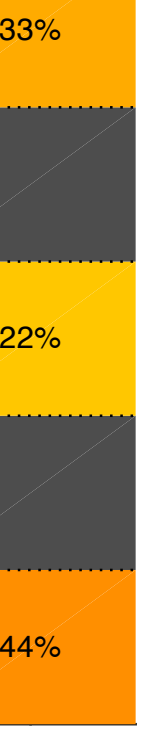
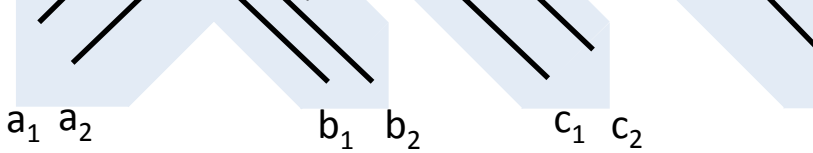
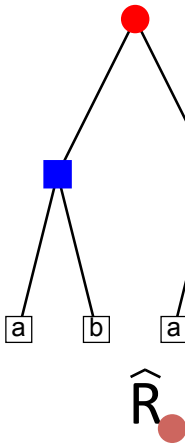




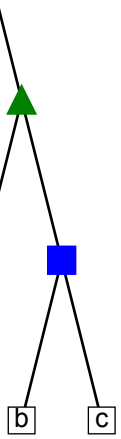
Graph-based Adjustment of Orthology-Relations



Paul Klemm

University of Greifswald, Germany

32th TBI Winterseminar, Bled 2017



$$\prod_{i=1}^{n-1} \binom{numST_i + (a_i - 1)}{a_i}$$

ERNST MORITZ ARNDT
UNIVERSITÄT GREIFSWALD

Wissen lockt. Seit 1456

Outline

Introduction

Phylogenetic, Orthology relation	Cographs	Graph-based orthology inference

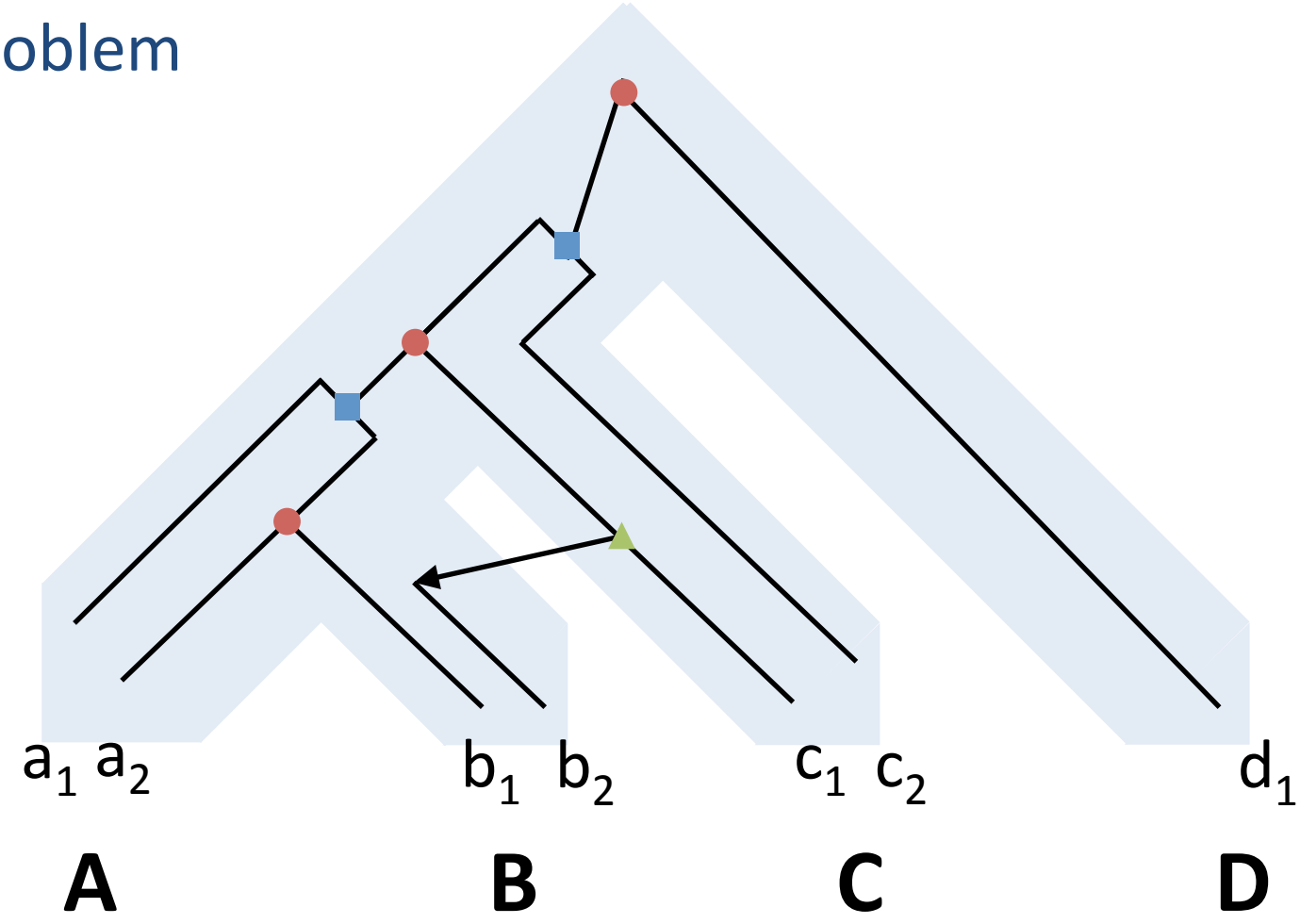
Artificial Data Analysis

Enumeration of all gene trees	Results

Summary and Outlook

Introduction

The problem



Introduction

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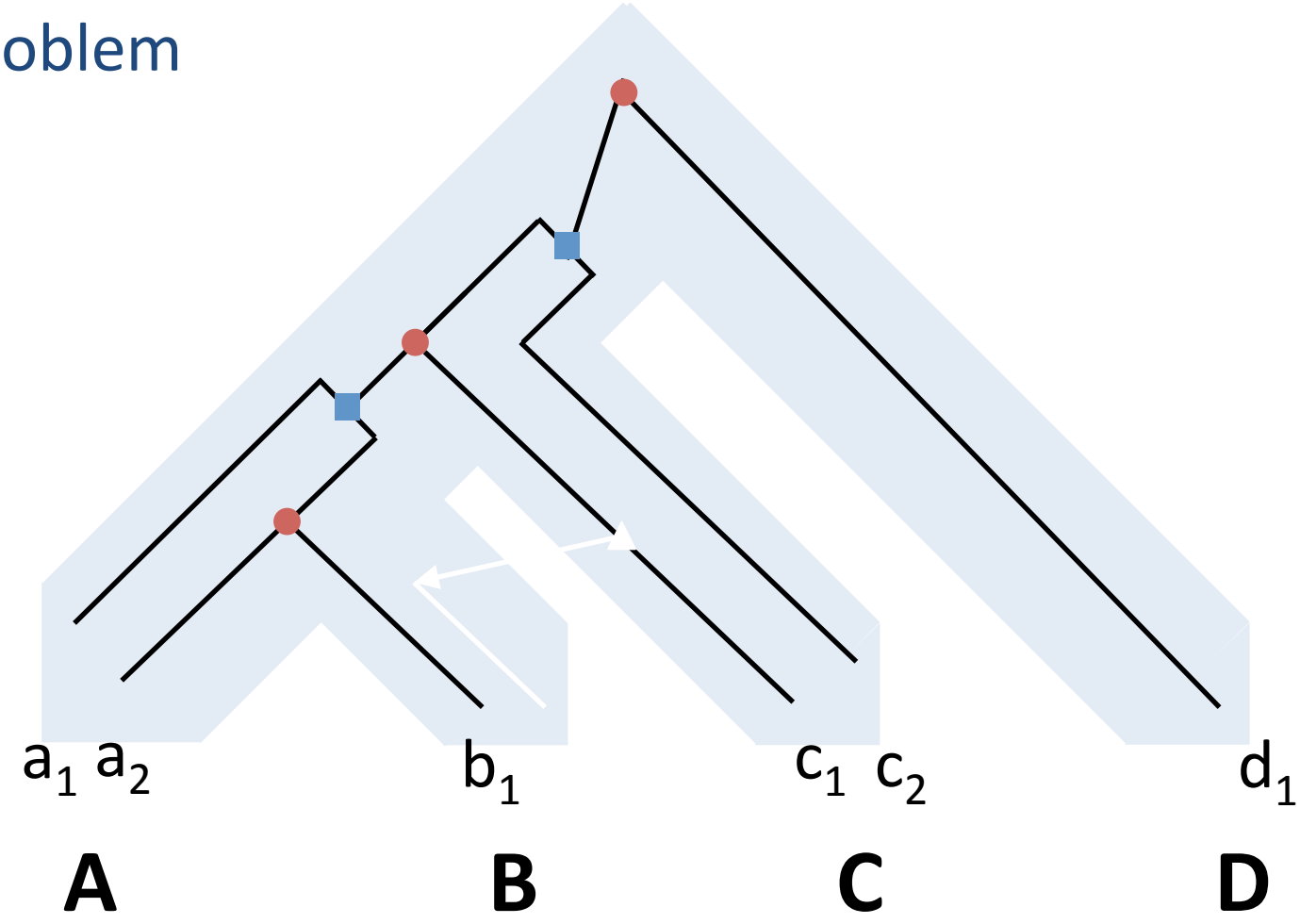
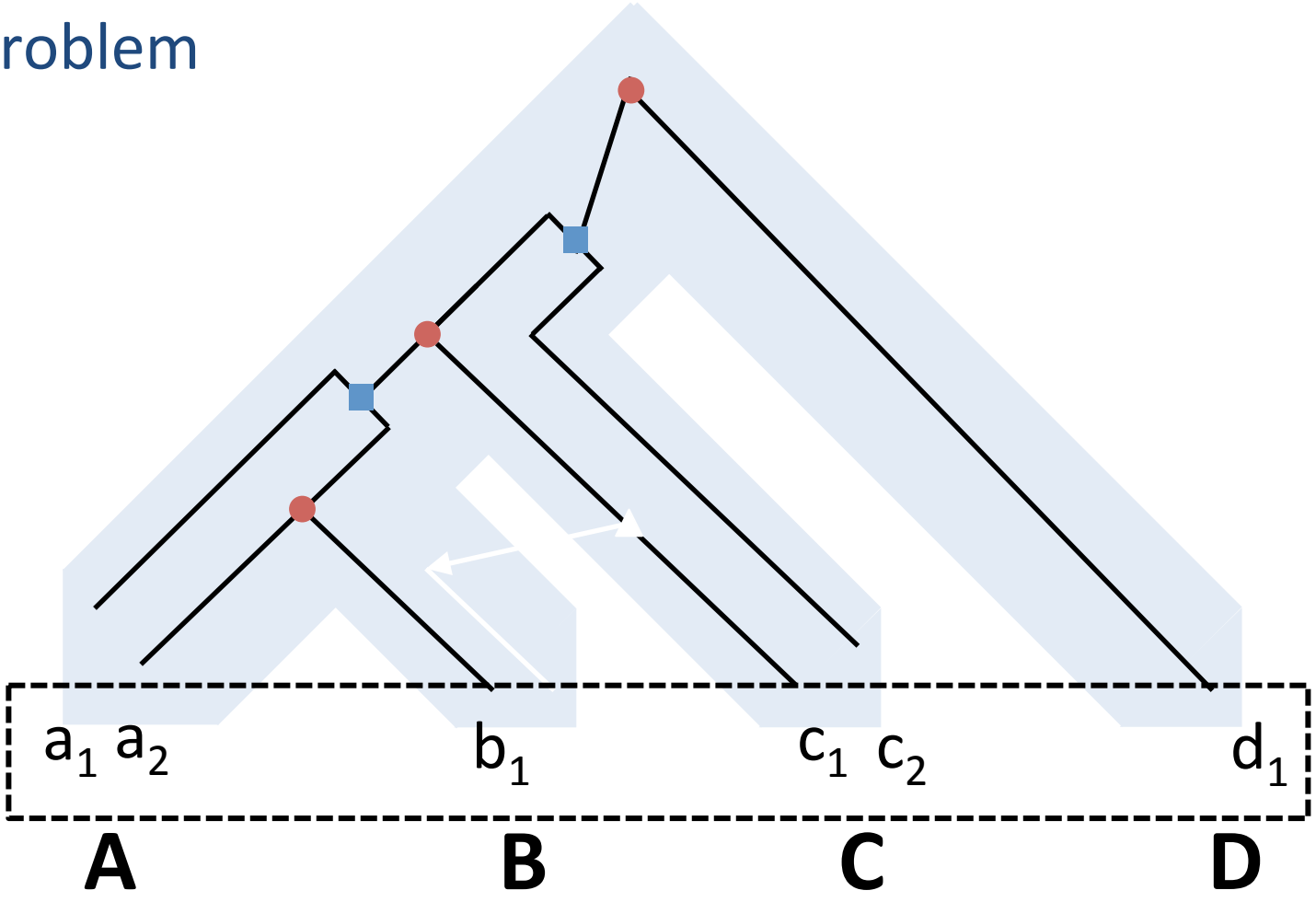


→ Simplification: no HGT-event

Introduction

The problem



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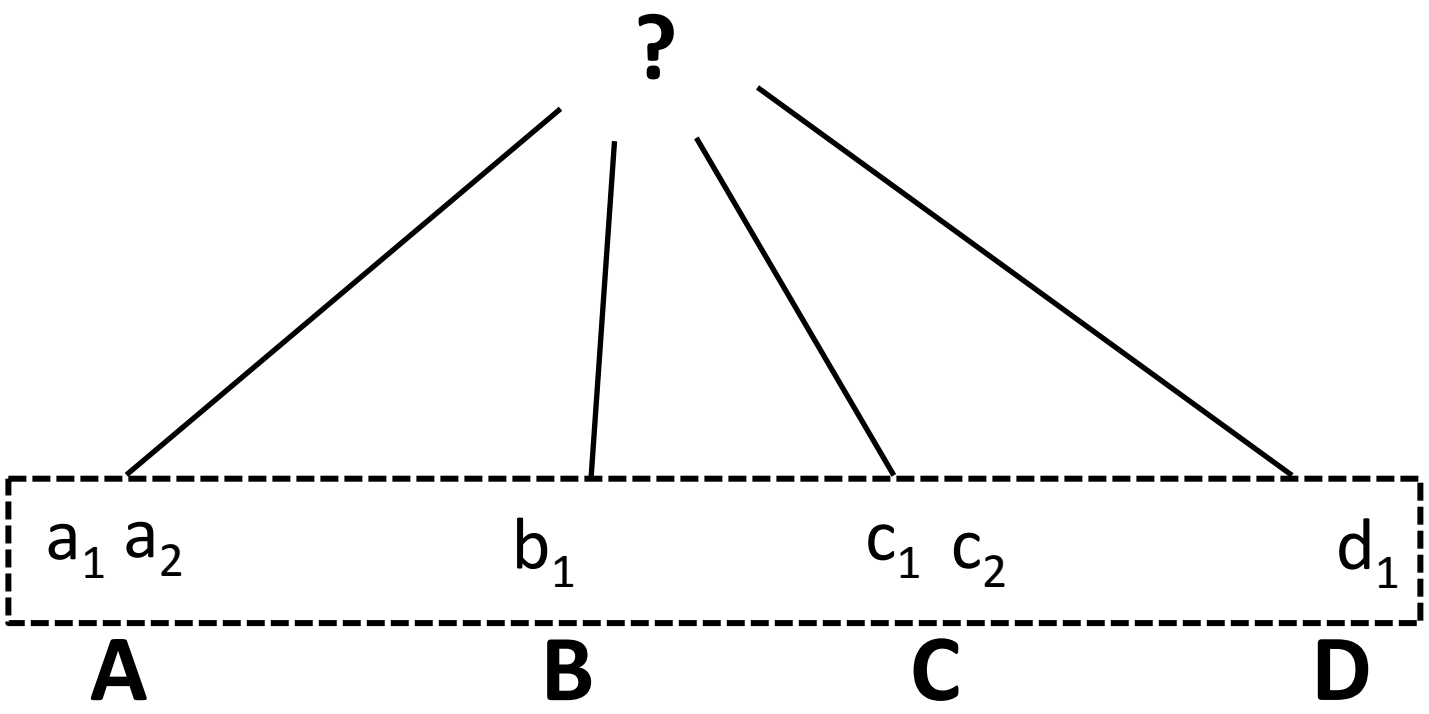

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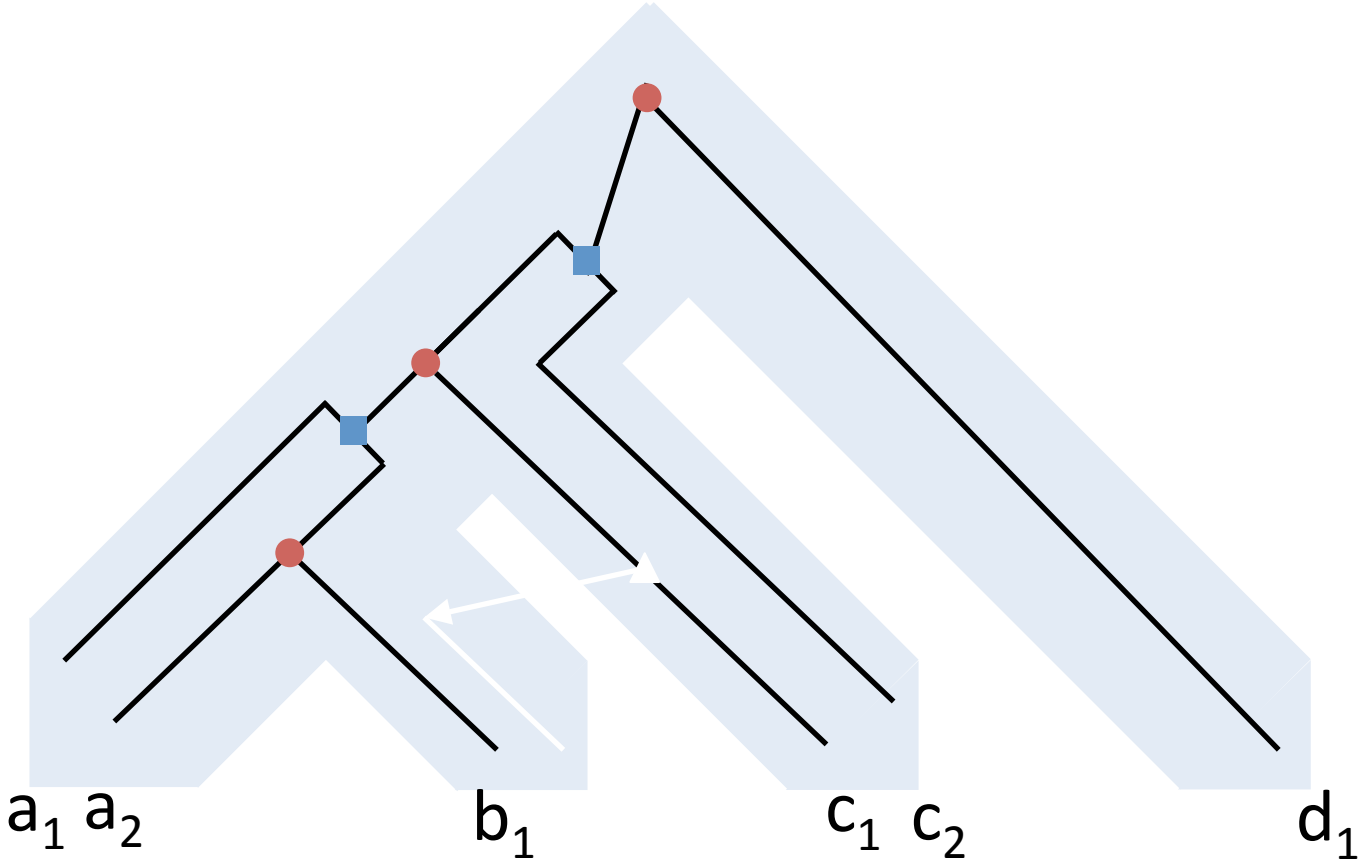
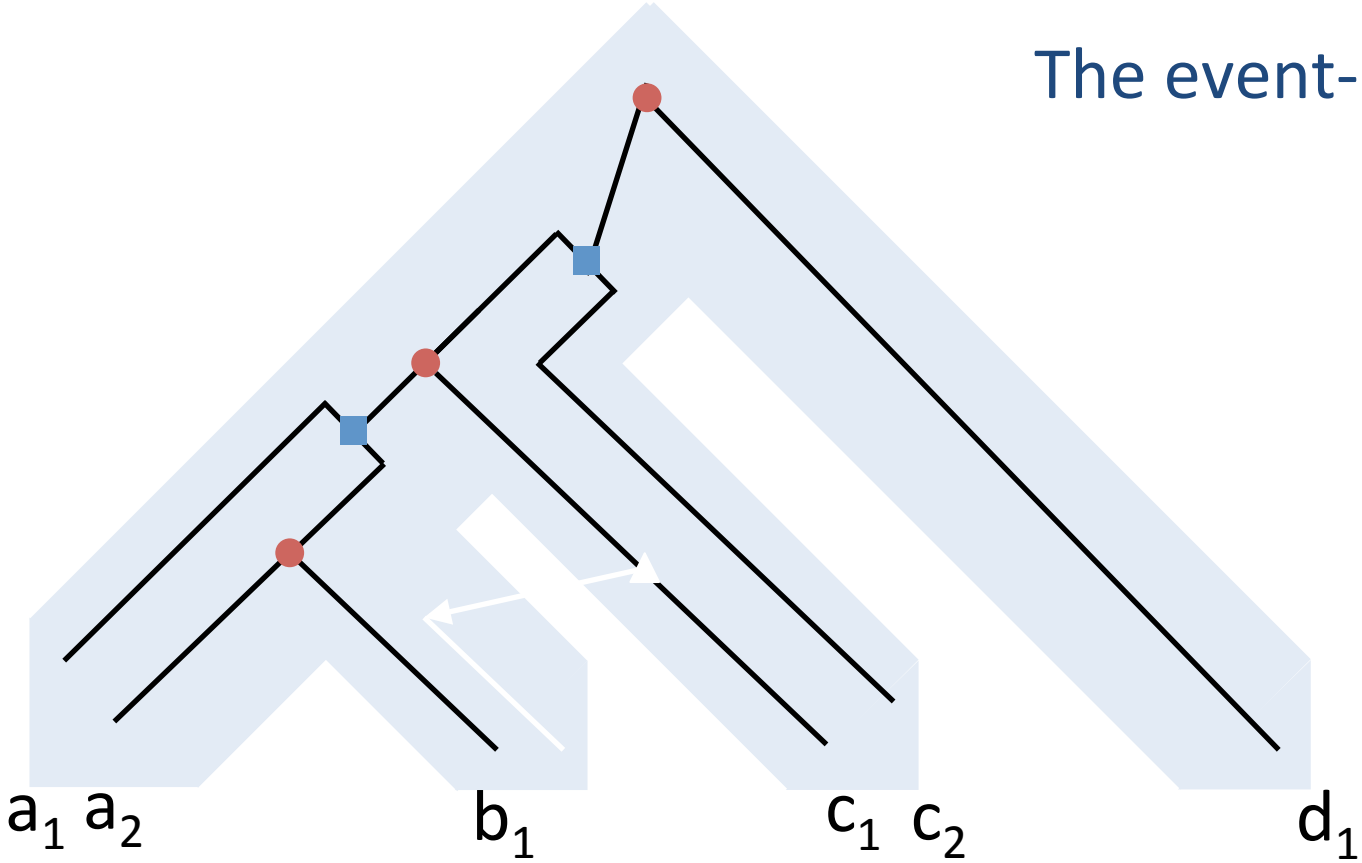


We call two genes x and y

- ortholog if lca(x,y) = ● (speciation) e.g. a_2 and b_1
- paralog if lca(x,y) = ■ (duplication) e.g. c_1 and c_2
- xenolog if lca(x,y) = ▲ (HGT) e.g. b_2 and c_1

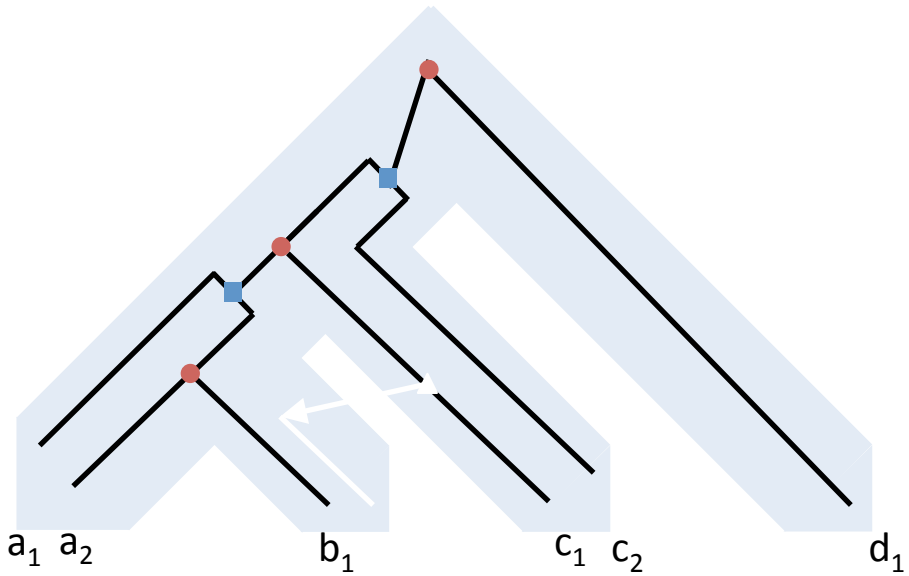
The event-Relations



The (distinct, binary, symmetric) **event-Relations**:

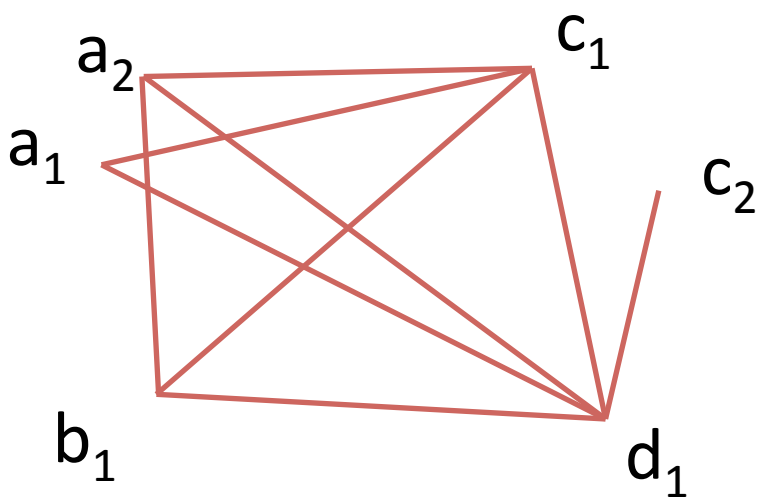
- $R_{●}$ = the set of all (x,y) with lca(x,y) = ● (speciation)
- $R_{■}$ = ... with lca(x,y) = ■ (duplication)
- $R_{▲}$ = ... with lca(x,y) = ▲ (HGT)

The event-Relations



Simplification: no HGT-events

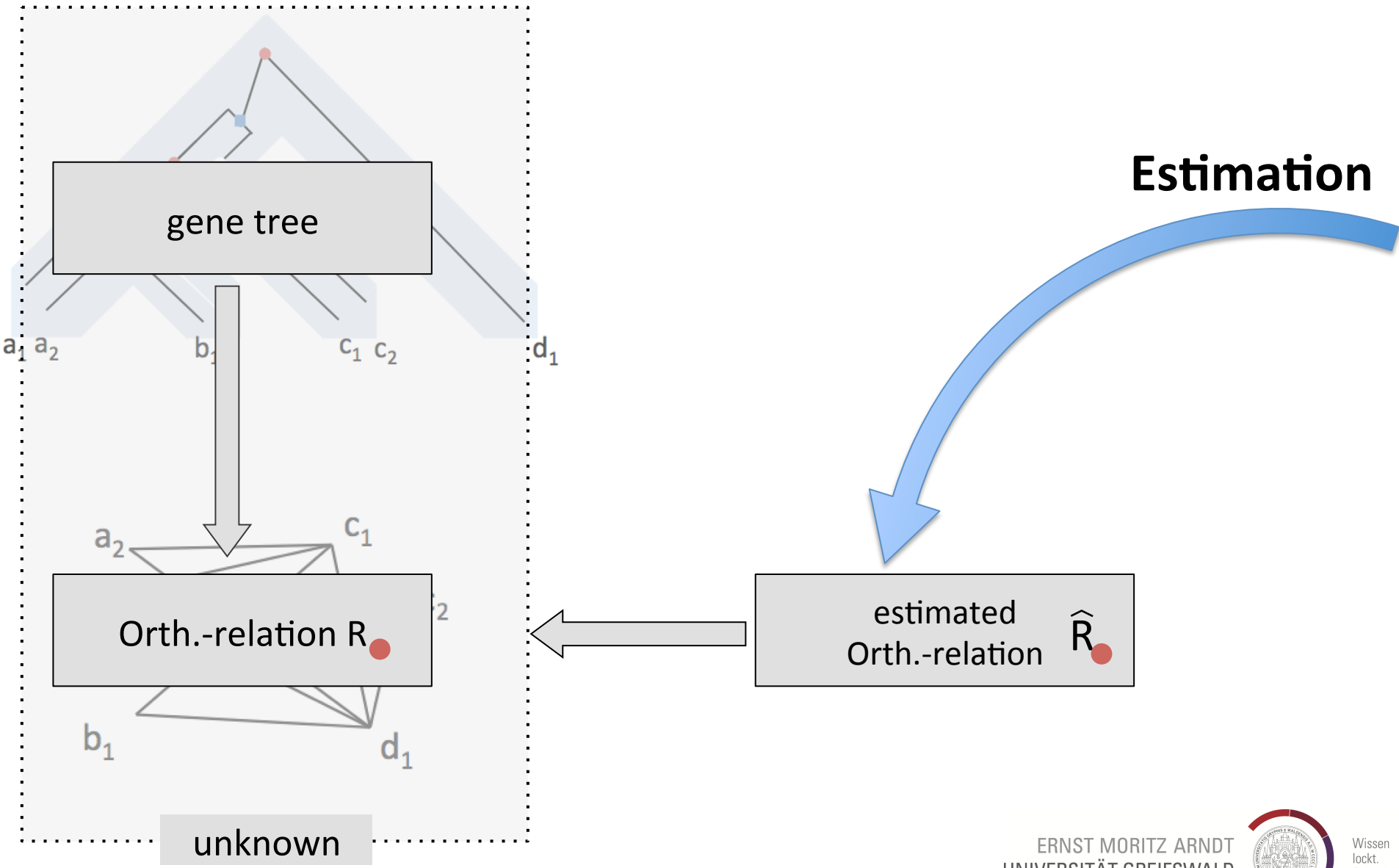
→ $R_{●} = \overline{R_{■}}$



→ graph representation of

$R_{●}$ and $R_{■}$

Introduction



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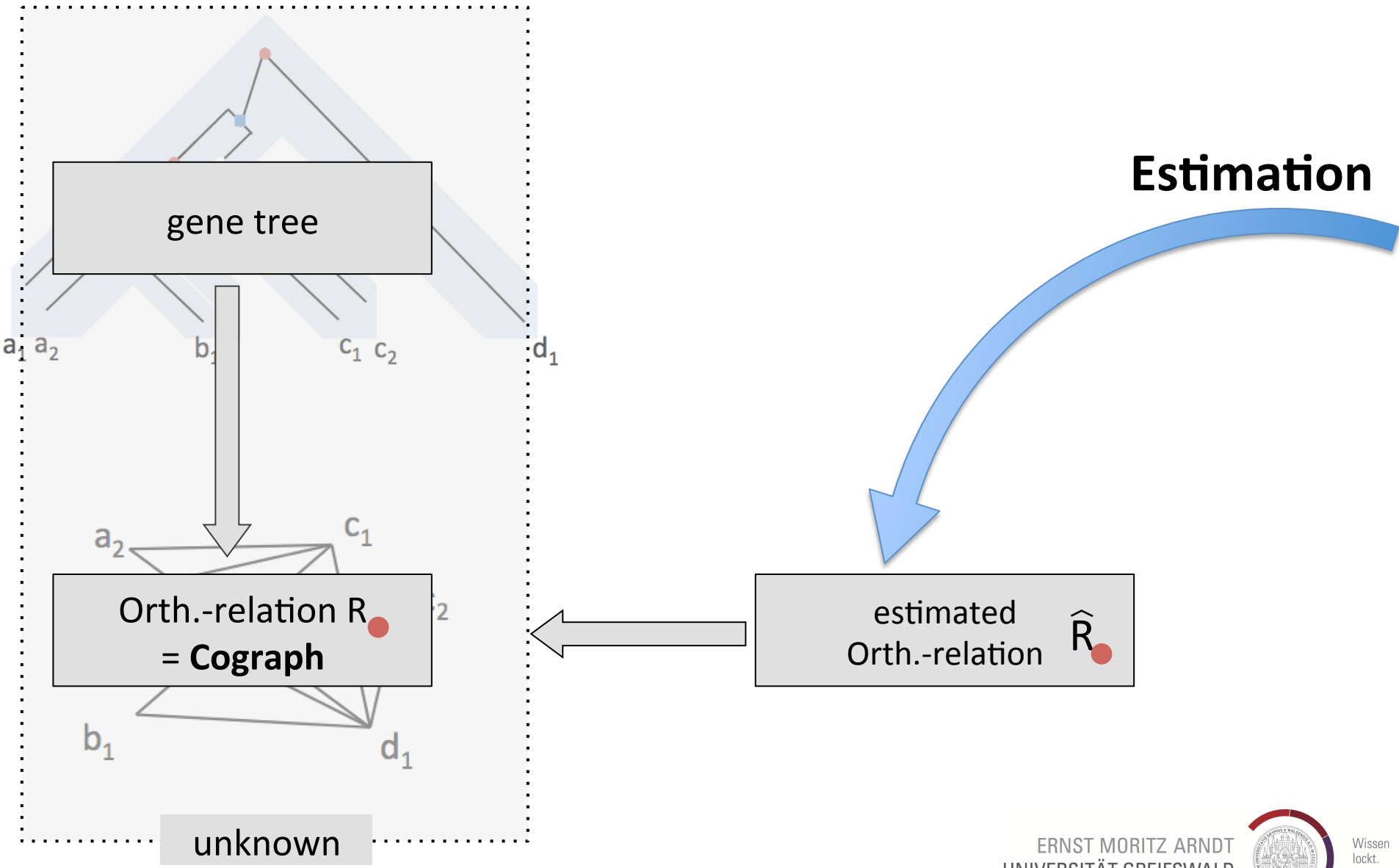

Cographs

A graph is called **cograph** if and only if
there exists no <u>induced</u> subgraph on 4 nodes that is a P4 ()

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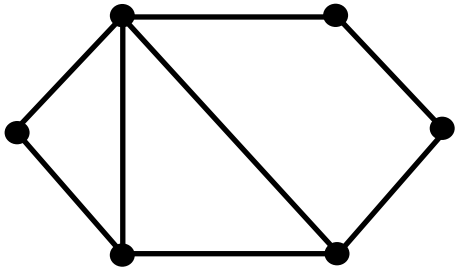

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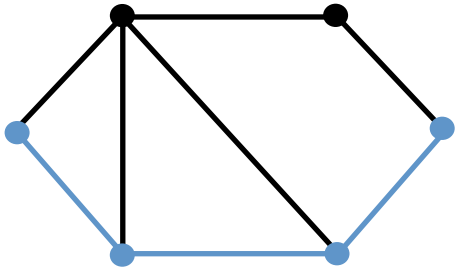

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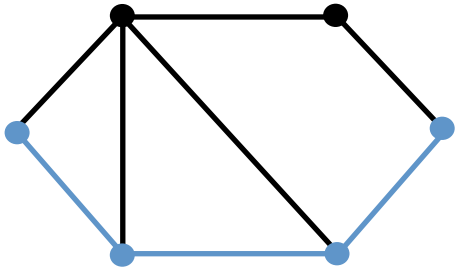

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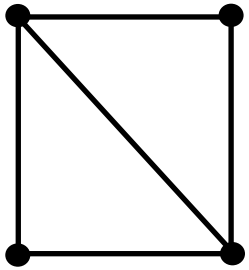

Cograph

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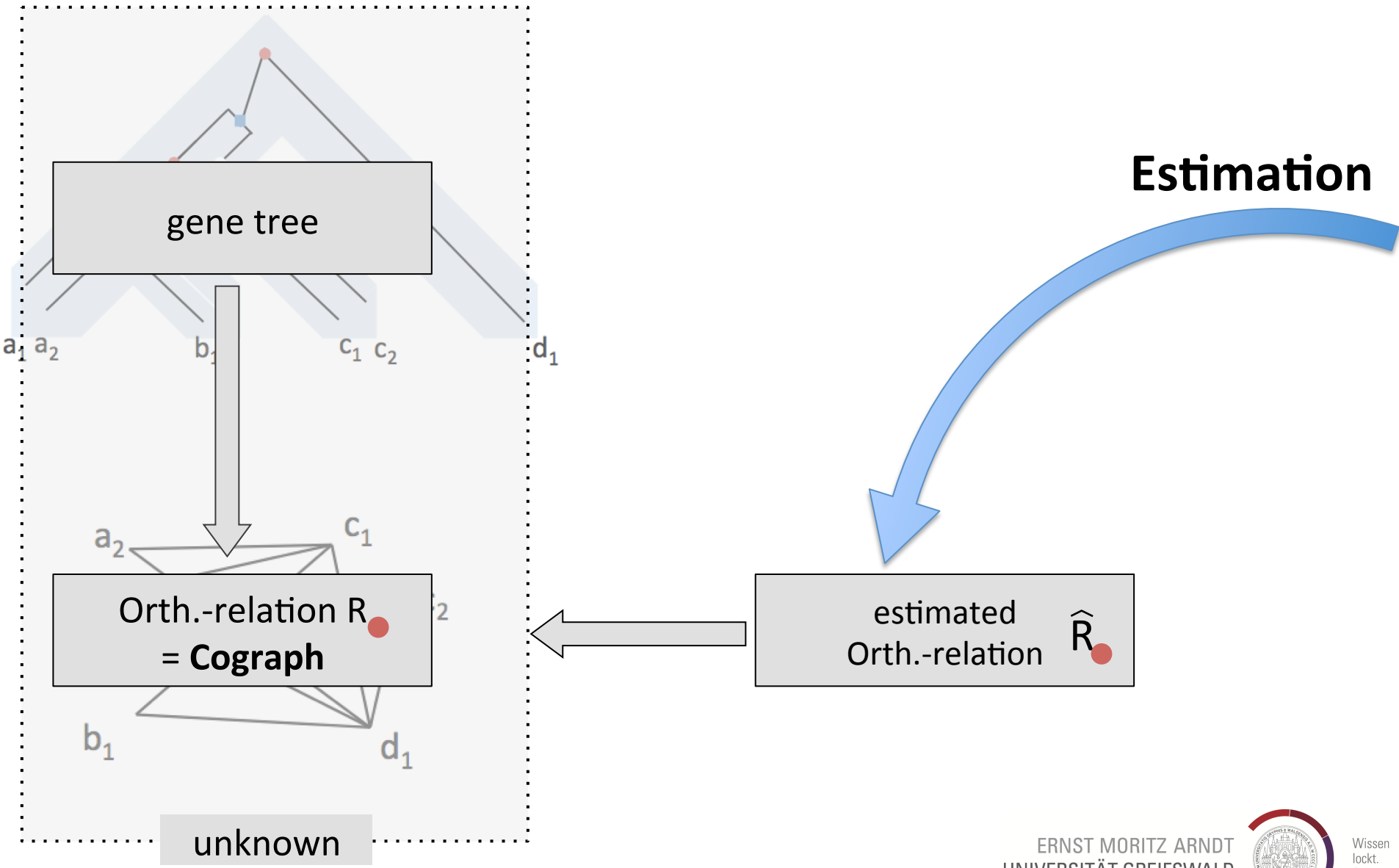

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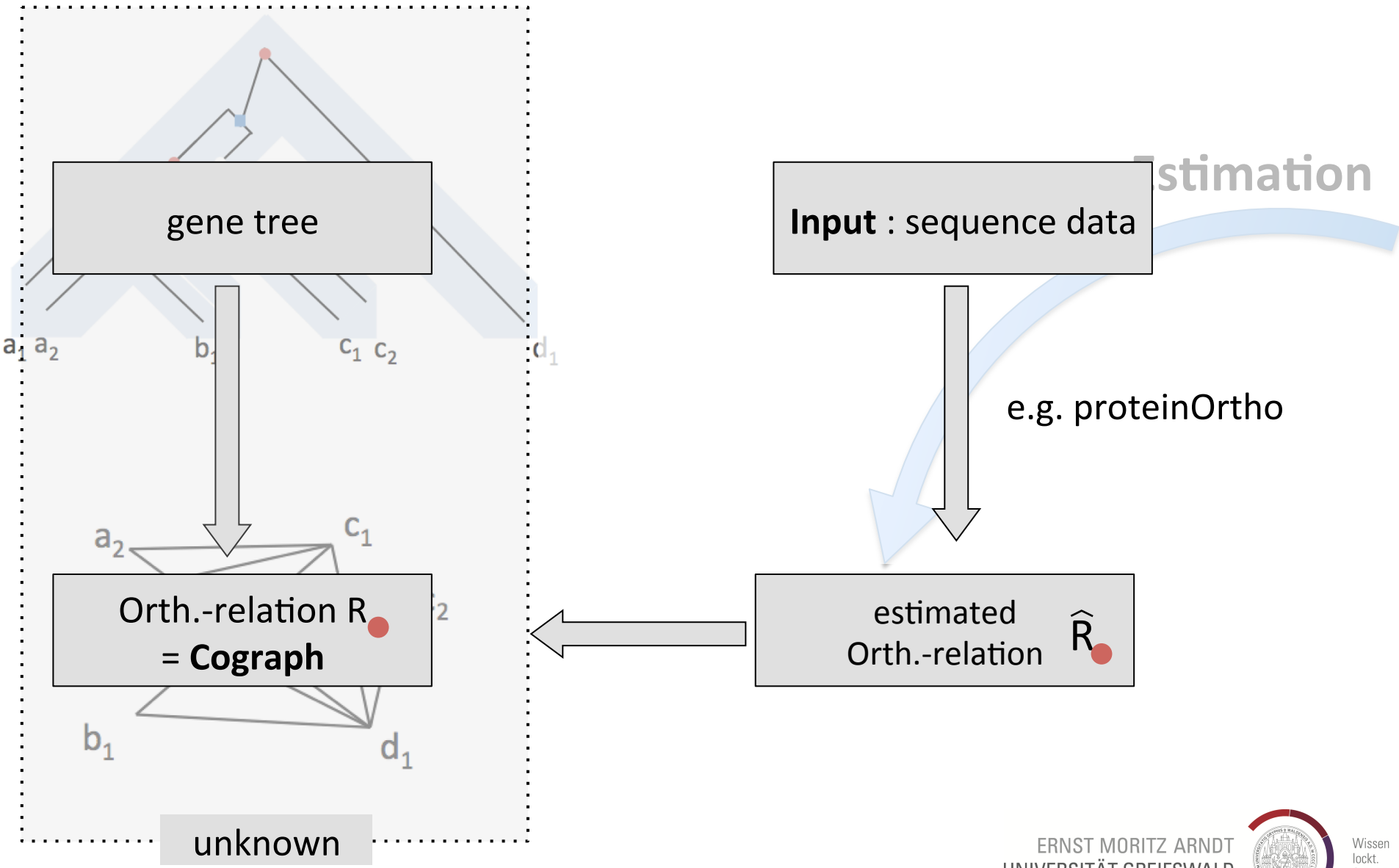

Introduction

Graph-based orthology inference (e.g. proteinOrtho)

Input : sequence data

Local alignment search
(e.g. BLAST)

Sequence similarity **s(x,y)**

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(e.g. BLAST)

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Then two genes x in X and y in Y are **estimated orthologs** if:

i. they are from different species and
ii. **s(x,y)** is the ~best score compared to **s(x‘,y)** and **s(x,y‘)** where x‘ in X, y‘ in Y

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→ **estimated orthologs** if:

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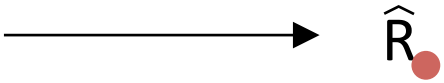

Introduction

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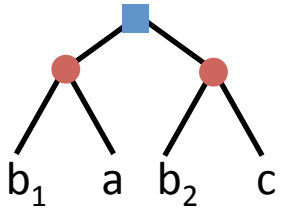

Genes: b_1 a b_2 c

Species: B A B C

$R_{\bullet}$:

$\hat{R}_{\bullet}$:

Simplification: leaf distance d(x,y) of the „true“ gene tree:

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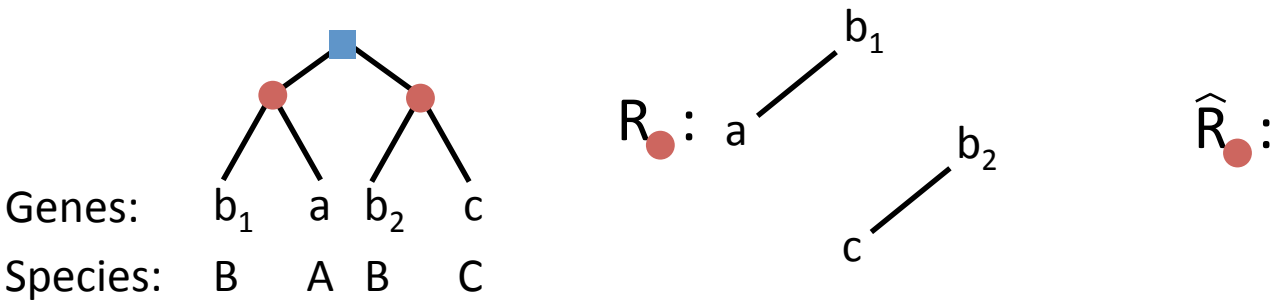
→ $\hat{R}_{\bullet}$

Introduction

Graph-based orthology inference



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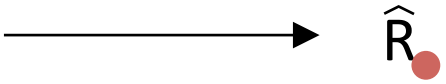

Introduction

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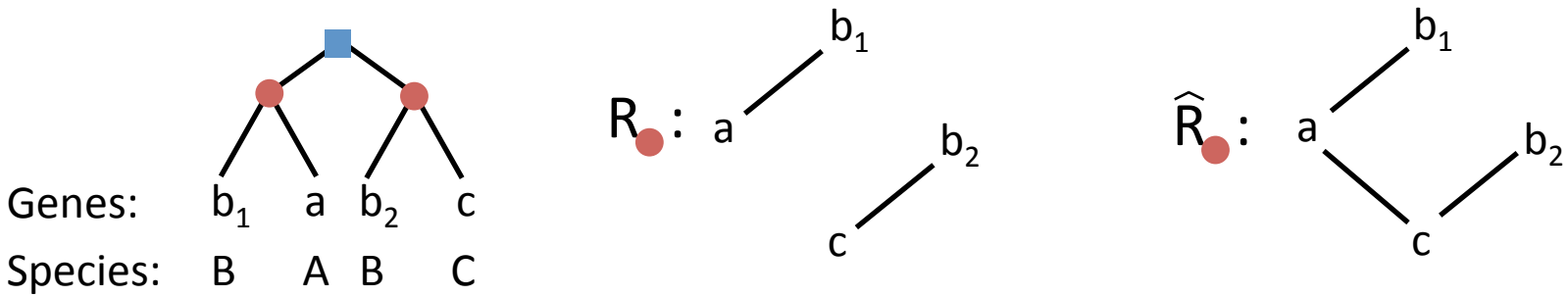

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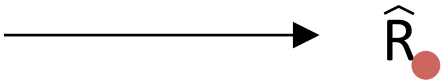

Artificial Data Analysis

Question:

How much information can we infer from non-cograph relations ?

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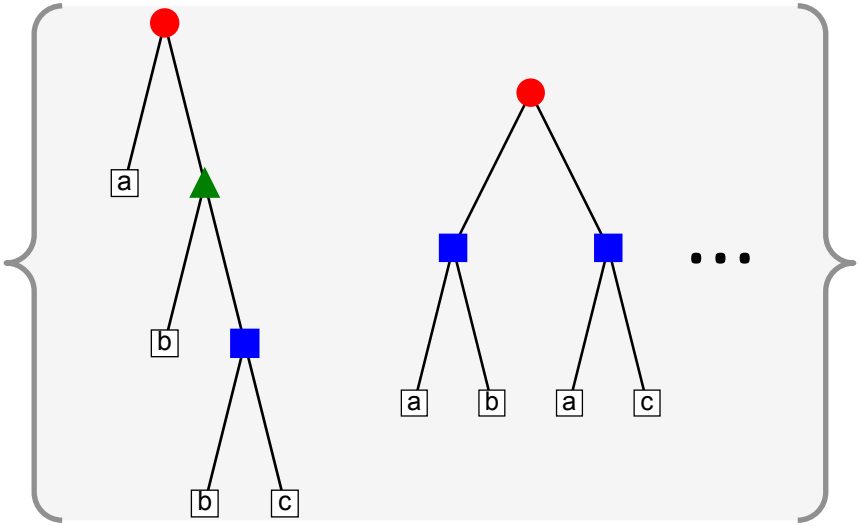
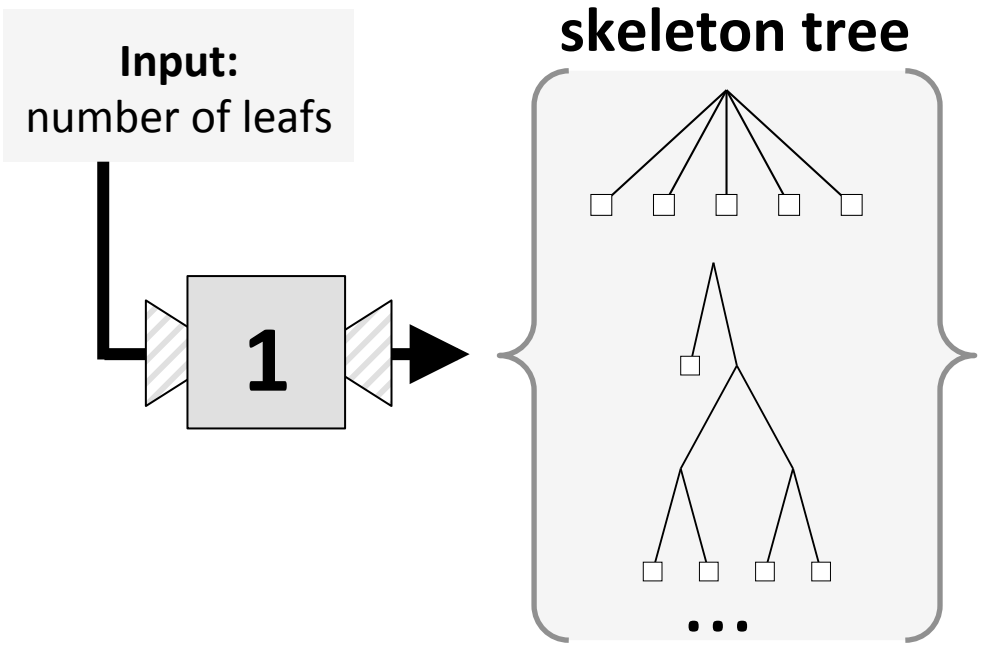
Input:
number of leafs

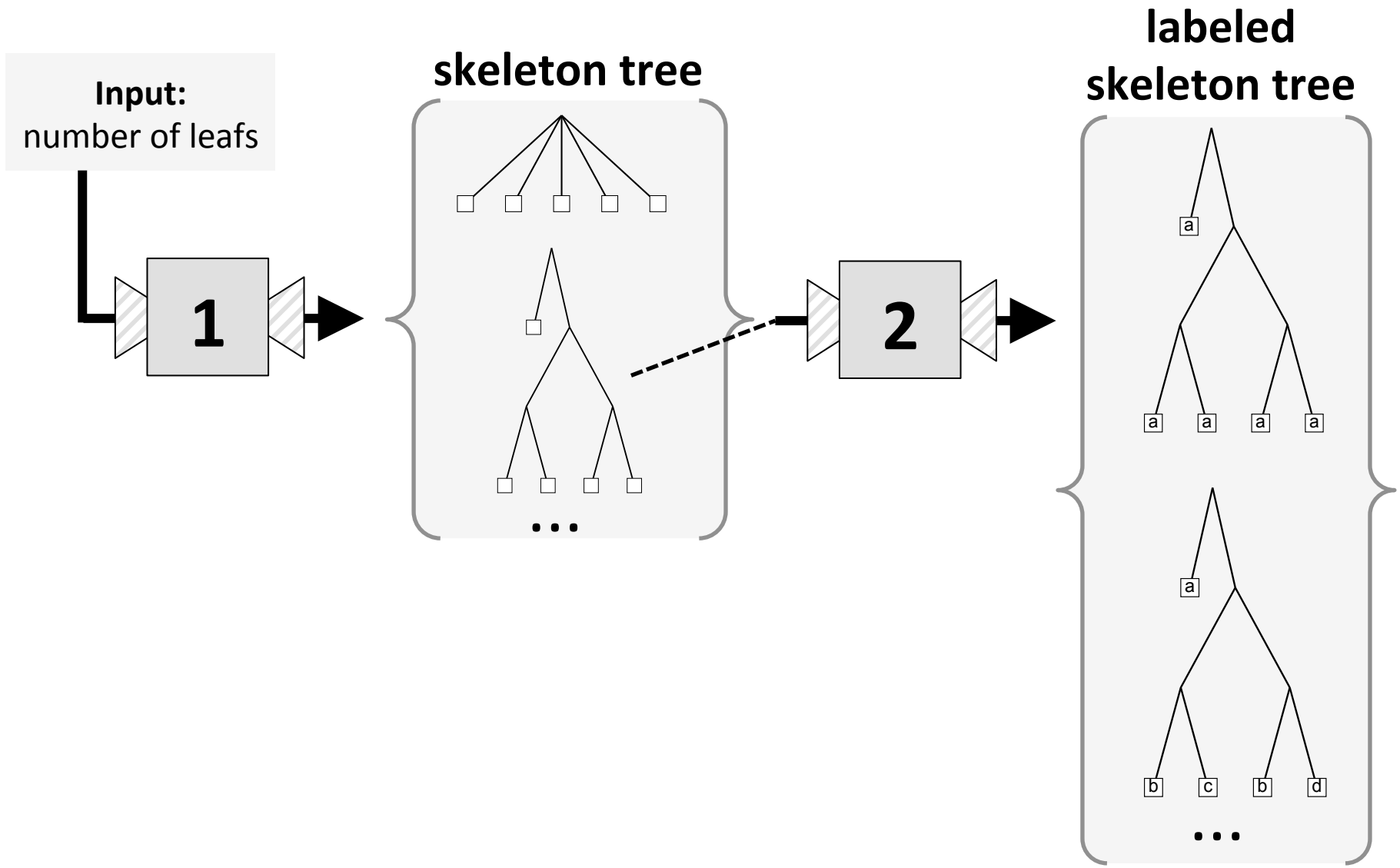
1,2,3

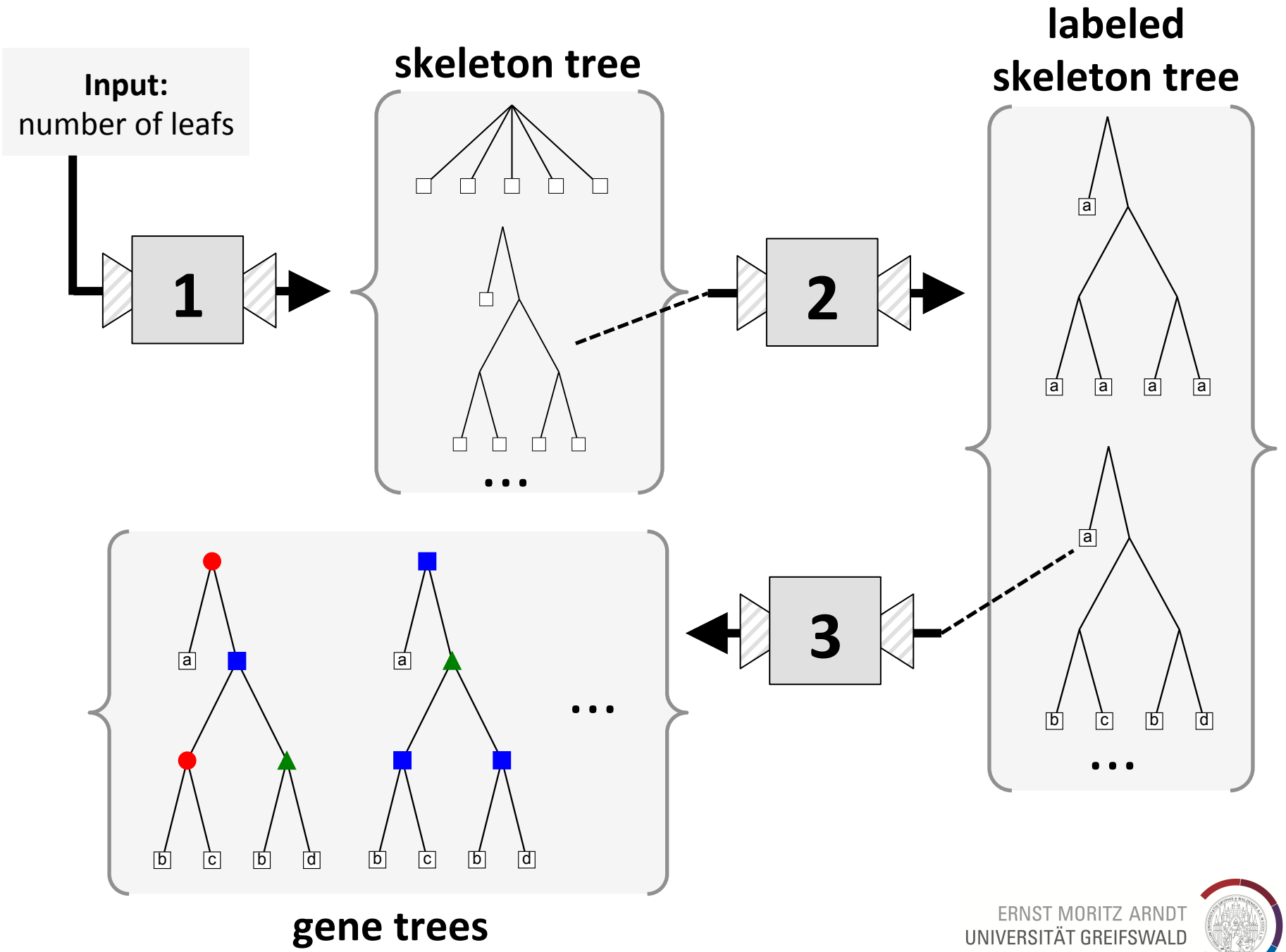


gene trees

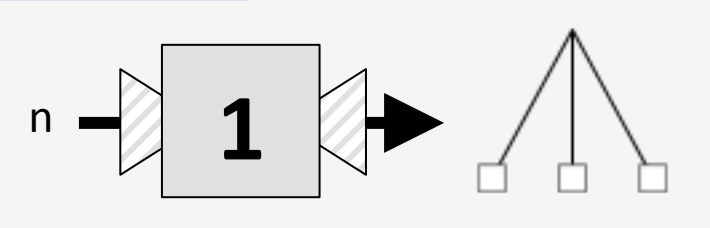
estimated Orth.-relation $\hat{R}$ + Orth.-relation R


Input:
number of leafs
1
skeleton tree
...


Input:
number of leafs
1
skeleton tree
2
labeled
skeleton tree
a
a
a
a
a
a
b
c
b
d


Input:
number of leafs
1
skeleton tree
2
labeled
skeleton tree
3
gene trees

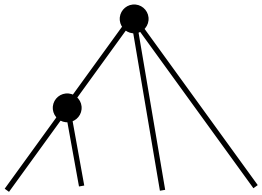
Artificial Data Analysis



1. Generate skeleton trees

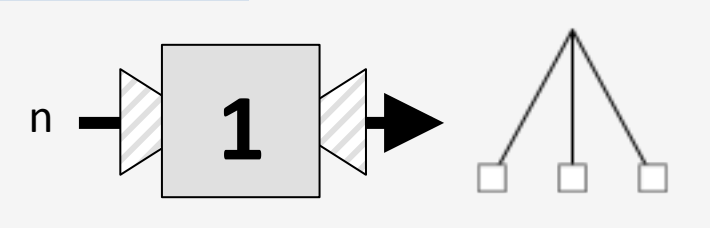
We want:

1. Rooted trees with n leafs



1 + 1 + 1 + 1 = 4

Artificial Data Analysis



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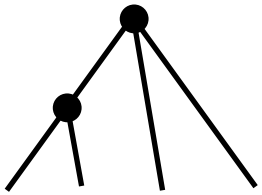
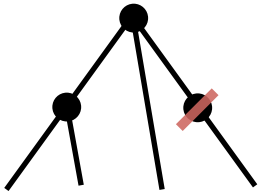
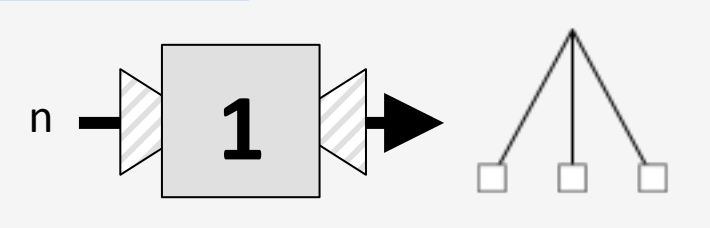


1 + 1 + 1 + 1 = 4

2. All inner nodes should have at least 2 childs



Artificial Data Analysis



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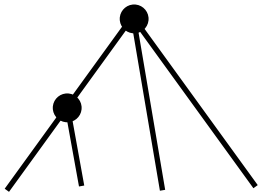

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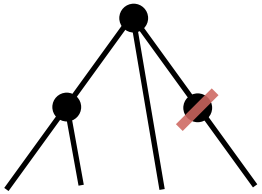
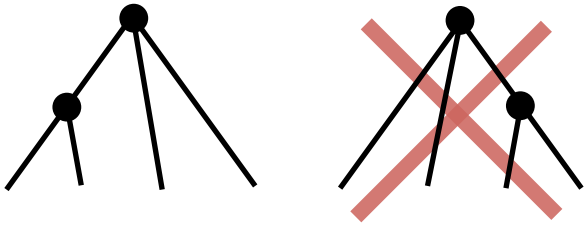


3. Only one representative of the isomorphism classes



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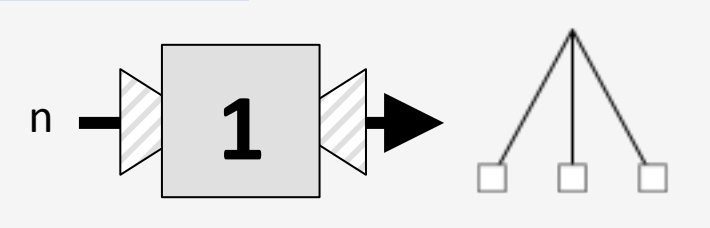

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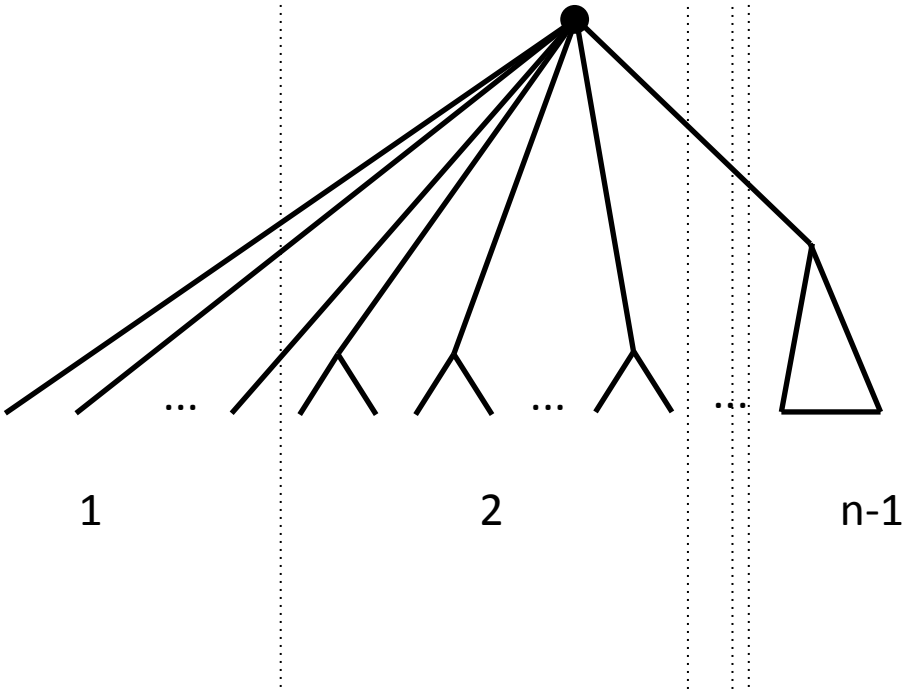

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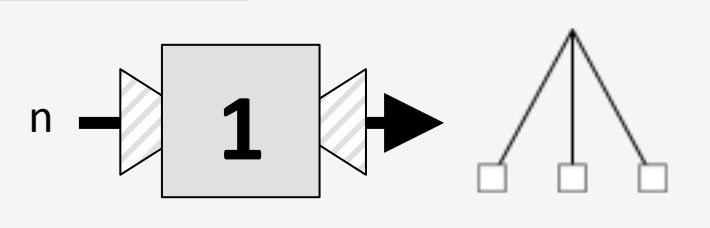

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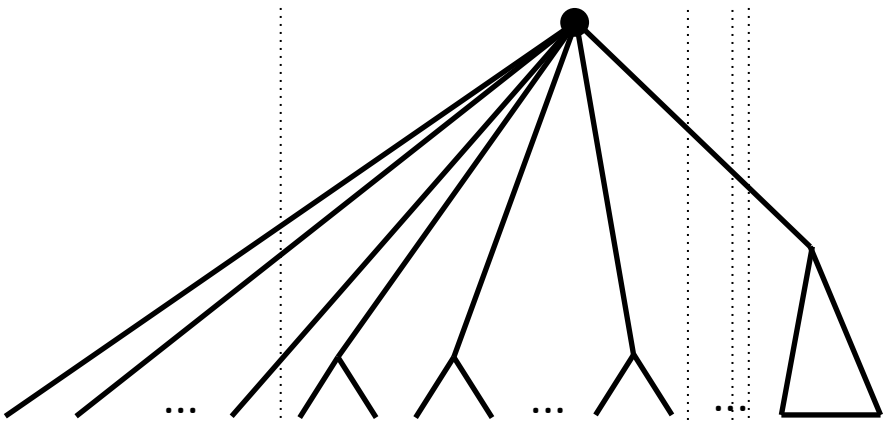
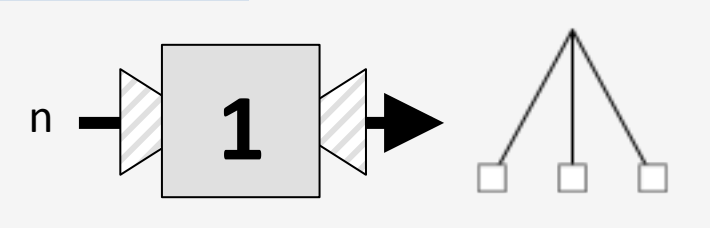


1 2 n-1

$1 \cdot a_1 + 2 \cdot a_2 + \ldots + (n-1) \cdot a_{n-1} = n$

Artificial Data Analysis



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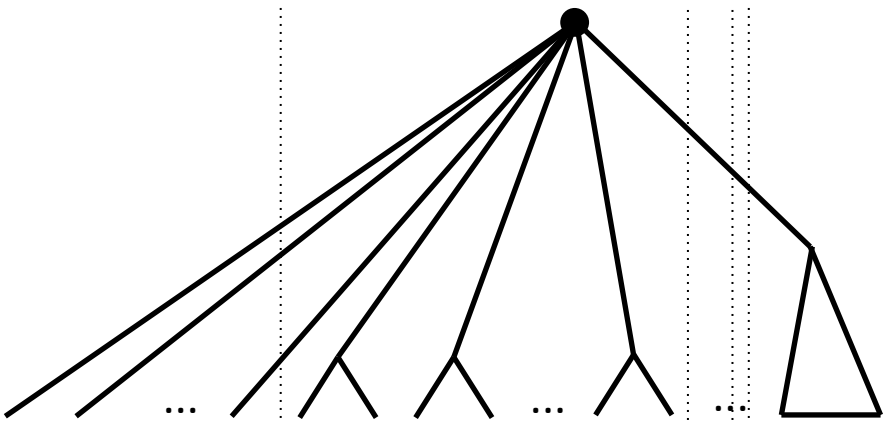


1 2 n-1

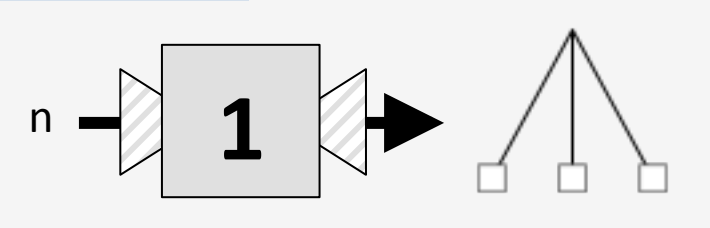
$1 \cdot a_1 + 2 \cdot a_2 + \ldots + (n-1) \cdot a_{n-1} = n$

Partition problem:

given an integer n

Question : Obtain all possible ways to write n as sum of 1 , ... , n-1

Artificial Data Analysis



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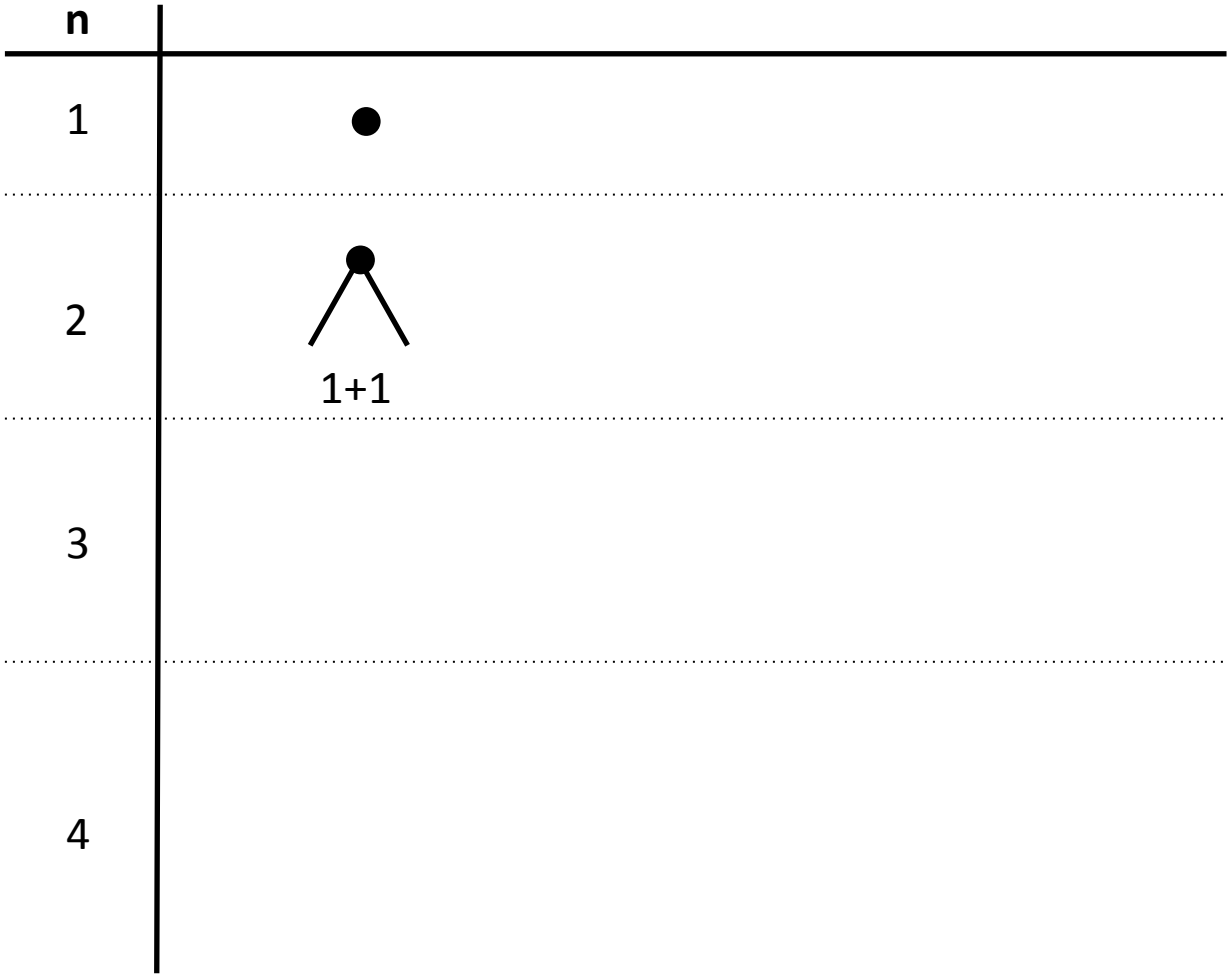
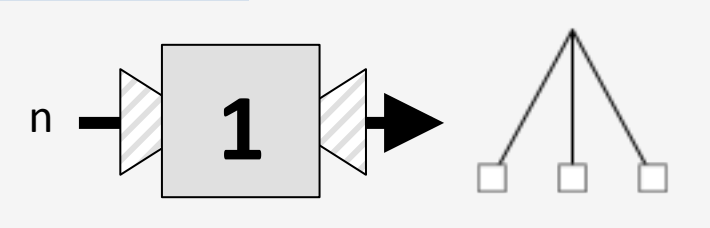
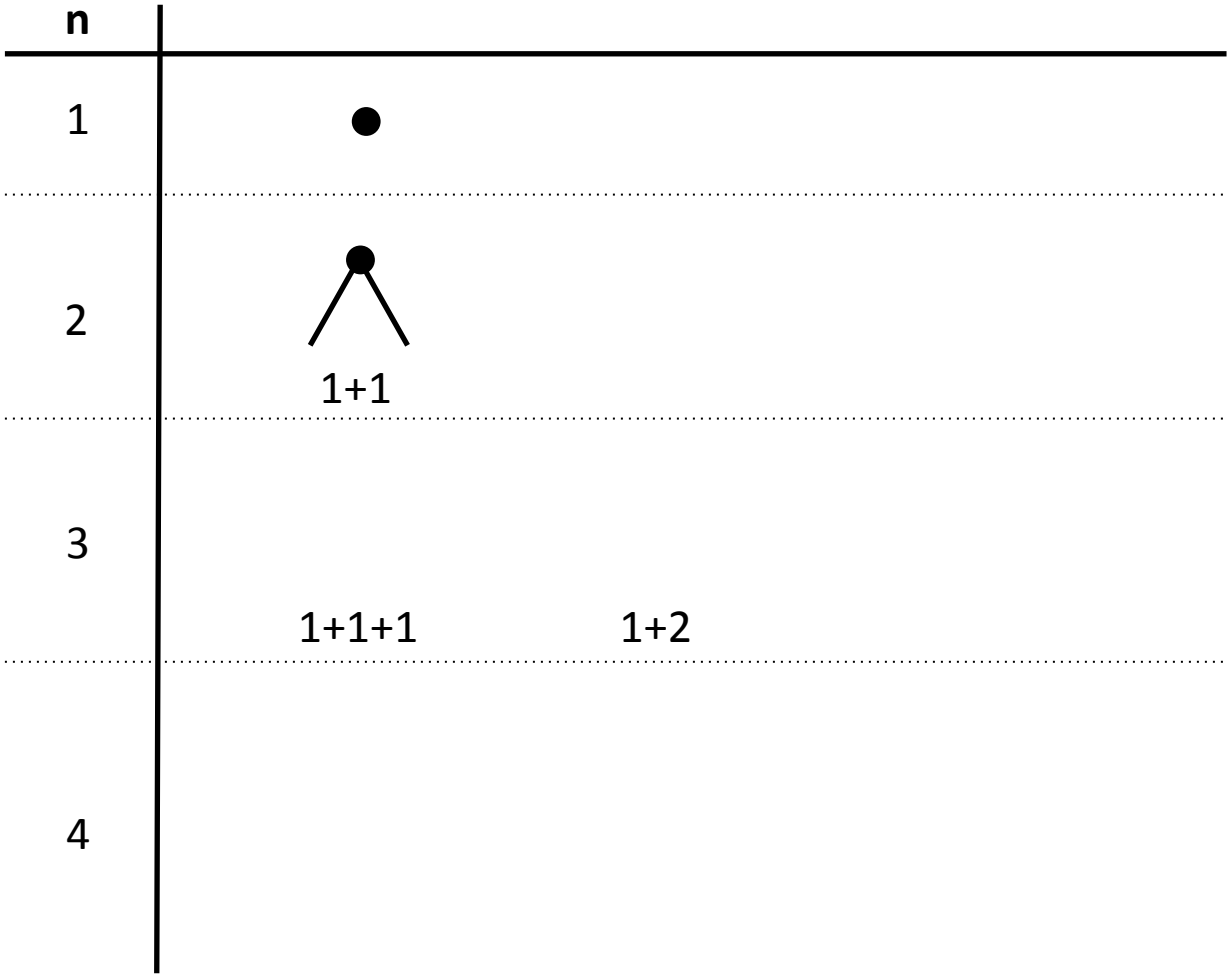


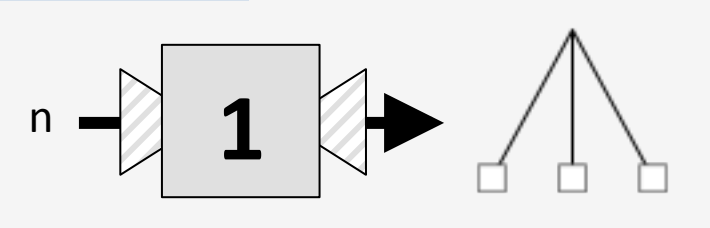
Artificial Data Analysis



1. Generate skeleton trees



Artificial Data Analysis



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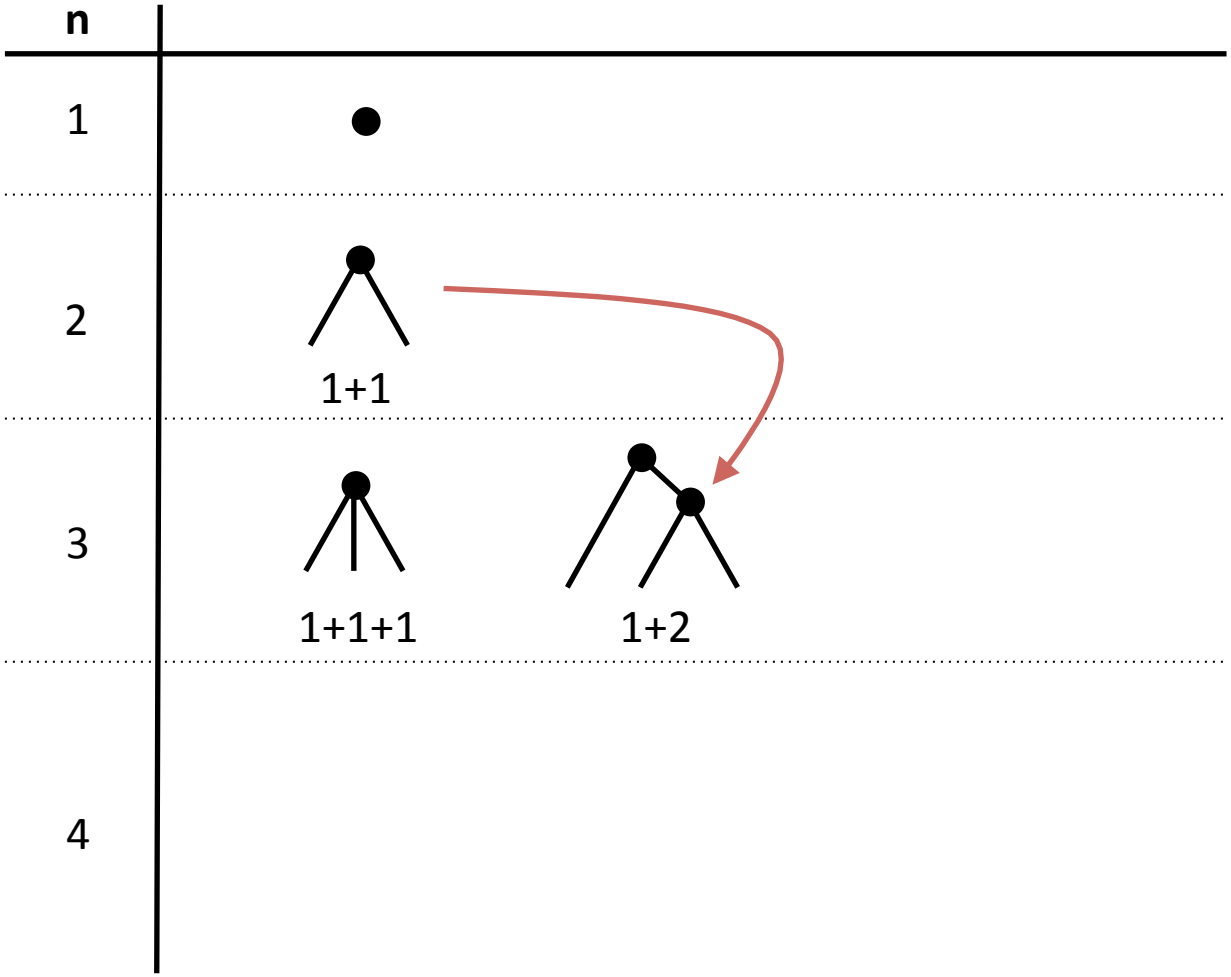

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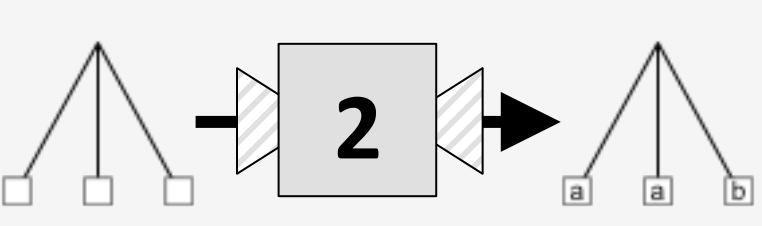
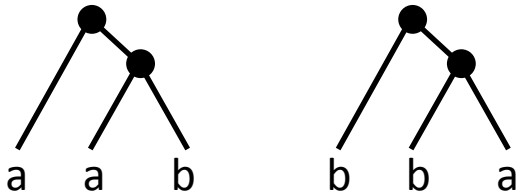


2. Generate labels for skeleton trees

We want:

1. Only one representative over all permutations



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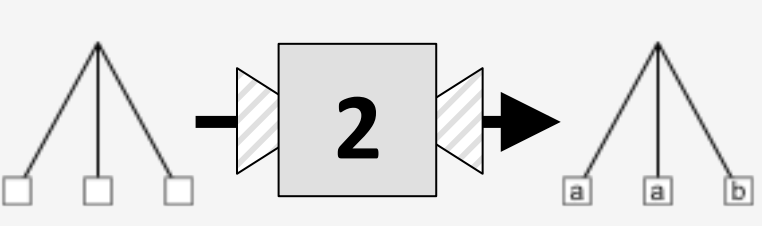

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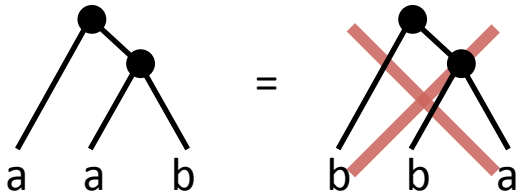
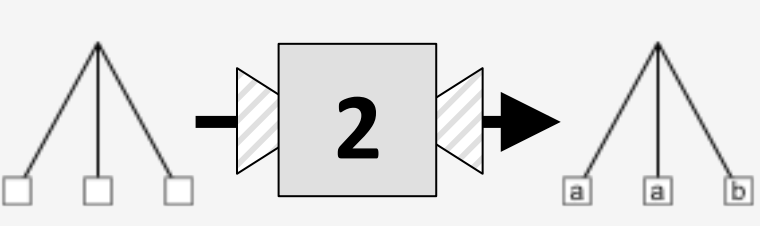


{ a → b , b → a }

Artificial Data Analysis



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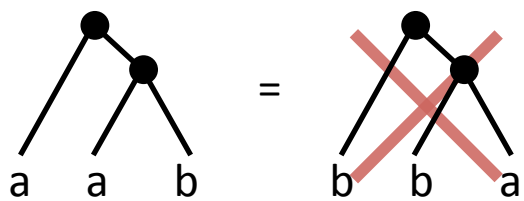
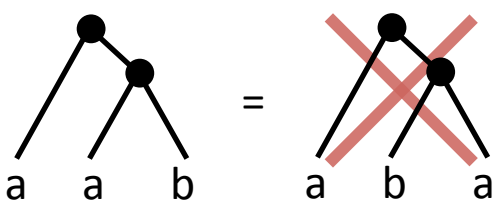


{ a → b , b → a }

2. Only one representative of the isomorphism classes



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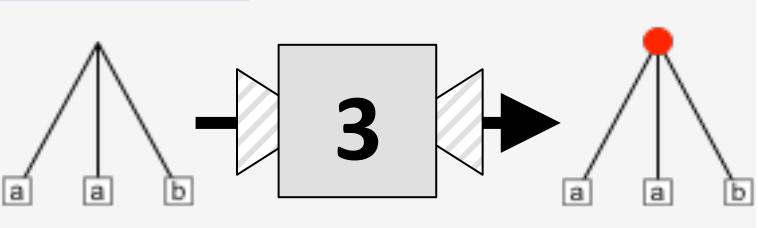
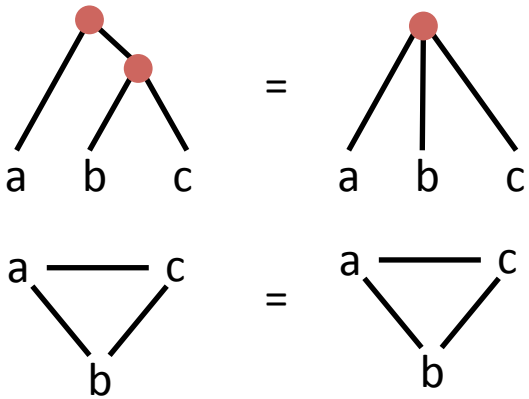
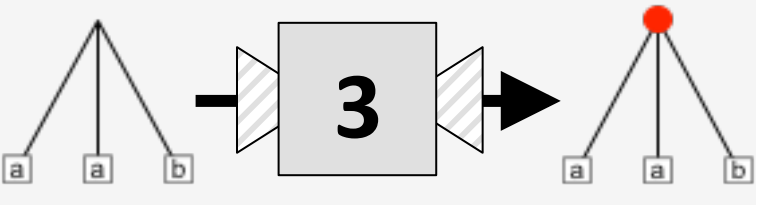


3. Coloring the labeled skeleton trees

We want:

No edge with the same event (color) on both ends





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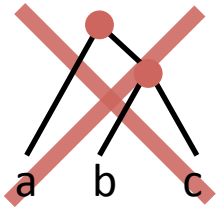
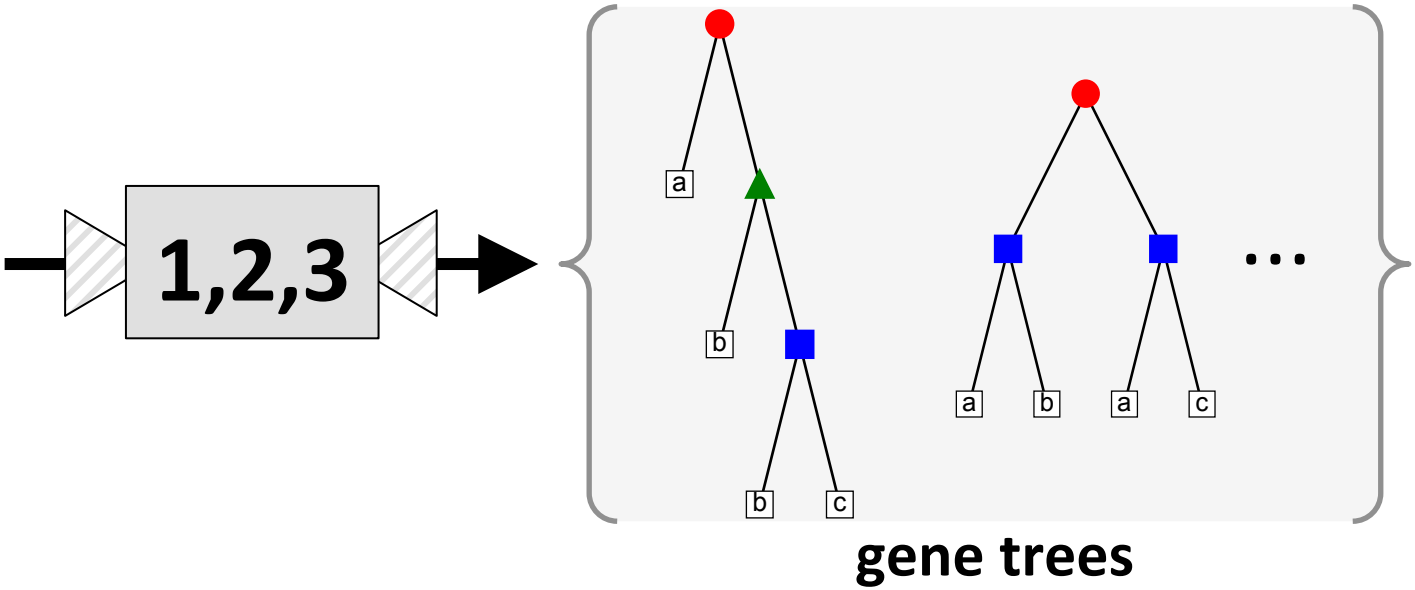


= 3-coloring of the inner nodes

Artificial Data Analysis

Overview

Input:
number of leafs



estimated Orth.-relation $\hat{R}$ + Orth.-relation R

Artificial Data Analysis

Results for n=4 leafs

Total number of gene trees : **324**

Non-cograph cases : **27**

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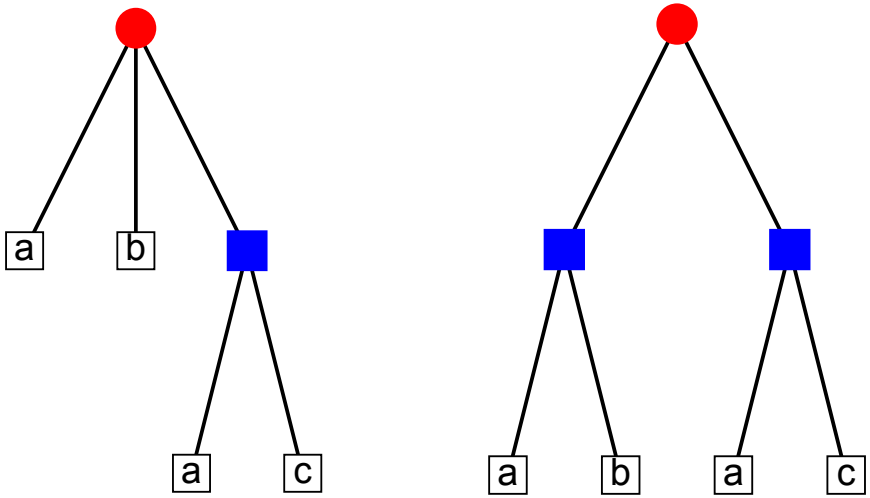


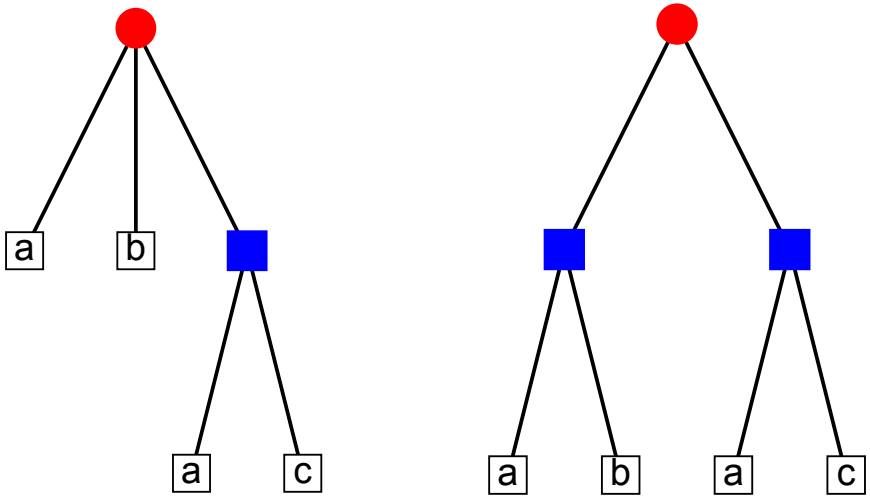
Artificial Data Analysis

Results for n=4 leafs

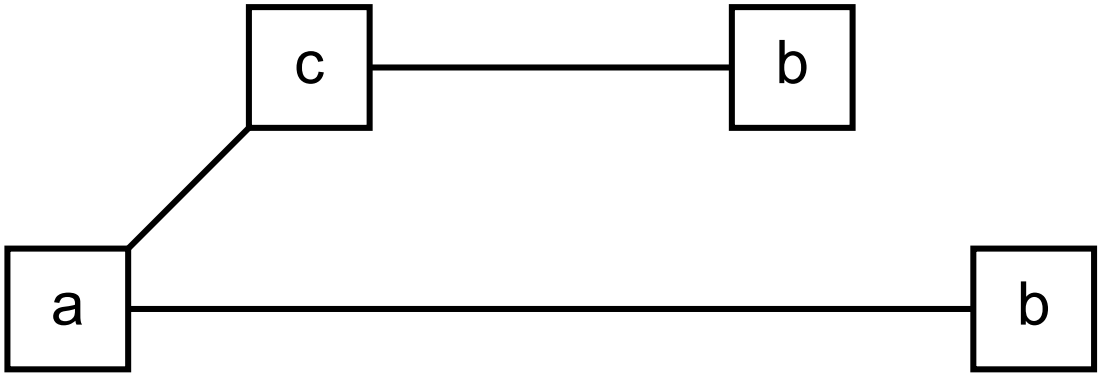
Total number of gene trees : **324**

Non-cograph cases : **27**

Number of problemclasses : **1**



$\widehat{R}$:



problemclass #1

27 generating gene trees

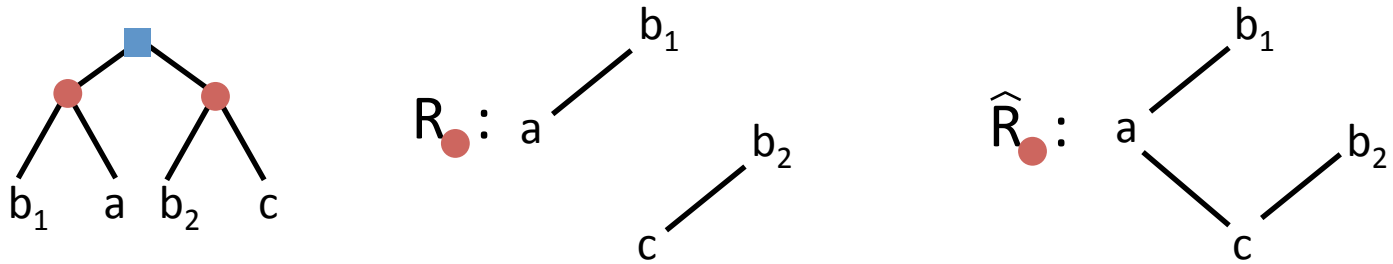
Artificial Data Analysis

Results for n=5 leafs

Total number of gene trees	: **3543**
Non-cograph cases	: **822**
Number of problemclasses	: **9**

Artificial Data Analysis

Question 1 : Is there a preference of right/wrong edges?



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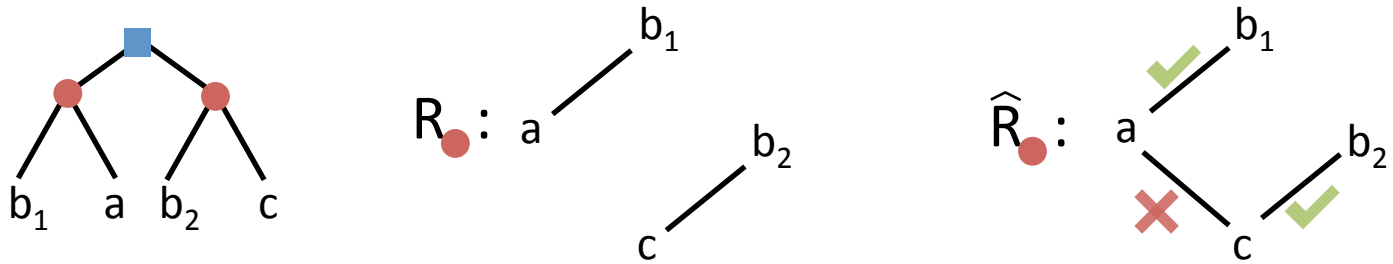

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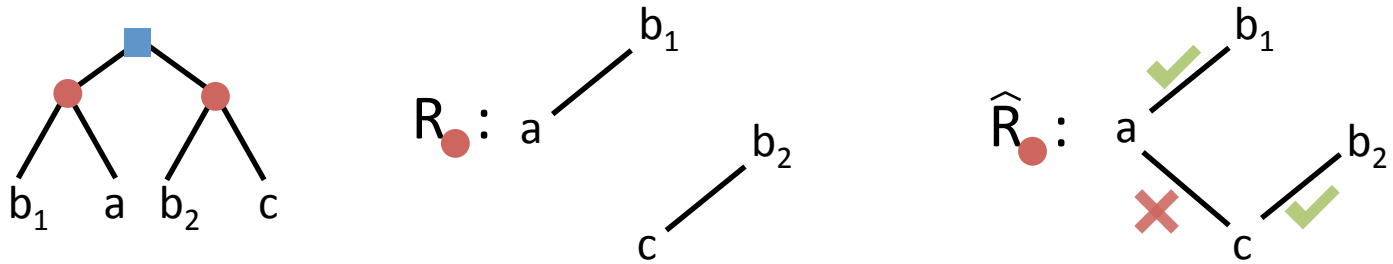
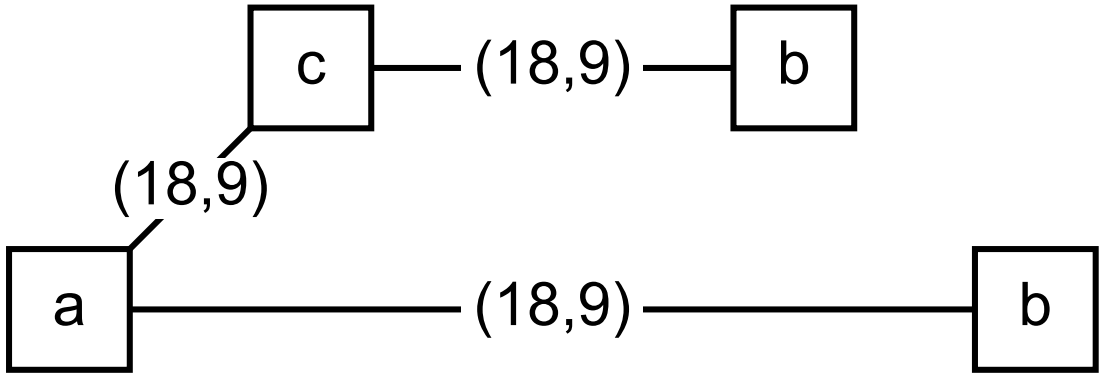


$\hat{R}$:



problemclass #1
27 generating gene trees

Artificial Data Analysis

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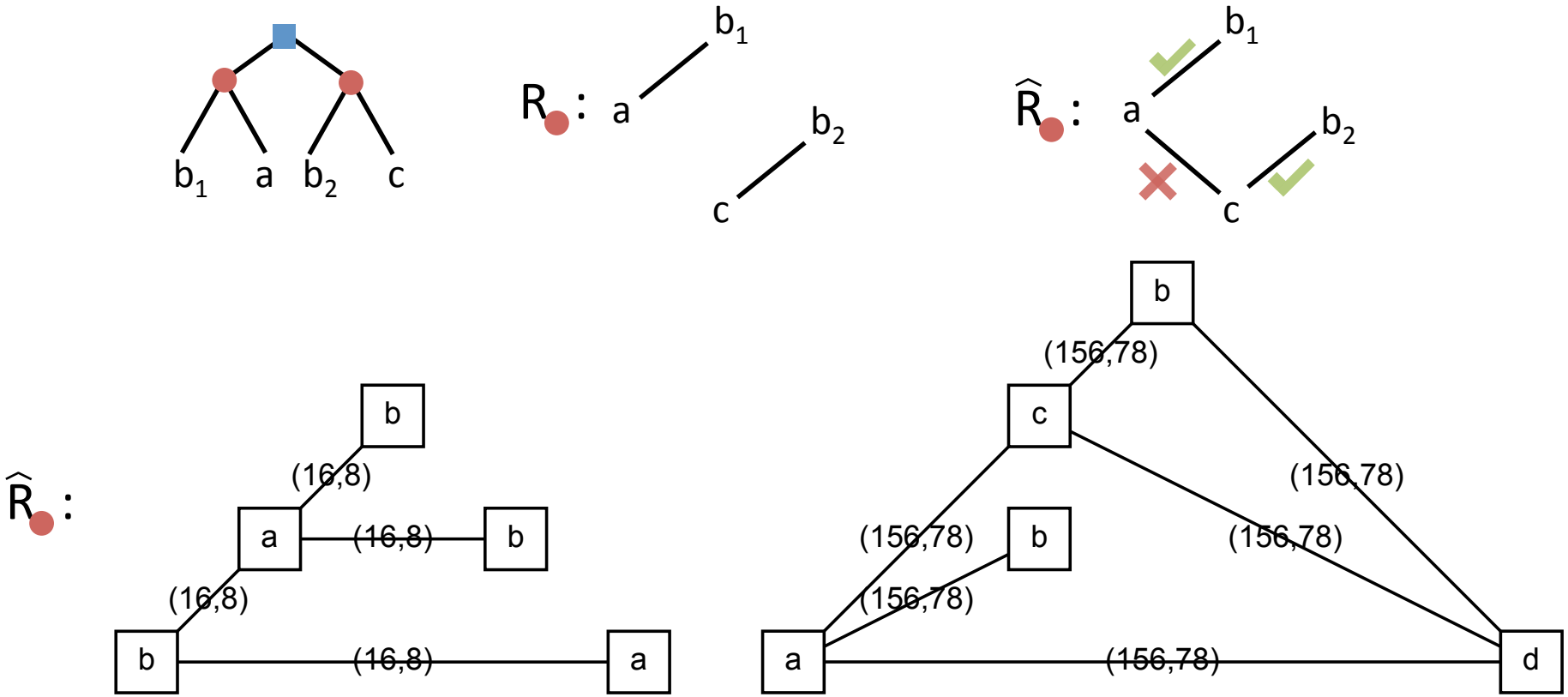
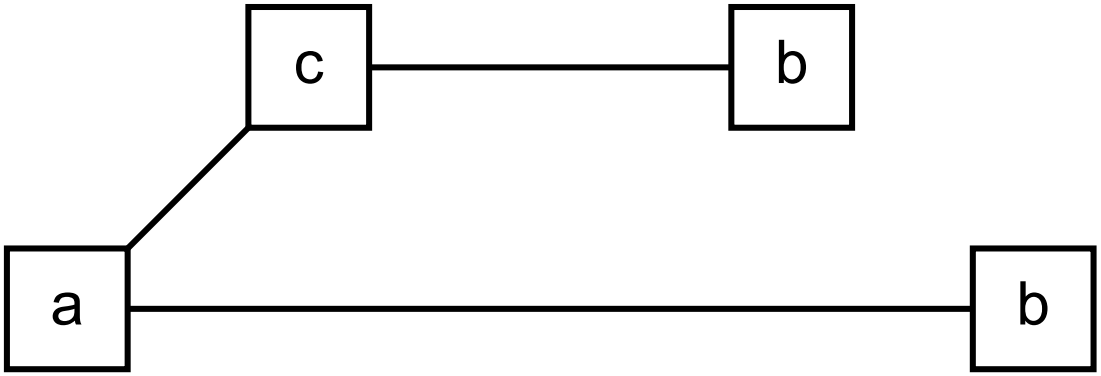


problemclass #3
24 generating gene trees

problemclass #7
234 generating gene trees

Artificial Data Analysis

Question 2 : Can one infer information about the skeleton?



problemclass #1
27 generating gene trees

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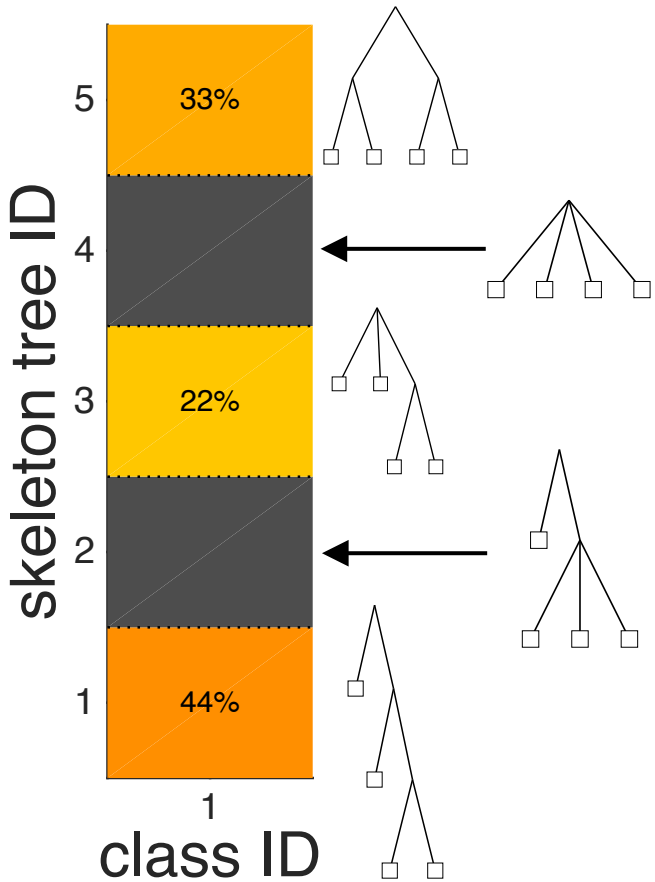
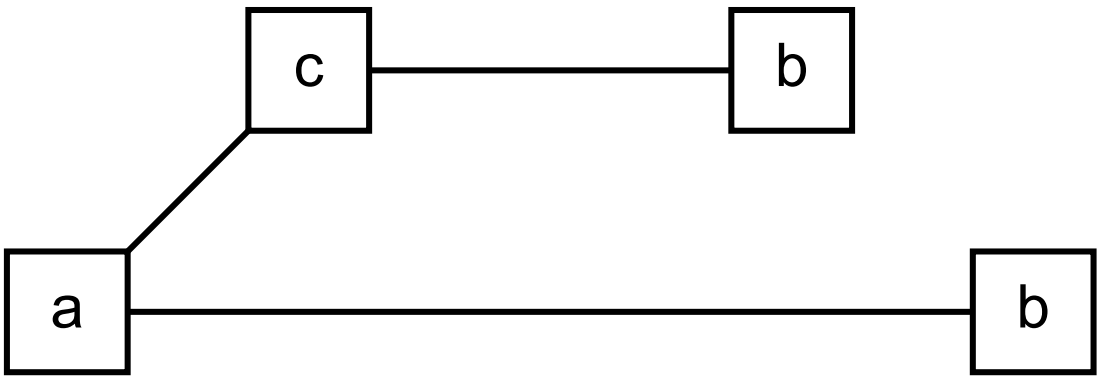




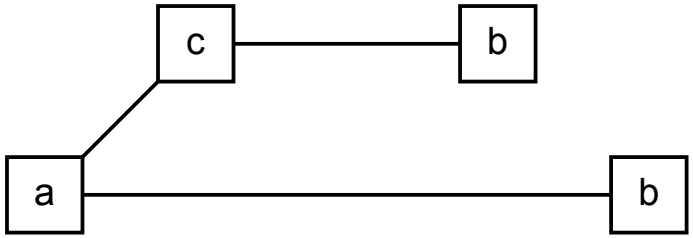
problemclass #1
27 generating gene trees

Artificial Data Analysis

Question 2 : Can one infer information about the skeleton?

Consider $\widehat{R}$ with leaf distance d as additional information.

d(x,y) =
length of the shortest path
between x and y



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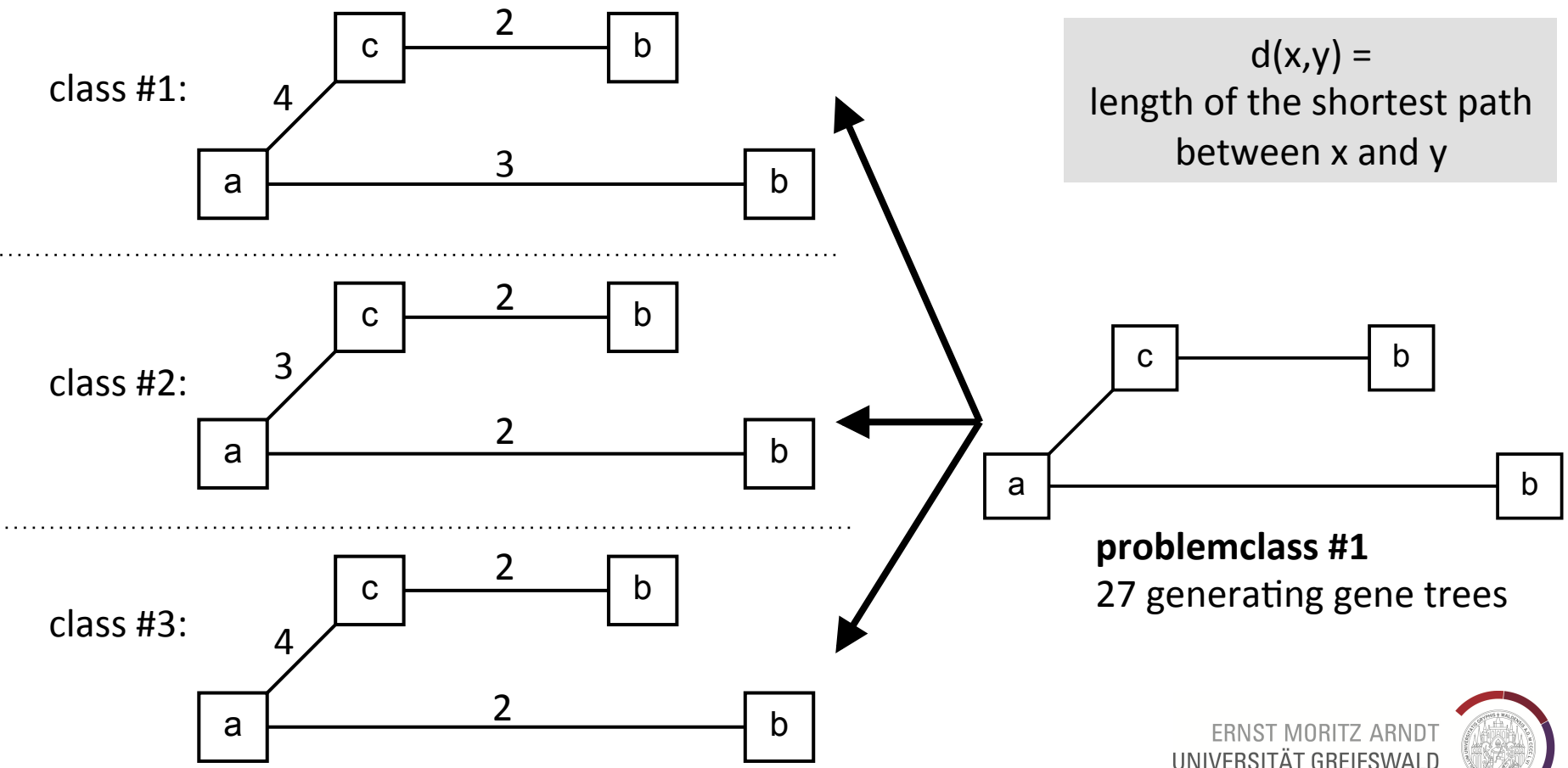

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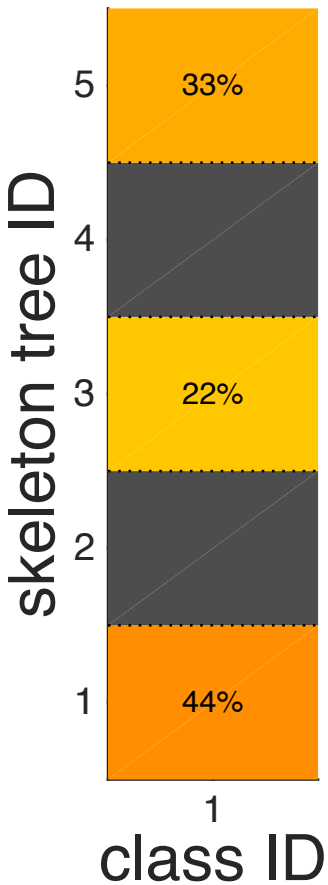
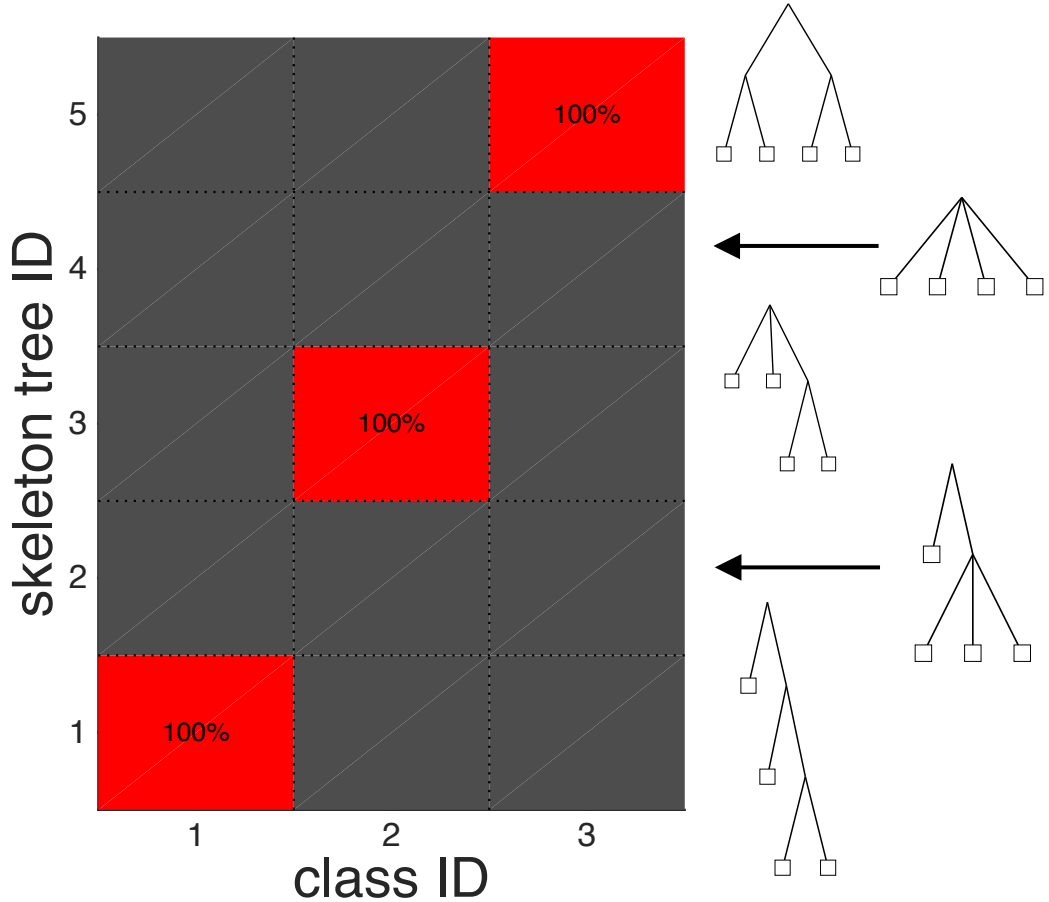


with leaf distance d



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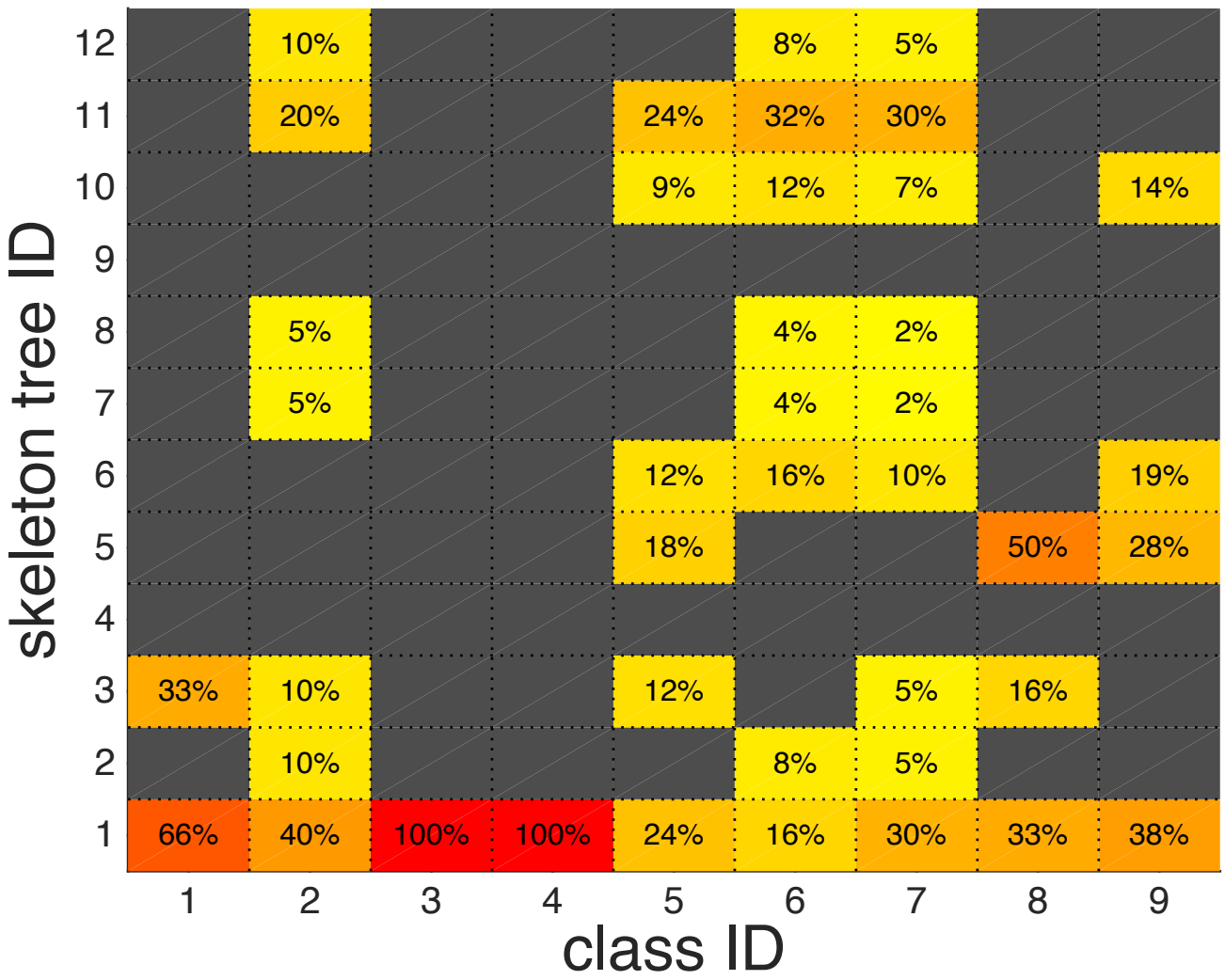
n=5



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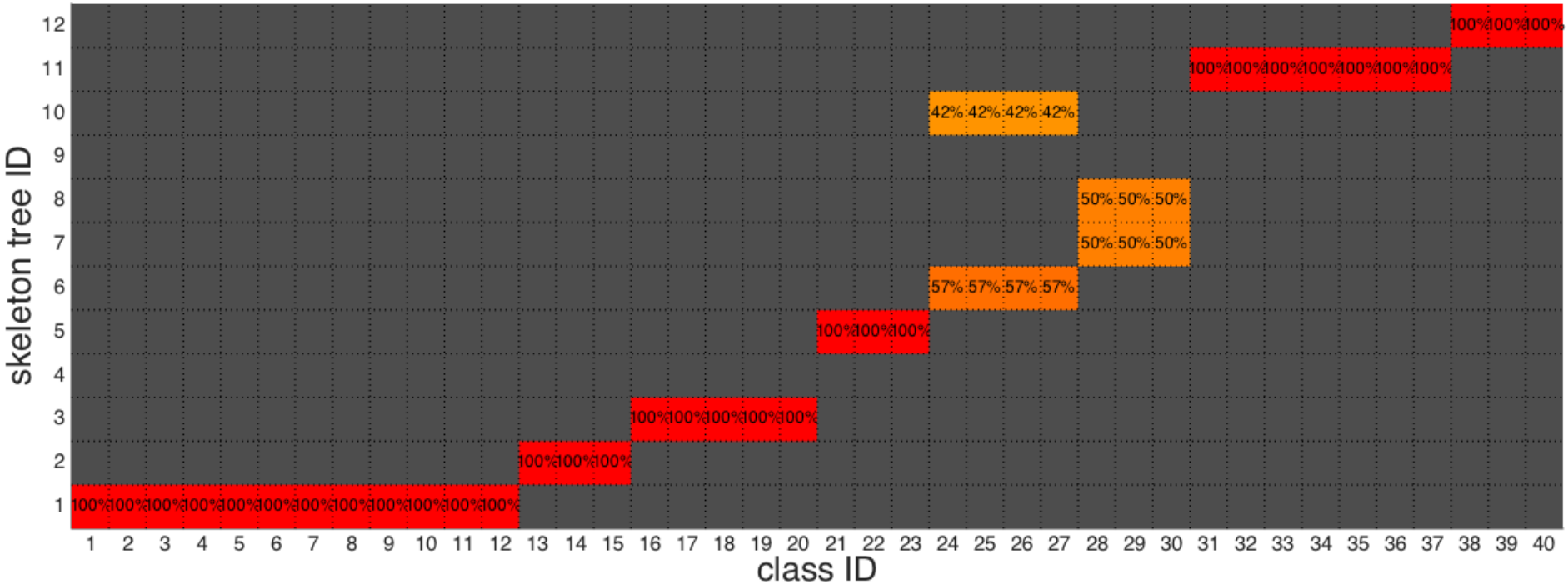

n=5 with leaf-distant d

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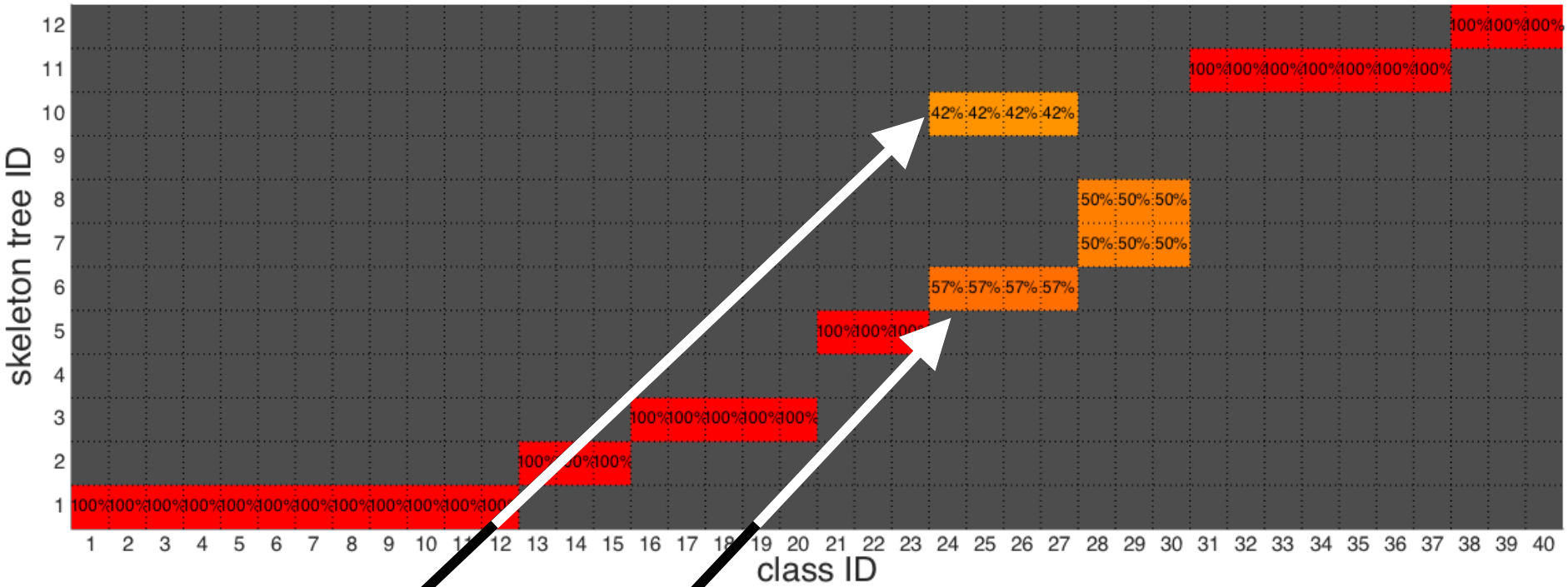

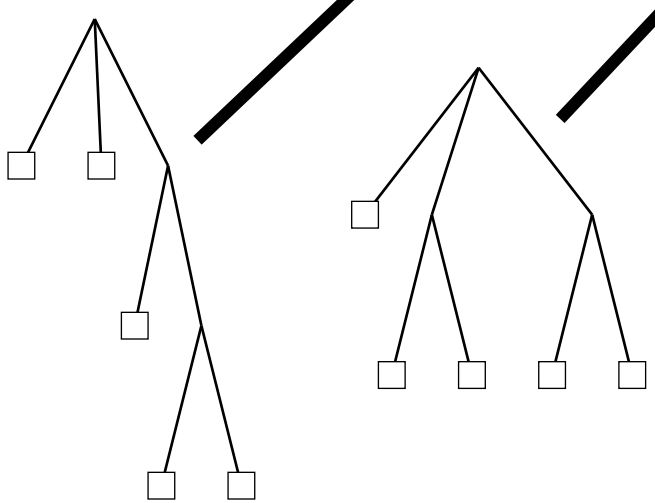

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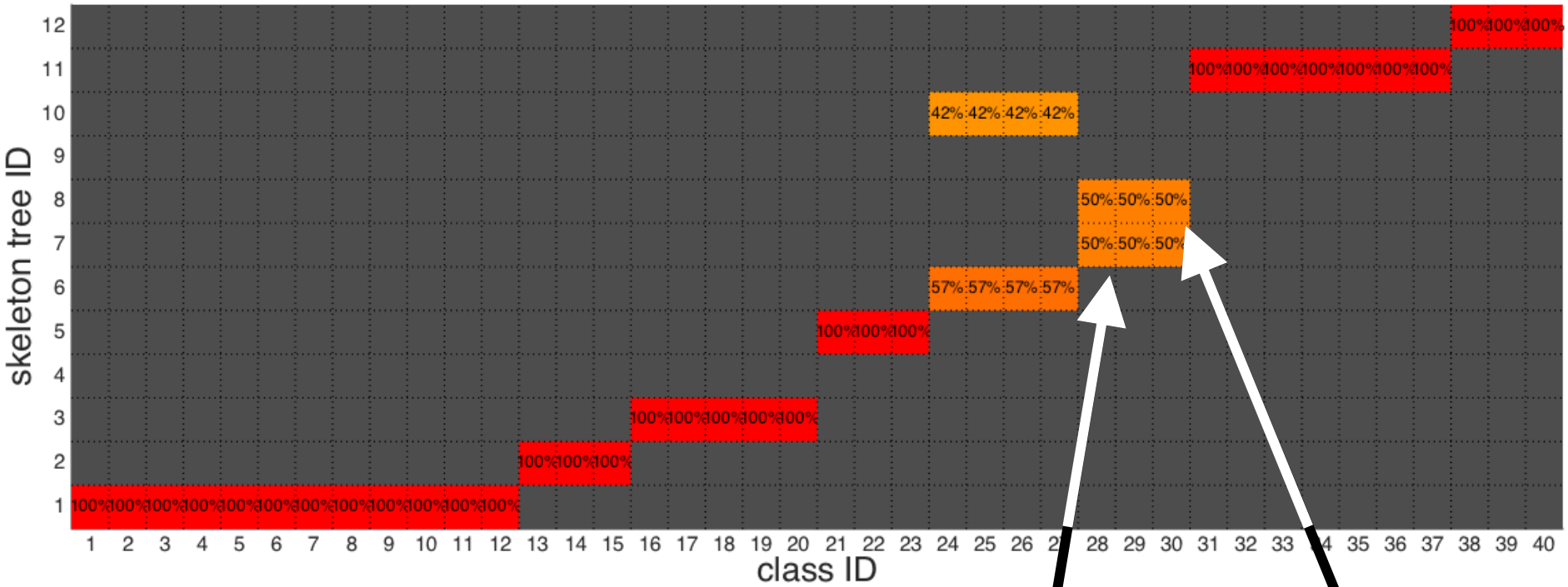

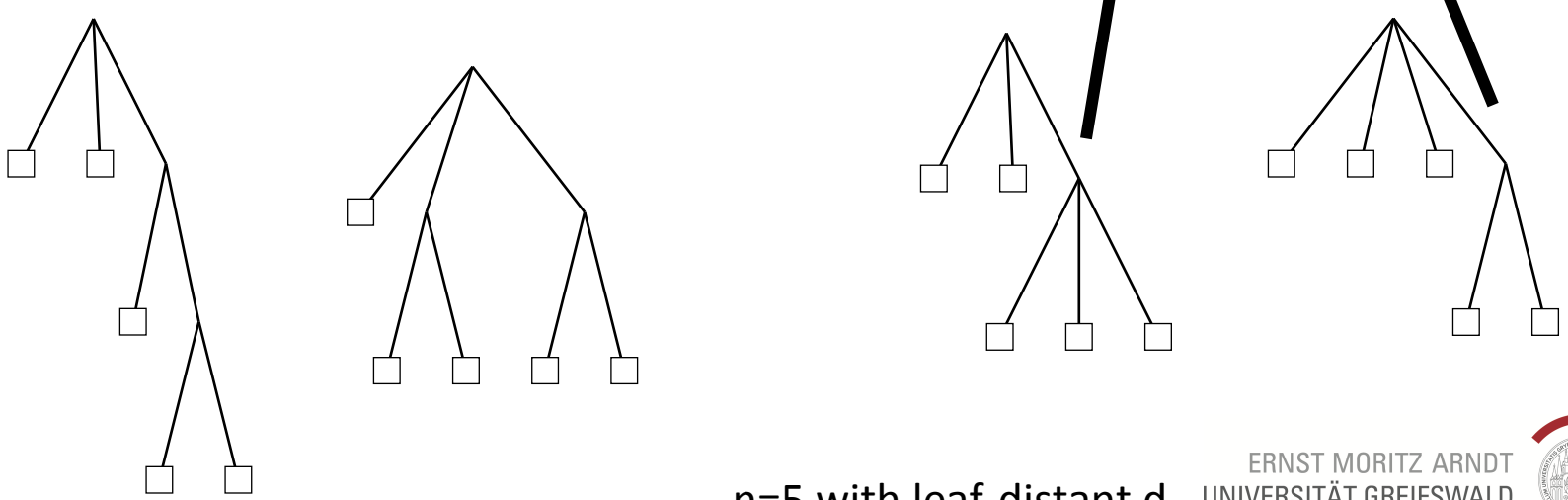

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Summary and Outlook

Summary:

- Generated all possible gene trees for up to 7 leafs
- No information about right or wrong placed edges in the problemclasses
- The leaf distance d gives us the unrooted skeleton tree

For the future:

- Find a more efficent way to generate the leaf-labeling
- Define and investigate more questions

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THANK YOU!

Summary and Outlook

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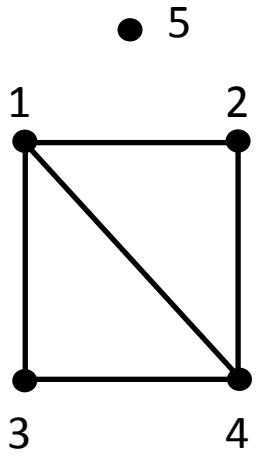
P4-free Graphs / Cographs

A graph is called **P4-free / cograph** if and only if
there exists no <u>induced</u> subgraph on 4 nodes that is a P4 ()

Every cograph is uniquely associated with a **cotree**
= construction instruction to create the cograph



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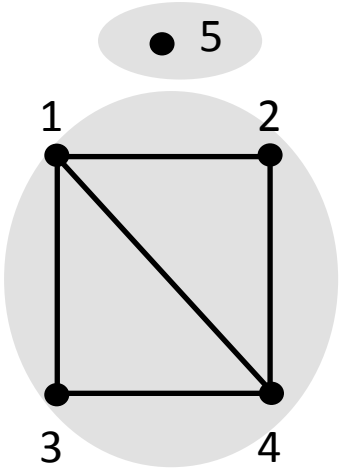

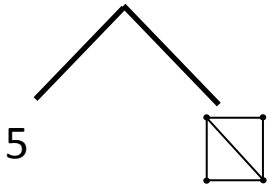

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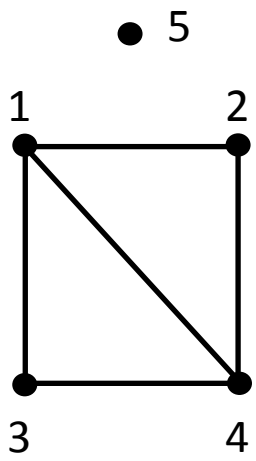

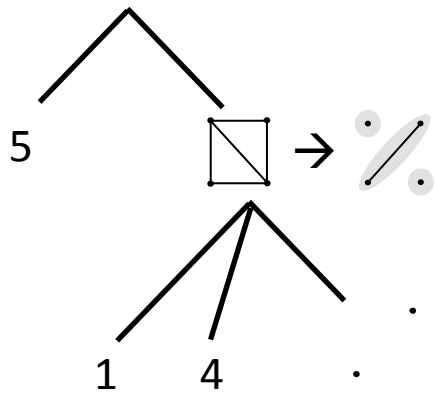

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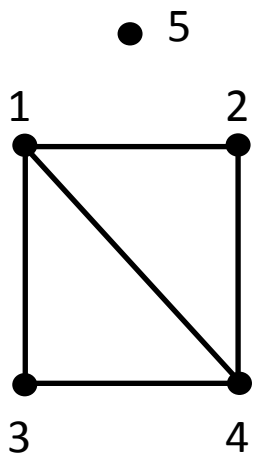

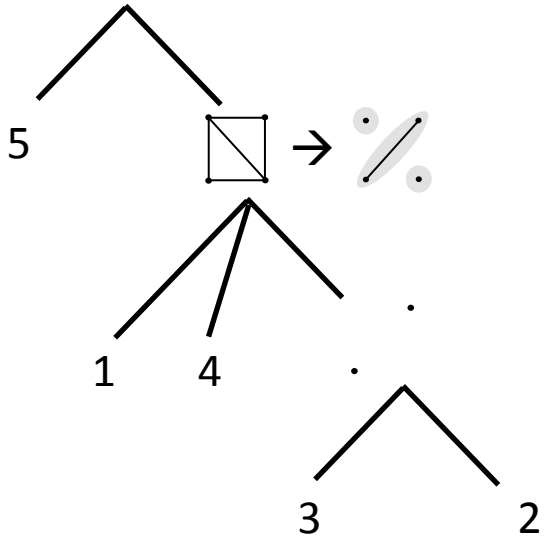

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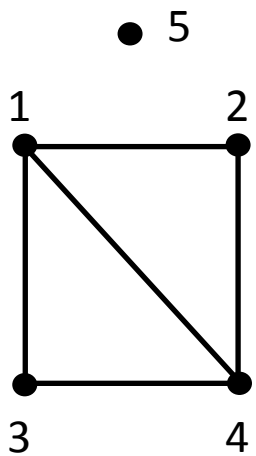

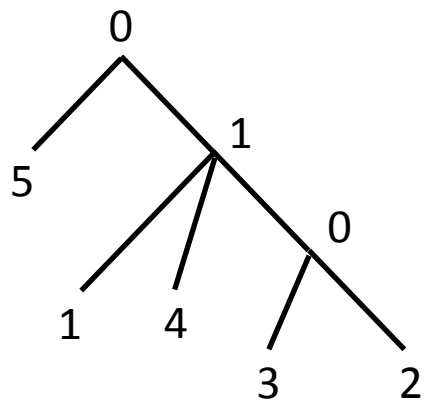

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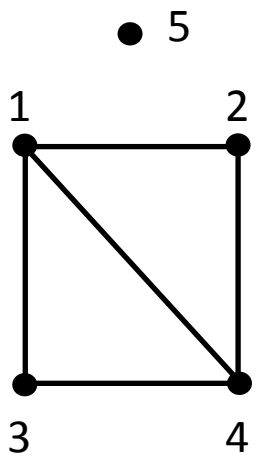

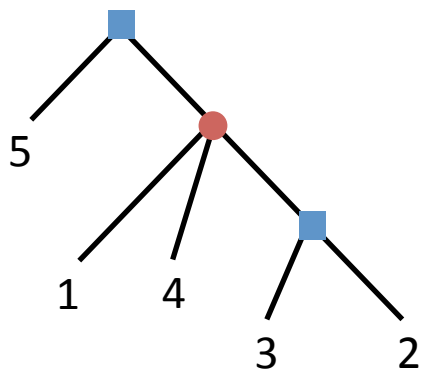

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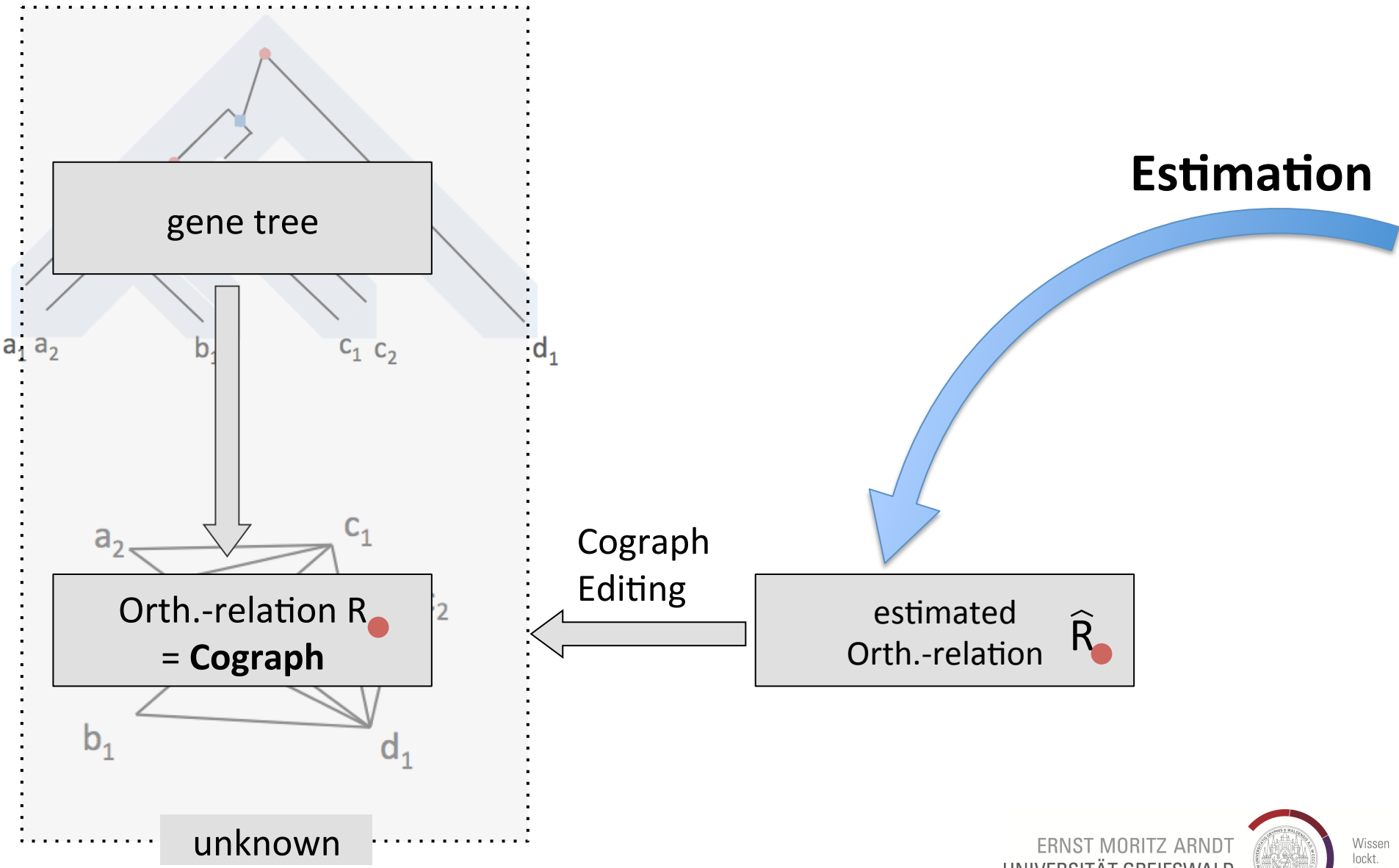

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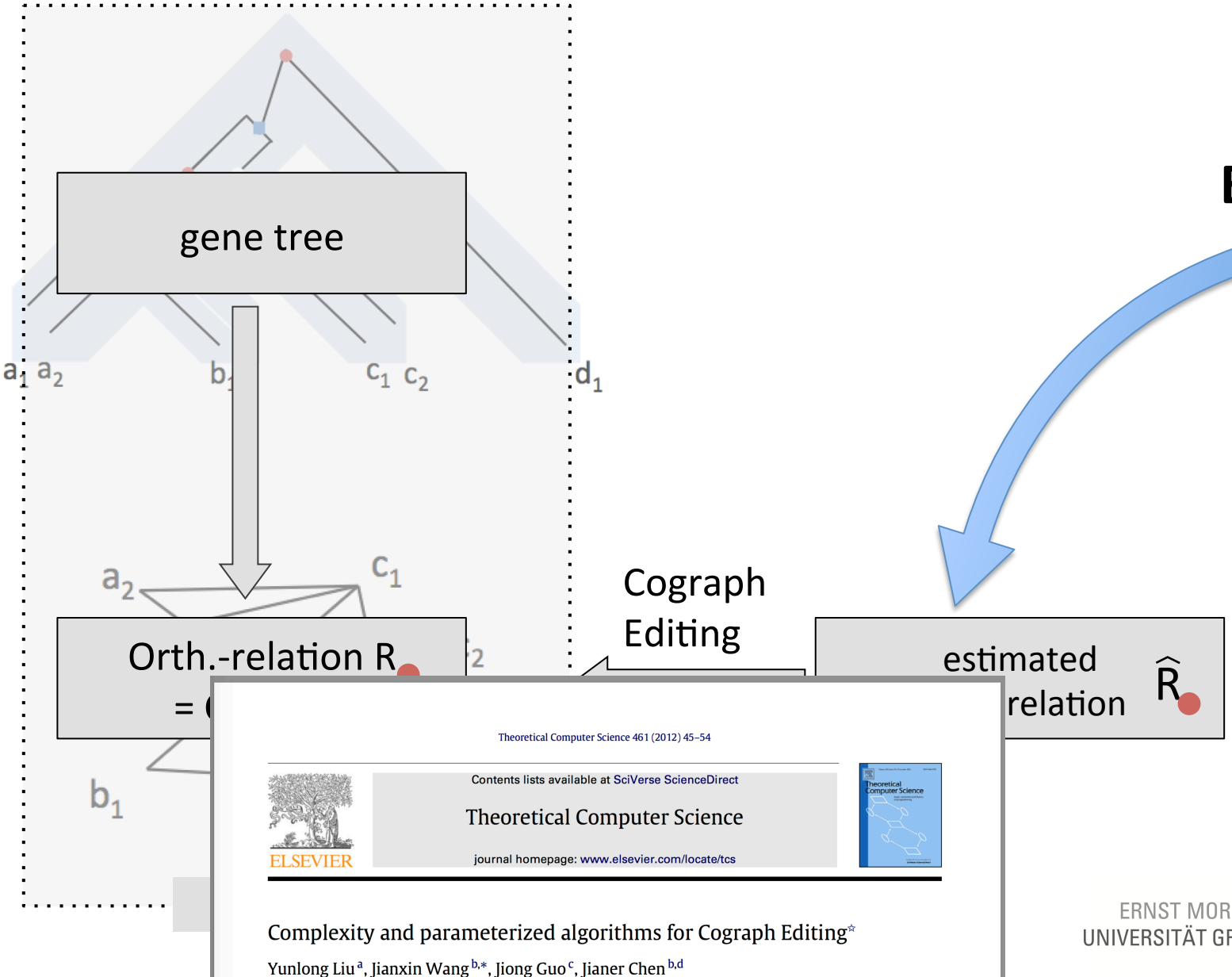

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Complexity and parameterized algorithms for Cograph Editing☆

Yunlong Liu[a], Jianxin Wang[b,*], Jiong Guo[c], Jianer Chen[b,d]

Graph-based orthology inference (e.g. proteinOrtho)

Input : sequence data

Local alignment search
(e.g. BLAST)

Sequence similarity **s(x,y)**

Then two genes x (from species A) and y (from species B) are **estimated orthologs** if:

i. A ≠ B
ii. The sequence similarity **s(x,y)** is greater than the one between
    x to all other genes of B and
    y to all other genes of A

Graph-based orthology inference (e.g. proteinOrtho)

x (from specie A) and y (from specie B) are **estimated orthologs** if:

i. $A \neq B$
ii. The sequence similarity **s(x,y)** is greater than the one between
    x to all other genes of B and
    y to all other genes of A

Simplification: leaf distance d(x,y) of the (unknown) gene tree:

d(x,y) = length of the shortest path between x and y

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$$d \sim 1/s$$

Introduction

Graph-based orthology inference (e.g. proteinOrtho)

x (from specie A) and y (from specie B) are **estimated orthologs** if:

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Simplification: leaf distance d(x,y) of the (unknown) gene tree:

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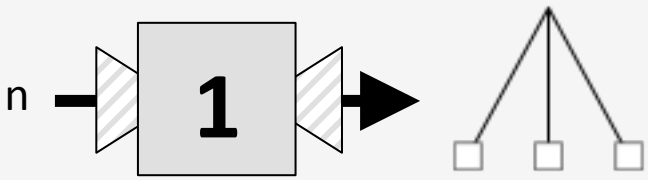
$d \sim 1/s$

→ **estimated orthologs** if:

i. A ≠ B
ii. d(x,y) is <u>smaller</u> than the distance between
    x to all other genes of B and
    y to all other genes of A

→ $\hat{R}$

Artificial Data Analysis



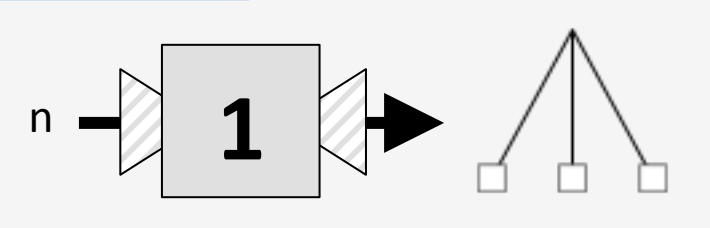
1. Generate skeleton trees

n = 3

$1 \cdot 3 \quad + \quad 2 \cdot 0 \quad = 3$

$1 \cdot 1 \quad + \quad 2 \cdot 1 \quad = 3$

Artificial Data Analysis



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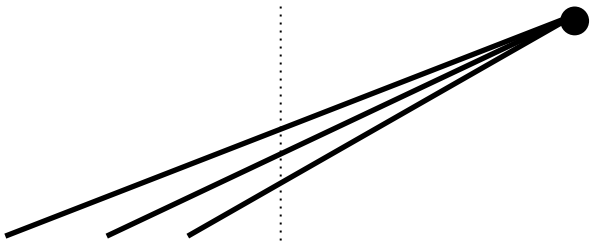
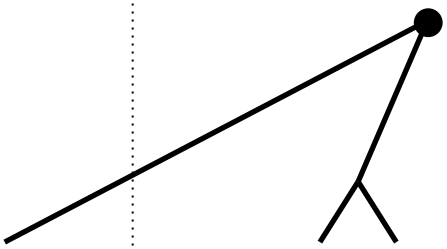
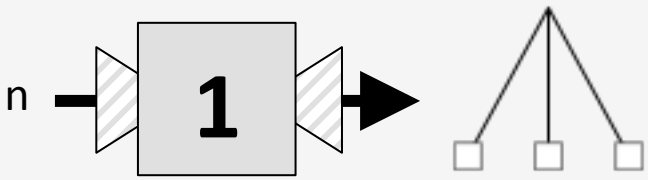


$1 \cdot 3 \quad + \quad 2 \cdot 0 \quad = 3$



$1 \cdot 1 \quad + \quad 2 \cdot 1 \quad = 3$

Artificial Data Analysis



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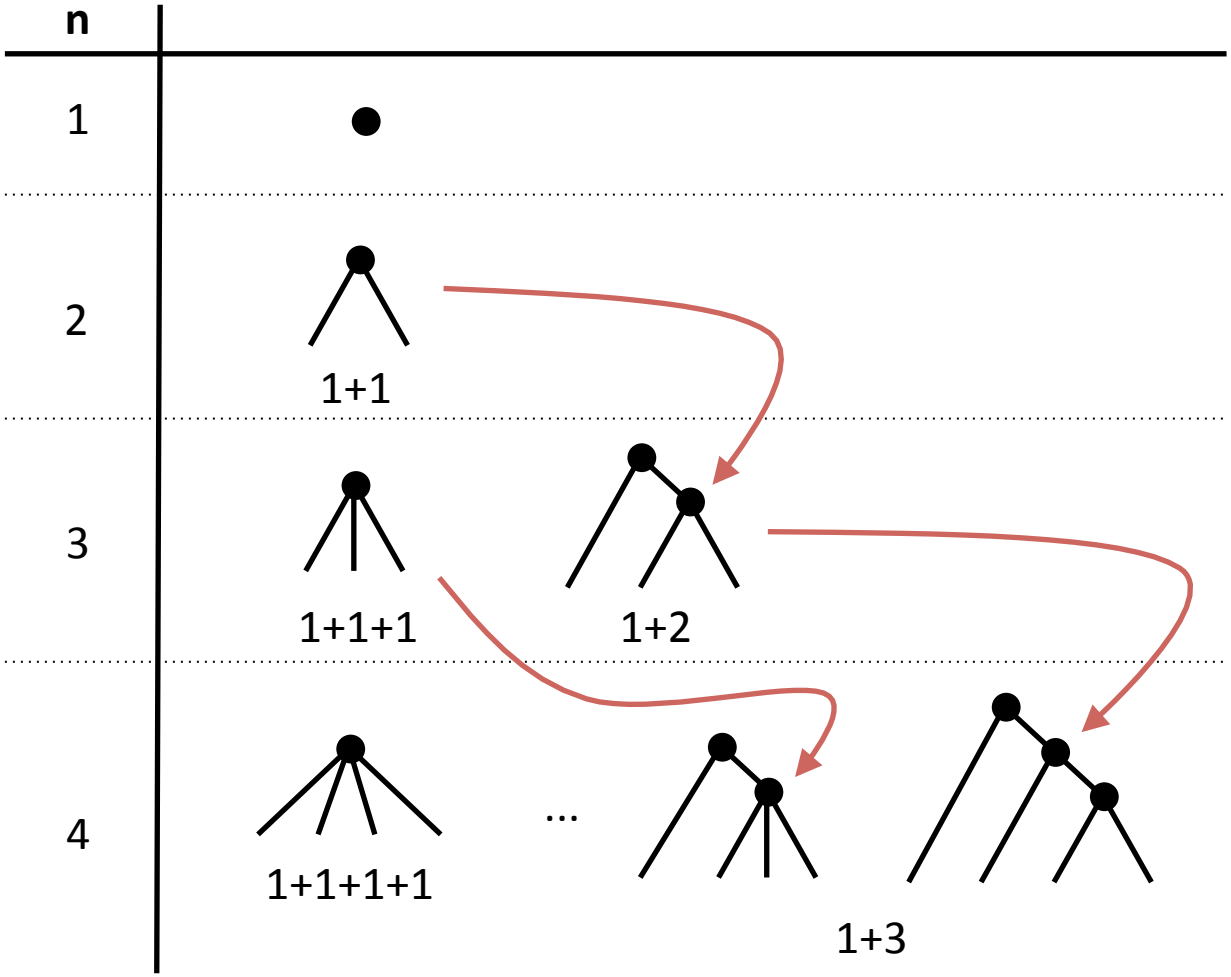
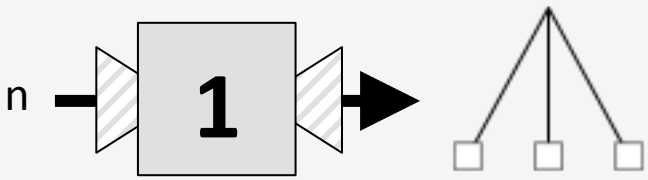


Artificial Data Analysis



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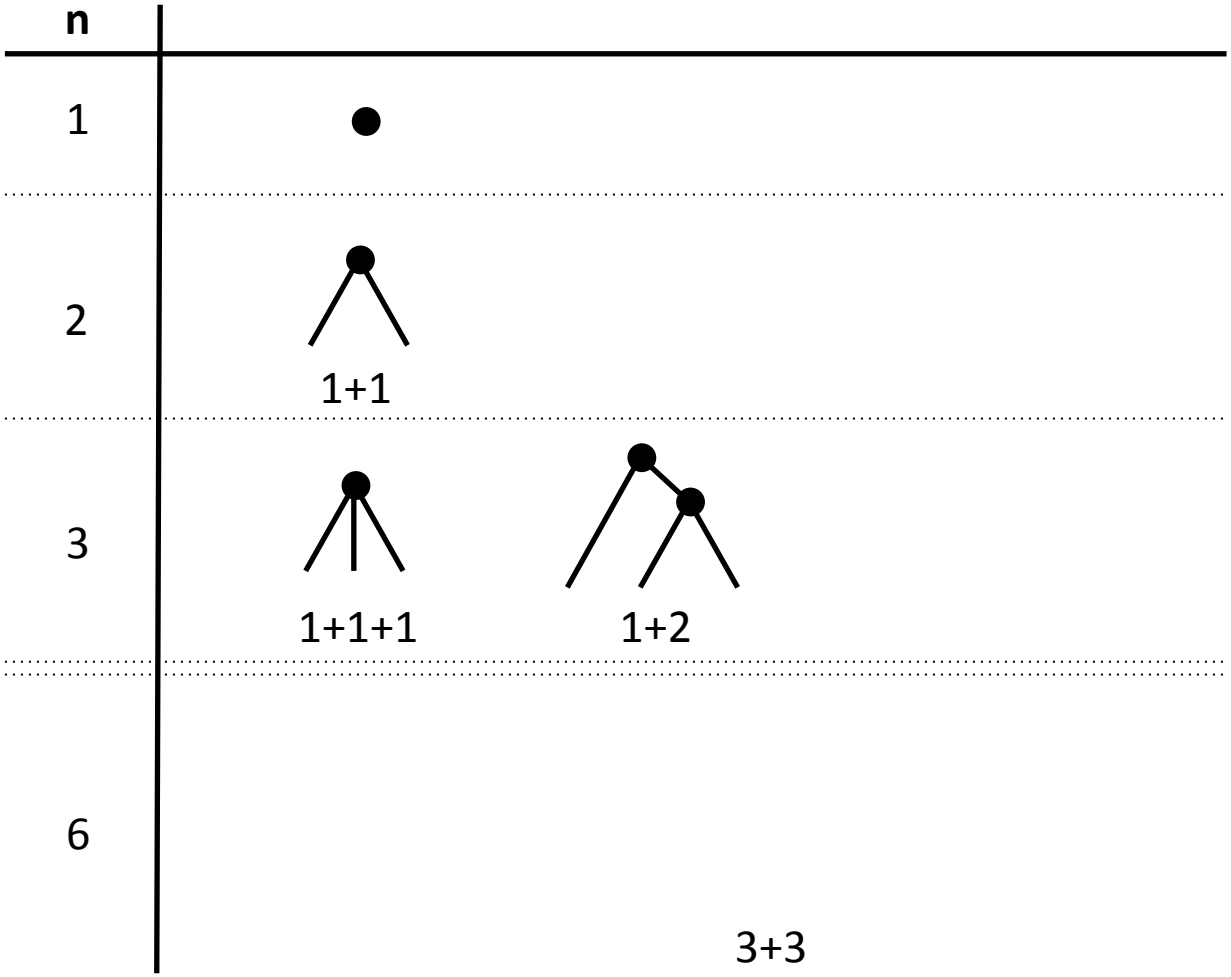
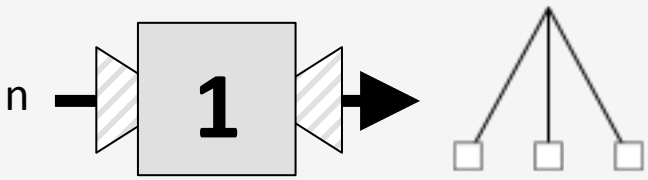


Artificial Data Analysis



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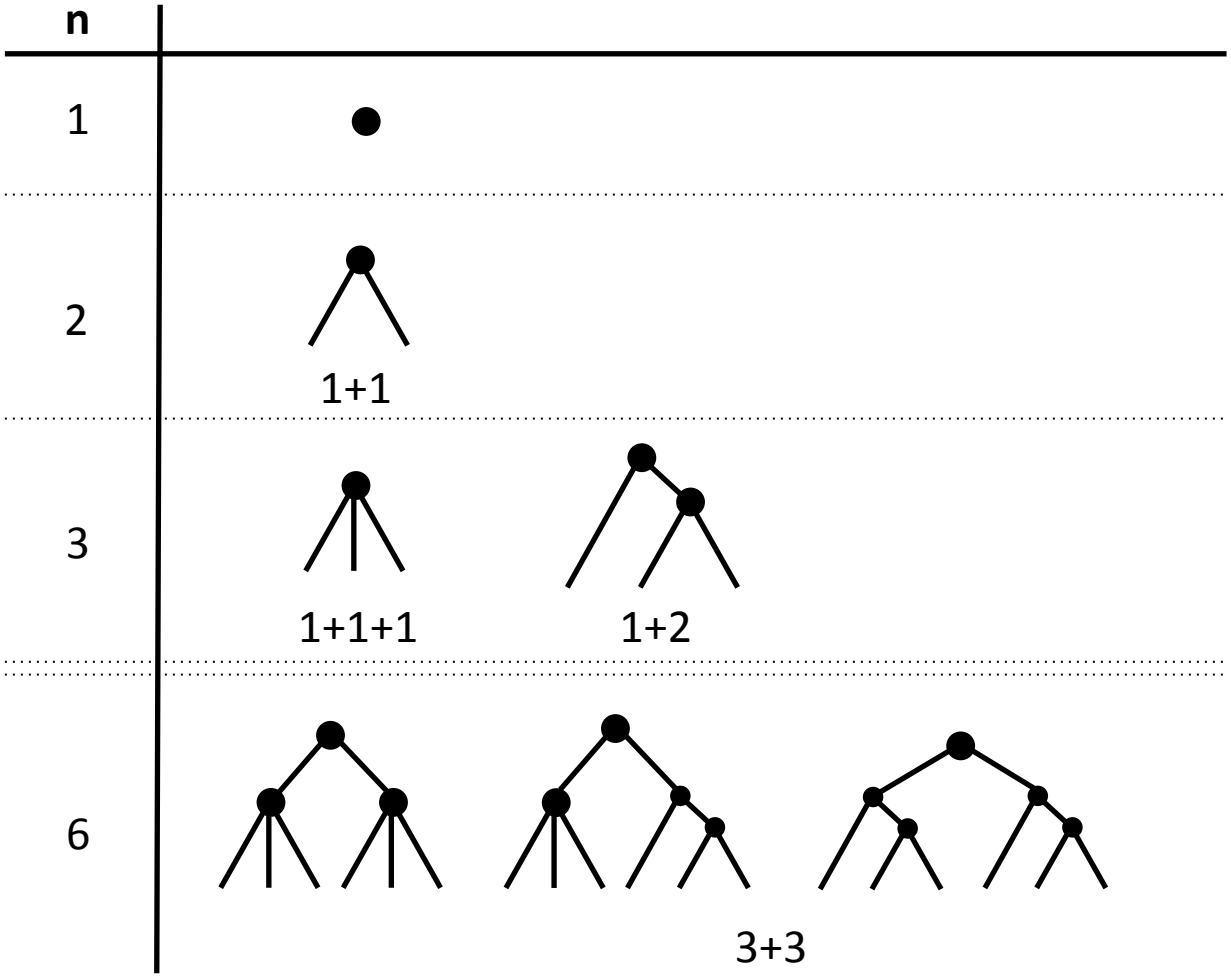
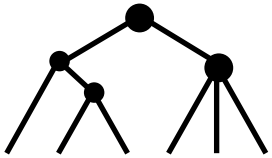
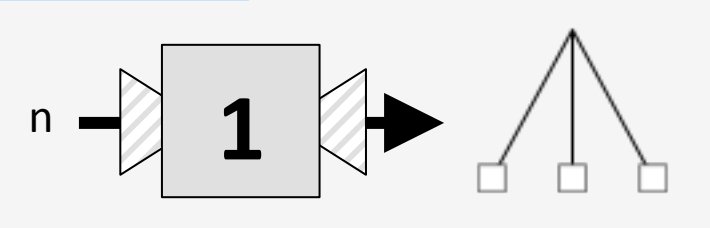


we do not want:



Artificial Data Analysis

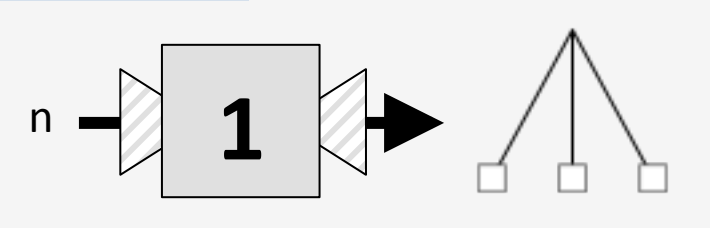


1. Generate skeleton trees

→ Choosing a_i **unordered** elements of the skeleton trees with i leafs **with** replacement

$$\binom{numST_i + (a_i - 1)}{a_i}$$

Artificial Data Analysis

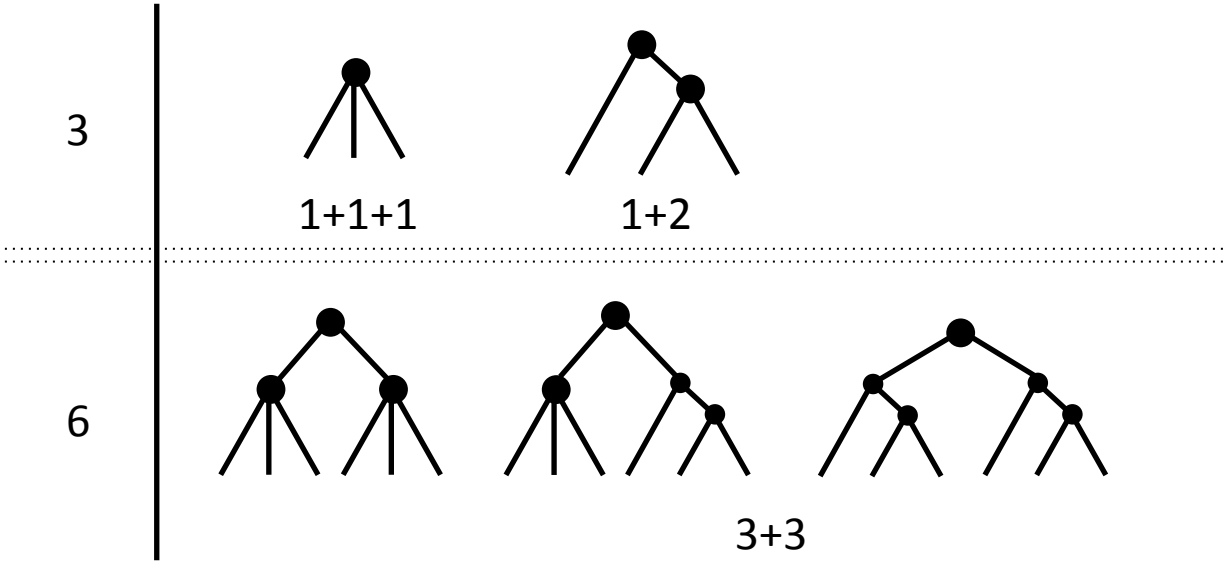


1. Generate skeleton trees

→ Choosing a_i **unordered** elements of the skeleton trees with i leafs **with** replacement

→ Choosing <u>2</u> **unordered** elements of the skeleton trees with <u>3</u> leafs **with** replacement

$$\binom{numST_i + (a_i - 1)}{a_i} = 3$$



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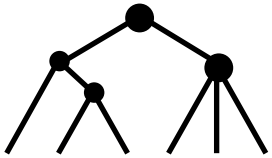

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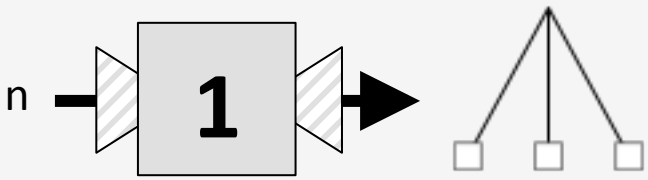
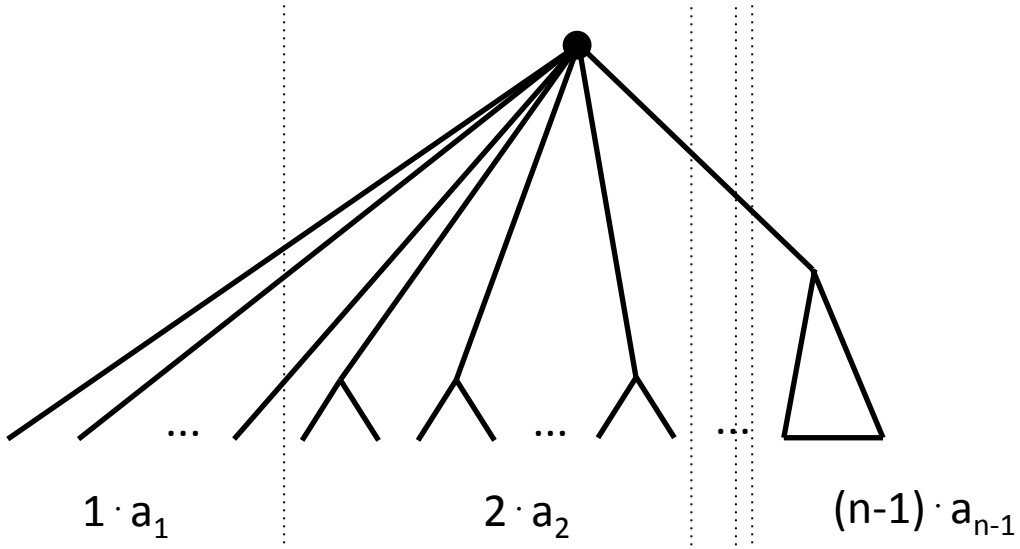


1. Generate skeleton trees

$$numST_n = \sum_{(a_1,a_2,\ldots,a_{n-1})\in P^n} \prod_{i=1}^{n-1} \binom{numST_i + (a_i - 1)}{a_i}$$



Artificial Data Analysis

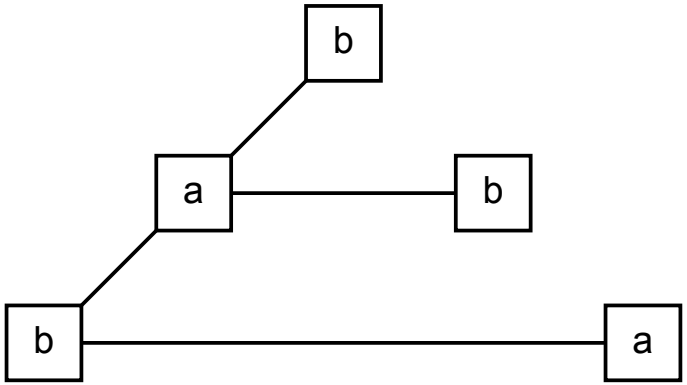
Results for n=5 leafs

Total number of gene trees : **3543**

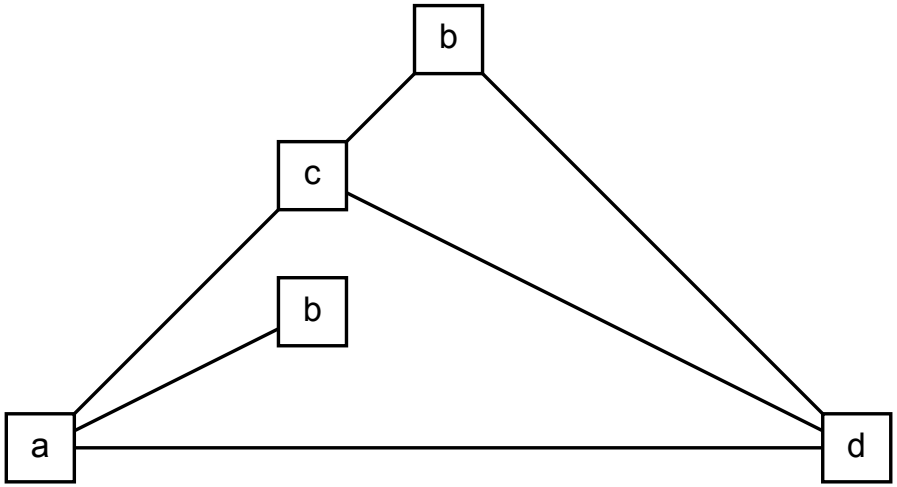
Non-cograph cases : **822**

Number of problemclasses : **9**

$\hat{R}_{\bullet}$:



problemclass #3
24 generating gene trees



problemclass #7
234 generating gene trees

Question 2 : Can one infer information about the skeleton?

Theorem:

Given the leaf distance d_1 of the skeleton T_1 and d_2 of T_2 then:

$$d_1 = d_2 \quad \Rightarrow \quad \text{Unroot}(\, T_1 \,) \sim \text{Unroot}\,(\, T_2 \,)$$

Unroot(T) : unrooted version of the tree T