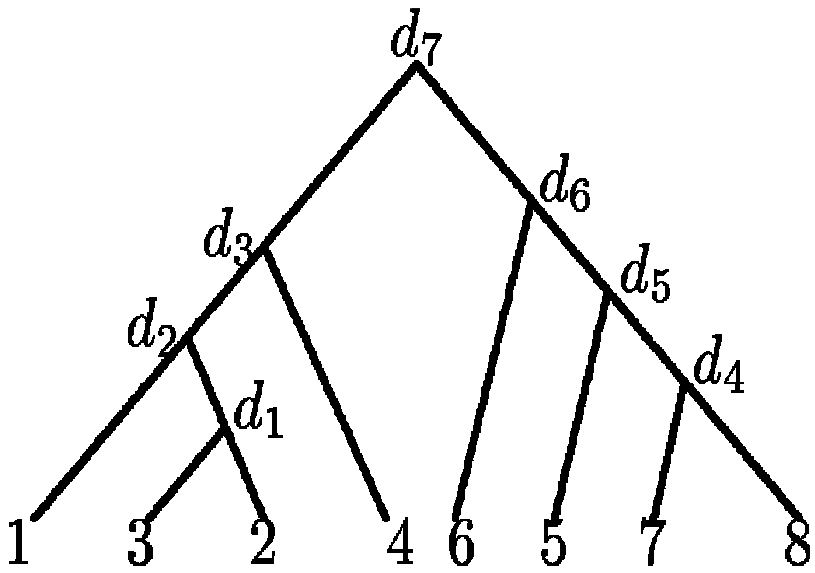
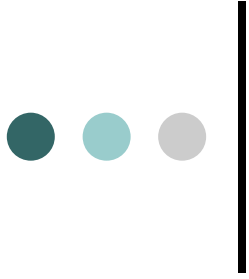
Algorithm

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

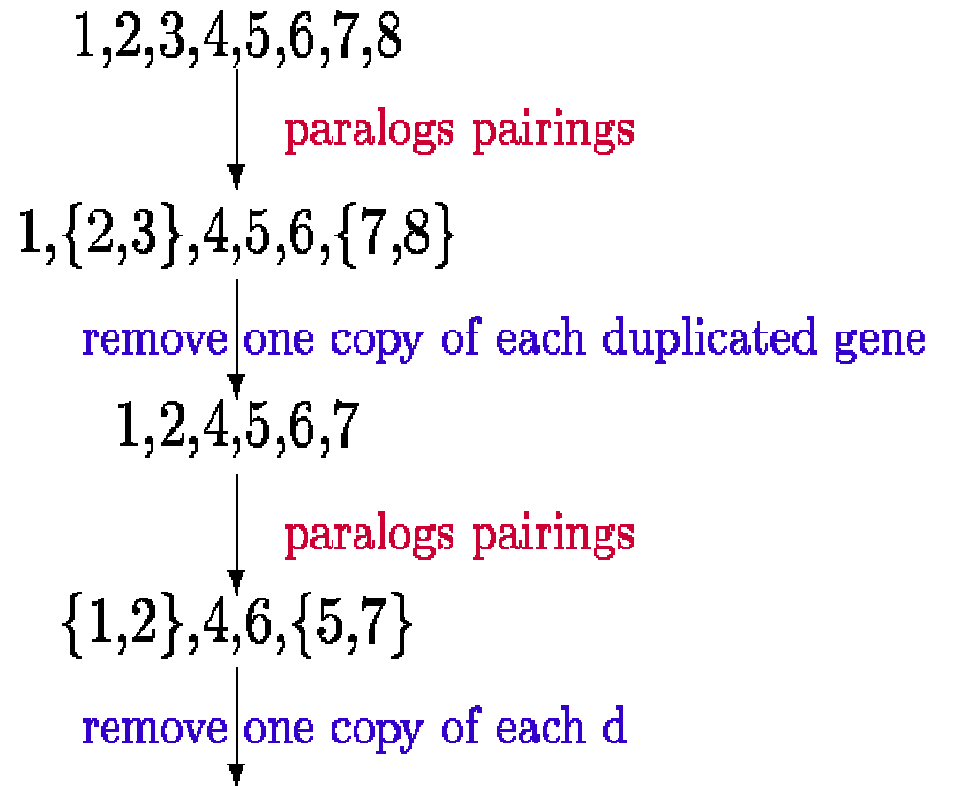
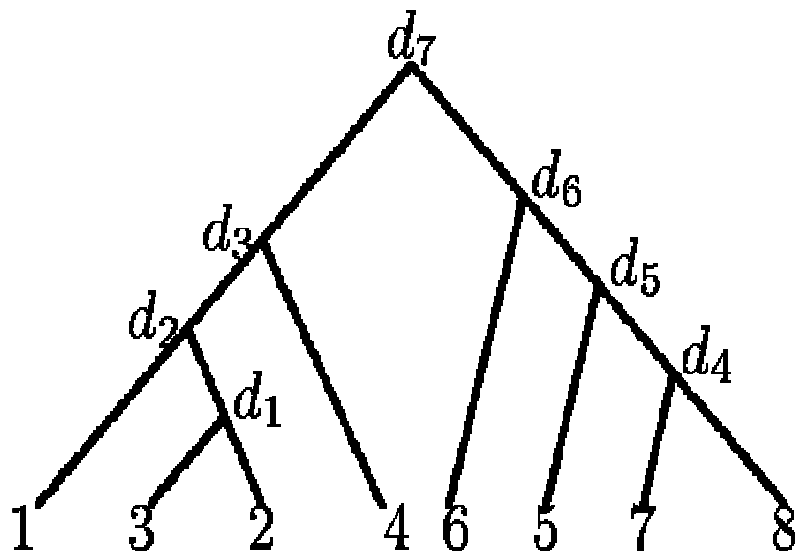
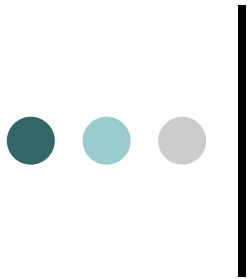


BUT: Possibly more than one circular fragment. A correction is required

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



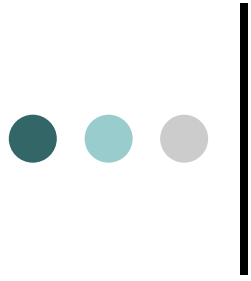
1, 2, 3, 4, 5, 6, 7, 8
↓ Paralog pairings
1, {2, 3}, 4, 5, 6, {7, 8}
↓ Remove one copy of each duplicate
1, 2, 4, 5, 6, 7
↓ Paralog pairings
{1, 2}, 4, 6, {5, 7}
↓ Remove one copy of each duplicate
1, 4, 6, 5
↓
{1, 4}, {6, 5}
↓
1, 6
↓
1





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



Reference:

- Nadia El-Mabrouk
- Université de Montréal
- Canada