Horizontal Gene Transfer and the Fitch-Relation

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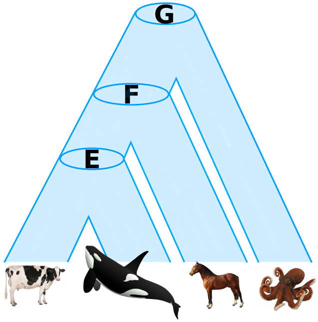
Intro

The “true” evolutionary History



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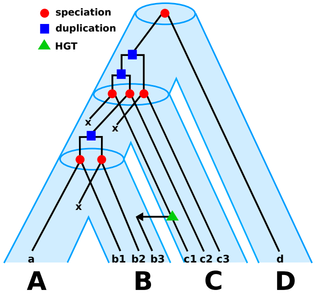
- species are characterized by its genome: a “bag of genes”
- “Genes” evolve along a *rooted* tree with unique *event labeling* $t: V^0 \rightarrow M = \{\bullet, \blacksquare, \blacktriangle\}$



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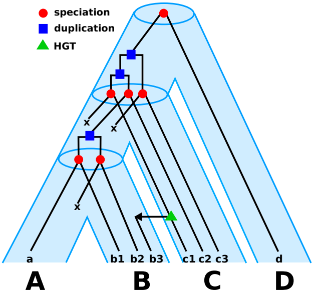
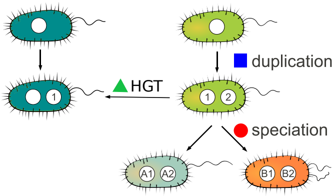


- ■ Gene duplication : an offspring has two copies of a single gene of its ancestor
- ● Speciation : two offspring species inherit the entire genome of their common ancestor
- ▲ HGT : transfer of genes between organisms in a manner other than traditional reproduction and across different species



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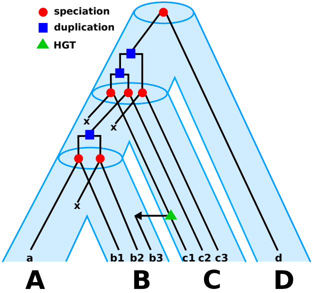

Homology Relations

- Best Matches (evolutionary closest relatives)
- Orthology $(t(\mathrm{lca}_T(x,y)) = \bullet)$
- Xenology (HGT on the path between two genes)

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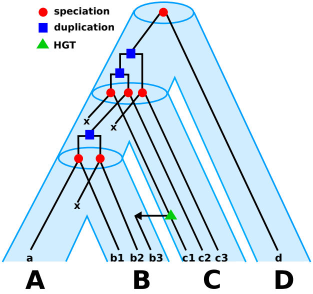

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Knowledge of Hom. Rel. is extremely important (e.g.: *comparative genomics, genome annotation, understanding mechanisms that act on genes, . . .*)

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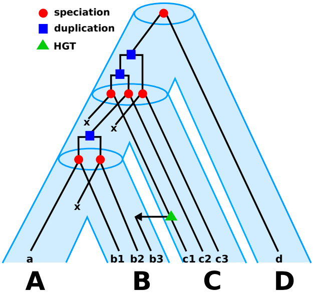

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Homology relations have a precise mathematical definition in terms of the true history which we don’t know!

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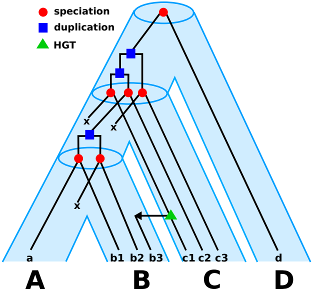

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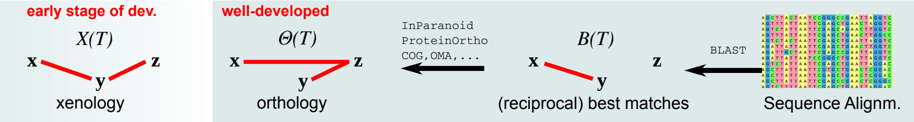

SoA: These relations can be *inferred* from genomic sequence data ***without* any knowledge of a gene or species trees.**

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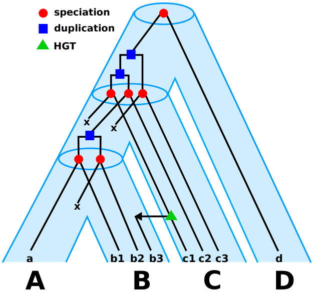

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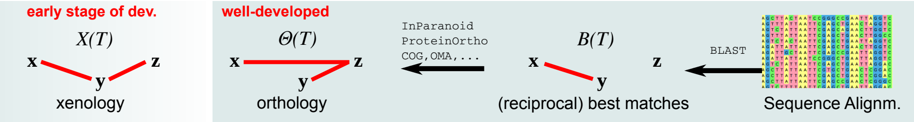

SoA: These relations can be *inferred* from genomic sequence data ***without* any knowledge of a gene or species trees.**

$\Longrightarrow$ we get only estimates of “true” relations $\Longrightarrow$ correct these estimates

(plaqued by measurement errors, noise, not biological feasible)

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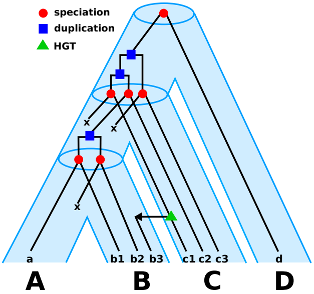

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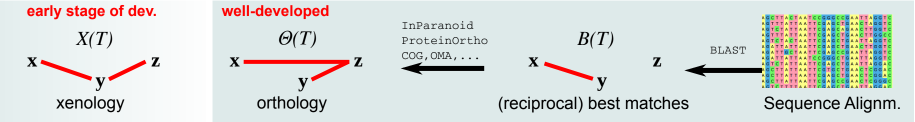


SoA: These relations can be *inferred* from genomic sequence data ***without* any knowledge of a gene or species trees.**

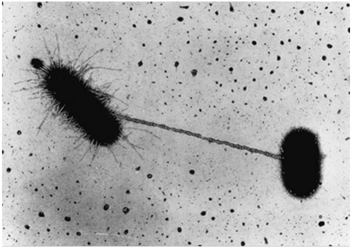
$\Longrightarrow$ understand mathematical structure of these relations

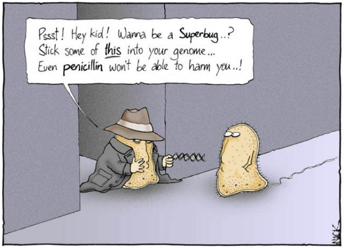
(there was a large gap in the literature)

Horizontal Gene Transfer and the Fitch-Relation

Examples of HGT

Bacteria to Bacteria:





HGT is a significant cause of increased drug resistance when one bacterial cell acquires resistance, and the resistance genes are transferred to other species.

Barlow, **What antimicrobial resistance has taught us about horizontal gene transfer**, *Methods in Molecular Biology. 532: 397-411*, 2009

Hawkey and Jones, **The changing epidemiology of resistance**, *Journal of Antimicrobial Chemotherapy. 64 (Suppl 1): i3-10.*, 2009

Stearns and Hoekstra, **Evolution: An introduction (2nd ed.)**, *Oxford Univ. Press*, 2005

Examples of HGT

Bacteria to Animals:

A bacterial gene discovered in the genome of the *coffee berry borer beetle*, a major pest, allows the beetle to occupy a unique ecological niche and feed exclusively on coffee beans.

The transferred gene, which lets the beetle break down complex sugars in the coffee bean, came from the beetle's gut bacteria.

Acuna et al. , **Adaptive horizontal transfer of a bacterial gene to an invasive insect pest of coffee**, *PNAS. 109 (11): 4197-4202*, 2012

Phillips, **Bacterial gene helps coffee beetle get its fix**, *Nature News*, 2012

Examples of HGT

Plant to Plant

Ferns have the neochrome-gene that allows them to “produce” an unconventional photoreceptor that senses both blue *and* red light, affording ferns a unique advantage in low-light environments.

This neochrome-gene is not part of any other “higher” plant.

There is strong evidence that Ferns acquired the neochrome-gene from the moss-like plant *Hornwort* via HGT.

Li et al. , **Horizontal transfer of an adaptive chimeric photoreceptor from bryophytes to ferns**, *PNAS*, 2014

Zimmer, **Plants That Practice Genetic Engineering**, *New York Times*, 2015

Examples of HGT

There are many other examples ..

- HGT from fungi to animals (e.g. in Pea Aphids)
- Bdelloid rotifers currently hold the 'record' for HGT in animals with ∼8% of their genes from bacterial origins.
- even humans may harbor more than 100 genes from other organisms ..

In what follows, let us have a closer look to genes that are related via HGT.

Fukatsu, **A Fungal Past to Insect Color**, *Science. 328 (5978): 574-575*, 2010

Moran and Jarvik, **Lateral Transfer of Genes from Fungi Underlies Carotenoid Production in Aphids**, *Science. 328 (5978): 624-627*, 2010

Gladyshev, Meselson, Arkhipova **Massive Horizontal Gene Transfer in Bdelloid Rotifers**, *Science*, 2008

Watson, **Bdelloids Surviving on Borrowed DNA**, *Science/AAAS News*, 2012

Crisp et al. , **Expression of multiple horizontally acquired genes is a hallmark of both vertebrate and invertebrate genomes**, *Genome Biol. 16: 50*, 2015

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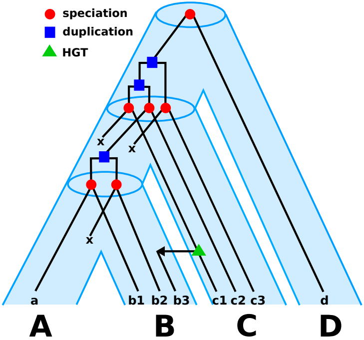
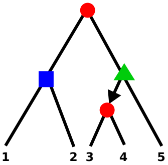


Walter M. Fitch:
“*Two genes x and y are xenologs if their history, since their common ancestor, involves an interspecies (horizontal) transfer of the genetic material for at least one of them.*”

W. M. Fitch, **Homology a personal view on some of the problems**, *Trends Genet 16:227-31*, 2000

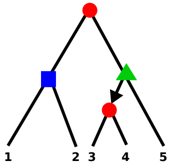
The Fitch Relation



Gene 2 and 3 are xenologs, but 2 and 5 are not.

Walter M. Fitch:
"*Two genes x and y are xenologs, if their history, since their common ancestor, involves an interspecies (horizontal) transfer of the genetic material for at least one of them.*"
$\Longleftrightarrow$
On the path from x to y in T there is a transfer-edge.

The Fitch Relation



HGT is a **directional event**, i.e., there is a clear distinction between the horizontally transferred "copy" and the "original" that continues to be vertically transferred.

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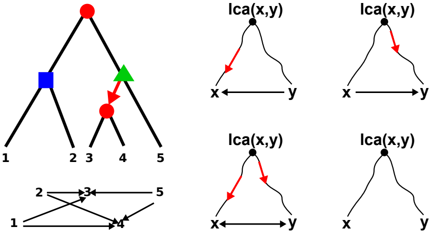
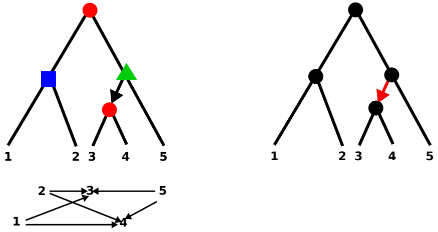


HGT is a **directional event**, i.e., there is a clear distinction between the horizontally transferred “copy” and the “original” that continues to be vertically transferred.

Thus, we consider the following “Refinement”:

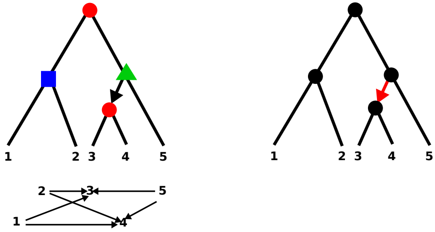
Gene x is xenologous to Gene y, in symbols “$x \to y$”,
if on the path from $\mathrm{lca}(x,y)$ to y there is a transfer-edge.

The Fitch Relation



Whether or not x and y are xenologs **does not depend on the "vertex-labels"** but only on the **"edge-labels"**.

The Fitch Relation



A Fitch-tree (T, λ) is a phylogenetic tree with transfer/non-transfer edges.
(λ is a binary edge-labeling)

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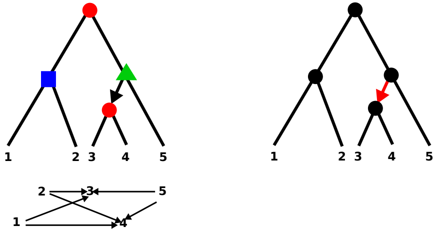

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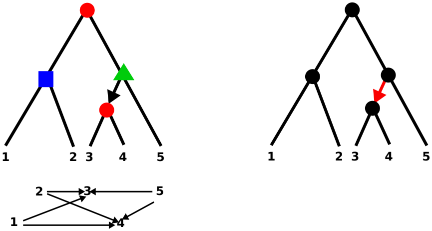

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A Fitch-relation $\mathcal{X}_{(T,\lambda)}$ contains all pairs of xenologs in (T, λ).

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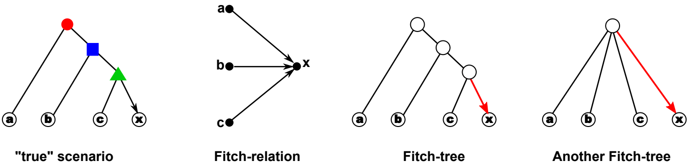

Another Example

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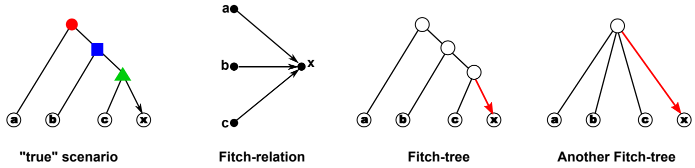


Another Example

Central Questions:

(1) Phylogenetic Signal:
Given a Fitch-relation $\mathcal{X}_{(T,\lambda)}$: Can we reconstruct (T,λ)?

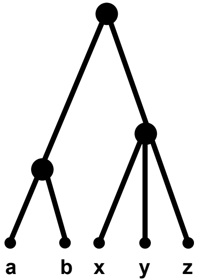
(2) Characterization:
Given an arbitrary binary (irreflexive) relation R:
Is R a Fitch-relation? $\iff$ There is a tree (T,λ) such that $R = \mathcal{X}_{(T,\lambda)}$?

Question 1 - Phylogenetic Signal:

Given a Fitch-relation $\mathcal{X}_{(T,\lambda)}$: Can we reconstruct (T, λ)?

Short Intermezzo: Triples

Rooted tree T:



Aho et al., **Inferring a tree from lowest common ancestors with an application to the optimization of relational expressions**, *SIAM Journal on Computing 10(3)*, 1981

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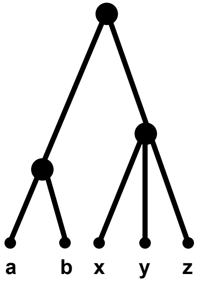

Triples:

T displays a triple $\mathbf{ab}|\mathbf{z}$ if the path from a to b does not intersect the path from z to the root.

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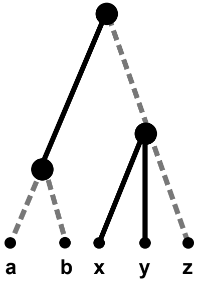

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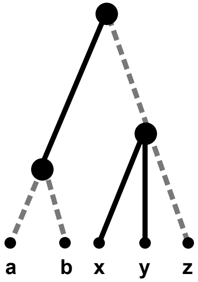

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$\mathcal{R}(T) = \{\mathbf{ab}|\mathbf{x}, \mathbf{ab}|\mathbf{y}, \mathbf{ab}|\mathbf{z}, \mathbf{xy}|\mathbf{a} \ldots\}$

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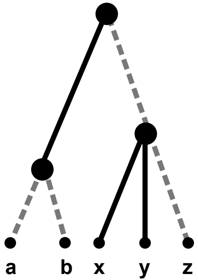

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The algorithm BUILD returns the tree T for $\mathcal{R}(T)$ in polynomial time.

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Phylogenetic Signal in $\mathcal{X}_{(T,\lambda)}$

All 3-leaf Fitch-trees and the explained relations.

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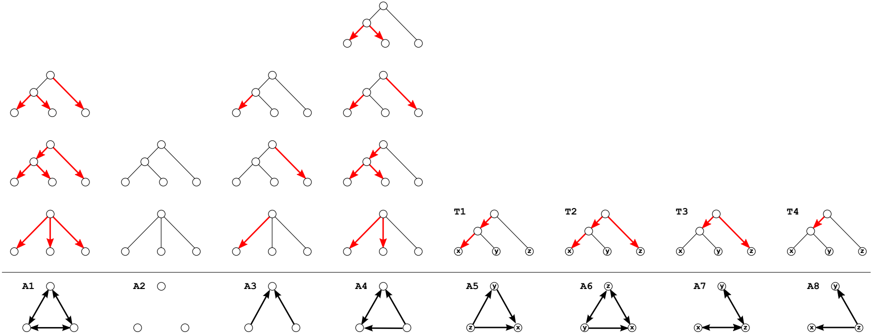

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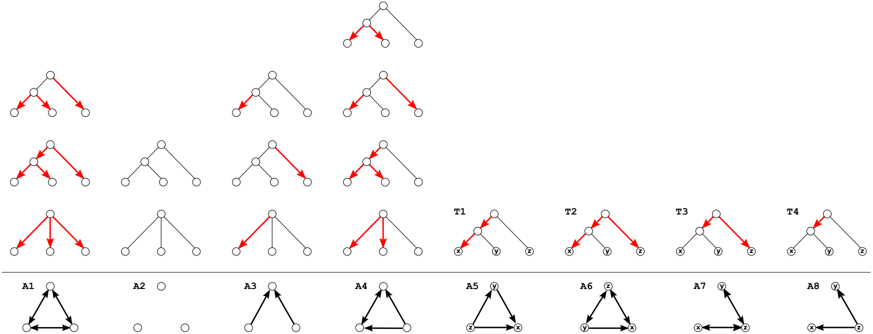

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then (T,λ) must also display the "informative" triple T_1.

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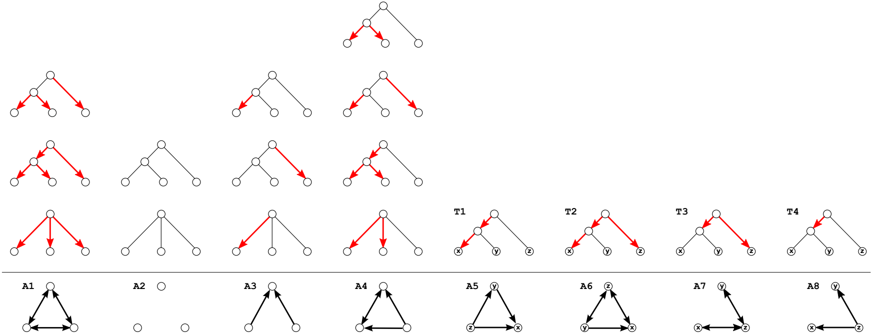

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Analogously for A_6, A_7, A_8 and T_2, T_3, T_4, respectively.

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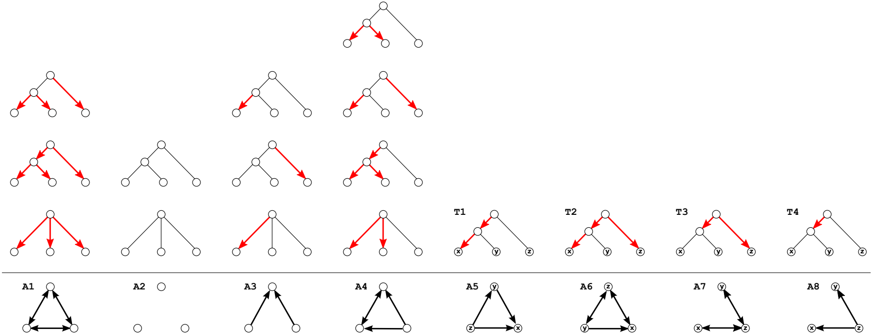

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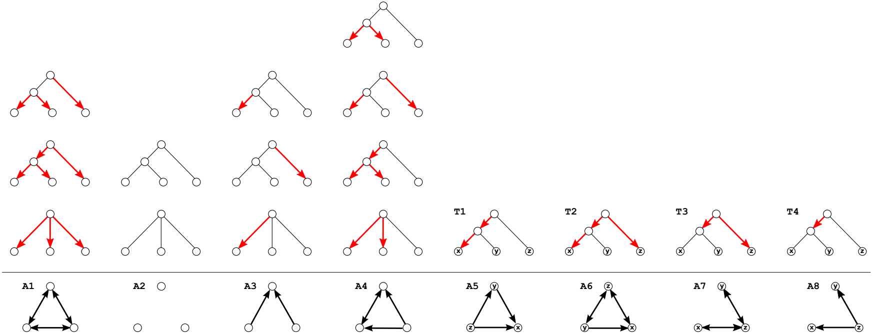
Collect all informative triples provided by $\mathcal{X}_{(T,\lambda)}$ in $r^*(\mathcal{X}_{(T,\lambda)})$.

Phylogenetic Signal in $\mathcal{X}_{(T,\lambda)}$

All 3-leaf Fitch-trees and the explained relations.



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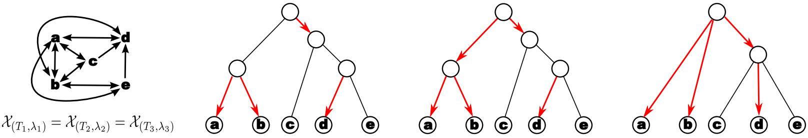
Analogously for A_6, A_7, A_8 and T_2, T_3, T_4, respectively. Collect all informative triples provided by $\mathcal{X}_{(T,\lambda)}$ in $r^*(\mathcal{X}_{(T,\lambda)})$.

Lemma: All triples in $r^*(\mathcal{X}_{(T,\lambda)})$ must be displayed by (T, λ).

Least-resolved tree for $\mathcal{X}_{(T,\lambda)}$

In general, there may be more than one tree that explains $\mathcal{X}_{(T,\lambda)}$.



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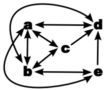
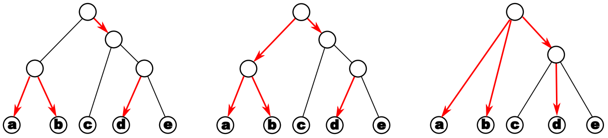


$\mathcal{X}_{(T_1,\lambda_1)} = \mathcal{X}_{(T_2,\lambda_2)} = \mathcal{X}_{(T_3,\lambda_3)}$



(T_1,λ_1) not least-res. (T_2,λ_2) not least-res. (T_3,λ_3) least-resolved

A tree (T,λ) is least-resolved w.r.t. $\mathcal{X}_{(T,\lambda)}$ if any edge contraction in T and any edge-relabeling would yield a tree that does not explain $\mathcal{X}_{(T,\lambda)}$.

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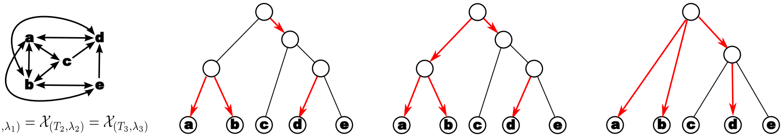

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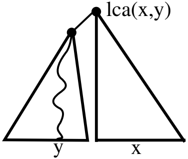

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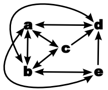

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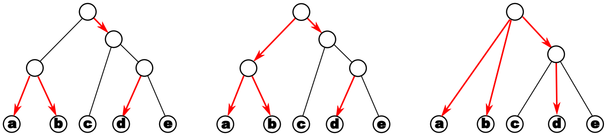

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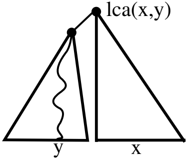

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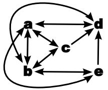

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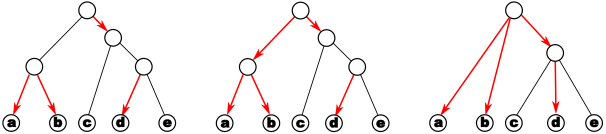

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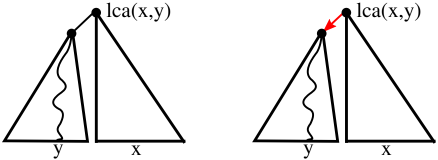

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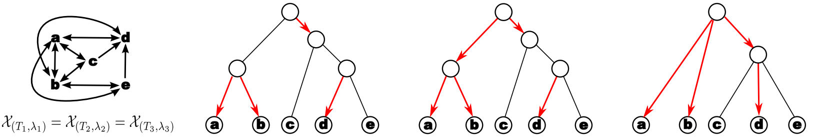

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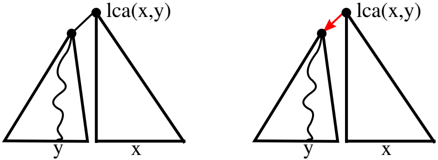

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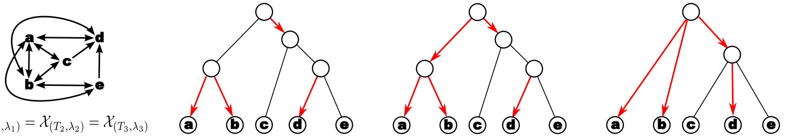

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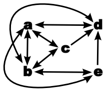

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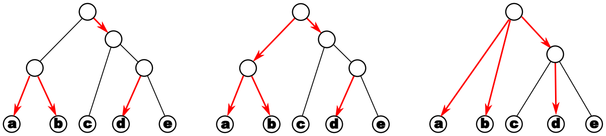

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Theorem. The next conditions are equivalent:

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2. All inner edges of (T,λ) are relevant and transfer-edges
3. All inner edges (u,v) of (T,λ) are transfer-edges and there is always an “outer” NON-transfer-edge (v,x).

Geiß et al., **Reconstructing gene trees from Fitch’s xenology relation.**, *J. Math. Bio*, 2018

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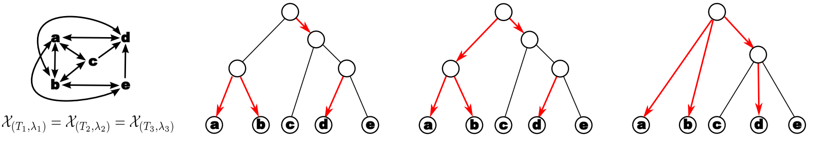

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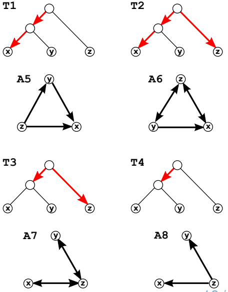

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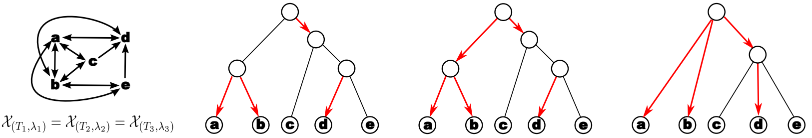

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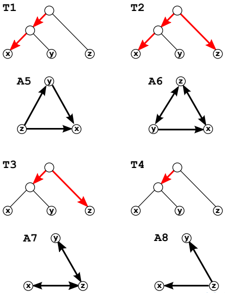

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If (T,λ) is least-resolved w.r.t. $\mathcal{X}_{(T,\lambda)}$, then $r^*(\mathcal{X}_{(T,\lambda)})$ identifies (T,λ).
$\Longrightarrow$ Least-resolved tree is unique

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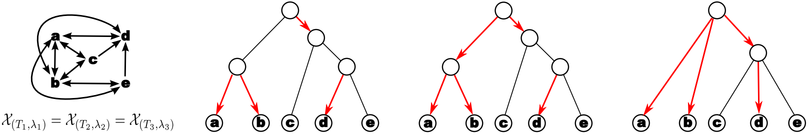

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Question 1 - Phylogenetic Signal:

Given a Fitch-relation $\mathcal{X}_{(T,\lambda)}$: Can we reconstruct (T, λ)?

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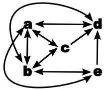

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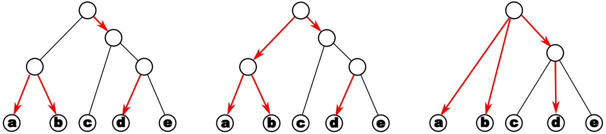

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Answer:

For a given $\mathcal{X}_{(T,\lambda)}$ ...

...one can reconstruct LRT (T^*,λ^*) with `BUILD` applied on $r^*(\mathcal{X}_{(T,\lambda)})$

...any other tree that explains $\mathcal{X}_{(T,\lambda)}$ is a refinement of (T^*,λ^*) since $r^*(\mathcal{X}_{(T,\lambda)})$ identifies (T^*,λ^*)

Question 2 - Characterization

Let R be an arbitrary irreflexive relation.

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Is R a Fitch-relation? $\iff$ There is a tree (T,λ) that explains R.

Characterization of Fitch-Relations

Given an irreflexive relation R, is there a Fitch-tree (T, λ) such that $R = \mathcal{X}_{(T,\lambda)}$?

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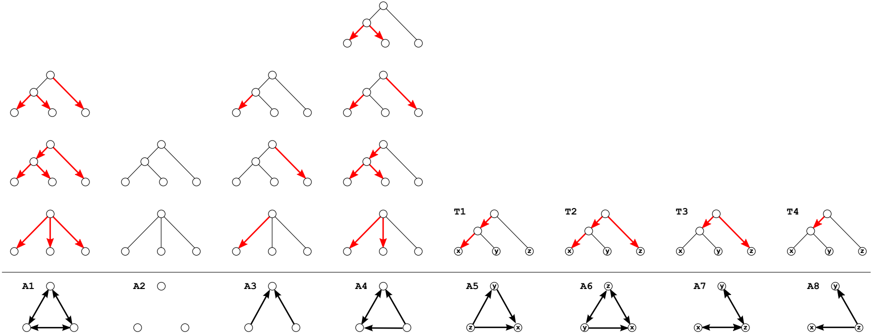

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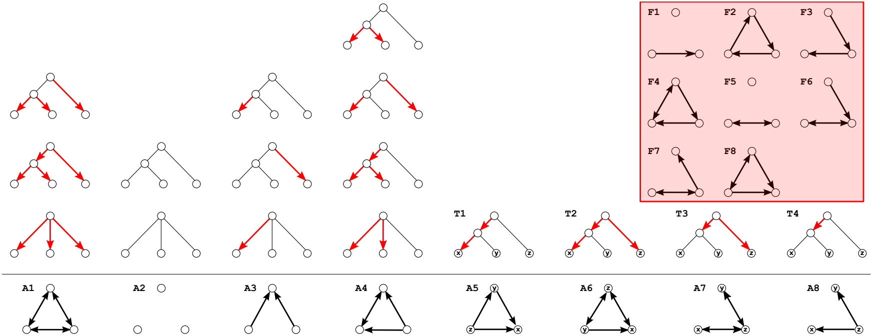

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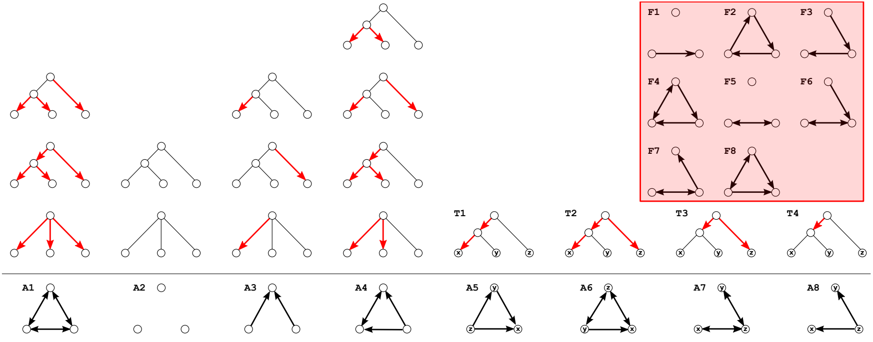

This also shows that informative triples are not sufficient since $r^*(F_i) = \emptyset$.

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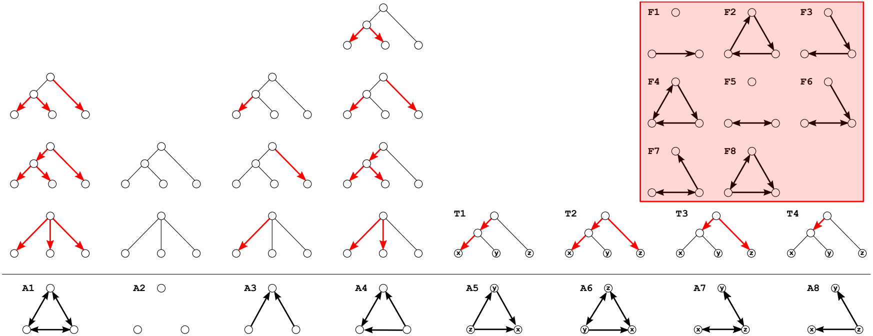

Theorem

R is Fitch-relation $\iff$ R does not contain $F_1,\ldots,F_8$ as an induced subgraph.

Proof: Induction on the size of the leaves + heavy construction part utilizing the structure least-resolved trees // Alternative simpler proof along "complementary neighborhoods".

Geiß et al., **Reconstructing gene trees from Fitch's xenology relation.**, *J. Math. Bio*, 2018

H. and Seemann, **Alternative Characterizations of Fitch's Xenology Relation.**, *J. Math. Bio*, 2019

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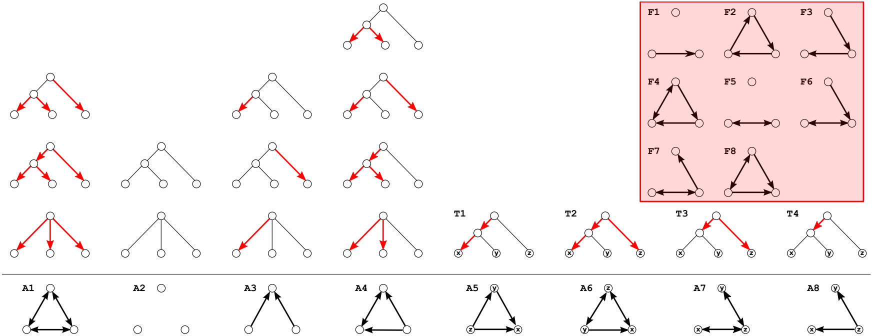

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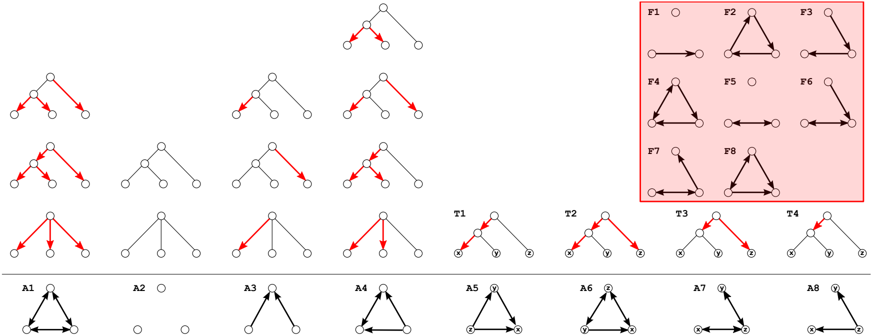

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Can we also get the trees and does it work in linear-time?

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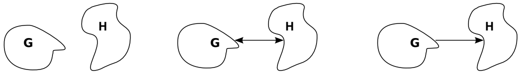
A linear-time recognition and Fitch-tree reconstruction Algorithm

Short Intermezzo: Di-cographs

A di-cograph is a special di-graph and is recursively defined:

- K_1 is a di-cograph;
- If G, H are di-cograph, then



$G+H$ $\qquad$ $G \oplus H$ $\qquad$ $G \oslash H$

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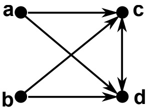

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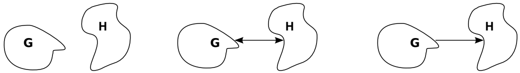

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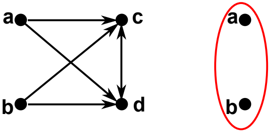

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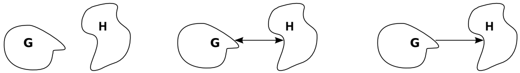

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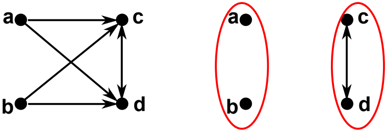

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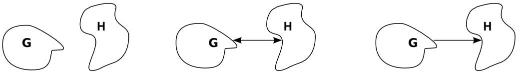

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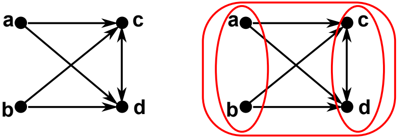

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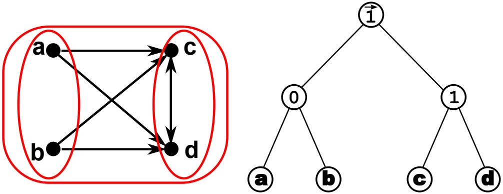
Short Intermezzo: Di-cographs

Each Di-cograph has a cotree-representations:

Ordered Tree (T,t) with vertex labels $t : V^0(T) \to \{0,1,\overrightarrow{1}\}$ defined by

$$t(\mathrm{lca}(x,y)) = \begin{cases} 0, & \text{if } (x,y)(y,x) \notin E(G) \\ 1, & \text{if } (x,y)(y,x) \in E(G) \\ \overrightarrow{1}, & \text{else .} \end{cases}$$



Recognition of di-cographs and cotree reconstruction can be done in $O(|V|+|E|)$ time.

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Short Intermezzo: Di-cographs

Theorem (Engelfriet et al. (1996))

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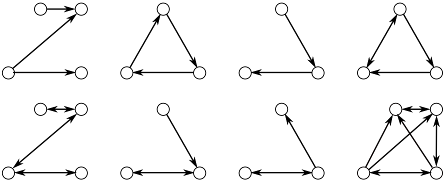

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Di-cographs and Fitch-relations

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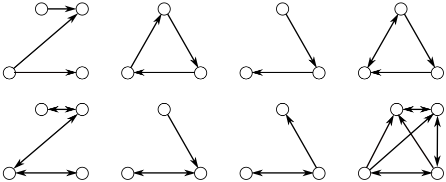

Geiß et al., **Reconstructing gene trees from Fitch's xenology relation.**, *J. Math. Bio*, 2018

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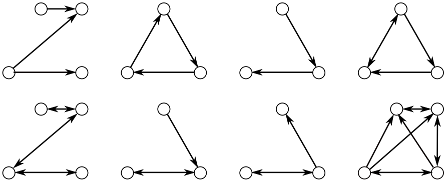

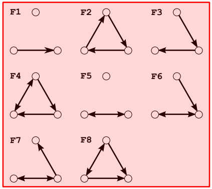

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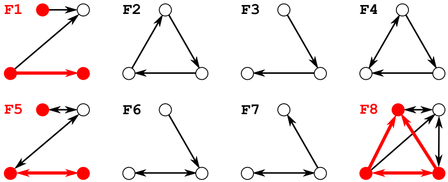

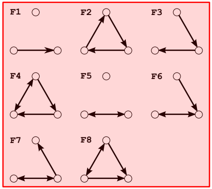

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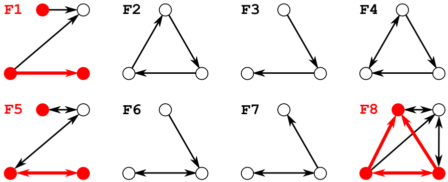

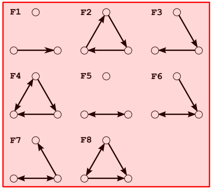

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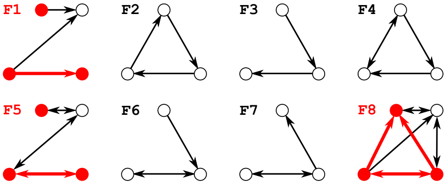

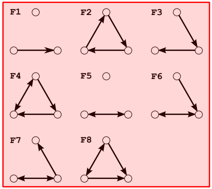

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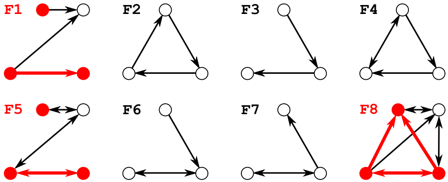

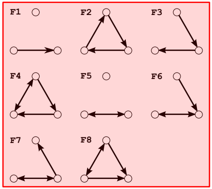

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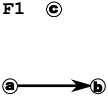
Can we use this to improve the $O(|V|^3)$-time algorithm for Fitch-relations and Fitch-trees? Note, we still have to check for the $O(|V|^3)$ triangles F_1, F_5 and F_8!

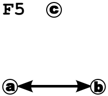
Geiß et al., **Reconstructing gene trees from Fitch's xenology relation.**, *J. Math. Bio*, 2018

Cotrees and F_1, F_5 and F_8

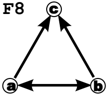
F1



F5



F8



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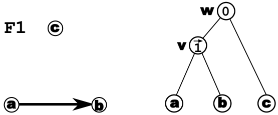

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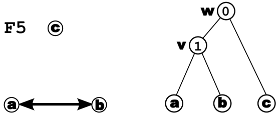

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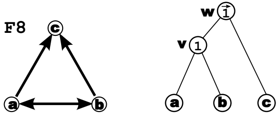

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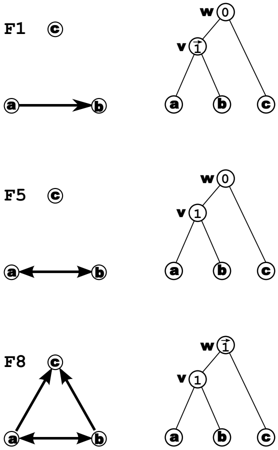

(a) $v \prec_T w$ with $t(w) = 0$ and $t(v) = \vec{1}$

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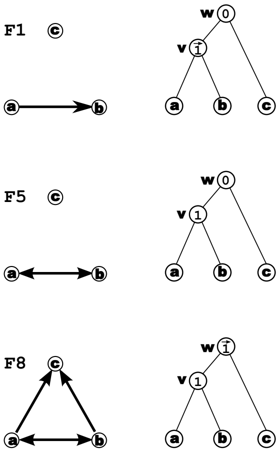

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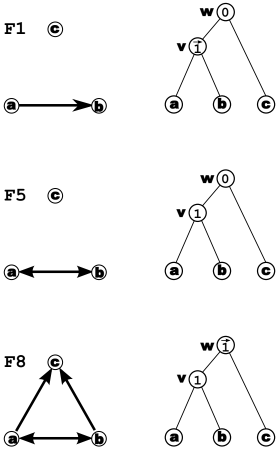

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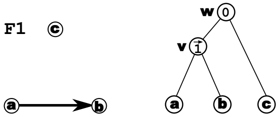

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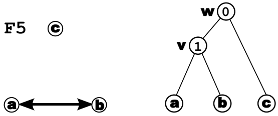

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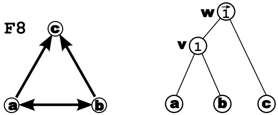

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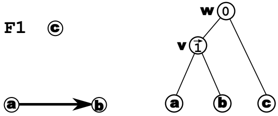

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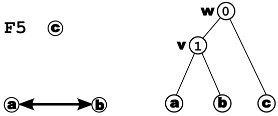

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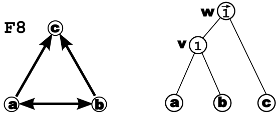

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Thus, recognition of Fitch-graphs can be done in $O(|V|+|E|)$-time.

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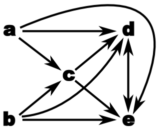
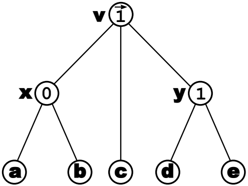
We obtain a cotree (T', t) for the Fitch-graph. How to obtain a Fitch-tree (T, λ)?





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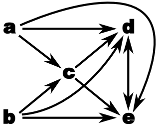

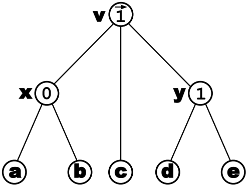

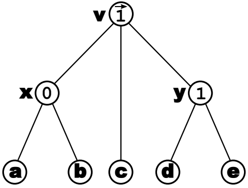

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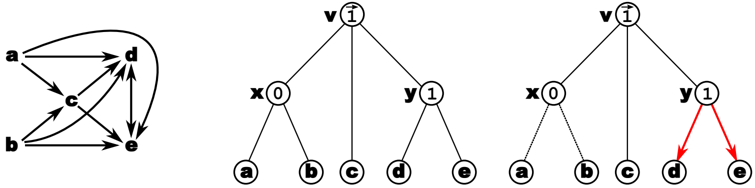

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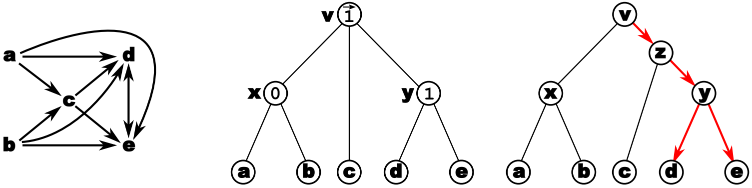

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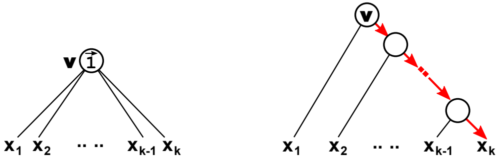

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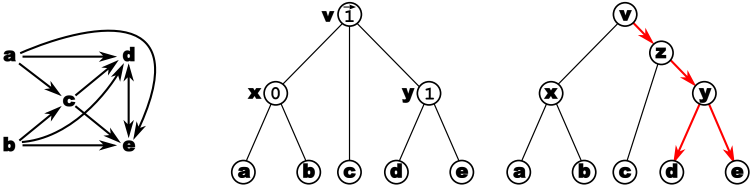

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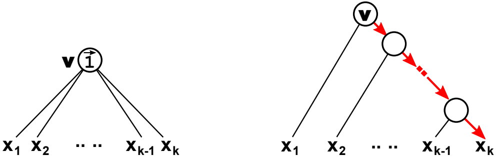

This procedure transforms a cotree into a Fitch-tree in $\mathcal{O}(|V(T')|)$ time.

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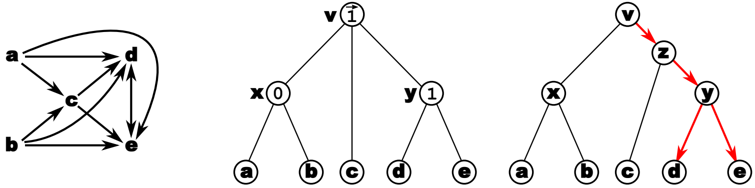

Theorem

Verifying whether a relation $\mathcal{X} \subseteq V \times V$ is a Fitch relation or not, can be a achieved within $\mathcal{O}(|V| + |\mathcal{X}|)$ time. Its unique least-resolved edge-labeled tree $(T_{\mathcal{X}}, \lambda_{\mathcal{X}})$ can be computed in $\mathcal{O}(|V|)$ time.

Geiß et al, **Reconstructing Gene Trees From Fitch's Xenology Relation**, *J. Math. Biology* 2018

Fitch-Relations

The "symmetrized" version

We have considered a "refinement:"
$(x,y) \in \mathcal{X}$ if on the path from $\mathrm{lca}(x,y)$ to y there is a transfer-edge.

The "original" definition by W.M. Fitch:
$(x,y) \in \mathcal{X}_{\mathrm{sym}}$ if on the path from x to y there is a transfer-edge.

H., Long, Geiß, Stadler, **A short note on undirected Fitch graphs**, *Art Discrete Appl. Math.*, 1, 1, #P1.08, 2018

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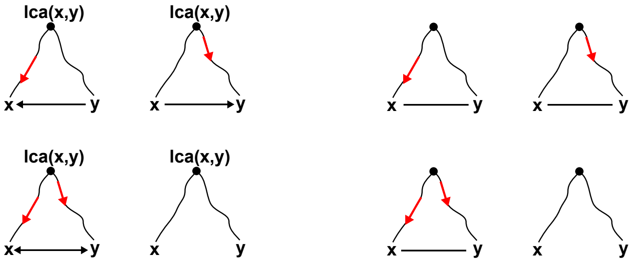

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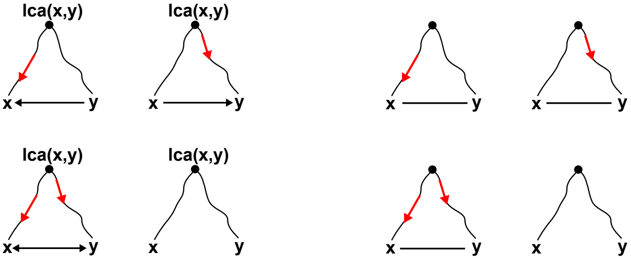

Least-resolved trees are not unique anymore.

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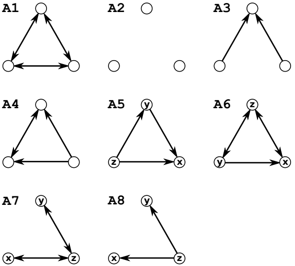

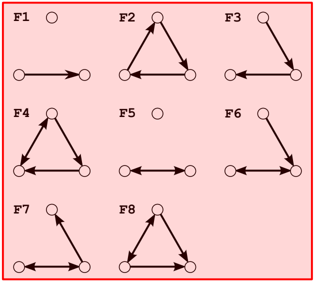

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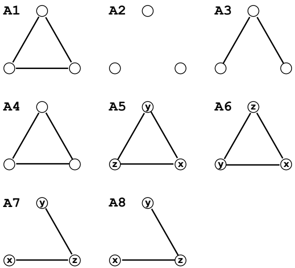

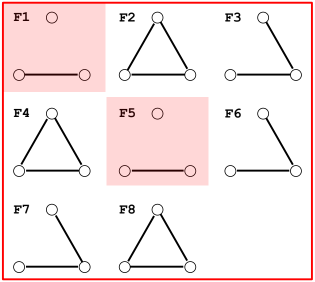

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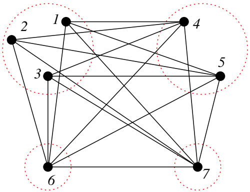

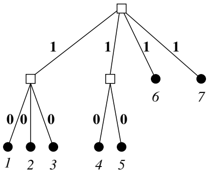

Theorem

$R = \mathcal{X}_{sym}(T,\lambda)$ for some tree (T,λ) $\iff$ R is a complete multipartite graph.

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Summary

- Fitch-relations $\mathcal{X} \subseteq V \times V$ uniquely determine its least-resolved Fitch-tree (T, λ) – informative triples $r^*(\mathcal{X})$.

  Any other Fitch-tree that explains $\mathcal{X}$ is a refinement of (T, λ).

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  Fitch-relations form a subclass of di-cographs.

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- Fitch-relations are characterized by a small set of forbidden subgraphs on 3 vertices.

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- Recognition of Fitch-relations and computing the Fitch-tree can be done on $O(|V| + |\mathcal{X}|)$-time by utilizing the di-cograph structure.

- Class of symmetrized Fitch relations
  = Class of complete multipatite graphs.

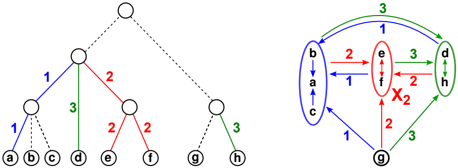
Geiß et al, **Reconstructing Gene Trees From Fitch's Xenology Relation**, *J. Math. Biology* 2018

H., Long, Geiß, Stadler, **A short note on undirected Fitch graphs**, *Art Discrete Appl. Math.*, 1, 1, #P1.08, 2018

Further Results and Outlook

A “generalized” version

We can ask the same questions for relation that are explained by edge-colored trees on more than 2 colors:



Its a great mathematical playground and complements the results known about relations that are explained by *vertex*-labeled trees (cographs, symbolic ultrametrics, 2-structures, . . .)

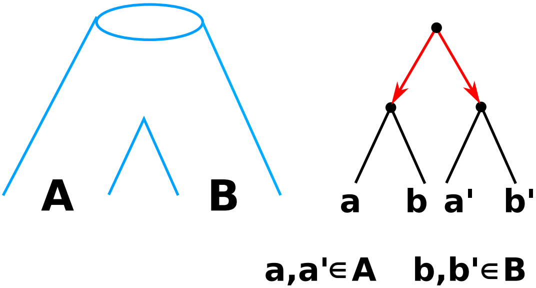
H., **Generalized Fitch Graphs: Edge-labeled Graphs that are explained by Edge-labeled Trees**, *Discr. Appl. Math* 2018

H., Seemann, Stadler **Generalized Fitch Graphs II: Sets of Binary Relations that are explained by Edge-labeled Trees**, preprint, 2020 *Discr. Appl. Math* 2020

H., Seemann, Stadler **Generalized Fitch Graphs III: Symmetrized Fitch maps and Sets of Symmetric Binary Relations that are explained by Unrooted Edge-labeled Trees**, preprint, 2020

Further Results and Outlook

Is every Fitch-relation / Fitch-tree “biologically-feasible”?



Even if we found a reconciliation with some species tree, then “time-consistency” is important!

H, **Biologically Feasible Gene Trees, Reconciliation Maps and Informative Triples**, *Alg. Molecular Biology*, 2017

Nøjgaard et al., **Time-Consistent Reconciliation Maps and Forbidden Time Travel**, *Alg. Molecular Biology*, 2018

Lafond and H, **Reconstruction of time-consistent species trees**, *Alg. Molecular Biology*, 2020

Open Problems

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4. Inference, inference and again inference!

Acknowledgments:

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THANK YOU!