Reconstructing the duplication history of tandemly repeated genes

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(1) LIRM Montpellier, Méthodes et Algorithmes pour l'Analyse de Séquences

(2) LIGM, IMGT the International ImMunoGeneTics Database, http ://imgt.cines.fr

1. Introduction

2. Mathematical model

3. Reconstructing duplication trees

4. Experimental results

5. Perspectives

1. Introduction

Tandemly repeated sequences

– two or more adjacent copies of a stretch of DNA

Tandemly repeated sequences

- two or more adjacent copies of a stretch of DNA
- they exist in several forms :
  - microsatellites (neurodegenerative diseases), minisatellites
  - larger sequences (genes)

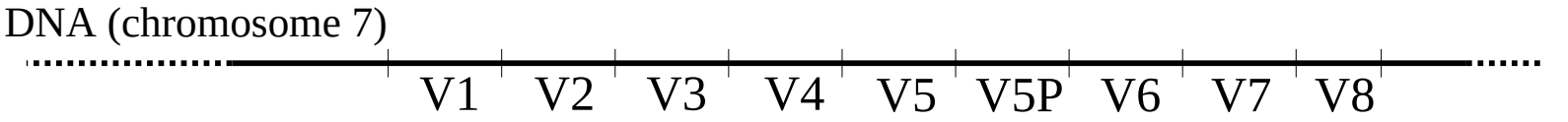
Tandemly repeated genes

Example : the human TRGV locus

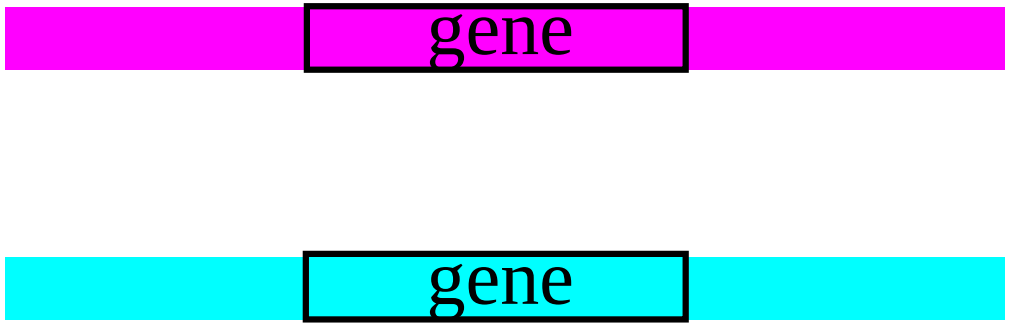
– it contains 9 adjacent copies of the same gene

– each of them is 4-5kb long

– they share between 85 and 97% of identity



Recombination



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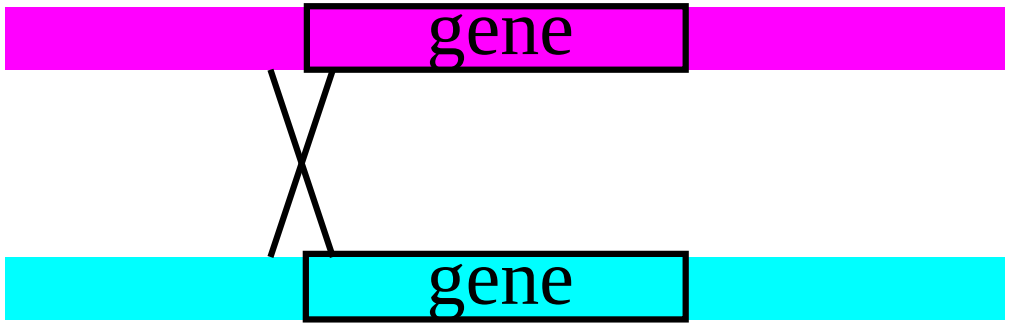

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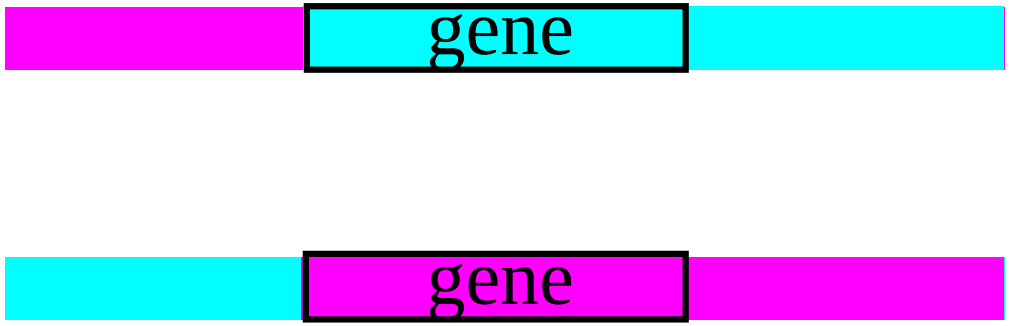
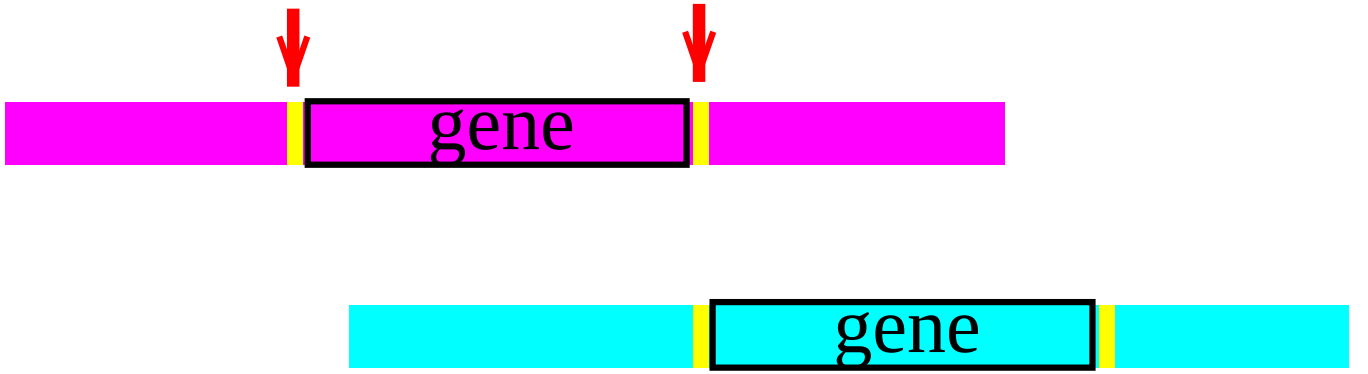


Unequal recombination (step 1)



initial duplication caused by the presence of short repeated sequences

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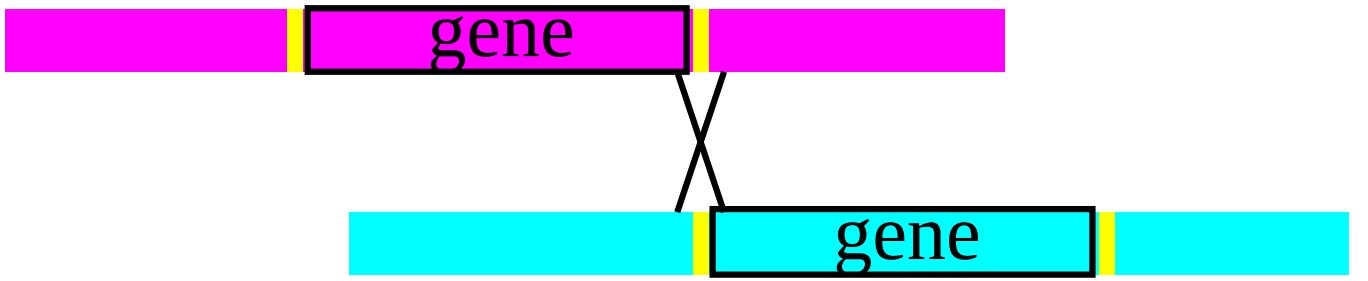

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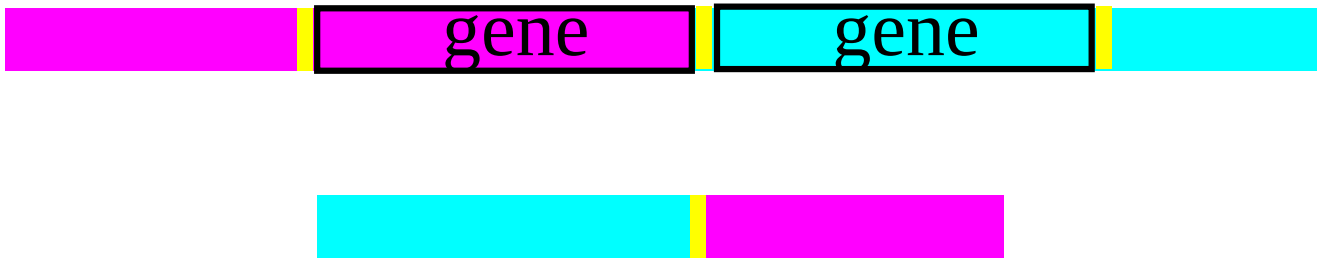

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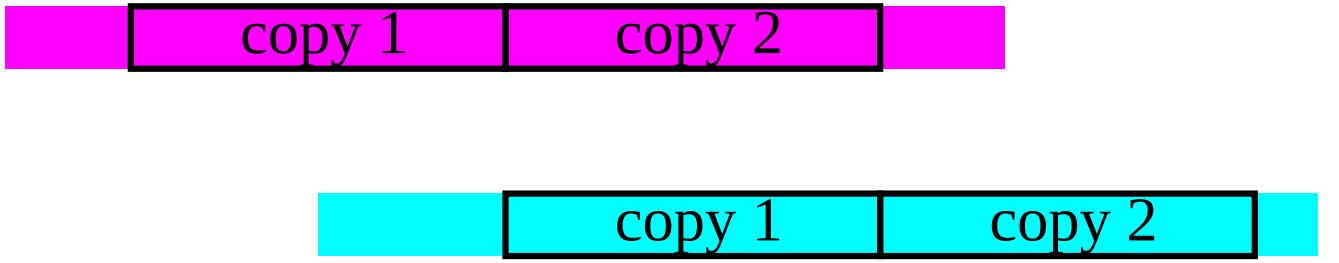
Unequal recombination (step 2)



the presence of several times the same copy favors additional duplications

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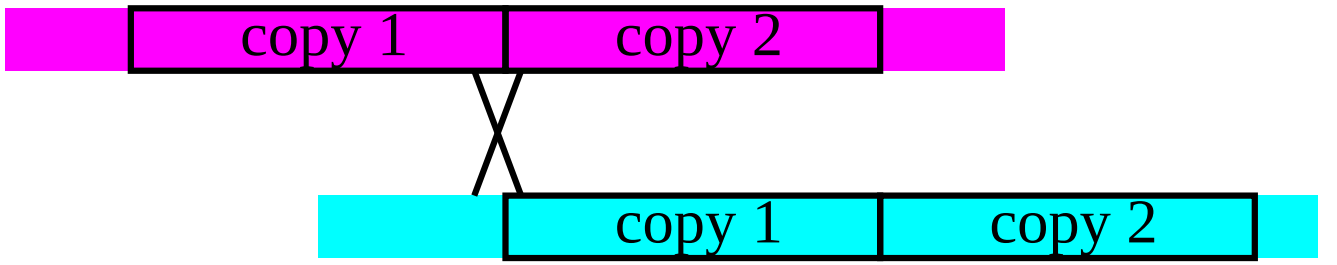

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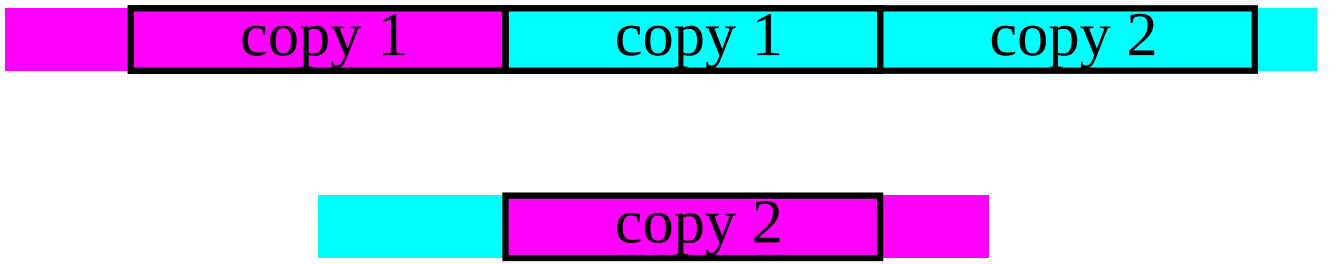

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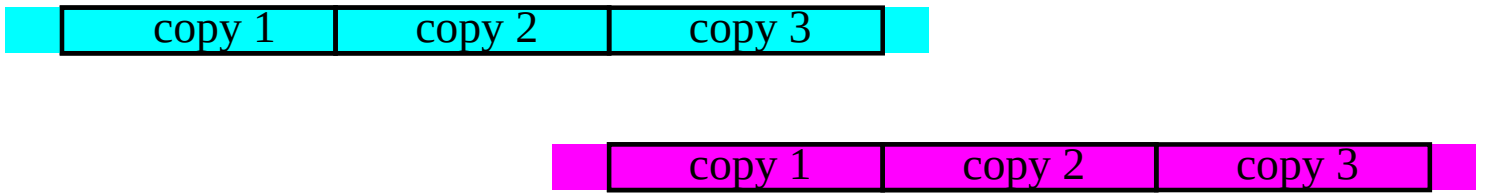

“block” duplication, i.e. simultaneous duplication of several copies

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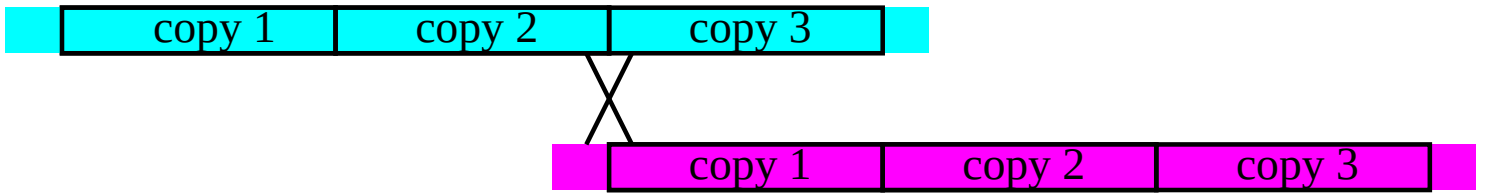

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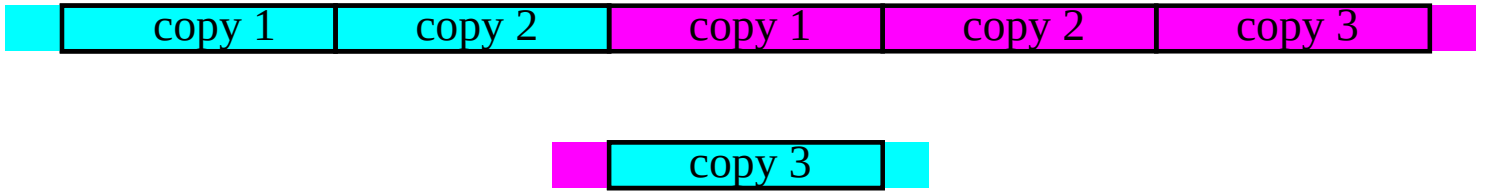

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Preliminary hypothesis

– unequal recombination is the sole generating mechanism

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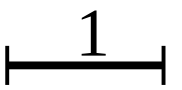
– there was no gene conversions

– there was “no gene deletions”

The duplication events

1-duplication



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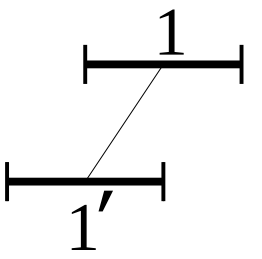

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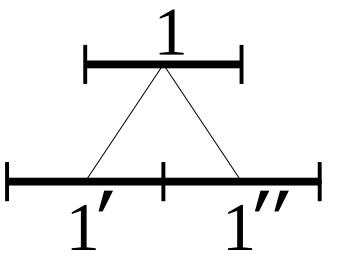

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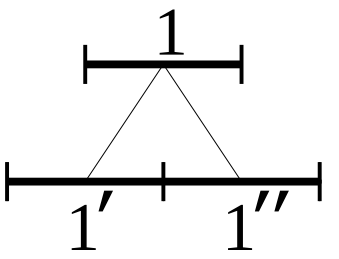
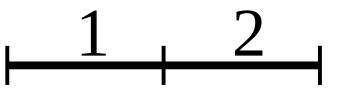


2-duplication



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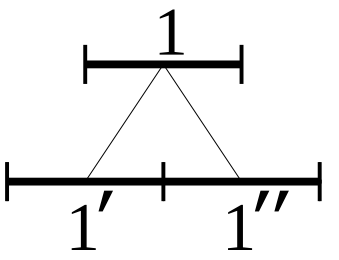

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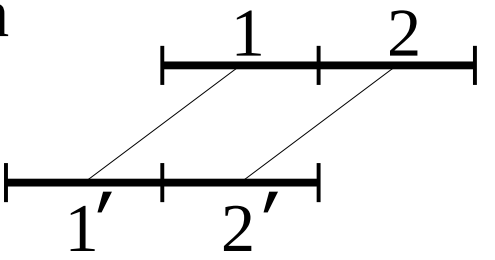

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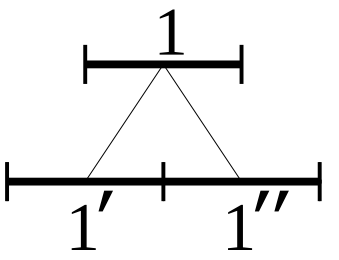

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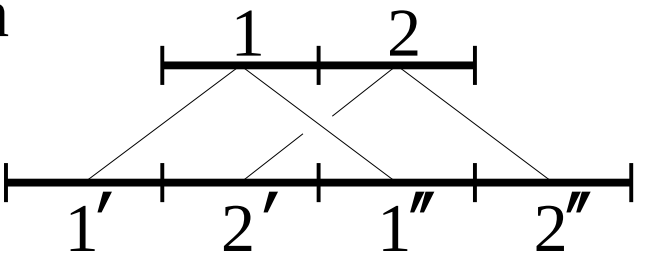

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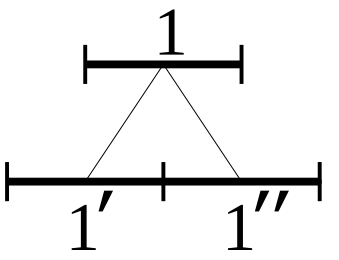

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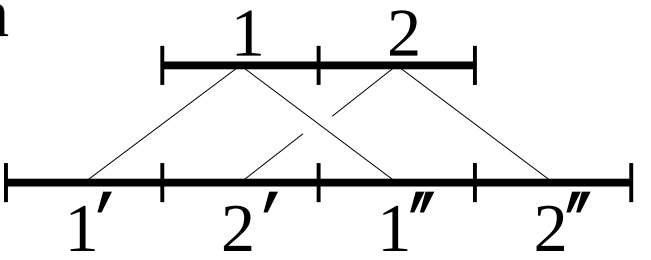
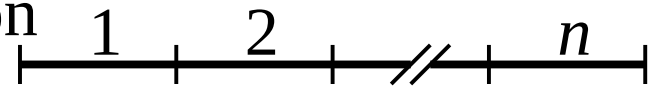


n-duplication



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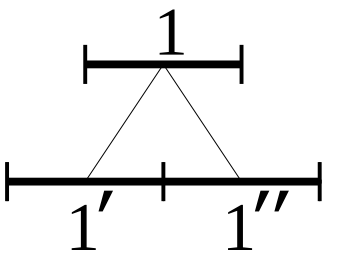

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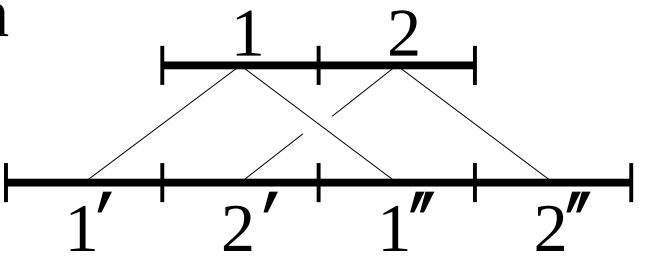

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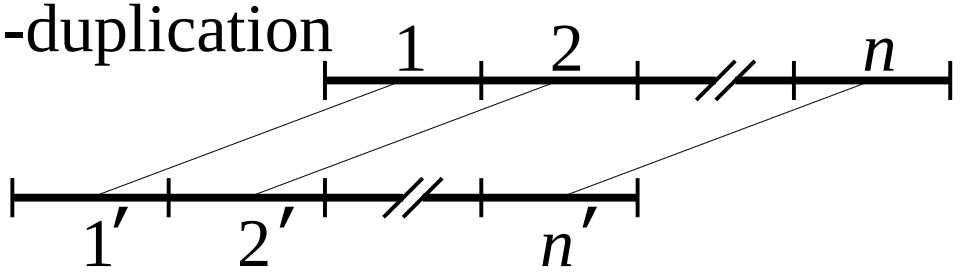

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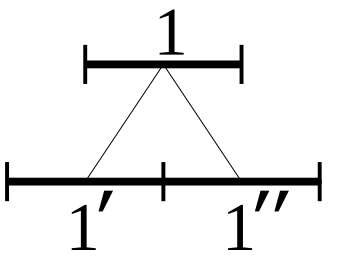

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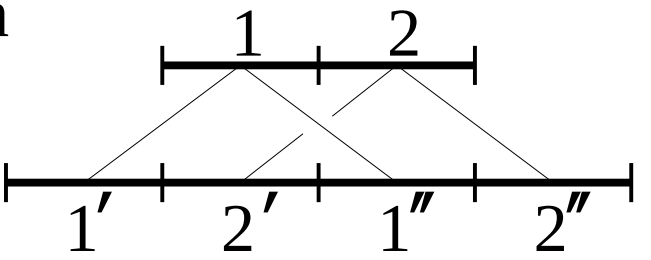

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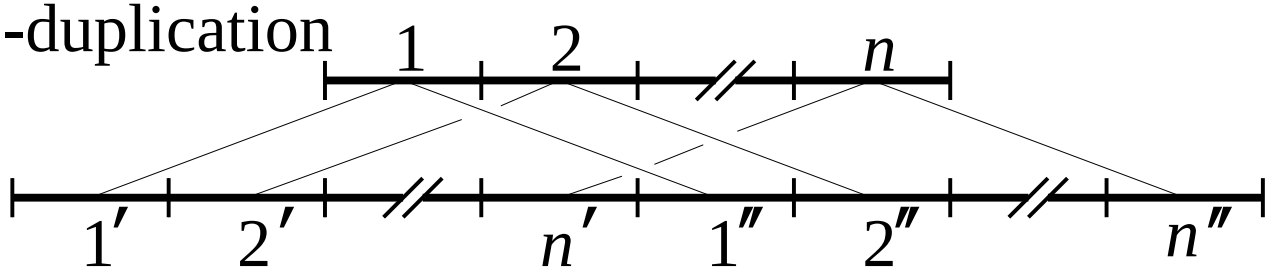
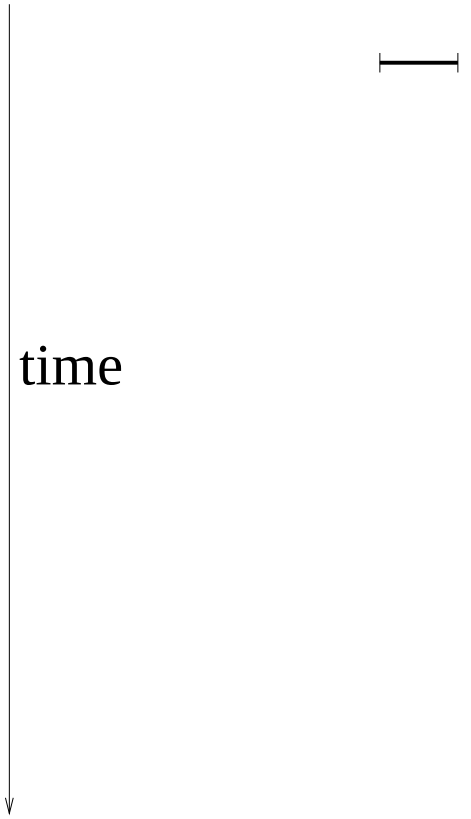


Time valued duplication history (reality)



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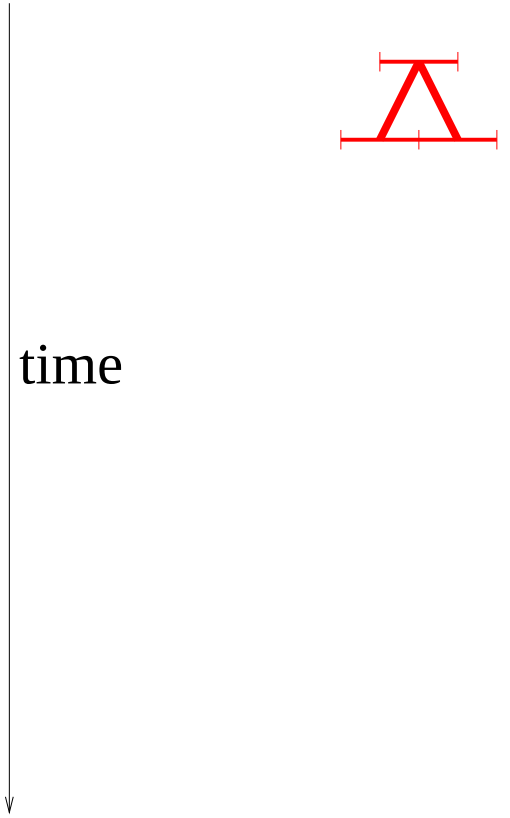

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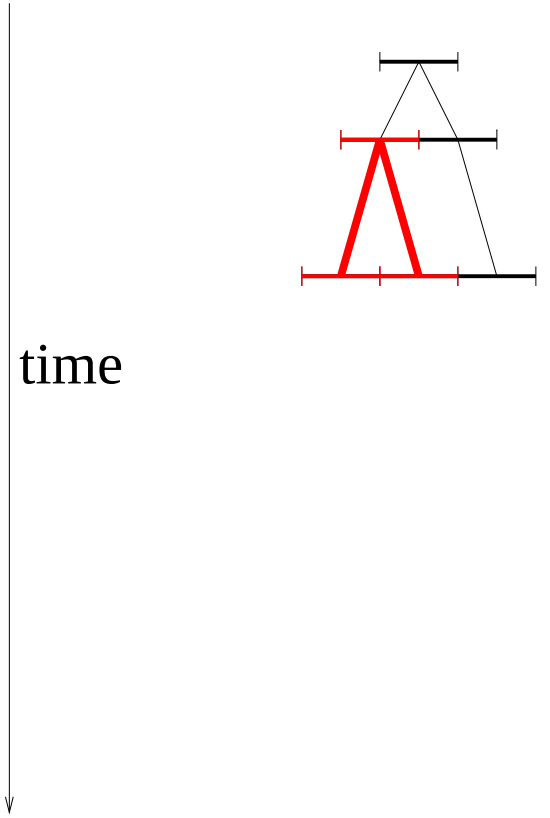

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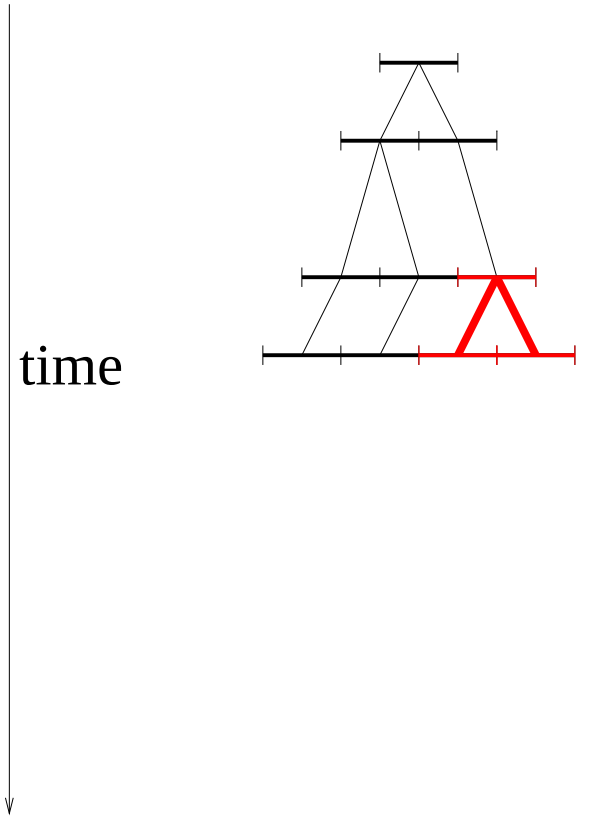

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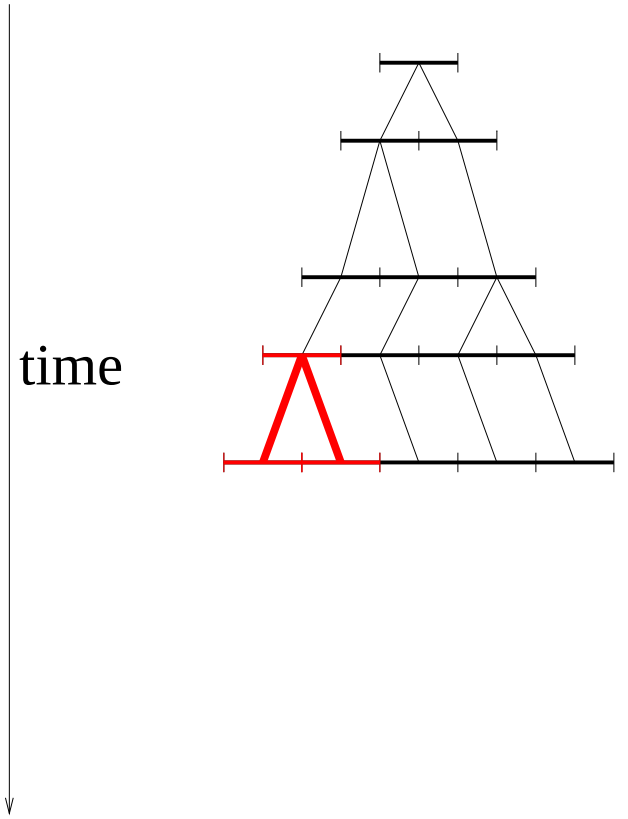

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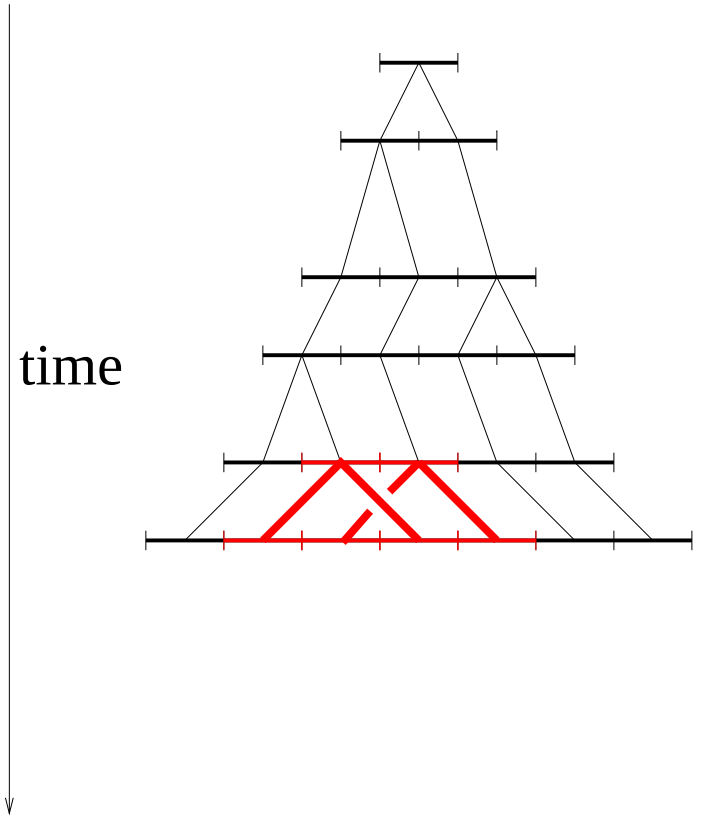

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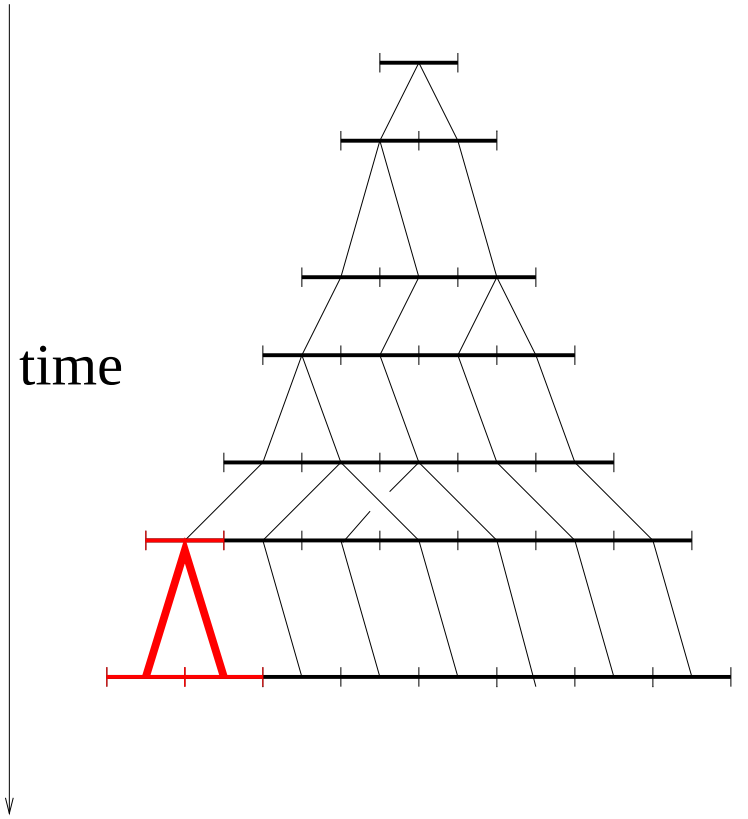

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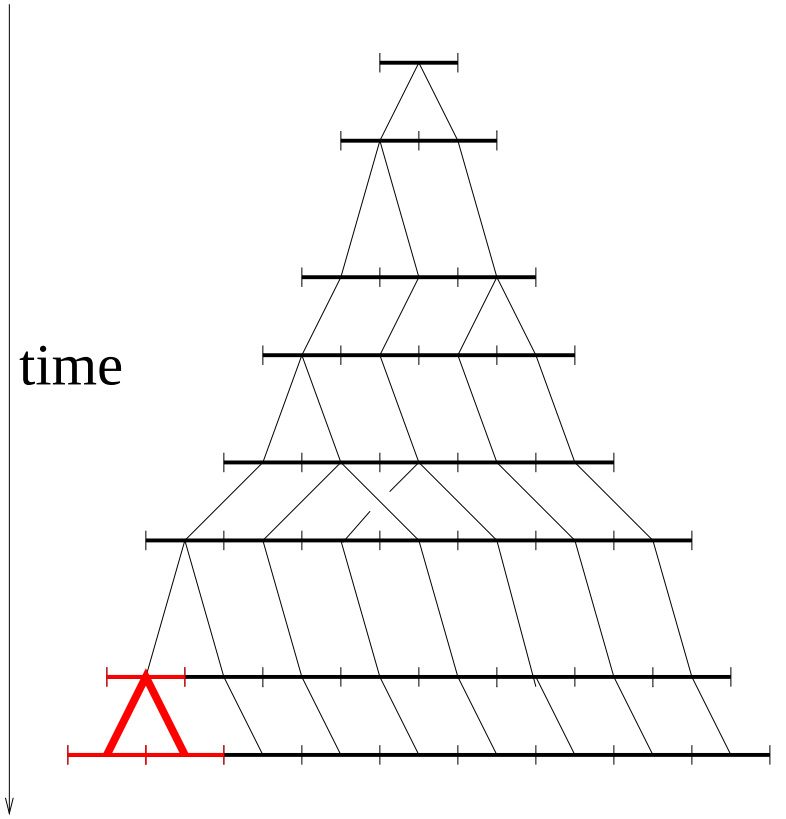

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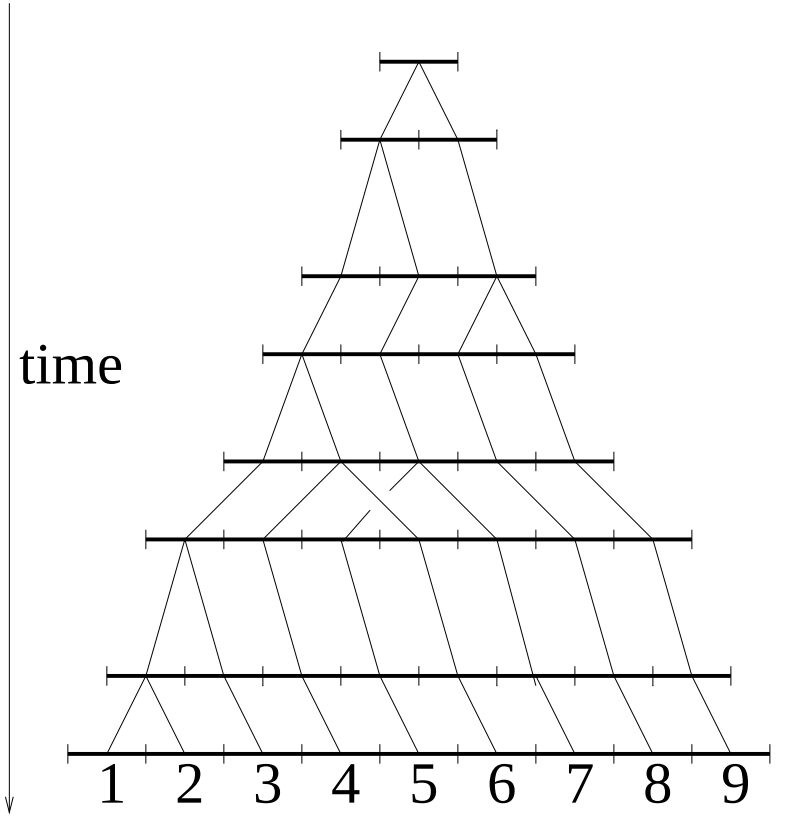

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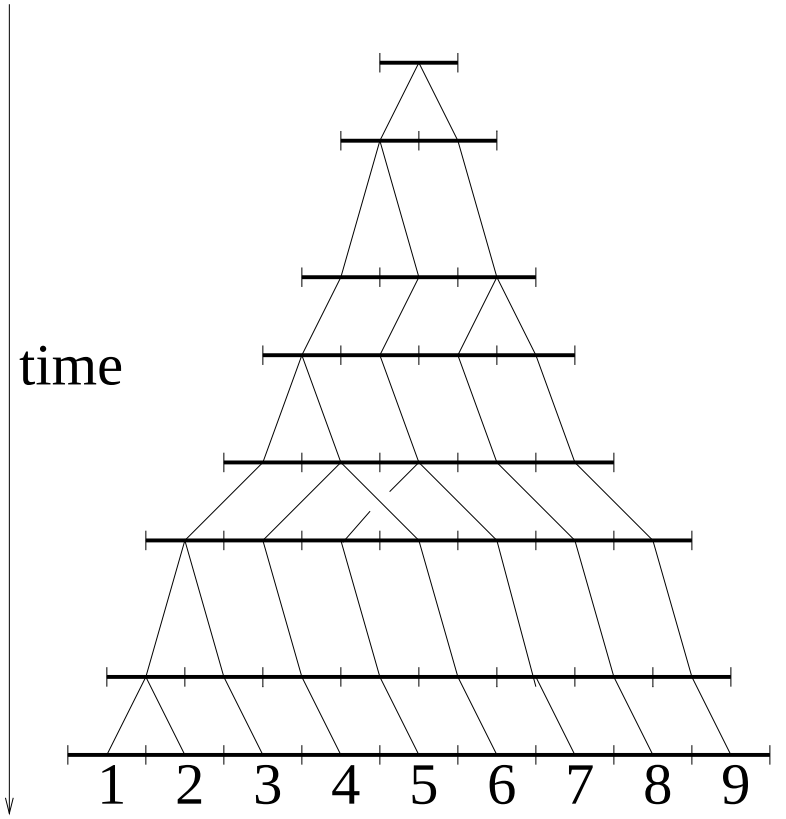

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- its taxa are ordered

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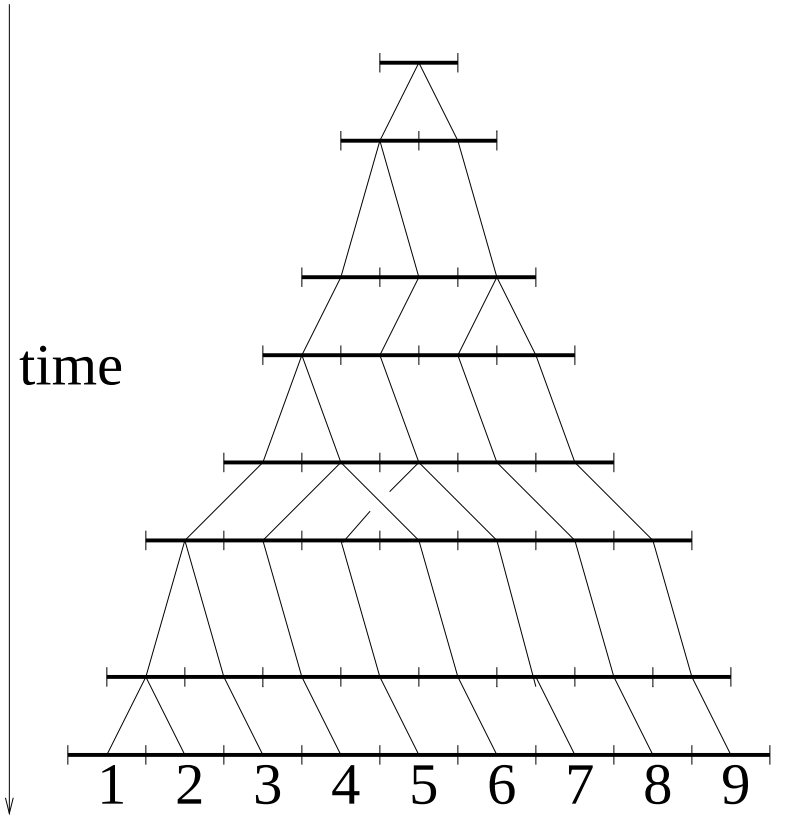

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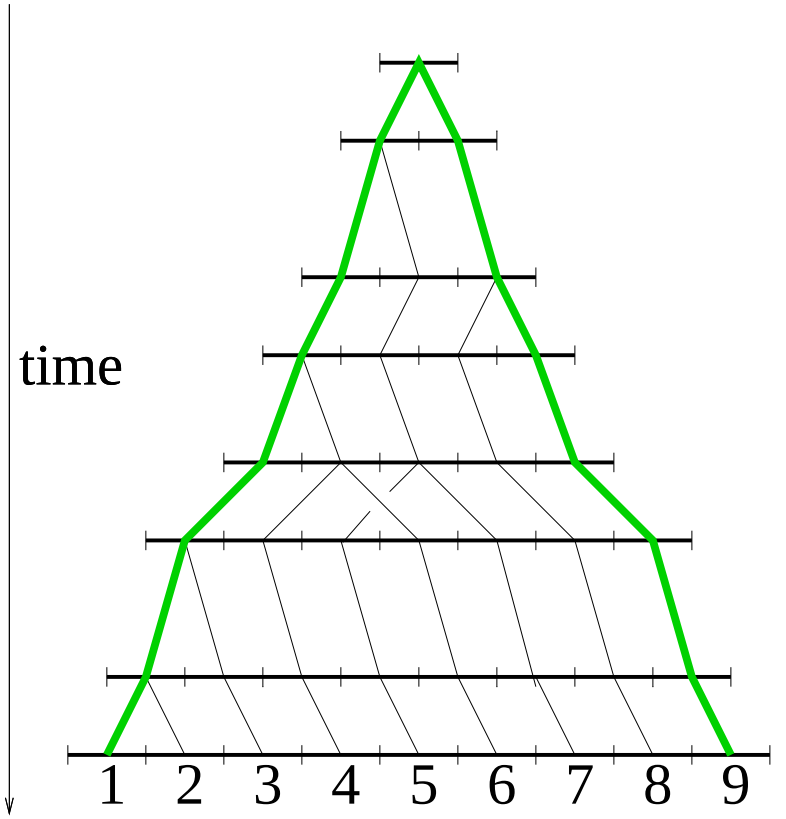
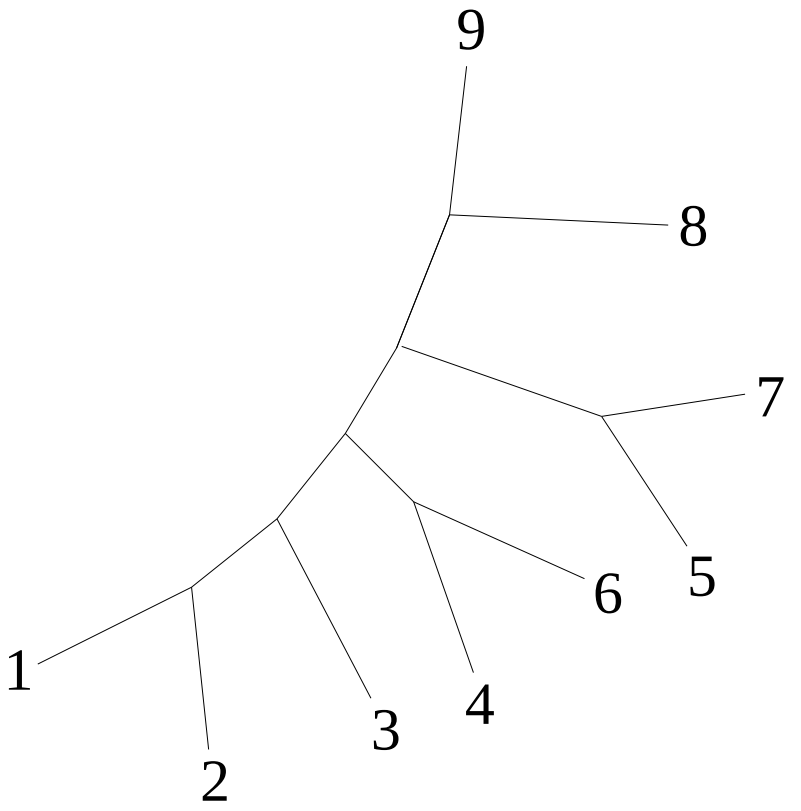


- it implies a rooted phylogeny
- its taxa are ordered
- its branches are time valued
- the root is situated between the most distant taxa

Duplication tree (what can be infered)

– it is an unrooted phylogeny



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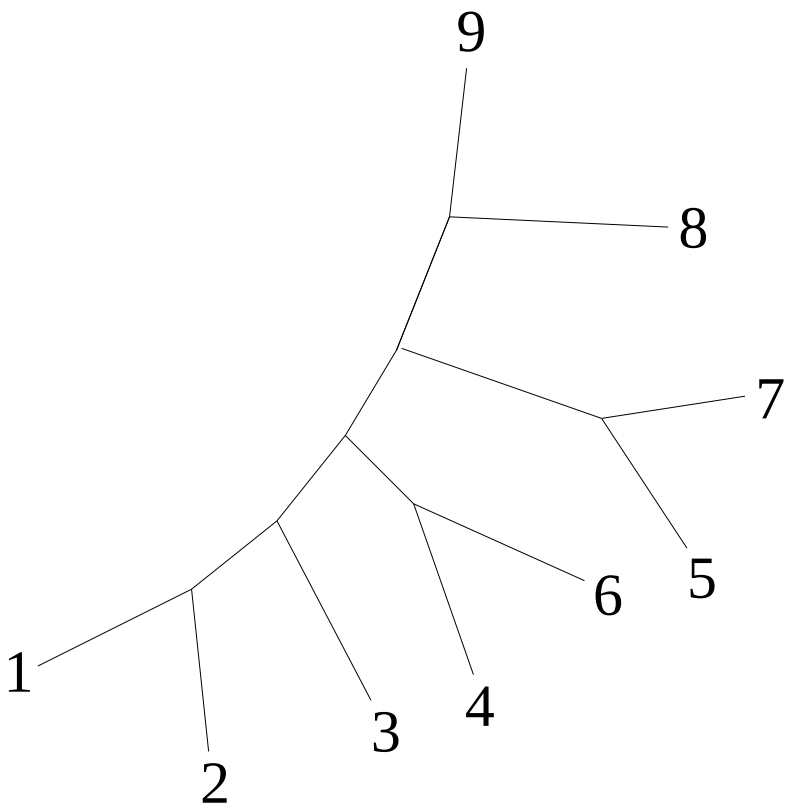

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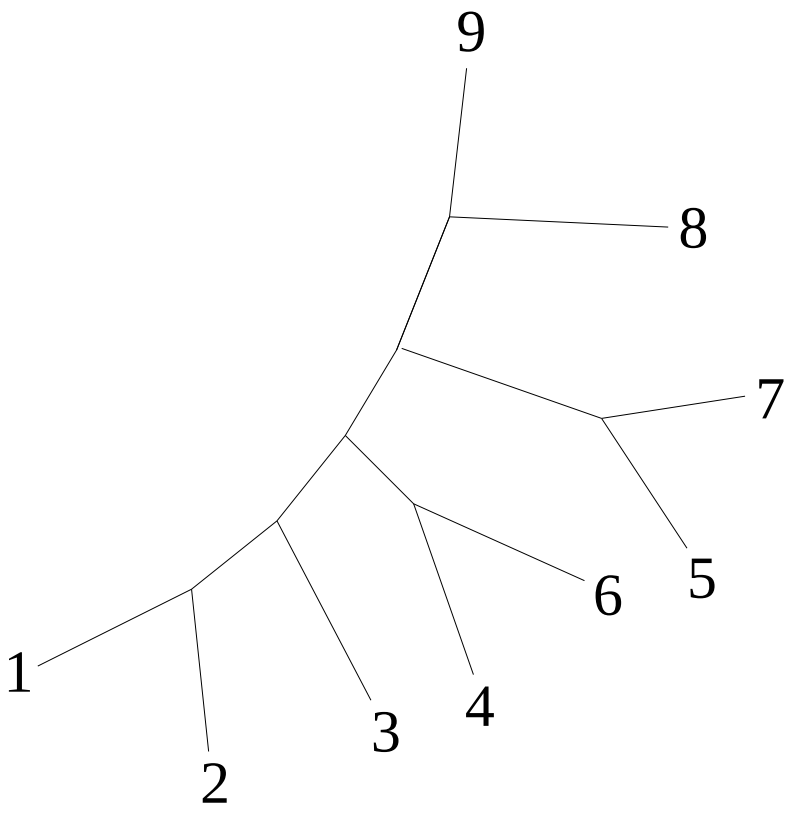

- it is an unrooted phylogeny
- its taxa are ordered
- its branches are mutation rate-valued

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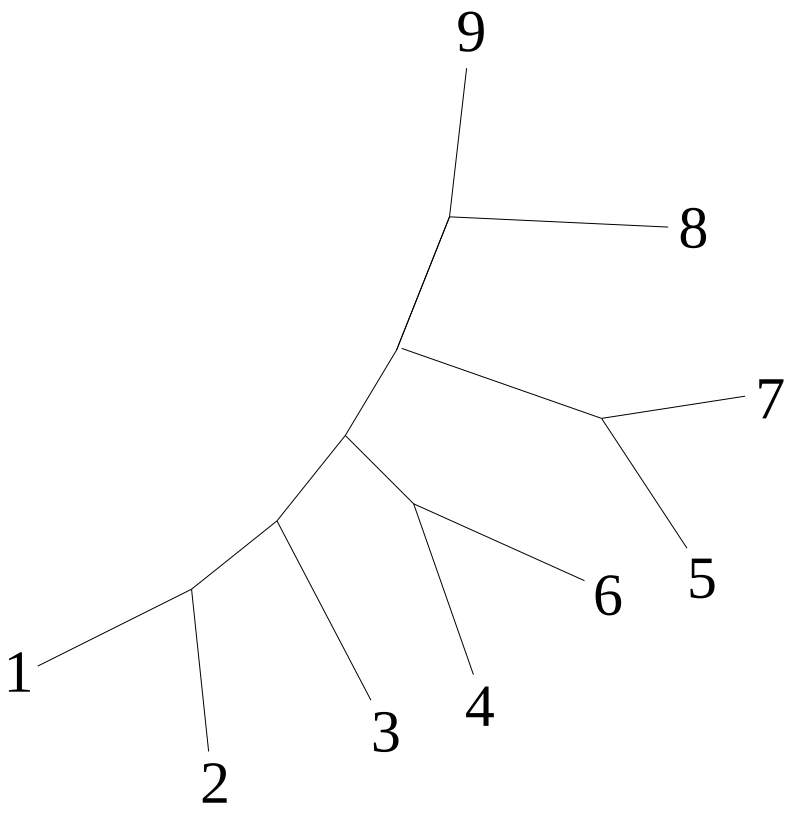

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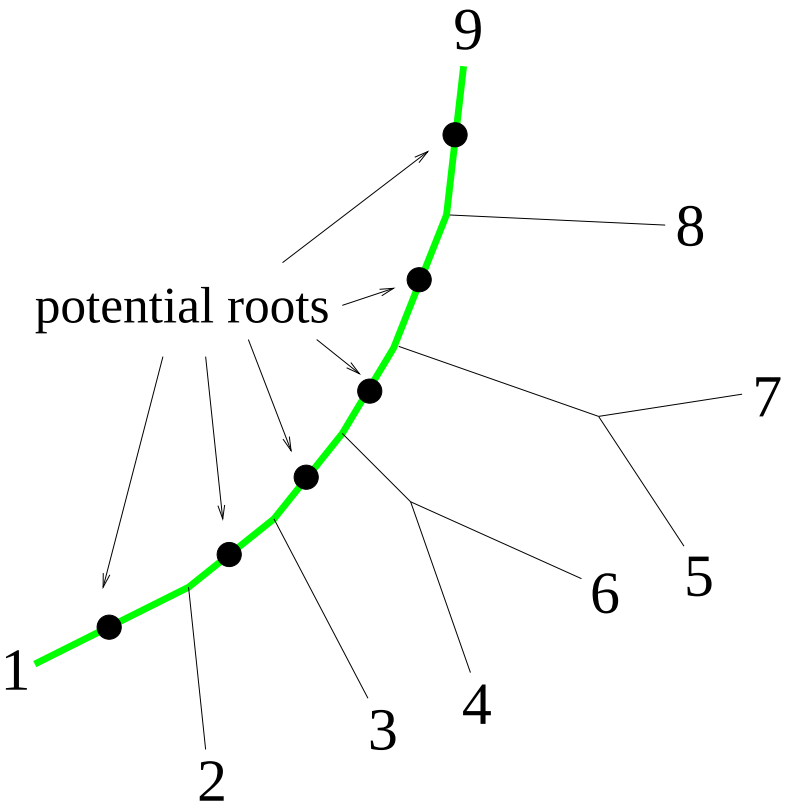
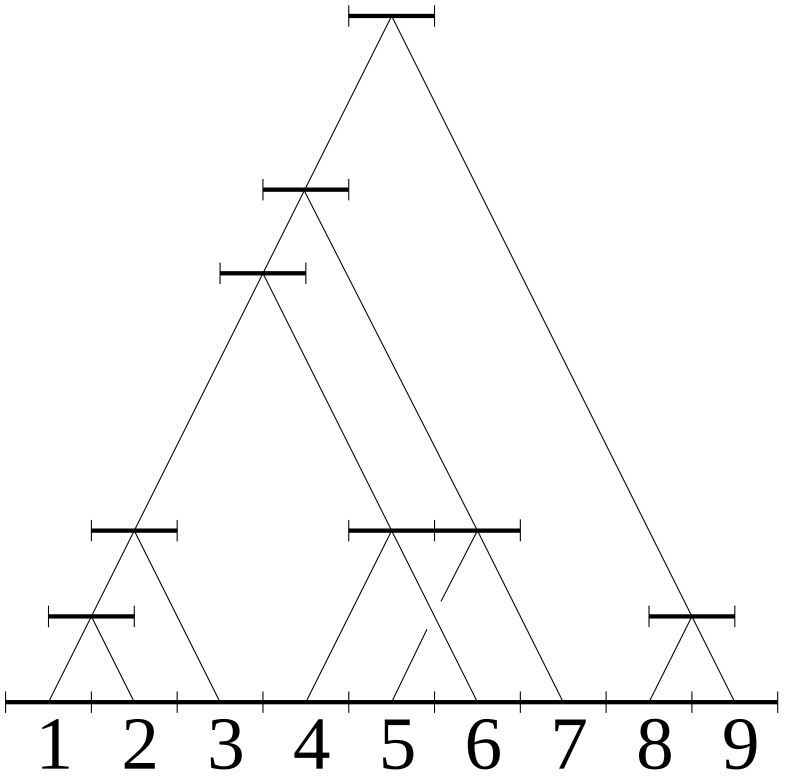


- it is an unrooted phylogeny
- its taxa are ordered
- its branches are mutation rate-valued
- its topology is compatible with at least one duplication history
- the root is situated somewhere in the tree between the most distant taxa

Ordinal duplication history

– obtained when rooting a duplication tree



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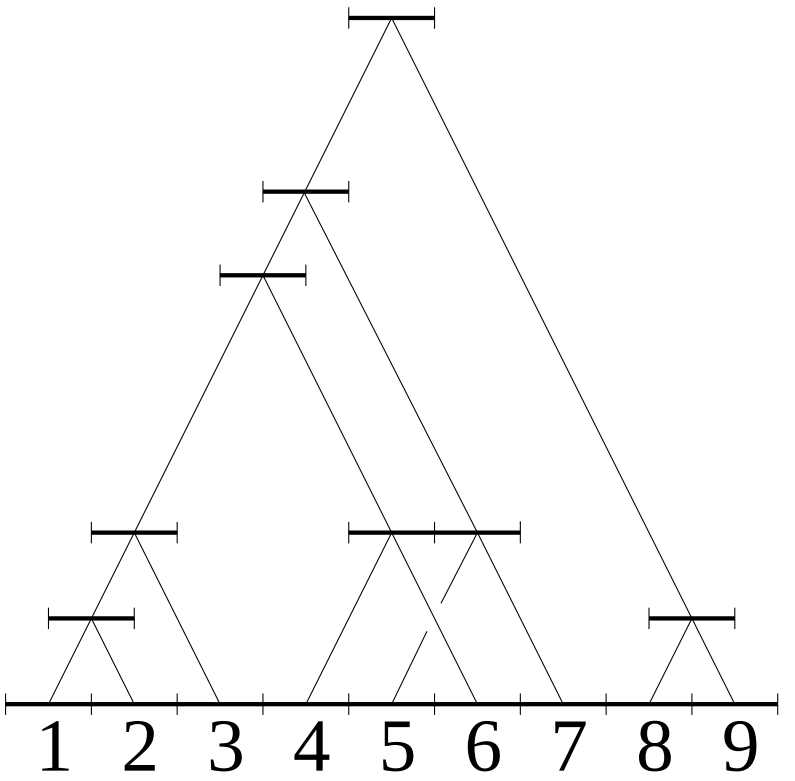
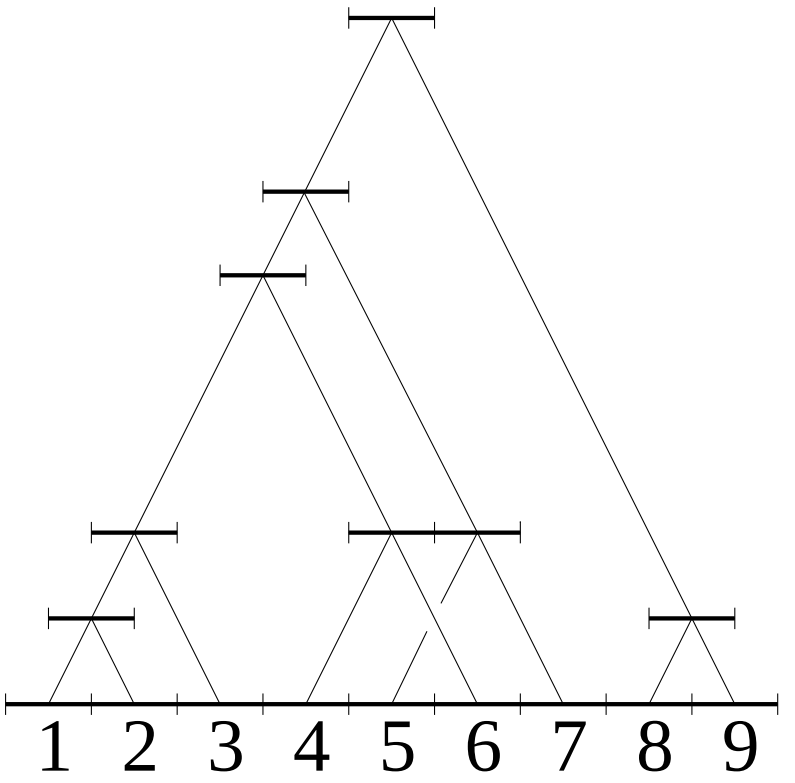


- obtained when rooting a duplication tree
- it is the topological version of the time valued duplication history

Ordinal duplication history



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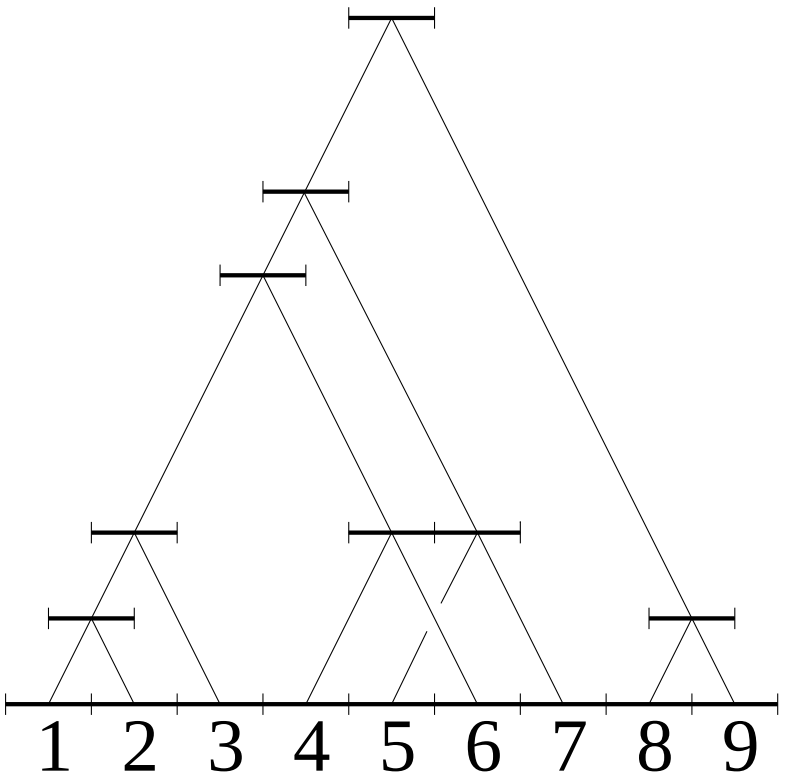

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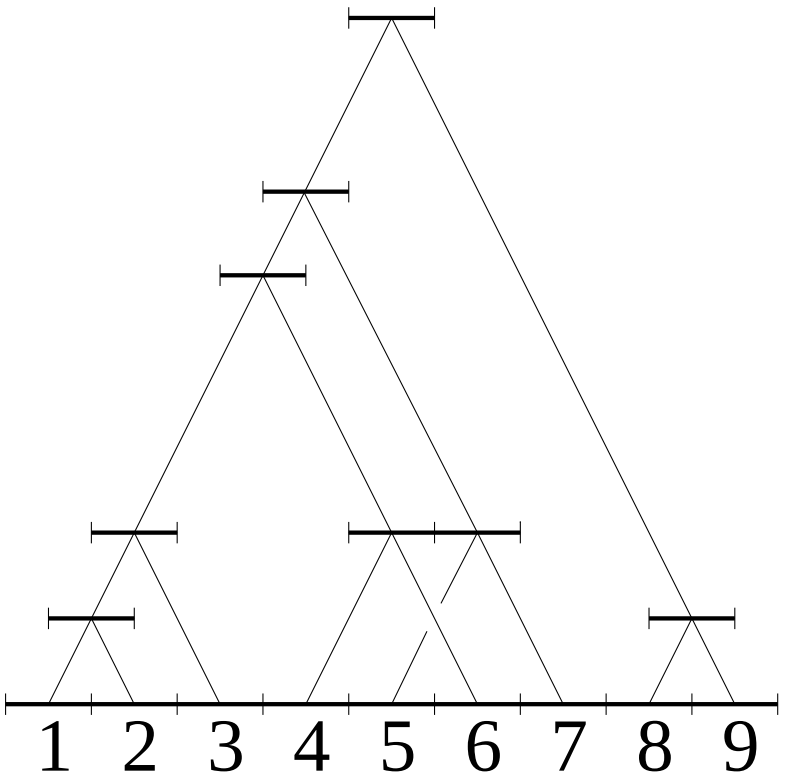
- its taxa are ordered

Ordinal duplication history



- obtained when rooting a duplication tree
- it is the topological version of the time valued duplication history
- it is a rooted phylogeny
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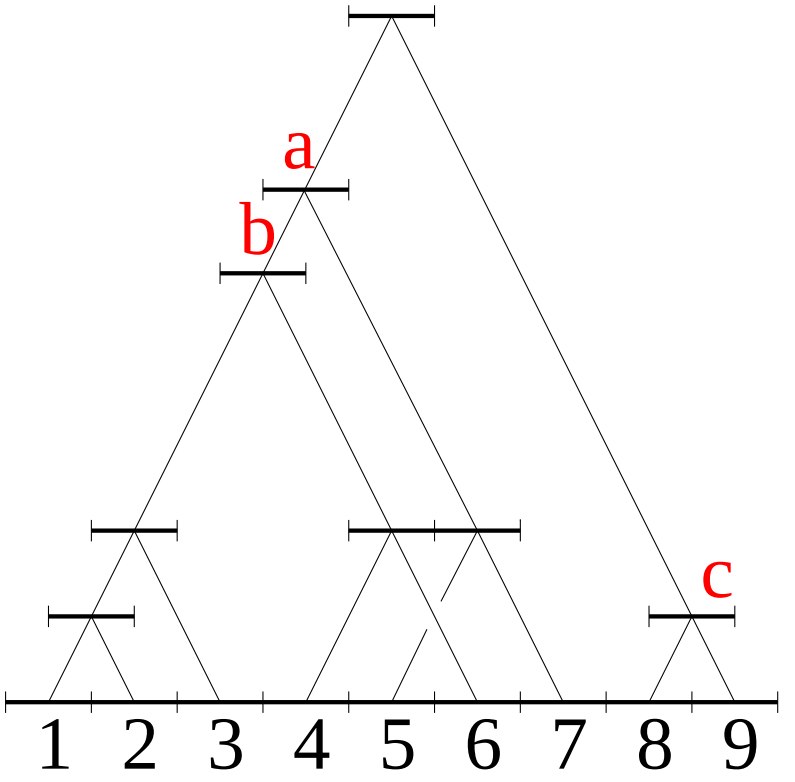
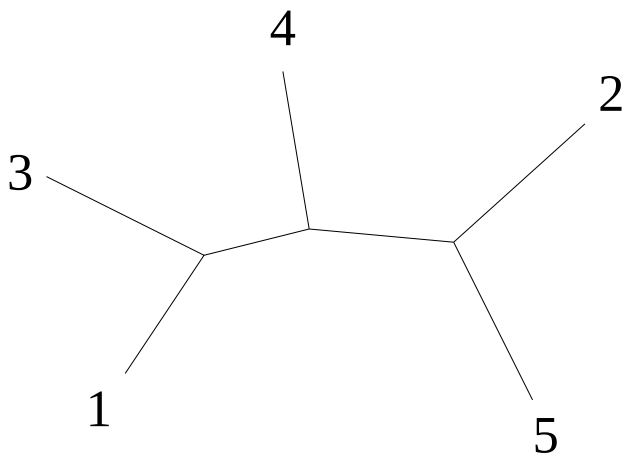
Ordinal duplication history



- obtained when rooting a duplication tree
- it is the topological version of the time valued duplication history
- it is a rooted phylogeny
- its taxa are ordered
- its branch lengths have no special meaning
- the duplication events are partially ordered

Not all phylogenies are duplication trees



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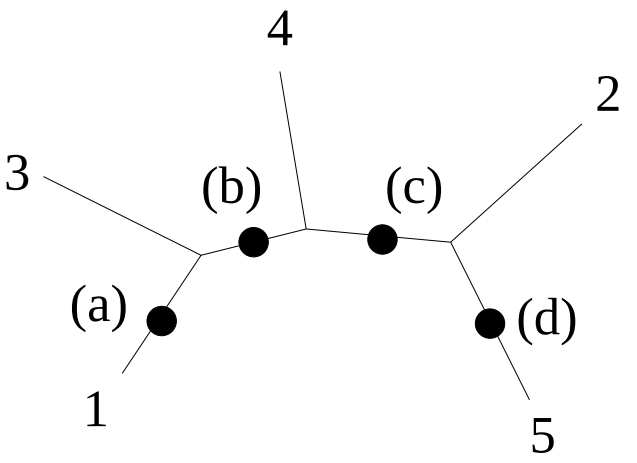

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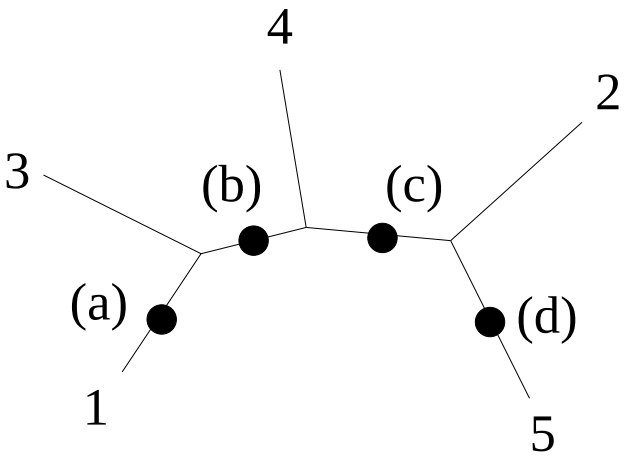
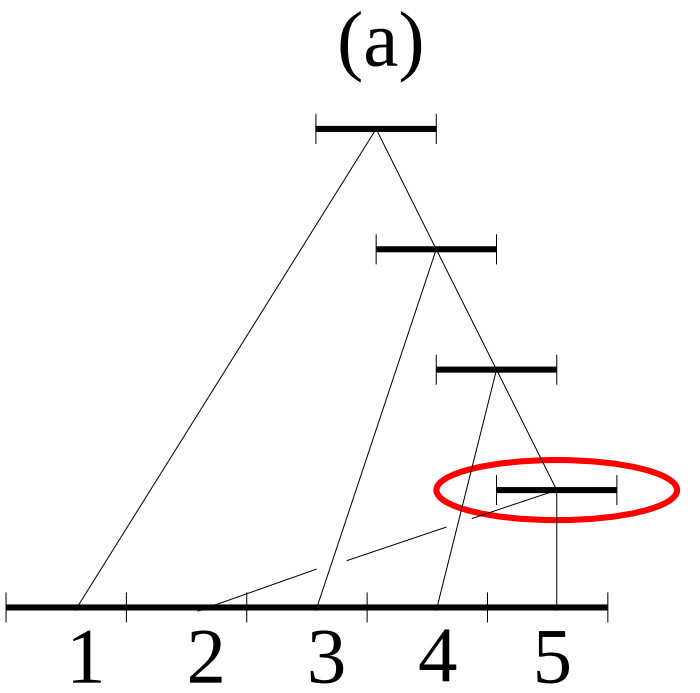
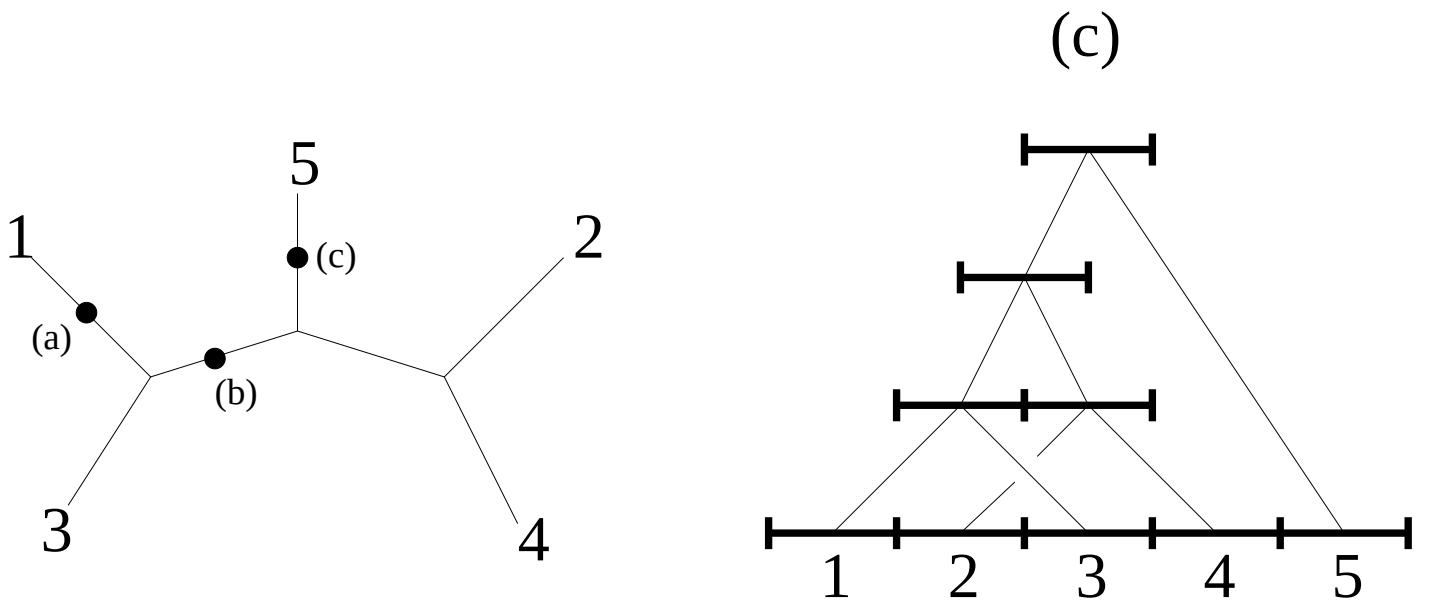




2 and 5 are not adjacent !

Not all potential roots lead to correct ordinal duplication histories



correct ordinal duplication history

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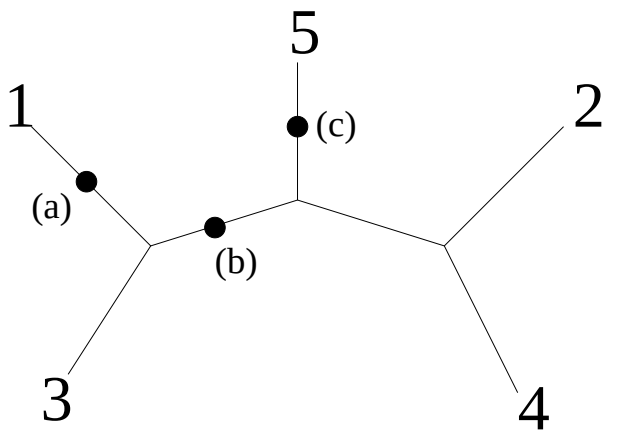

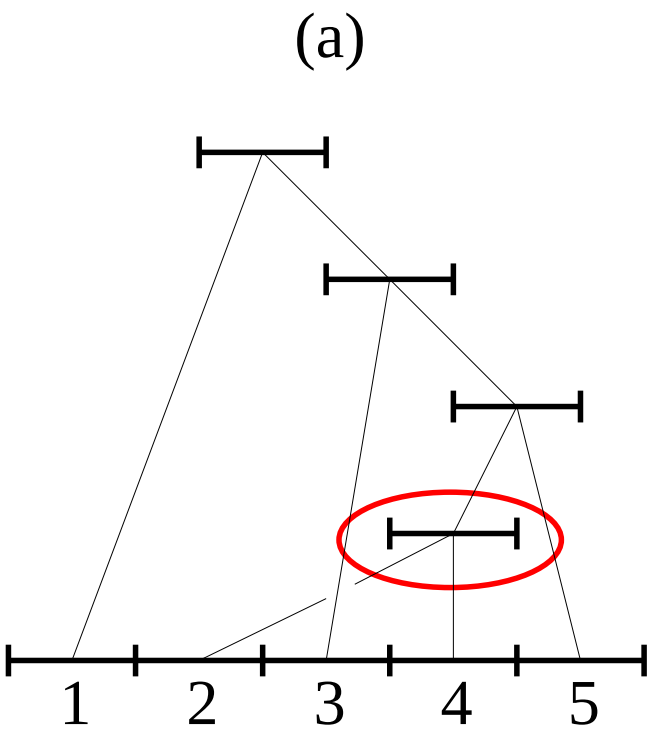

incorrect ordinal duplication history

Definition

A phylogeny is a duplication tree if, among its potential roots, at least one of them leads to a correct ordinal duplication history

The PDT algorithm

– it takes as input a rooted phylogeny with ordered leaves

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– it stops and returns :
(true) when the tree has been reduced to its root
(false) when it cannot go further

The PDT algorithm

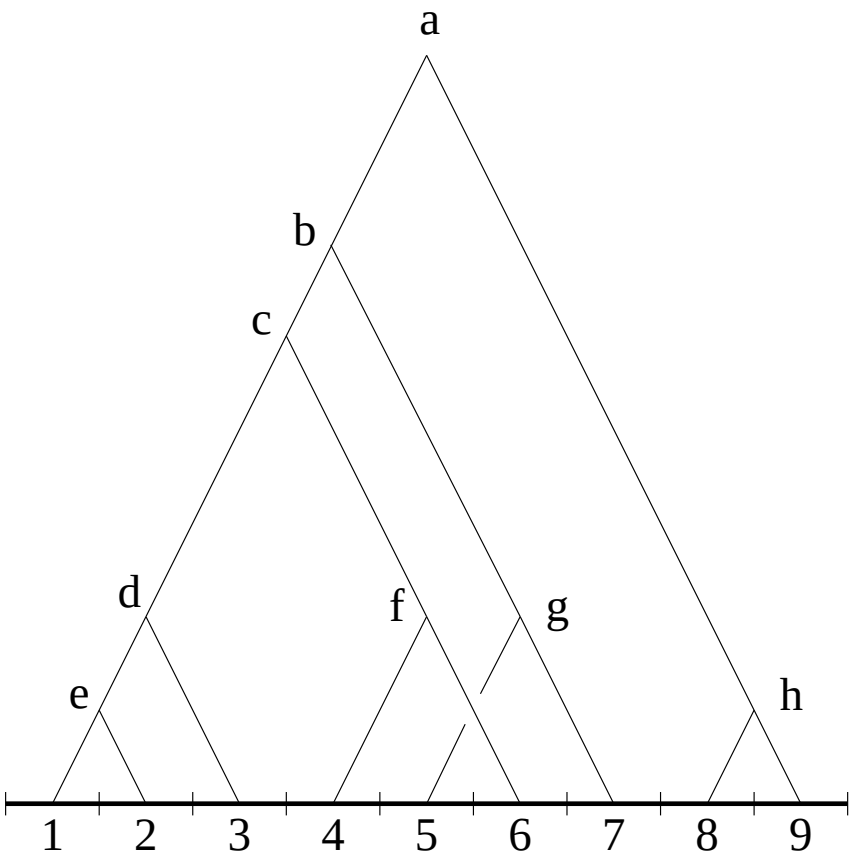
– we apply the PDT algorithm to each potential root of the considered phylogeny

The PDT algorithm

– we apply the PDT algorithm to each potential root of the considered phylogeny

– if PDT return “true” at least once, the phylogeny is a duplication tree

The PDT algorithm



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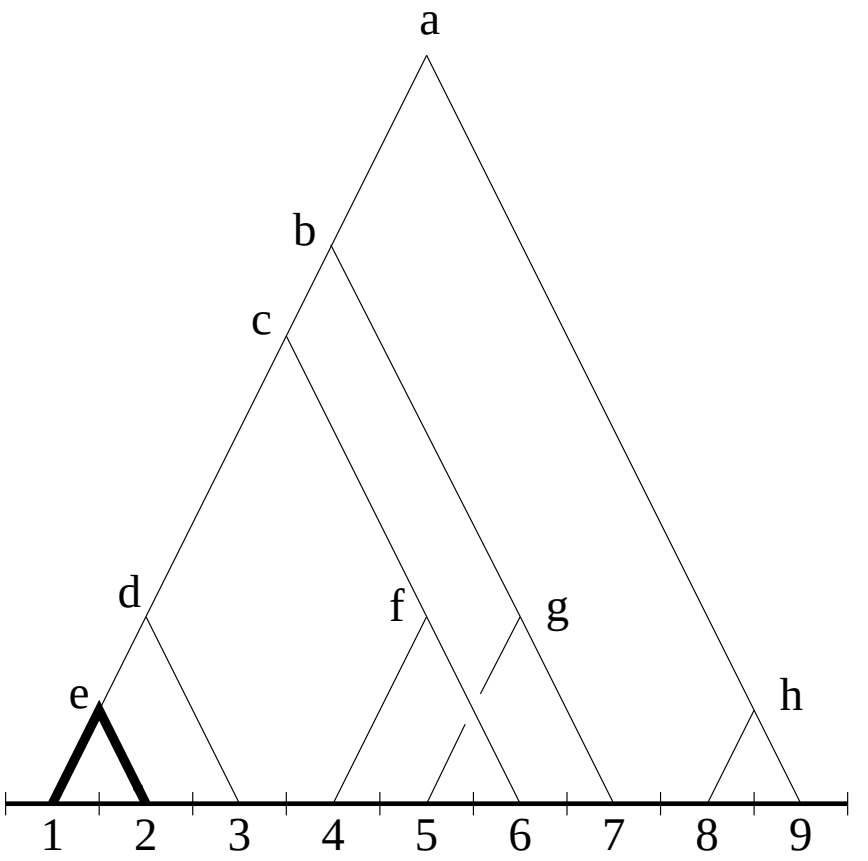
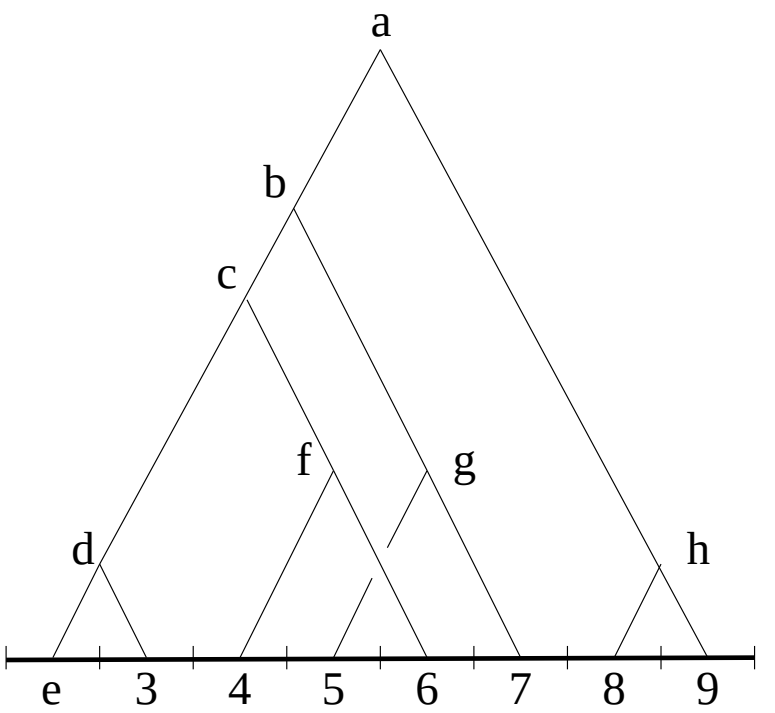


The PDT algorithm



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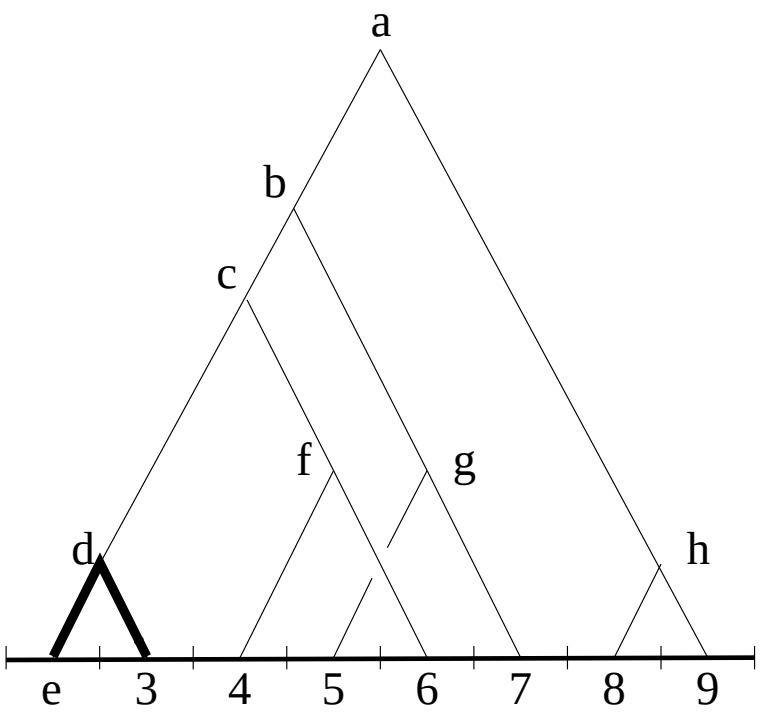

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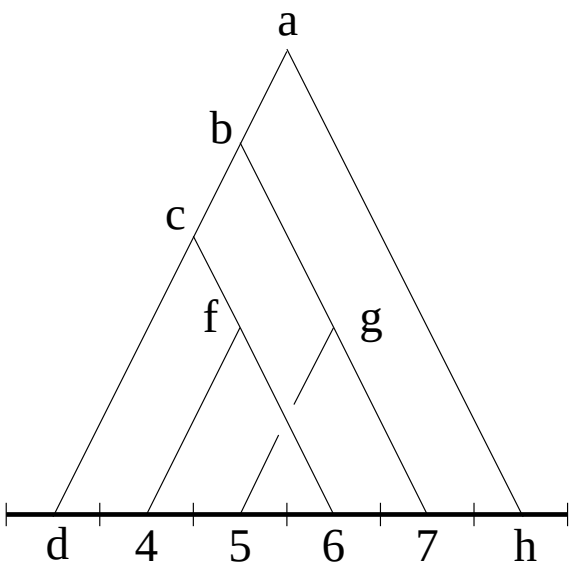

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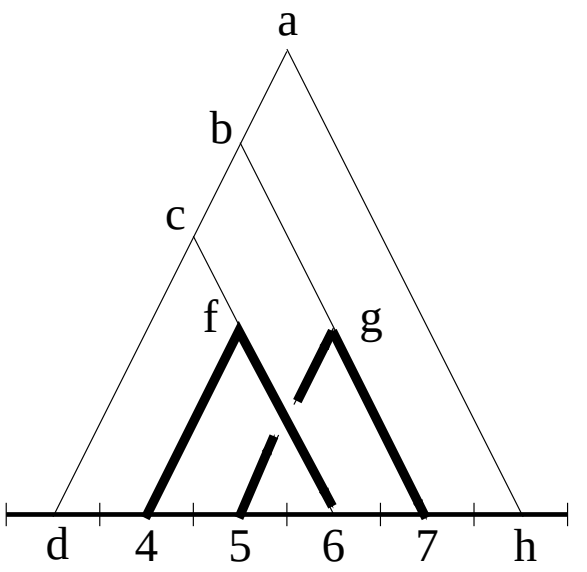

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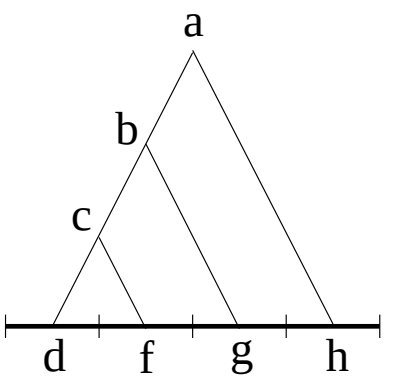

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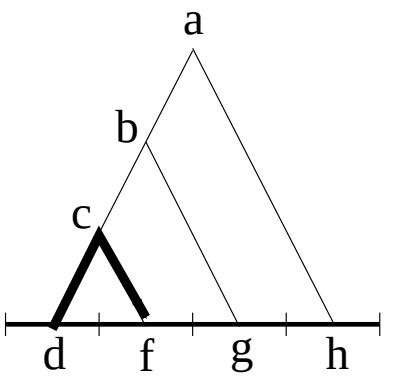

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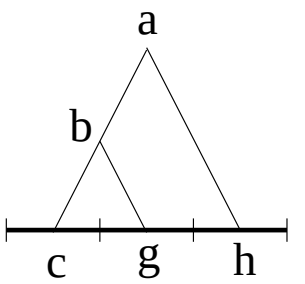

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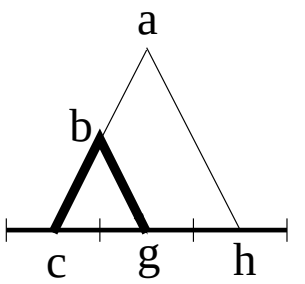

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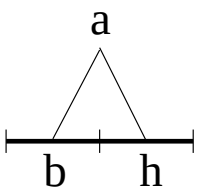

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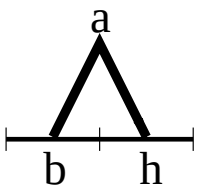

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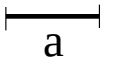
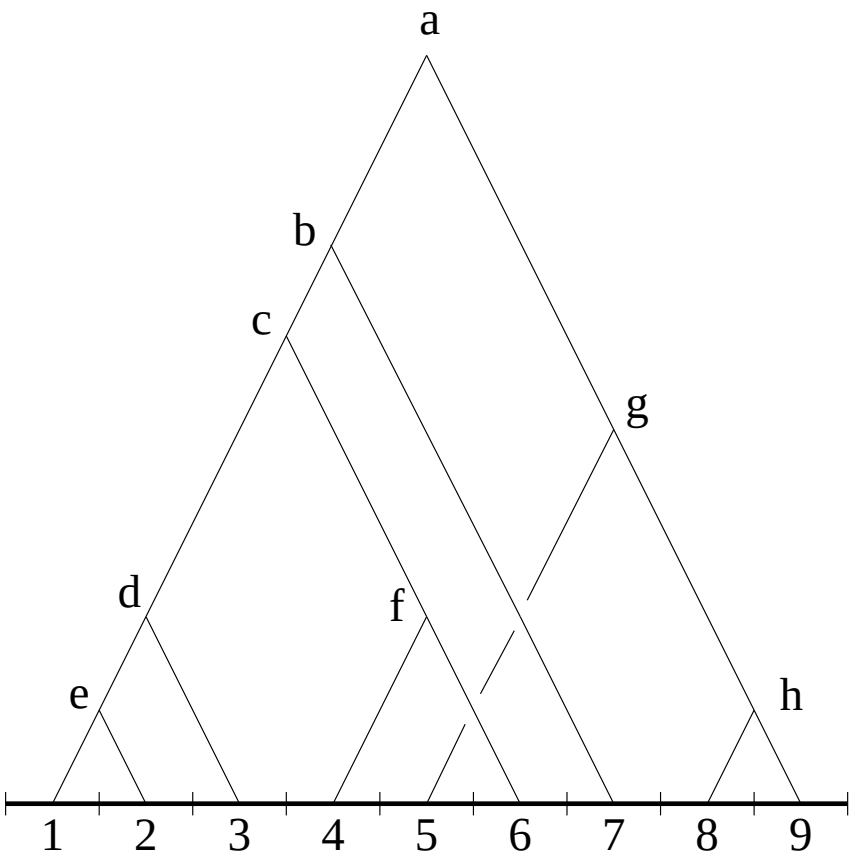


true!

The PDT algorithm



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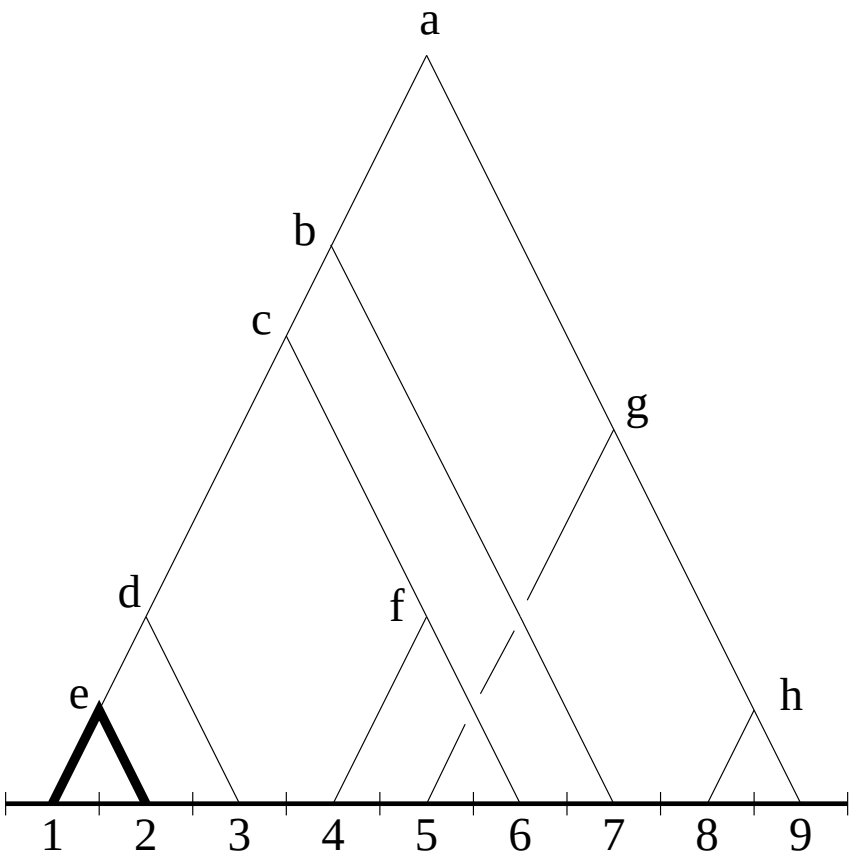

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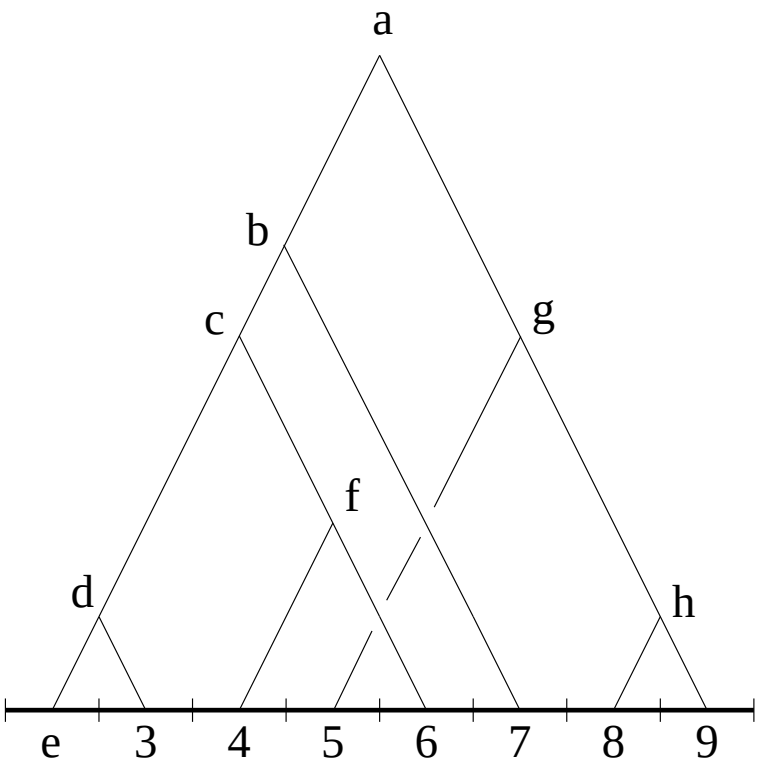

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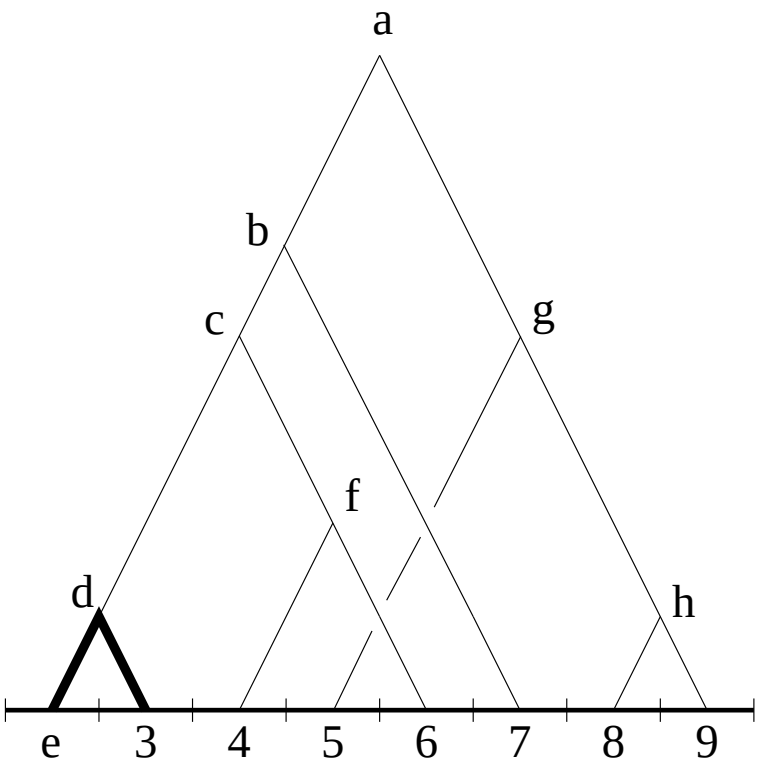

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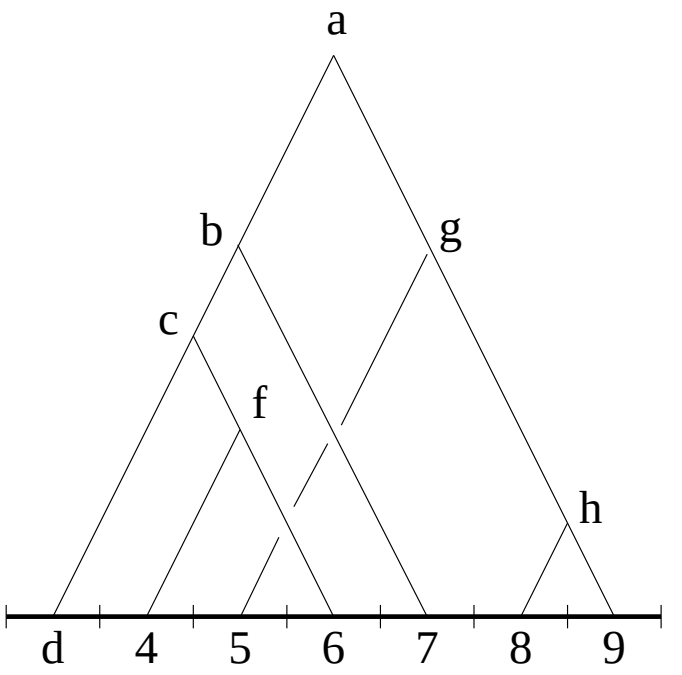

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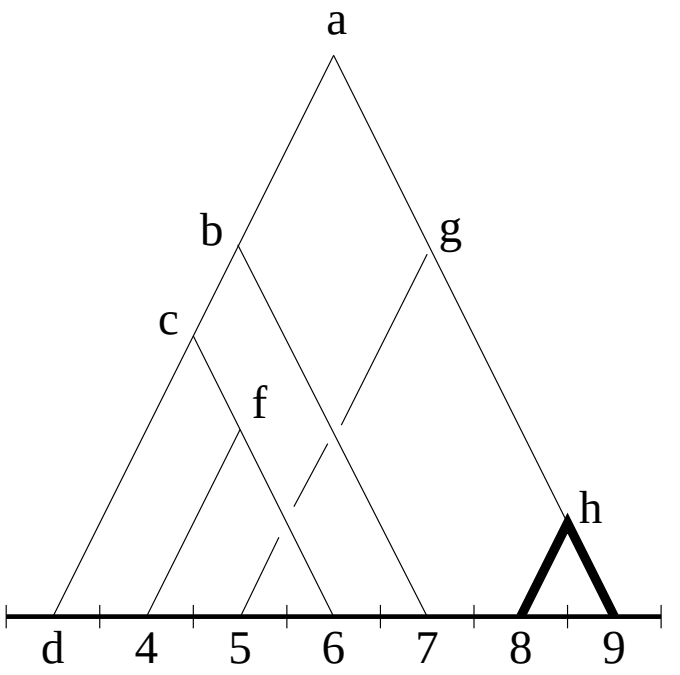

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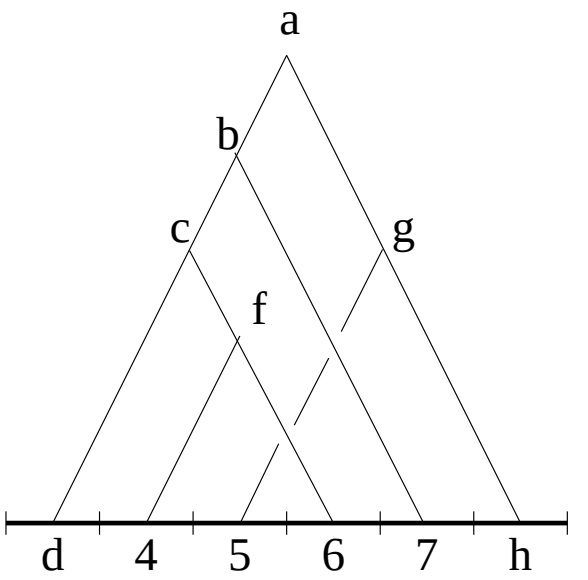

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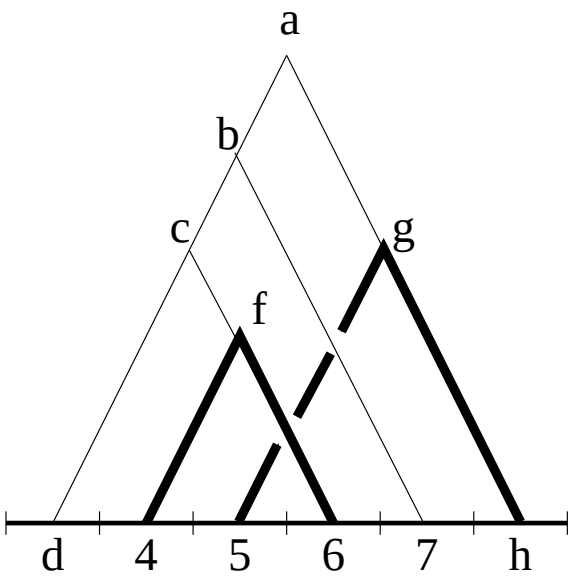

false!

7 is between 6 and h

Counting duplication trees

– we used PDT to count (or estimate) the number of duplication trees

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– the number of phylogenies expands approximately 3^n faster than the number of duplication trees

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– the goal is to recontruct the optimal duplication tree(s) from a given set of aligned and ordered DNA sequences

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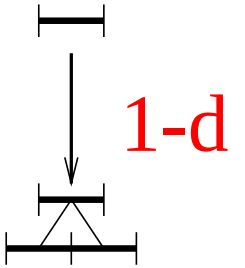
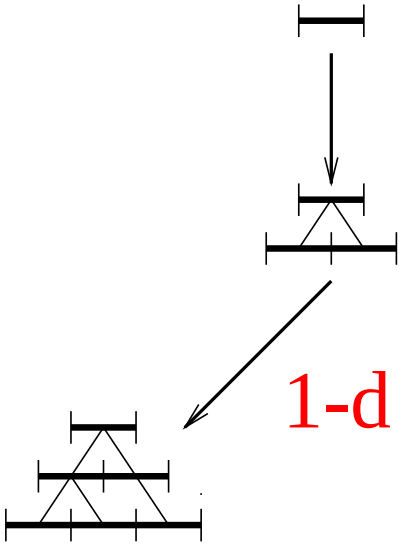
– we assess the optimality of the reconstruction using a parcimony criterion

Exhaustive approach

– we generate every possible duplication tree, using a simulation of the duplication process


1-d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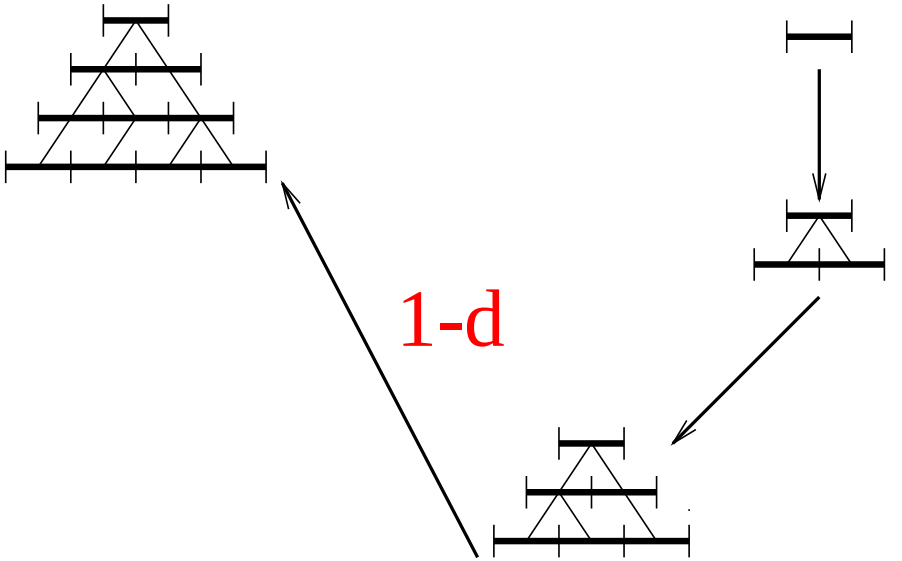
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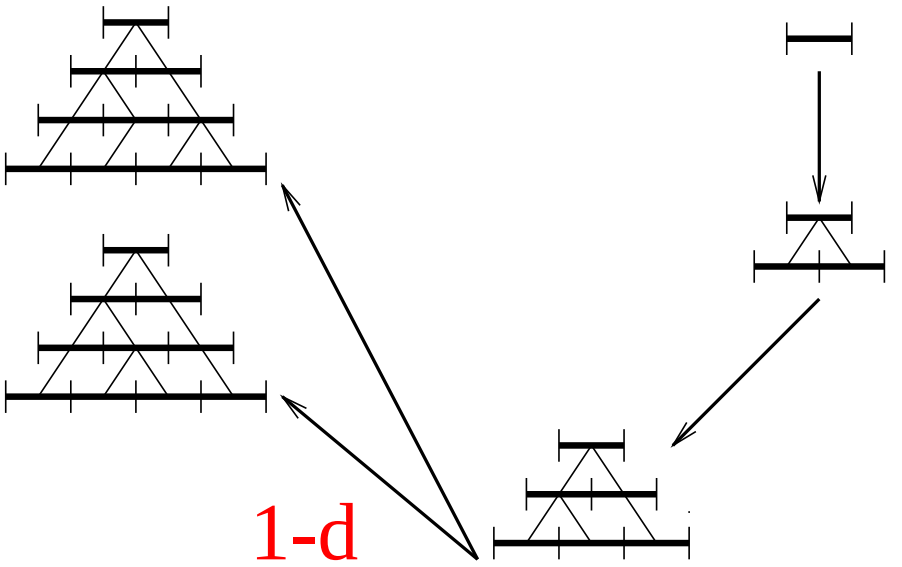
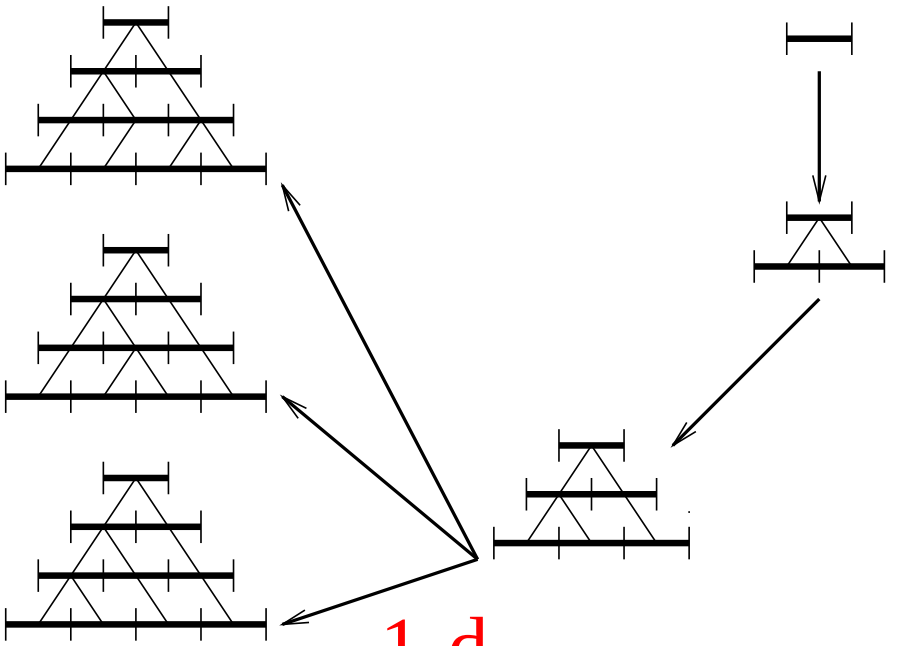
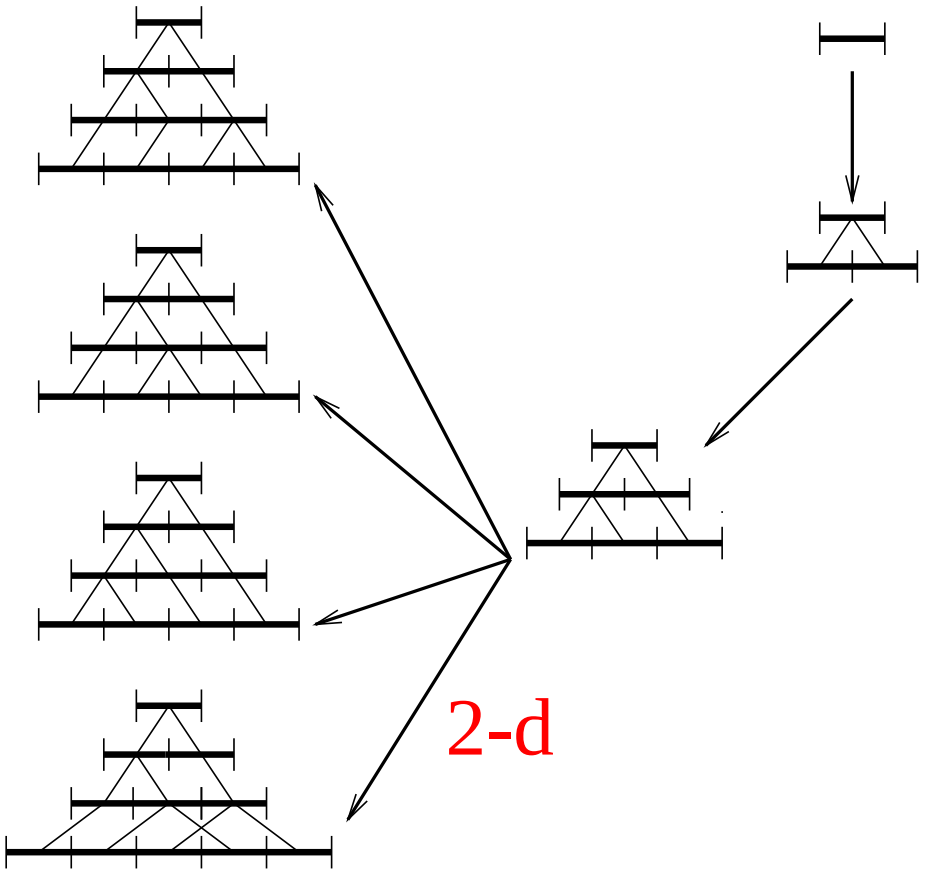
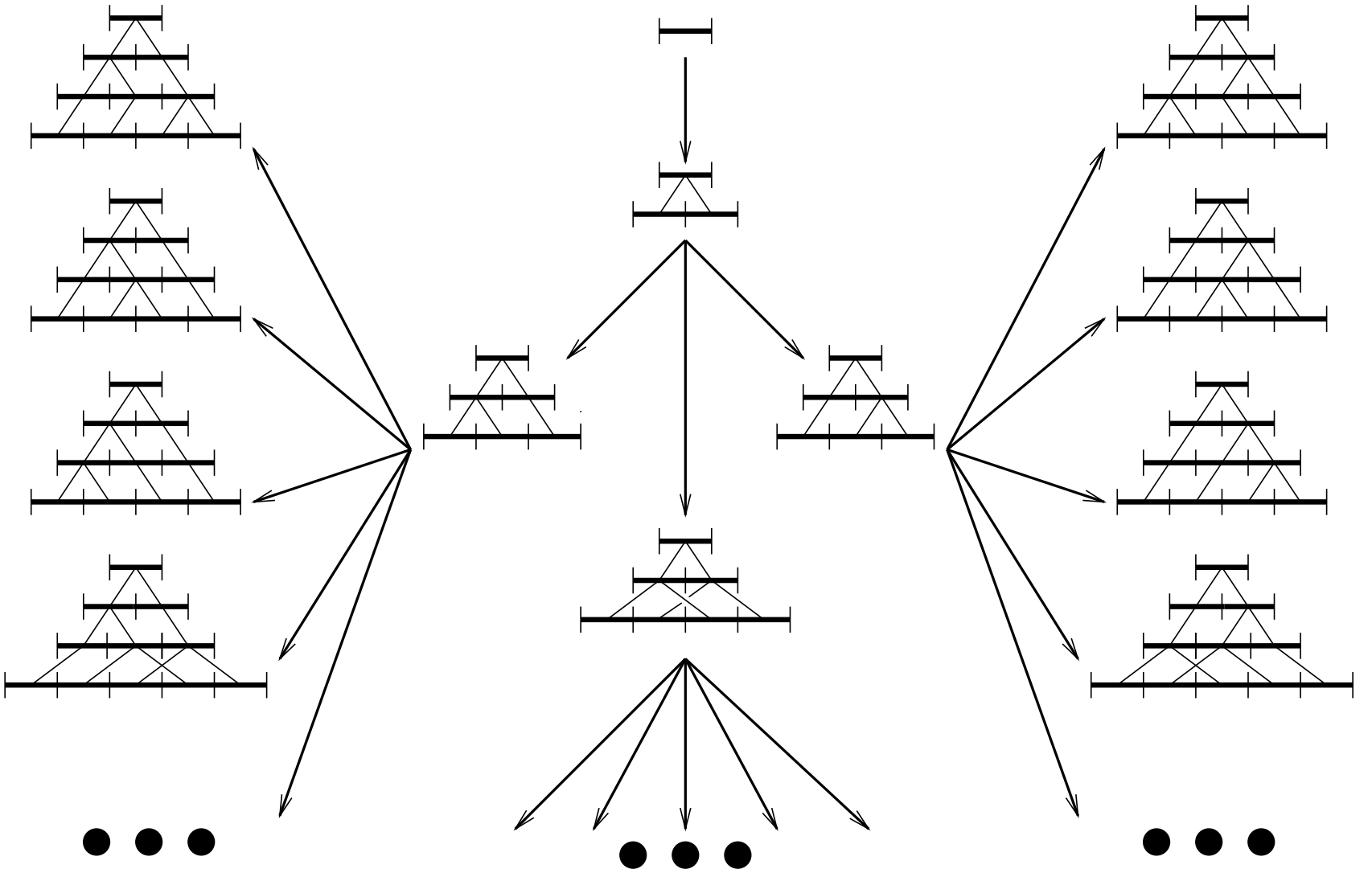

1-d


1-d


2-d

3. Reconstructing duplication trees



Exhaustive approach

– we generate every possible duplication tree, using a simulation of the duplication process

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Experimental results

– we applied this reconstruction procedure to the TRGV locus

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– only 1 duplication tree is found by exhaustive search

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– this duplication tree is identical to the most parcimonious phylogeny, reconstructed from the same data, but without restriction to duplication trees

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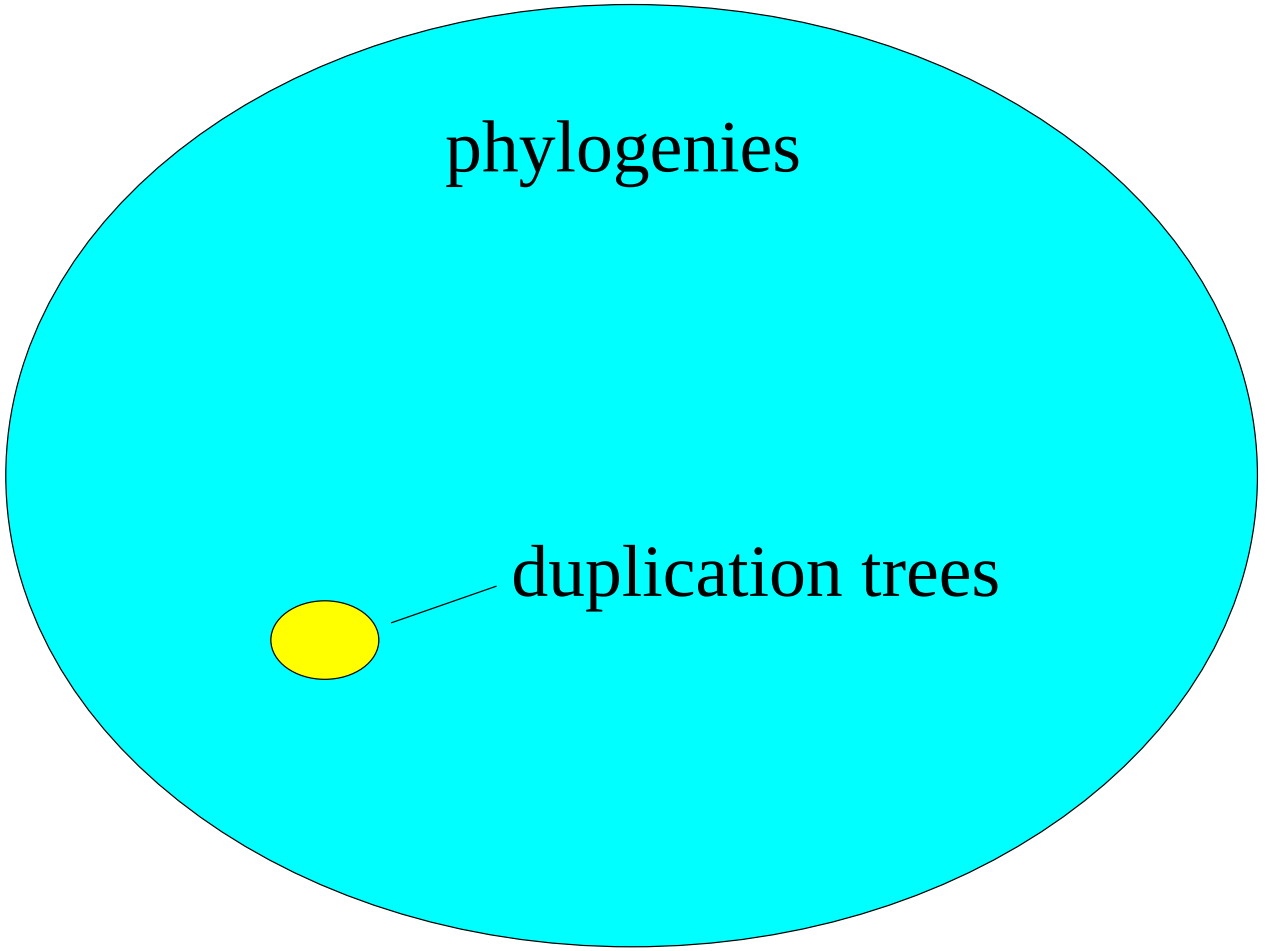
– the probability of a phylogeny to be a duplication tree is less than 0.04 for 9 taxa

First validation



Second validation

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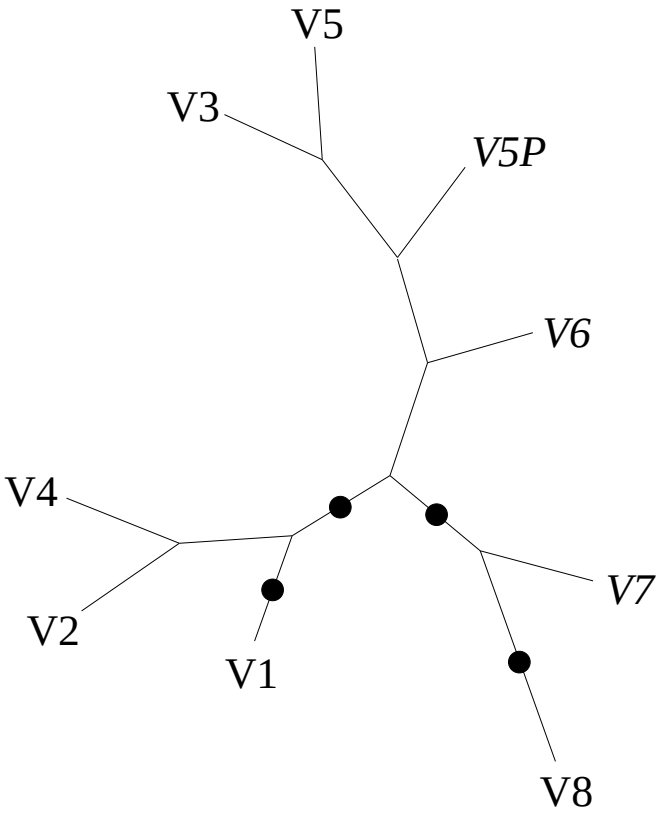

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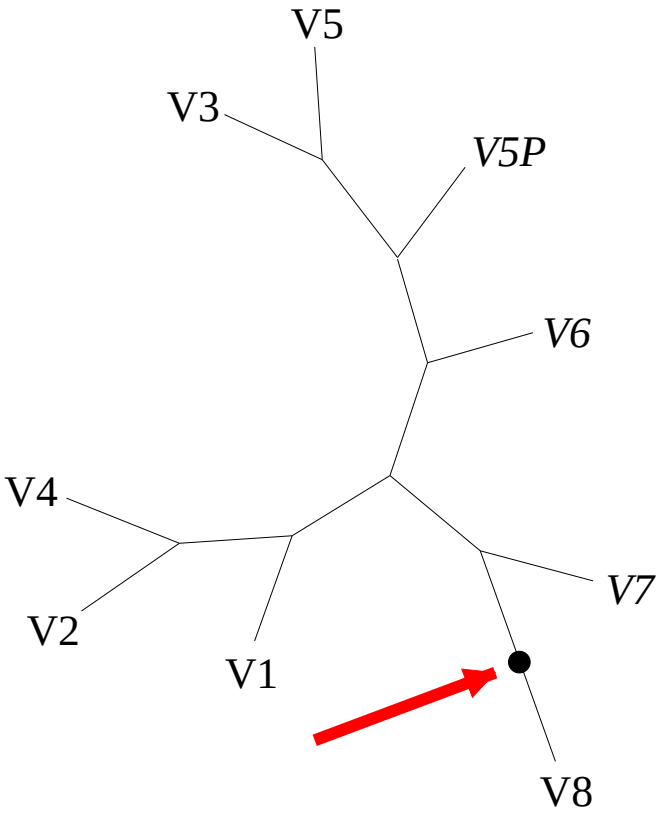

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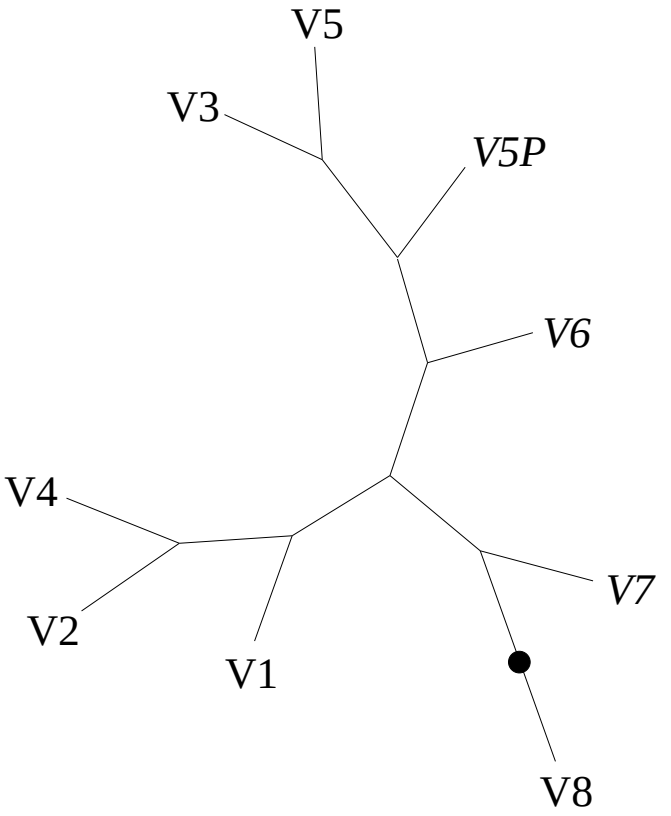
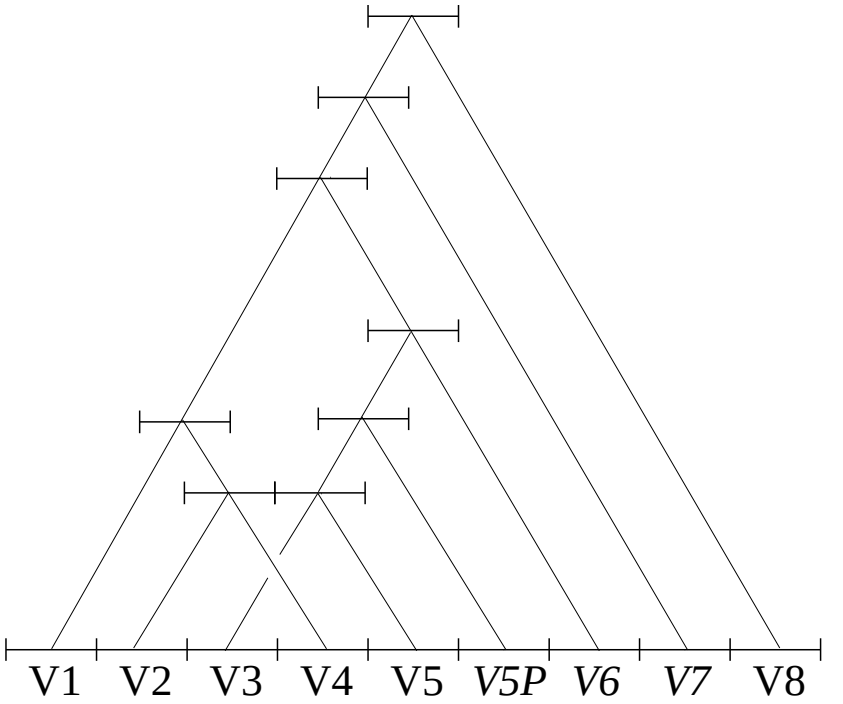
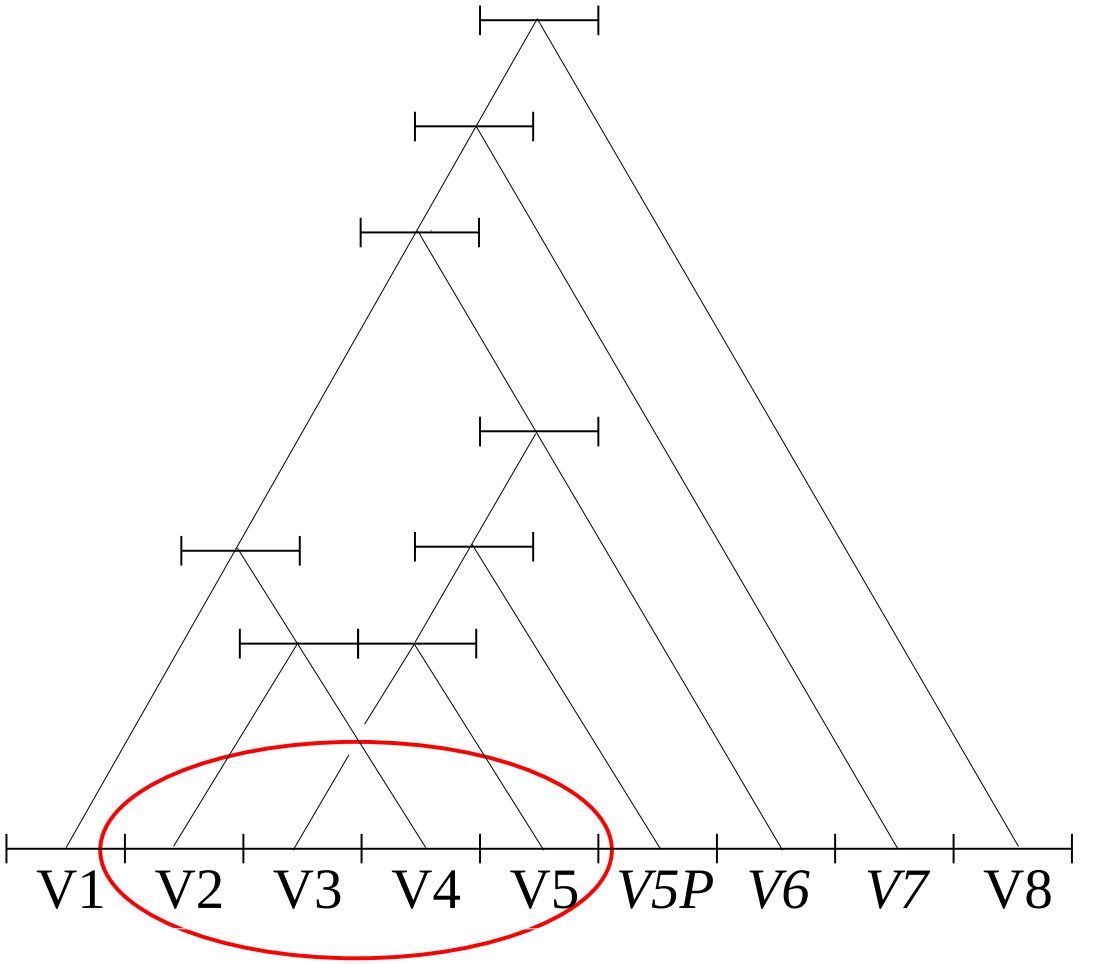




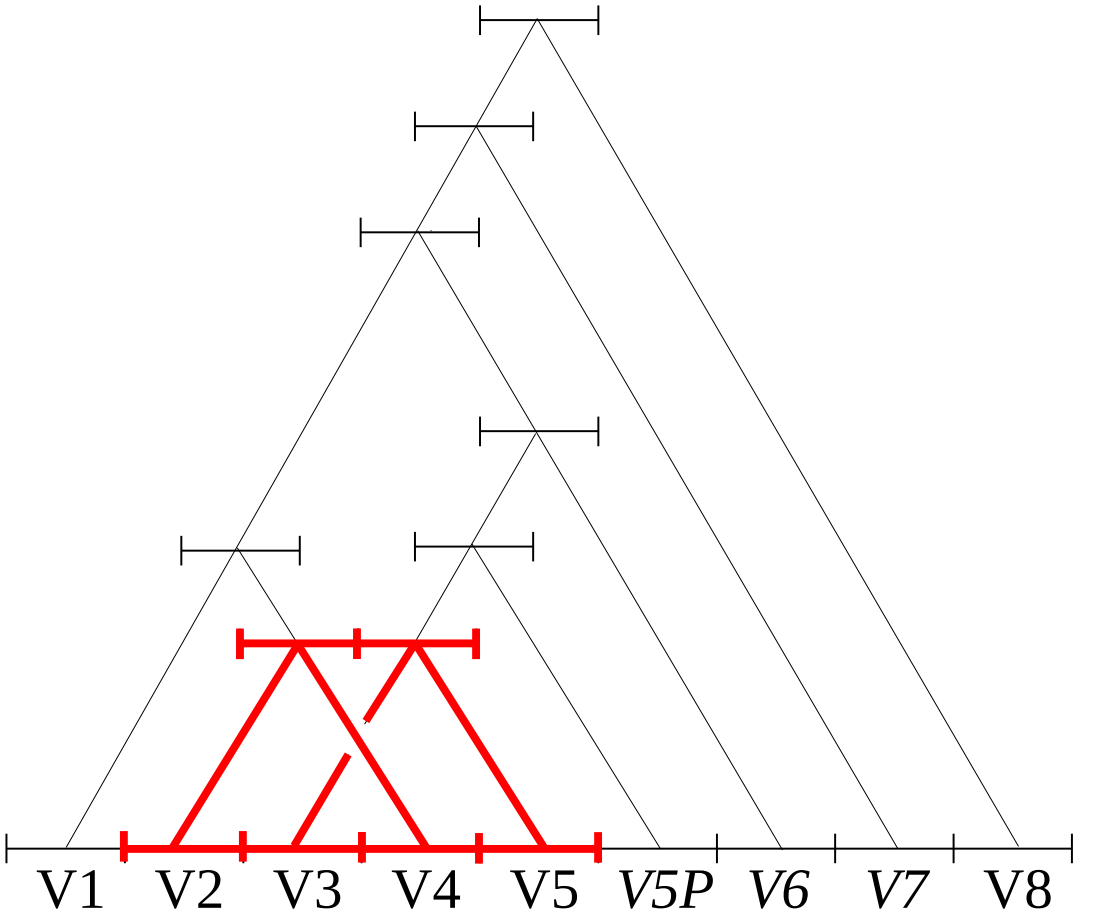
Third validation

– the ordinal duplication history is in agreement with a polymorphism that exists for this locus

Polymorphism for the TRGV locus



Polymorphism for the TRGV locus



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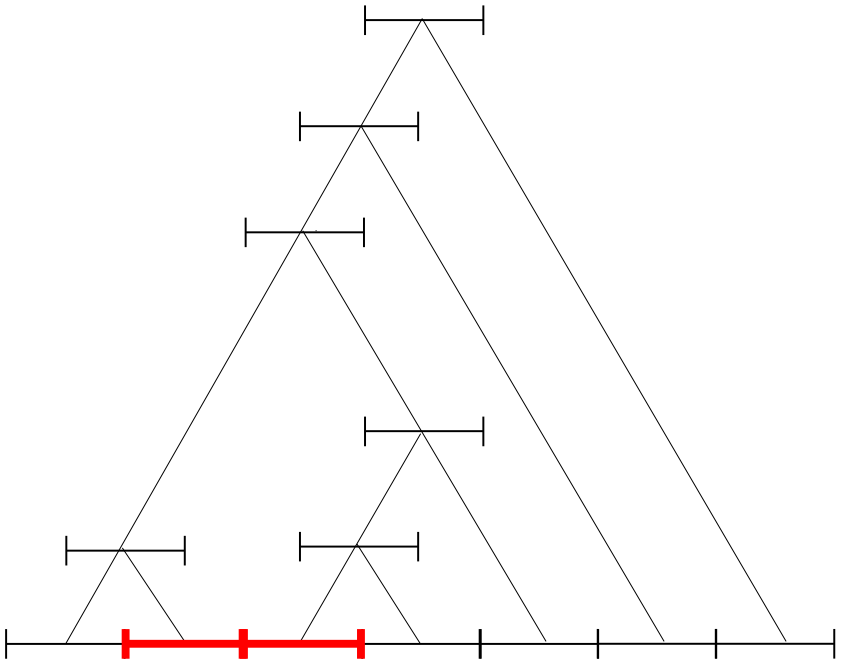

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– they are robust to gene deletions (most duplications are 1-duplications)

Perspectives

– development of a fast heuristics to improve the reconstruction speed

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- more complex duplication models