ORTHOLOGY RELATION AND GENE TREE CORRECTION: COMPLEXITY RESULTS

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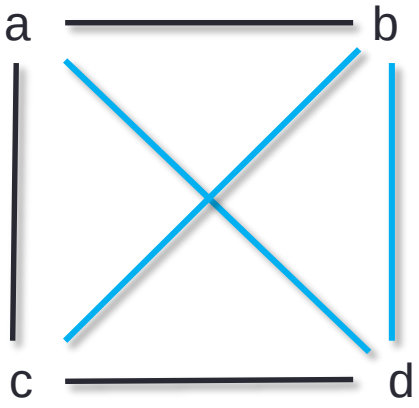
- **Two classes of problems :**
  - Orthology / paralogy relation correction
  - Gene tree correction (based on orthology / paralogy)

- **Four problems, all NP-Complete**

Orthology / paralogy correction

Makes no sense
(we'll see why)

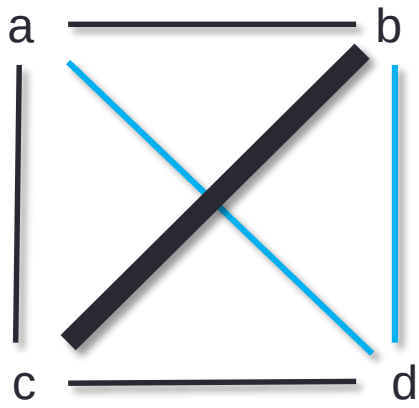
R



Correction

Makes sense

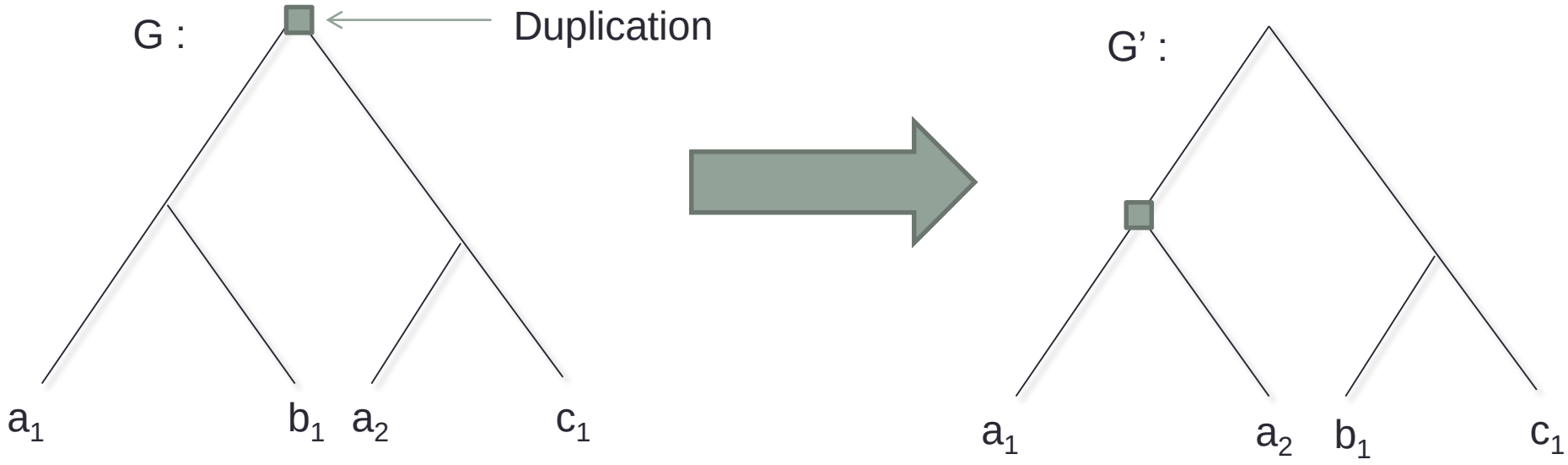
R'



Orthologs

Paralogs

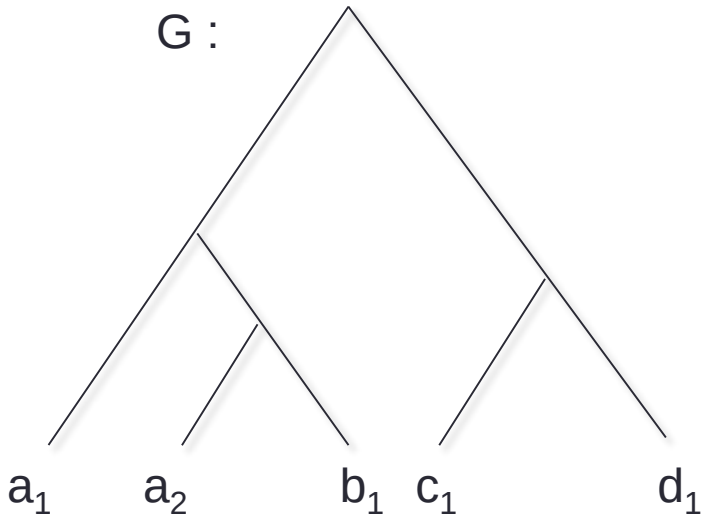
Gene tree correction



a_1 and c_1 should be orthologs.
Please do something about it…

Introduction

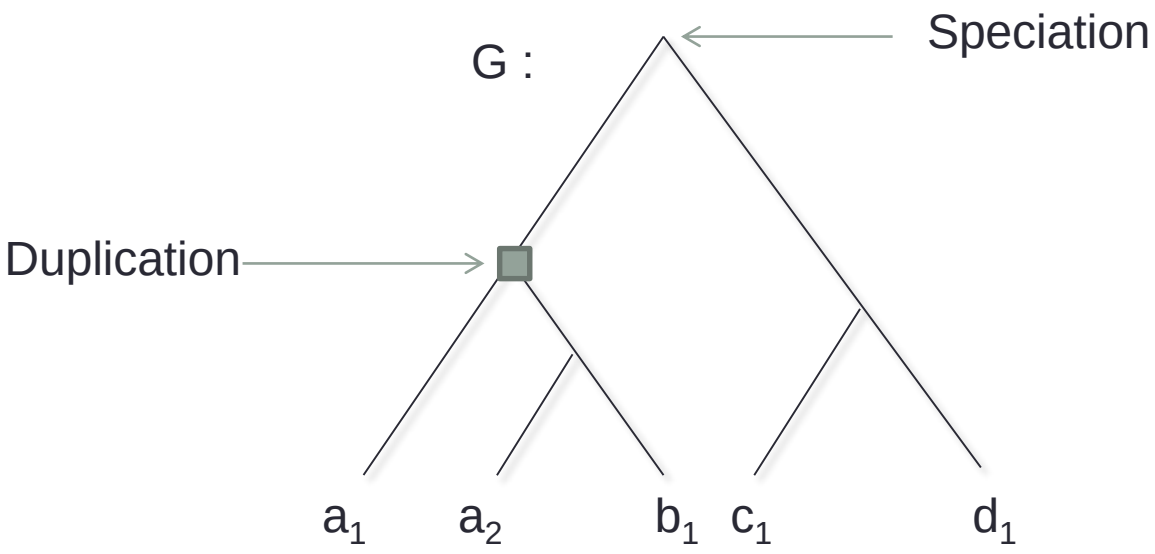
- **Gene trees** reflect the evolutionary history of a family of **homologous** genes
  - Genes that all descend from a common ancestor



a,b,c,d are species

Introduction

- Ancestral genes may have undergone **speciation** or **duplication**



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Orthologs : LCA has undergone speciation

Paralogs : LCA has undergone duplication

(LCA = Lowest Common Ancestor)

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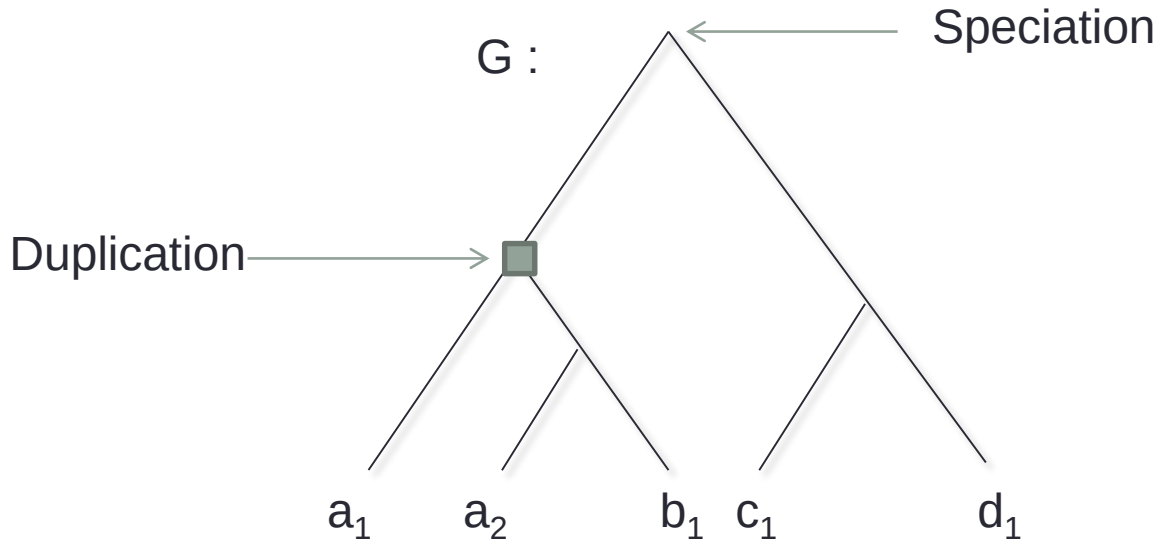
For instance, **according to G** :

- a_1, b_1 are paralogs
- a_1, c_1 are orthologs



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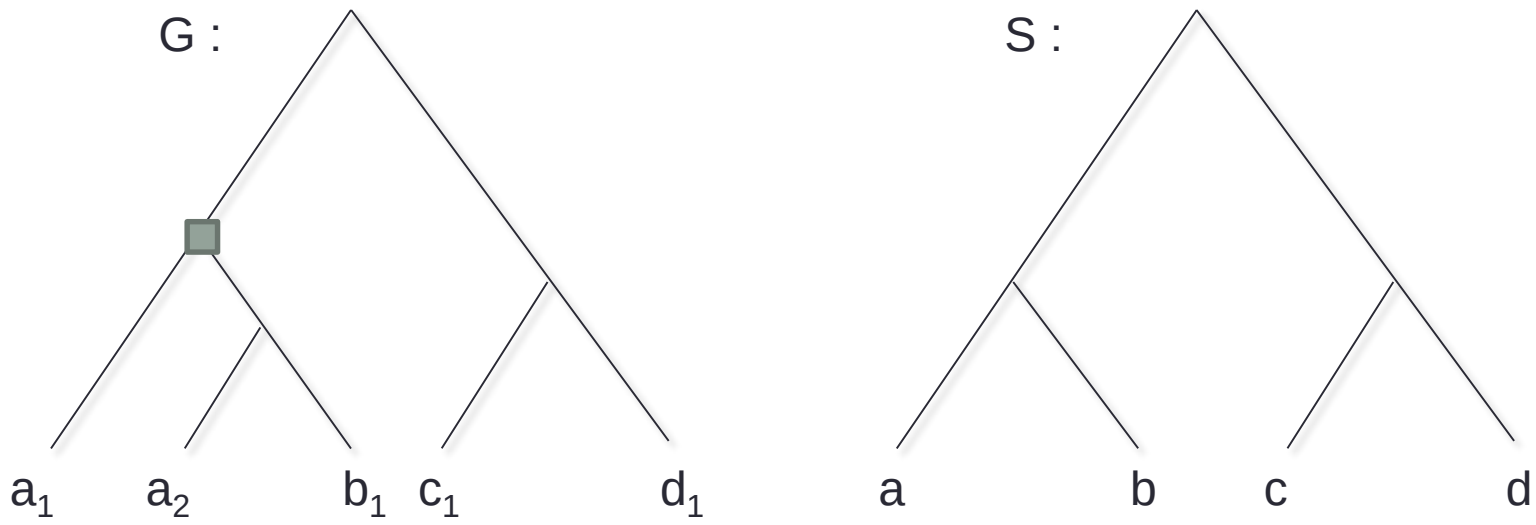
S-Consistency : If genes from species sets X,Y are separated by speciation in G, then species X, Y are separated in the **species tree** S.



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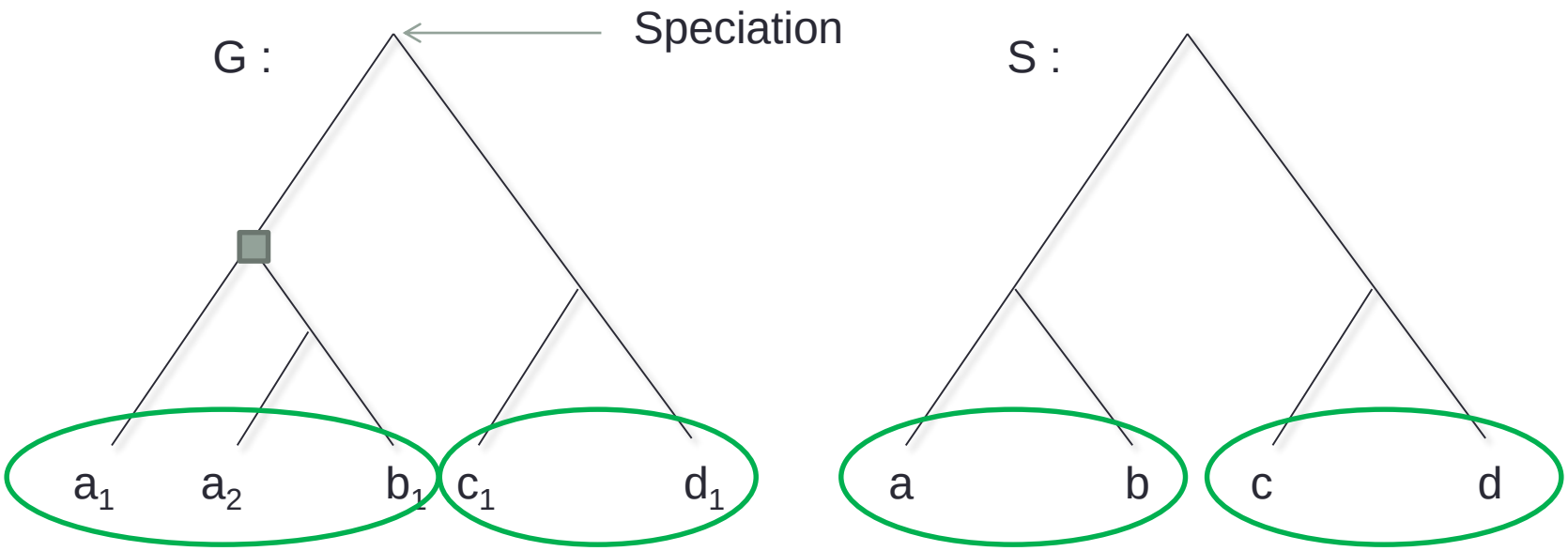

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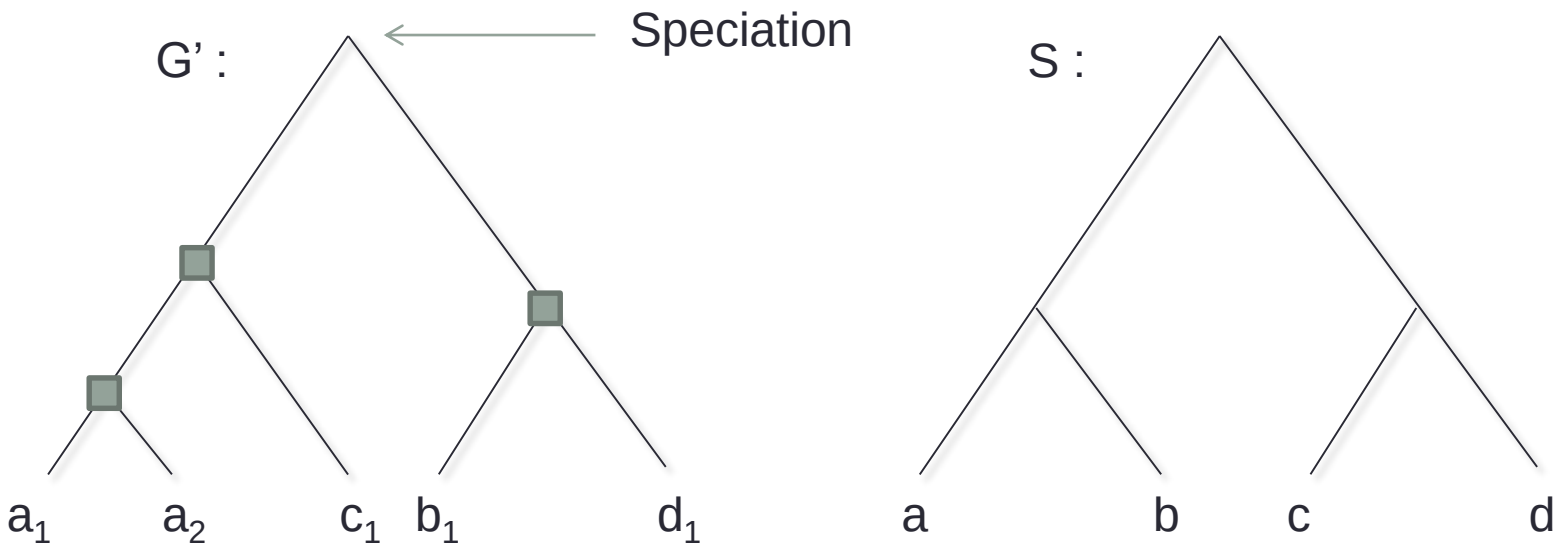

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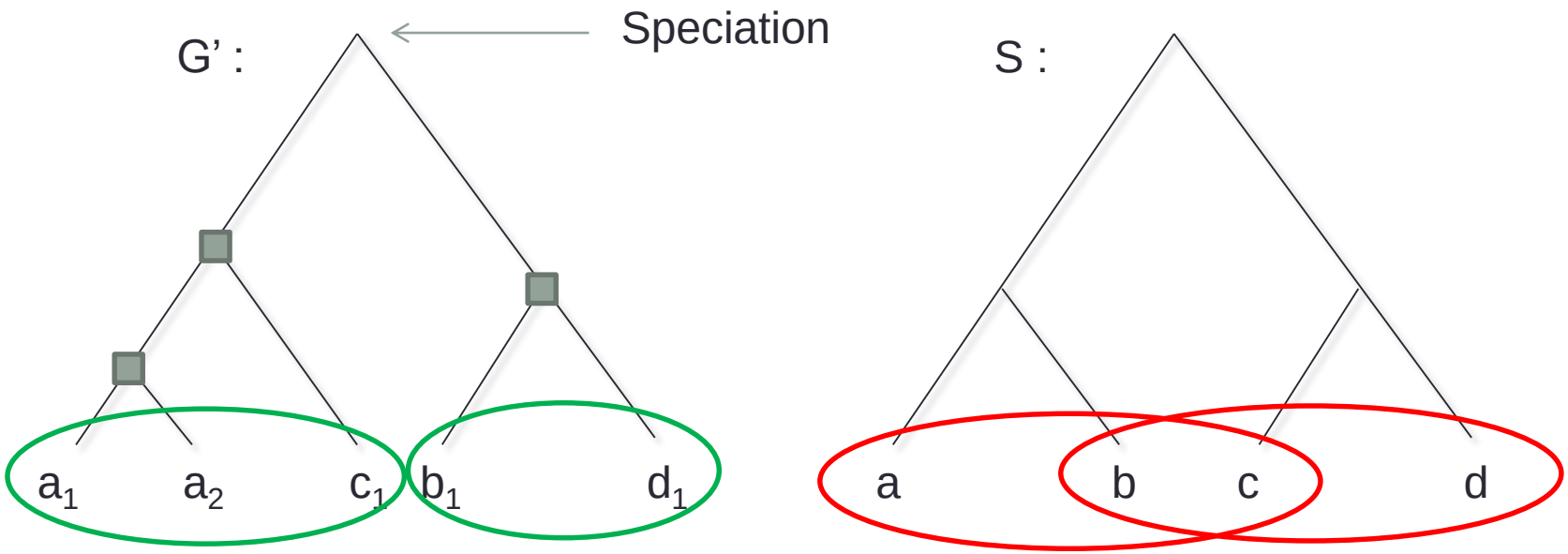

Magic orthology / paralogy machine

Orthologs = (a,b) (a, c) (b, c) (c, d)

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Sequence-based : COG, OrthoMCL, InParanoid, Proteinortho, …

Gene order/synteny-based : GIGA, SYNERGY, …

Satisfiability

Orthologs = (a,b) (a, c) (b, c) (c, d)

Paralogs = (a, d) (b, d)

Is there some **gene tree** and
Dup/Spec labeling that displays
these relationships ?

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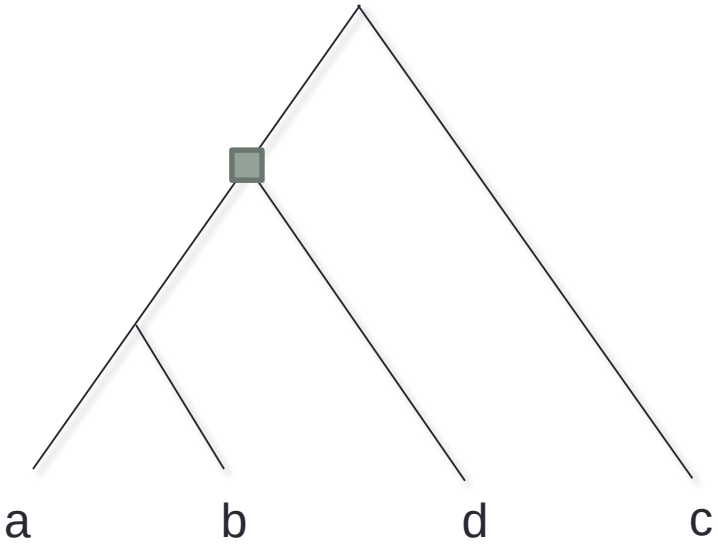

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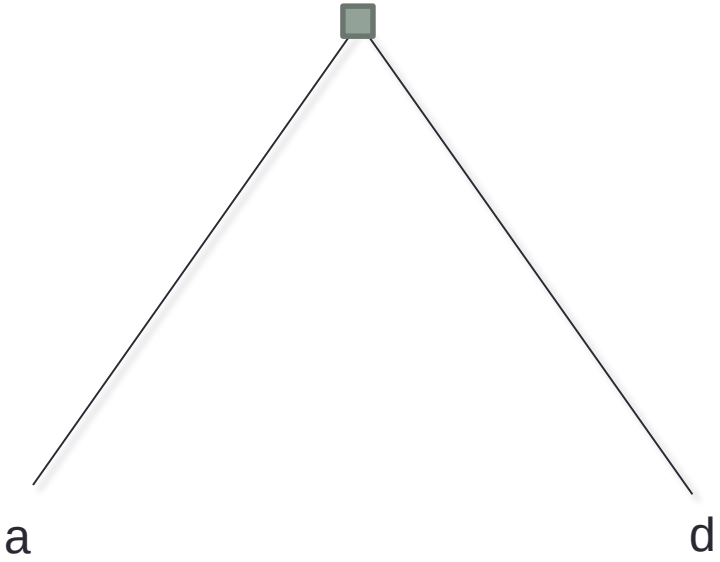

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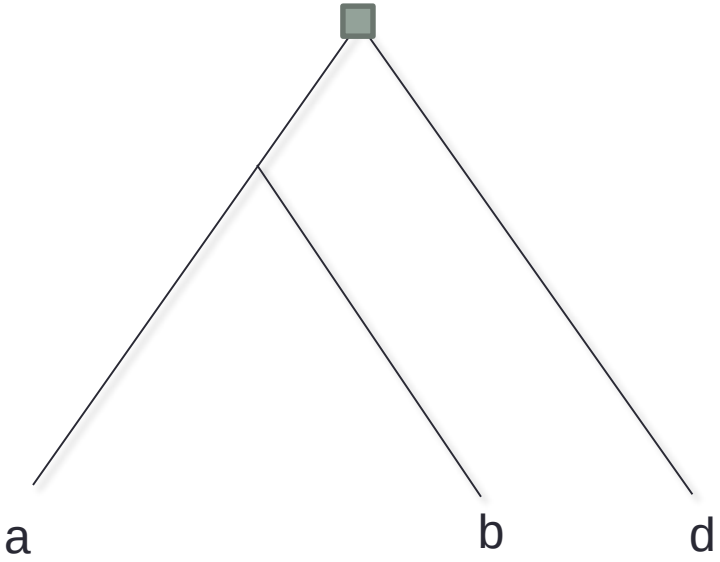

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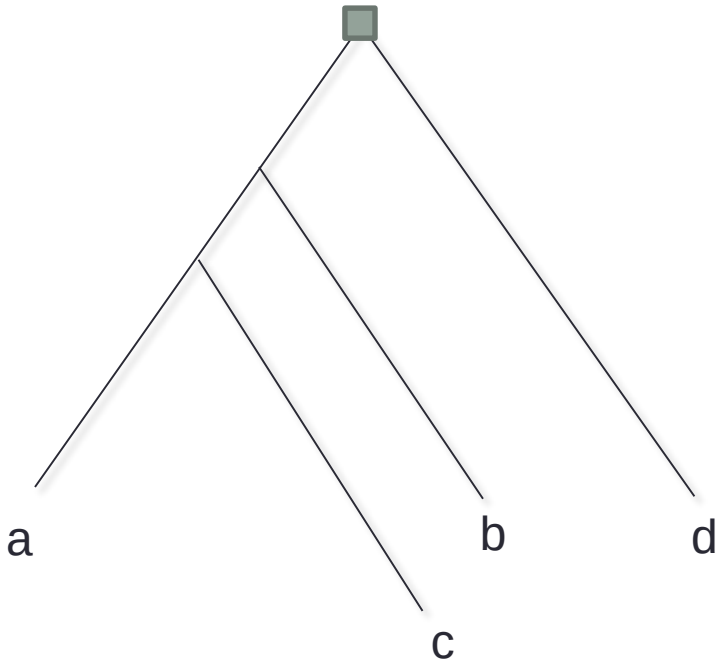

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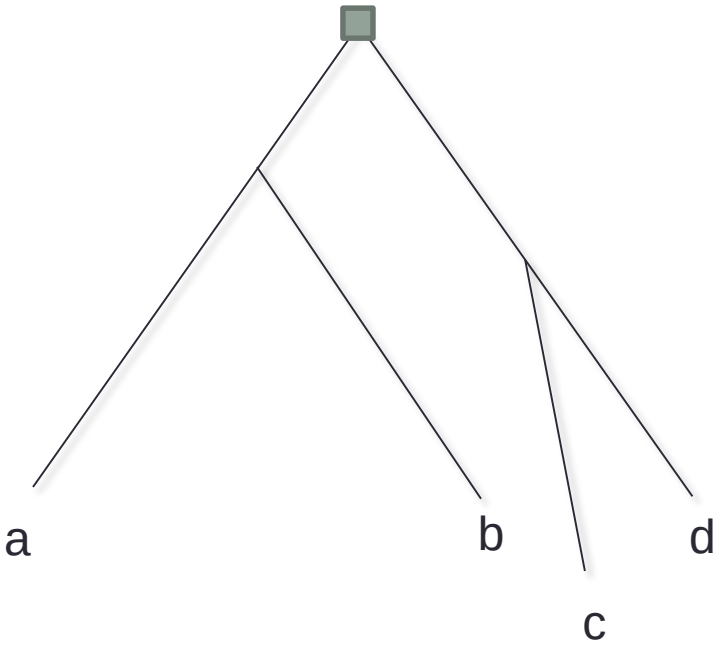

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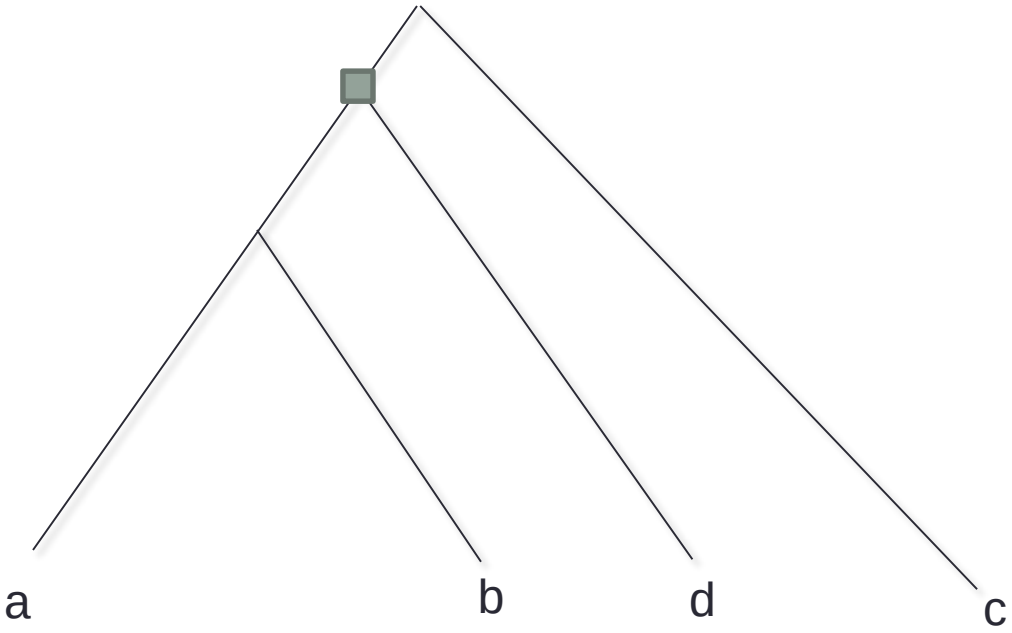

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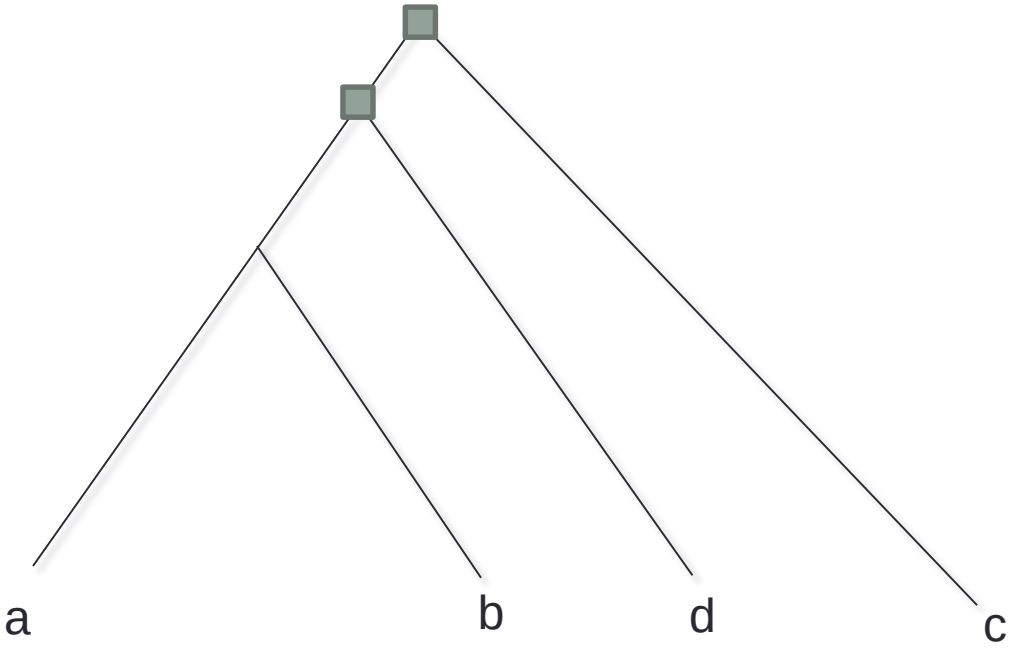

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I JUST CAN'T !

THESE DON'T MAKE SENSE !

S-Consistency

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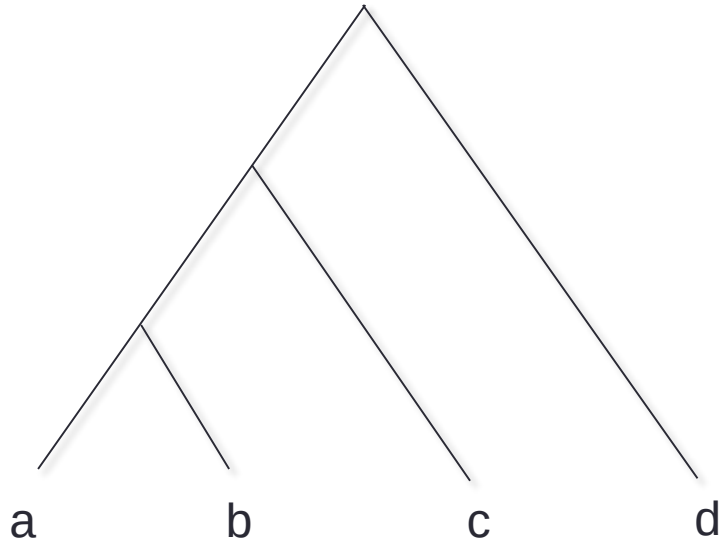
Gene tree G

?

Species tree S



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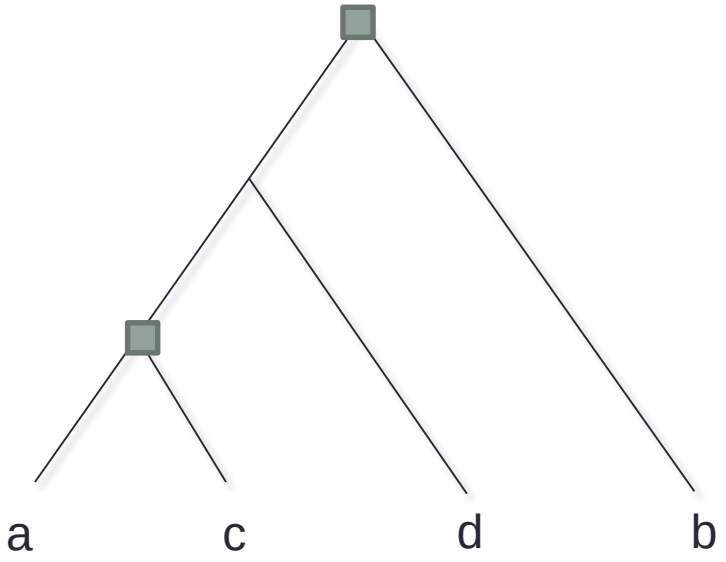
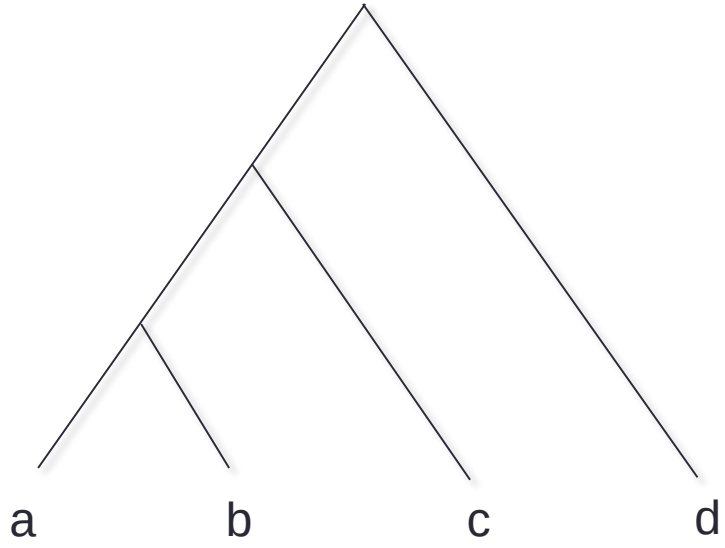


Species tree S



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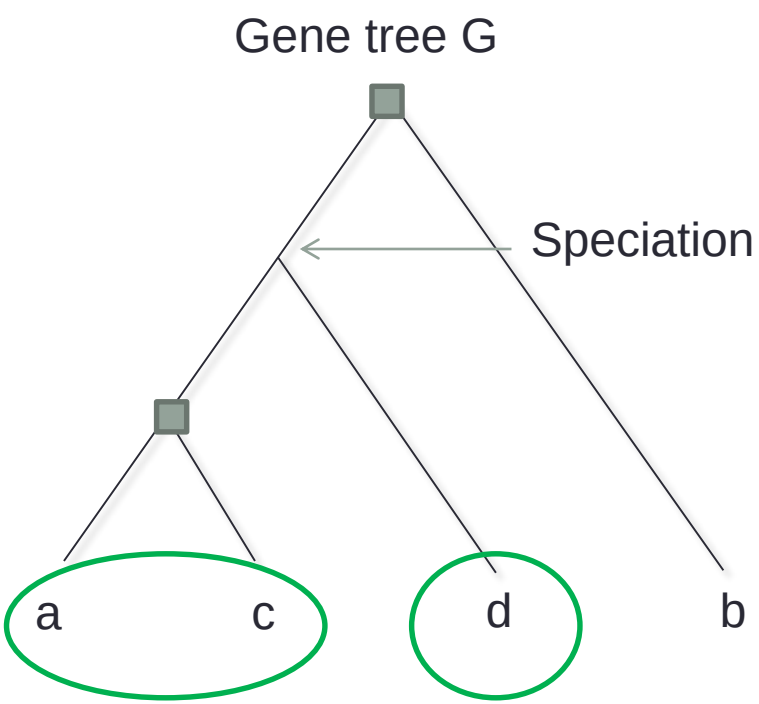

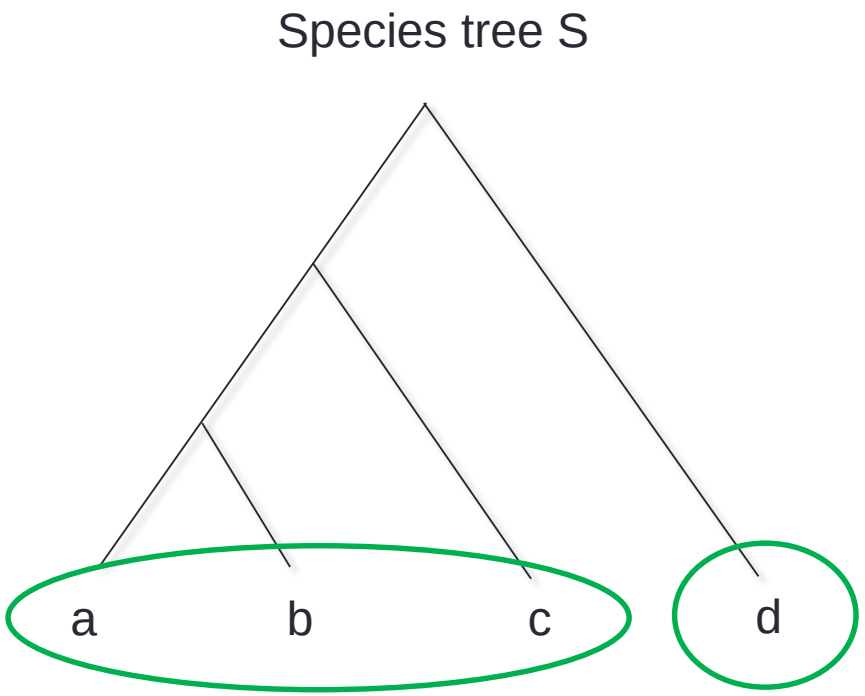

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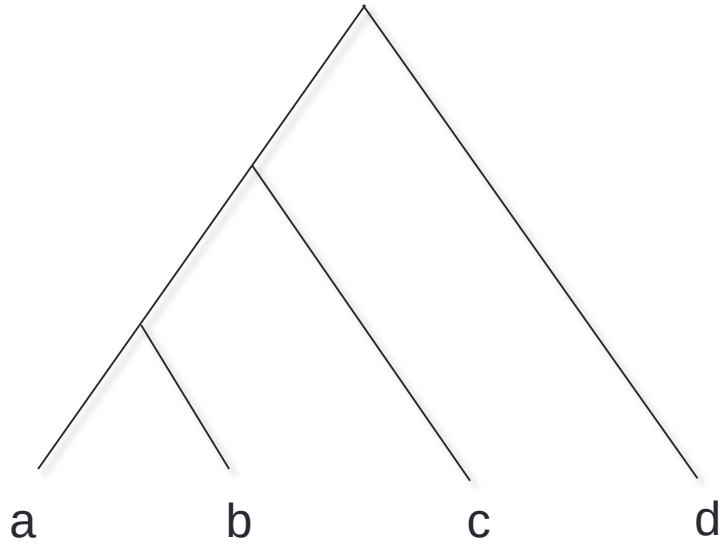

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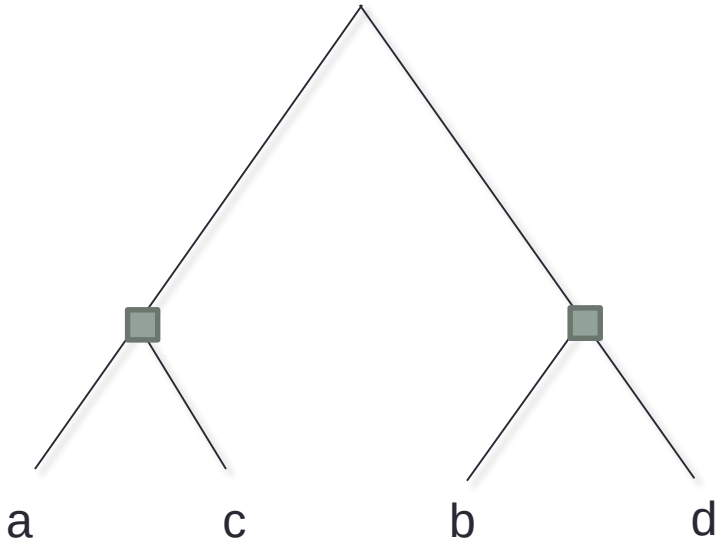

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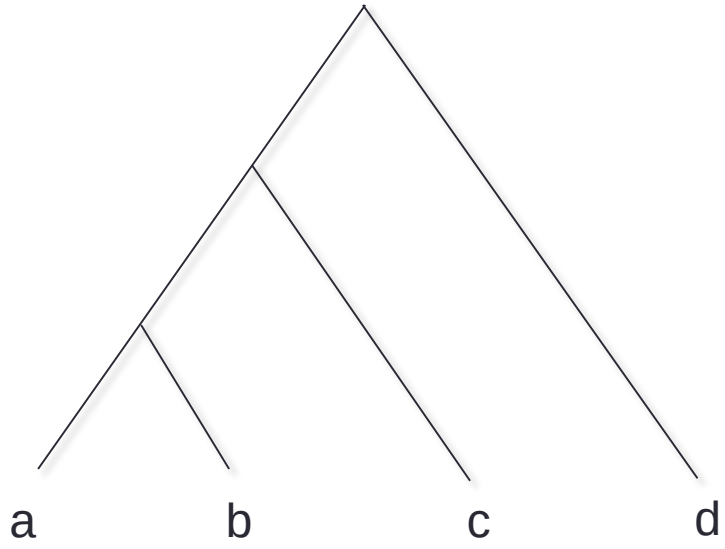

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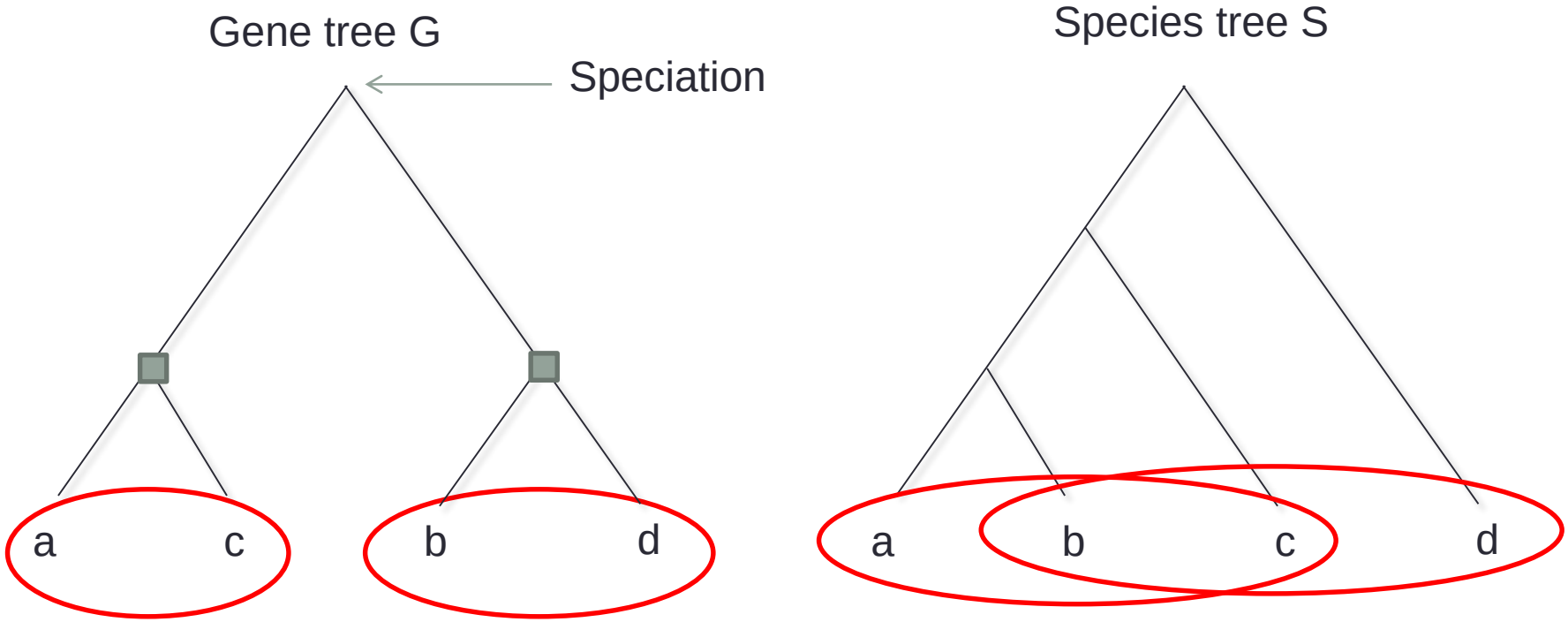

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Some people / software infer **orthology/paralogy** relations.

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If they don’t make sense, what should we do about it ?

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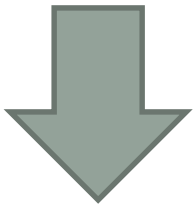

Orthologs = ~~***(a,b)***~~ (a, d) (b, c) ~~***(c, d)***~~

Paralogs = (a, c) (b, d) **(a,b) (c, d)**

Relation graphs

Orthologs = (a,b) (a, c) (c, d)

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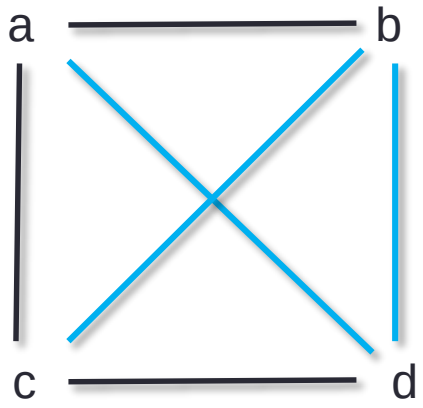
Relation graph R



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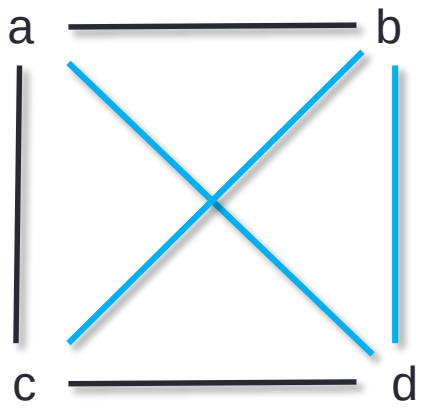
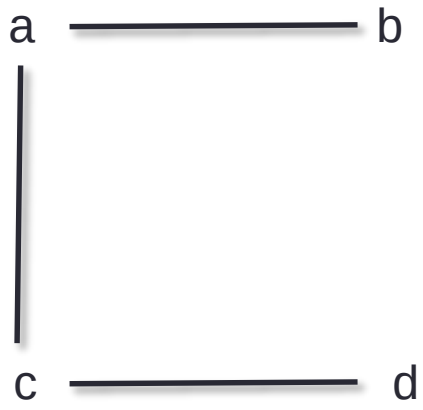
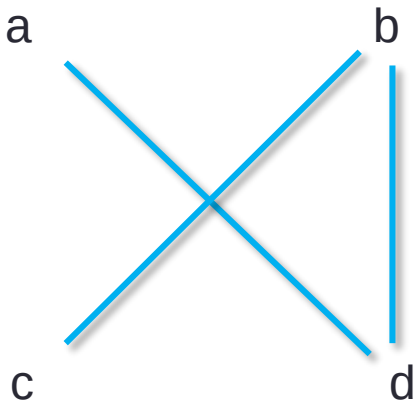


R_O



R_P



Orthologs

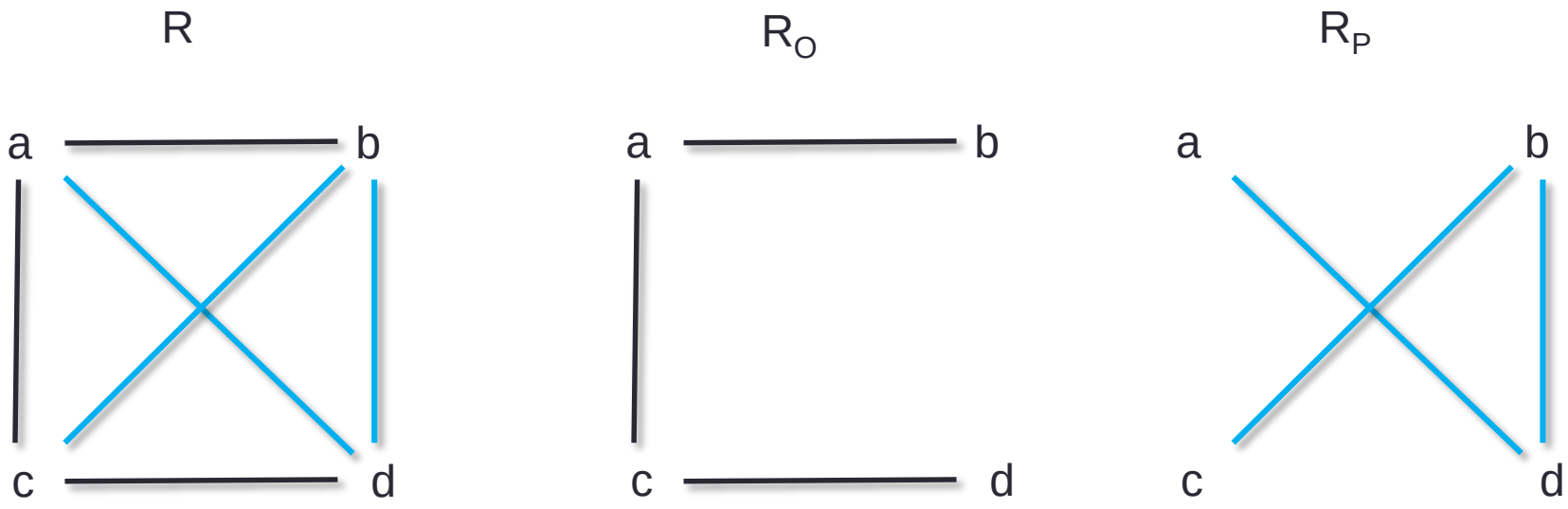
Paralogs

Relation graphs

(Hernandez-Rosales & al., 2012)

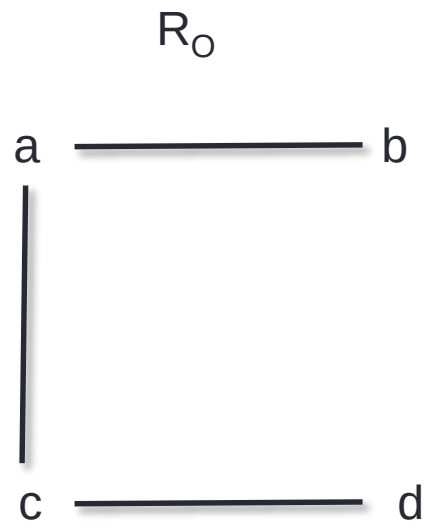
The relations are **satisfiable** iff

R_O is P_4-free (no **induced path** of length 4)



Relation graphs

NOT SATISFIABLE : No gene tree displays these relations



Orthologs

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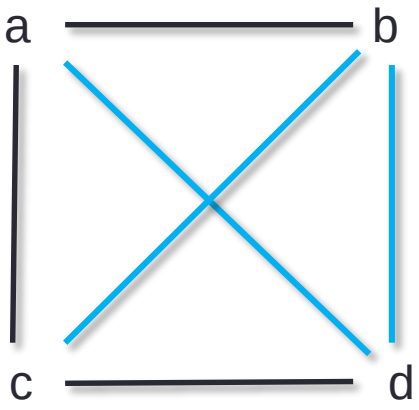

Correction

Makes sense

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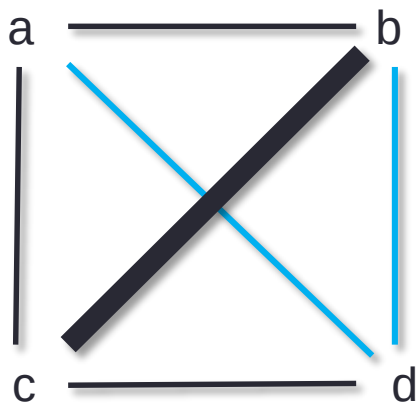

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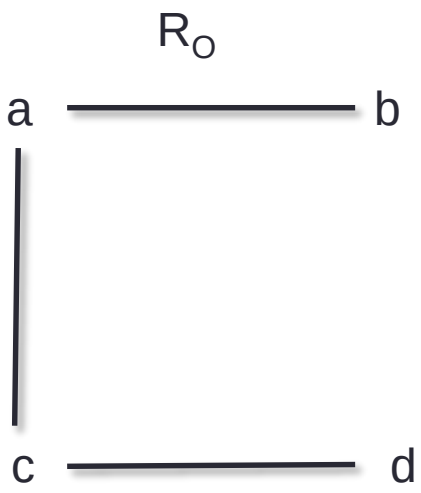

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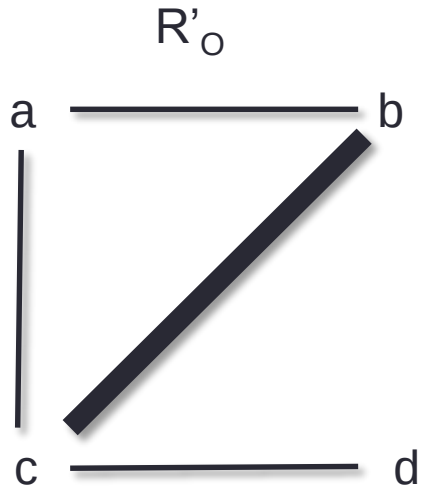

Orthologs

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NP-COMPLETE (El-Mallah and Colbourn, 1988)

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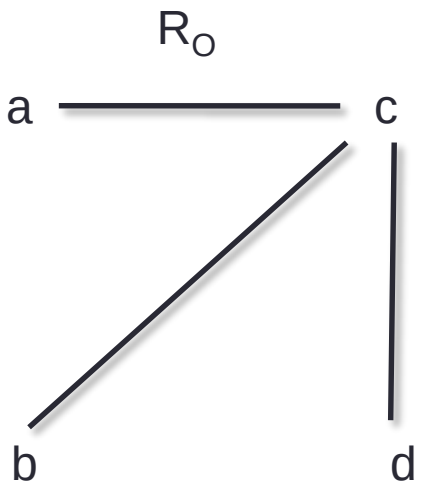
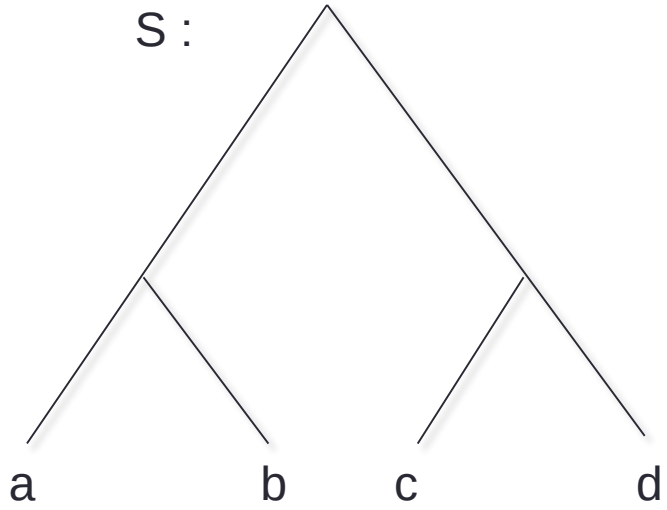
What about S-Consistency ???

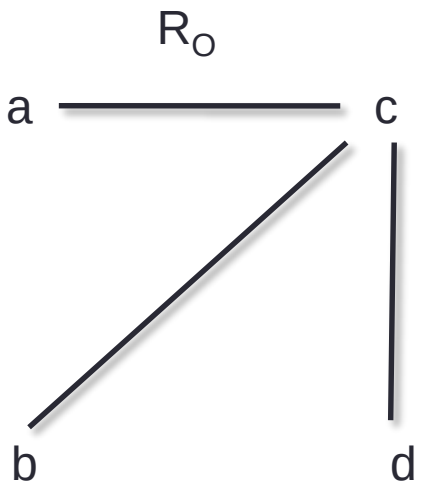
Relation graphs and S-Consistency

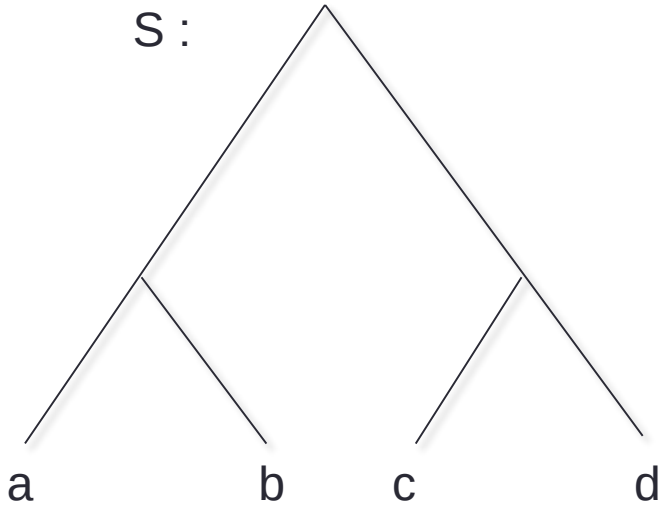




Does R_O lead to an S-Consistent gene tree ?

Relation graphs and S-Consistency





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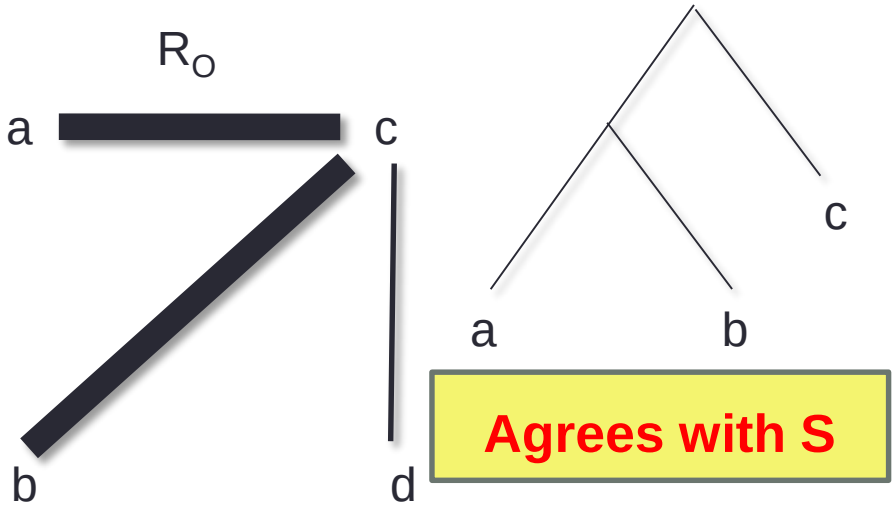
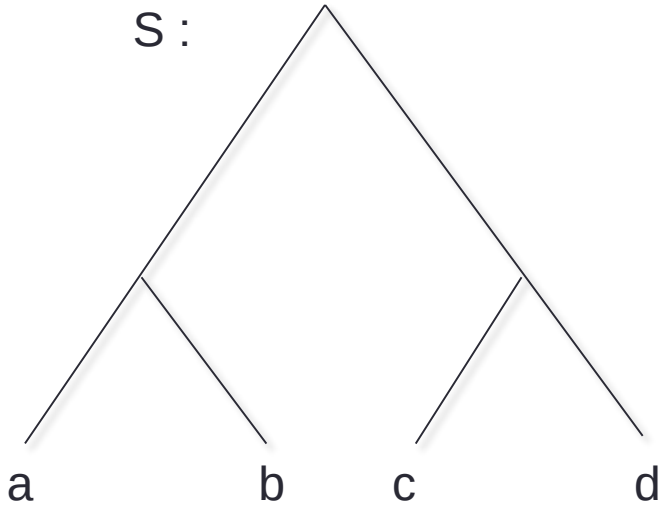


Agrees with S



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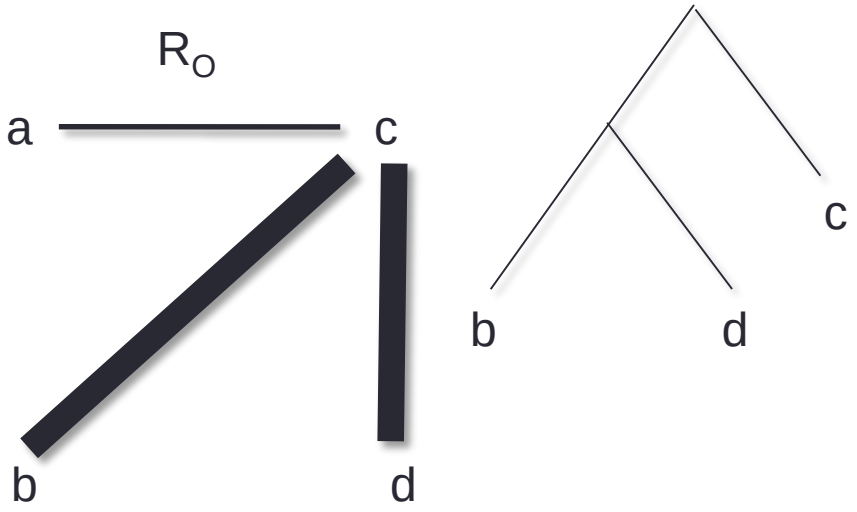

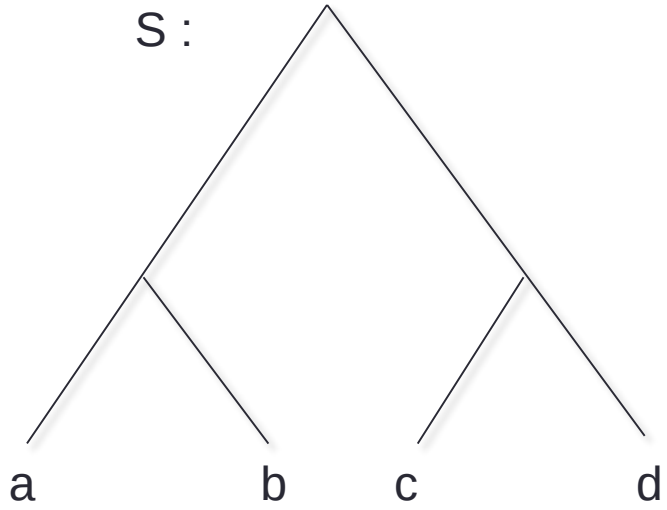

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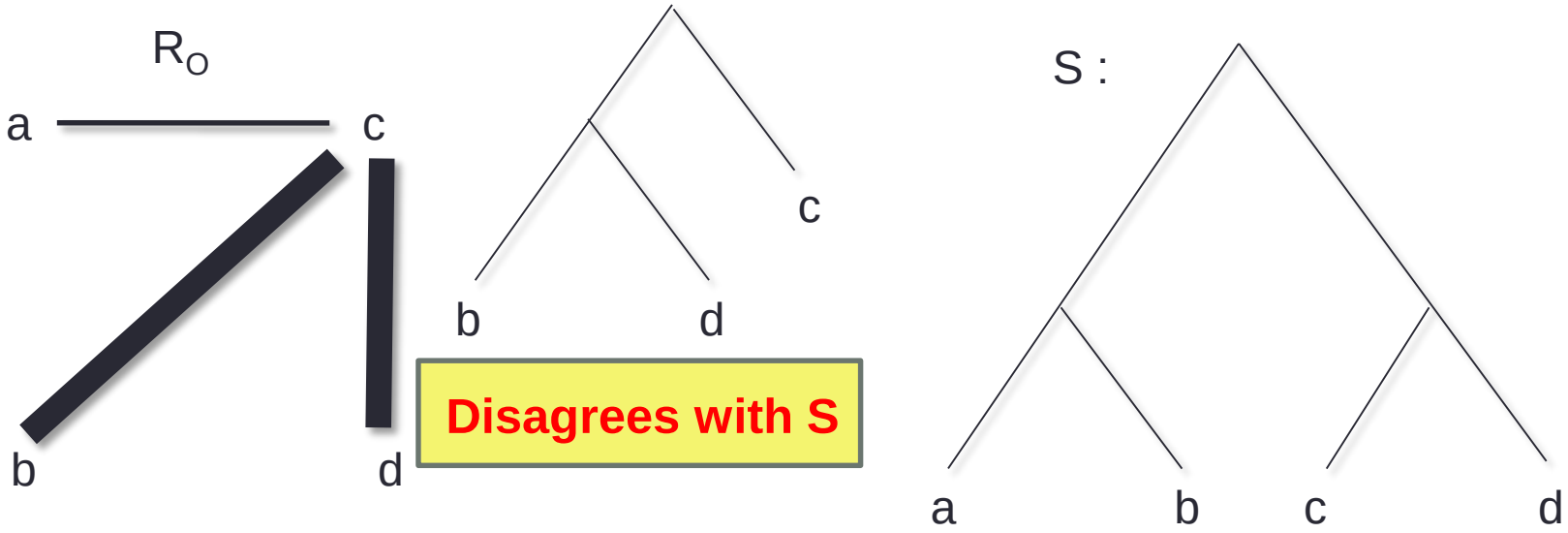

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Checking for S-Consistency is easy. Just find every P_3 and check them, in $O(n^3)$.

But how to correct for S-Consistency ?

Problem 1

Given : a species tree S and a set of orthology / paralogy relations R.

Find : the minimum number of relations to change in R such that the relations are **satisfiable** + **S-Consistent**

Equivalently : find the minimum number of edge insertions / deletions in R_O such that it is P_4-free + every P_3 agrees with S.

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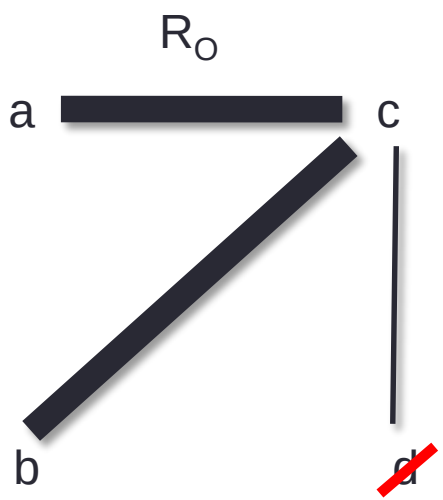

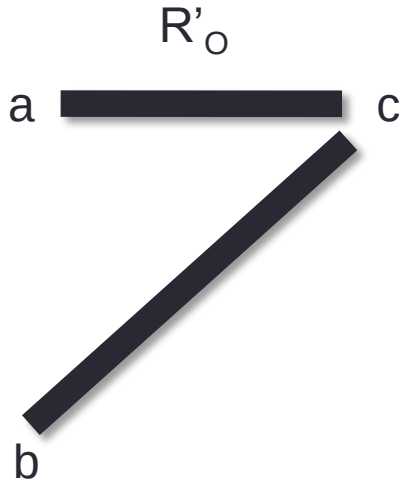

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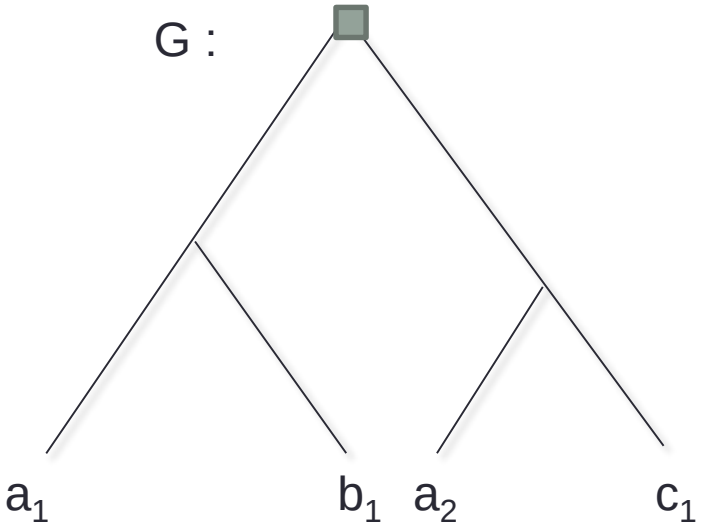
WORSE ! Hard to approximate within a $n^{1-\varepsilon}$ factor (R.Dondi, unpublished).

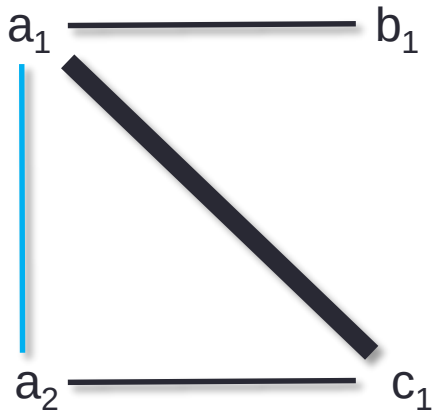
Allright then…

So we can’t correct inferred relations.

Still, let’s say there’s a bunch of them that I trust.

Can I use them to validate / correct my gene tree ?

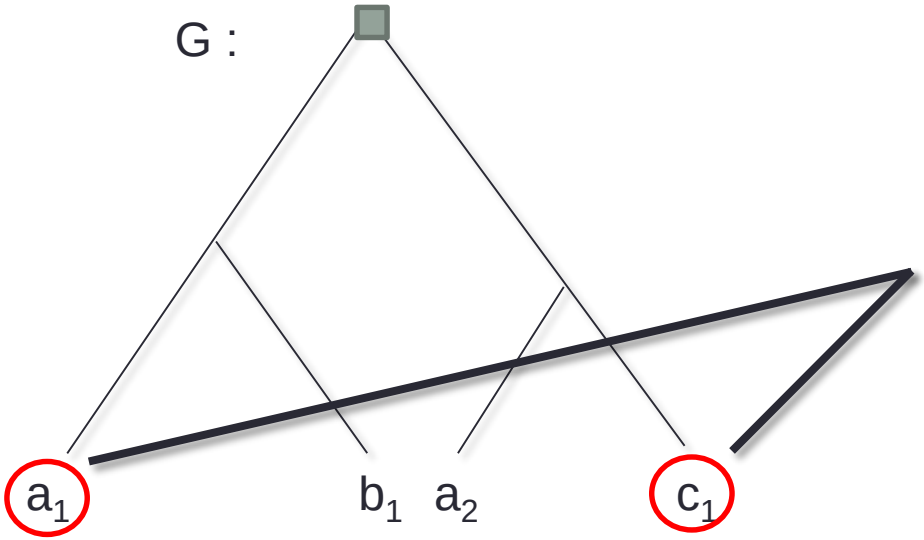




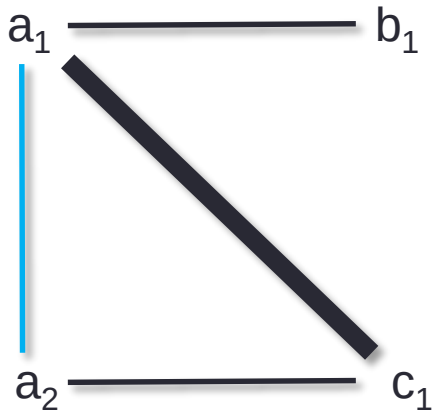
Partial, but trustworthy, relations

Orthologs

Paralogs



These guys should be orthologs



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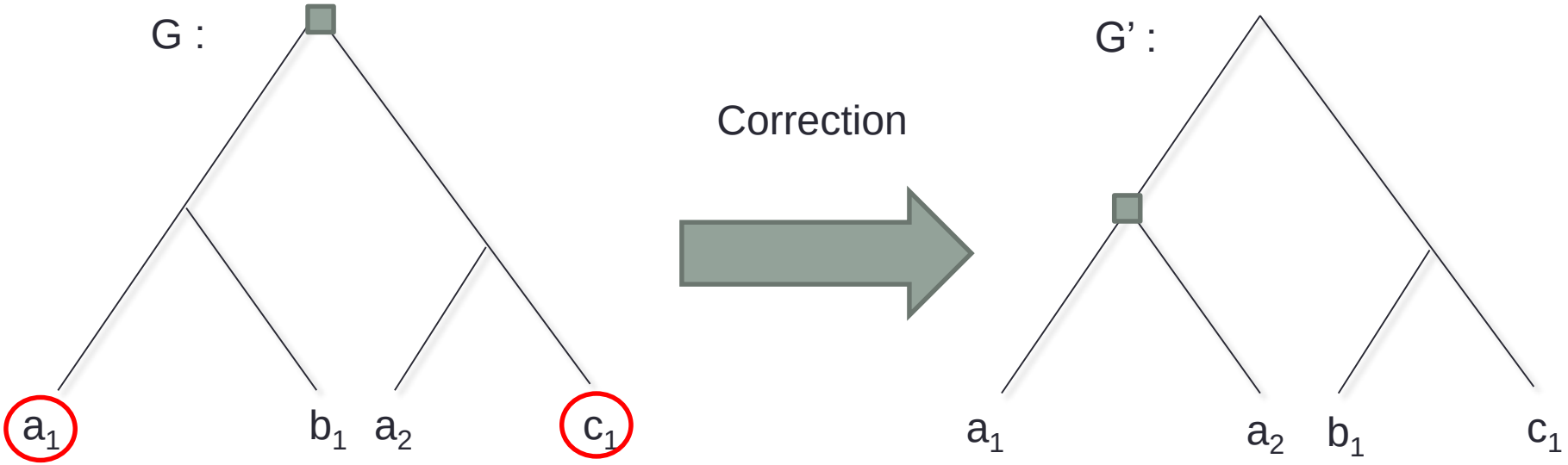

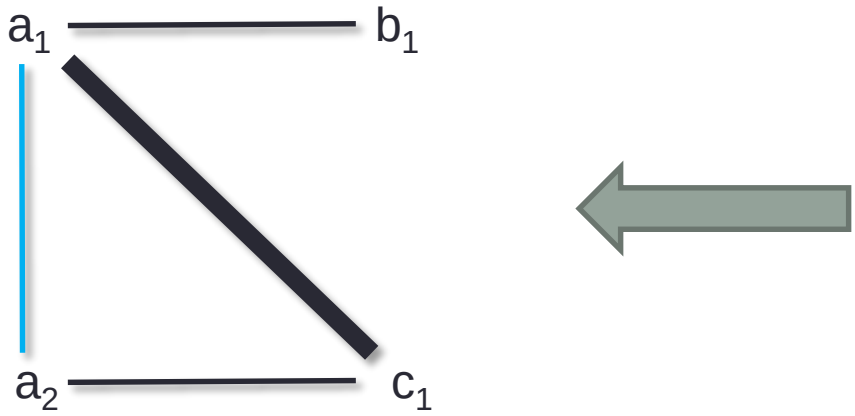

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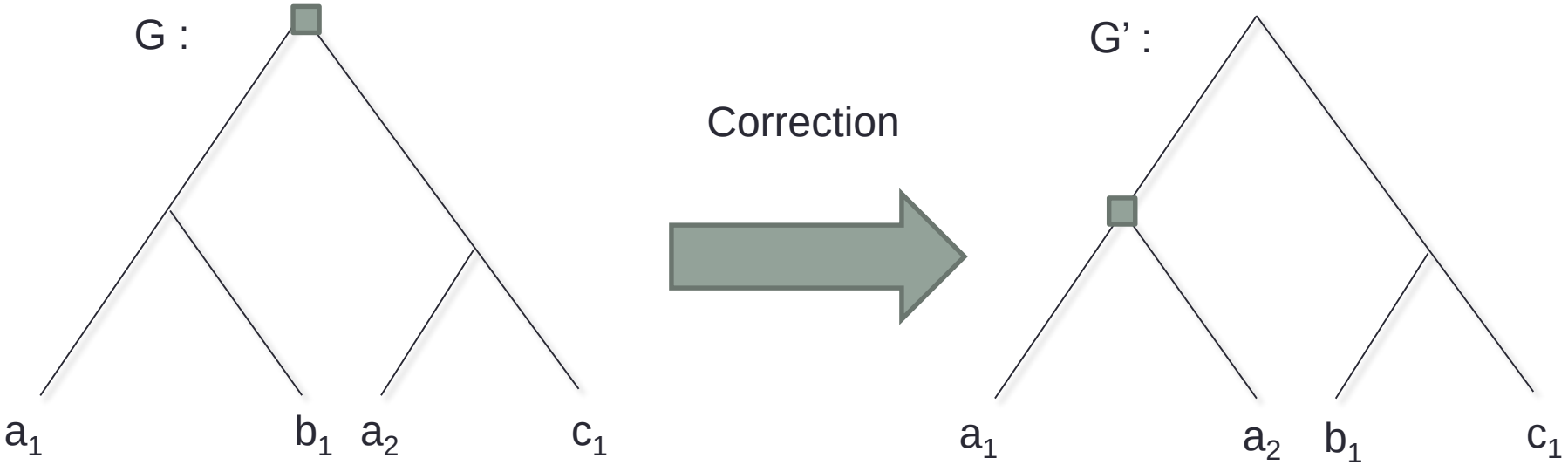
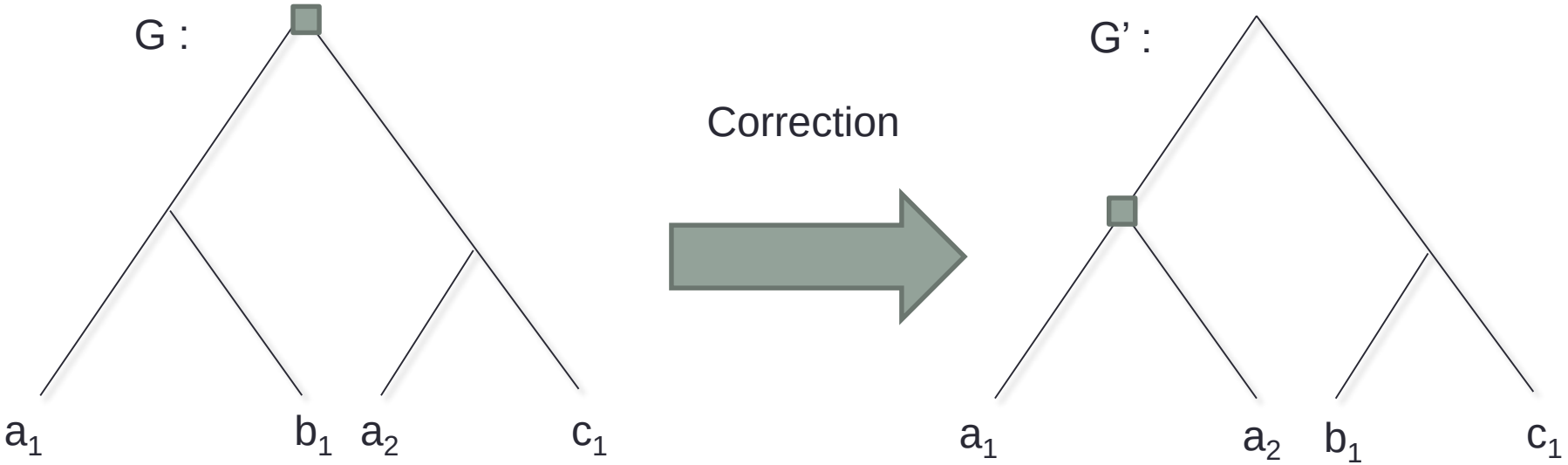


Keep G as ‘intact’ as possible.



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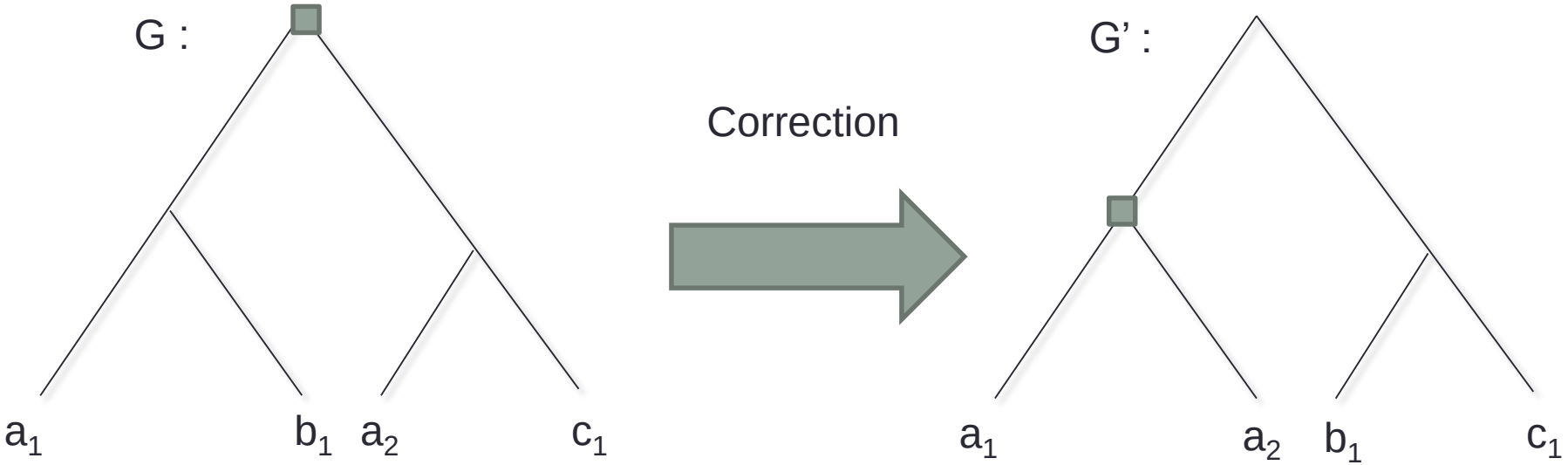

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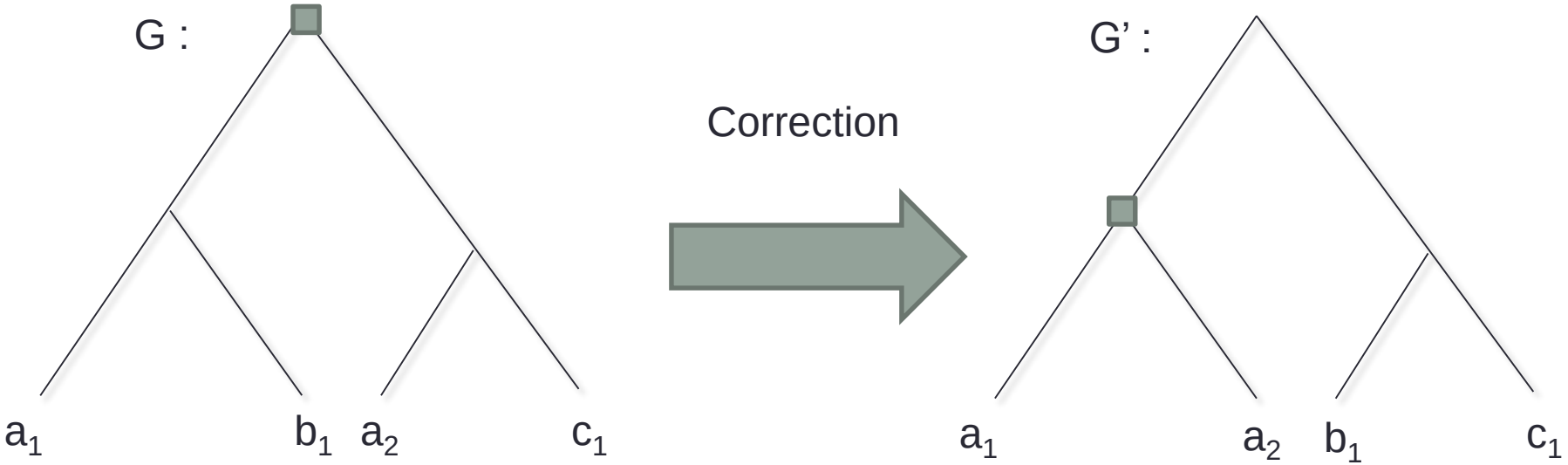

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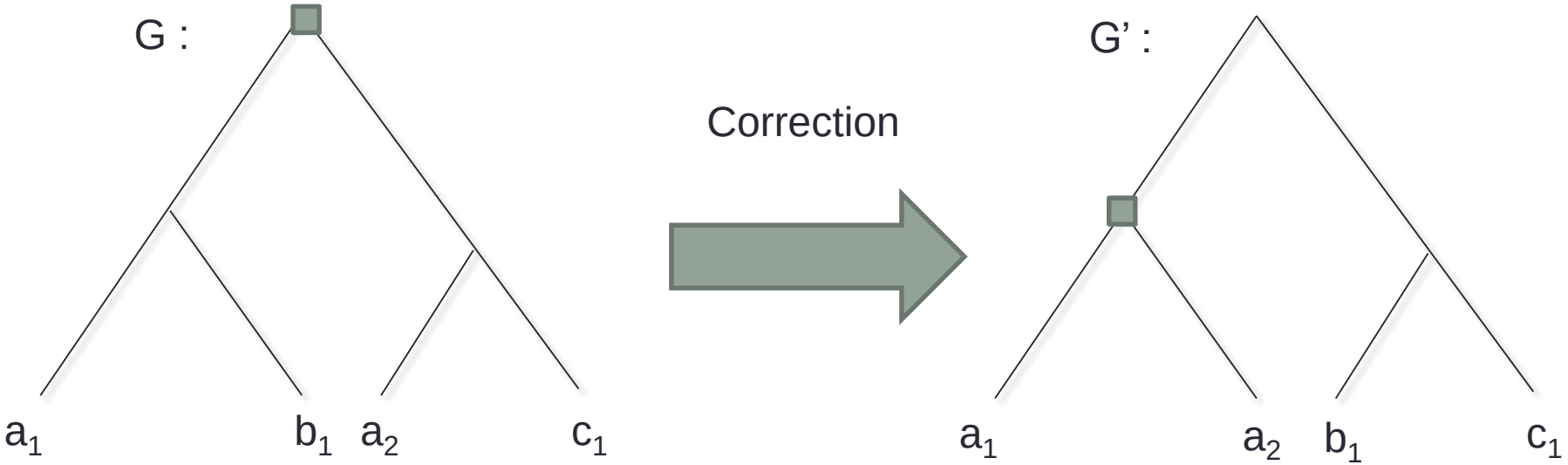

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The number of clades that G and G' do not have in common.

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Reduction from the edge insertion/deletion problem (Problem 1)

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If R has only orthologs, or only paralogs, then this is feasible in polynomial time (Lafond & al. 2013).

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Surprise !

NP-COMPLETE (Lafond and El-Mabrouk, 2015)

Reduction from the gene removal problem (Problem 2)

More problems

The inferred relations could be **weighted**, e.g. associated with a **probability** of orthology.

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- Generalizes both **Problem 1** (edge insertion / deletion) and **Problem 3** (gene tree correction, minimize broken relations).
- Factor O(n) approximation algorithm (unpublished). We do not know whether it is essentially best possible.

Conclusion

- Gene tree => Orthologs / paralogs : **YES**
- Orthologs / paralogs => Gene tree : **NOT ALWAYS**

- Unfortunately, error correction of orthology / paralogy relations is difficult.

- Even assuming relations are error-free, gene tree coorrection is difficult.