RECONCILIATION BETWEEN GENE TREES AND SPECIES TREES IN THE PHYLOGENOMICS ERA

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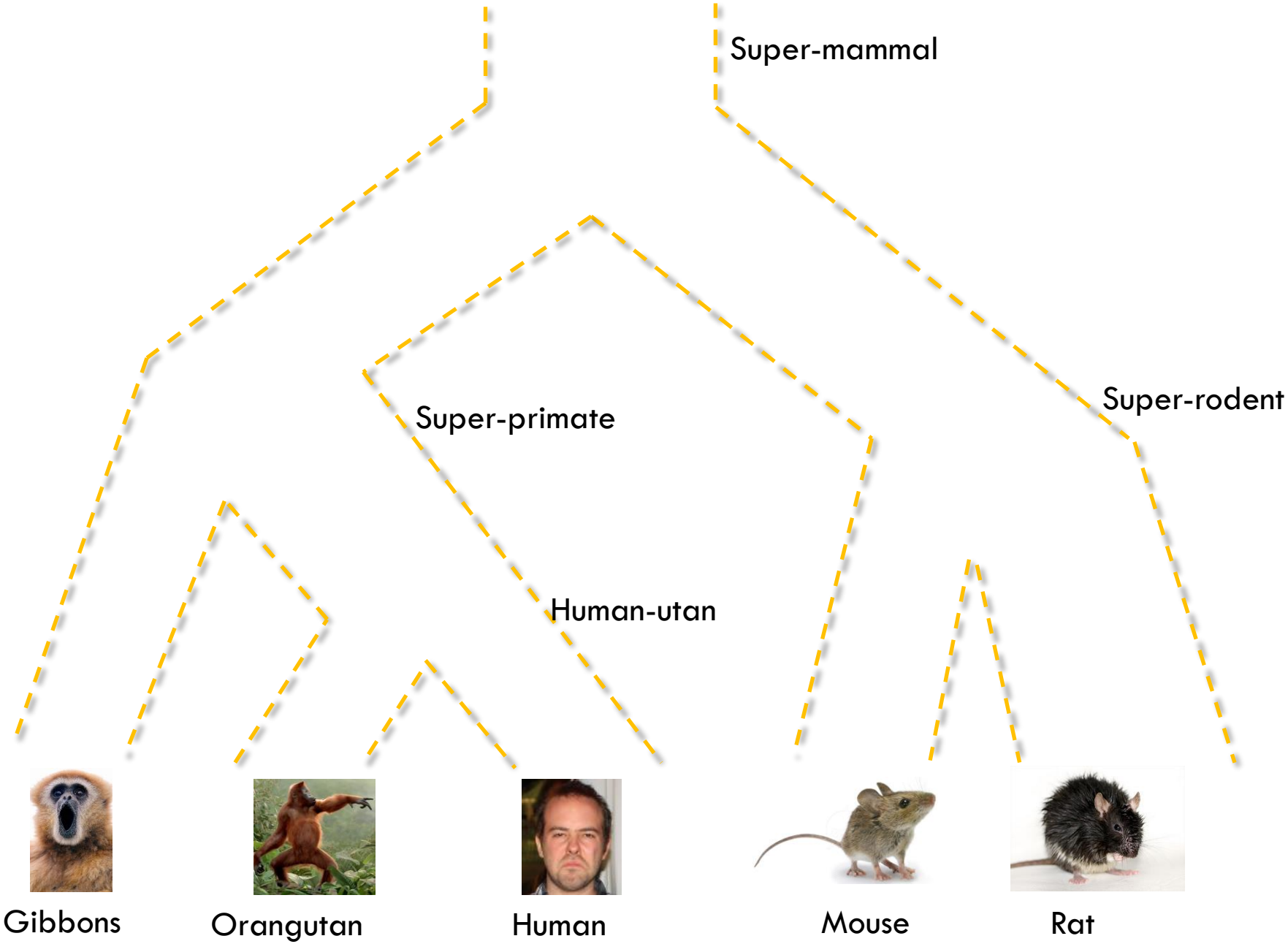
Reconciliation in phylogenomics

- **Phylogenomics** : evolutionary analysis that involves whole genomes or large portions of it.
- **Traditional reconciliation** : single gene families
- **Phylogenomics reconciliation** : many gene families

The plan

- Part 1 : basics of multi-gene family reconciliation
- Part 2 : reconciliation with segmental duplications + losses
- Part 3 : reconciling syntenic blocks


Super-mammal
Super-primate
Super-rodent
Human-utan
Gibbons
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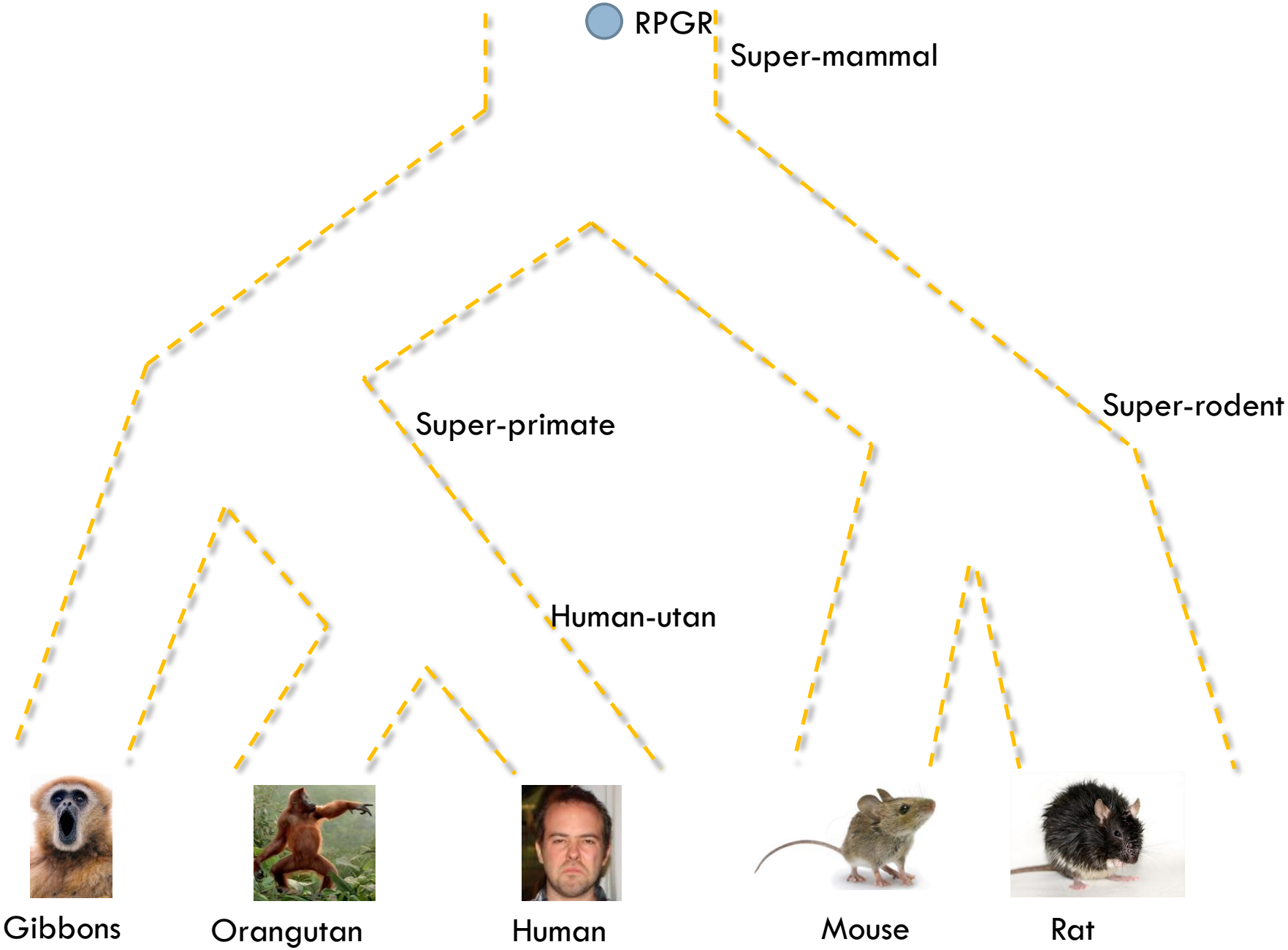
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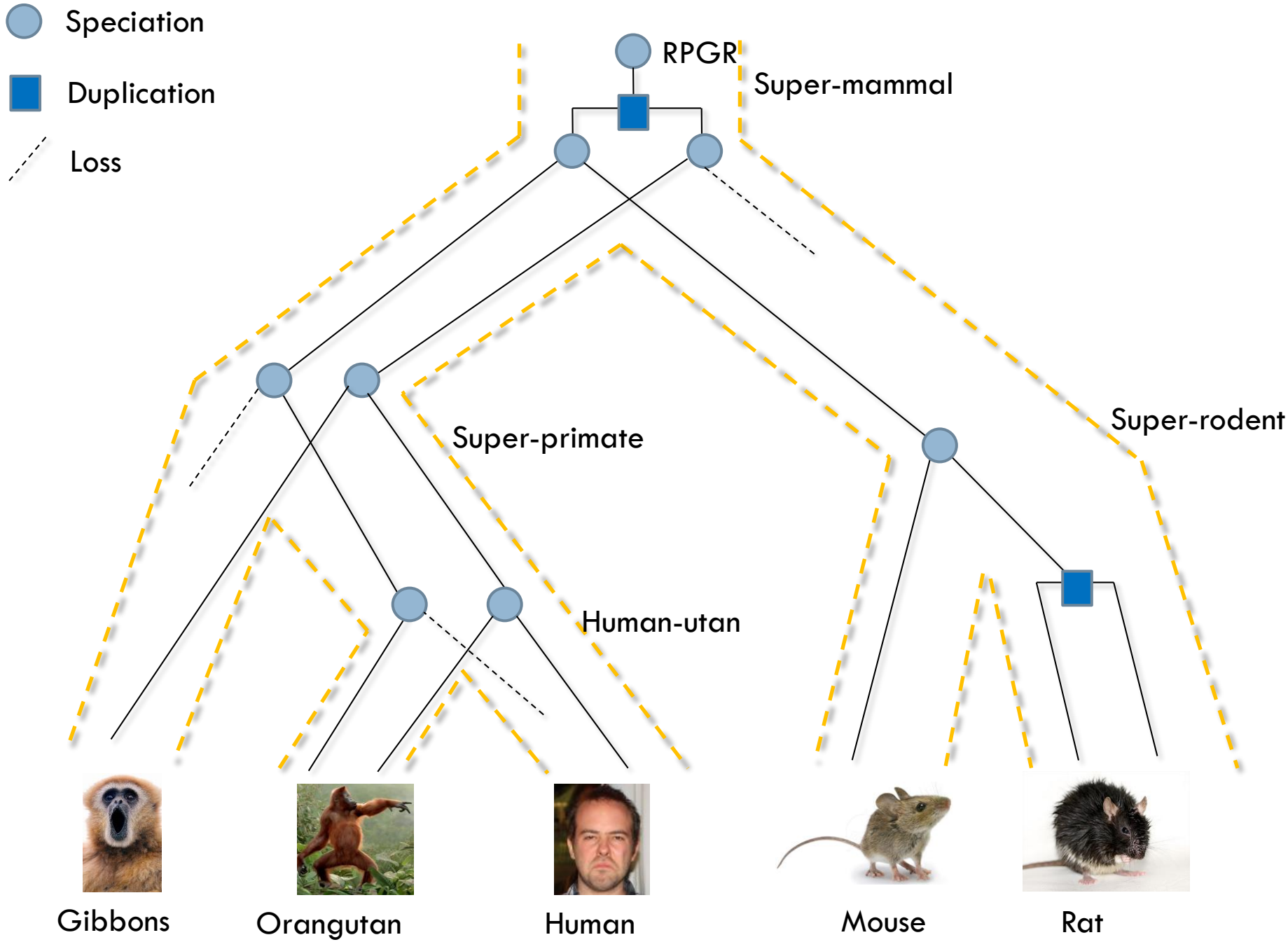
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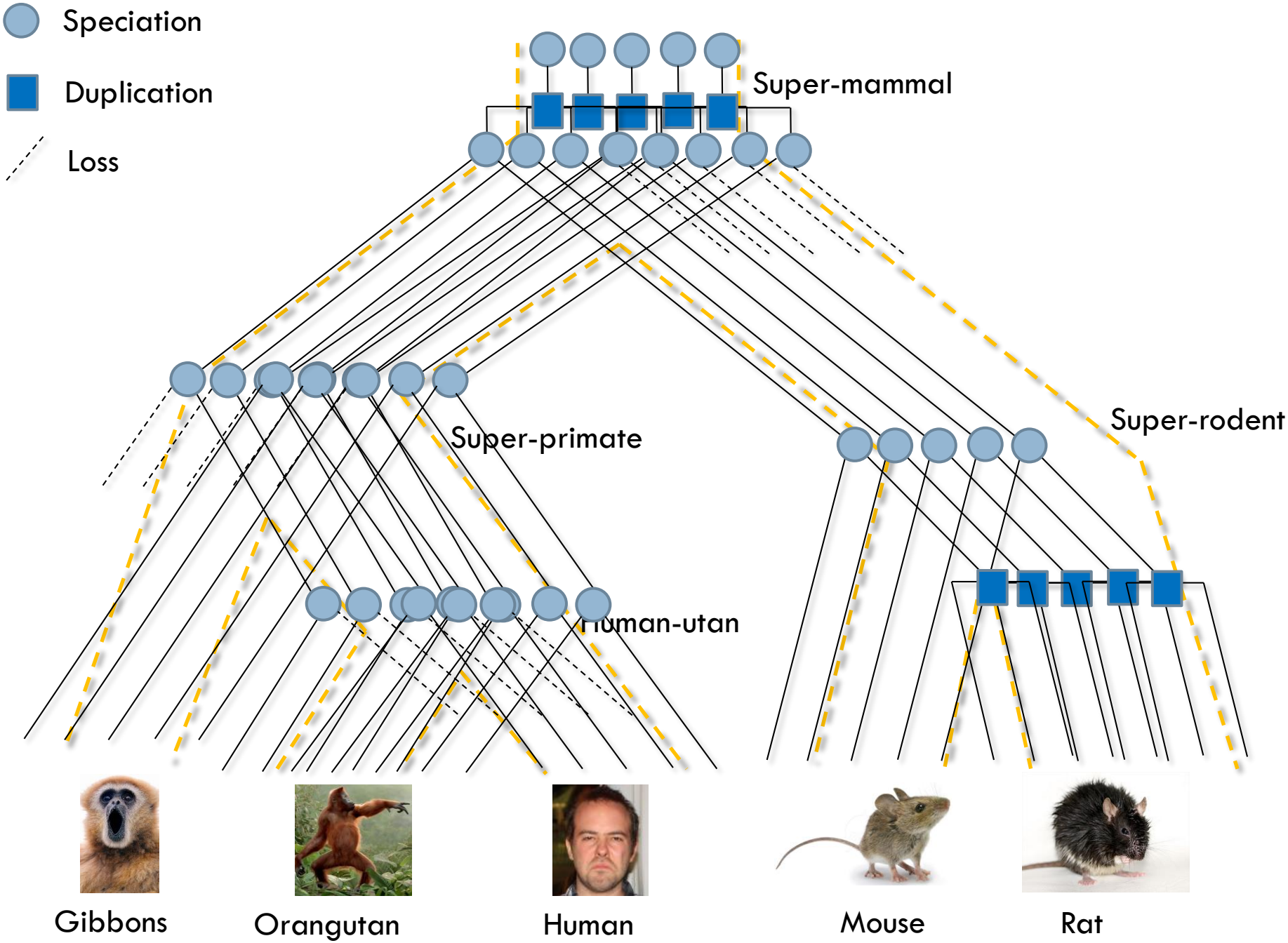
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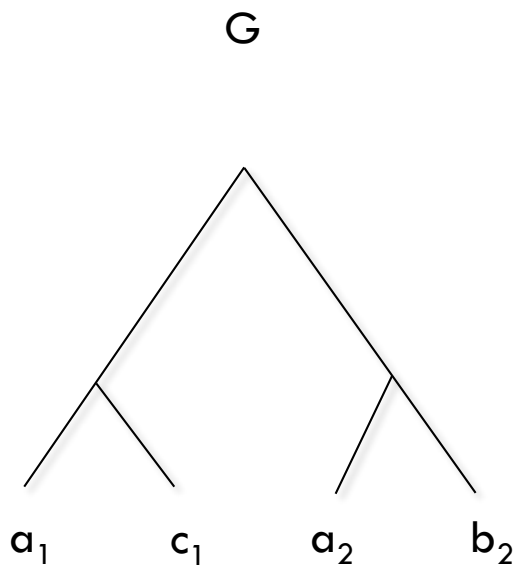
The big question

Given many gene trees, how to identify events that affect genes from several gene trees?

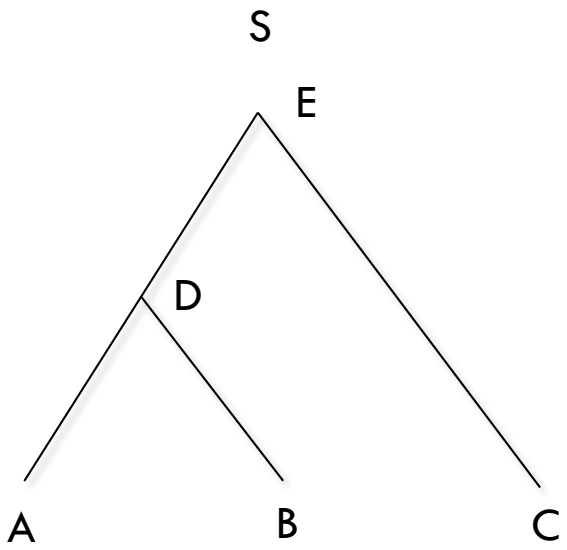
- Segmental duplications, losses, transfers.
- Whole genome duplications followed by block deletions

Reconciliation

Reconciliation identifies **duplication**, **speciation** and **loss** events in a gene tree G, using a species tree S.



Gene tree



Species tree

Notation tip: gene name = lowercase species

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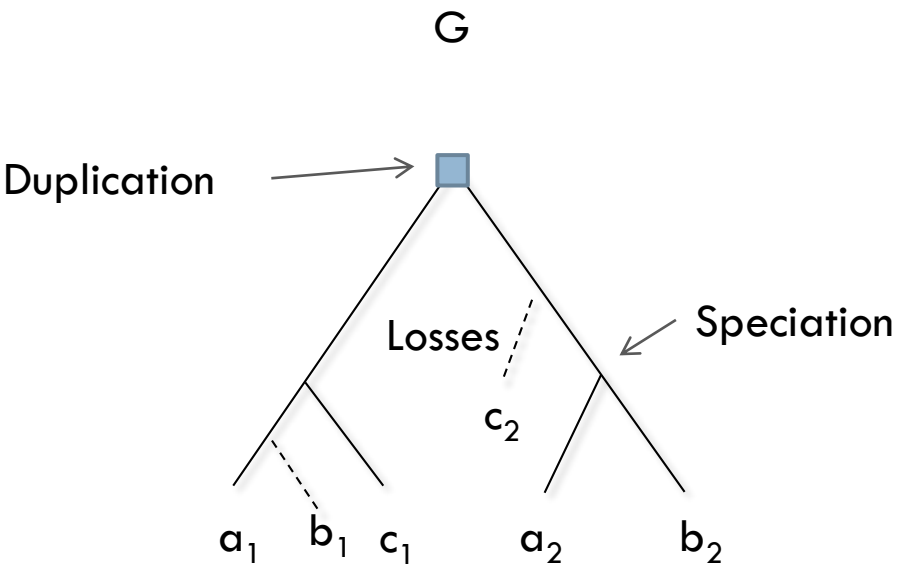

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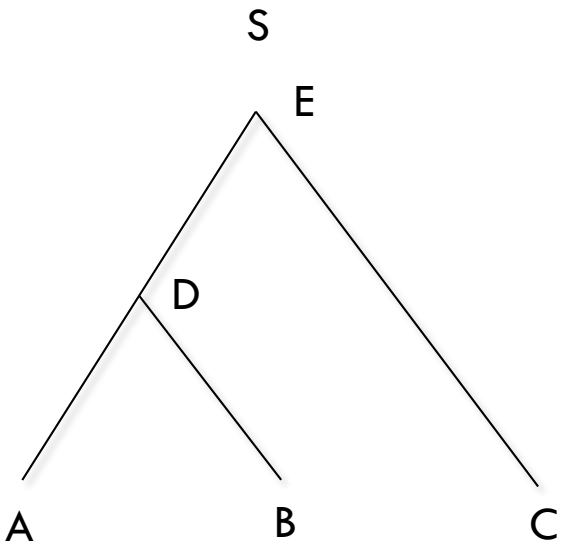

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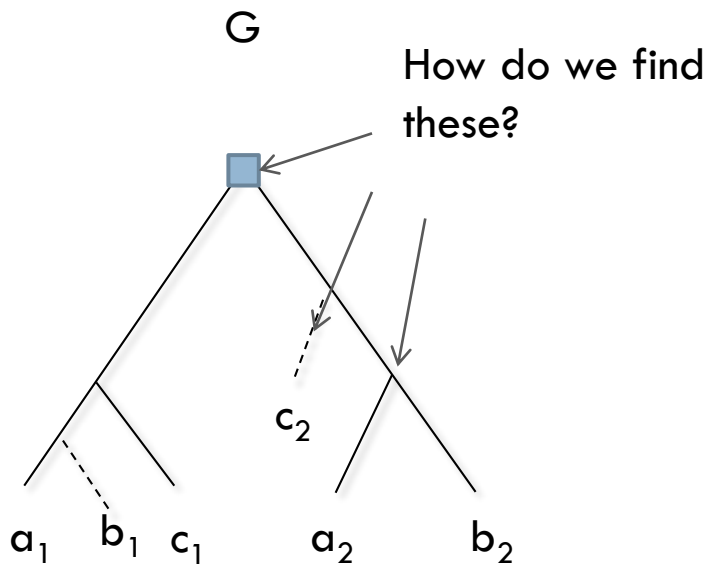

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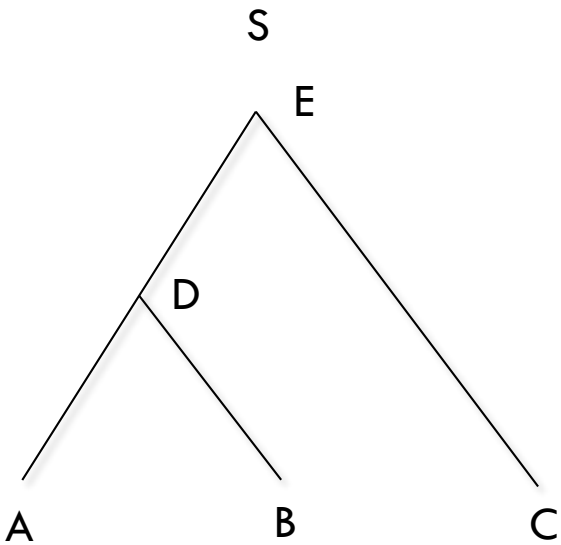
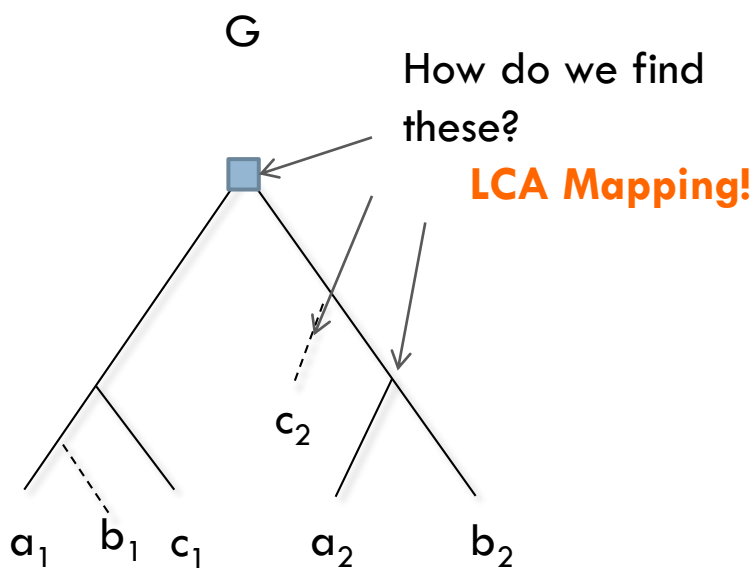


Species tree

LCA Mapping



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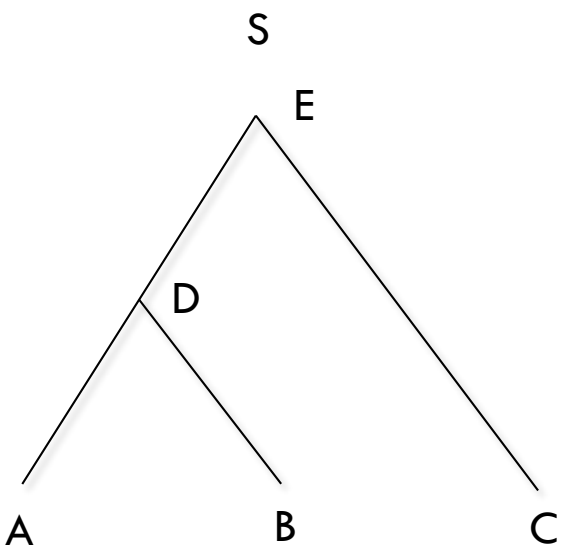

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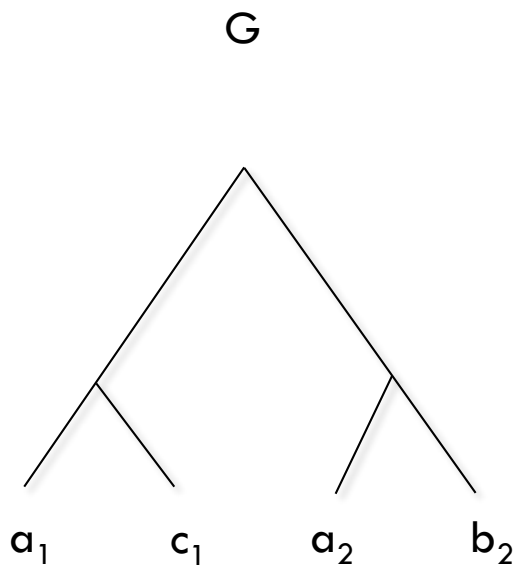

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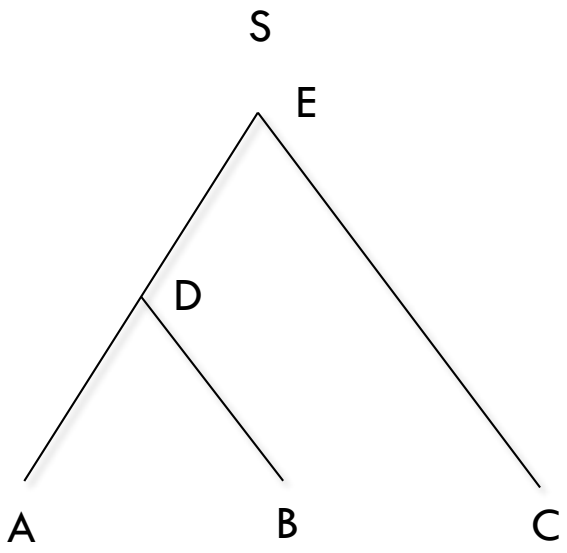

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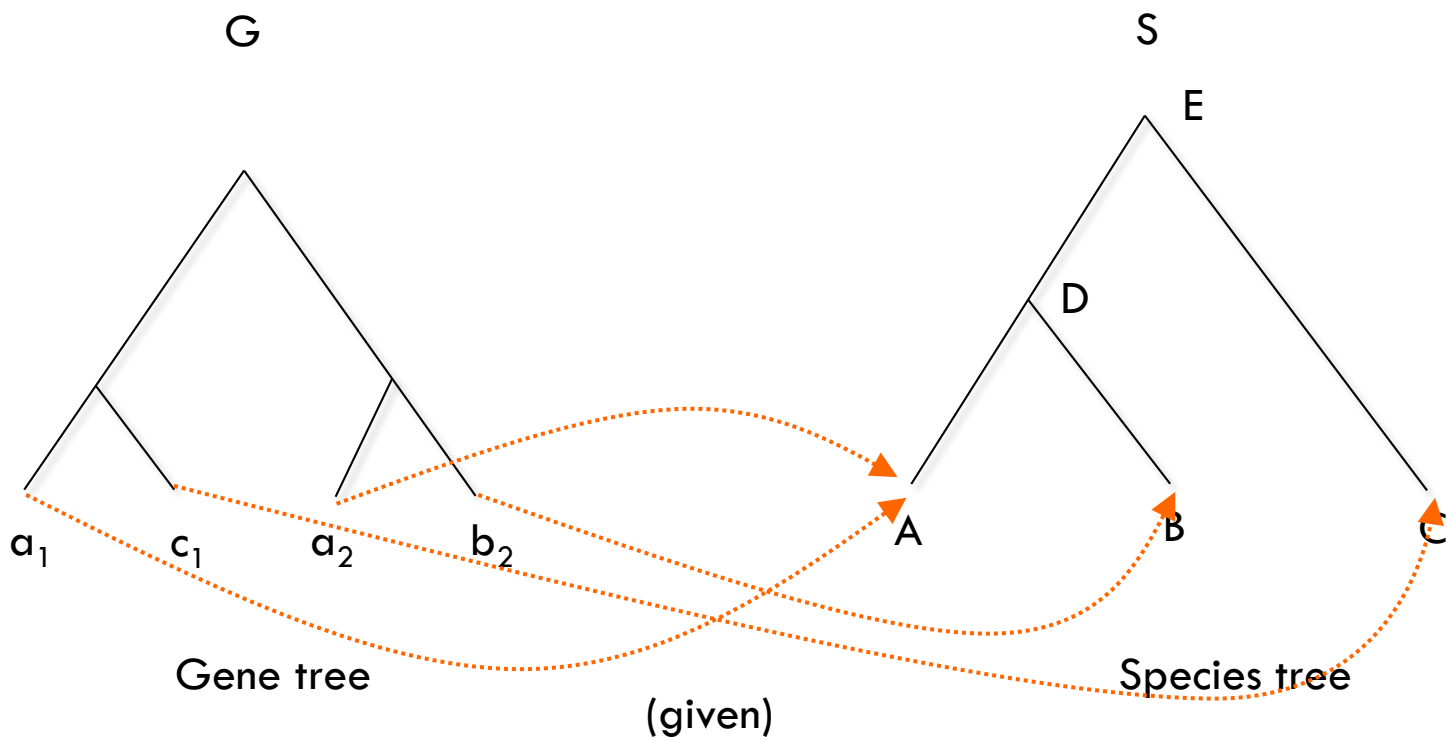

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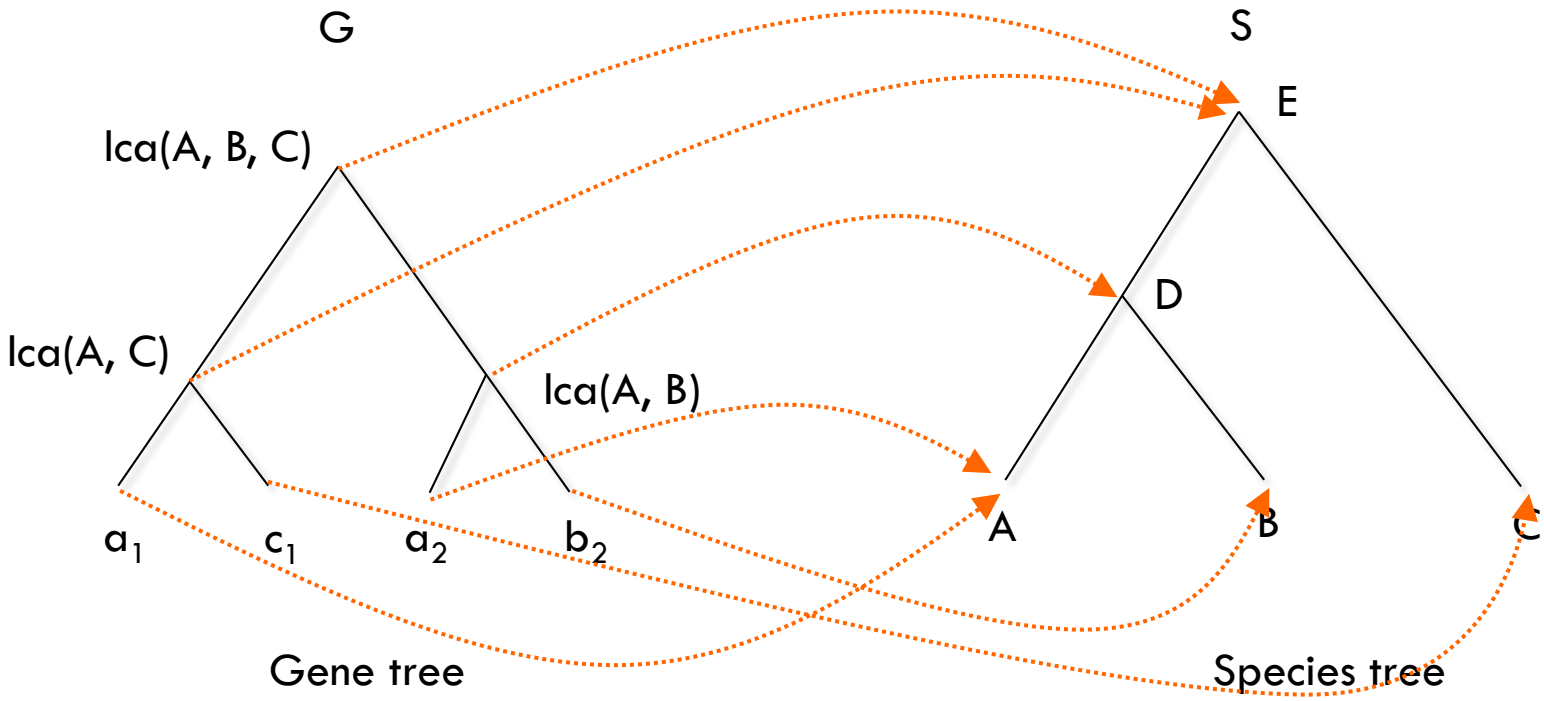

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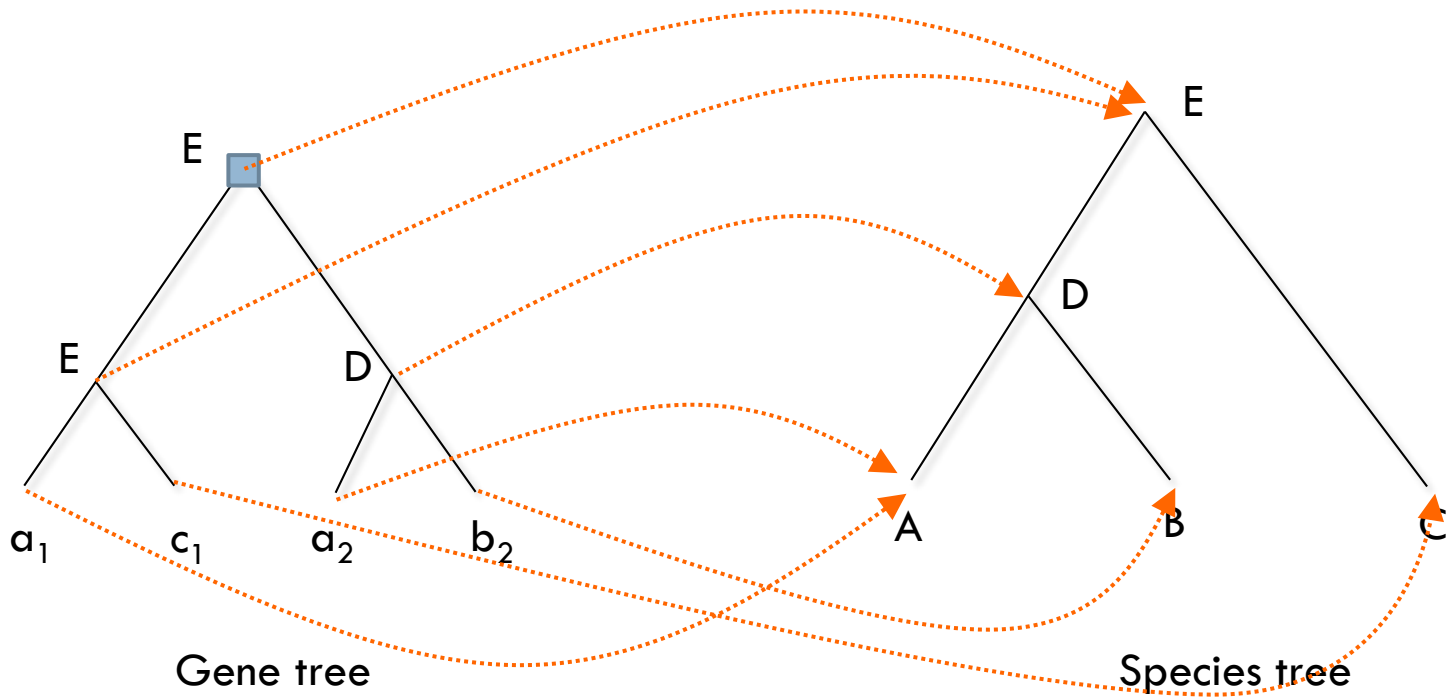

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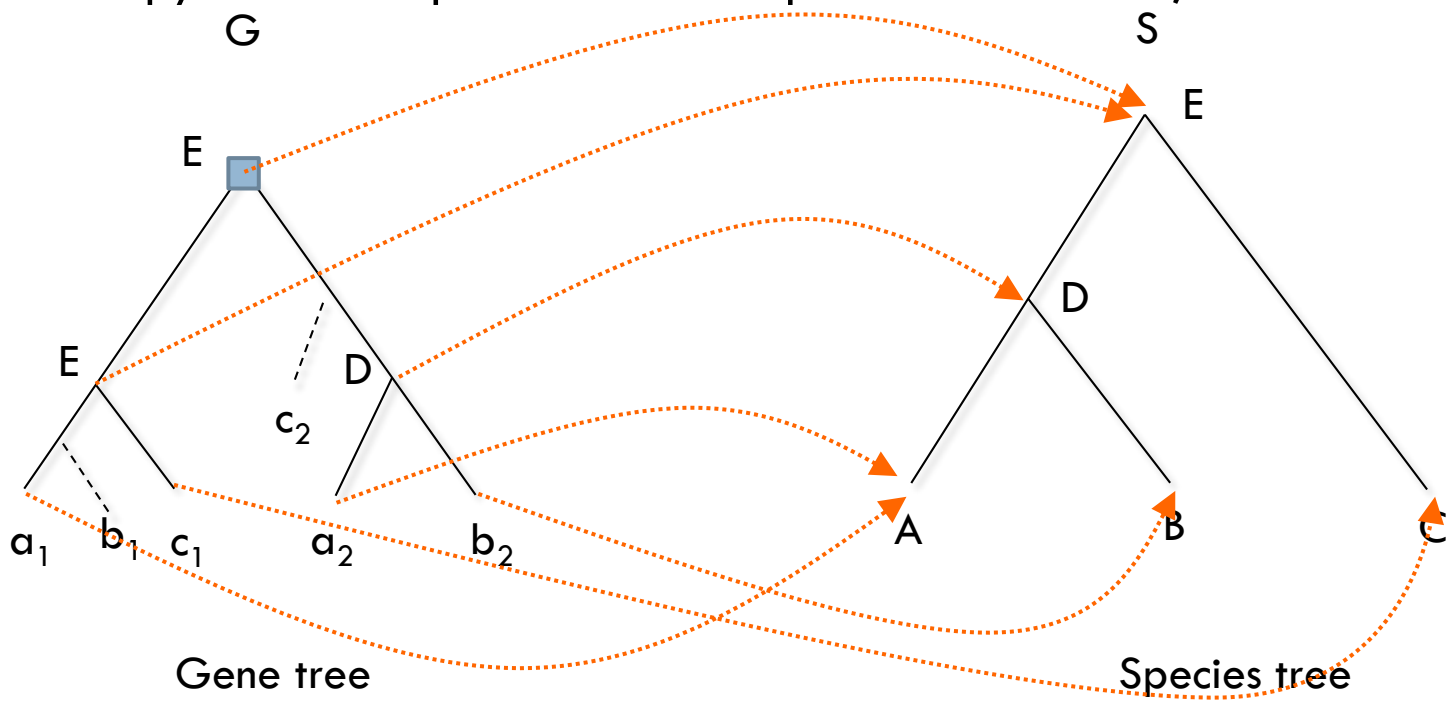
- Each copy should be present in each species – otherwise, losses.



LCA Mapping

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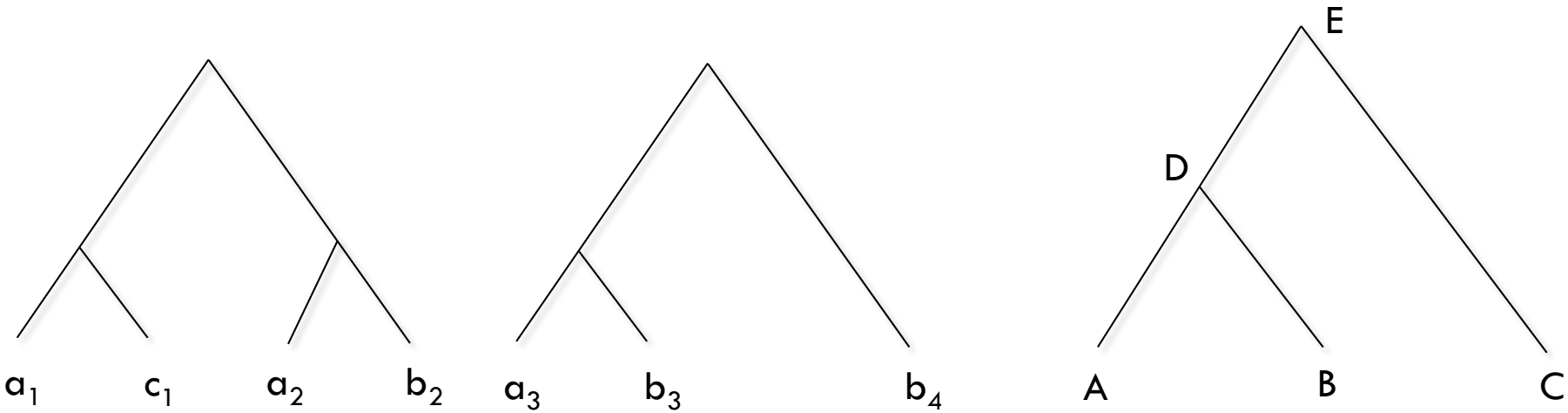

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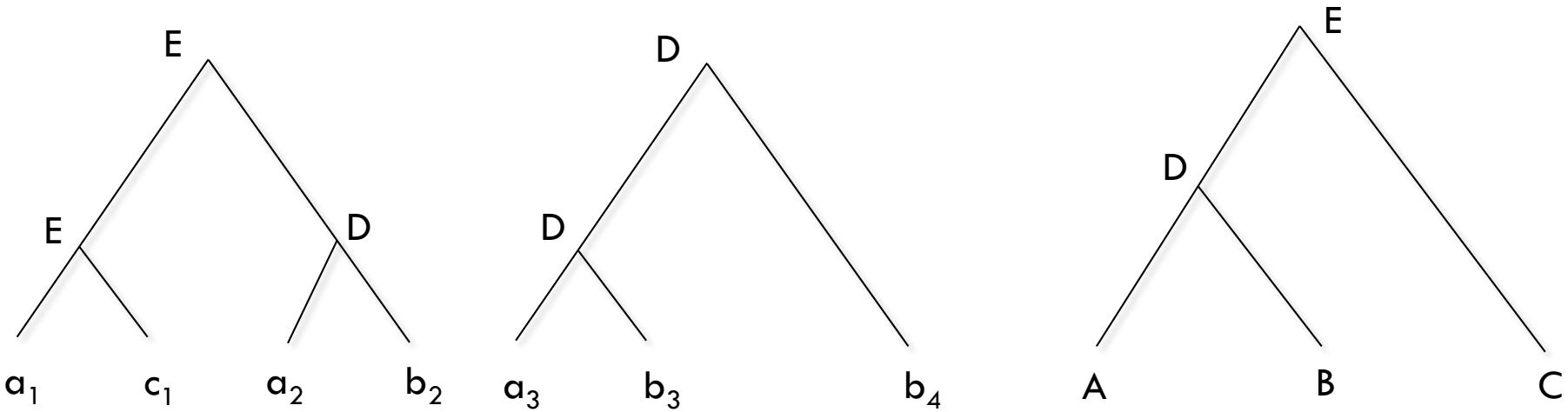

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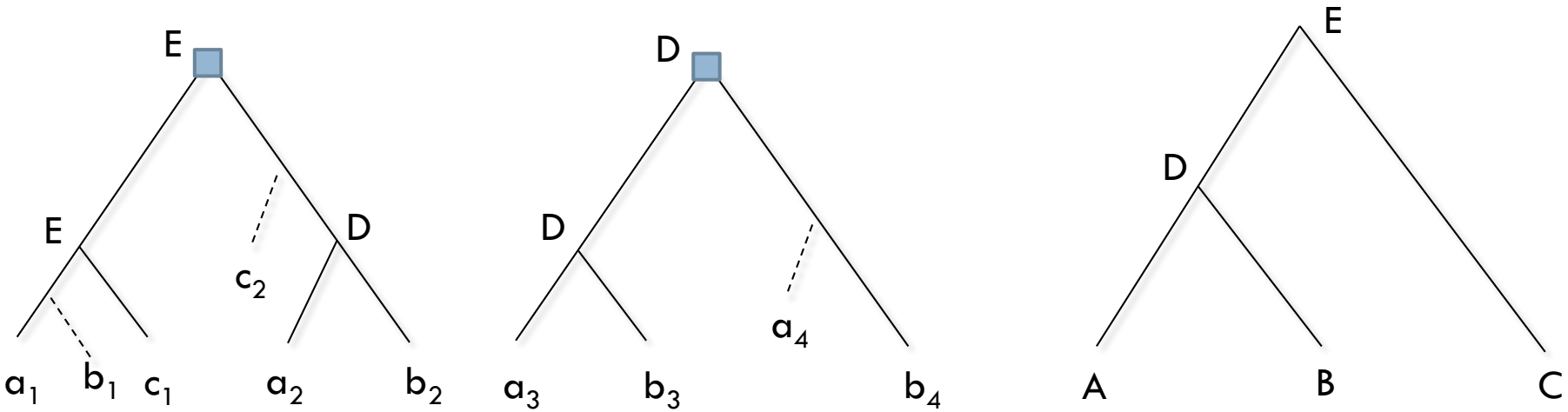

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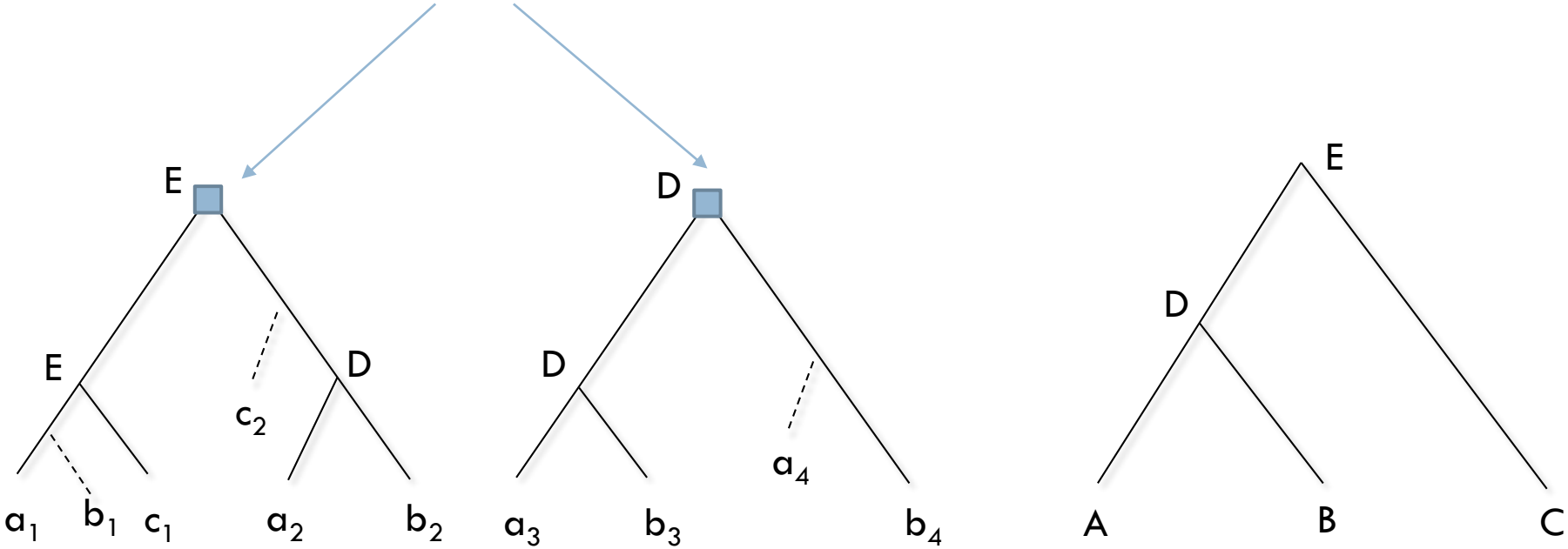

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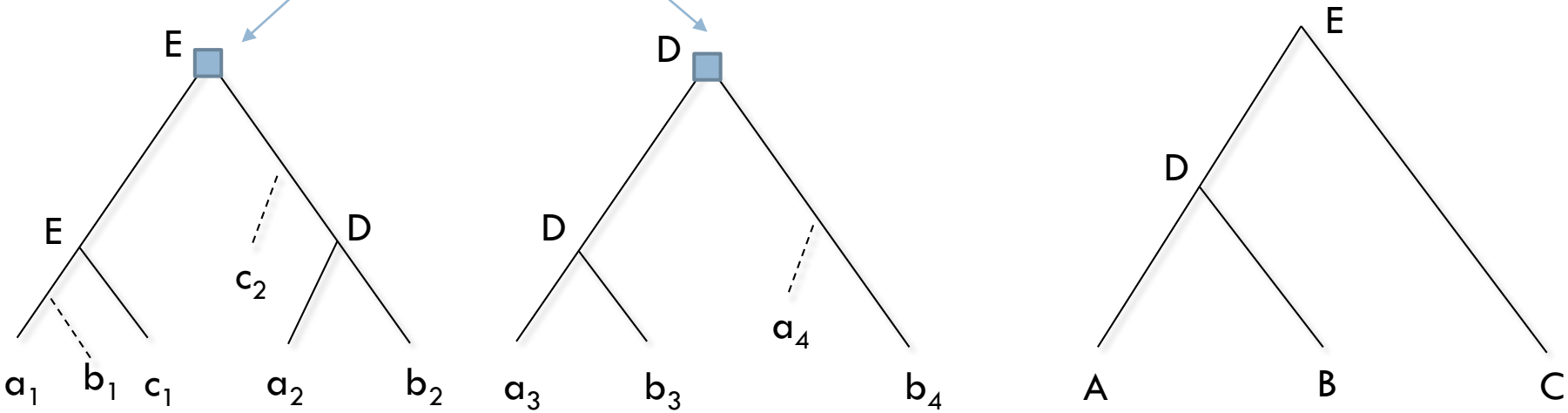
If so, this Dup must have occurred in the E species.

=> We must **remap** the D duplication.



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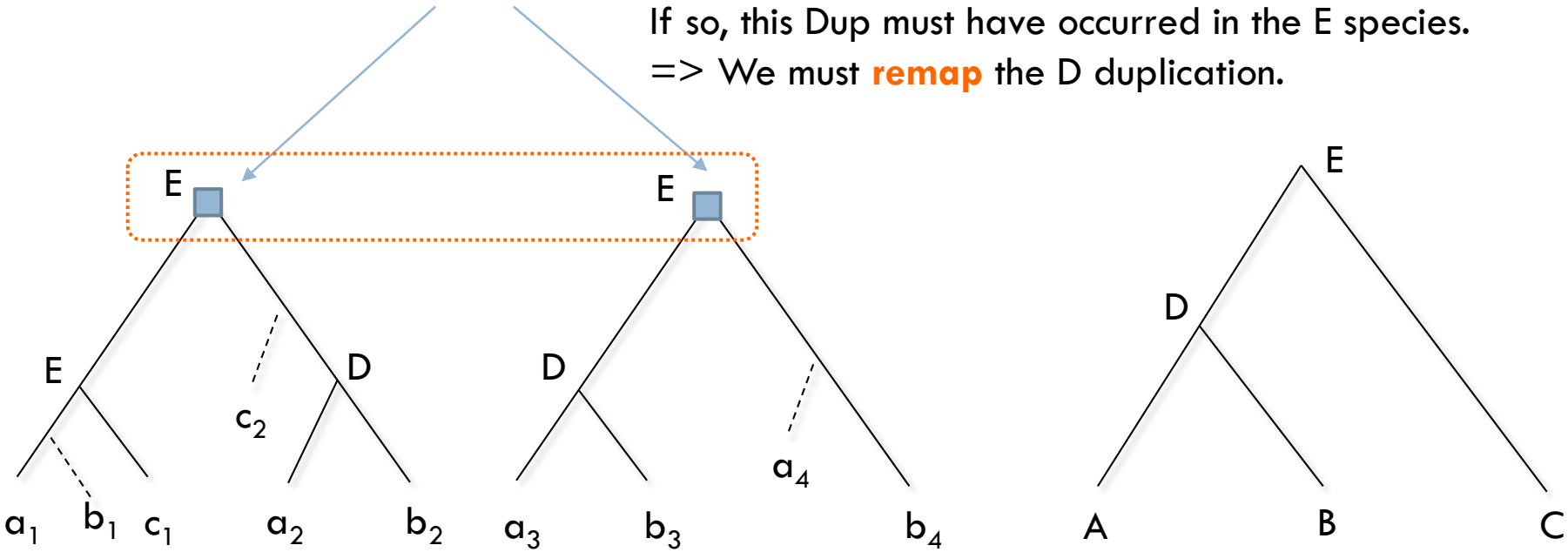

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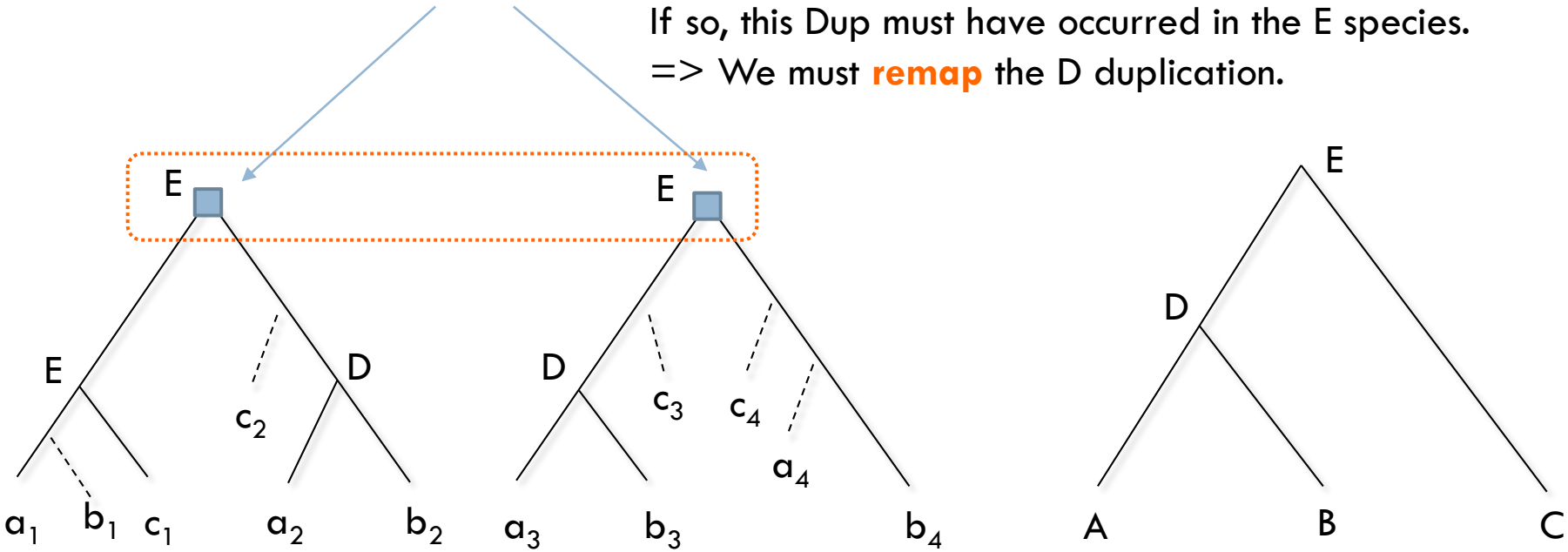
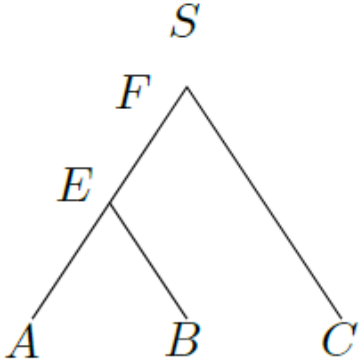
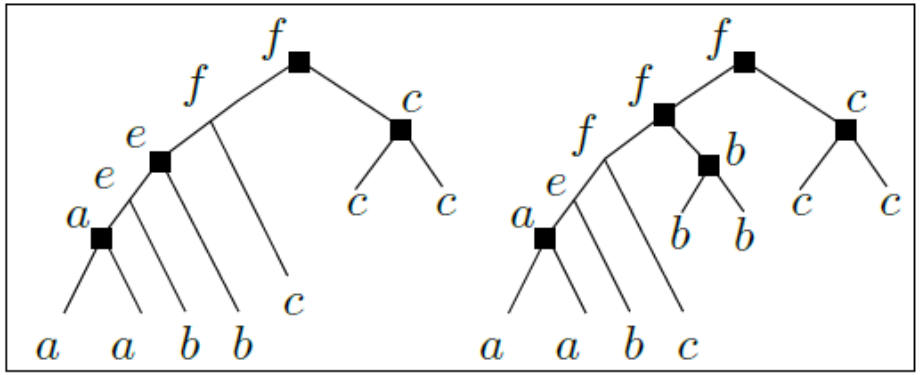


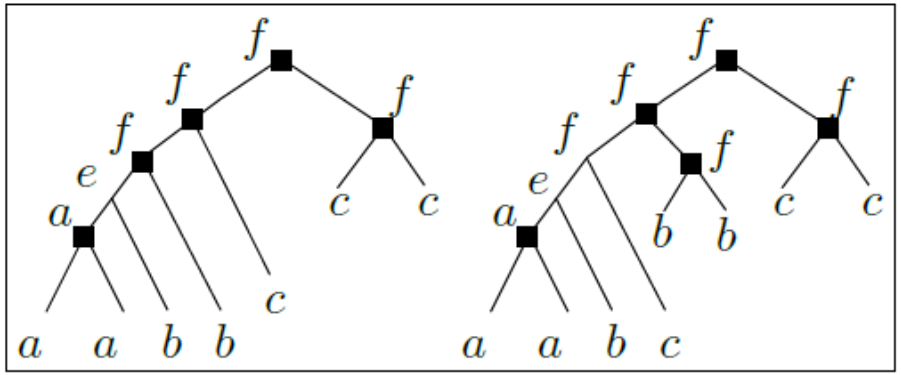
1 DUP, 5 LOSSES (before, we had 2 DUPS, 3 LOSSES)



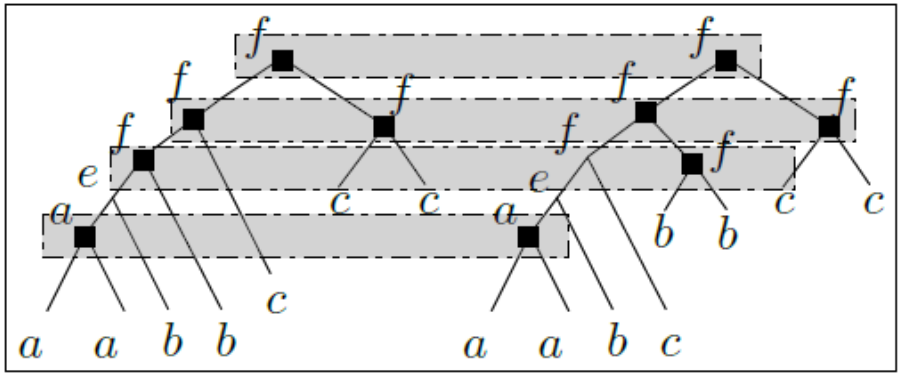
(1)



1) Classical lca mapping



2) Remap



3) Find dups

Axioms of gene-species maps

- A map $m : V(G) \quad V(S)$ is valid if
  - For a leaf u, $m(u)$ is the known species of gene u
  - **Time-consistency** : $m(u) \preccurlyeq m(parent(u))$ for all non-root u.

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- A gene loss must be inferred on the uv branch for each species strictly between $m(u)$ and $m(v)$
  - But including $m(u)$ if u is a Dup

A brief survey of models of segmental duplications

Models of segmental duplications

- Episode clustering EC
  - *[Guigo, Muchnik & Smith, Mol. Phylo & evol 1996]*
  - Dup events contain **all genes in the same species**.
- Gene duplication clustering GD
  - *[Fellows, Hallett & Stege, ISAAC 1998]*
  - Dup events have **at most 1 gene per gene tree**.
- Minimum episode ME
  - *[Bansal & Eulenstein, Bioinformatics 2008]*
  - Dup events **do not contain a gene and one of its descendants**.

Models of segmental duplications

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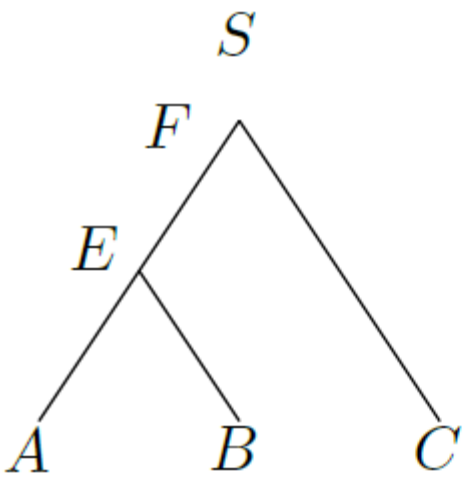
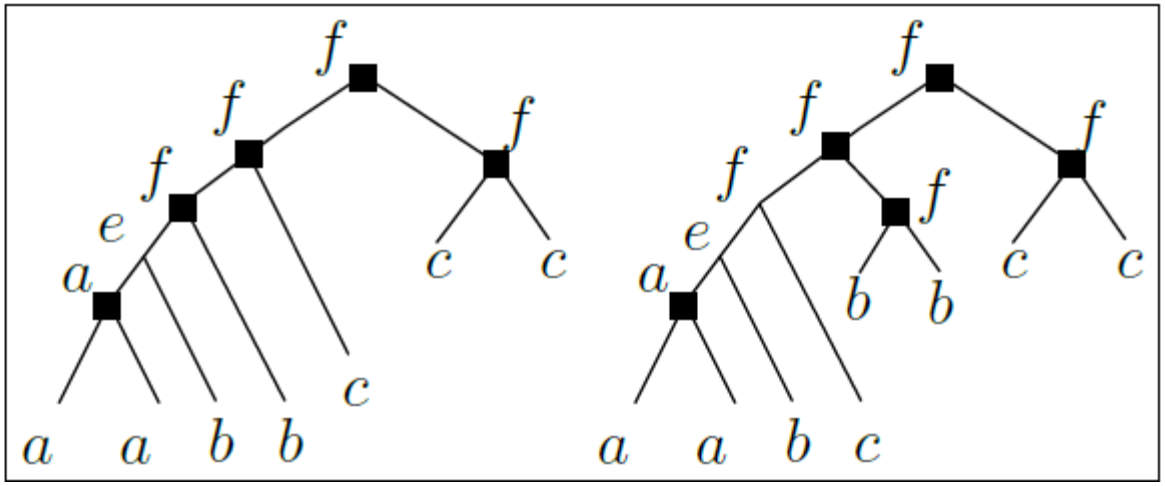
  - Dup events can affect **all** genes in the same species.





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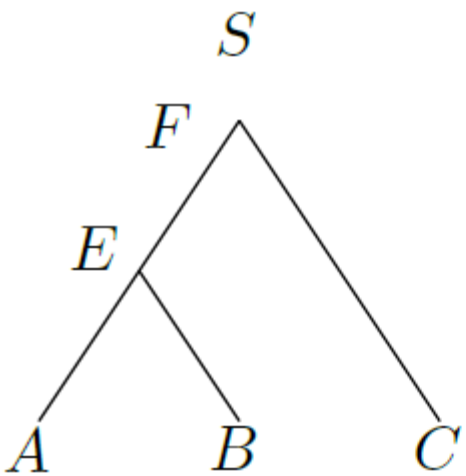
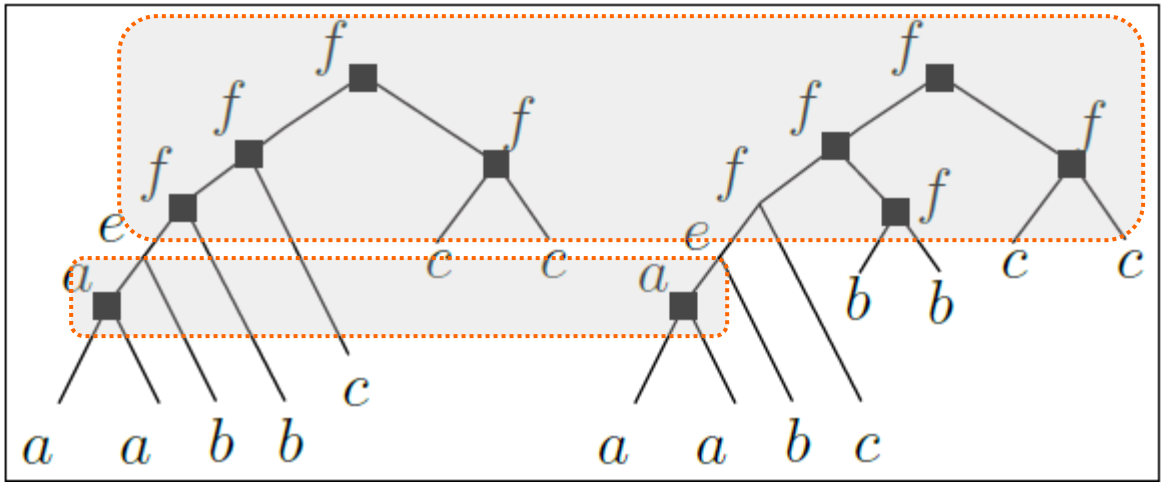


# of dups = 2



Models of segmental duplications

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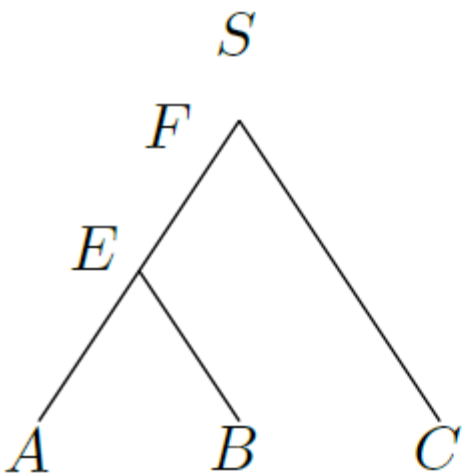
  - Why not just remap every gene to F and have a single dup? Restriction needed.



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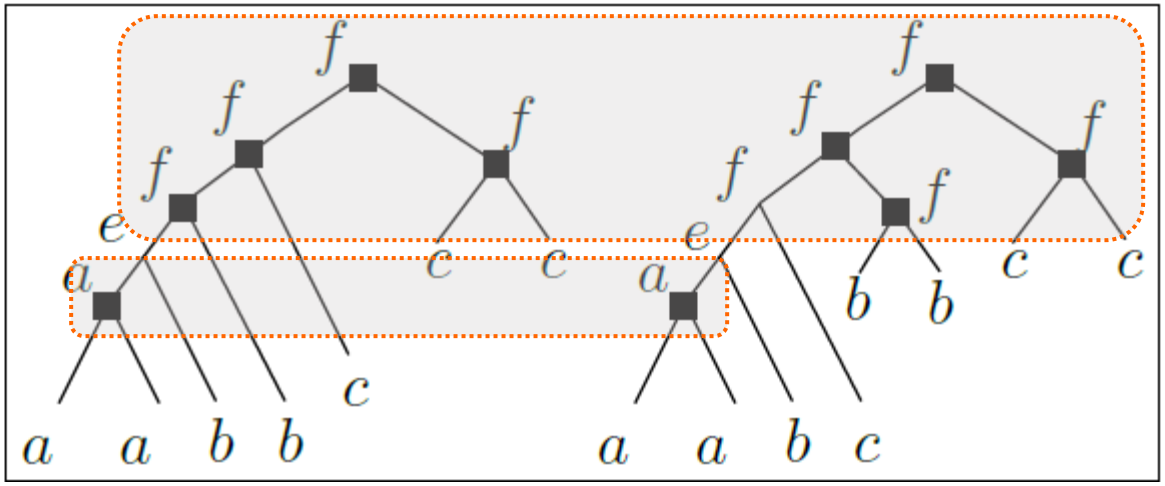

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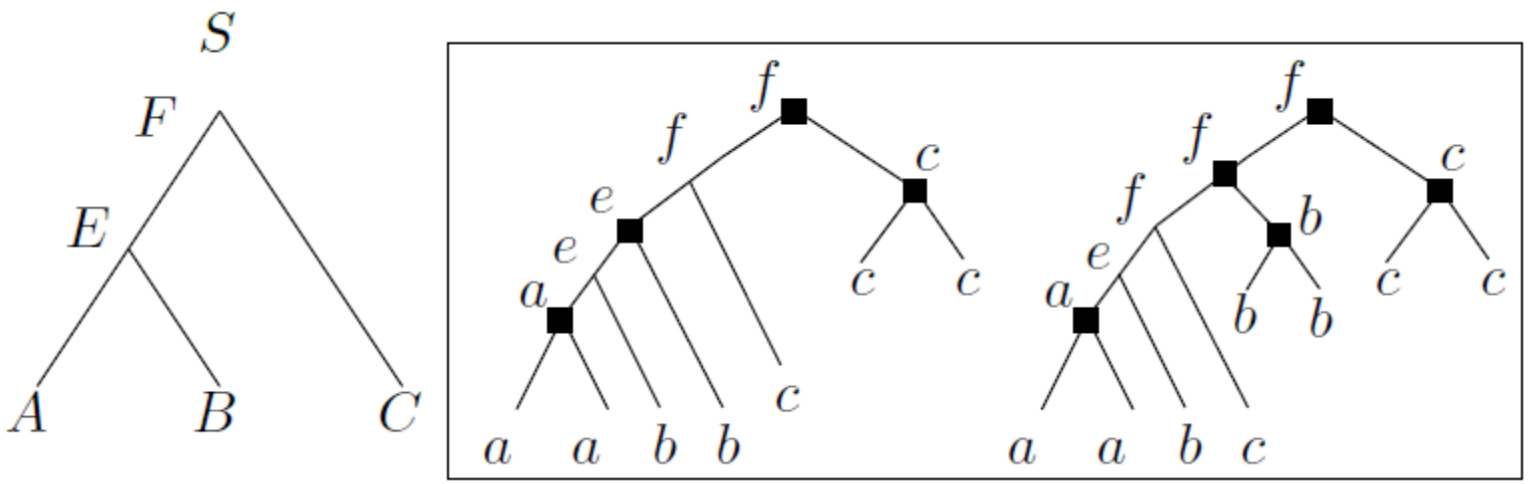

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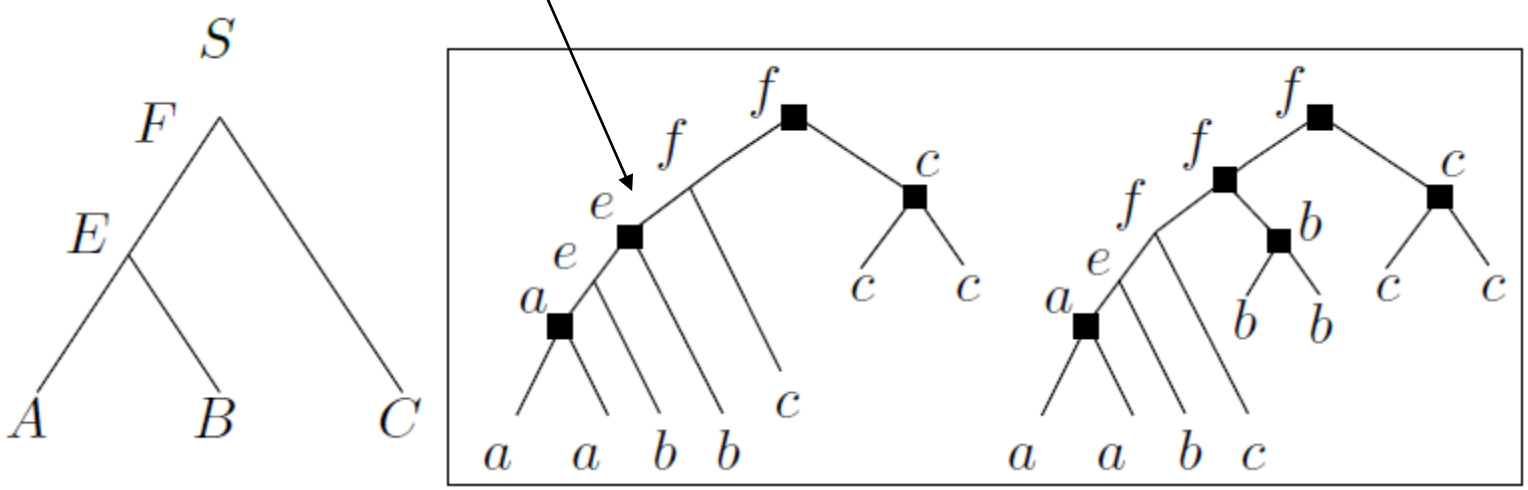

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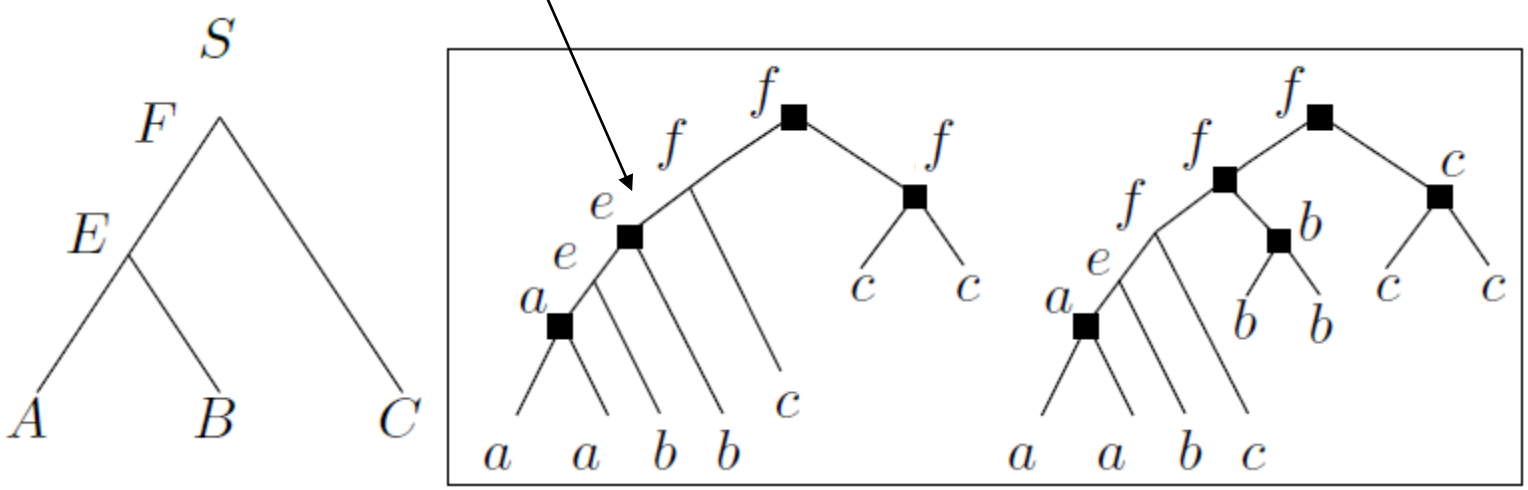

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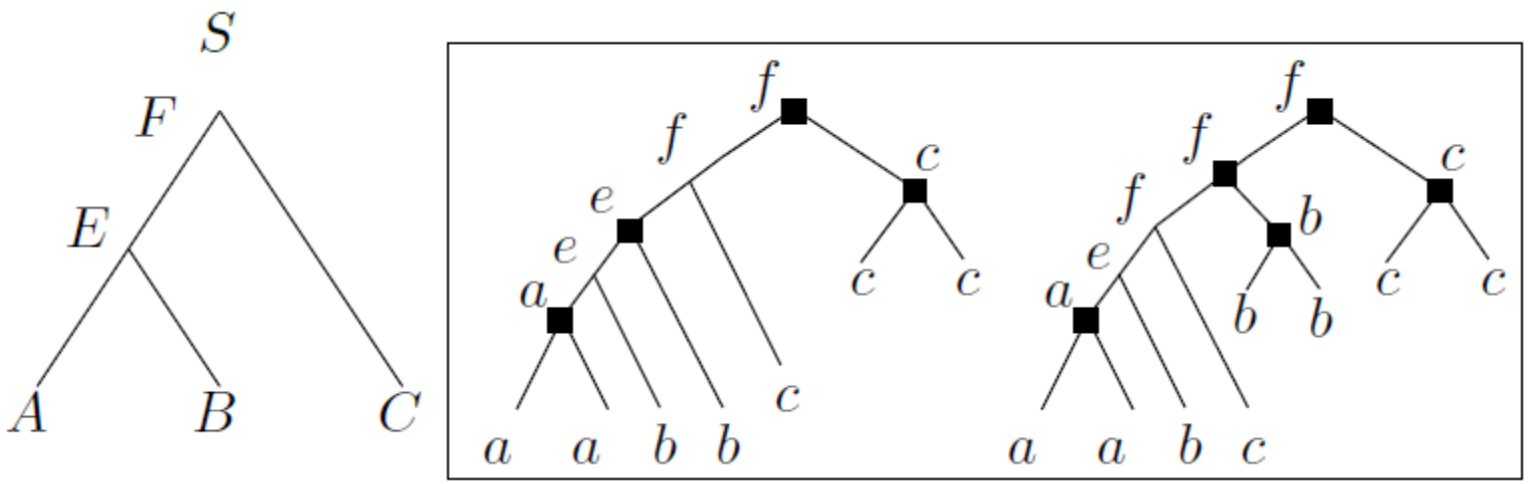

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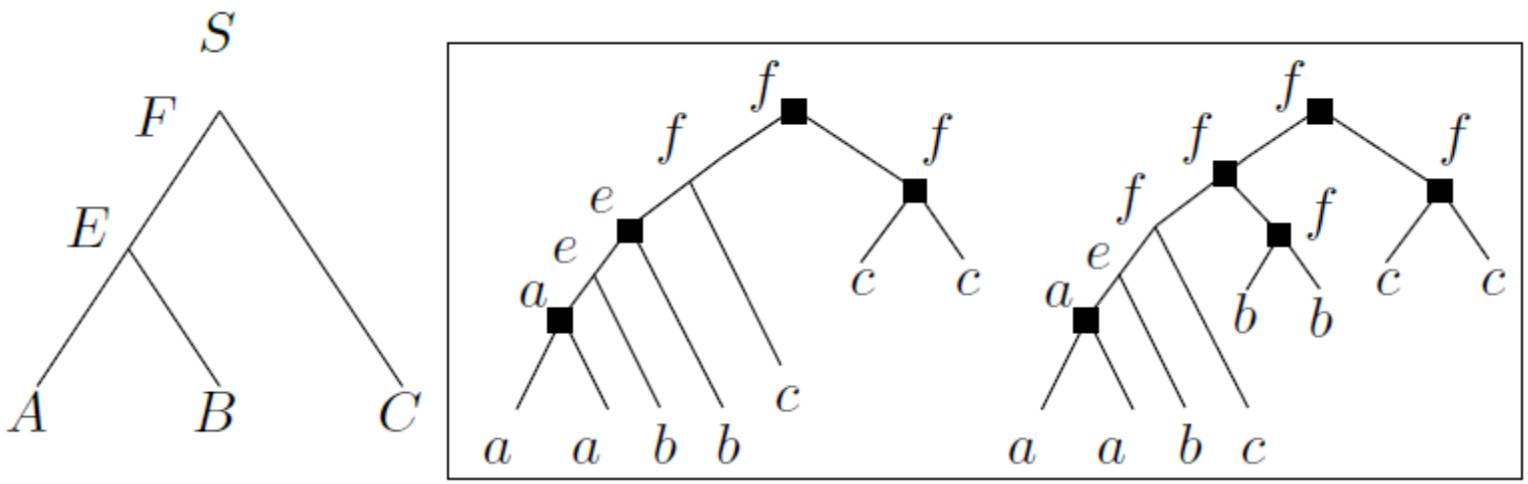

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- Can be solved in polynomial time (also for other types of restrictions).
  - *[Burleigh & al., RECOMB 2008]*

Models of segmental duplications

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  - Dup events can affect genes in the same species, but contain **at most one gene per gene tree**.
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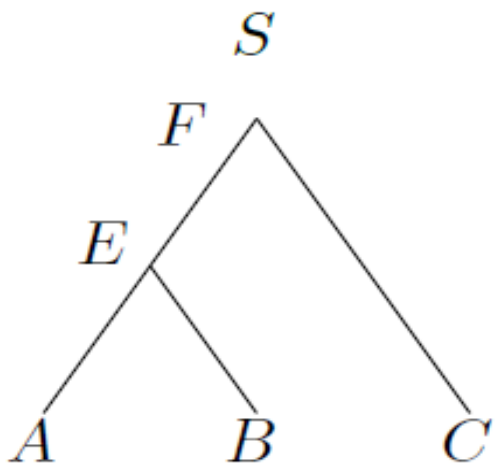

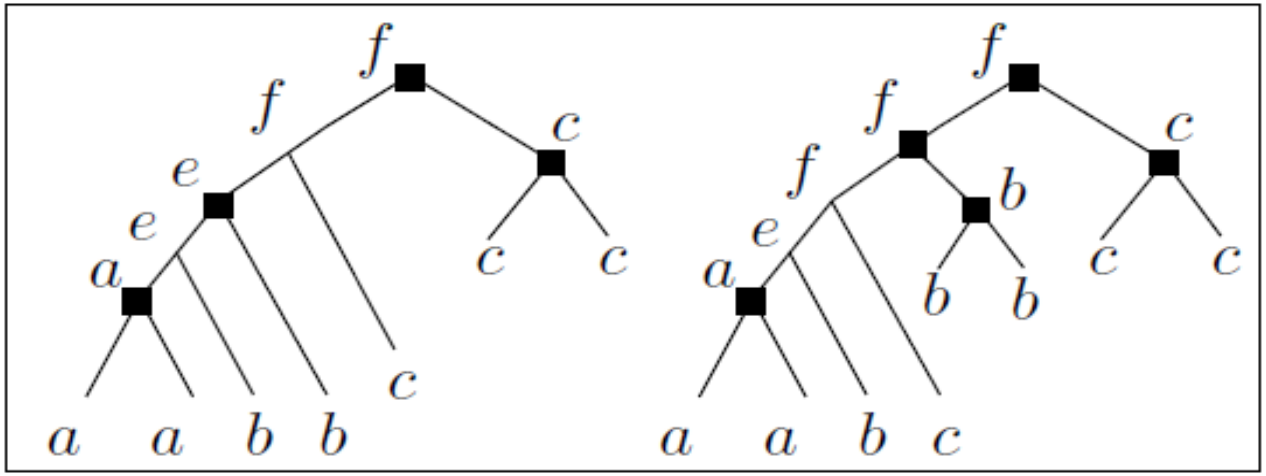

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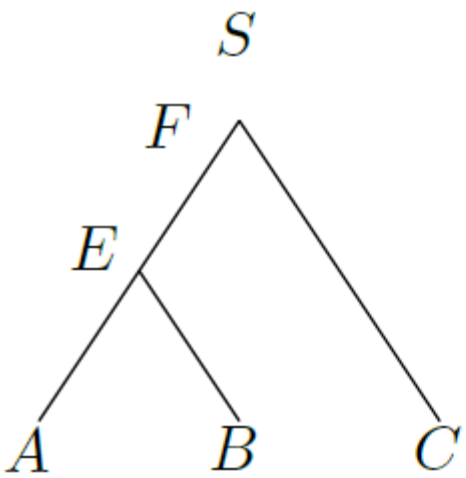

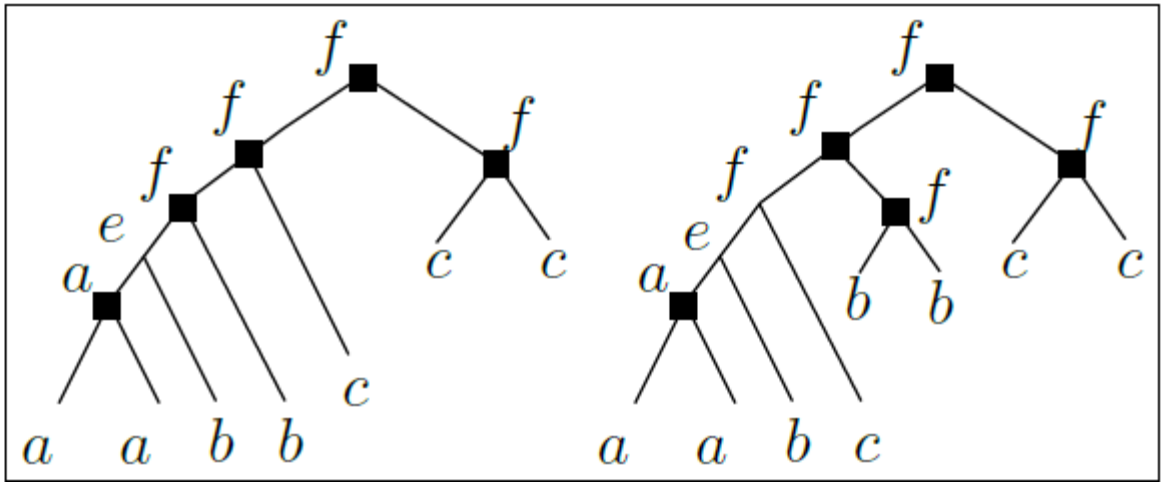

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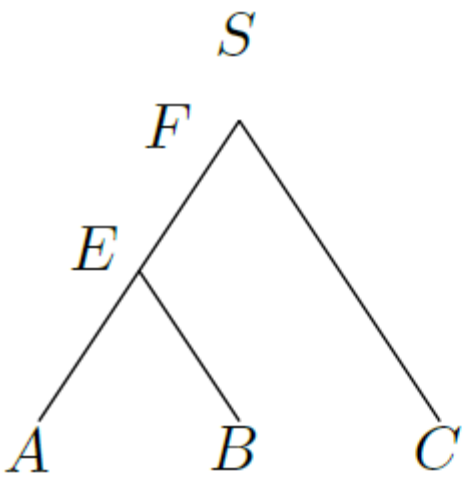

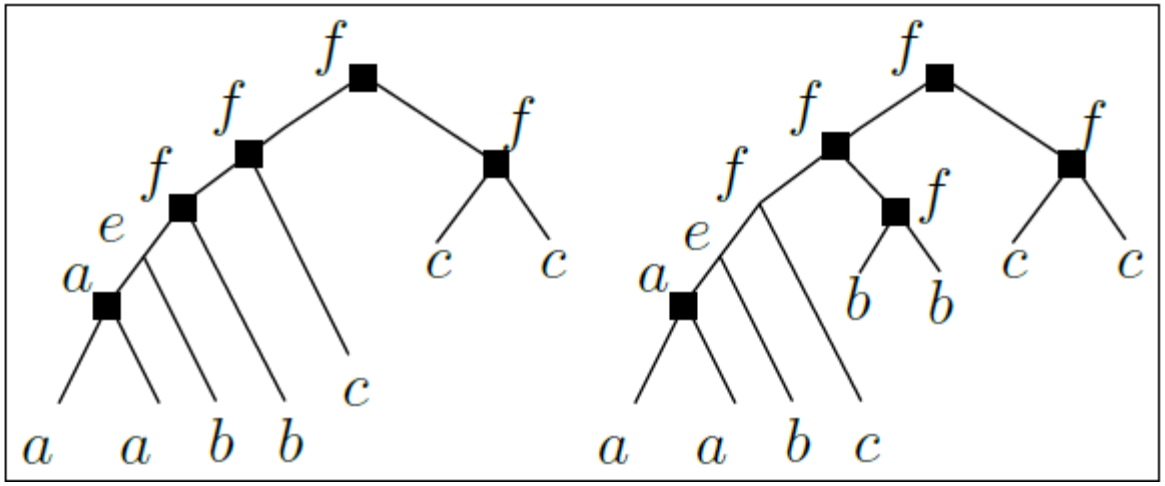

Models of segmental duplications

- Gene duplication clustering GD
  - Dup events can affect genes in the same species, but contain **at most one gene per gene tree**.
  - No restriction on mapping.

- NP-hard, and even W[1]-hard in the # of dups.
  - *[FHS, ISAAC 2008]*

Models of segmental duplications

- Minimum episode ME *[Bansal & Eulenstein 2008]*
  - Dup events can affect genes in the same species, but **cannot contain a gene and one of its descendants**.
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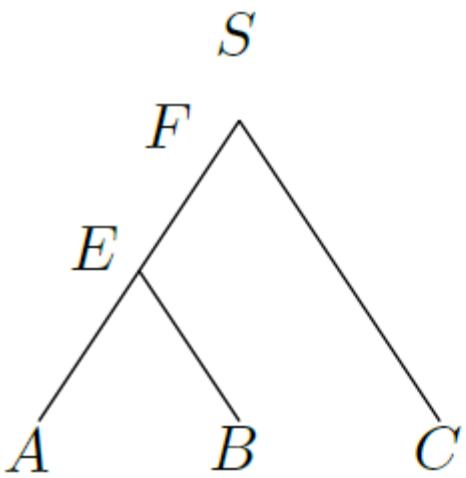

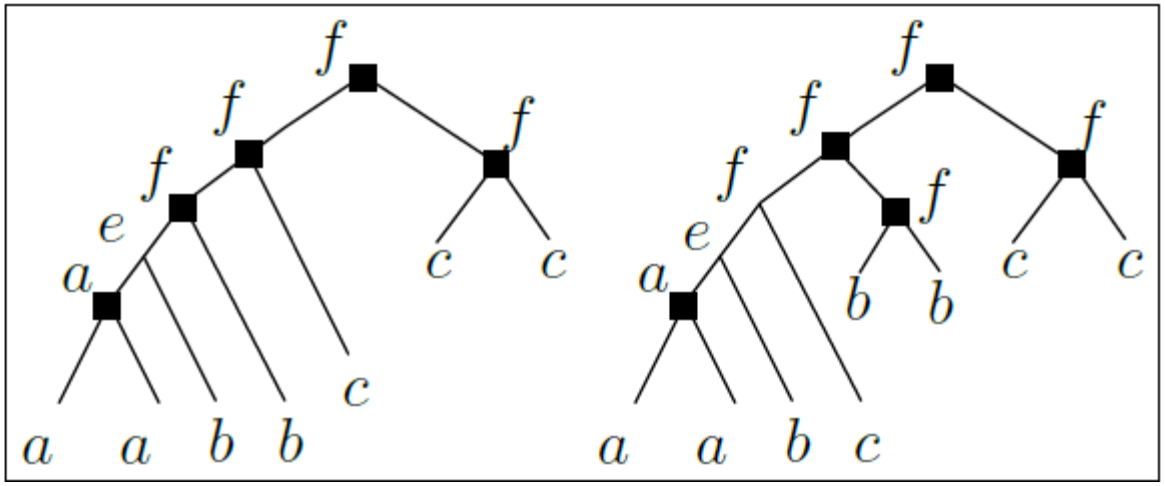

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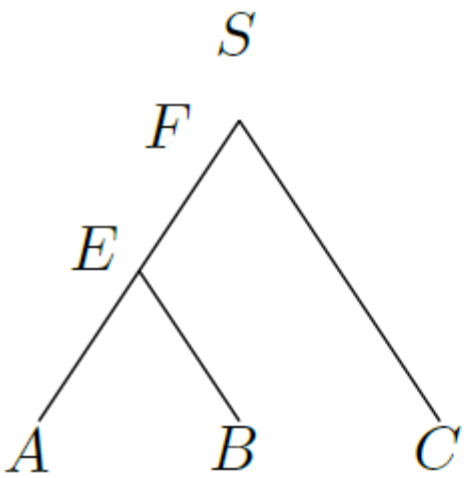

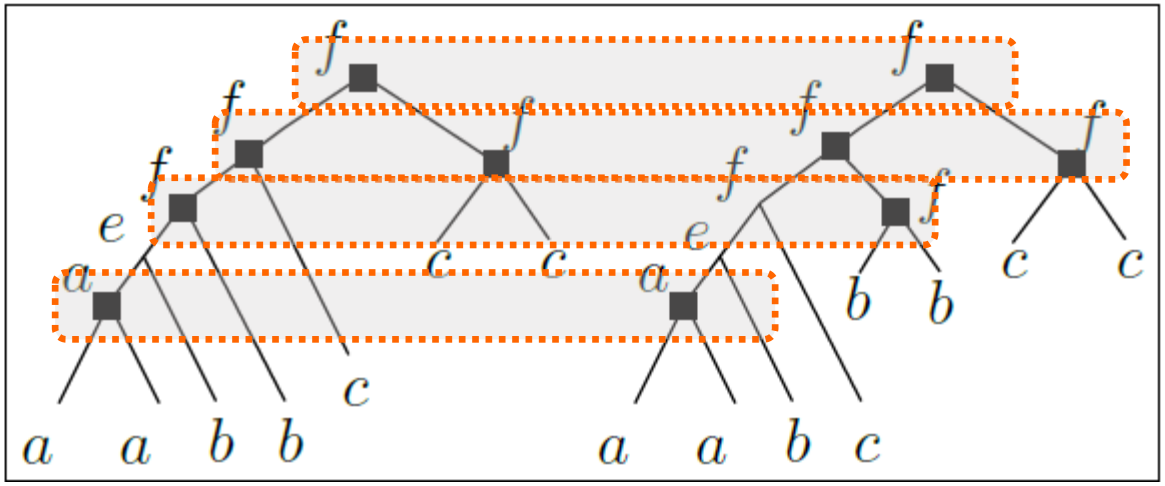

Models of segmental duplications

- Minimum Episodes inference problem
  - **Input** : species tree S, gene trees $G_1, \ldots, G_n$
  - **Find** : a valid gene-species mapping m that minimizes the number of ME duplications.

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- Minimum Episodes inference problem
  - **Input** : species tree S, gene trees $G_1, \ldots, G_n$
  - **Find** : a valid gene-species mapping m that minimizes the number of ME duplications.

- With restriction of "never break a speciation", can be solved in polynomial time.
  - *[Bansal & Eulenstein, Bioinformatics 2008]*
  - *[Paszek & Gorecki, TCBB 2017]*
- Unrestricted mapping = open problem until recently

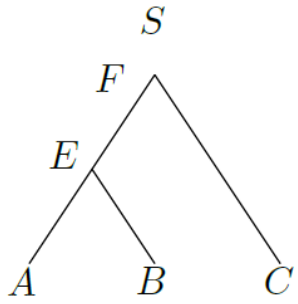
Models of segmental duplications

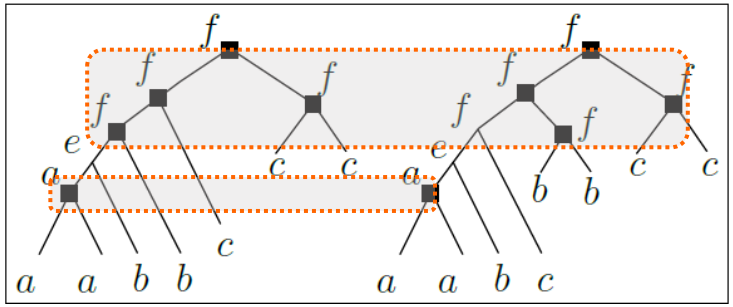
- Minimum Episode and Species Tree Inference
  - **Input** : gene trees $G_1, \ldots, G_n$
  - **Find** : **a species tree S** and a valid gene-species mapping that minimizes the number of ME duplications.

- Can be solved in polynomial time!
  - *[Van Iersel, Janssen, Jones, Murakami & Zeh, TCBB 2019]*
  - Reduction to Beaded Tree problem.

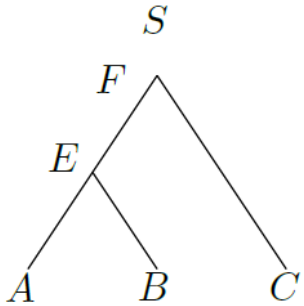
3 models

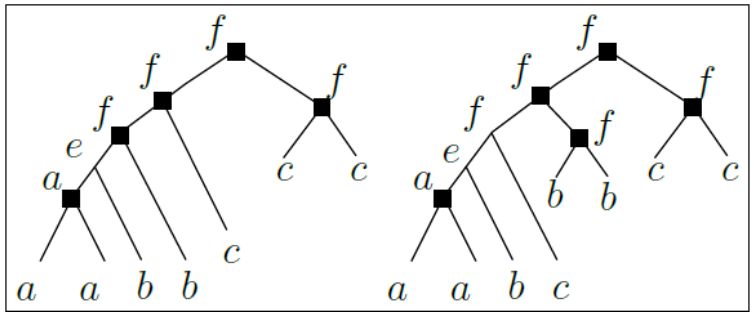
Episode Clustering



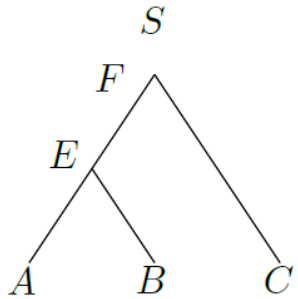


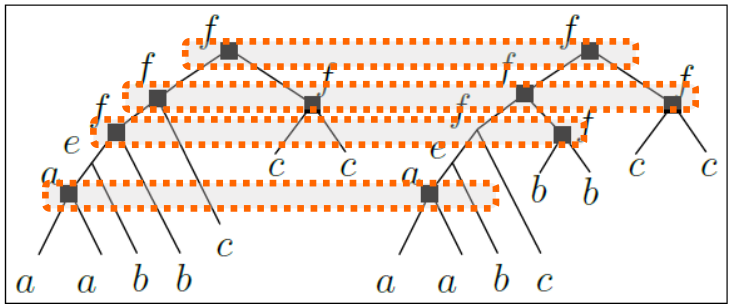
Gene Dup Clustering





Minimum Episode Clustering





Some more on Minimum Episode inference

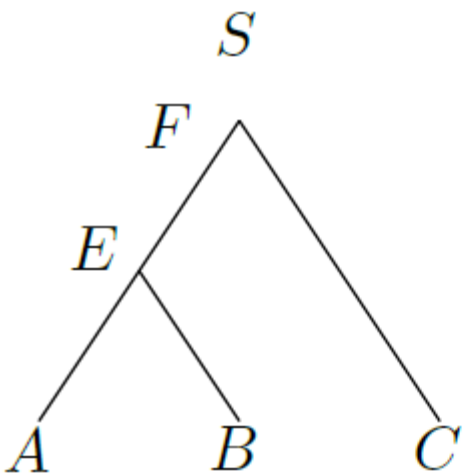
- Minimum Episodes inference problem
  - **Input** : species tree S, gene trees $G_1, \ldots, G_n$
  - **Find** : a valid gene-species mapping m that minimizes the number of ME duplications.

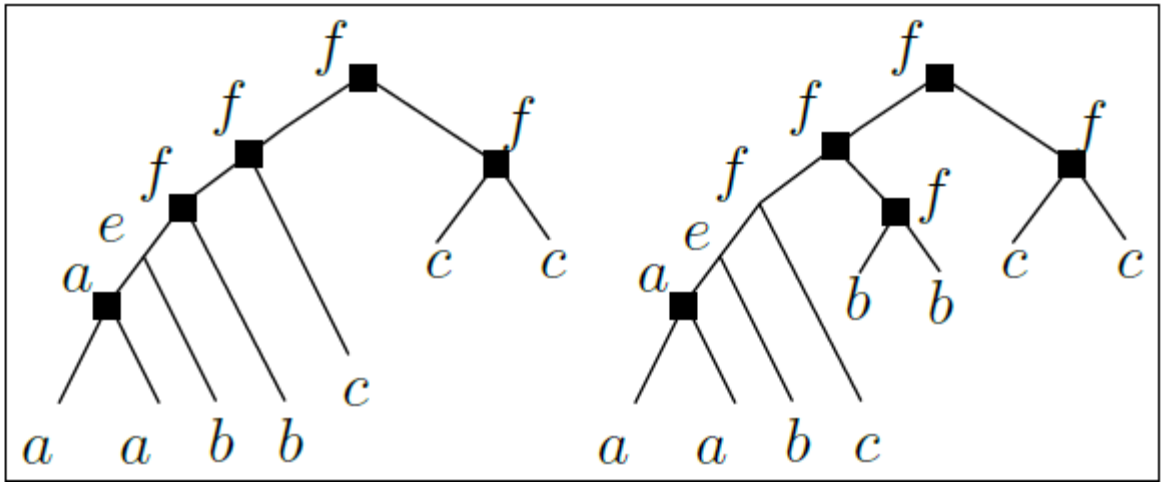
- Minimum Episodes inference problem
  - **Input** : species tree S, gene trees $G_1, \ldots, G_n$
  - **Find** : a valid gene-species mapping m that minimizes the number of ME duplications.

- Naive algorithm:
  - For each valid mapping m
    - Compute the number of ME duplications under m
  - Return the best mapping found

Reconciling with segmental Dups

- **Question**: given a fixed mapping m, how do we minimize the number of ME Dups?





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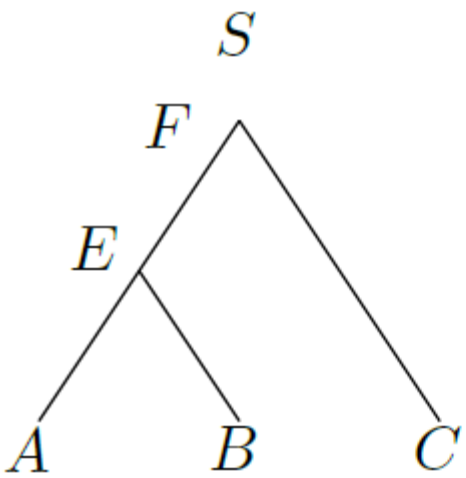

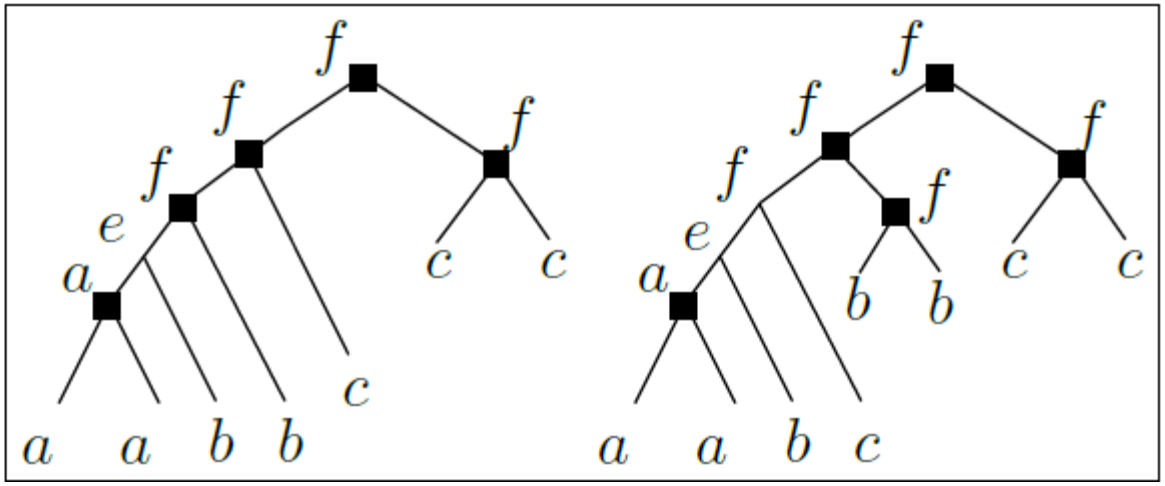

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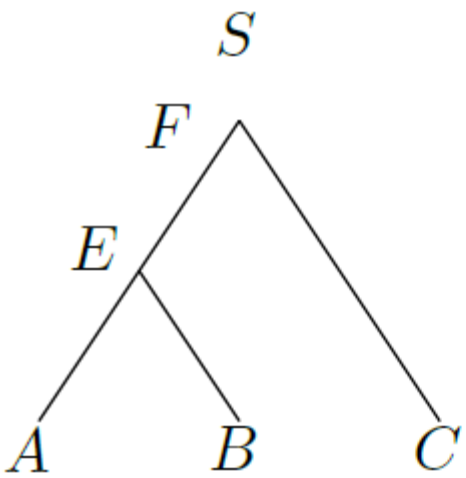

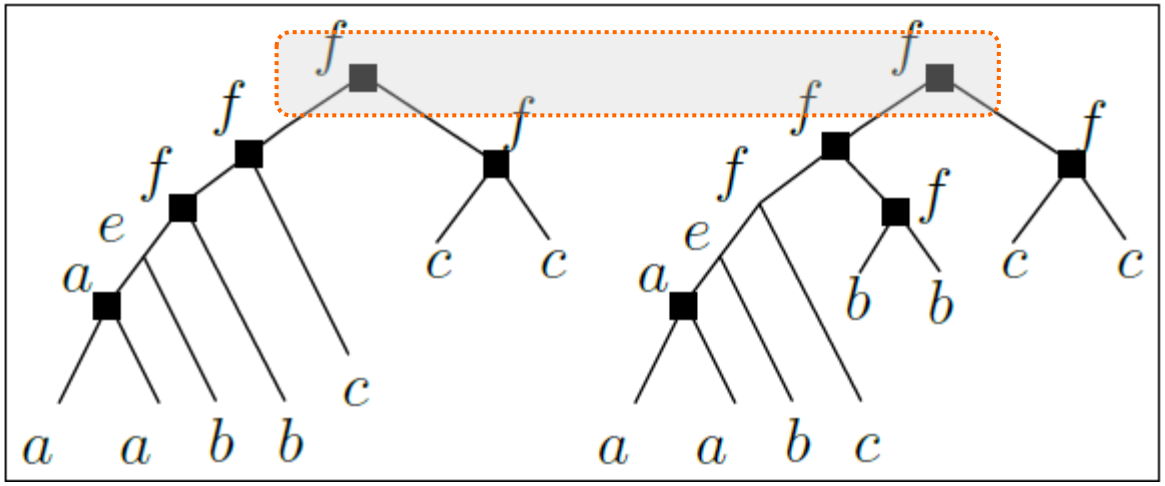

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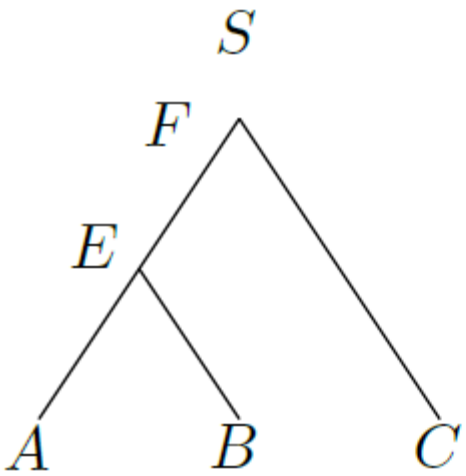

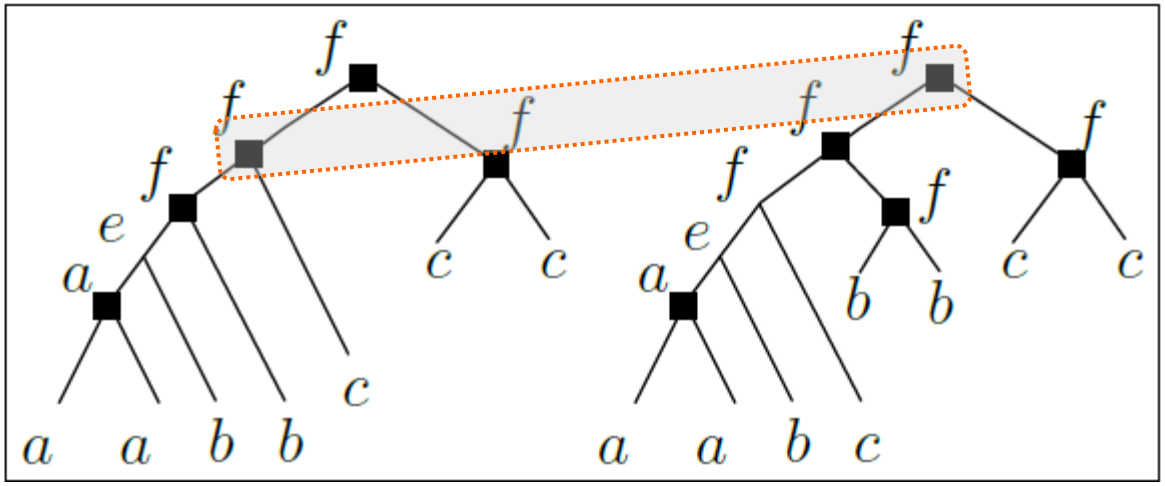

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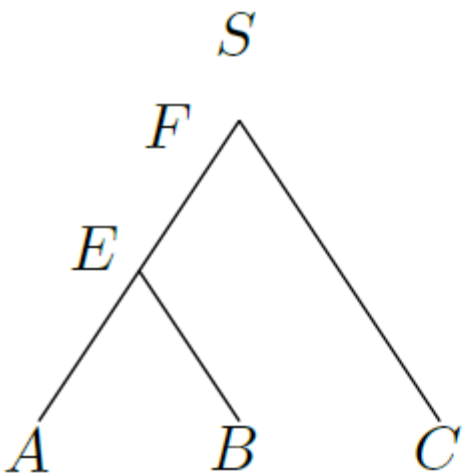

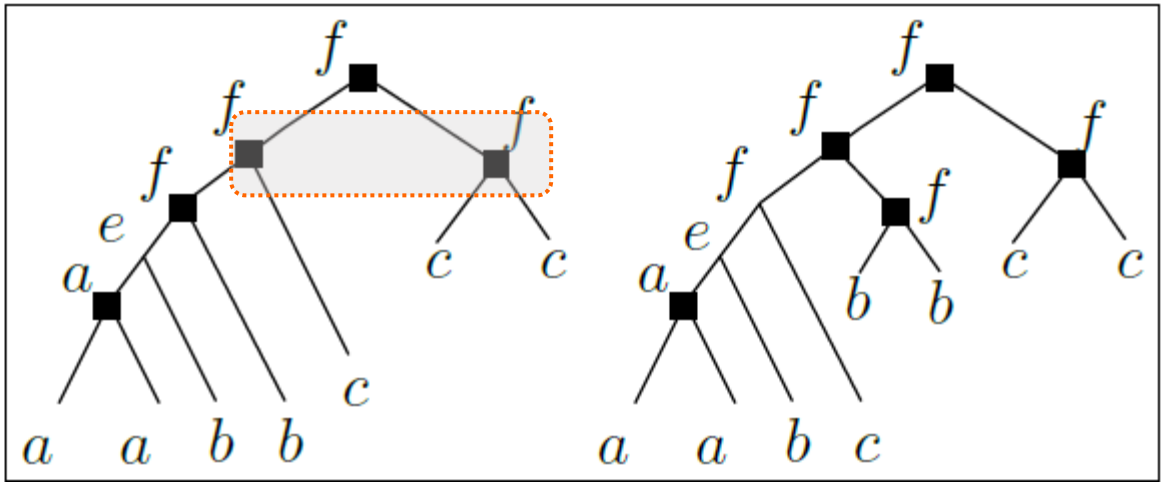

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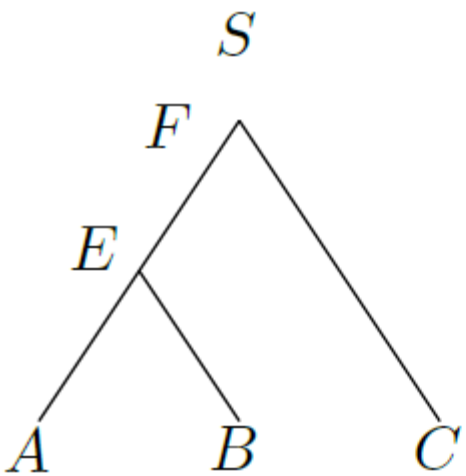

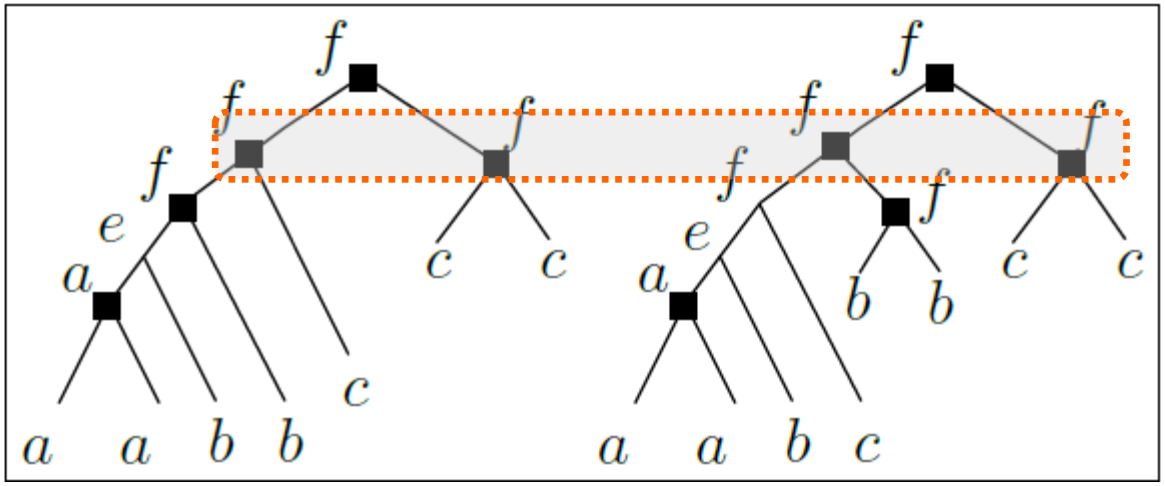

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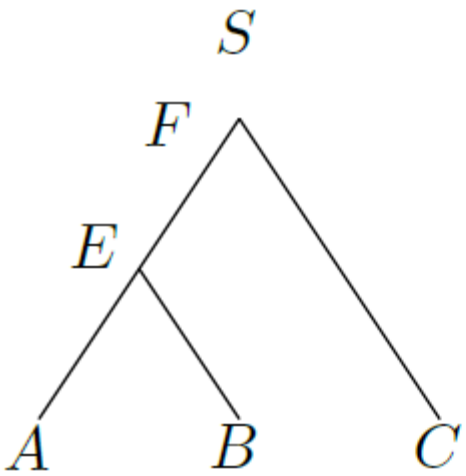

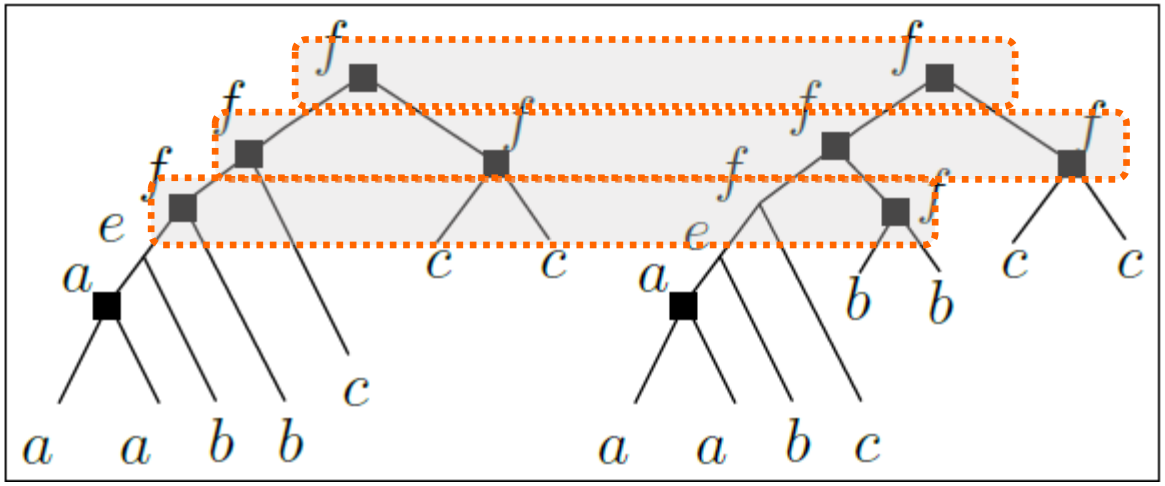

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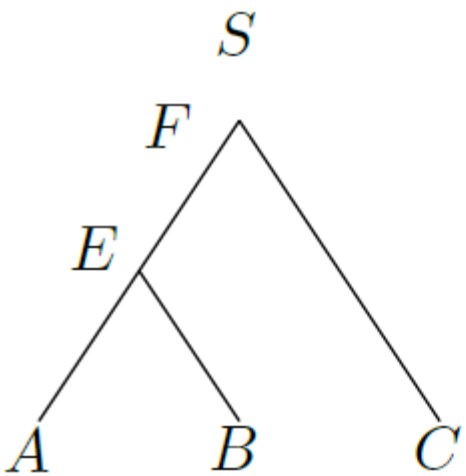

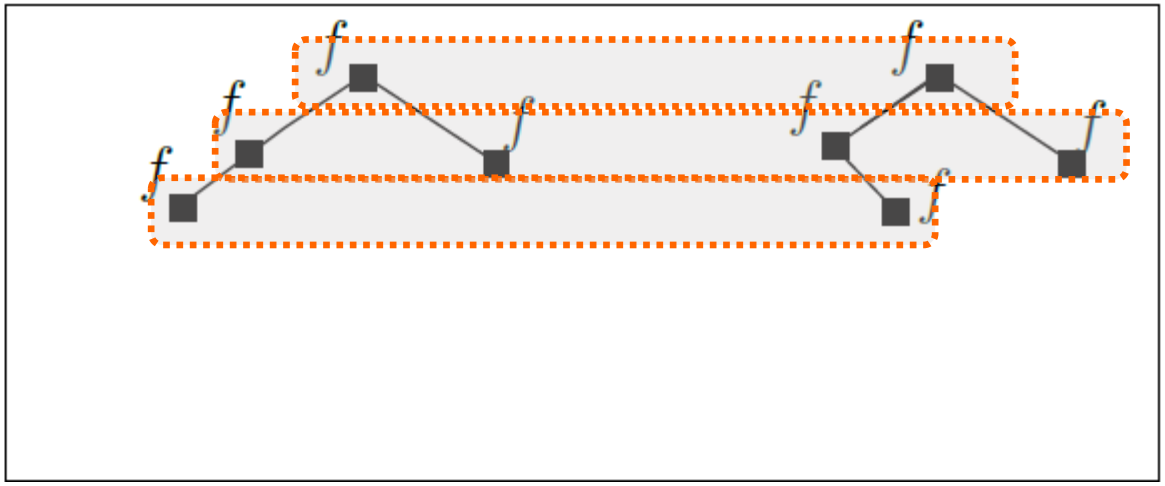

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- **Question**: given a fixed mapping m, how do we minimize the number of ME Dups?
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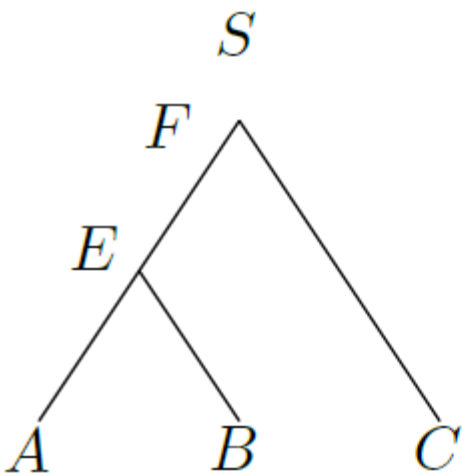
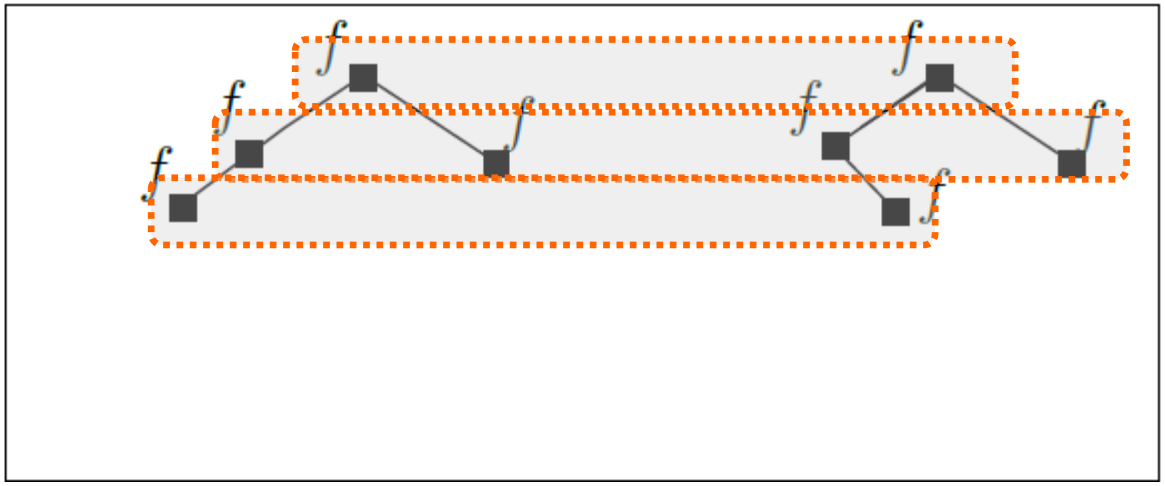
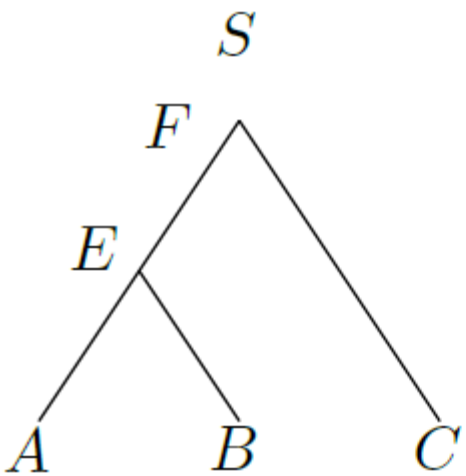
  - **# segmental Dups in *f* = height of *f* forest**

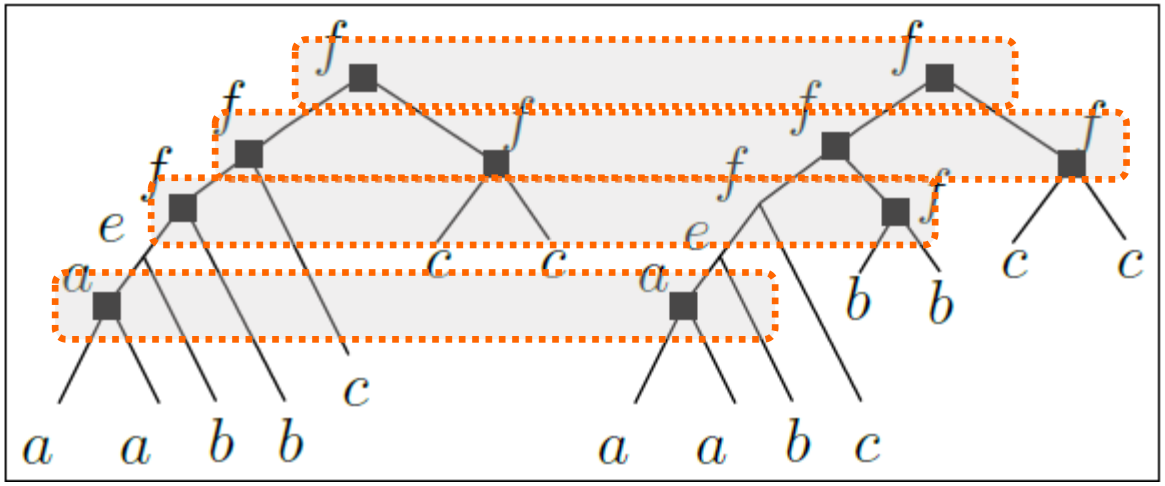




Reconciling with segmental Dups

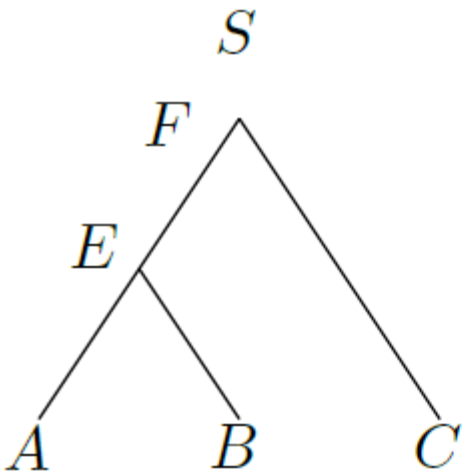
- **# segmental Dups in *f* = height of *f* forest = 3**
- **# segmental Dups in *a* = height of *a* forest = 1**
- **Total dup cost = 4**

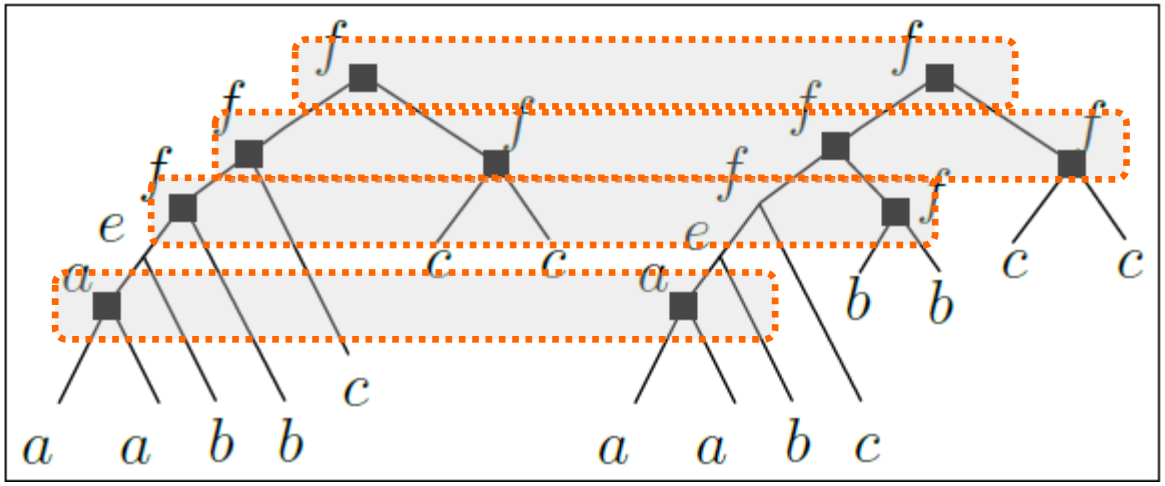




Reconciling with segmental Dups

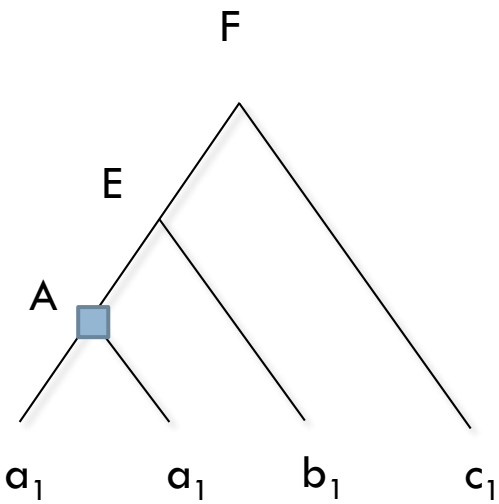
- **Input** : species tree S, gene trees $G_1, \ldots, G_n$
- **Find** : a valid gene-species mapping m that minimizes the sum of dup heights $\sum_{v \in V(S)} dupheight(v)$.

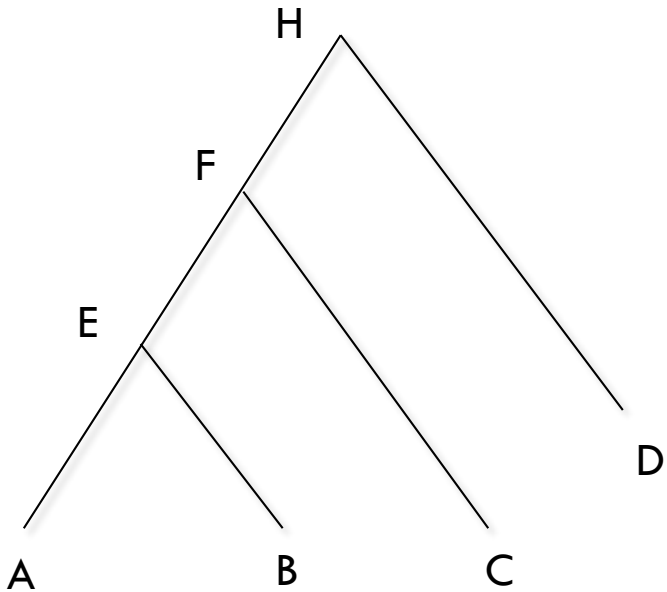




Reconciling with segmental Dups

- Main difficulty : remapping a Dup can create a chain of Dups above it.

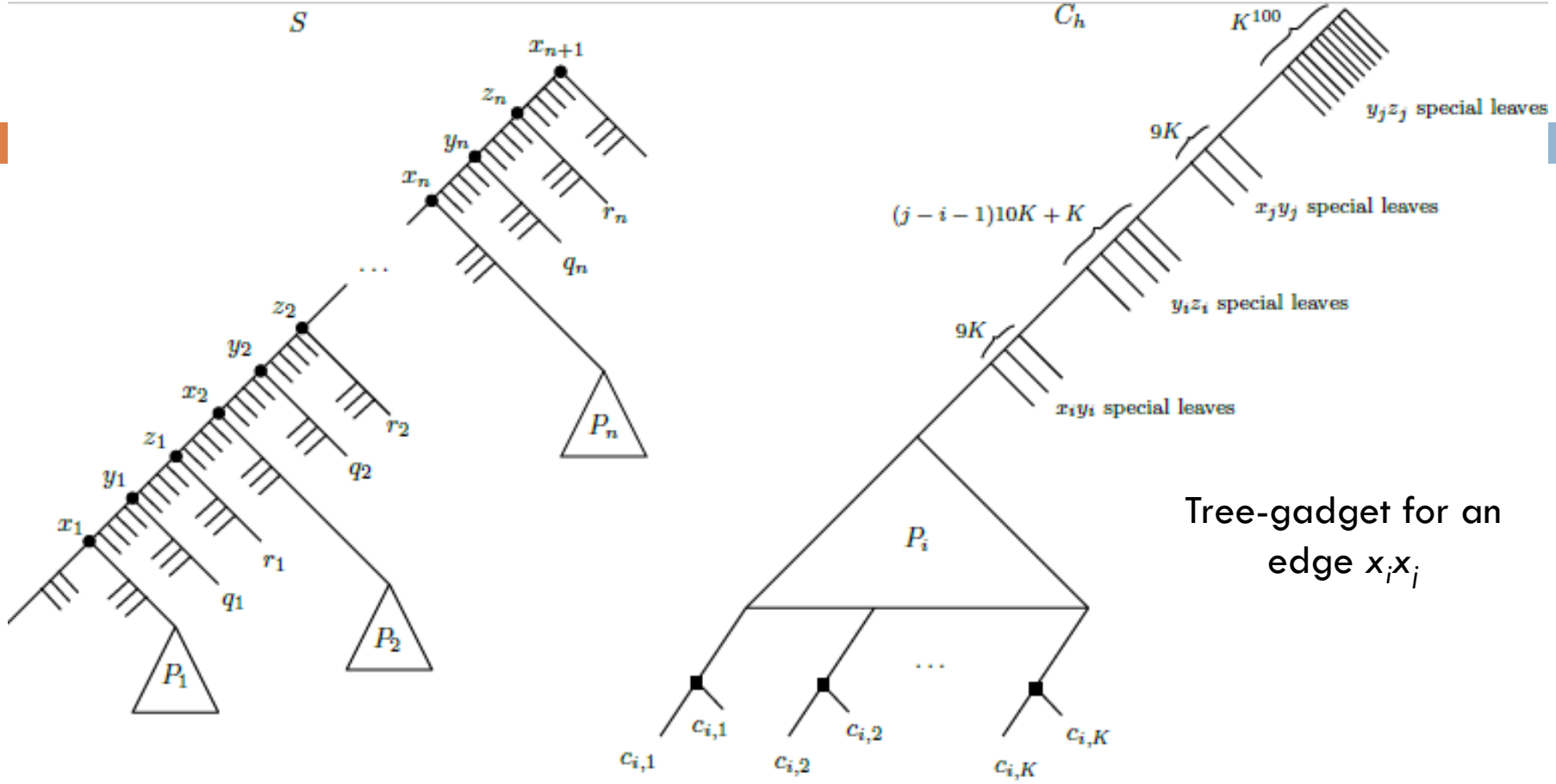




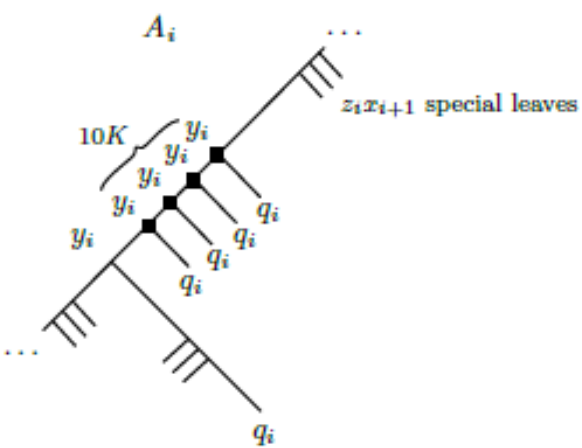
NP-hardness of ME clustering

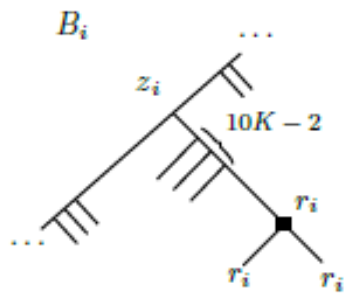
- Complexity was left opened in Paszek & Gorecki in 2017.

- **Theorem:** Finding an optimal reconciliation with the minimum number of ME Dups is NP-hard.
  - *[Dondi, L & Scornavacca, AMB 2019]*
  - Reduction from Vertex Cover



Tree-gadget for an edge $x_i x_j$





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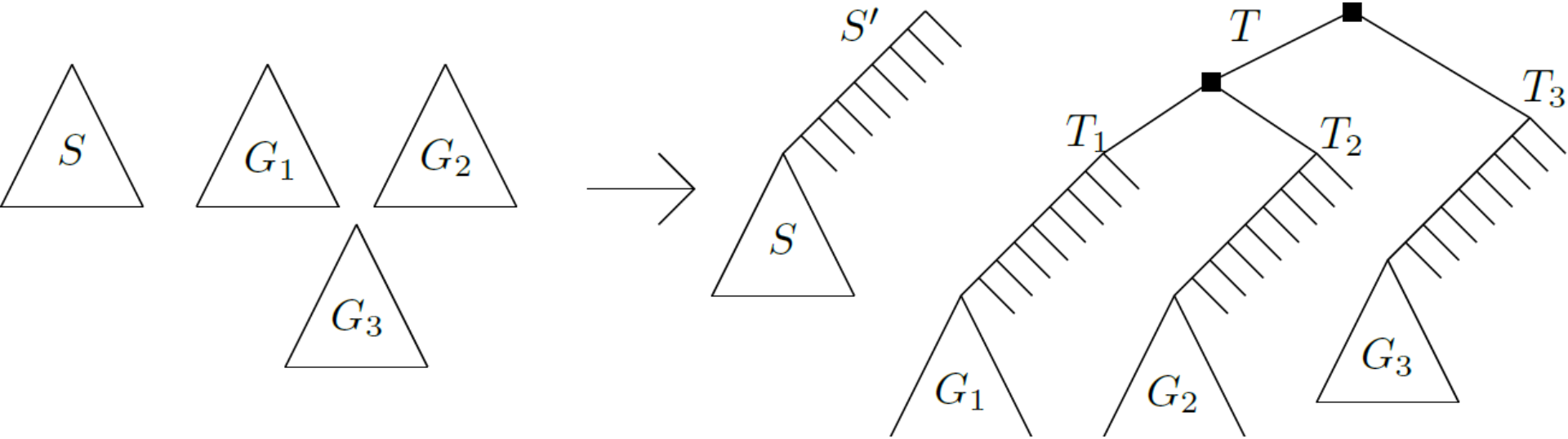
- **Theorem**: finding an optimal reconciliation with minimum ME Dups is NP-hard, **even if only one gene tree is given in the input**.

NP-hardness of ME clustering

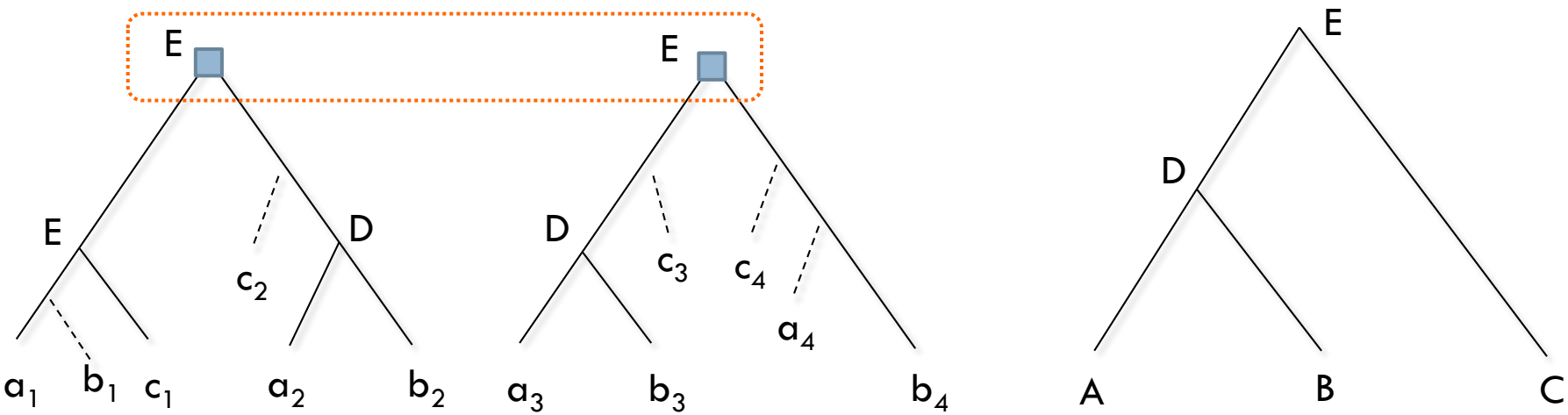
- **Theorem**: finding an optimal reconciliation with minimum ME Dups is NP-hard, **even if only one gene tree is given in the input.**
  - Reduction from reconciliation with many gene trees: just join all the gene trees under many speciations.



Incorporating gene losses

Incorporating gene losses

- **Input** : species tree S, gene trees $G_1, \ldots, G_n$, dup cost δ, loss cost λ
- **Find** : a valid gene-species mapping m that minimizes δ * (sum of Dup heights) + λ * (number of losses)



1 DUP, 5 LOSSES (before, we had 2 DUPS, 3 LOSSES)

The case of $\lambda \geq \delta$

- $\lambda \geq \delta$ => losses are worse than Dups.

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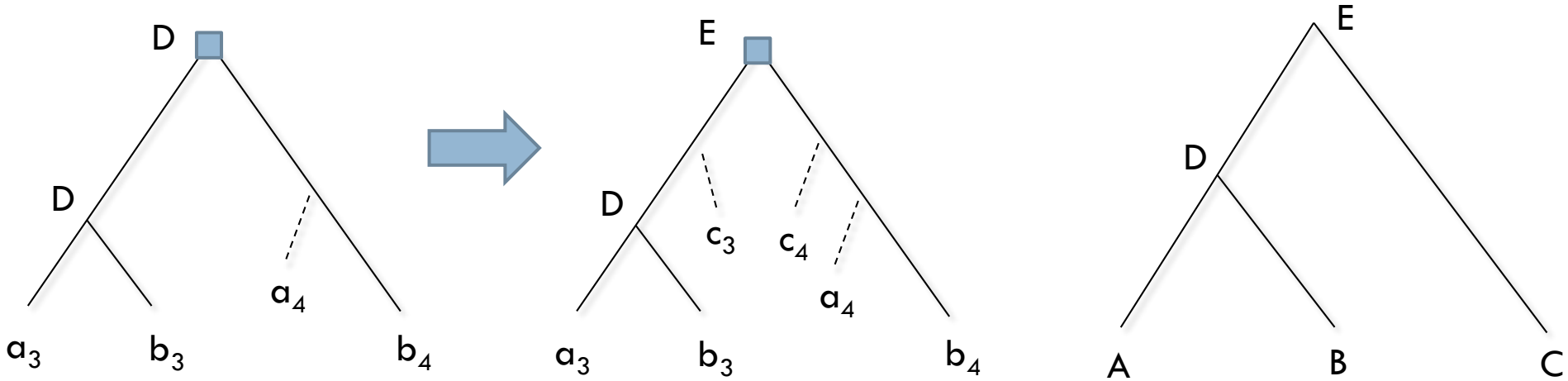
- $\lambda \geq \delta$ => losses are worse than Dups.
- **Theorem**: when $\lambda \geq \delta$, the usual LCA mapping yields an optimal reconciliation. It is also the unique optimal reconciliation if $\lambda > \delta$.

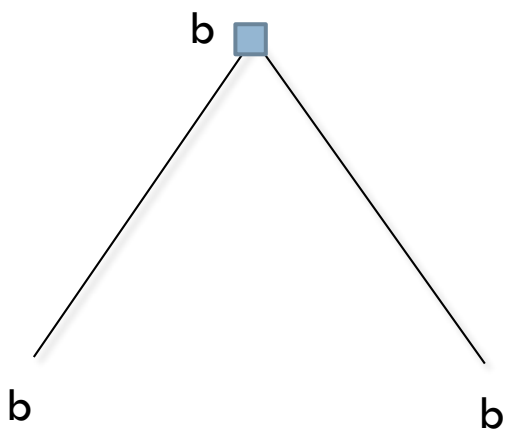


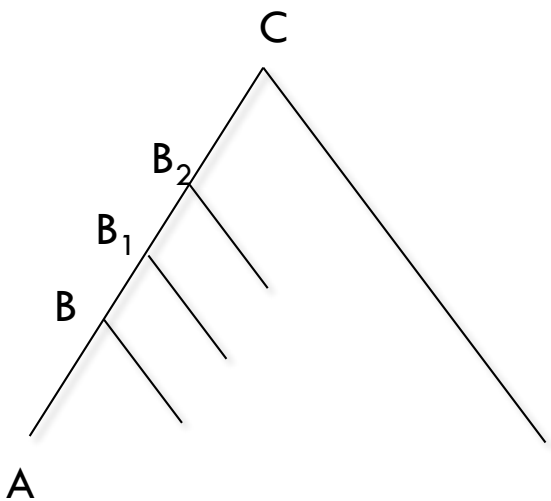
An FPT algorithm for $\lambda < \delta$

- An $O((\delta/\lambda)^{d+1} n)$ time algorithm.
  - *d* is the sum of Dup heights in an optimal solution
  - e.g. when $\delta = 3$, $\lambda = 2$, we get a $O(1.5^{d+1} n)$ algorithm.

An FPT algorithm for $\lambda < \delta$

- When we remap a Dup node up by *k* species, we create at least *k* new losses.





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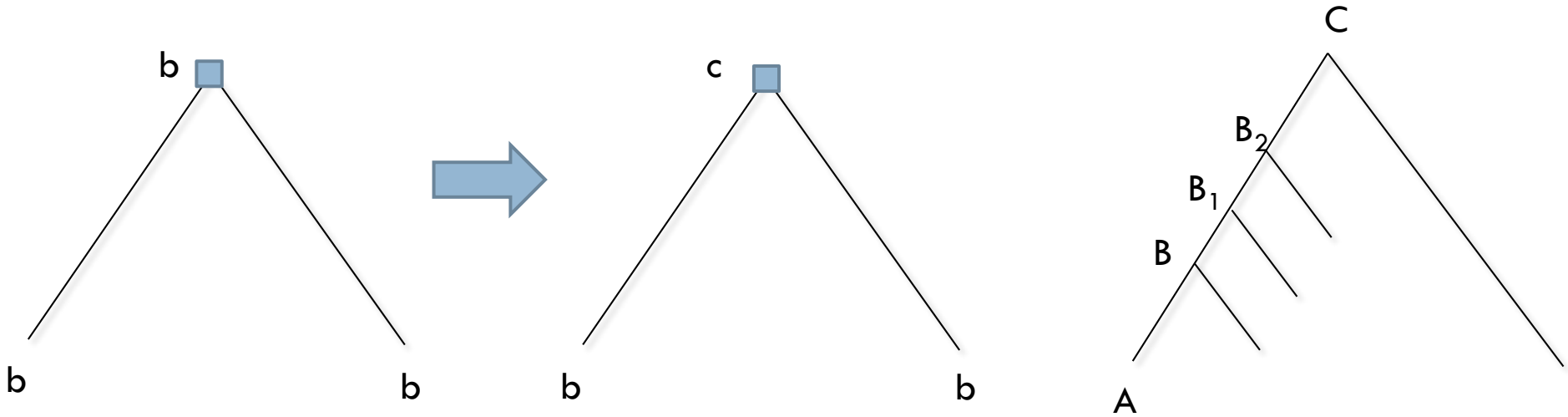

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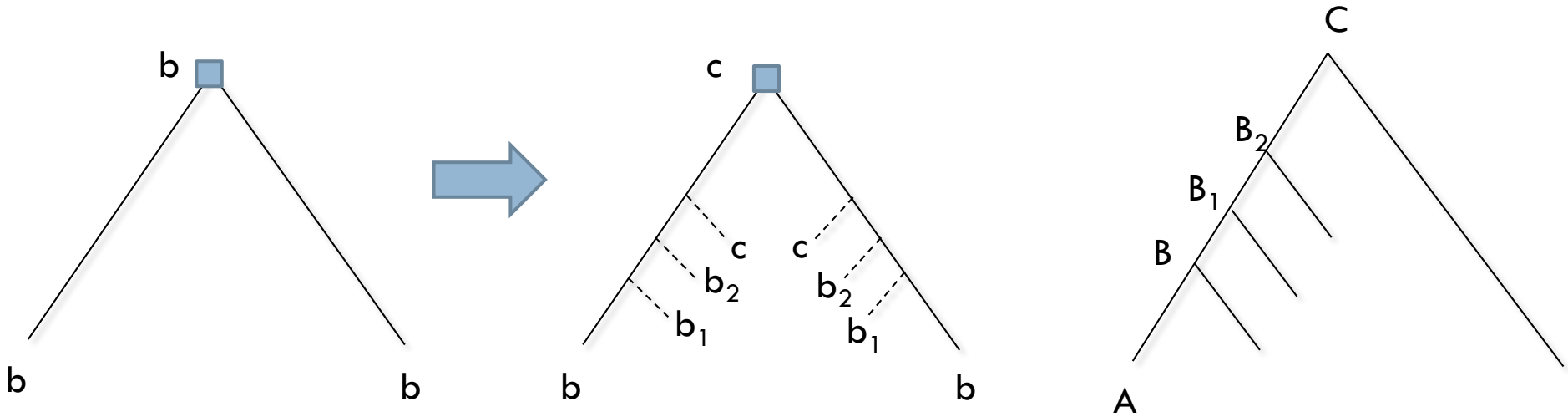
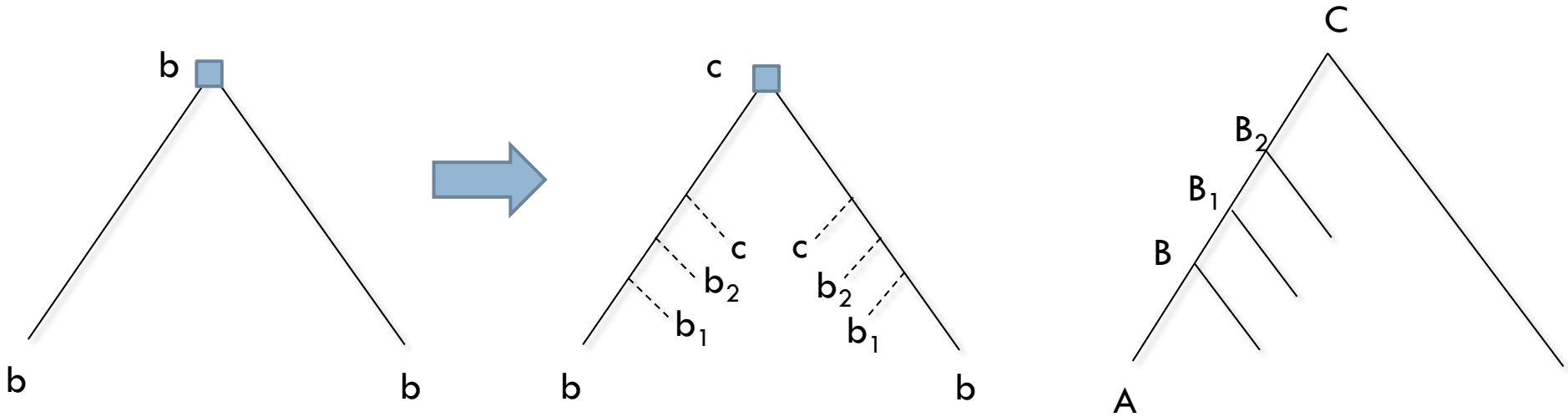


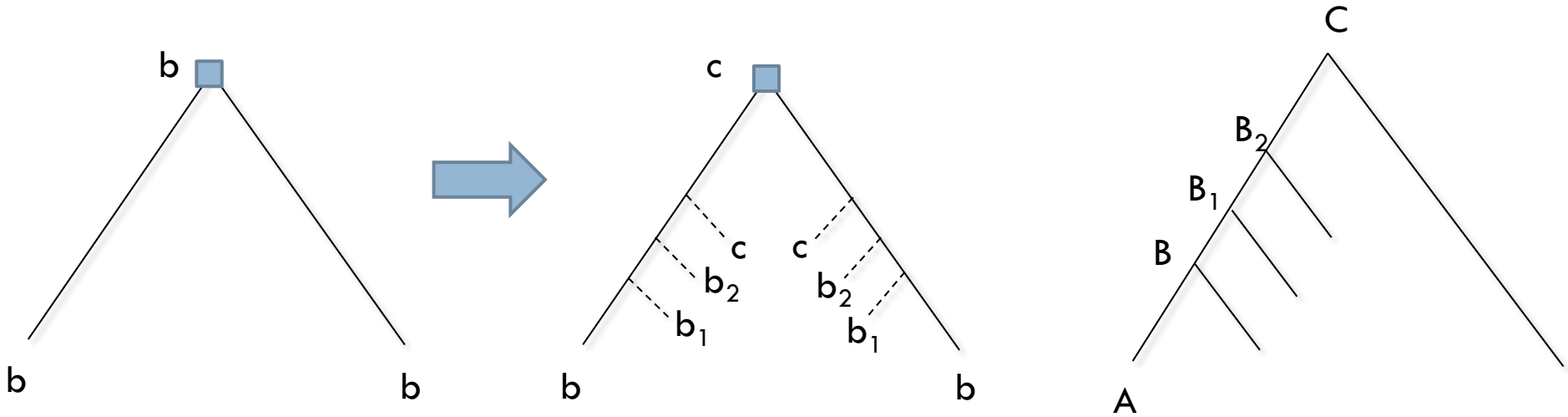
An FPT algorithm for $\lambda < \delta$

- When we remap a Dup node up by *k* species, we create at least *k* new losses.
- If we remap a Dup node up by more than δ/λ species, we save 1 Dup but create $> \delta/\lambda$ losses.



An FPT algorithm for $\lambda < \delta$

- When we remap a Dup node up by *k* species, we create at least *k* new losses.
- If $k > \delta/\lambda$ losses, *never worth it*.



An FPT algorithm for $\lambda < \delta$

- Branching algorithm:
  - Take a Dup node *x* mapped to species *s* under the LCA mapping.
  - Branch into the δ/λ possible ways of remapping *x* to an ancestor *s'* of *s*.
    - *If x is well-chosen, each time we branch, Dup heights increase by 1.*

An FPT algorithm for $\lambda < \delta$

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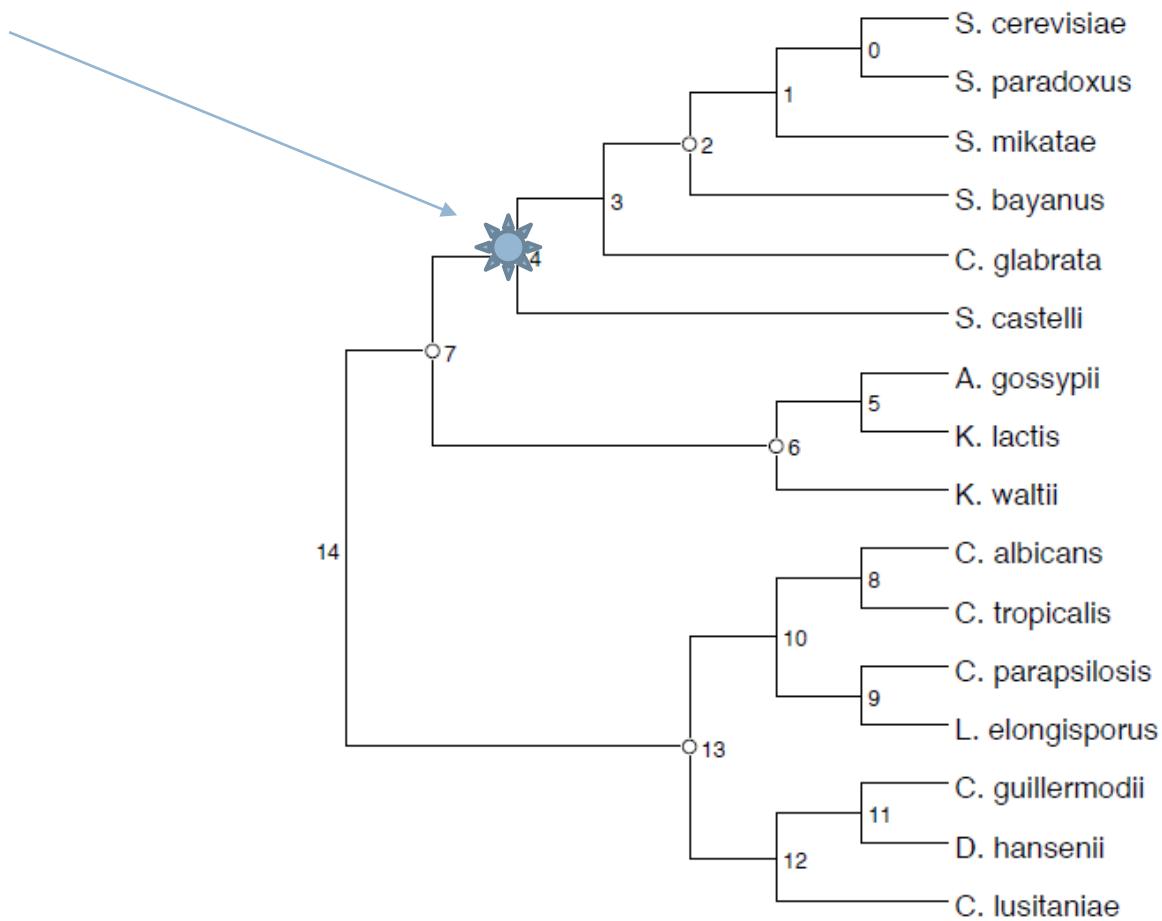
    - *If x is well-chosen, each time we branch, Dup heights increase by 1.*
  - Search tree of degree δ/λ and height at most *d*.
    - $O((\delta/\lambda)^{d+1} n)$ complexity

Experiments

- We implemented the FPT algorithm.
  - https://github.com/manuellafond/Multrec
- We applied it on 2 datasets:
  - Yeast species from [Butler & al., Nature, 2009]
    - 16 species, 2379 gene trees
  - Eukaryotes from [Guigo & al., Mol Phylo Evo, 1996]
    - 16 species, 53 gene trees

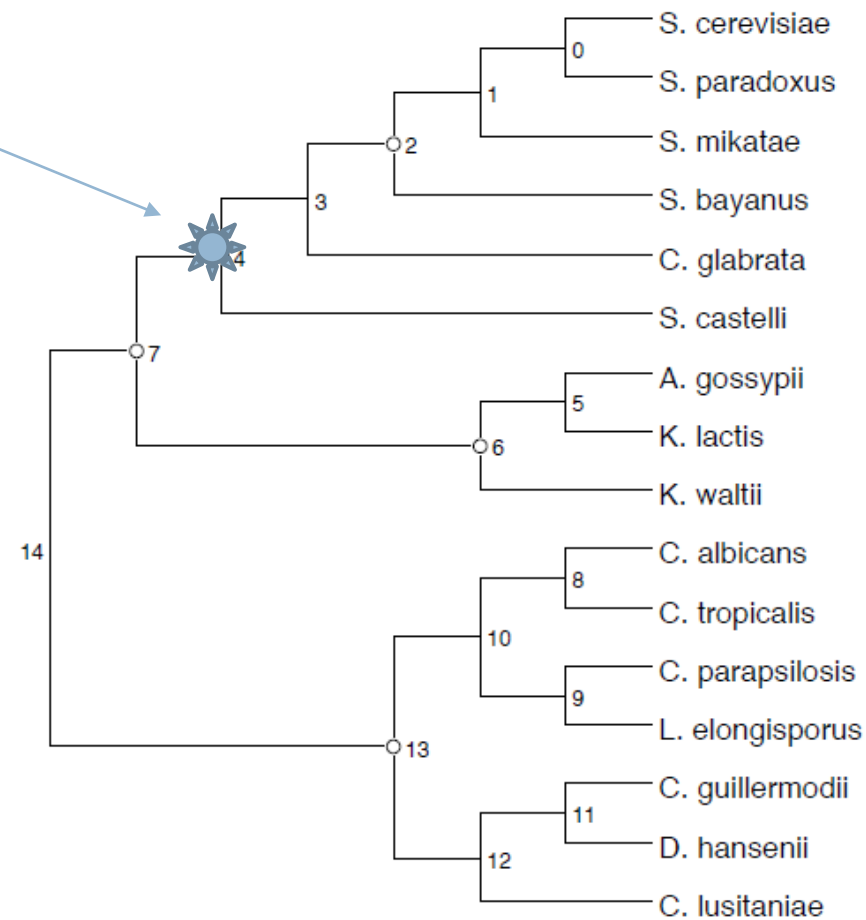
Experiments

- In the 2379 yeast trees, we infer a segmental Dup with **216 genes** ($\delta = 3, \lambda = 2$).
  - Located here



Experiments

- In the 2379 yeast trees, we infer a segmental Dup with **216 genes** ($\delta = 3, \lambda = 2$).
  - Located here
  - Coincides with WGD found using synteny in *[Kellis, Birren & Lander, Nature, 2004]*



Nodes 7,6,13,2 had segmental Dup with 190, 157, 148 and 136 *genes.*

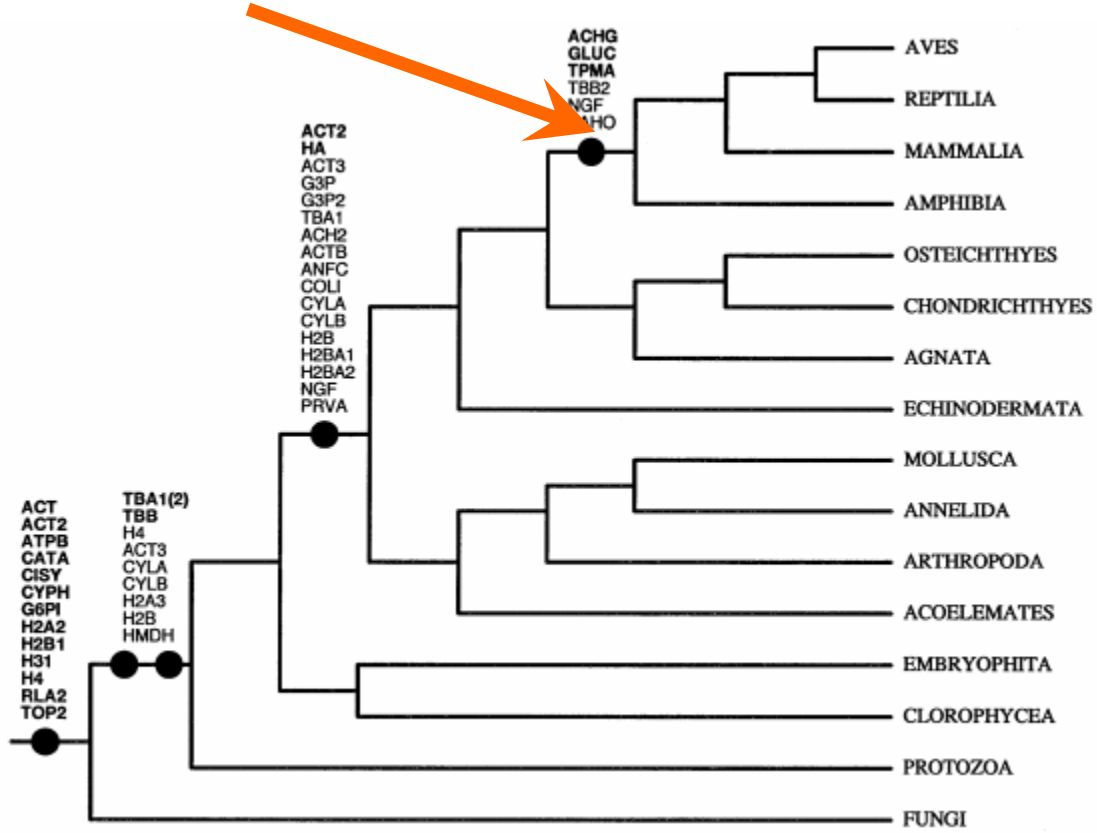
Experiments

- In the 53 Eukaryote gene trees.
  - *ExactMGD [Bansal & Eulenstein, Bioinf, 2008]* finds a solution with **5** segmental Dups
    - Does not allow speciations to become duplications.
  - We find a solution with **4 segmental Dups**
    - By setting $\delta > 61$, $\lambda = 1$
    - All segmental Dups found in *[Guigo & al., 1996]* are confirmed, **EXCEPT ONE**.

Experiments

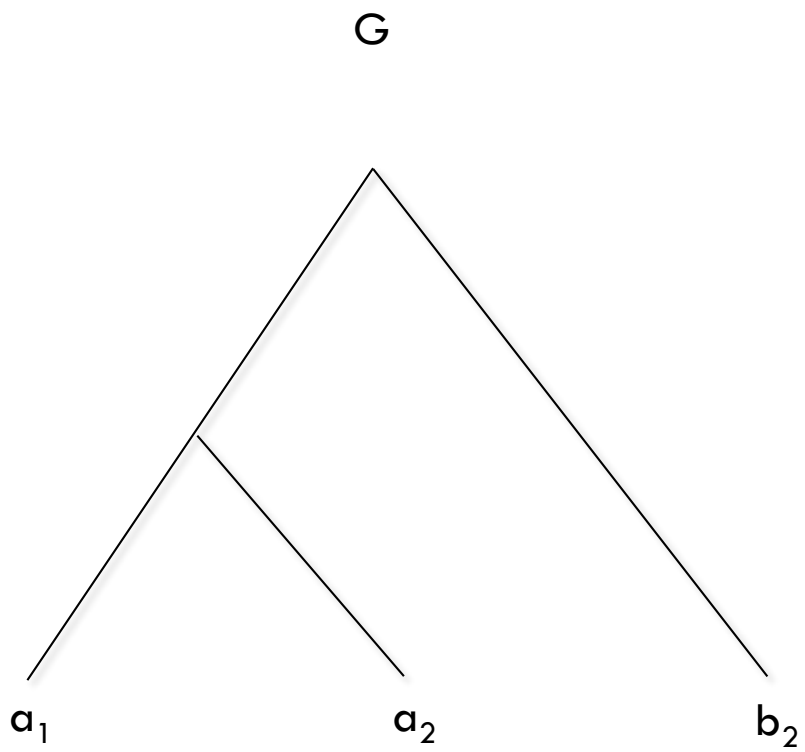
- In the 53 Eukaryote gene trees.

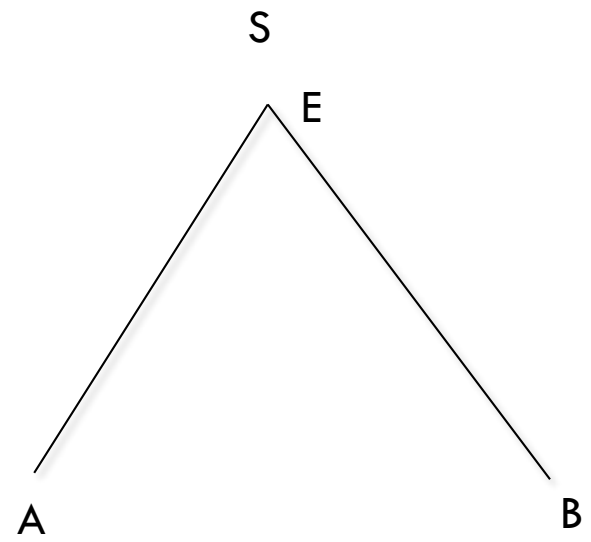
In our solutions, no Dup maps here (Tetrapoda)

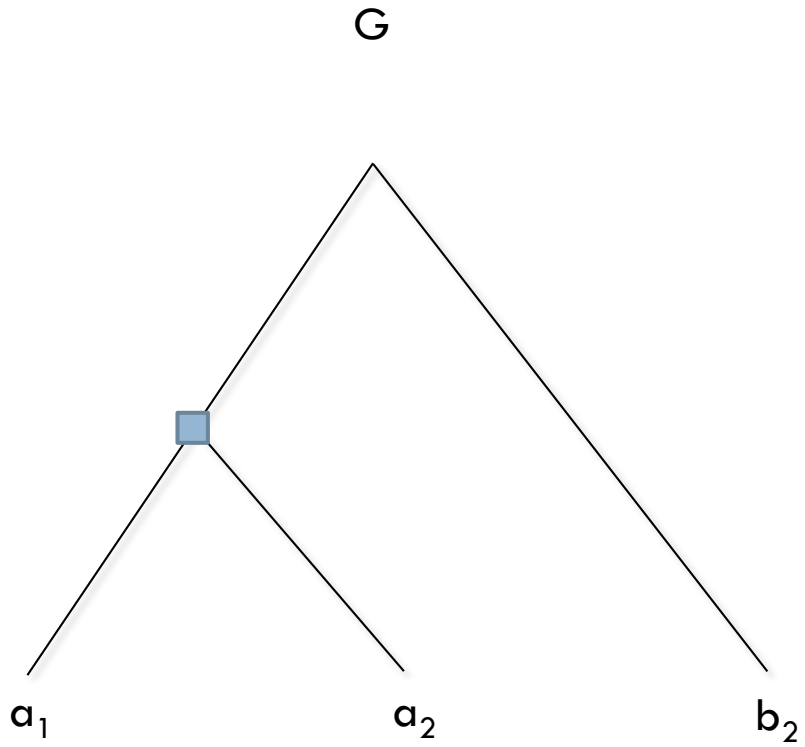


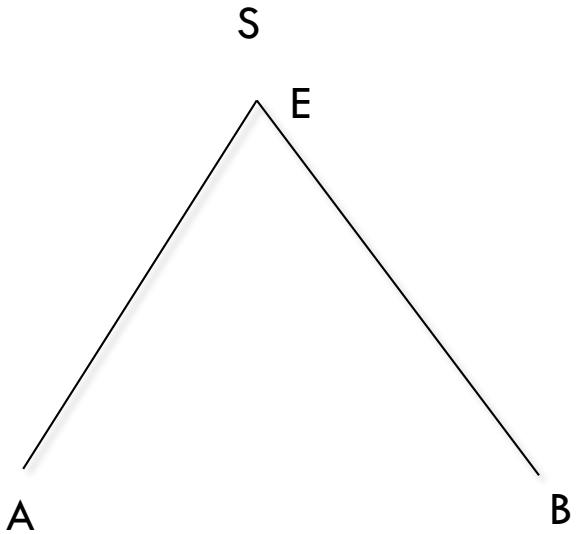
- Algorithmic challenges
  - Without losses, is the problem FPT in d? And with losses?
  - Constant factor approximation?
- Modeling challenges
  - Model the problem with segmental dups + segmental losses
  - Add segmental horizontal gene transfers
  - Add conserved adjacencies / syntenies into the optimization criteria

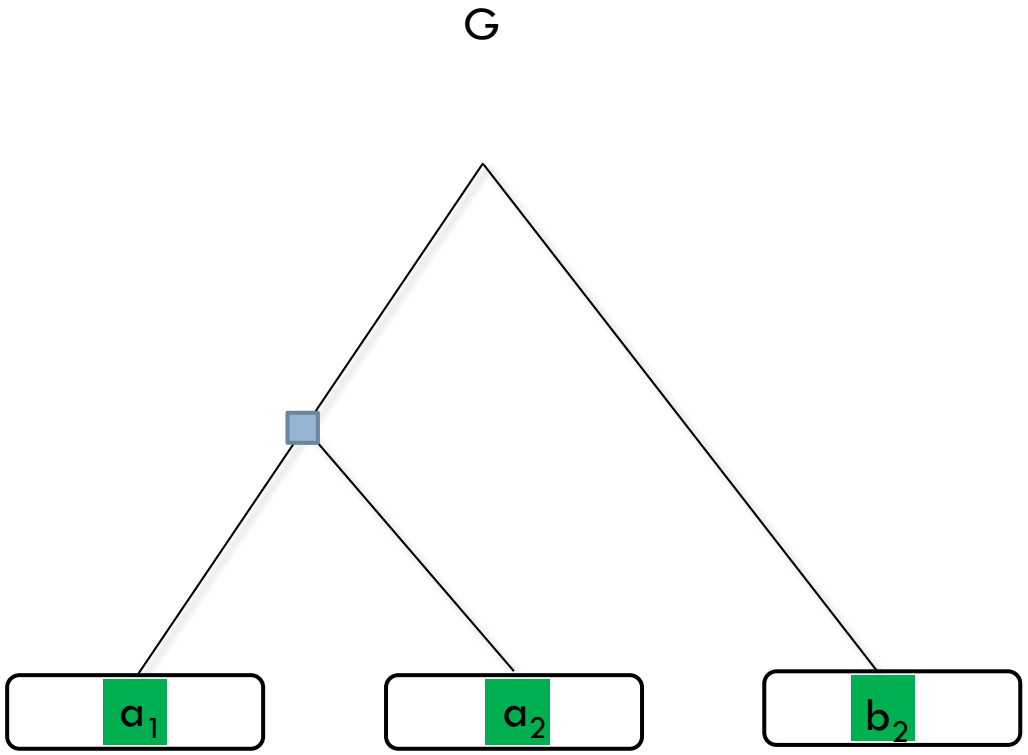
Incorporating syntenic blocks

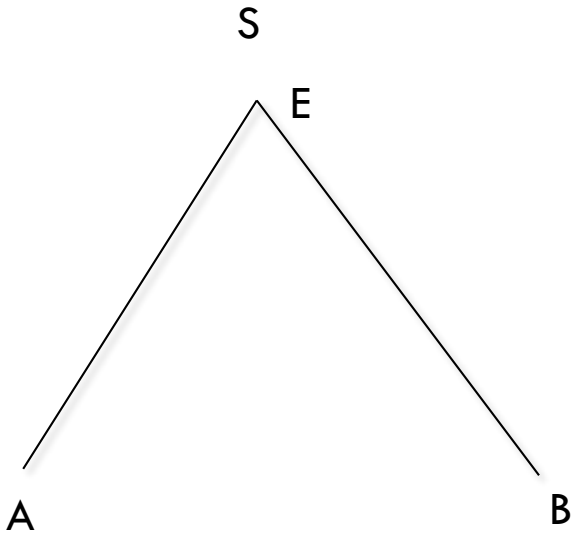

G
a_1
a_2
b_2

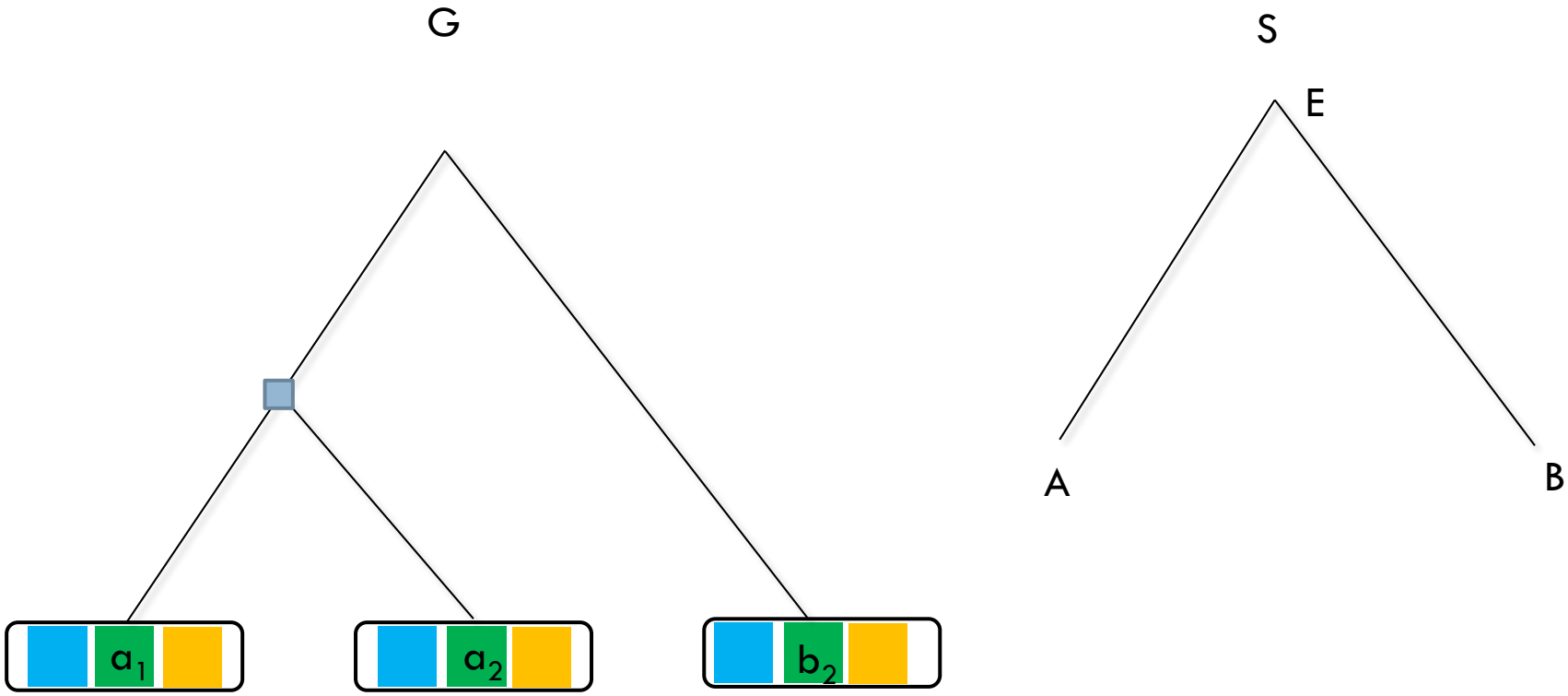

S
E
A
B

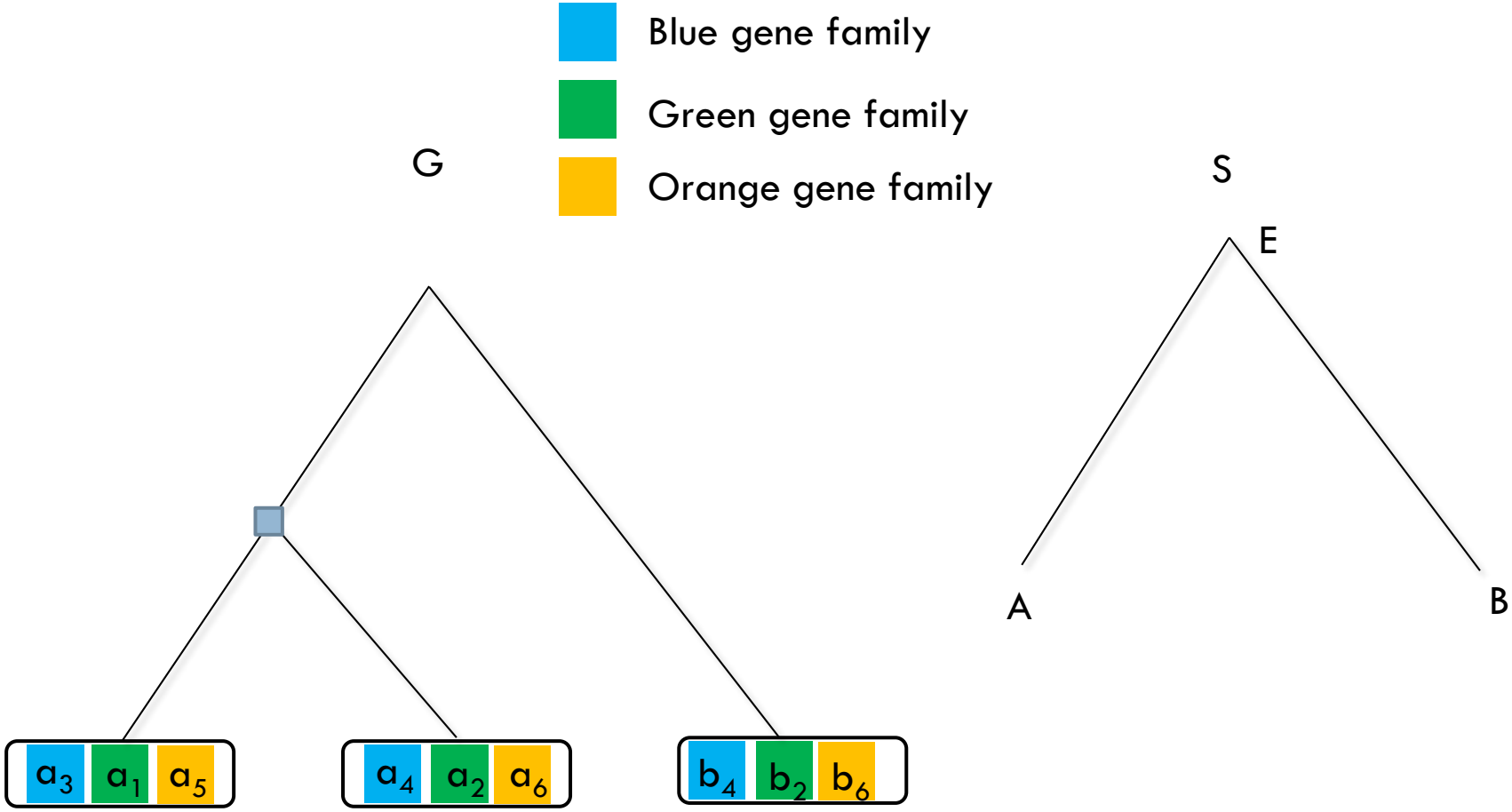

G
a_1
a_2
b_2

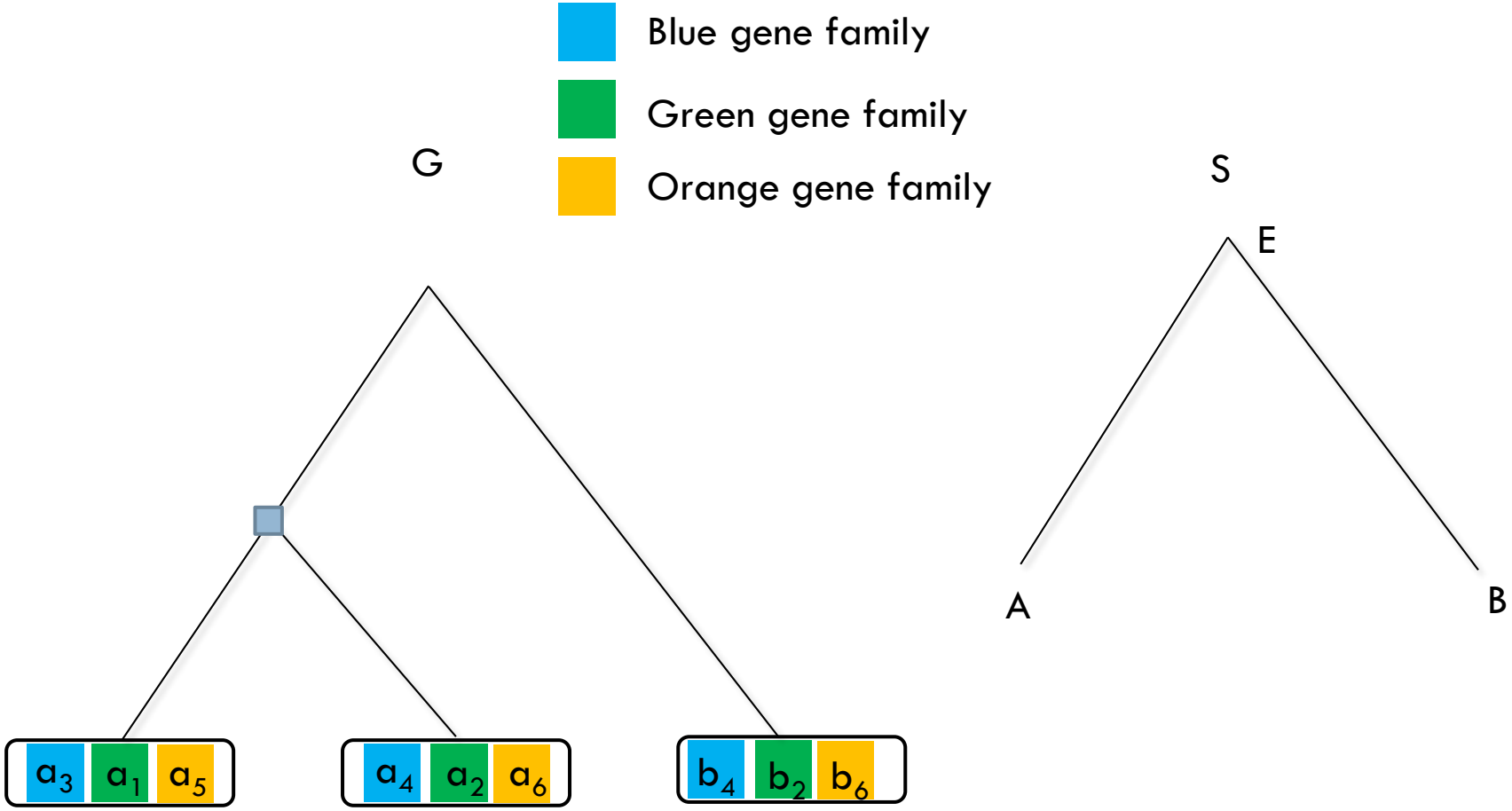

S
E
A
B


G
a_1
a_2
b_2

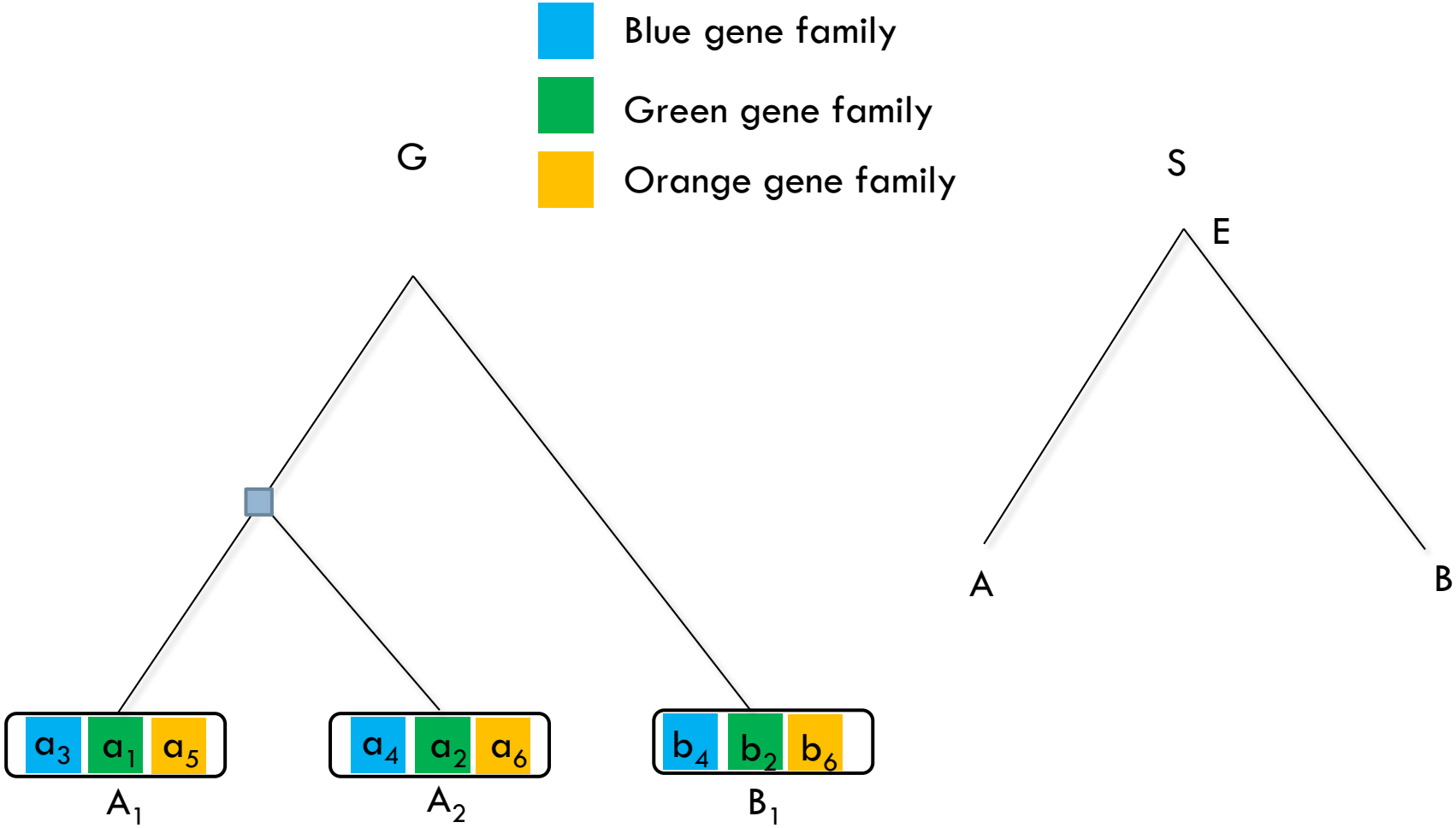

S
E
A
B


G
S
E
A
B
a_1
a_2
b_2


Blue gene family
Green gene family
Orange gene family
G
S
E
A
B
a_3 a_1 a_5
a_4 a_2 a_6
b_4 b_2 b_6



Syntenic blocks : segments with preserved gene order across species



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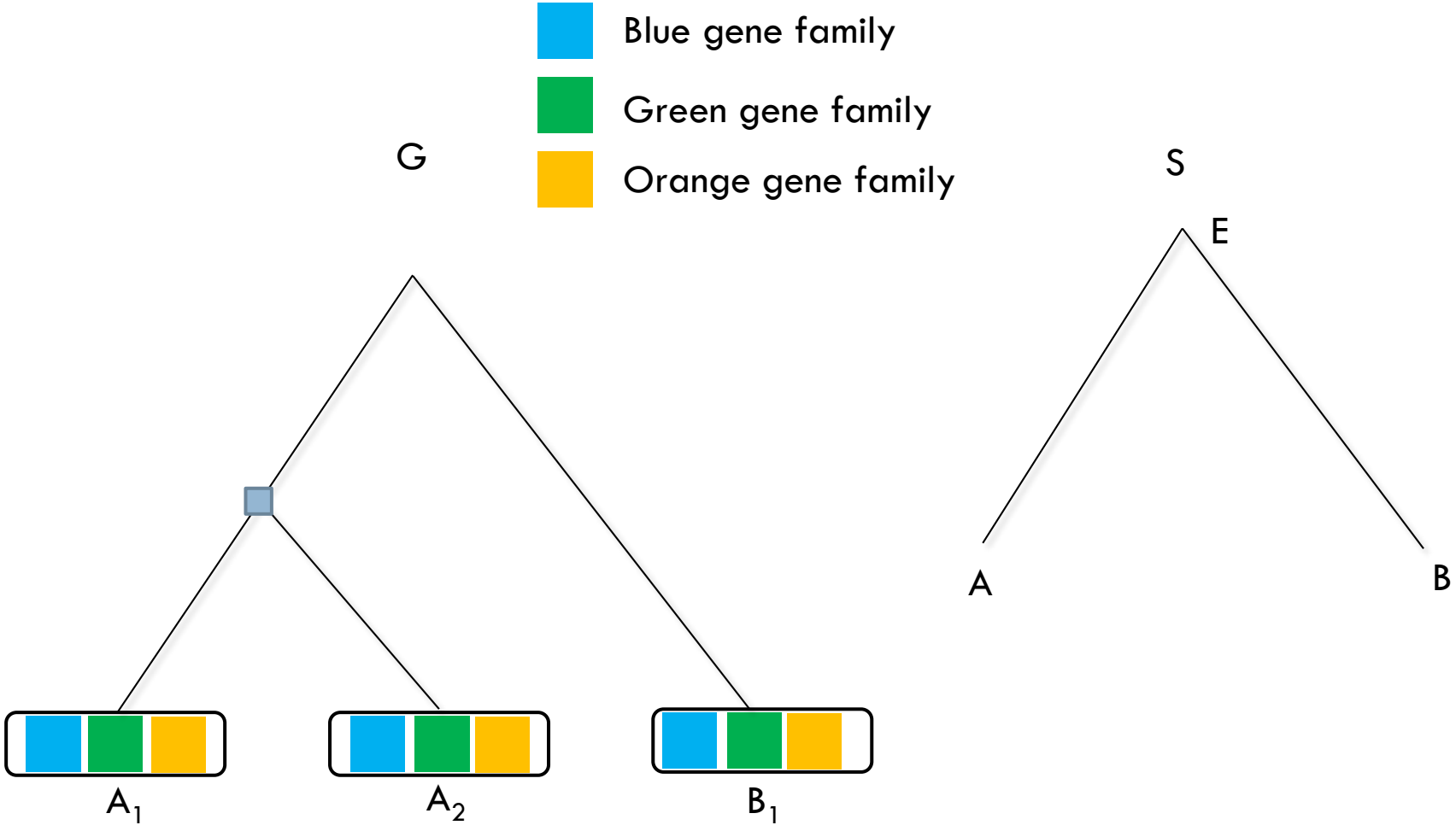

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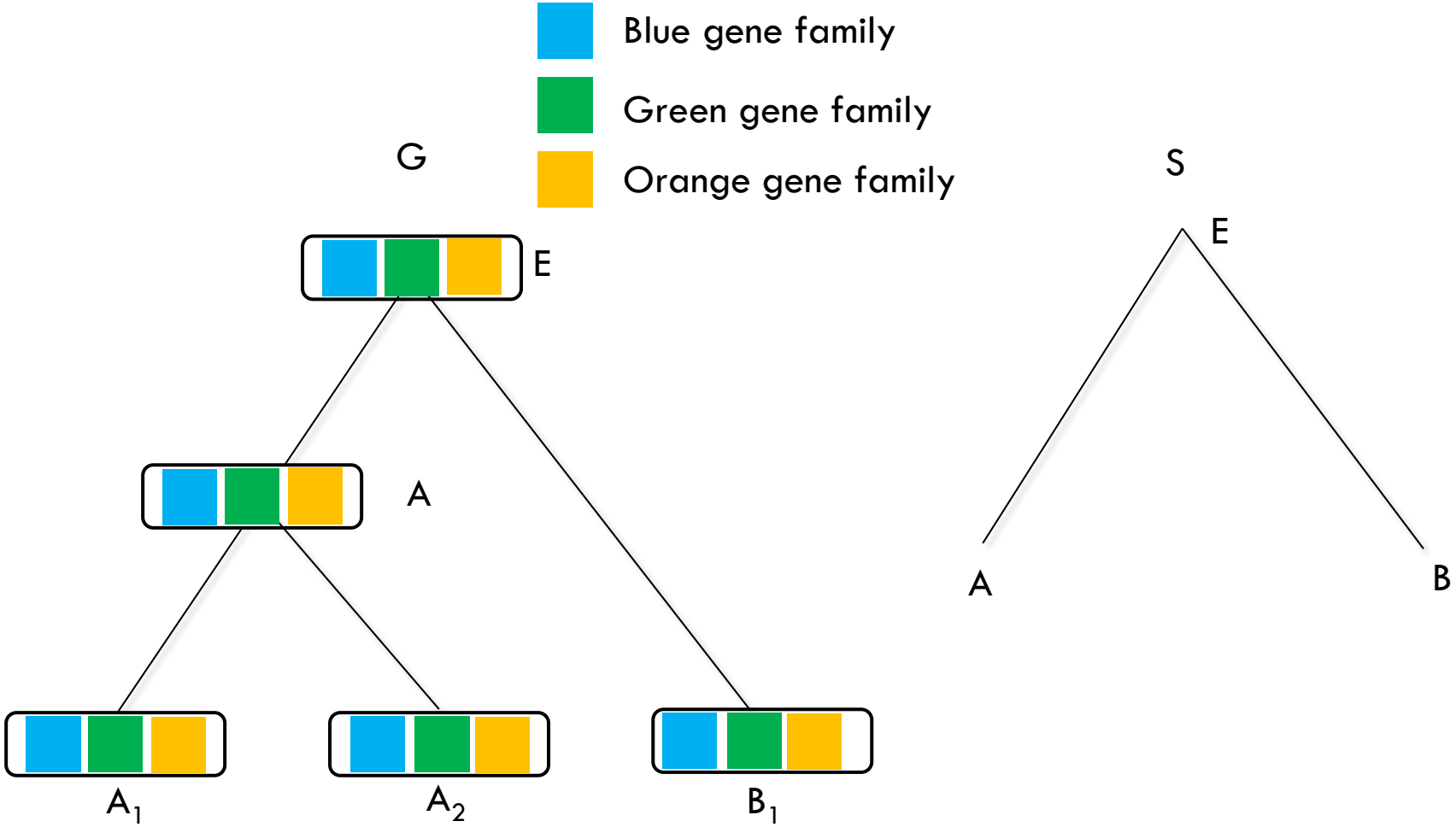
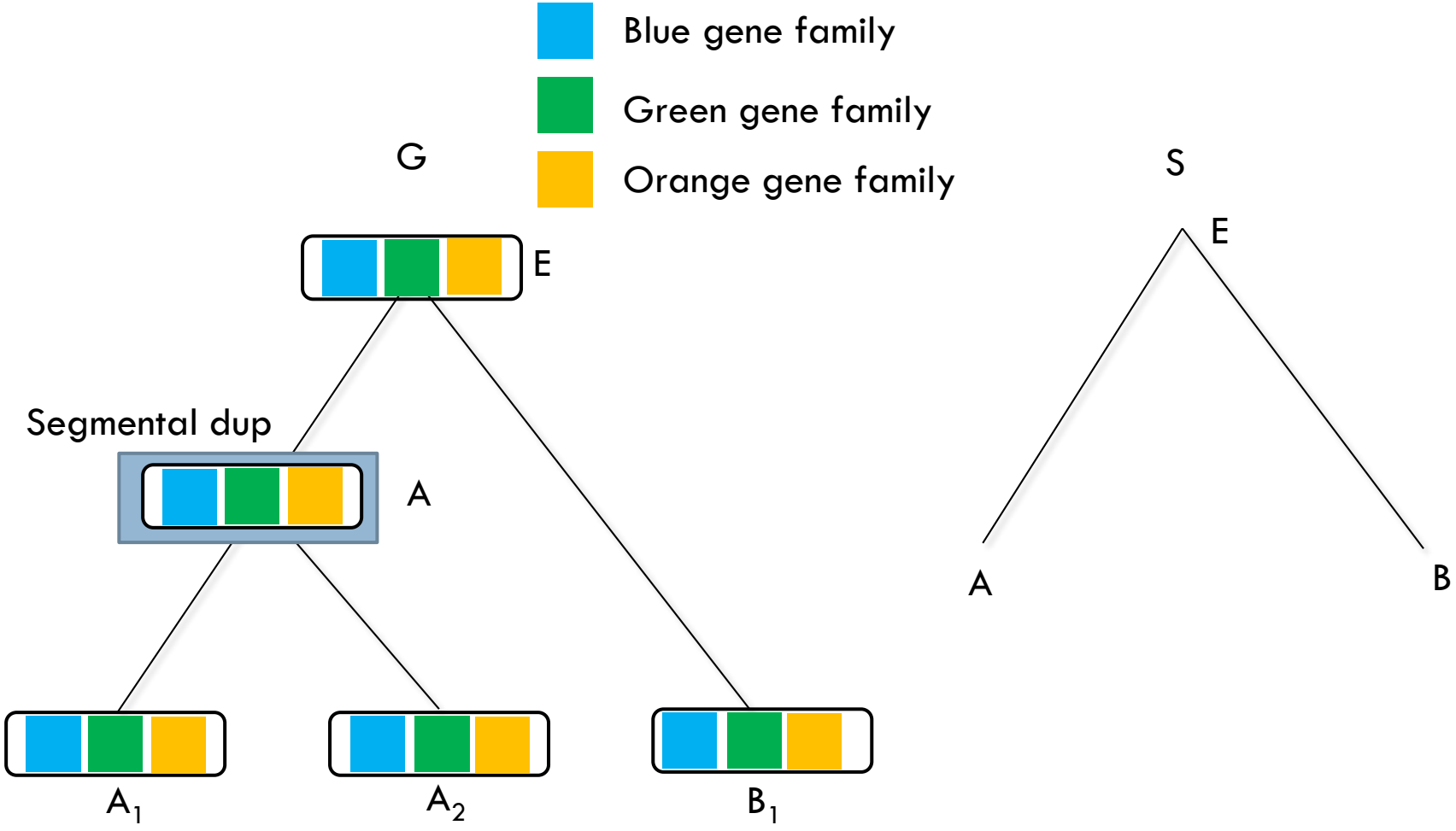


Syntenic blocks : segments with preserved gene order across species



Syntenic blocks : segments with preserved gene order across species

- Synteny tree reconciliation problem
  - **Input** : species tree S, a synteny tree T in which each leaf is labeled by a syntenic block
  - **Find** : an evolution of blocks across T with the minimum segmental dups + losses

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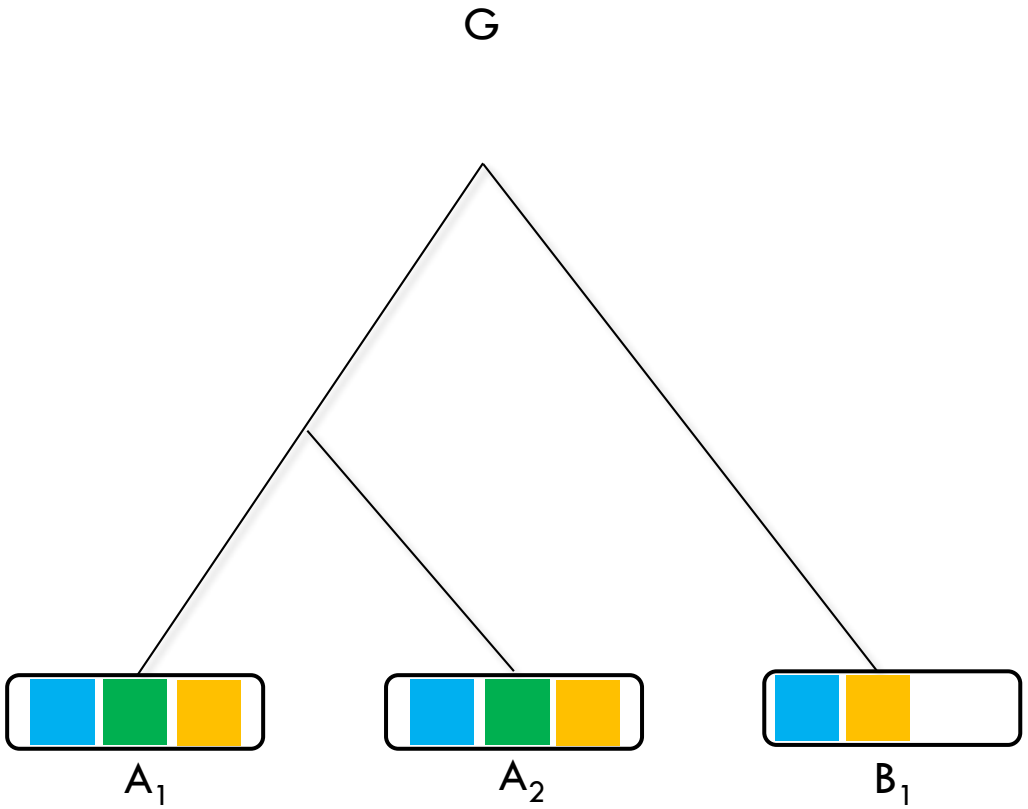
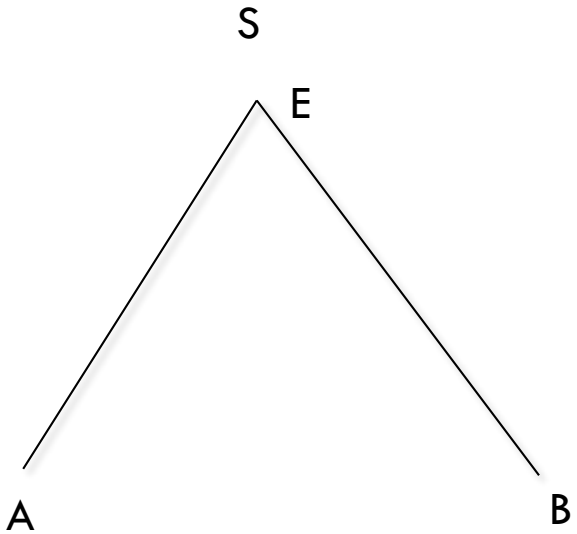
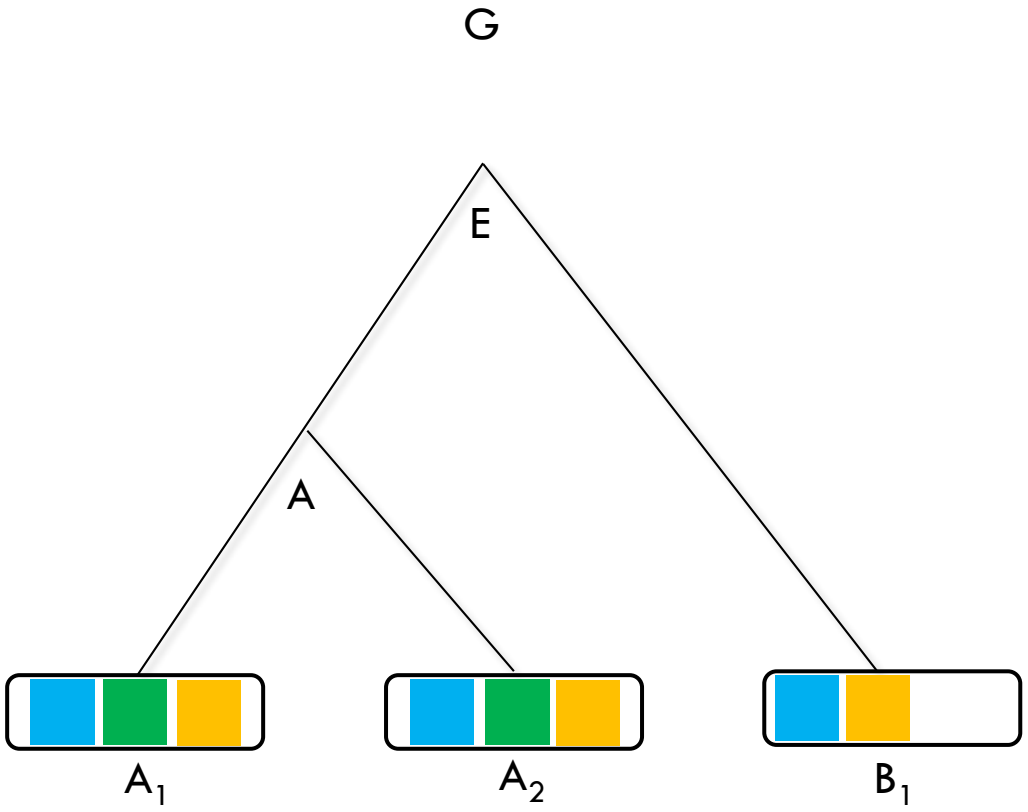
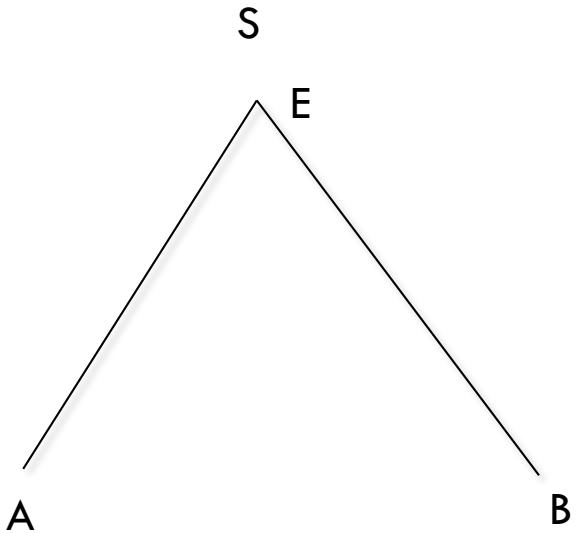
  - **Input** : species tree S, a synteny tree T in which each leaf is labeled by a syntenic block
  - **Find** : an evolution of blocks across T with the minimum segmental dups + losses

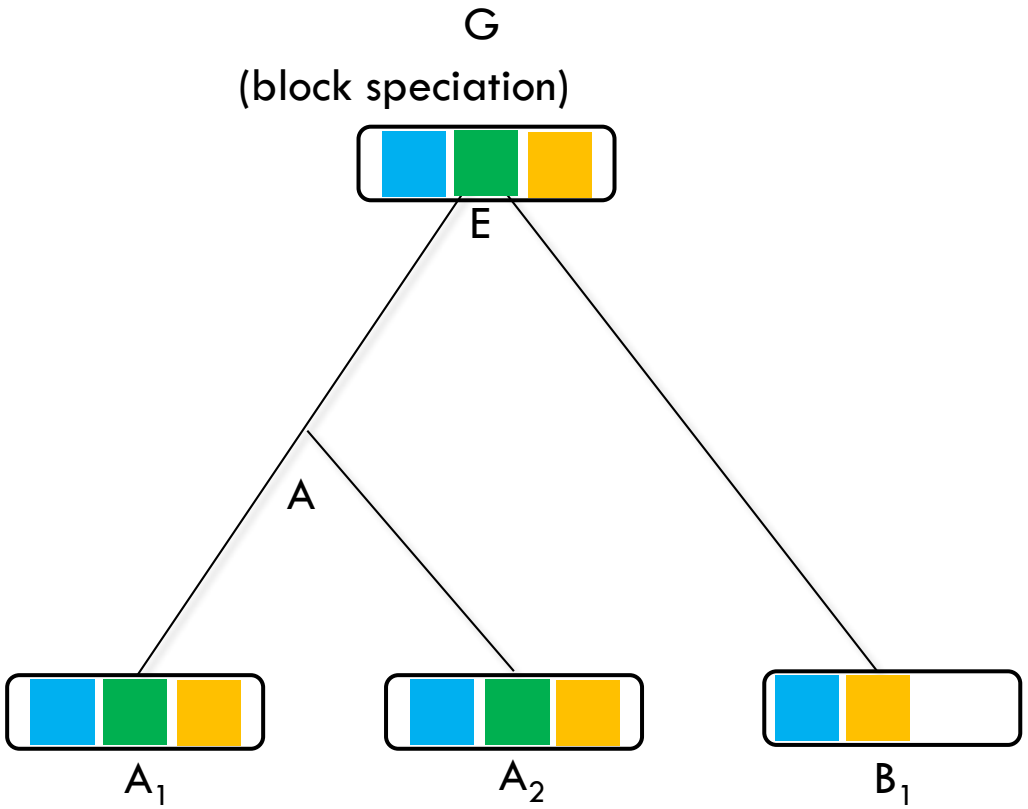
- If all leaf blocks are identical, same as classical reconciliation.
- Problem : syntenic blocks can vary in content because of losses.

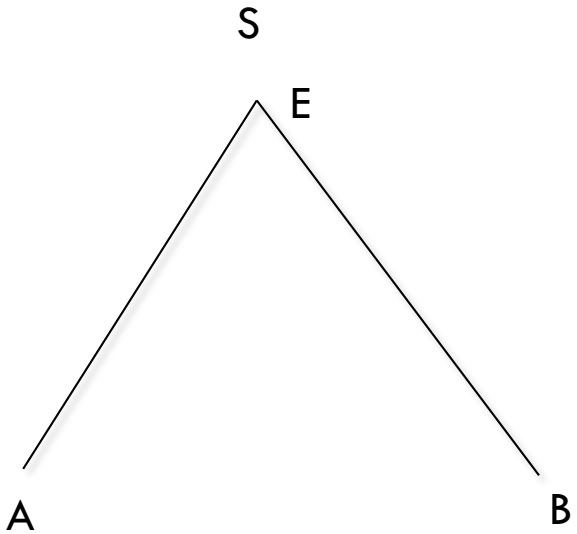

G
A_1
A_2
B_1

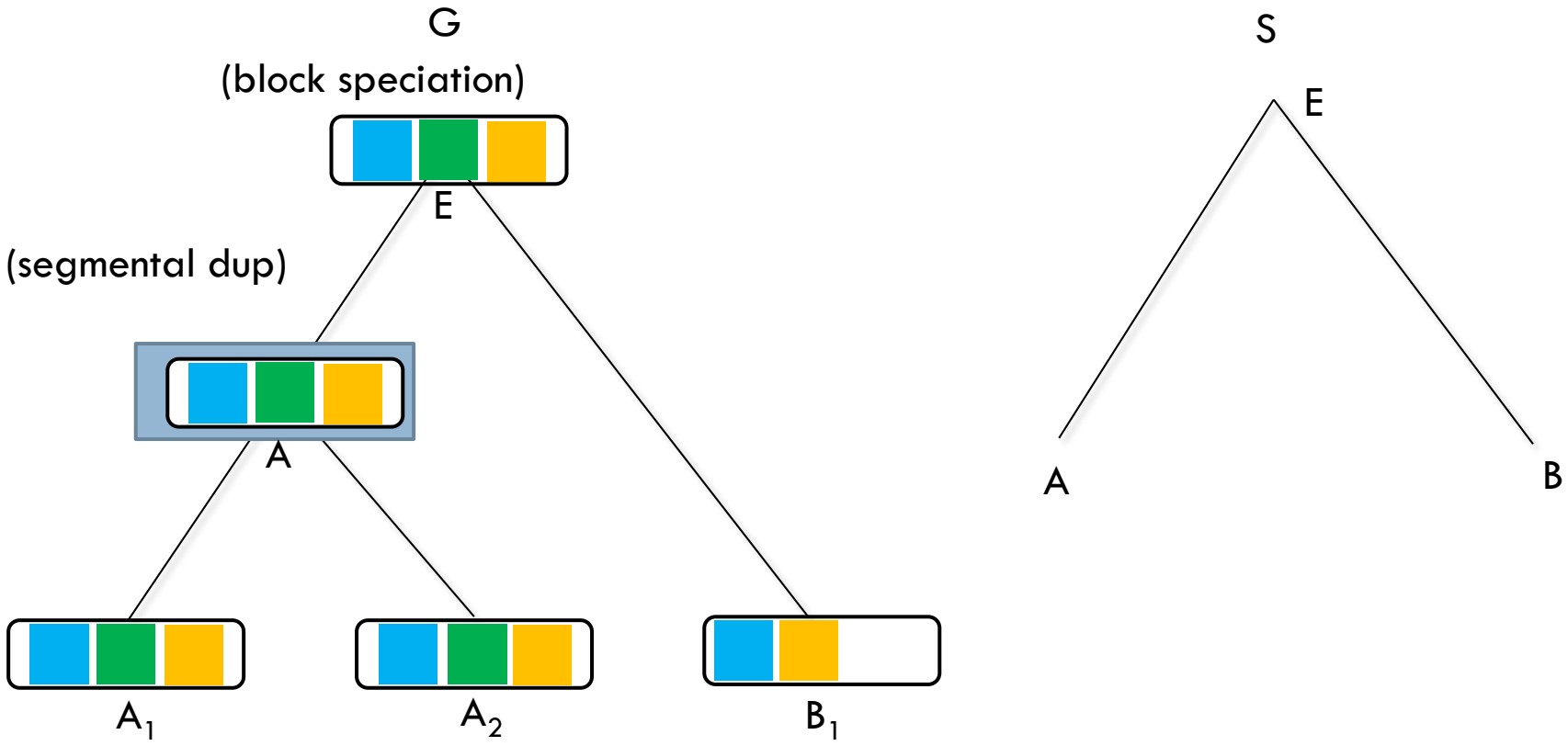

S
E
A
B

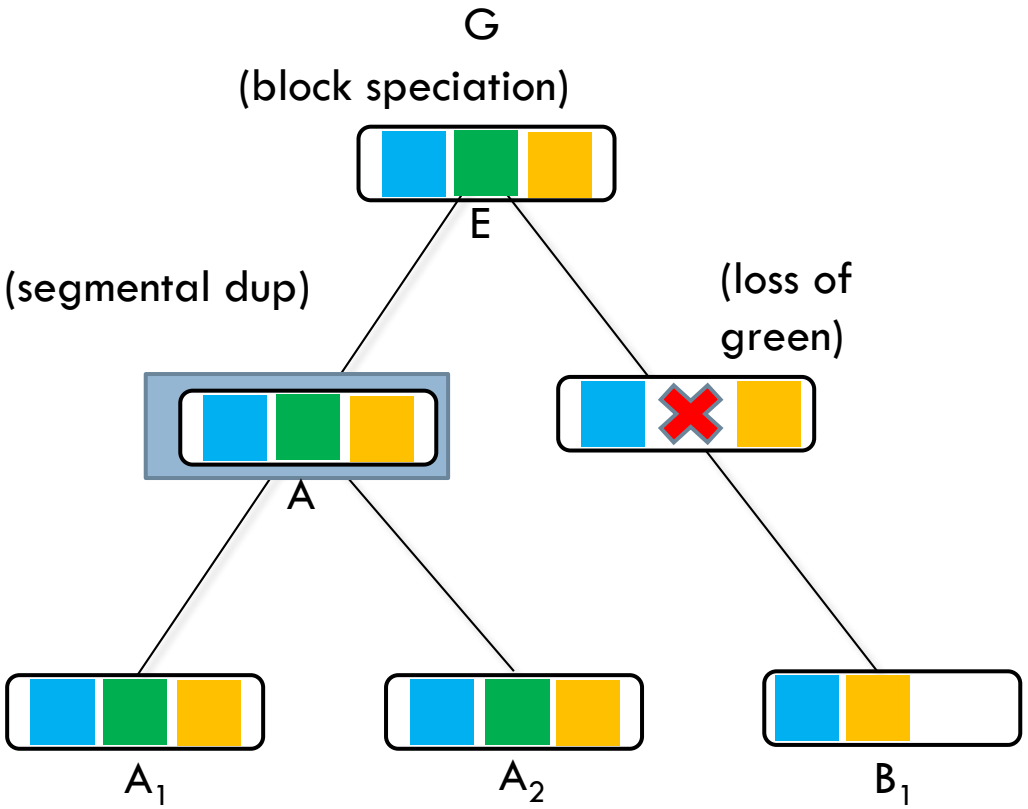

G
E
A
A_1
A_2
B_1

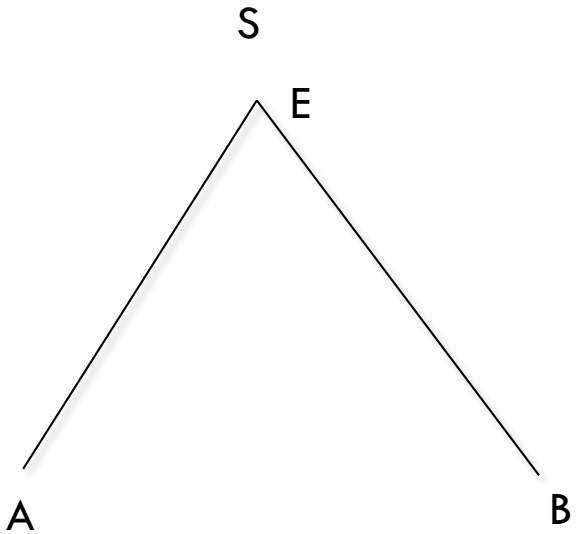

S
E
A
B


G
(block speciation)
E
A
A_1
A_2
B_1

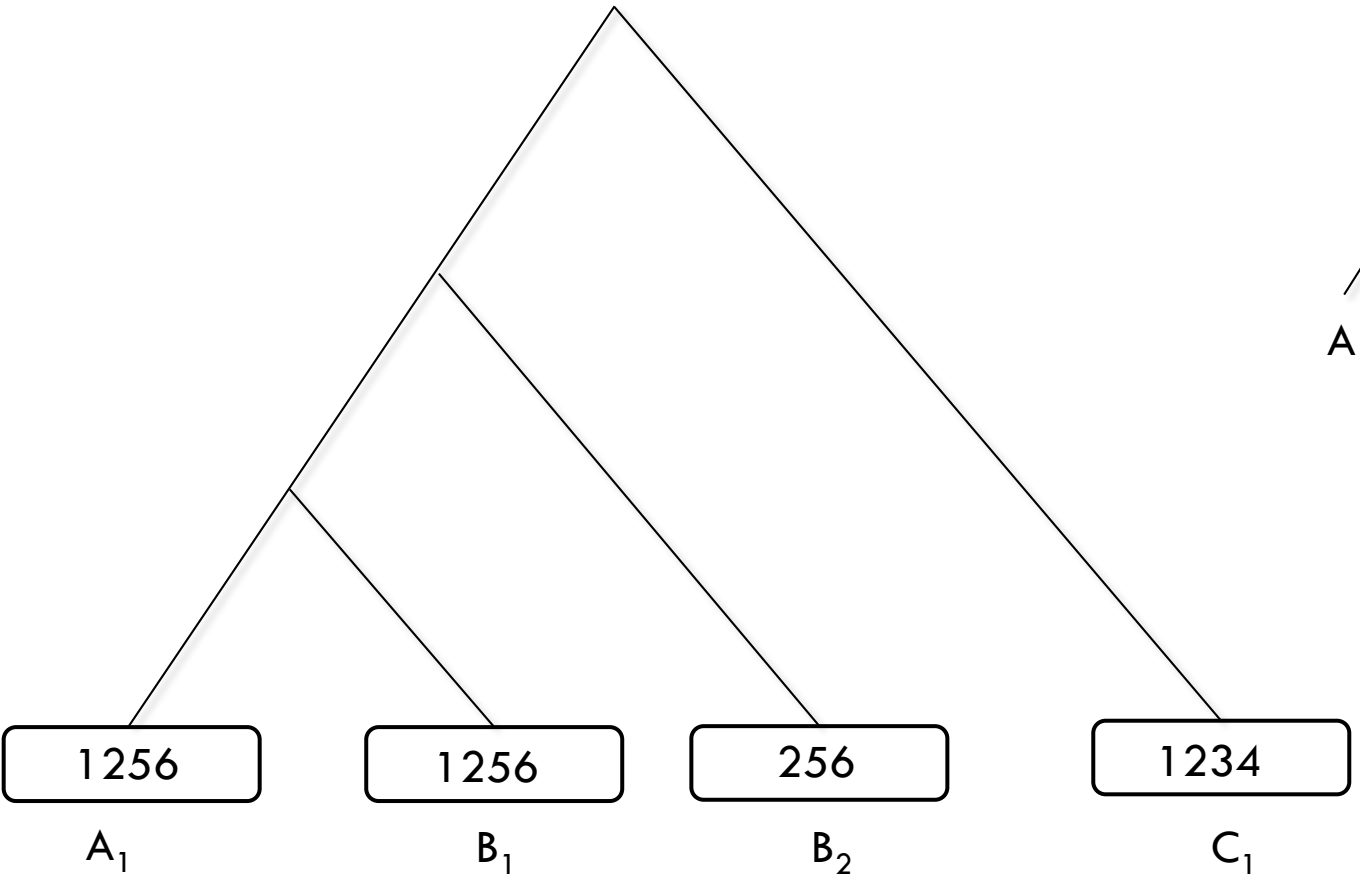

S
E
A
B

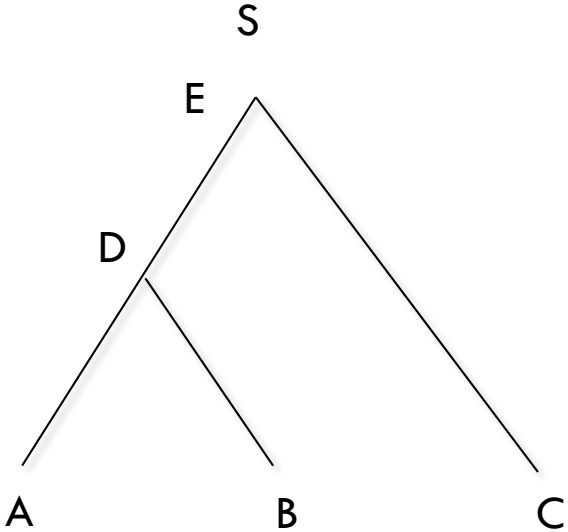

G
(block speciation)
E
(segmental dup)
A
A_1
A_2
B_1
S
E
A
B


G
(block speciation)
E
(segmental dup)
(loss of green)
A
A_1
A_2
B_1

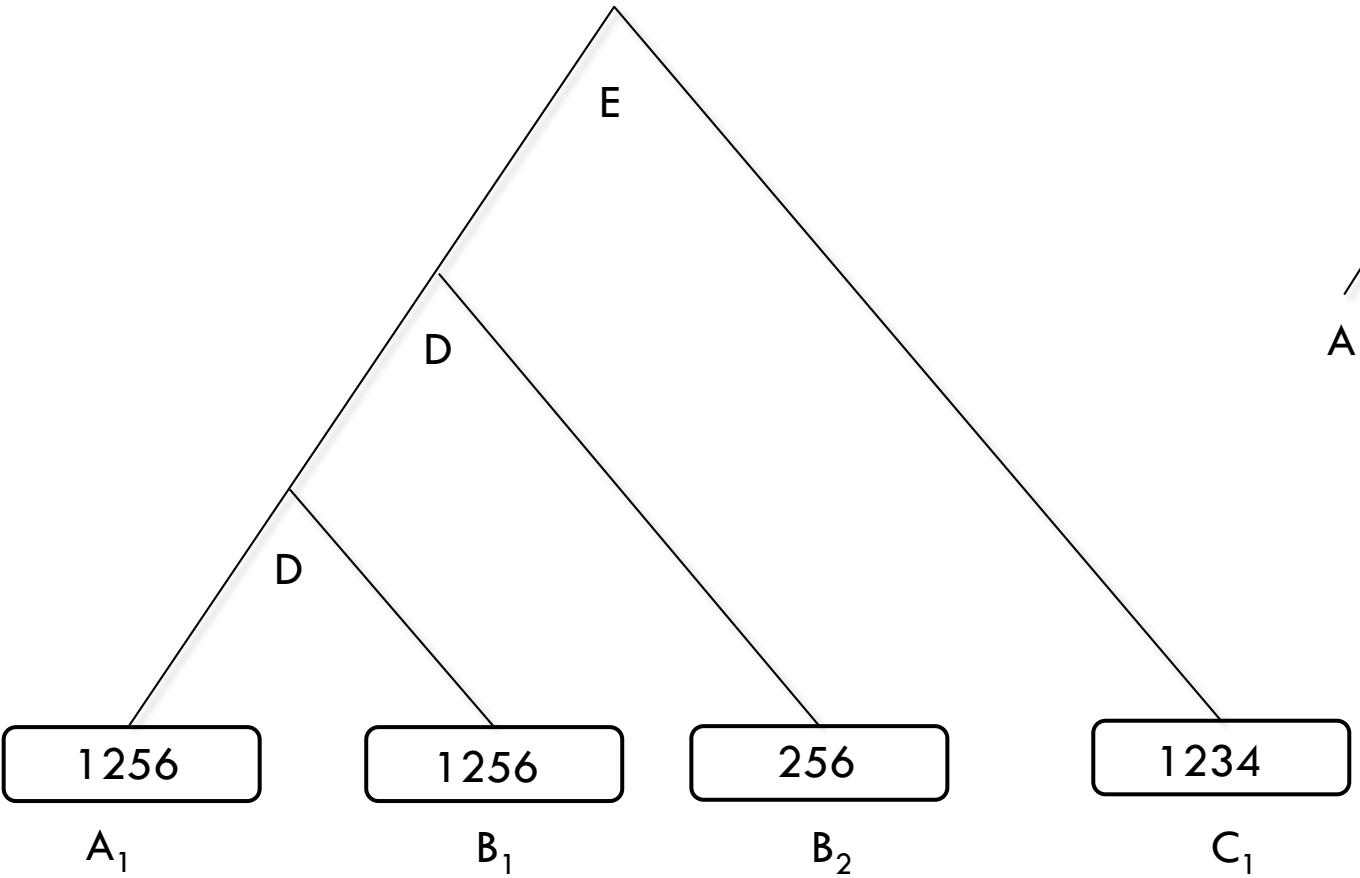

S
E
A
B

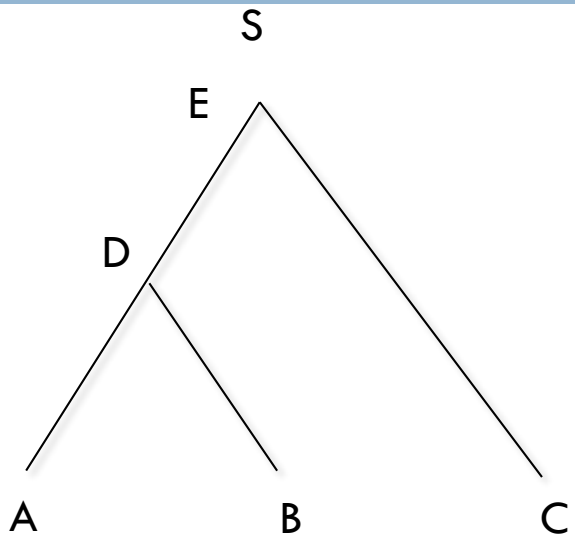
- Synteny tree reconciliation problem
  - **Input** : species tree S, a synteny tree T in which each leaf is labeled by a syntenic block
    - Syntenic block = string of characters (representing colors)
  - **Find** : an evolution of blocks across T with the minimum segmental dups + losses
    - Assign each internal node a string and a species
    - Block speciation = block transmitted to 2 descending species
    - Block dup = copy substring, paste it in a new block
    - Partial block loss = remove a substring
    - Block loss = whole block is lost





(numbers = gene family ids (instead of colors))





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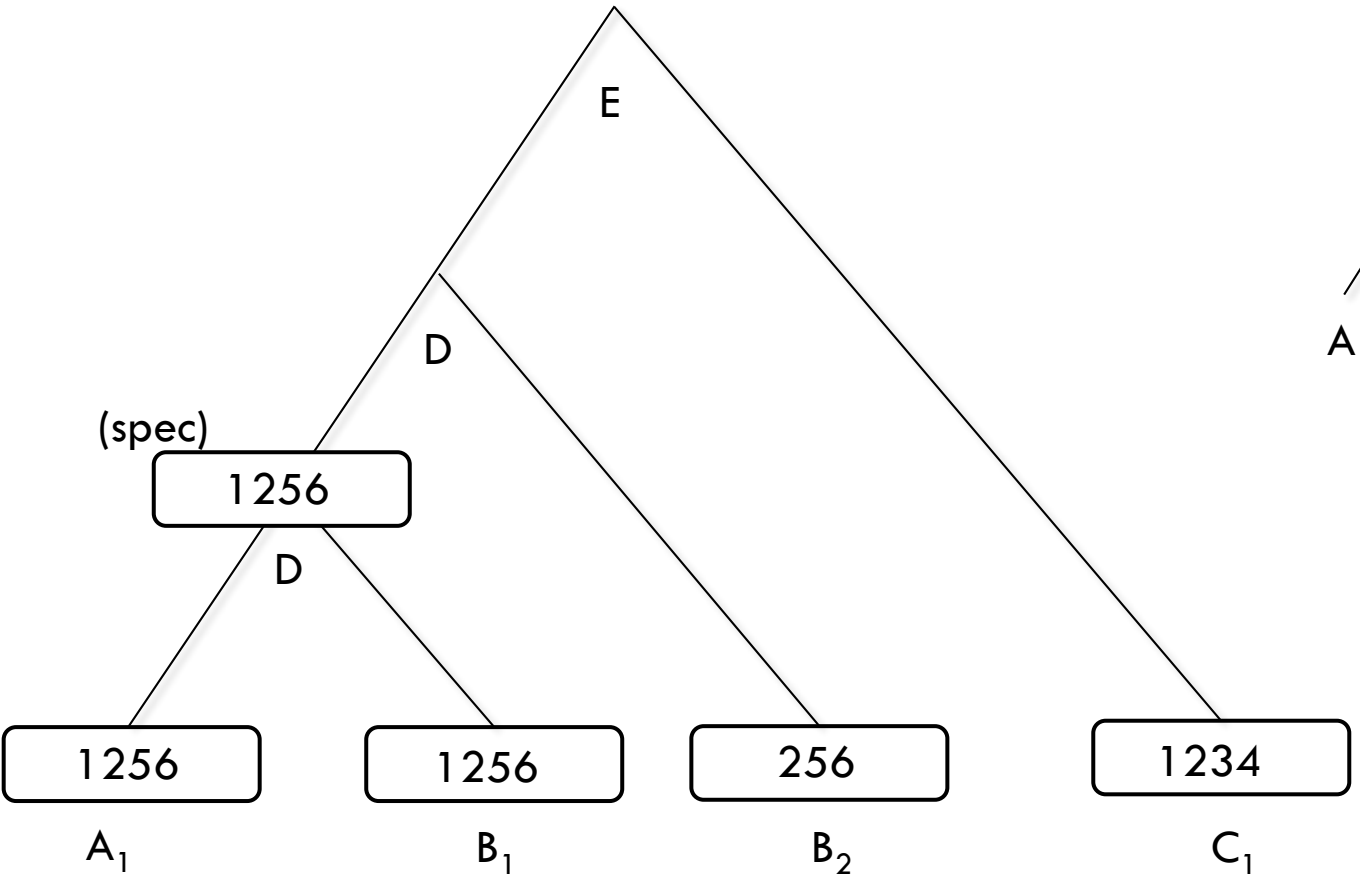

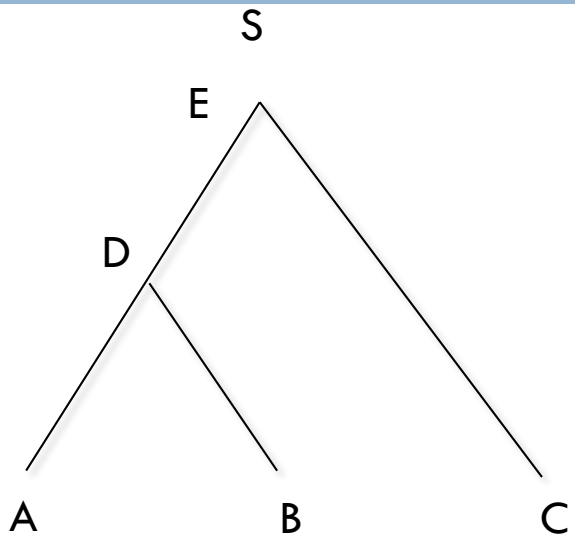

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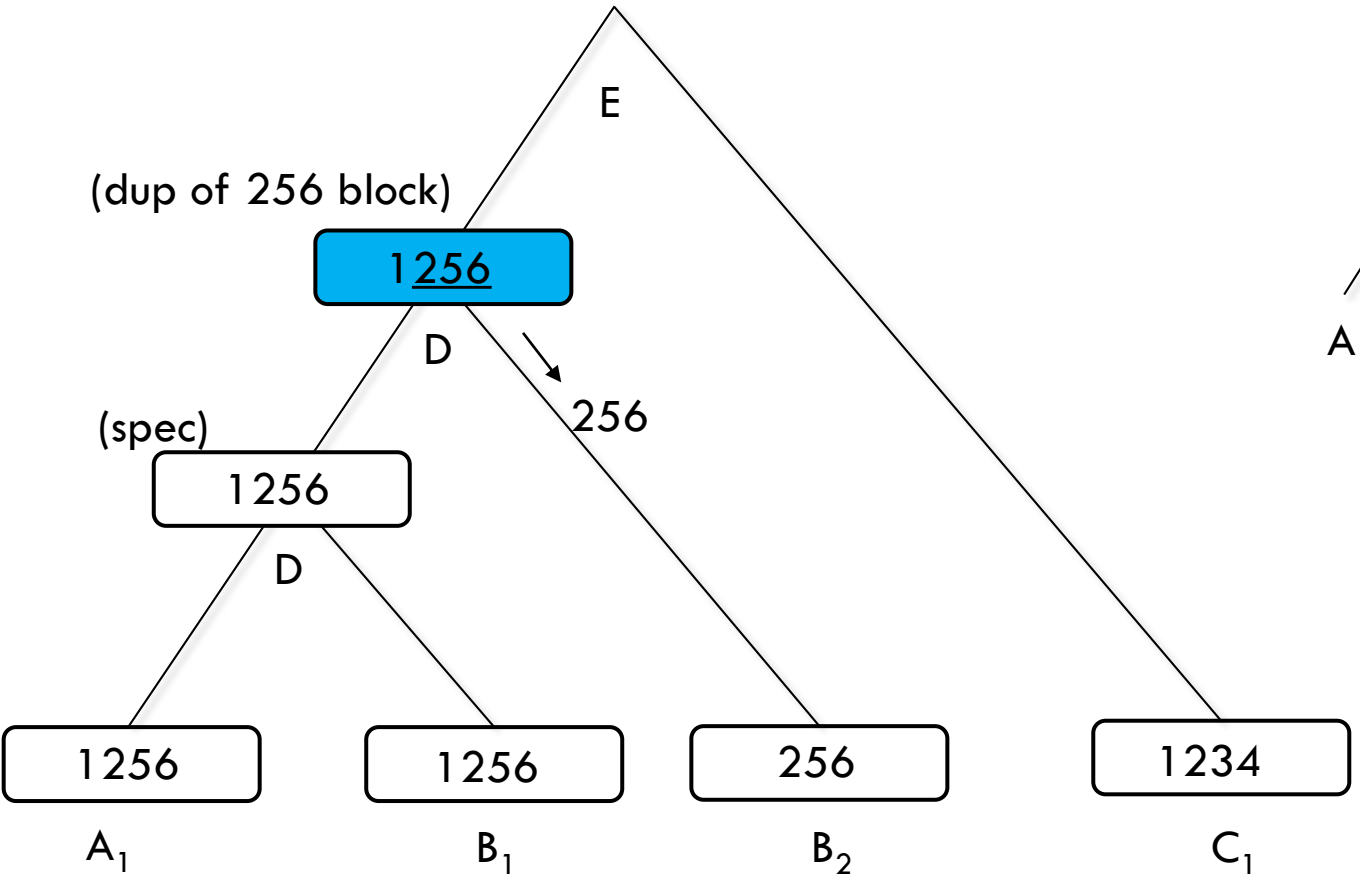

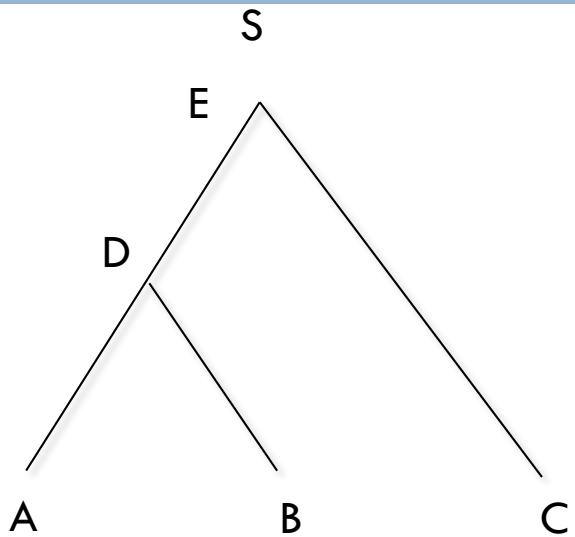

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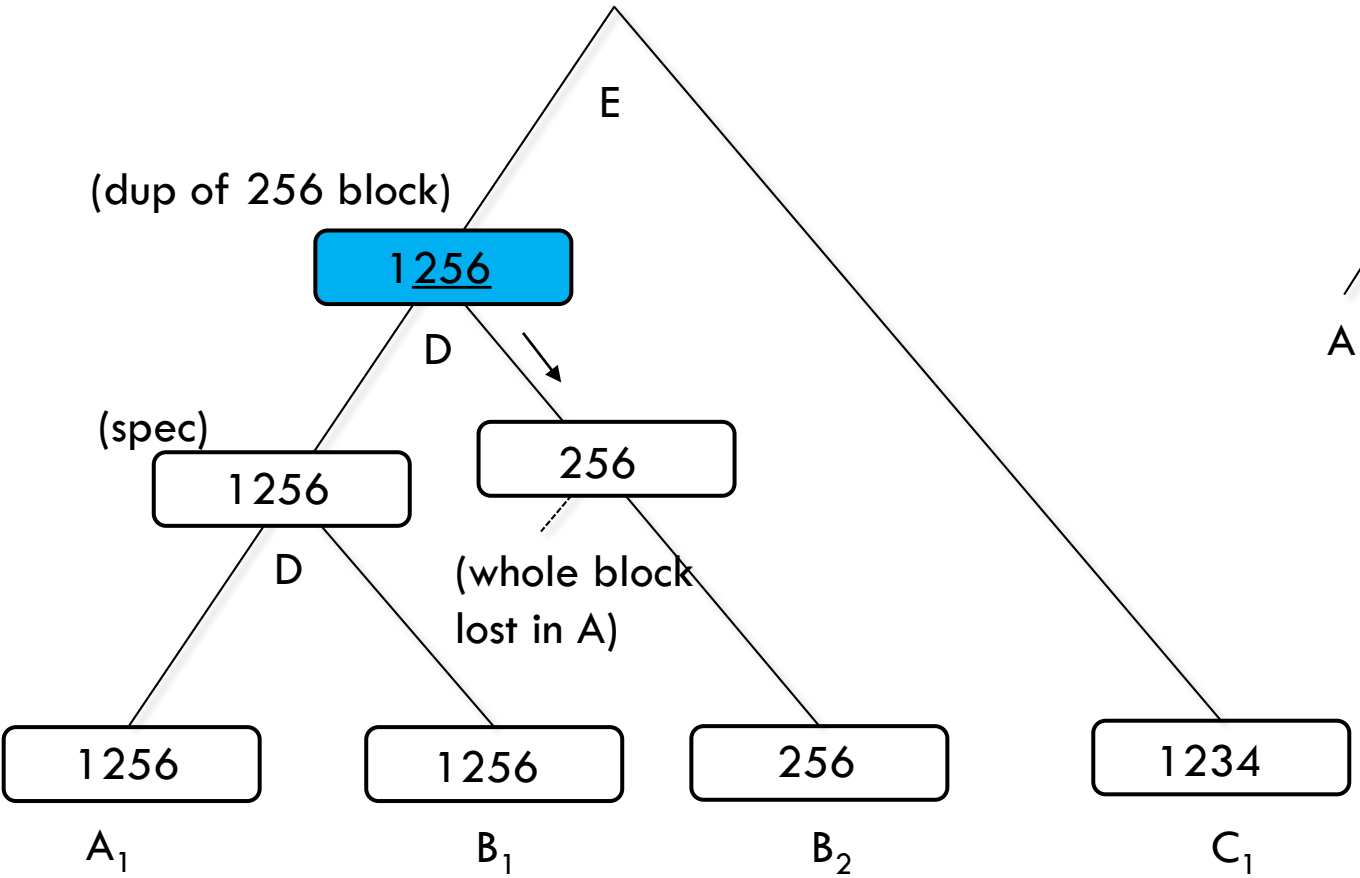

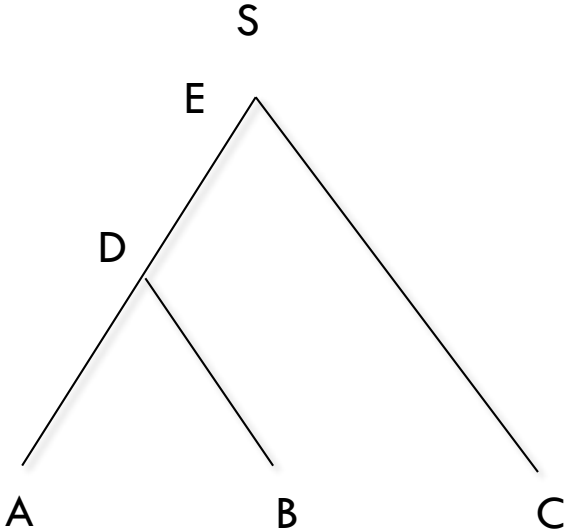

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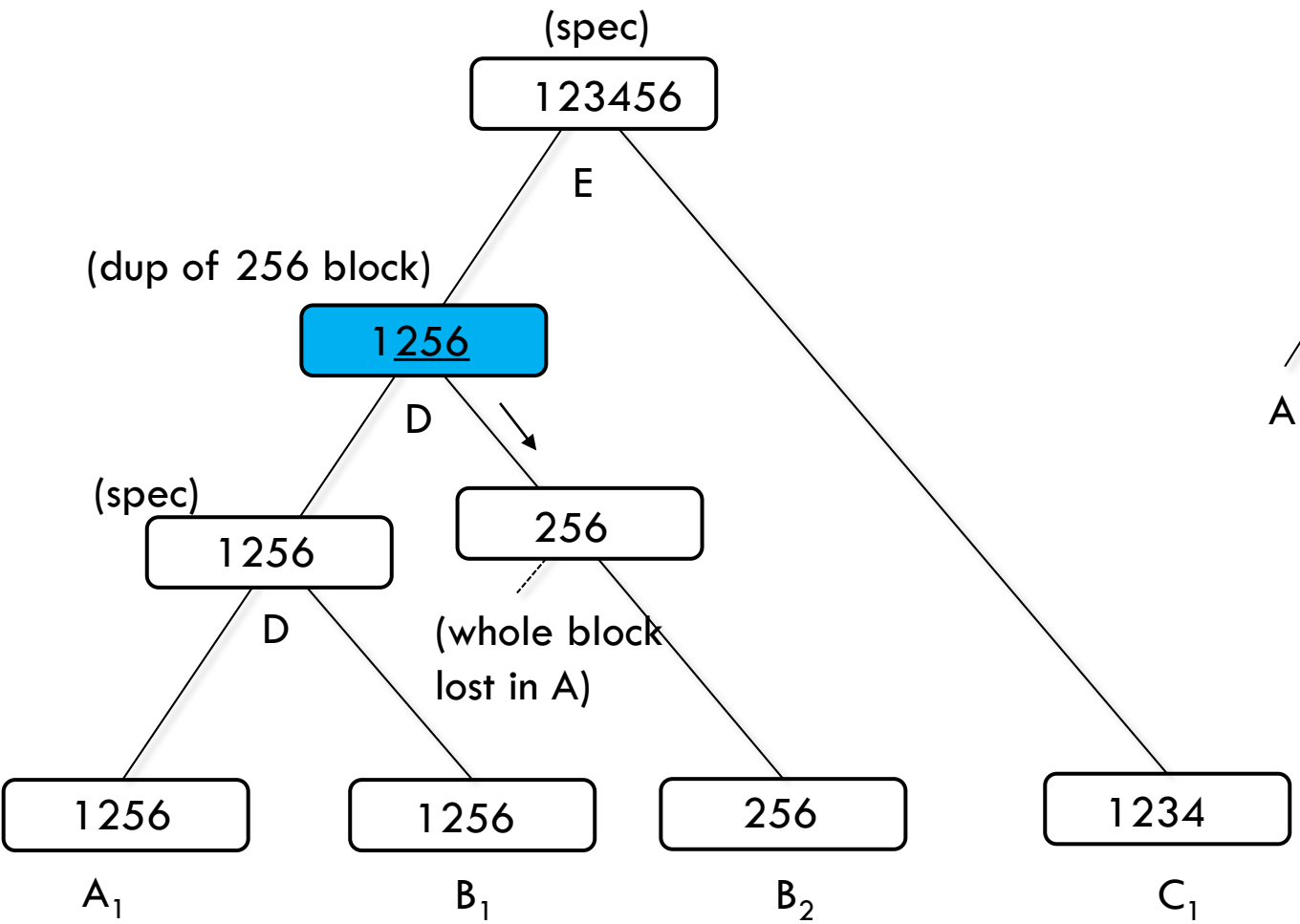

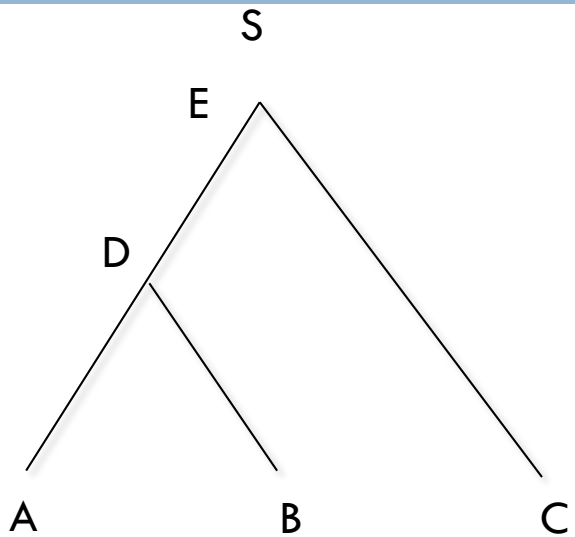

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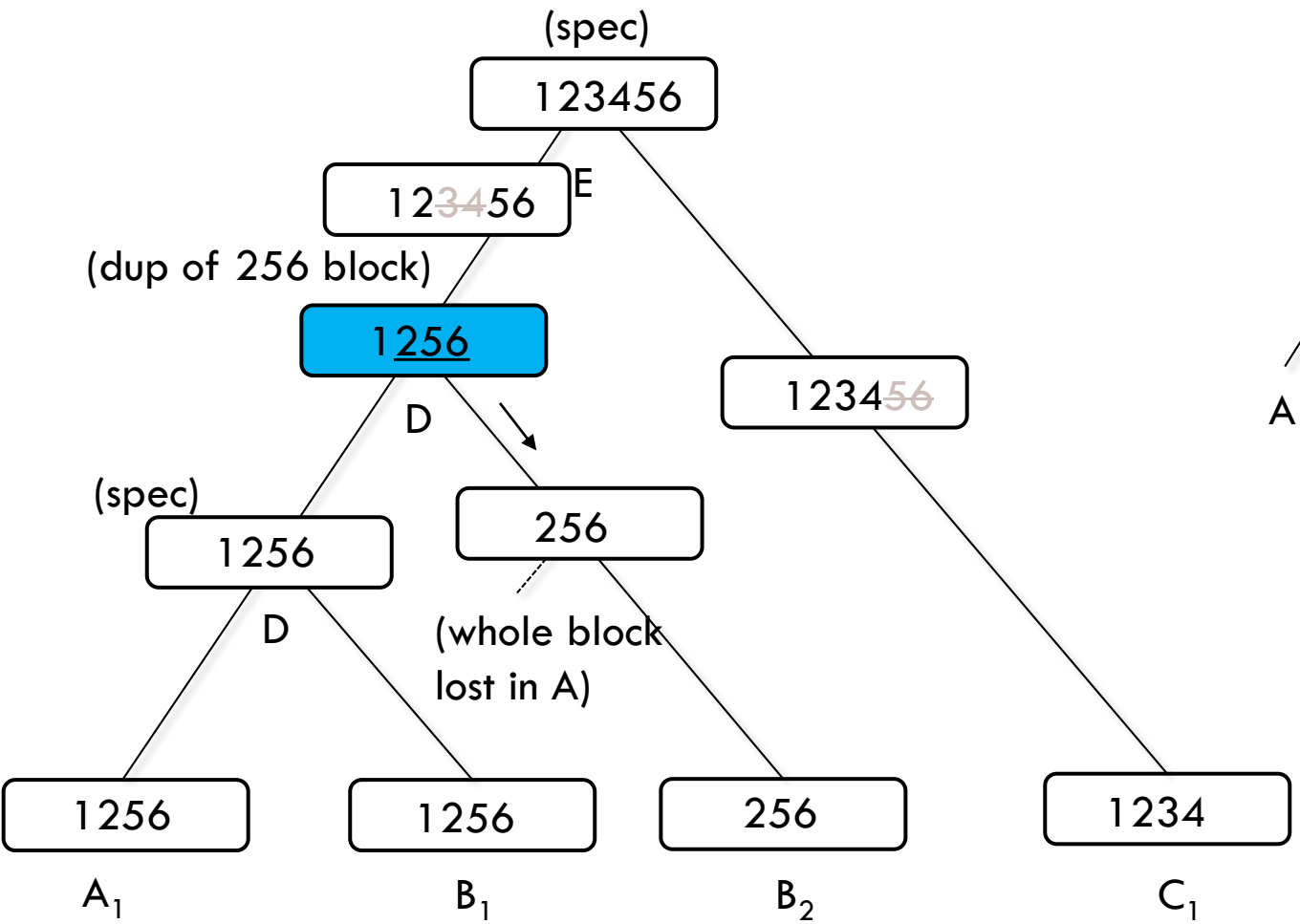

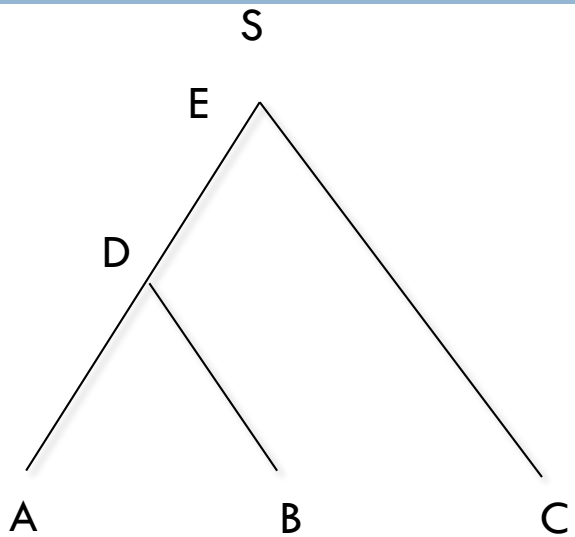

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- Complexity of synteny tree reconciliation problem:
  - Unknown.
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  - Unknown.
- Belief : if root sequence is known, feasible.
- Rearrangements are forbidden => the leaves give precedence constraints on the ordering of the string at the root.
  - Topological sort of leaf constraints = possible strings at the root.
  - How to choose the best ordering?

- Set version : each genome is a set of characters.
- Dup can copy any subset, loss can remove any subset.
- Can be solved in polynomial time.
  - *[Delabre, El-Mabrouk, Huber, L, Moulton, Noutahi, Sauti, AMB 2020]*
  - Bottom-up dynamic programming.

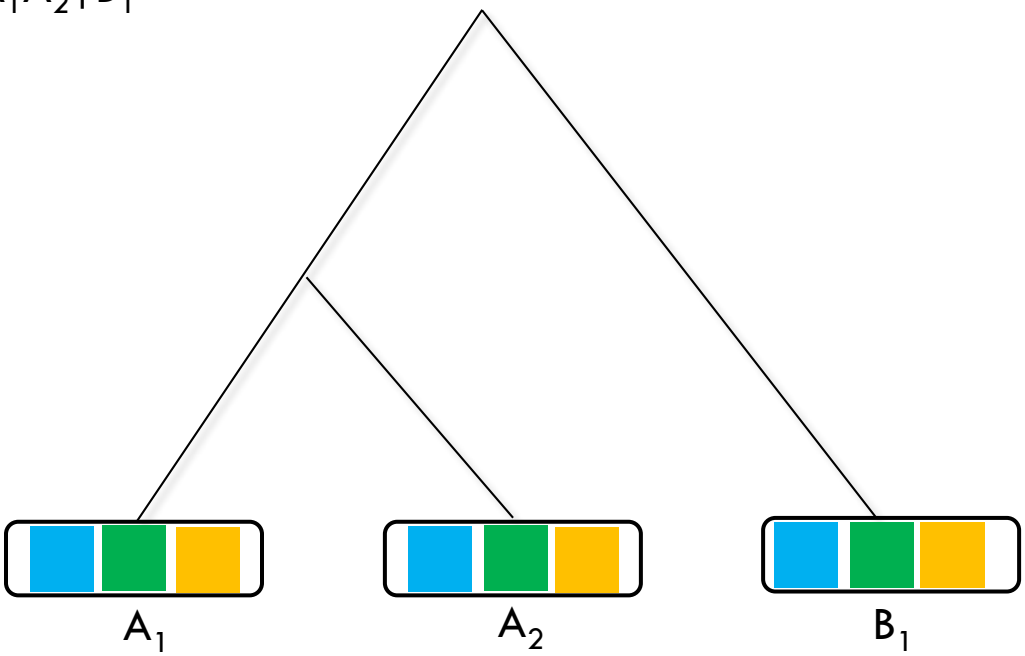
- The synteny reconciliation is just the tip of the iceberg.
- Where does the synteny tree come from?

- The synteny tree should reflect the evolution of all the genes in its blocks.
  - Each gene family has its own tree.
  - Each tree = an 'opinion' on how the blocks evolved.
  - If each tree is identical, synteny tree is obvious.
  - If not, the 'opinions' should at least be **compatible**.

Incompatible histories

How did the blocks A_1, A_2, B_1 evolve?

Green family says : $A_1A_2|B_1$

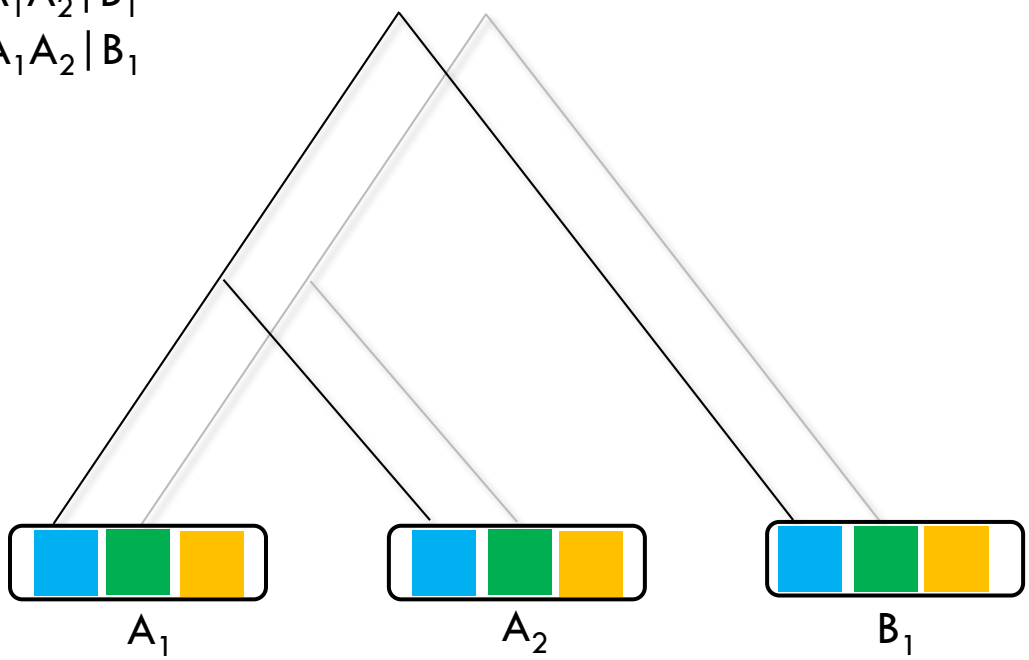


Incompatible histories

How did the blocks A_1, A_2, B_1 evolve?

Green family says : $A_1A_2|B_1$

Blue family says : $A_1A_2|B_1$



Incompatible histories

How did the blocks A_1, A_2, B_1 evolve?

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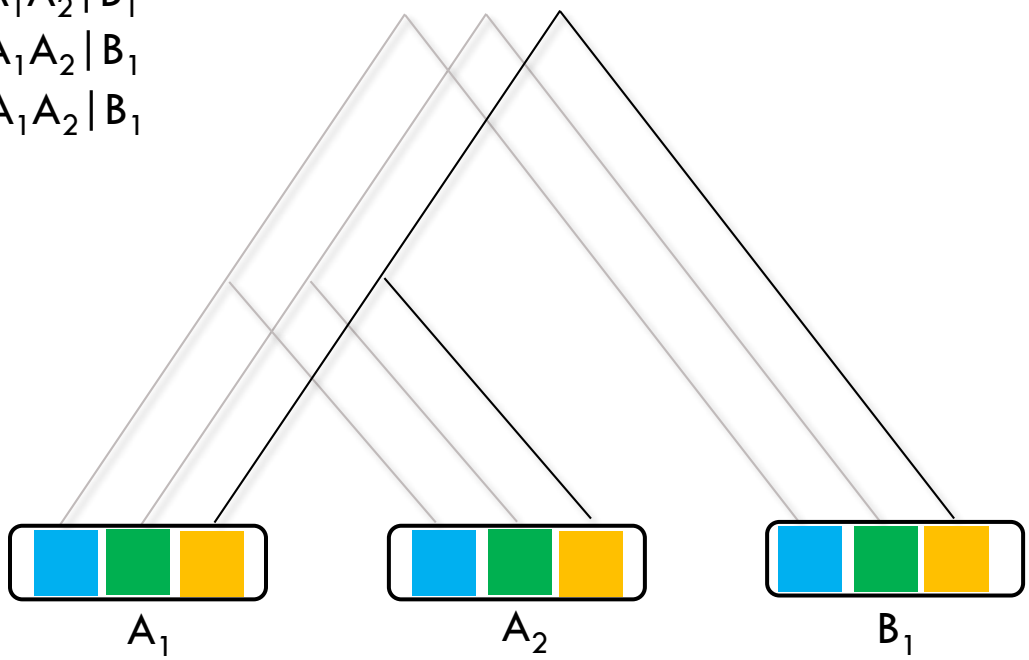

All trees agree => Good, synteny tree is obvious.

Incompatible histories

How did the blocks A_1, A_2, B_1 evolve?

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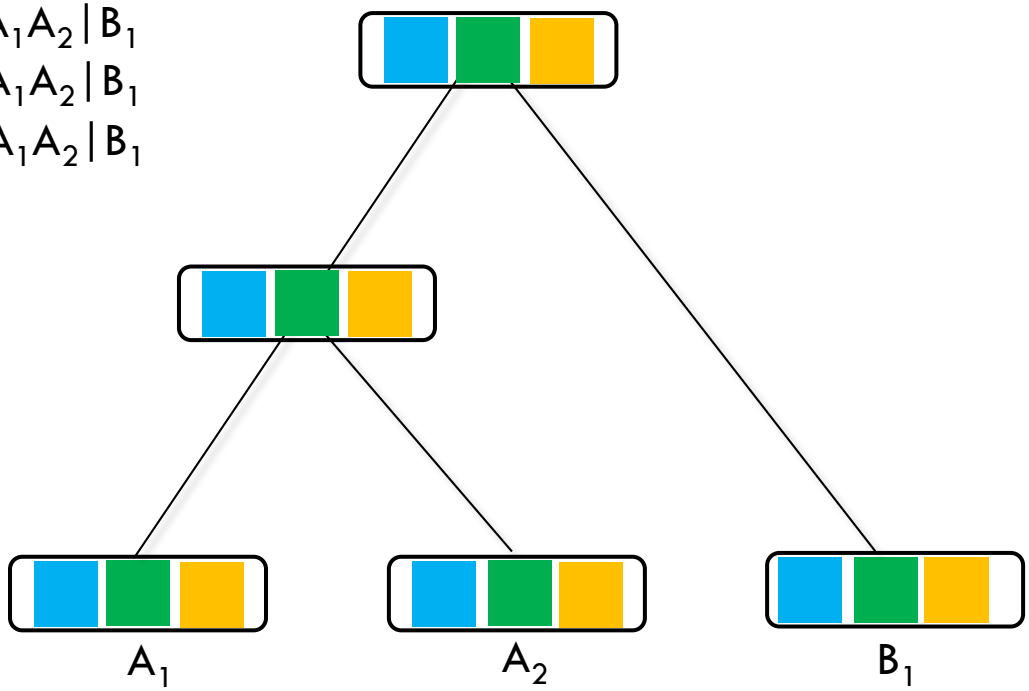
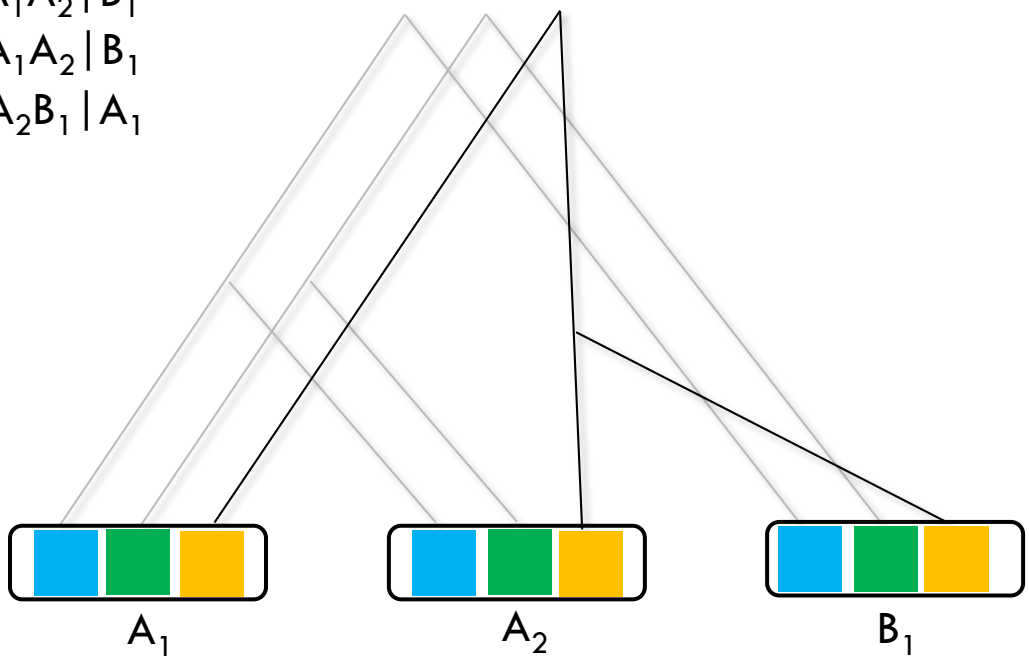
Blue family says : $A_1A_2|B_1$
Orange family says : $A_1A_2|B_1$



All trees agree => Good, synteny tree is obvious.

Incompatible histories

Green family says : $A_1A_2|B_1$
Blue family says : $A_1A_2|B_1$
Orange family says : $A_2B_1|A_1$



Discordant topologies => Blocks can't have evolved together.

Incompatible histories

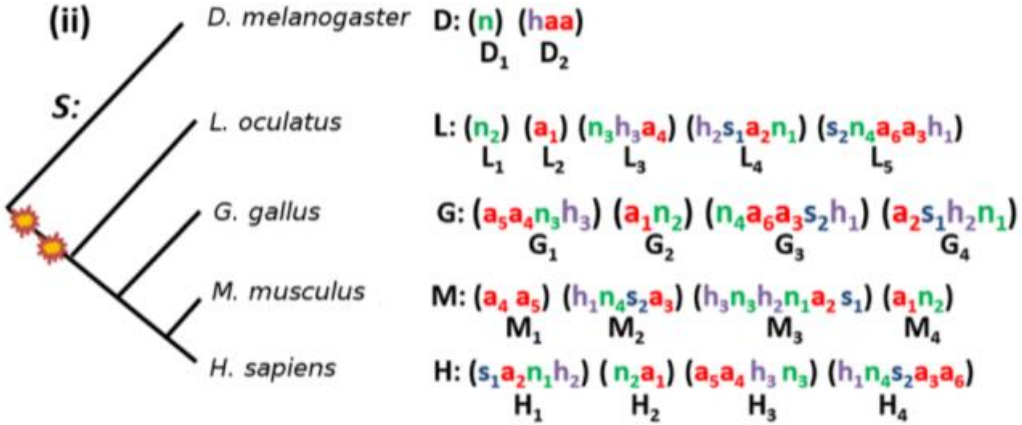
- If each synteny has exactly k genes, we have k trees with leafset X = leaf labels = blocks, all distinct
- If the k trees are identical, easy to reconcile.
- If not, find **some minimal way** to edit the trees so that they are identical + **minimize reconciliation cost**.
  - No clear formulation known.

Proof-of-concept : opioids family

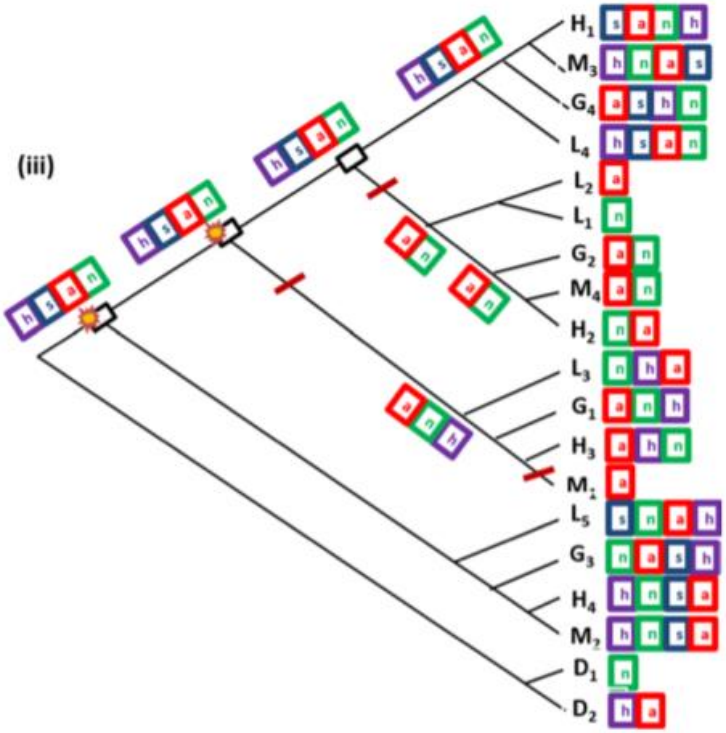
(i)

OPR	NKAIN	STMN	SRC-B
OPRM1 (a_1)	NKAIN1 (n_1)	STMN1 (s_1)	HCK (h_1)
OPRD1 (a_2)	NKAIN2 (n_2)	STMN3 (s_2)	LCK (h_2)
OPRL1 (a_3)	NKAIN3 (n_3)		LYN (h_3)
OPRK1 (a_4)	NKAIN4 (n_4)		
NPBWR1 (a5)			
NPBWR2 (a6)			

(ii)



(iii)



Conclusion

- Modeling challenges
  - Combine both ME and synteny views
  - Infer ME dups + losses using synteny information
  - Integrate segmental losses + transfers + …
  - Integrate order-changing rearrangements

  - Also, simulate good multi-family evolutionary scenarios

Conclusion

- Algorithmic challenges
  - Scalable algorithm for ME + losses inference
  - Synteny tree reconciliation and variants
  - Construct a synteny tree that agrees the most with the gene trees in the blocks

Thank you