RECONCILIATION WITH SEGMENTAL DUPLICATION, TRANSFER, LOSS AND GAIN

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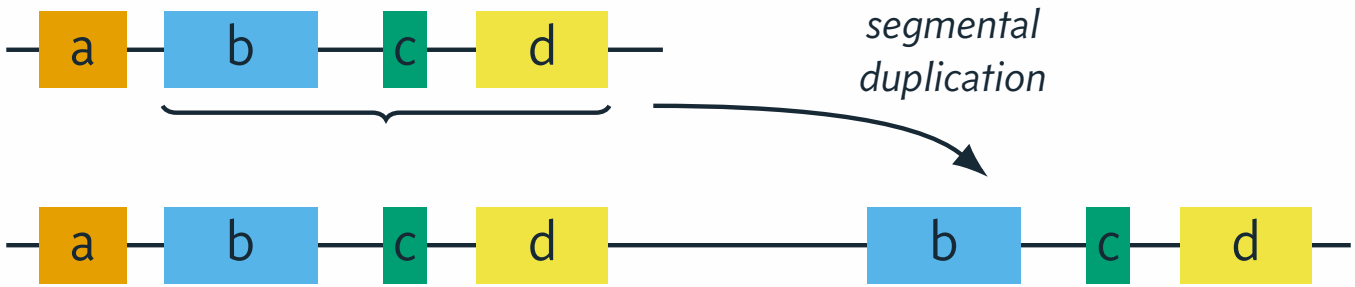
HISTORY OF SYNTENIES

- **Syntenies:** Groups of genes that can be **affected simultaneously** by segmental events *(e.g., because of their location in the genome)*



- **Problem:** Given a family of *homologous* syntenies, **infer a plausible scenario** for their history, made up of segmental events

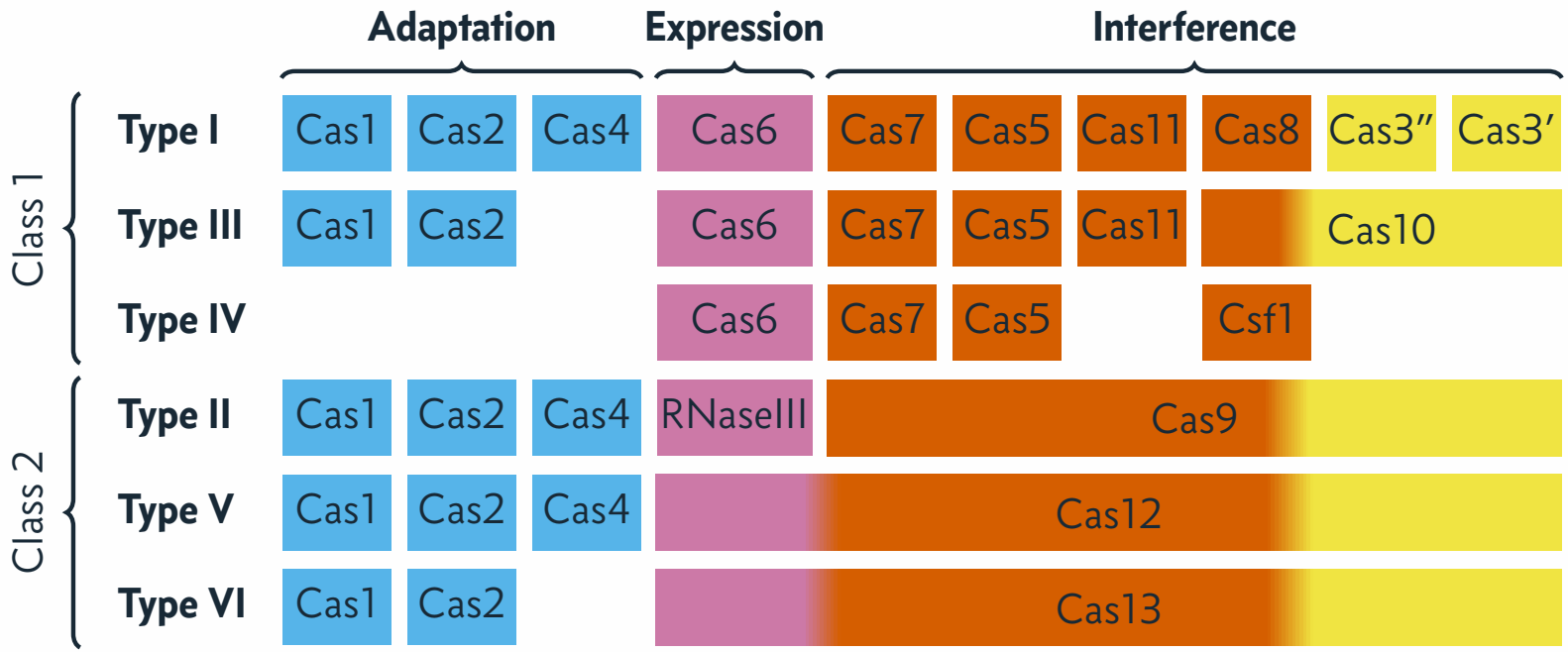
CRISPR-CAS SYSTEMS

- **Adaptive immunity** mechanisms of bacteria and archaea

- **Foreign sequences** are stored as spacers in the **CRISPR array**
- **Cas genes** perform adaptation, expression, and interference

CAS SYNTENIES CLASSIFICATION

- Cas genes form a **diverse family** of syntenies

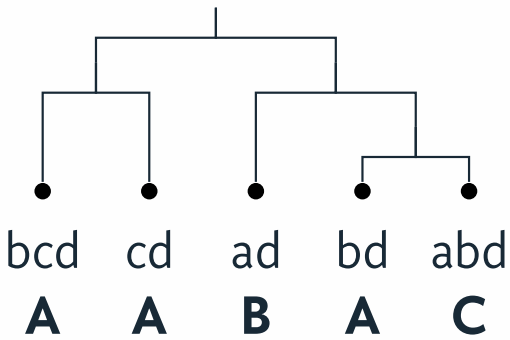


- Can we **infer a scenario** for the history of **Cas syntenies?**

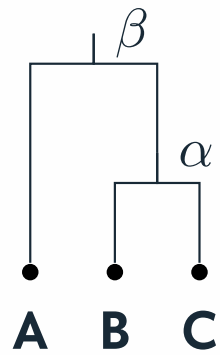
Makarova et al. “Evolutionary classification of CRISPR–Cas systems: a burst of class 2 and derived variants” (Feb. 2020).

USING SUPER-RECONCILIATION METHODS

- **Extend** usual reconciliation techniques for **synteny** history inference
- A **synteny tree** replaces the gene tree in the problem input



Synteny tree



Species tree

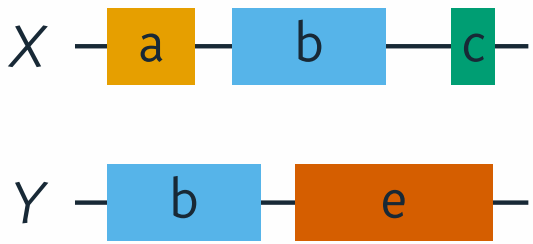
- The synteny tree can be obtained as a **supertree** of individual gene trees, hence **"super-reconciliation"**

OUTLINE

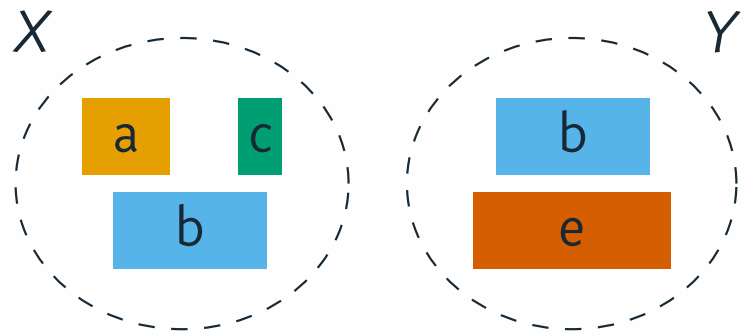
1. **Modelling the Evolution of Syntenies**
2. Super-Reconciliation Approach
3. Preliminary Results on Cas Syntenies
4. Conclusion

MODELLING SYNTENIES

1 As **strings**



2 As **sets**



- Super-reconciliation is **less computationally expensive** on **sets**
- **Strings** require either **"order-consistent"** syntenies or modelling **rearrangement** events

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Delabre, El-Mabrouk, Huber, Lafond, Moulton, Noutahi, and Castellanos. "Evolution through segmental duplications and losses: a Super-Reconciliation approach" (May 2020).

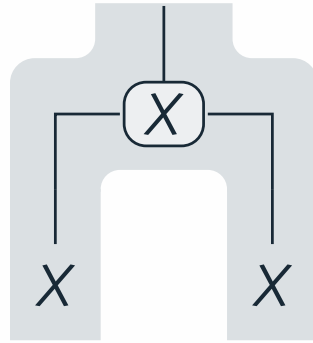
MODELLING SEGMENTAL EVENTS

- BINARY EVENTS
  Create new synteny copies

- UNARY EVENTS
  Change existing syntenies

MODELLING SEGMENTAL EVENTS

- BINARY EVENTS
  Create new synteny copies
  - **Speciation**



- UNARY EVENTS
  Change existing syntenies

MODELLING SEGMENTAL EVENTS

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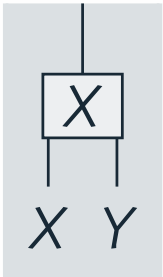
  Create new synteny copies
  - Speciation
  - **Duplication**

- UNARY EVENTS
  Change existing syntenies

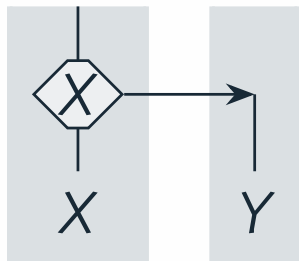


$Y \subseteq X$

MODELLING SEGMENTAL EVENTS

- BINARY EVENTS
  Create new synteny copies
  - Speciation
  - Duplication
  - **Transfer**

- UNARY EVENTS
  Change existing syntenies



$Y \subseteq X$

MODELLING SEGMENTAL EVENTS

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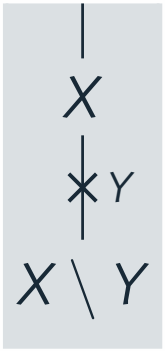
  - Duplication
  - Transfer

- **UNARY EVENTS**
  Change existing syntenies
  - **Loss**



MODELLING SEGMENTAL EVENTS

- **BINARY EVENTS**
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  - Speciation
  - Duplication
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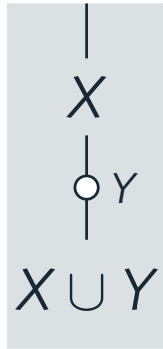
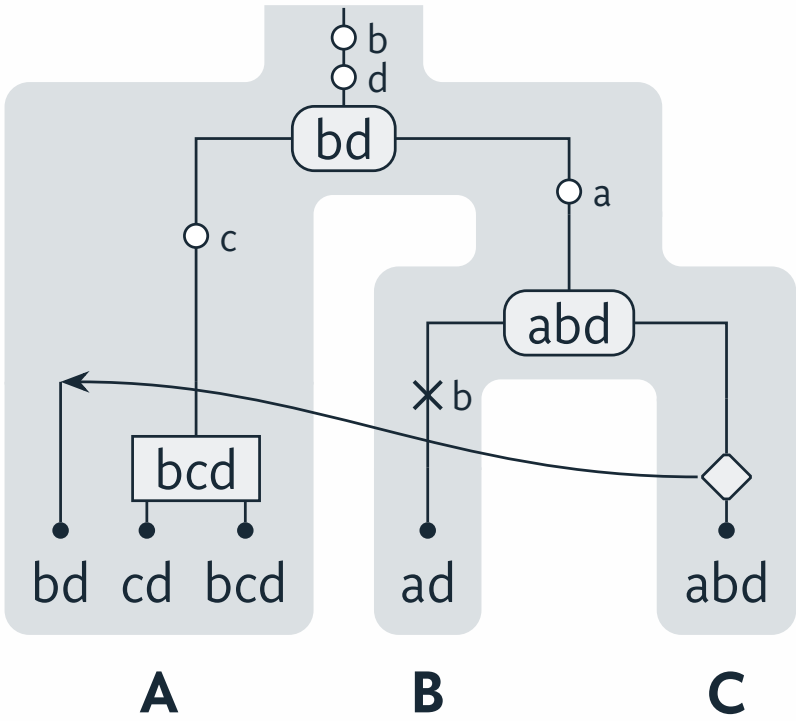
- **UNARY EVENTS**
  Change existing syntenies
  - Loss
  - **Gain**



- Restrictions
  - **Gains** are **non-segmental** ($|Y| = 1$)
  - Each family is gained exactly once (**no convergent evolution**)

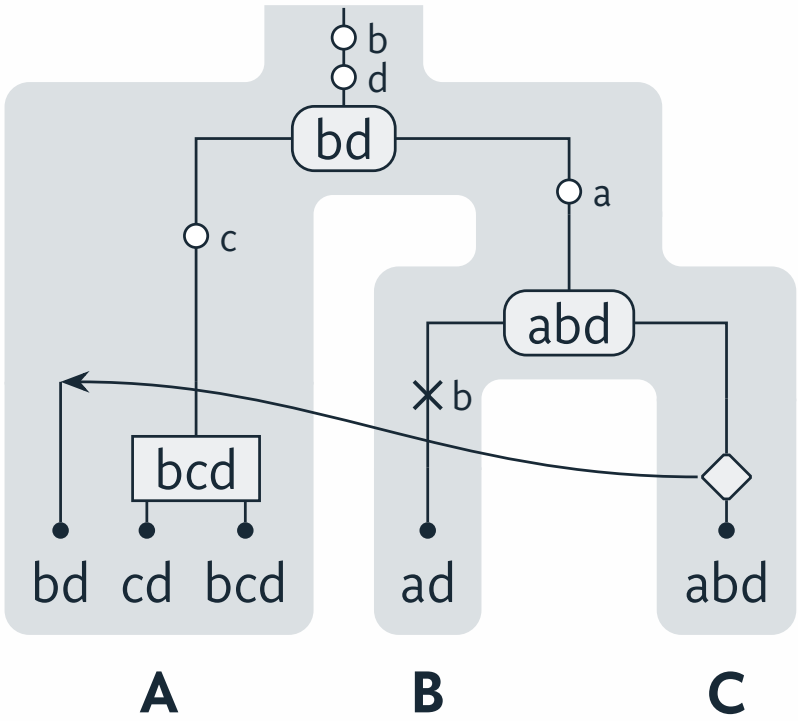
EVOLUTIONARY HISTORY

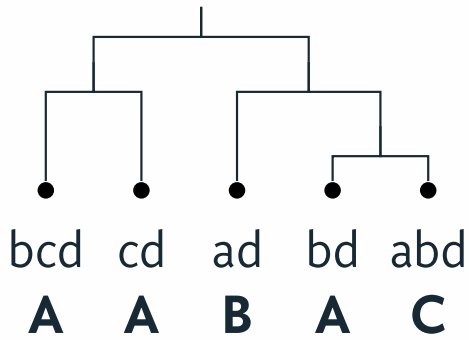
- **Branching sequence** of segmental events



EVOLUTIONARY HISTORY

- **Branching sequence** of segmental events
- **Corresponds to** a synteny tree

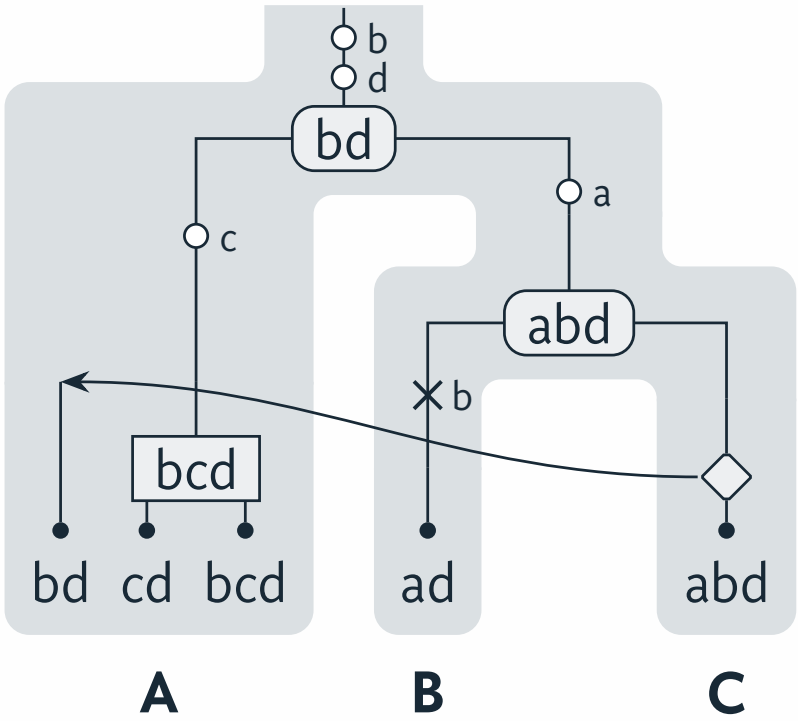


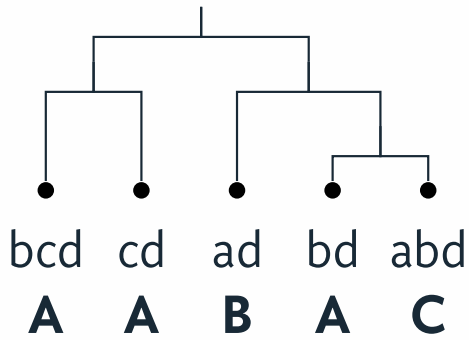


Synteny tree

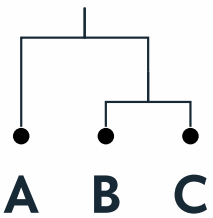
EVOLUTIONARY HISTORY

- **Branching sequence** of segmental events
- **Corresponds to** a synteny tree
- **Fits in** a species tree





Synteny tree



Species tree

PARSIMONY PROBLEM

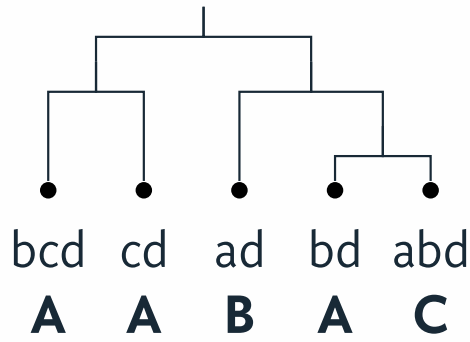
- Find most **plausible histories** for given synteny and species trees
- Each **event** is given a **cost** value (quantifying its "rareness")
- The cost of a history is the **sum of costs** for its events

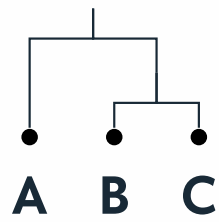
Minimum-Cost History Problem

Input: Synteny tree T, species tree S
Output: Minimum-cost history corresponding to T and fitting in S

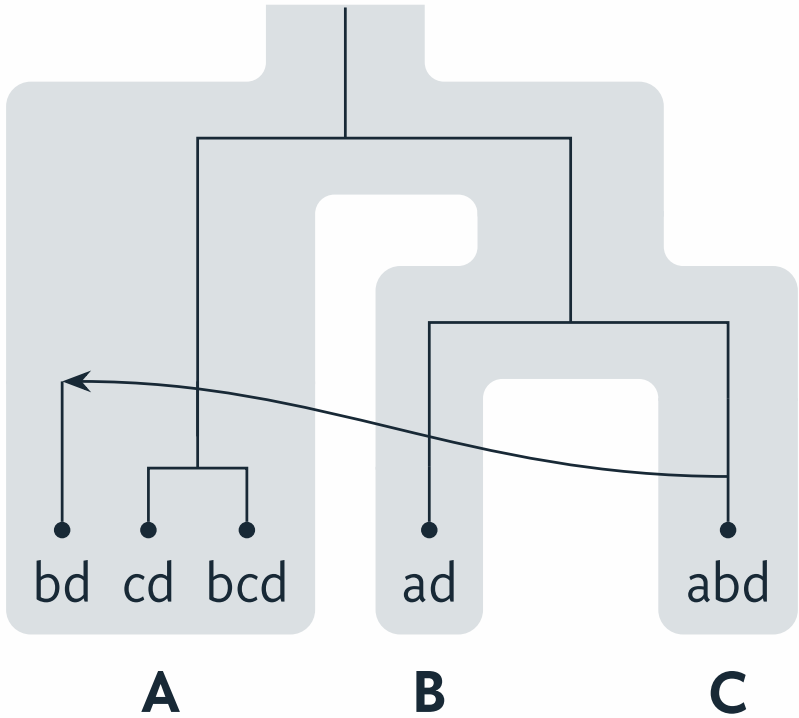
OUTLINE

PARTS OF A HISTORY



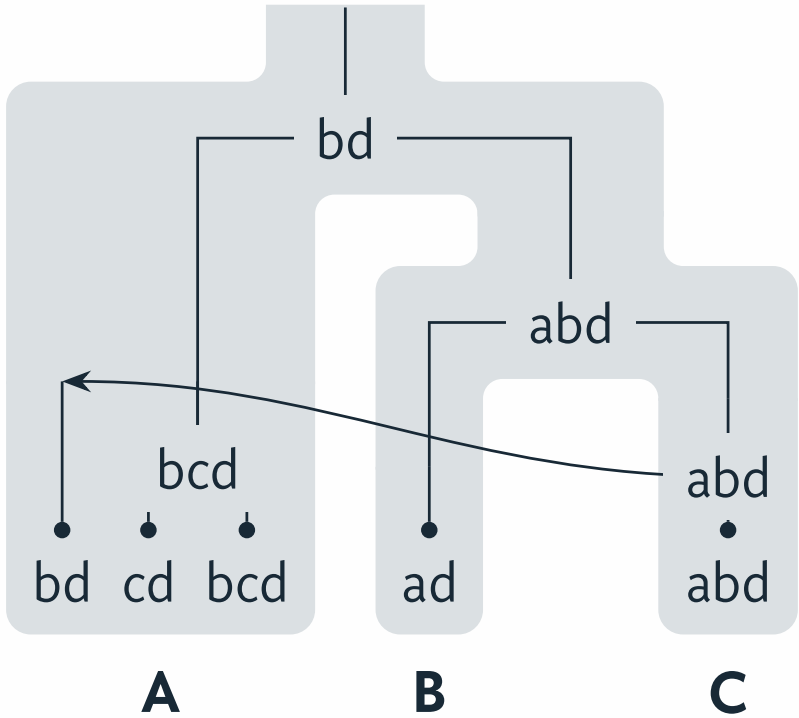


1 Synteny to species tree mapping



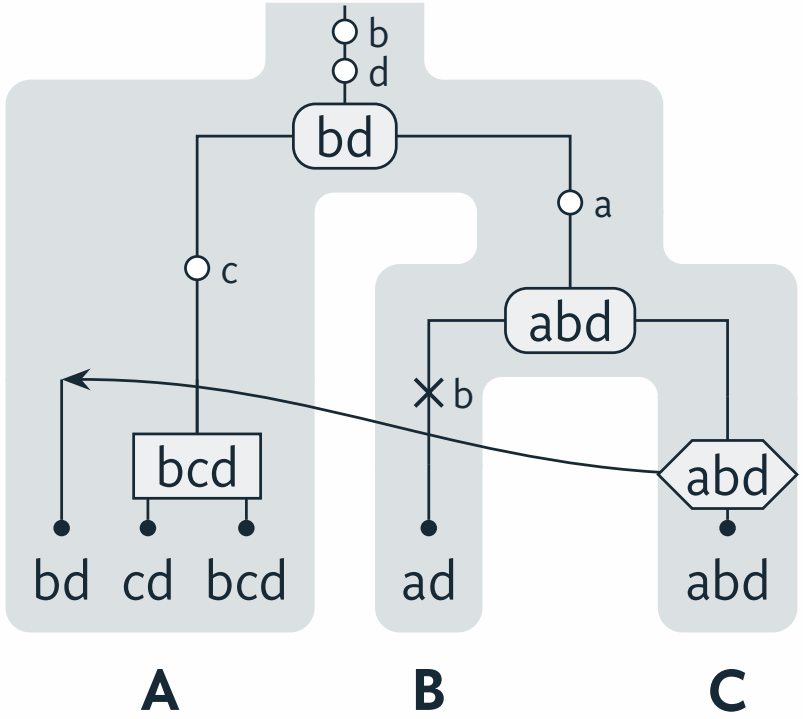
PARTS OF A HISTORY

1. Synteny to species tree mapping
2. **Ancestral syntenies assignment**

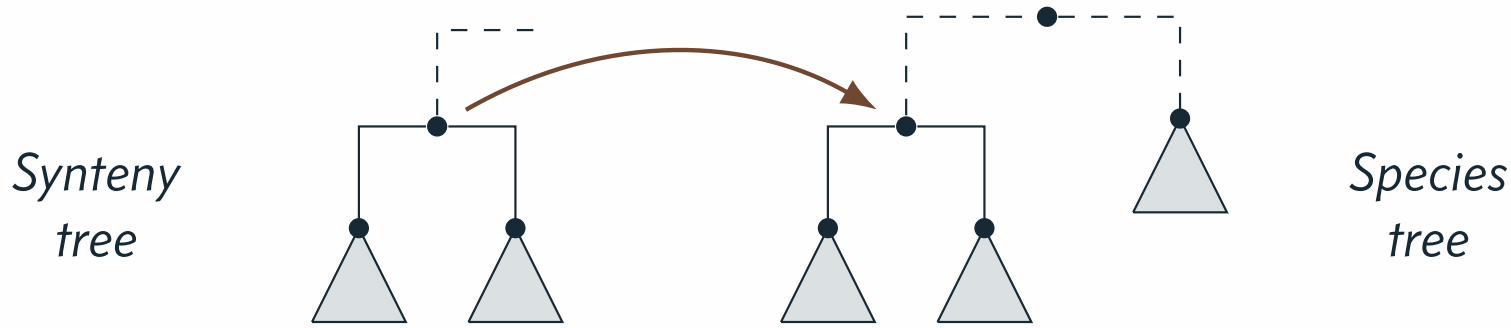


PARTS OF A HISTORY

1. Synteny to species tree mapping
2. Ancestral syntenies assignment
3. **Events (come for free!)**



MAPPING SYNTENY TREE TO SPECIES TREE



Tofigh, Hallett, and Lagergren. "Simultaneous identification of duplications and lateral gene transfers" (Mar. 2011).

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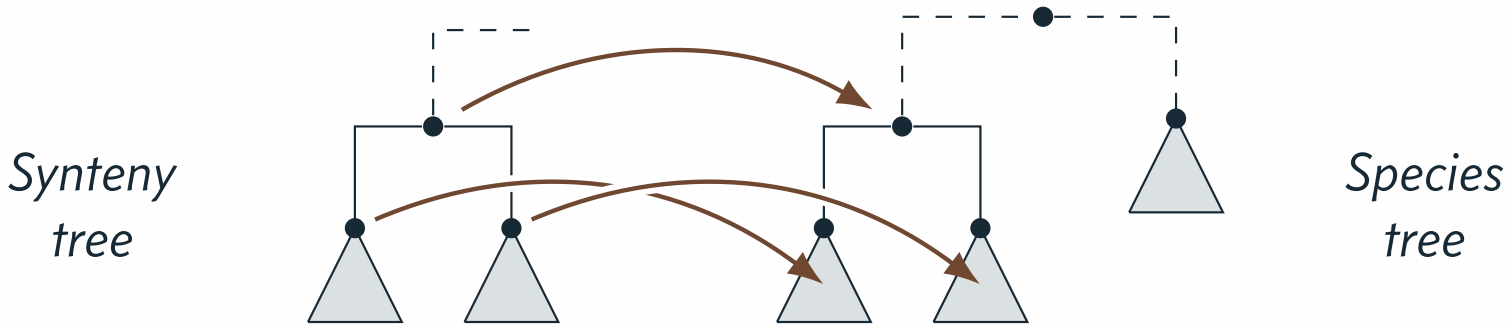

1 **Different descendent subtrees** Speciation

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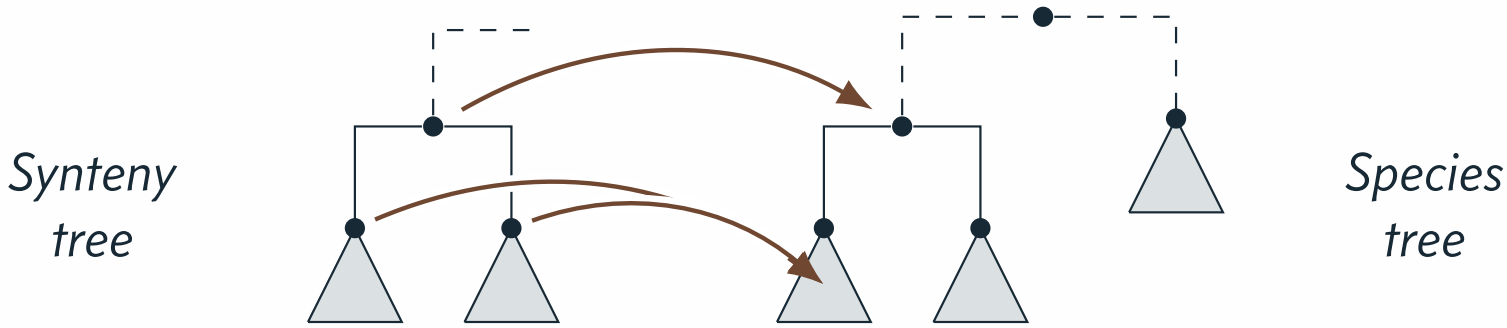

1	Different descendent subtrees	Speciation
2	**Same descendent subtree**	Duplication

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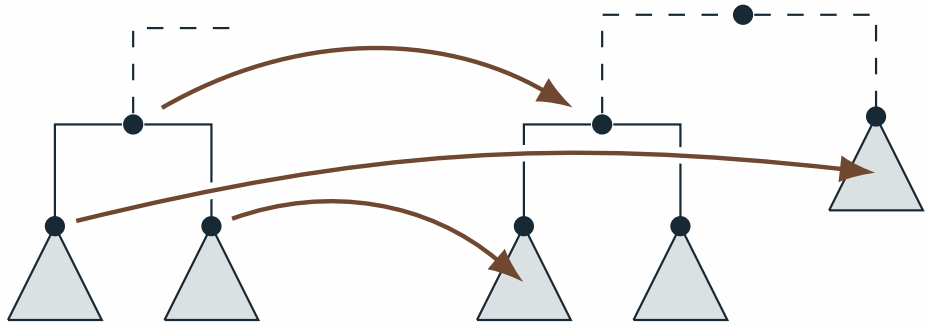
MAPPING SYNTENY TREE TO SPECIES TREE

Synteny tree



Species tree

1	Different descendent subtrees	Speciation
2	Same descendent subtree	Duplication
3	**One in separate subtree**	Transfer

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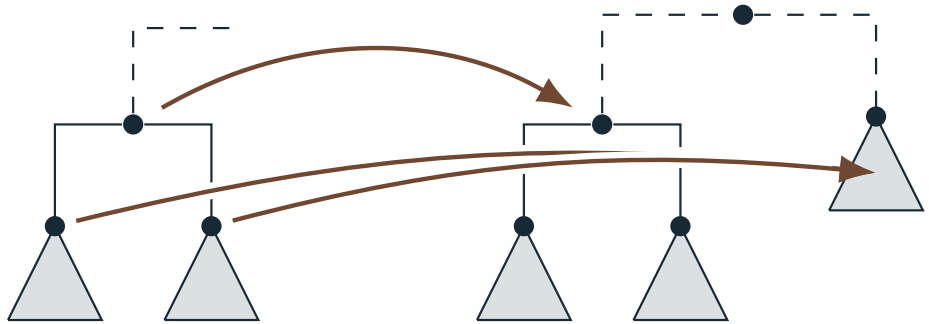
MAPPING SYNTENY TREE TO SPECIES TREE

Synteny tree



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4	**Both in separate subtrees**	*(Excluded)*

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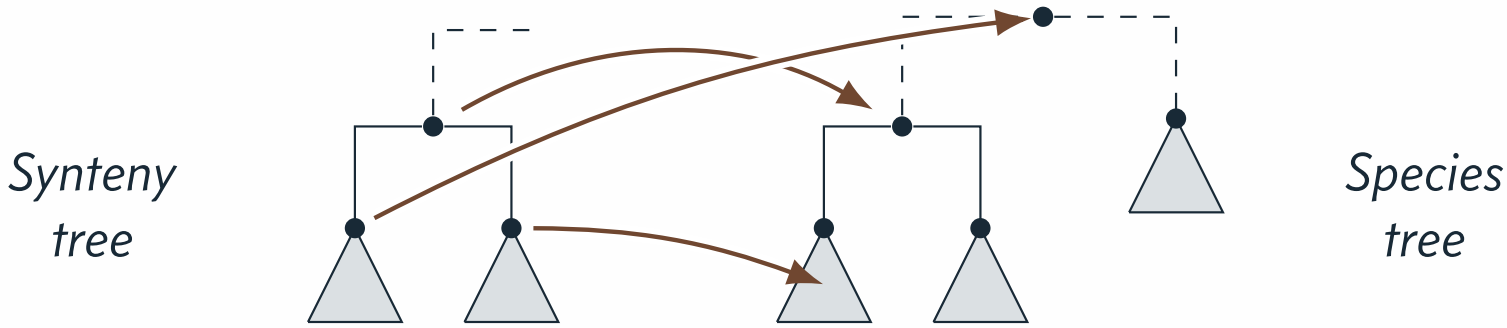
MAPPING SYNTENY TREE TO SPECIES TREE



1	Different descendent subtrees	Speciation
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3	One in separate subtree	Transfer
4	Both in separate subtrees	*(Excluded)*
5	**One in ancestor**	*(Inconsistent)*

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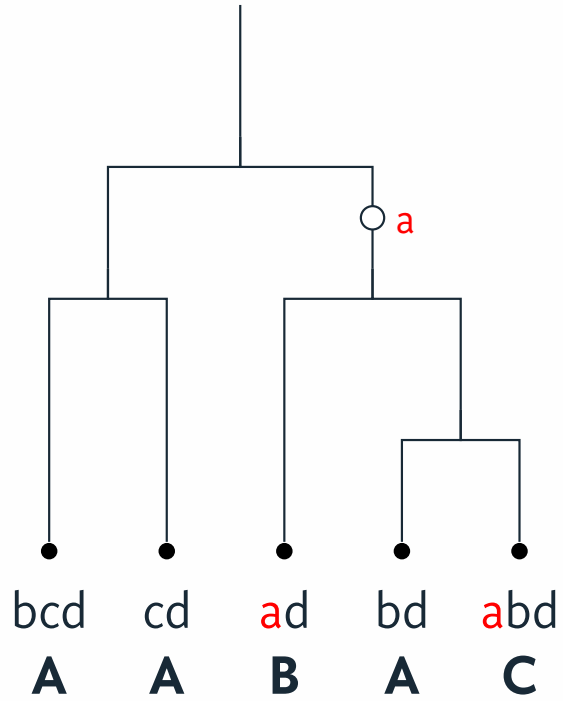
INFERRING GAIN EVENTS

- No family can be gained below the **LCA of the leaves it appears in**
- Minimum-cost history can be obtained by **placing gains exactly at the LCA**



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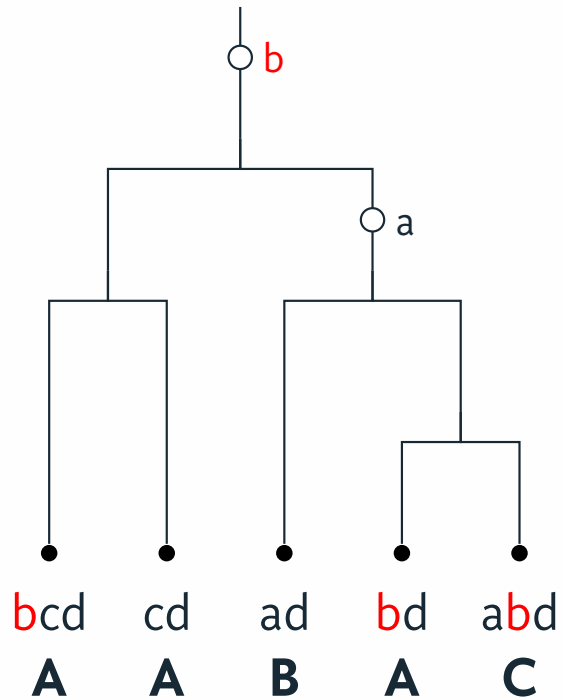

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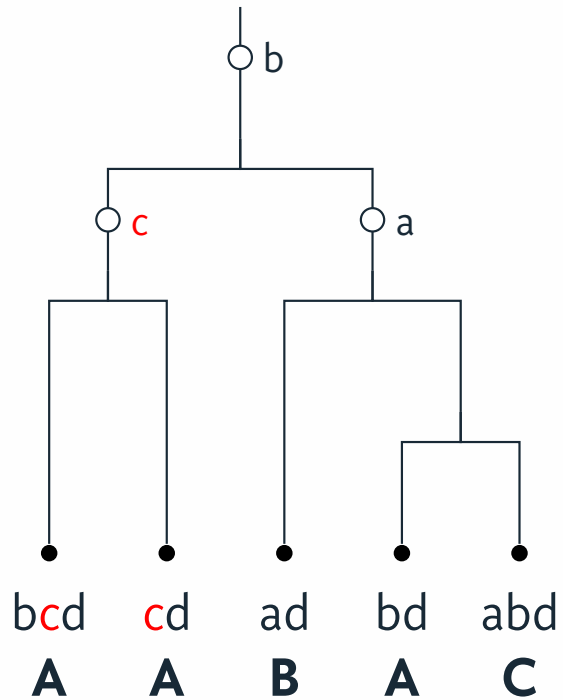

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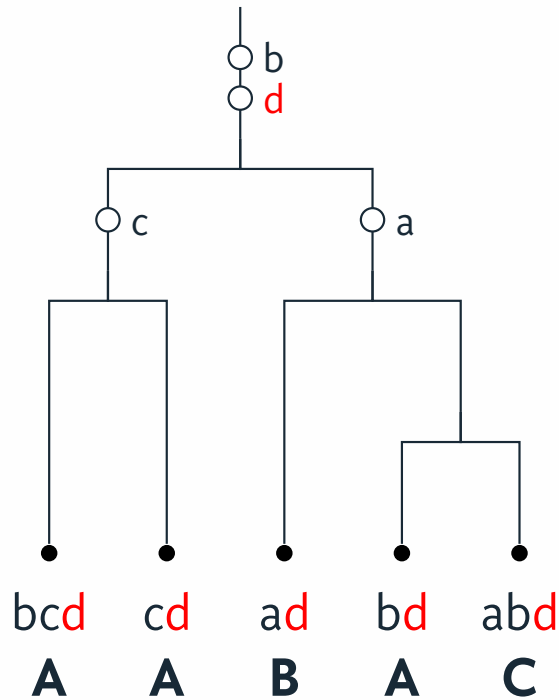
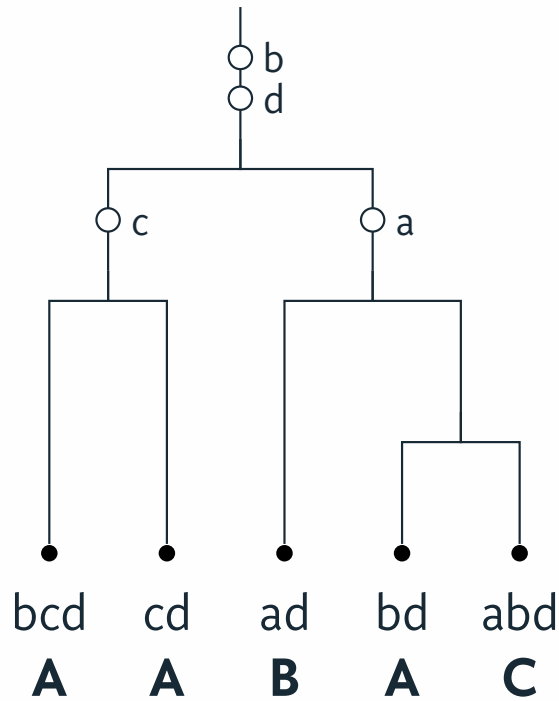


INFERRING ANCESTRAL SYNTENIES

- Choose a **subset of families** for each node so that **losses are minimized**
  - *Exponential choices?*



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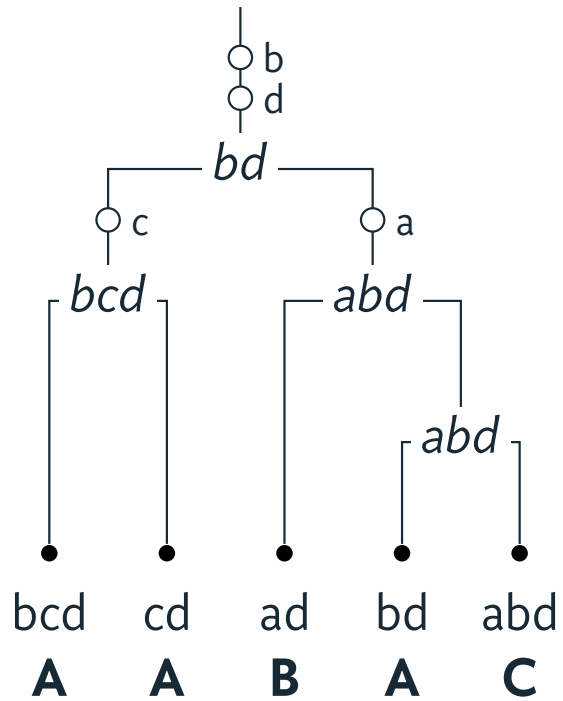
- Each node must contain a **minimum set** of families, may **contain more**
  - "Extra content"



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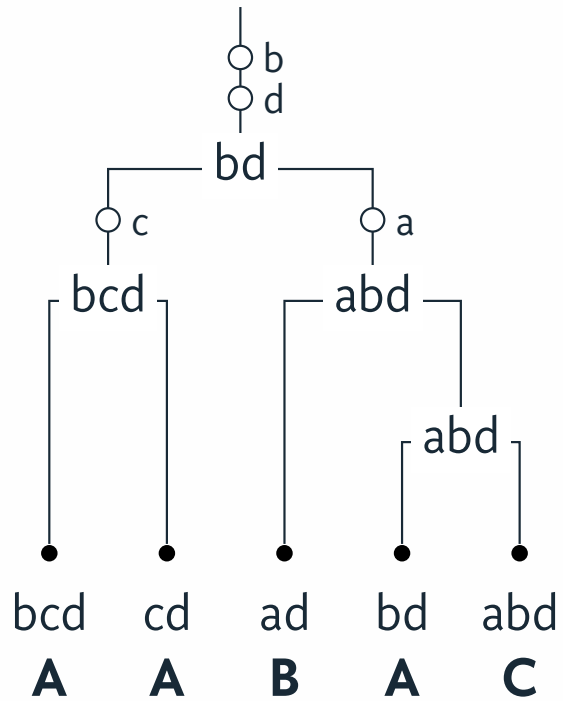
INFERRING ANCESTRAL SYNTENIES

- Choose a **subset of families** for each node so that **losses are minimized**
  - *Exponential choices?*
- Each node must contain a **minimum set** of families, may **contain more**
  - "Extra content"
- Any extra content leads to the same cost, **no matter the actual content**



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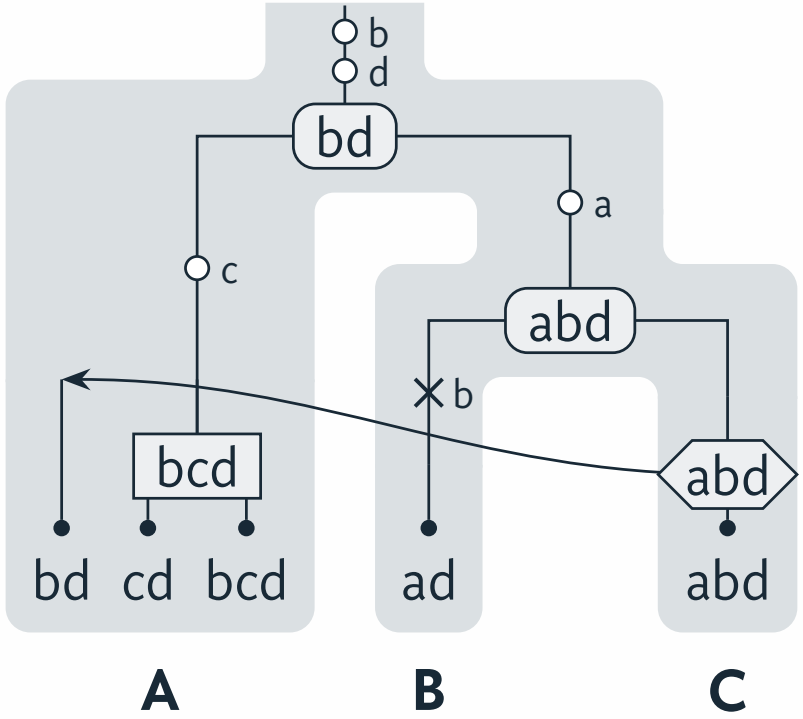
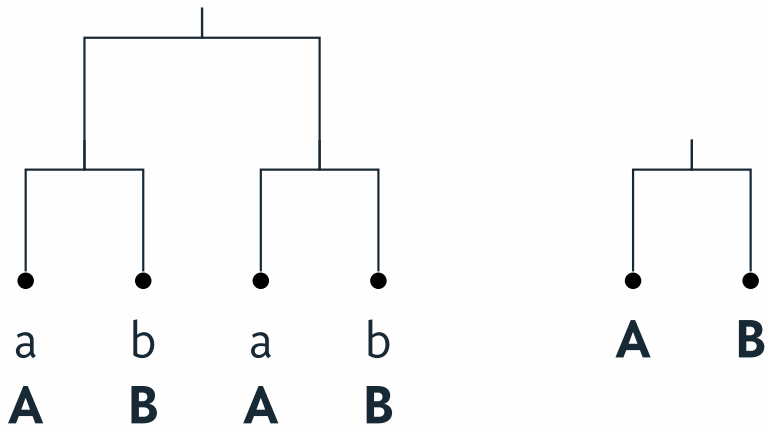


NEED FOR JOINT INFERENCE



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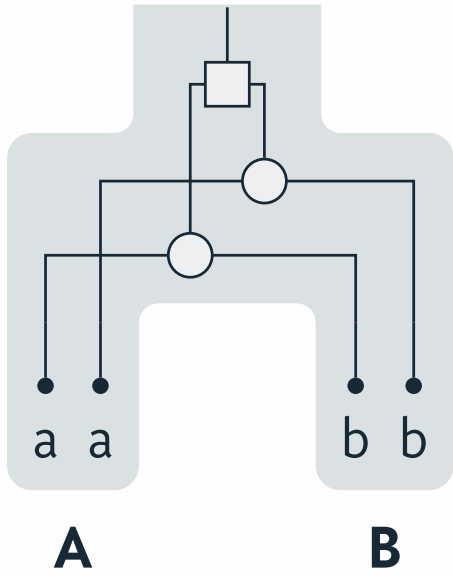
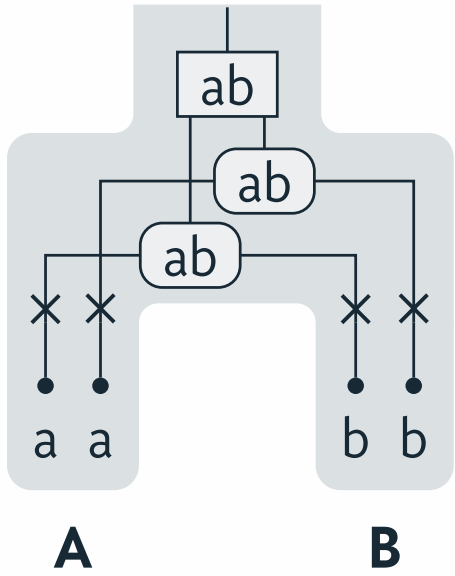


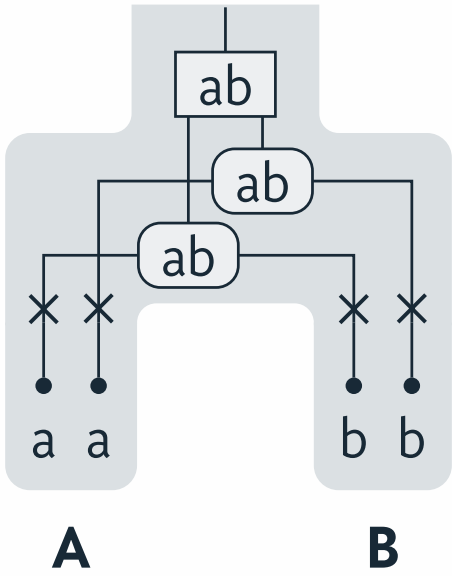
Cost: 1

NEED FOR JOINT INFERENCE

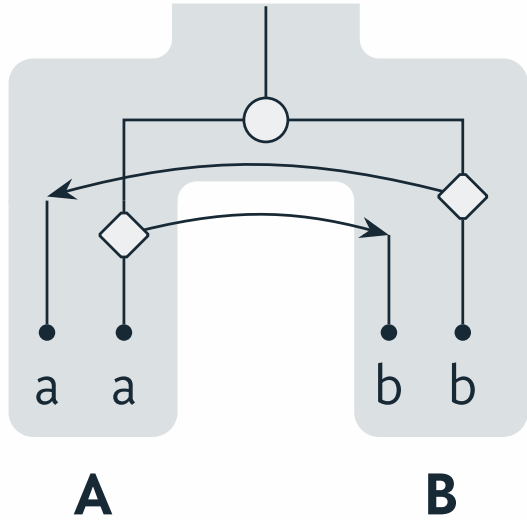


Cost: 1 + 4

NEED FOR JOINT INFERENCE

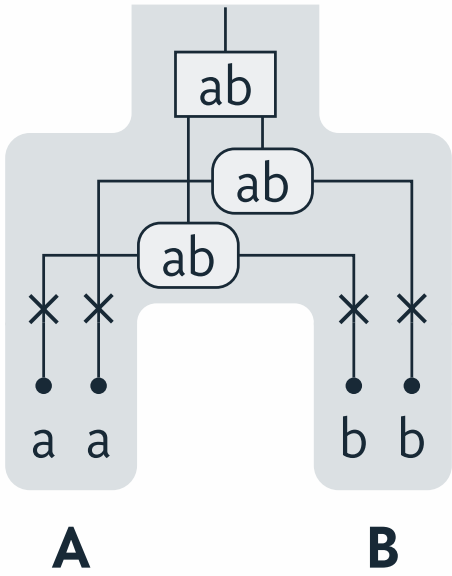


Cost: 1 + 4

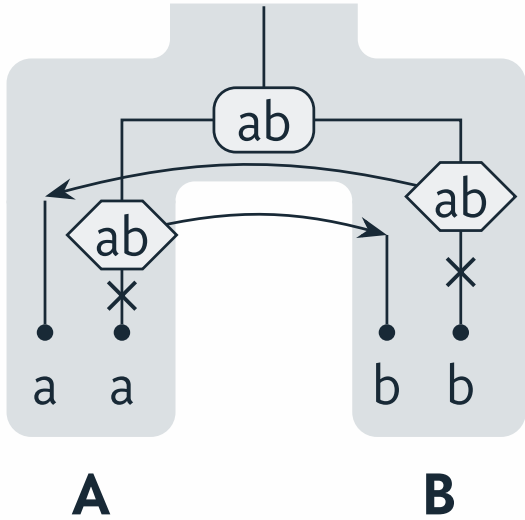


Cost: 2

NEED FOR JOINT INFERENCE



Cost: 1 + 4



Cost: 2 + 2

SUPERDTL ALGORITHM SKETCH

- **For each pair** of nodes (v, σ) in the **synteny** and **species** trees, find minimum cost of **sub-history** below v such that v **is mapped to** σ
  1. Consider **all pairs of species** to which v's children can be mapped
  2. Assign to v either the **minimum synteny** or **any extra content**

- **Overall** minimum cost obtained by looking at values for the **root**
- **Solutions** obtained by backtracing the cost computation

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- **Complexity:** $\mathcal{O}(NM \times M^2) = \mathcal{O}(NM^3)$ time, $\mathcal{O}(NM)$ space
  N: number of syntenies, M: number of species

OUTLINE

DATASET

- Set of **15 bacterial Cas syntenies** from [Makarova *et al.*, 2020][1]
  - Types I, III and IV (class 1)
  - Gene repetitions discarded
- **Synteny tree** as constructed in the article
  - One synteny per species, one species per subtype
  - **Includes multifurcations**
- **Species tree** based on the topology in [Coleman *et al.*, 2021][2]

[1] Makarova et al. "Evolutionary classification of CRISPR–Cas systems: a burst of class 2 and derived variants" (Feb. 2020).

[2] Coleman et al. "A rooted phylogeny resolves early bacterial evolution" (May 2021).

SETTINGS AND PRELIMINARY RESULTS

- Enumerate **all resolutions** of the **synteny tree**, keep best solutions
- **Evaluated event costs**
  - Transfer: 4
  - Duplication: $\{1, 1.5, 2, 2.5, 3\}$
  - Loss: 1

[1] Koonin and Makarova. "Evolutionary plasticity and functional versatility of CRISPR systems" (Jan. 2022).

SETTINGS AND PRELIMINARY RESULTS

- Enumerate **all resolutions** of the **synteny tree**, keep best solutions
- **Evaluated event costs**
  - Transfer: 4
  - Duplication: $\{1, 1.5, 2, 2.5, 3\}$
  - Loss: 1

- **32 optimal solutions**
- All **agree** on the multifurcations **resolution**
- Differences between optimal solutions are not significant
- Inferred scenario **mostly in line** with [Koonin and Makarova, 2022][1]
- See full inferred scenario on poster #10

[1] Koonin and Makarova. "Evolutionary plasticity and functional versatility of CRISPR systems" (Jan. 2022).

OUTLINE

KEY POINTS

- Reconciliation framework is **extended** to include **segmental** (non-ordered) duplication, transfer, loss and gain events
- **Most parsimonious** history under that model **found in** $\mathcal{O}(NM^3)$
- History inference for small **Cas synteny** dataset gives results mostly **in line with current evolutionary hypotheses**

FUTURE WORK

- Unsampled lineages[1]
  - Transfers may only happen between **co-existing species**
  - Some species may be **unsampled** yet act as intermediate hosts
- Dataset extension
  - Include archaeal Cas syntenies
  - Extract data from CRISPRCasDb
- Complexity improvements[2]

---

[1] Weiner and Bansal. "Improved duplication-transfer-loss reconciliation with extinct and unsampled lineages" (Aug. 2021).

[2] Bansal, Alm, and Kellis. "Efficient algorithms for the reconciliation problem with gene duplication, horizontal transfer and loss" (June 2012).

Code available at: github.com/UdeM-LBIT/superrec2

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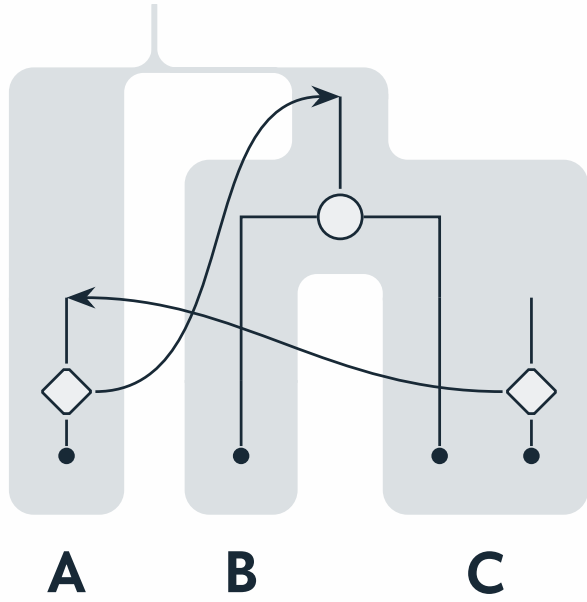
BACKUP SLIDES

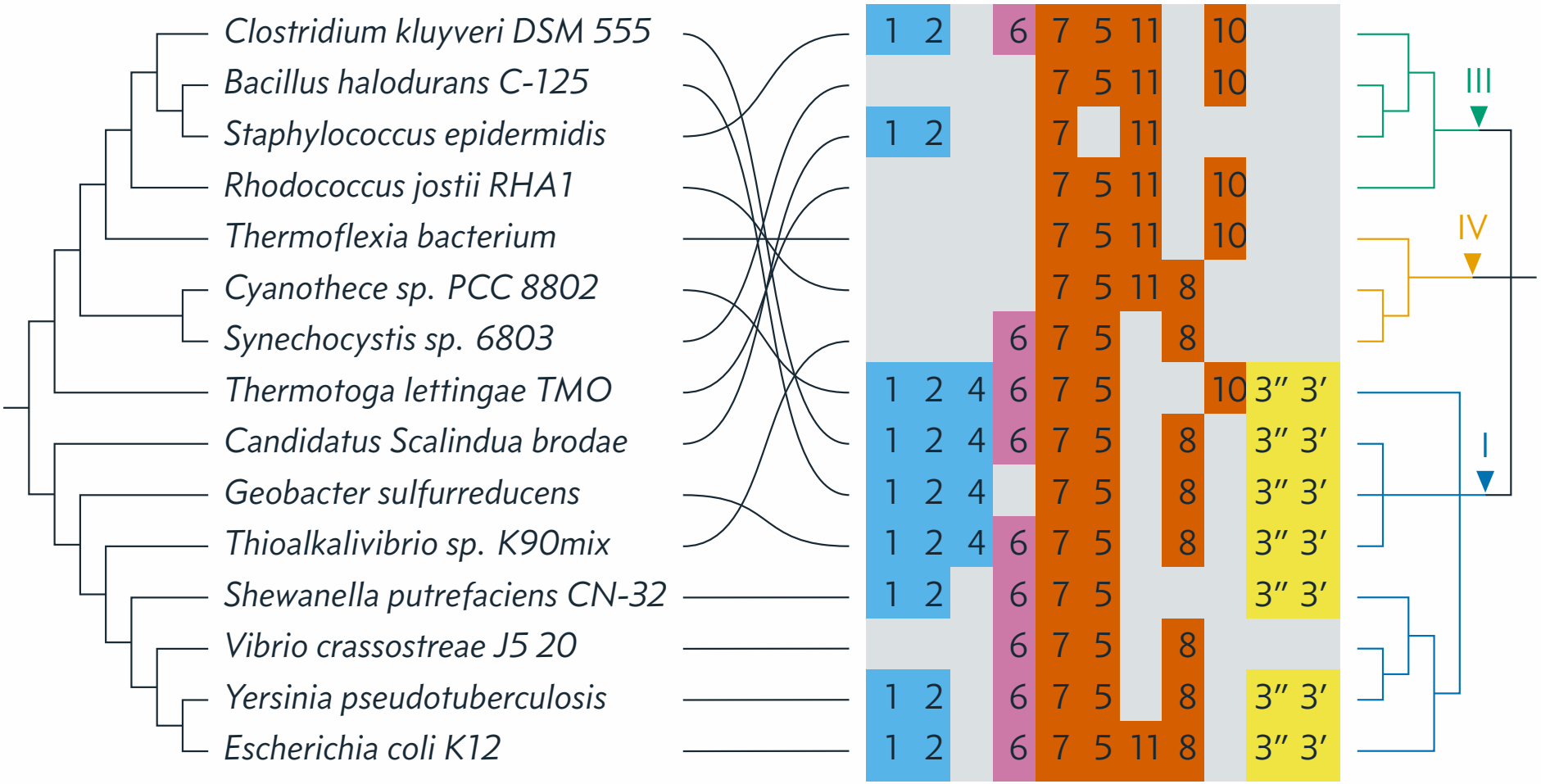
TIME-CONSISTENCY

- Model admits **time-inconsistent** histories
- Forbidding them makes the problem **intractable**



Tofigh, Hallett, and Lagergren. "Simultaneous identification of duplications and lateral gene transfers" (Mar. 2011).

DATASET DETAILS



RESULTS DETAILS

Resolutions of the synteny tree: 27

Solutions per cost value:

$c_T \backslash c_D$	**1**	**1.5**	**2**	**2.5**	**3**
1	1376	1376	1376	1376	1376
2	132	132	132	132	132
3	112	60	60	60	60
4	*32*	*32*	*32*	*32*	*48*
5	288	288	320	32	32
6	320	288	288	288	288