Reconstruction of ancestral gene orders

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Banff, February 17, 2017

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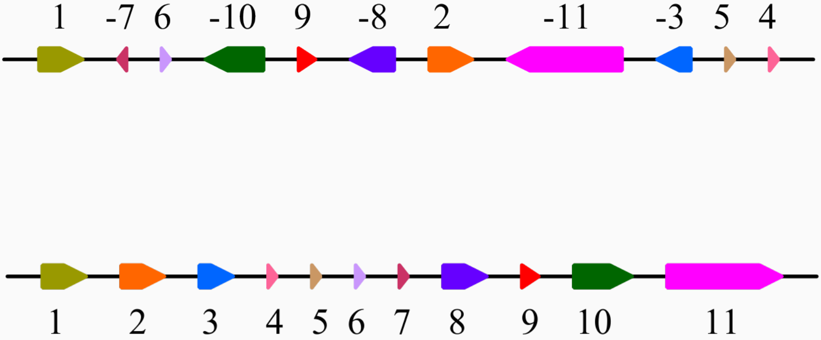
ENGAGING THE WORLD

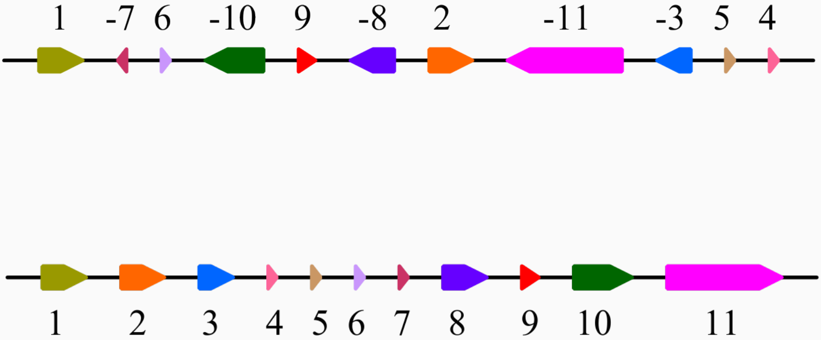
Universität Bielefeld
Technische Fakultät
Genominformatik

Introduction

Genomes



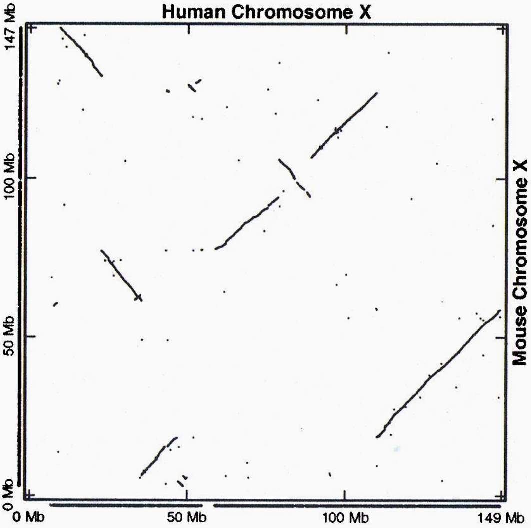
Mouse X-Chromosome



Human X-Chromosome

(Pevzner and Tesler, 2003)

Genomes


Human Chromosome X
Mouse Chromosome X
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50 Mb
100 Mb
149 Mb
0 Mb
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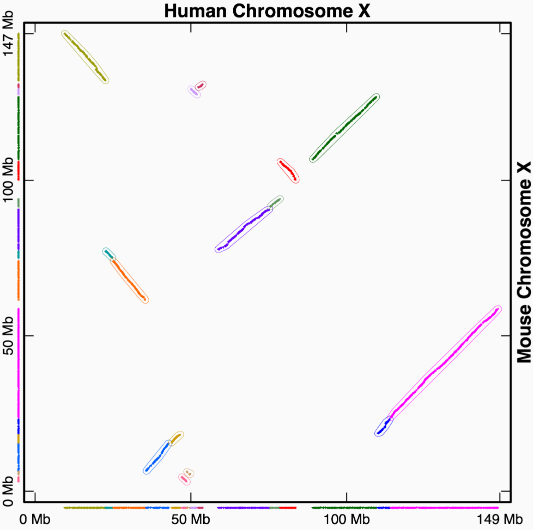
147 Mb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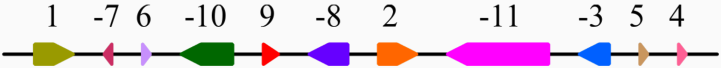
Reversal



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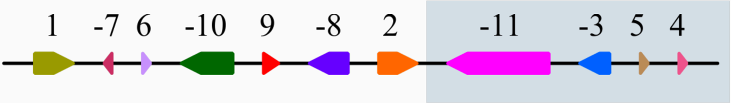

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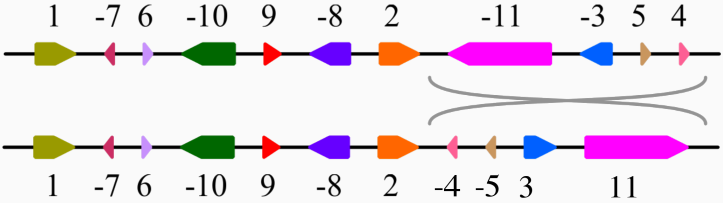
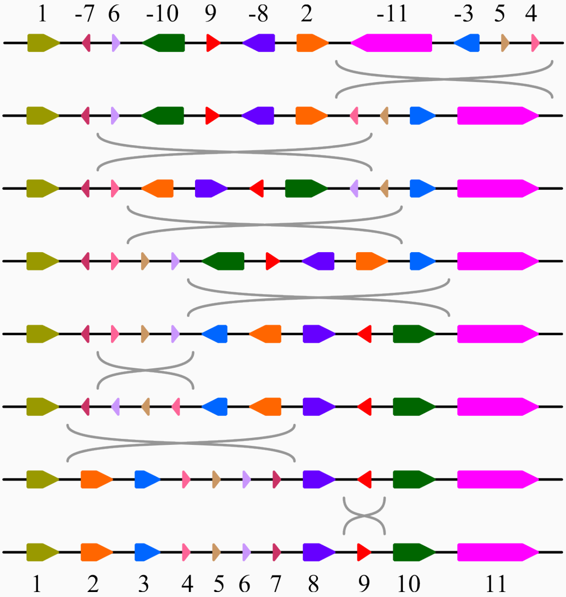


Rearrangement Scenario



Genome Rearrangement Problems

- **Distance**: Minimum # of rearrangements from A to B?

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- **Distance**: Minimum # of rearrangements from A to B?
- **Scenario**: Which rearrangements? (also called *Sorting*)
- **Phylogeny**: How did the genomes evolve?
- **Ancestral Reconstruction**: How do the ancestors look like?

translocations
algorithm
adjacencies
breakpoint
segments
model
probabilistic
reciprocal
computing
sorting
DCJ
genes
approximation
double
maximum
ancestral
problem
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InDels
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Ancestral Reconstruction

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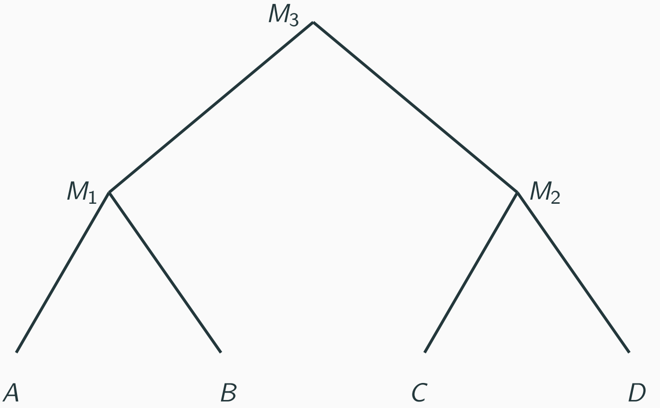


Input: Tree and genomes A, B, C, D

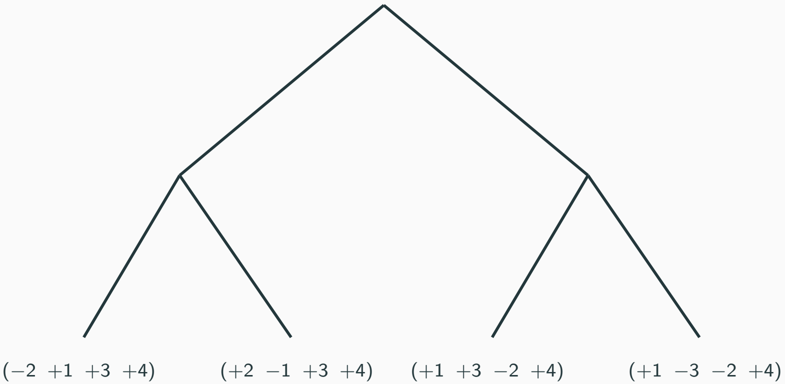
Ouput: Ancestral genomes (M_1, M_2, M_3)

Ancestral Reconstruction

- Distance-based Methods

- Homology-based Methods

Distance-based Methods



$(-2\ \ +1\ \ +3\ \ +4)$

$(+2\ \ -1\ \ +3\ \ +4)$

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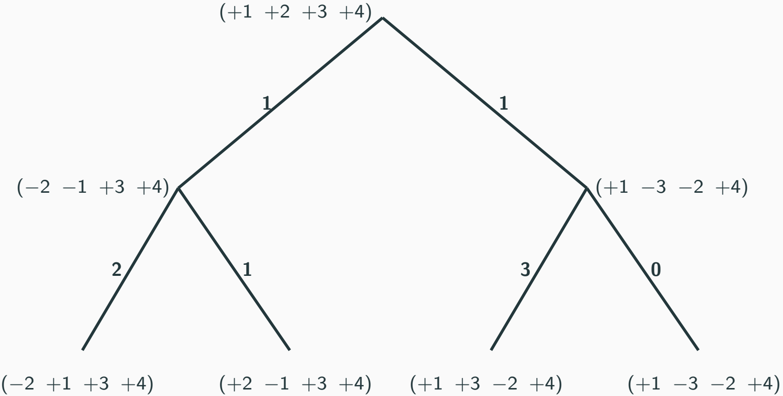
Distance-based Methods



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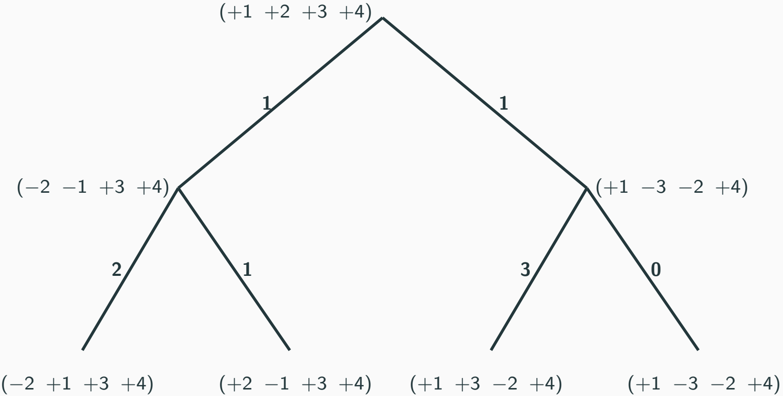
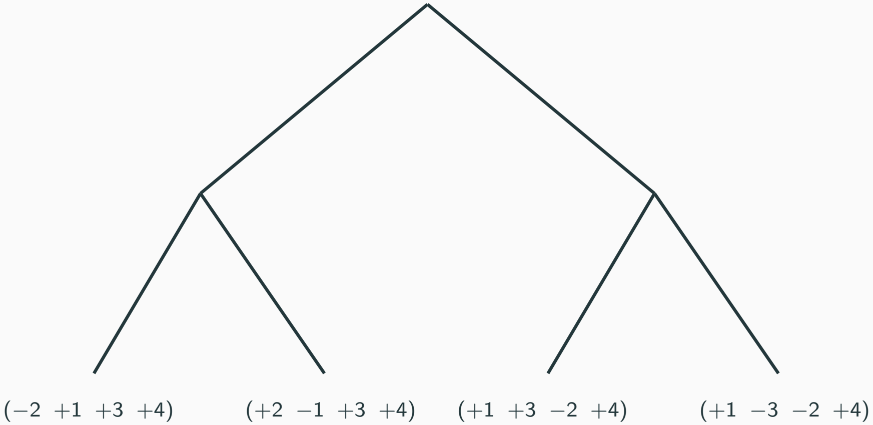


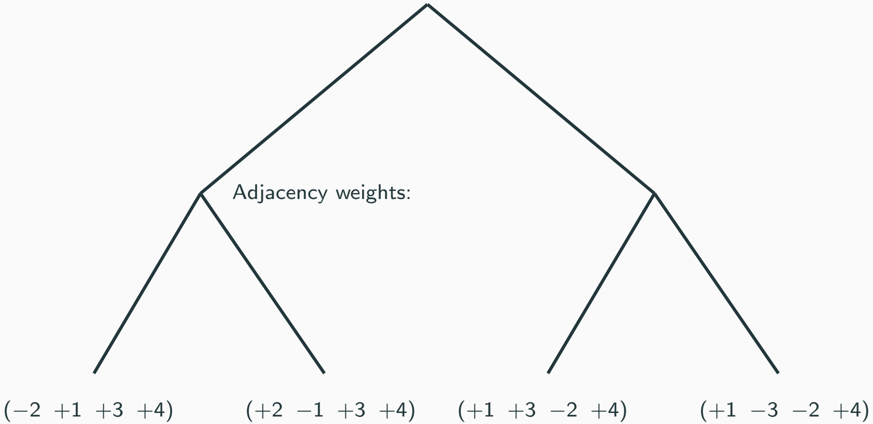
Find ancestral genomes that **minimize events** on the tree
→ **Small Parsimony Problem**

Homology-based Methods



$(-2\ \ +1\ \ +3\ \ +4)$ $(+2\ \ -1\ \ +3\ \ +4)$ $(+1\ \ +3\ \ -2\ \ +4)$ $(+1\ \ -3\ \ -2\ \ +4)$

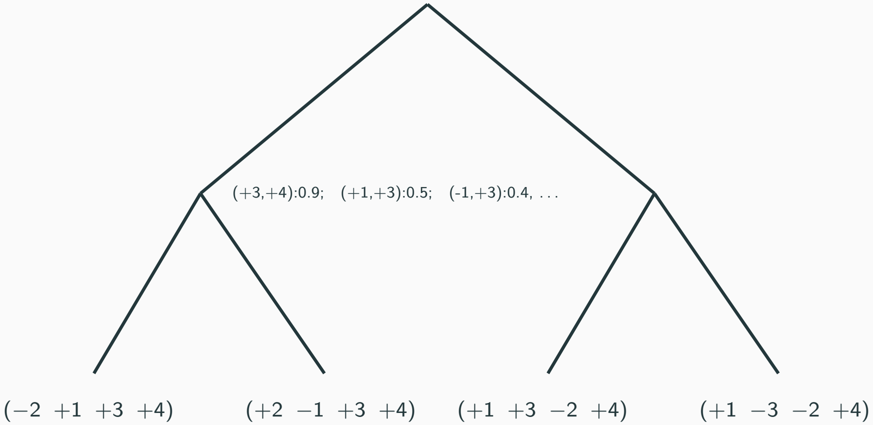
Homology-based Methods



Adjacency weights:

$(-2\ \ +1\ \ +3\ \ +4)$ $(+2\ \ -1\ \ +3\ \ +4)$ $(+1\ \ +3\ \ -2\ \ +4)$ $(+1\ \ -3\ \ -2\ \ +4)$

Homology-based Methods



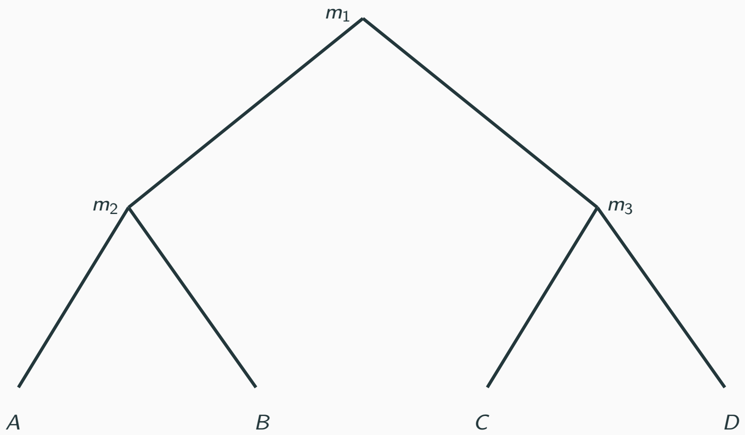
(+3,+4):0.9; (+1,+3):0.5; (-1,+3):0.4, . . .

$(-2\ \ +1\ \ +3\ \ +4)$ $(+2\ \ -1\ \ +3\ \ +4)$ $(+1\ \ +3\ \ -2\ \ +4)$ $(+1\ \ -3\ \ -2\ \ +4)$

Ancestral Reconstruction methods

- Distance-based methods:
  - Assume a rearrangement model
  - Minimize branch lengths
- Homology-based methods:
  - Find conserved structures
  - Maximize some weight/probability function

Intermediate Genomes



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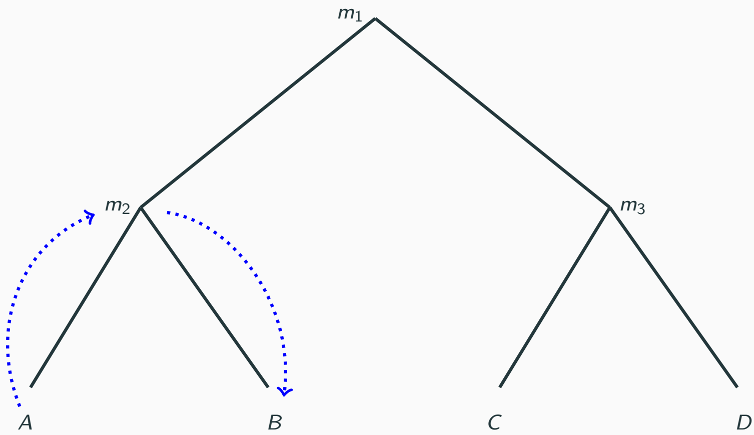


Problem Definition

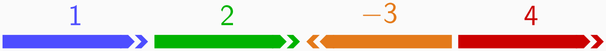
Ancestral Reconstruction where internal nodes

are

Intermediate Genomes of its children.

Definitions

Genome model



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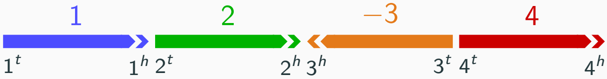
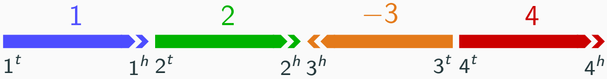
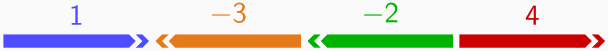


Genome model



$$A = \{\circ 1^t, 1^h 2^t, 2^h 3^h, 3^t 4^t, 4^h \circ\}$$

The Double-Cut-and-Join (DCJ) operation



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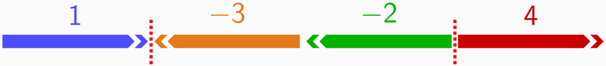

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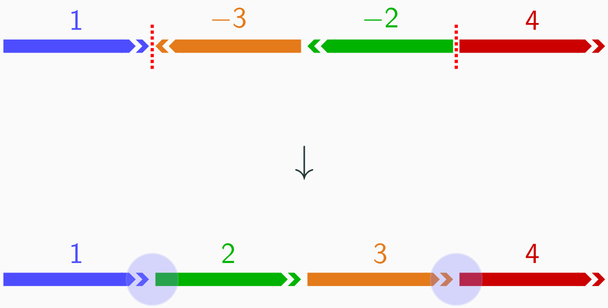

Breakpoint Graph $BP(A, B)$

$$A = \{\circ 1^t, 1^h 2^t, 2^h 3^t, 3^h 4^t, 4^h \circ, \circ 5^t, 5^h 6^t, 6^h 7^t, 7^h \circ\}$$

$$B = \{1^h 2^h, 2^t 3^h, 3^t 4^t, 4^h 1^t, \circ 6^t, 6^h 5^t, 5^h 7^h, 7^t \circ\}$$

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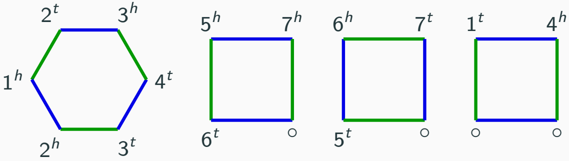


A-edges are drawn in green, and *B*-edges in blue.

DCJ Distance

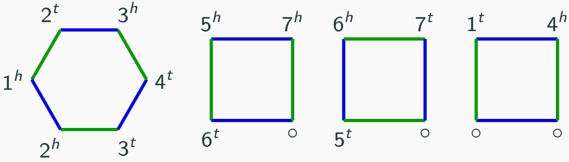
$$d_{\mathrm{DCJ}}(A, B) = N - C$$

where N is the number of genes and C is the number of cycles in $BP(A, B)$.

(Bergeron et al, 2006)

Intermediate Genomes

Genomes are **matchings** in the BP graph:



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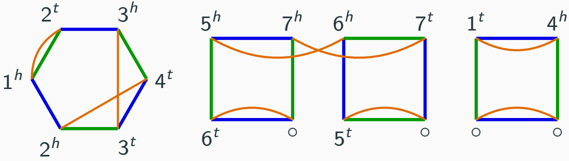

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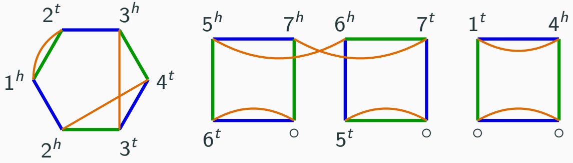

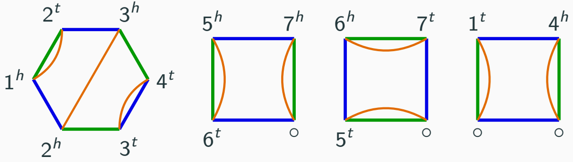

Intermediate Genomes

Edges are non-crossing chords in the cycles of $BP(A, B)$

$$\Rightarrow$$

Intermediate Genome of A and B

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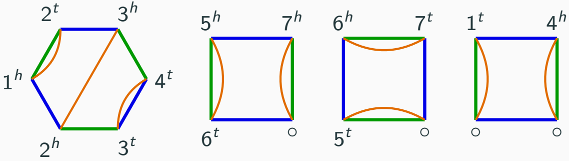

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    - 34,459,425 possible genomes

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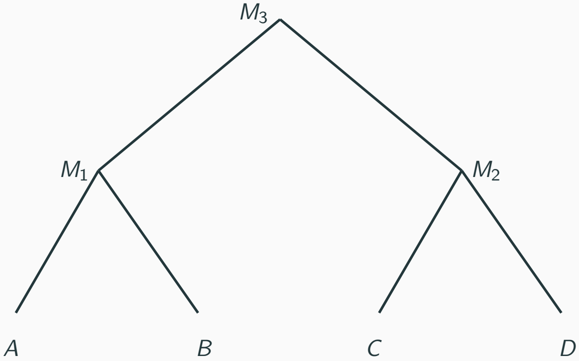
- Reduces the search space. In the example:
    - 34,459,425 possible genomes
    - Only 40 intermediate genomes between A and B.

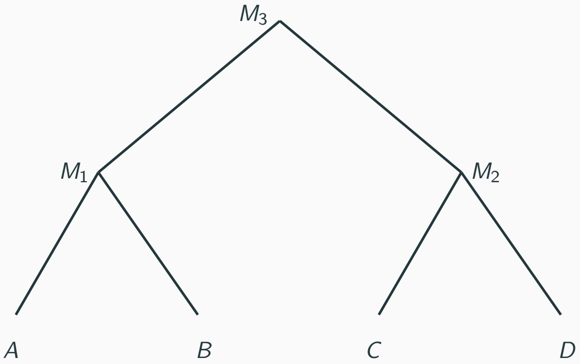
Methods

Ancestral Reconstruction with IG



- Small parsimony with the restriction that internal nodes are IG's of the children.

Ancestral Reconstruction with IG



- Small parsimony with the restriction that internal nodes are IG's of the children.

- Still NP-hard

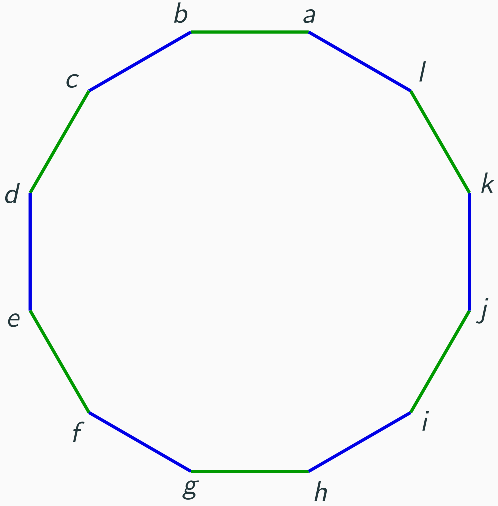
Maximum Weight Intermediate Genome

- Given adjacency weights, can we find an IG with maximum weight?
- **Maximum Weight Independent Set**: Polynomial Time

Finding Adjacency Weights

- DeClone (Chauve et al., 2015)
- New proposed algorithm based on InferCARs (Ma et al., 2006).

Example



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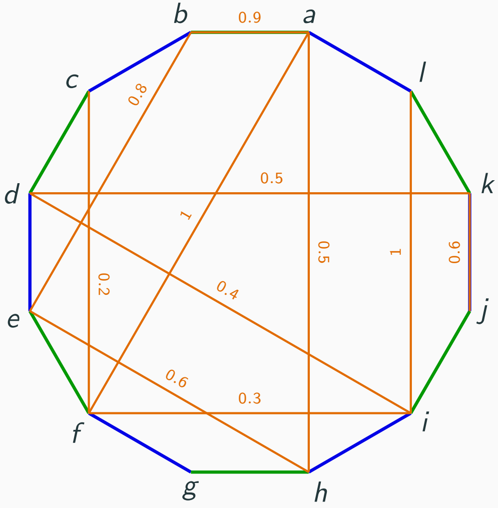

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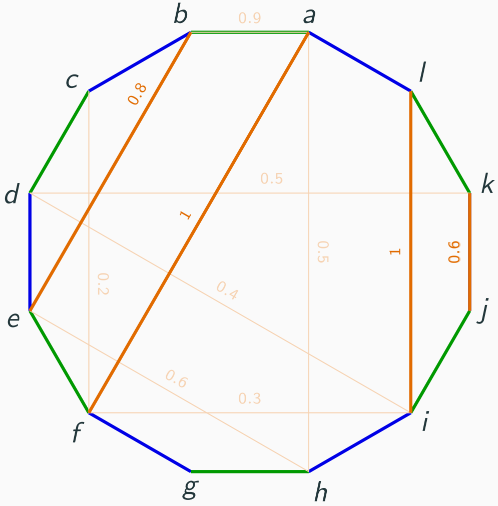
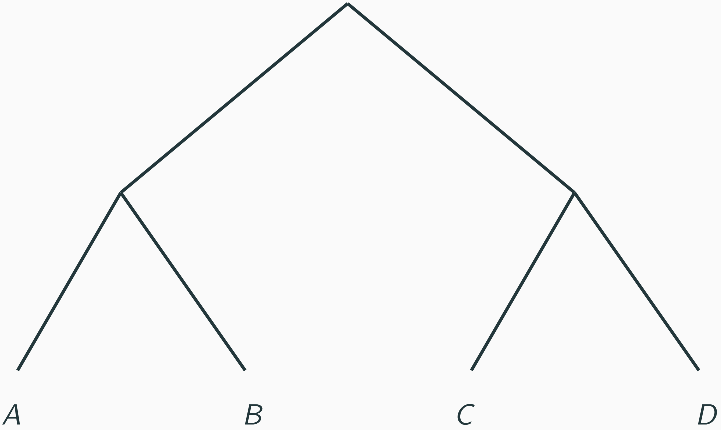


Algorithm Overview



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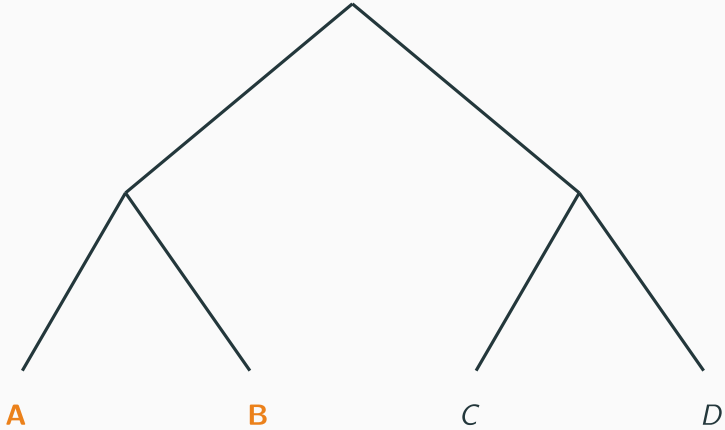

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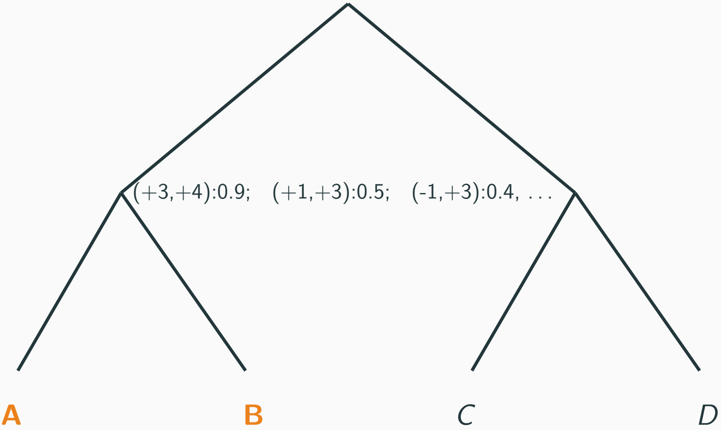

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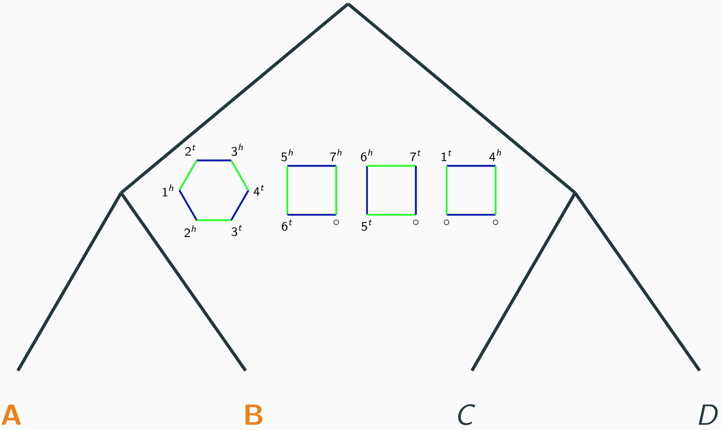

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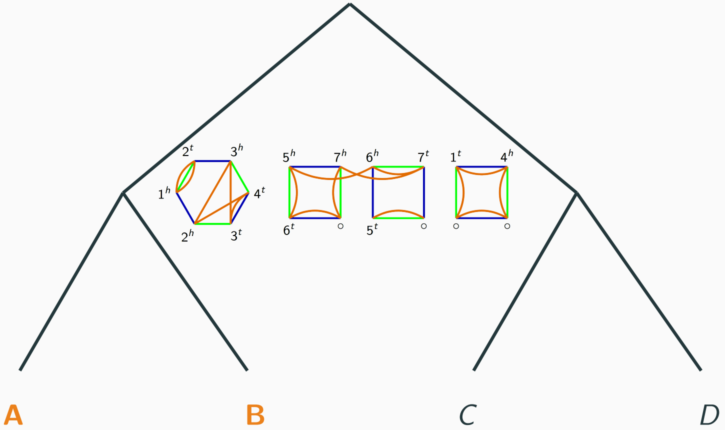

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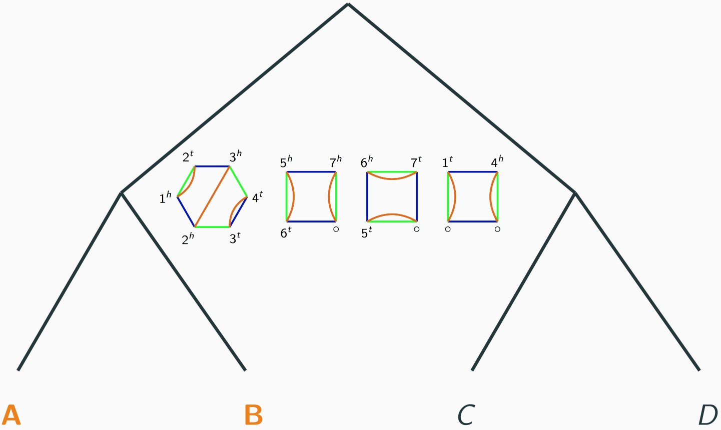

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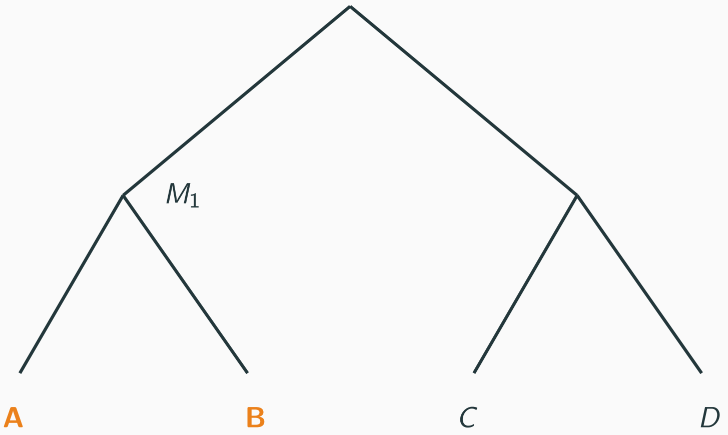
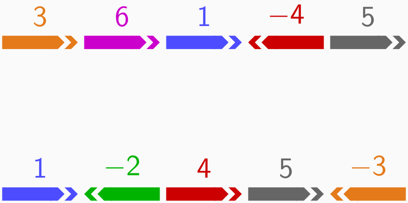


Genomes with unique genes



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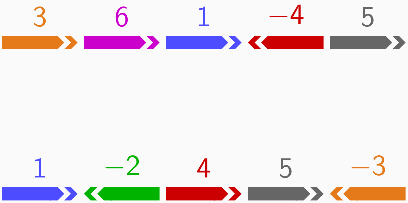
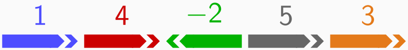
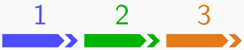


DCJ InDel Model (Braga et al., 2010; Compeau, 2012)

DCJ InDel example





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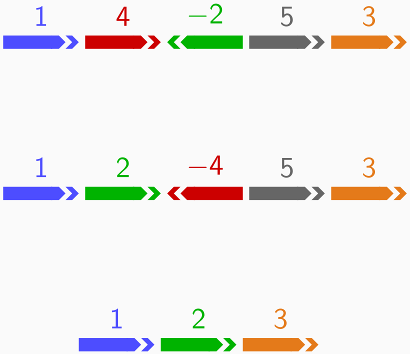
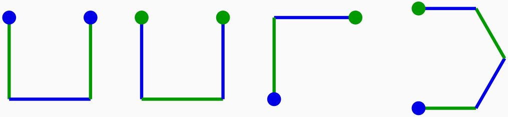


Breakpoint graph with Unique genes



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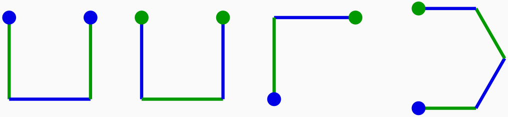

New components: AA-, BB-, AB- , A-, and B-paths.

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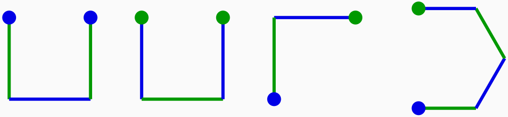

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Find an **optimal completion**

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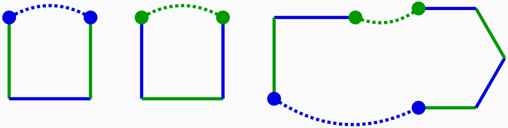
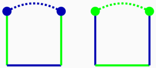


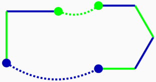
New components: AA-, BB-, AB- , A-, and B-paths.

Find an **optimal completion**

Optimal completion

- AA- and BB- components are closed





- AB- are paired

- A- and B- paths are paired, with opposing parity.

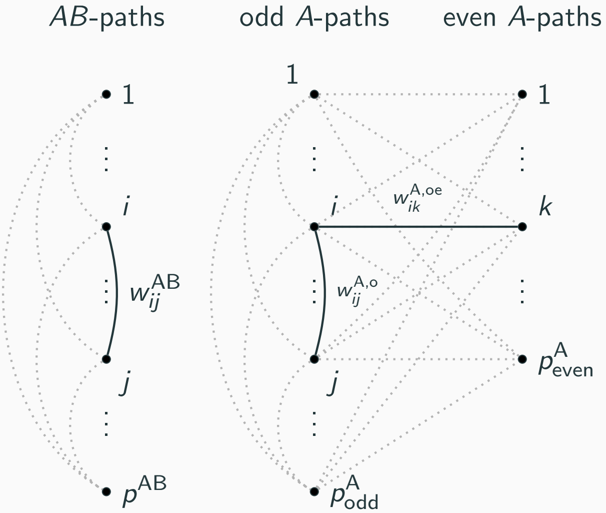
- Sometimes A-, B- and AB- paths are joined in a **triplet**.

Maximum Weight Intermediate Genome

- How to find a completion with maximum weight?

- Calculate all possible pairings and solve a *Maximum Weight Matching*

Maximum Weight Matching



MWM is not always optimal

- Sometimes A-, AB-, B- triplets are possible.
- Triple matching is usually NP-hard, but it is still open in this case.

Results

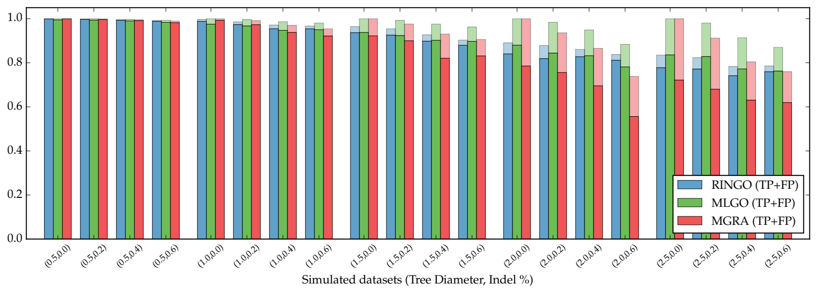
Methods

- RINGO - ancestral **R**econstruction with **IN**termediate **G**en**O**mes (Feijao and Araujo, 2016)

- MGRA2 (Avdeyev et al., 2016)

- MLGO (Hu et al., 2014)

Quality Results



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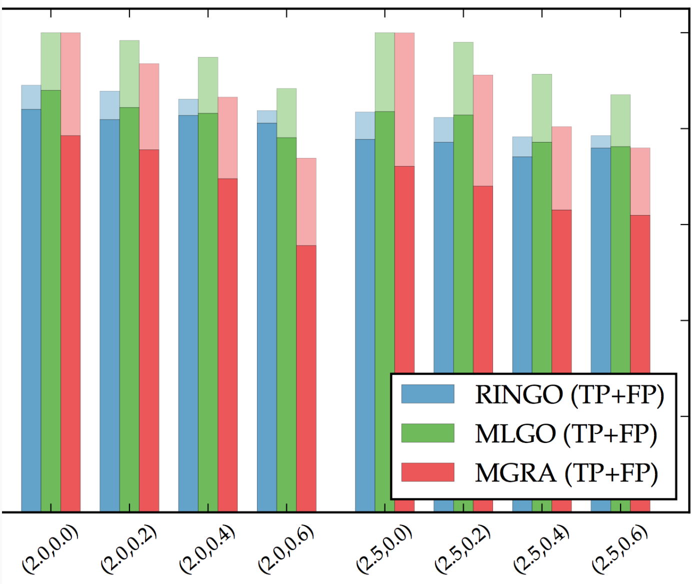
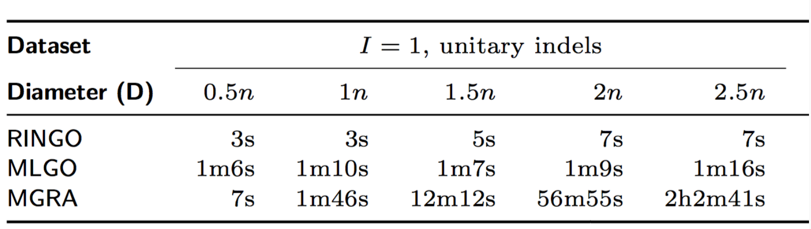


Running Time



Dataset	$I = 1$, unitary indels				
Diameter (D)	$0.5n$	$1n$	$1.5n$	$2n$	$2.5n$
RINGO	3s	3s	5s	7s	7s
MLGO	1m6s	1m10s	1m7s	1m9s	1m16s
MGRA	7s	1m46s	12m12s	56m55s	2h2m41s

Current Challenges

- Duplicated genes
- Statistical models

Acknowledgments

- Elói Araújo (UFMS, Brazil)

UFMS

- Jens Stoye (Bielefeld University, Germany)

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Genominformatik

Thanks!