The path of trial and tribulation towards homology based gene/species tree inference

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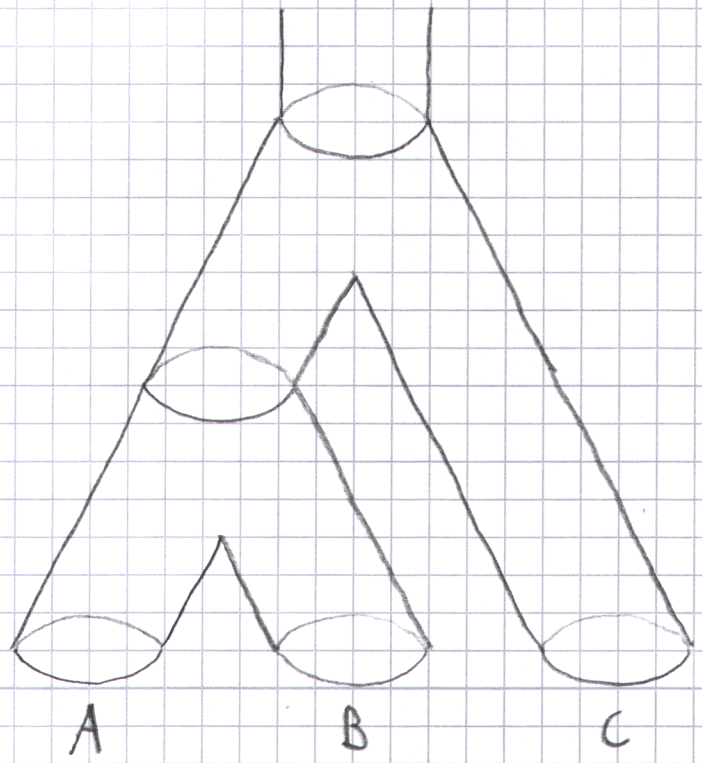
Marc Hellmuth, Bioinf, Greifswald

Problems in Phylogenetics



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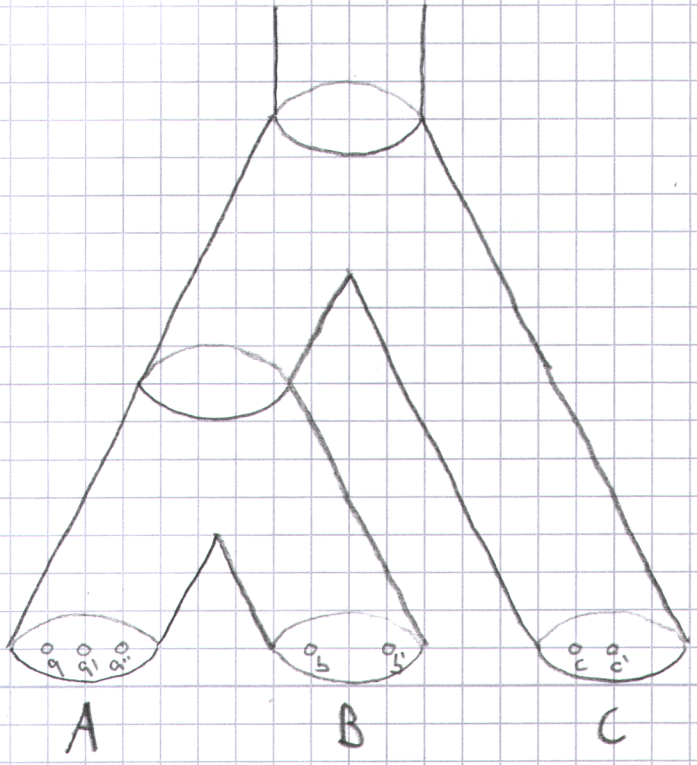

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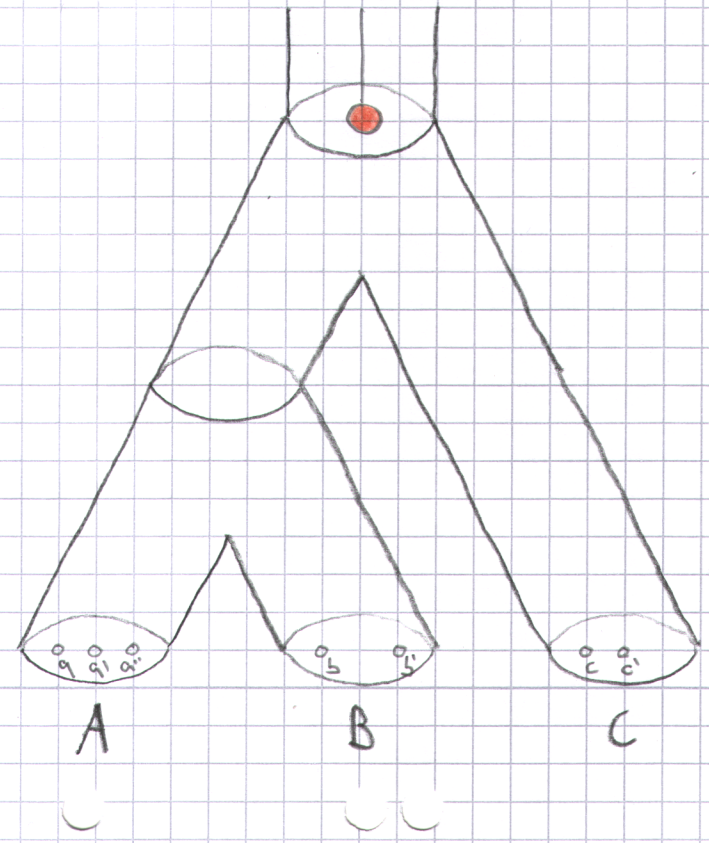

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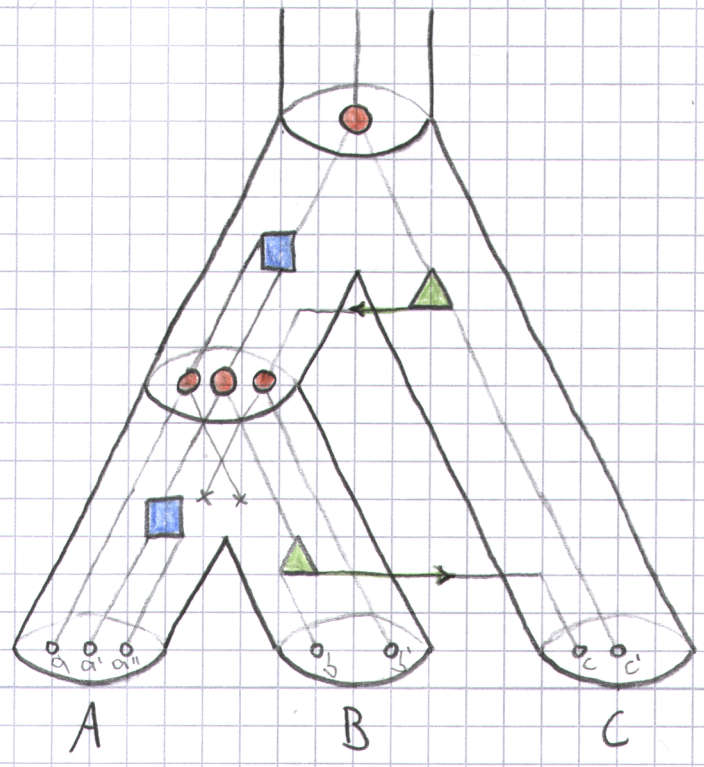

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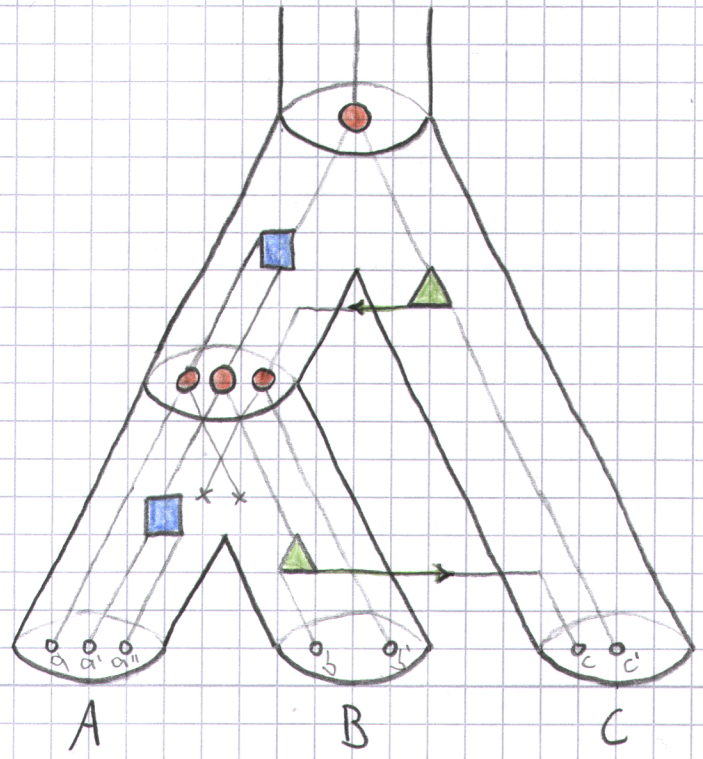


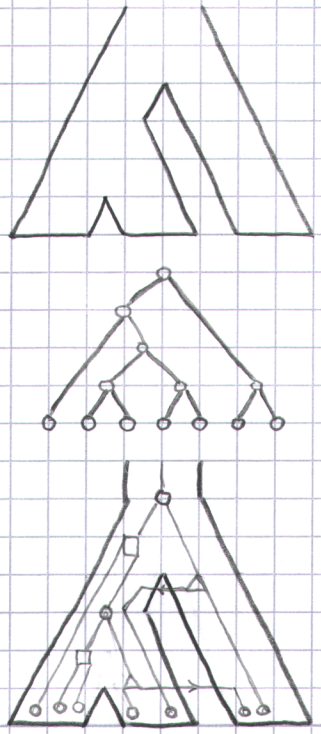
Phylogenetics asks for

- species tree
- gene trees
- evolutionary events
- reconciliation

using only the sequences from extant genes

Classical approach

1. infer species tree
   - using 1-to-1 orthologs
   - multiple sequence alignments
   - NJ, ML, or Bayesian methods
2. infer gene tree
3. reconcile gene tree with species tree
   - using event costs or probabilities
4. obtain event labels



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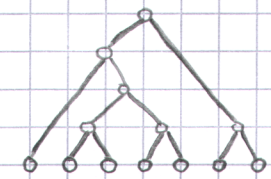

3. reconcile gene tree with species tree
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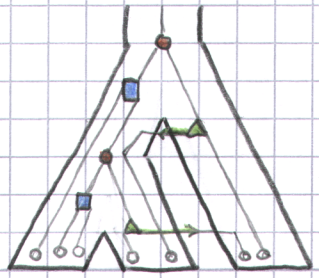
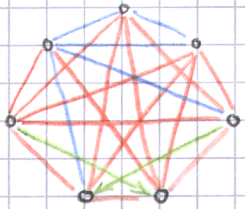


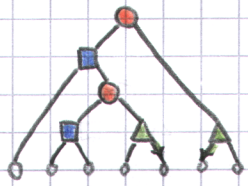
4. obtain event labels

New approach

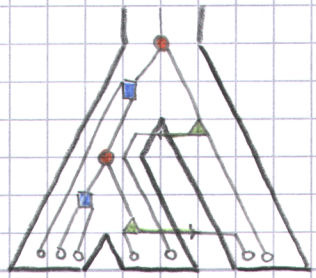
1. infer event labels
   - using pairwise sequence comparisons



2. obtain event labeled gene trees



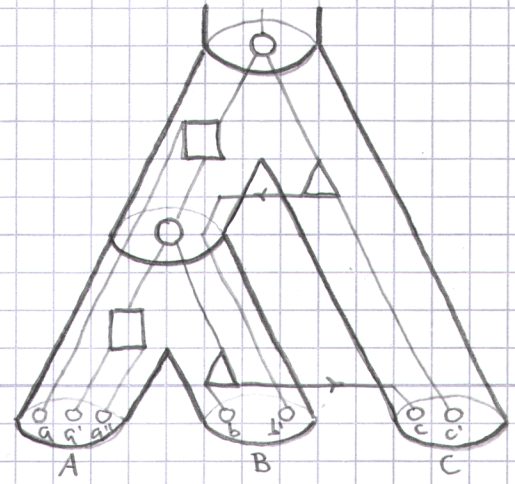
3. infer species tree and corresponding reconciliation



Homology Relations

LCA Relations

- lca-orthologs Θ_L
- lca-paralogs Π_L
- lca-xenologs χ_L
  - lca-donor-xenologs χ_L^D
  - lca-acceptor-xenologs χ_L^A



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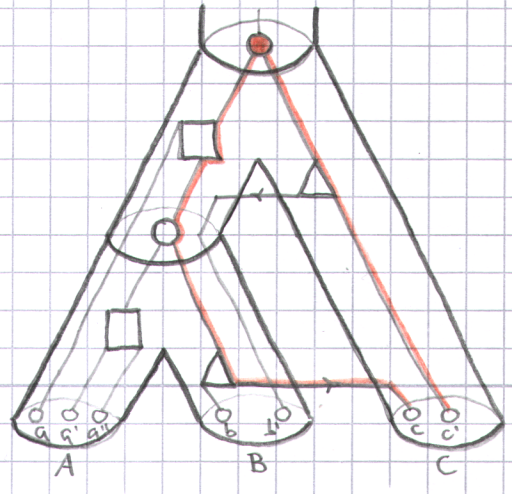

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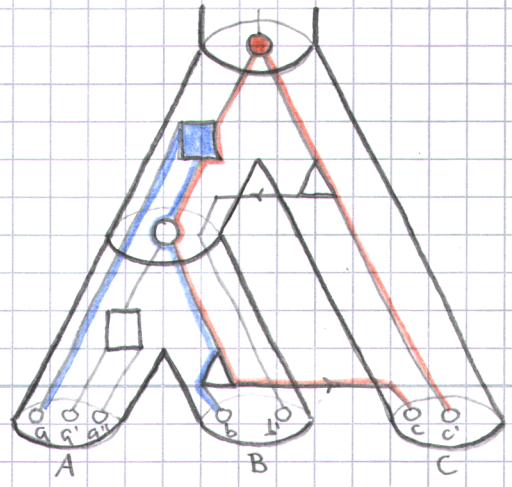

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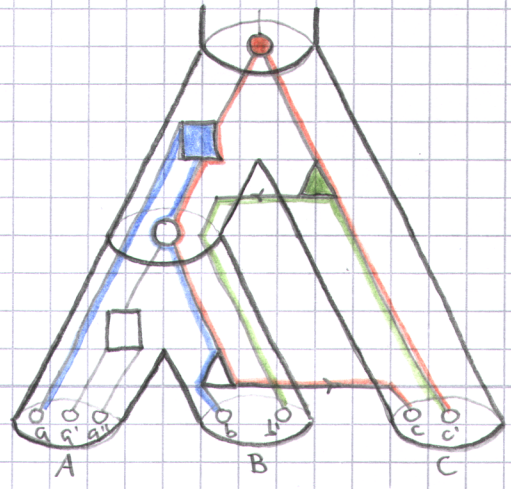

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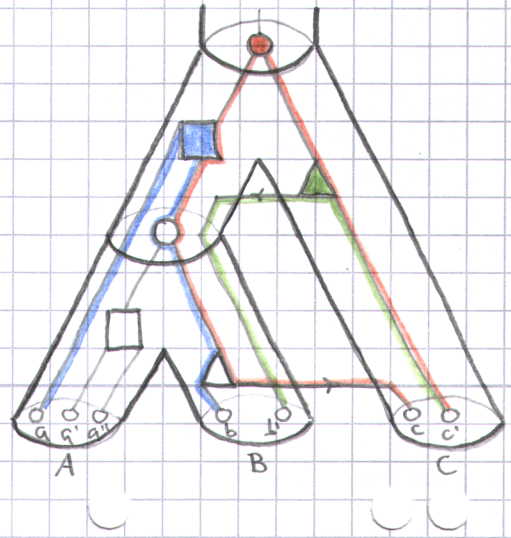

Fitch Relations

- Fitch-orthologs Θ_F
  $(a,b) \in \Theta_F \leftrightarrow \mu(lca_T(a,b)) = lca_S(A,B)$
- Fitch-xenologs χ_F
  $(a,b) \in \chi_F \leftrightarrow$ transfer on path $a-b$
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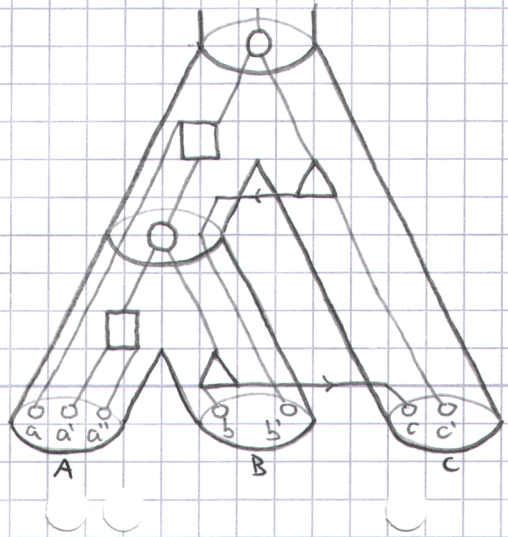

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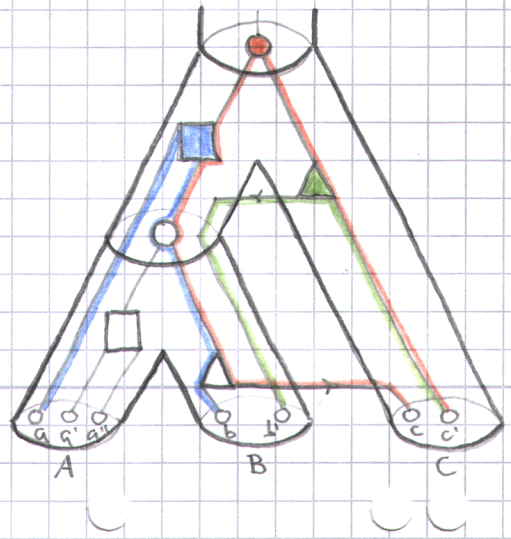

$\Theta_L \supseteq \Theta_F$

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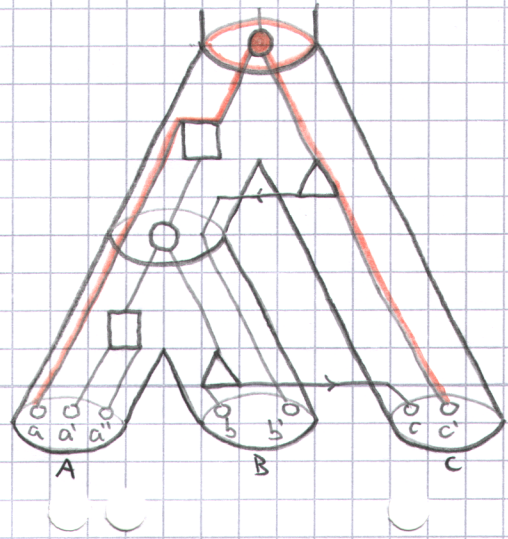

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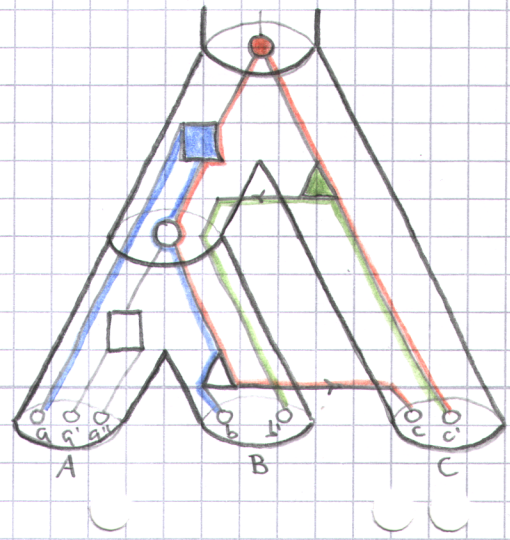
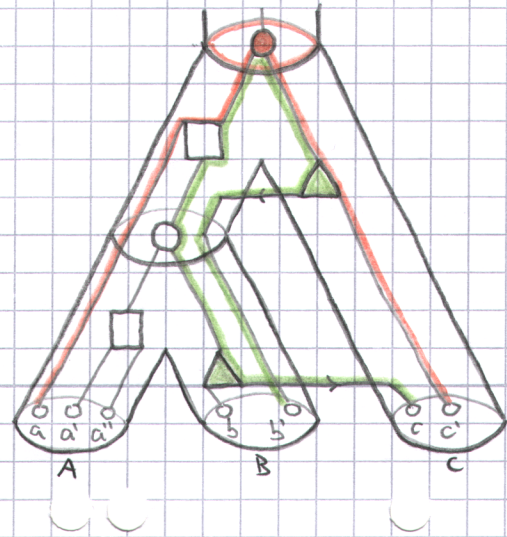
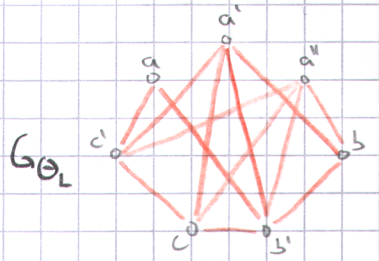
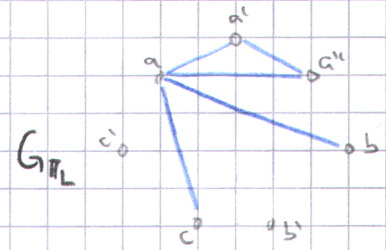


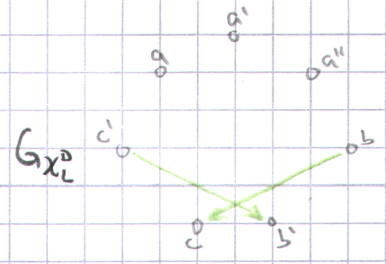


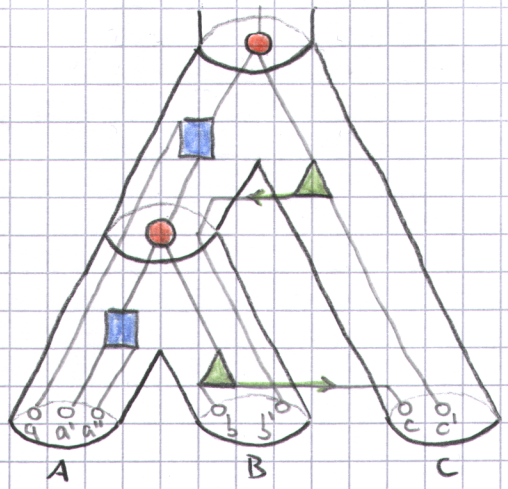
Graph Representation

LCA Relations









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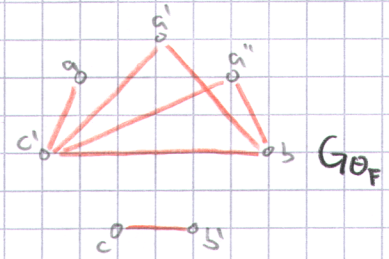

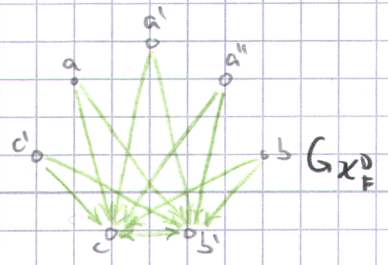

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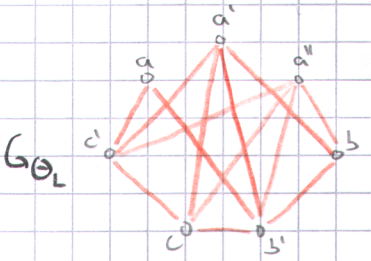
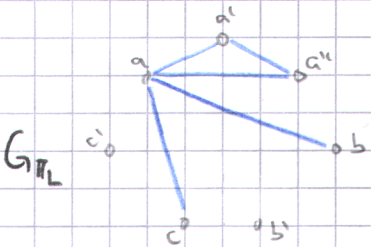
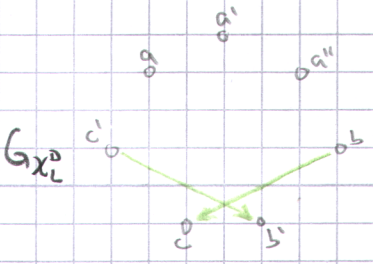
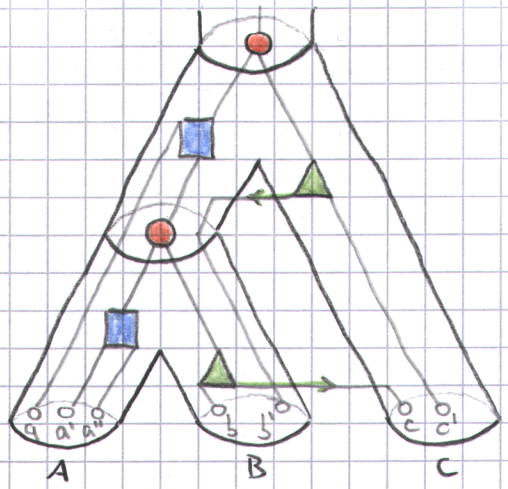






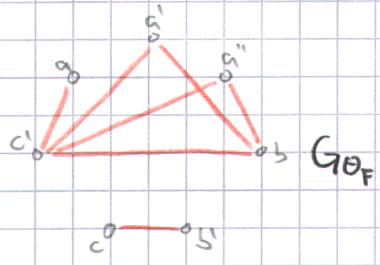


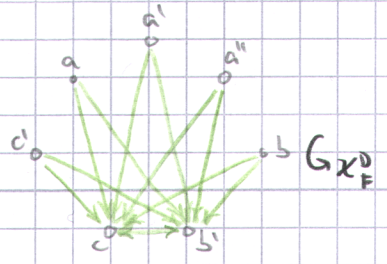
In case of no HGT events

$$G_{\Theta_L} \cong G_{\Theta_F}$$

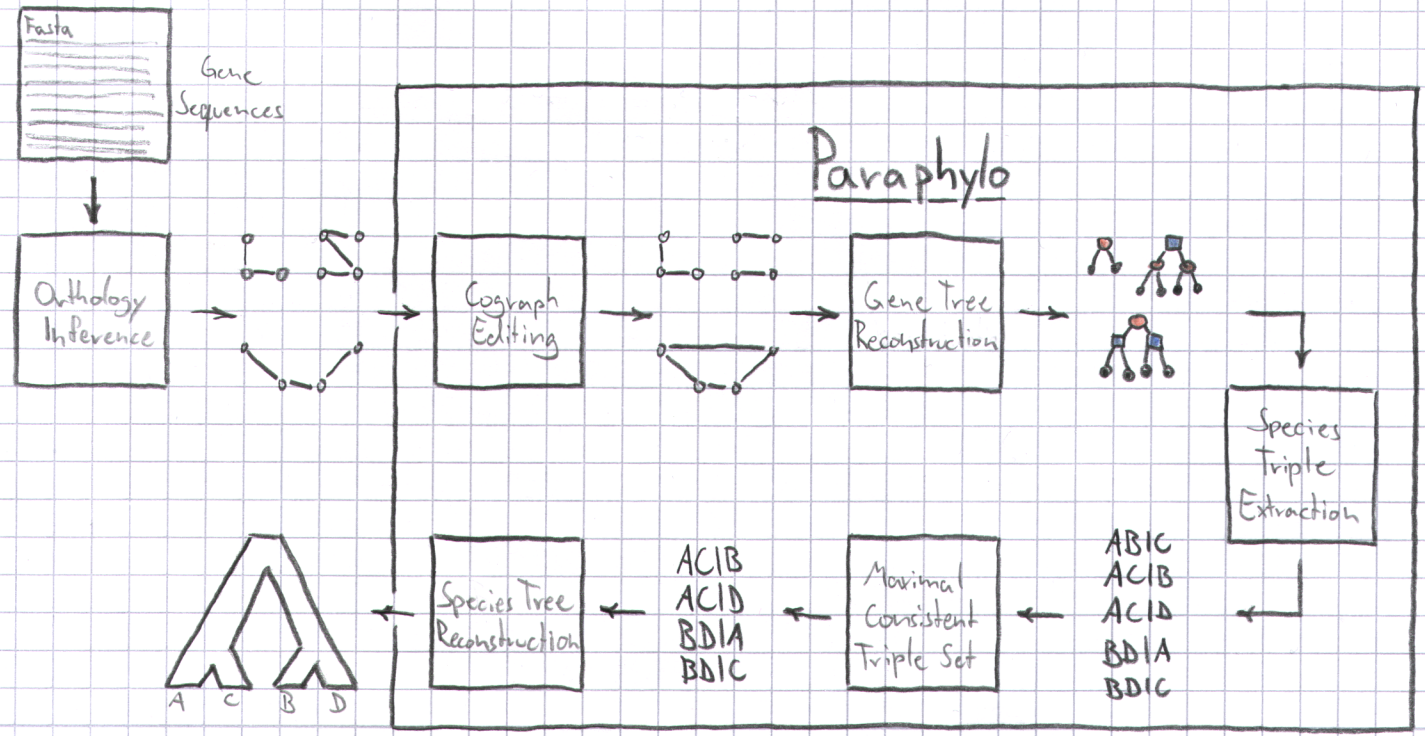
$$G_{\Pi_L} \cong \overline{G_{\Theta_F}}$$

Fitch Relations

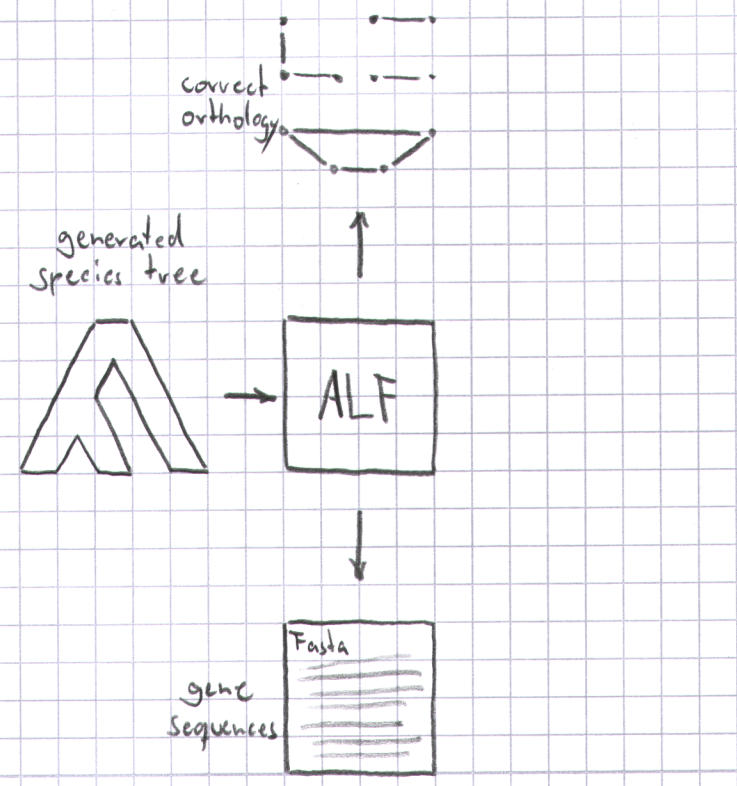




Pipeline for datasets without HGT



Simulations without HGT



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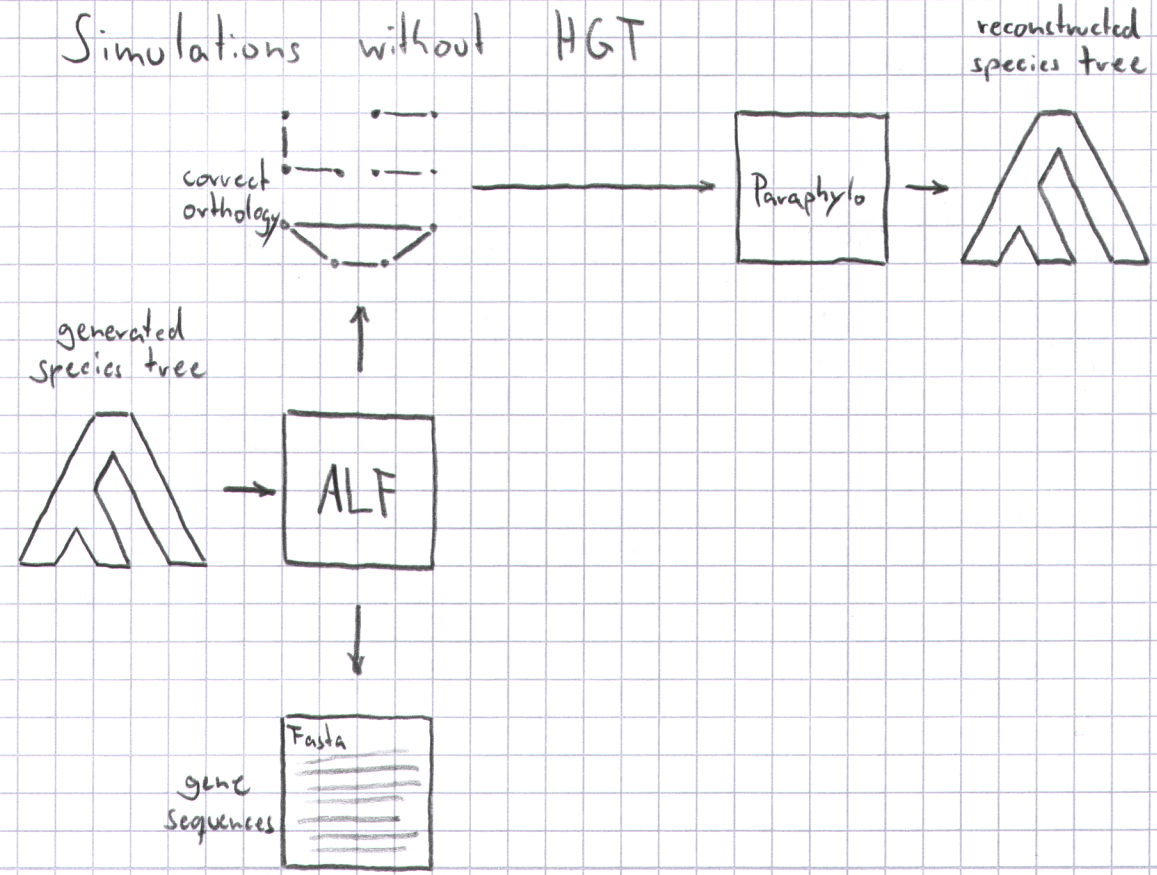

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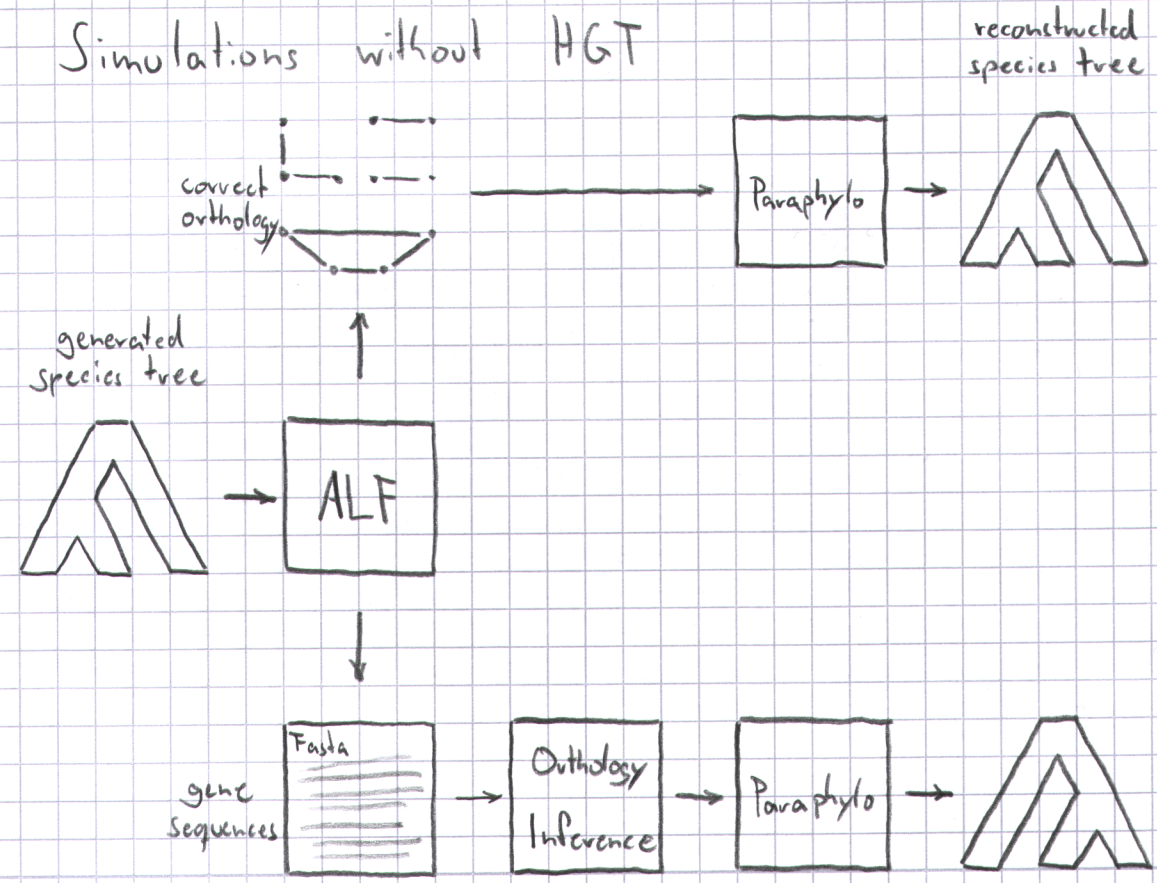

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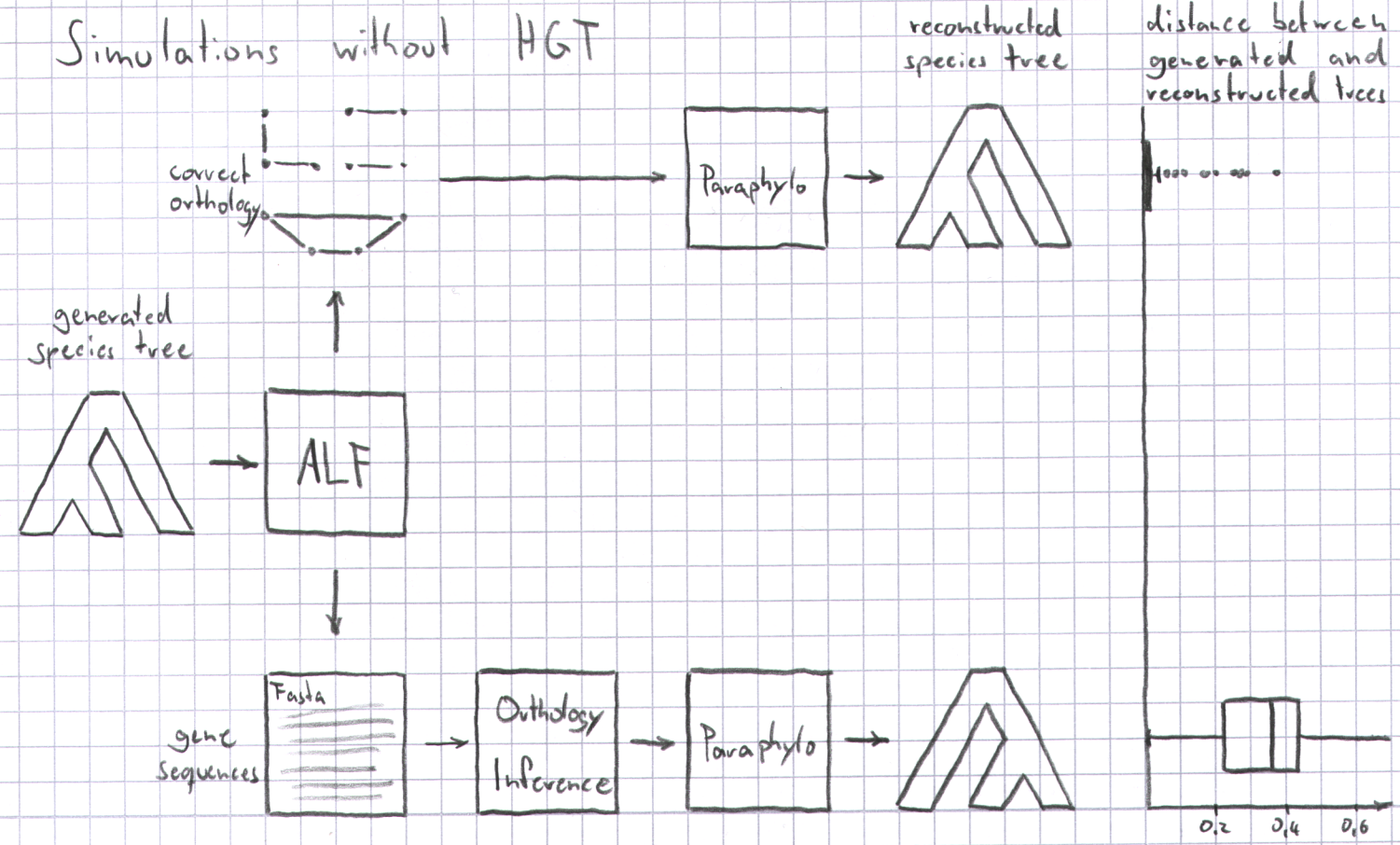

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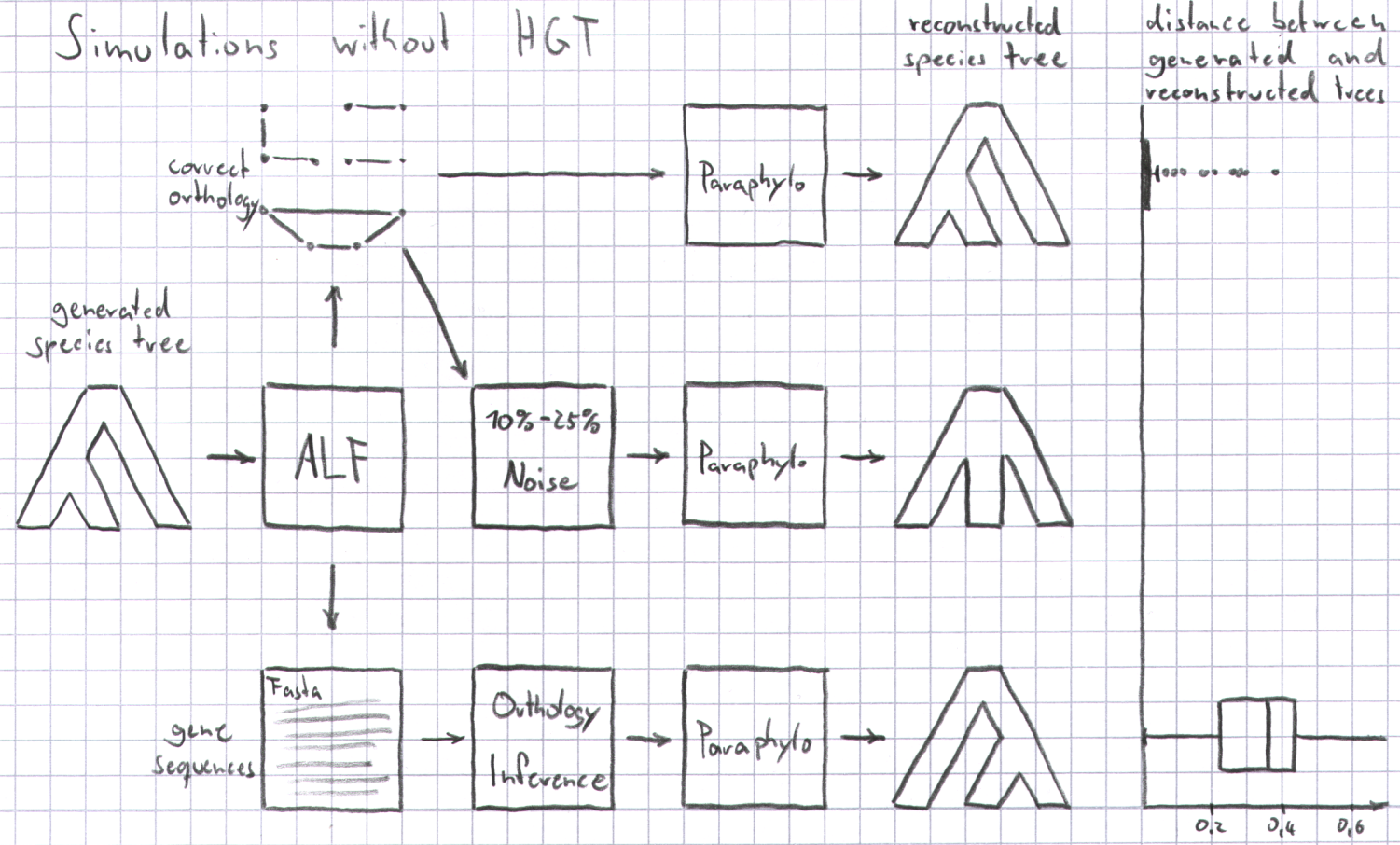

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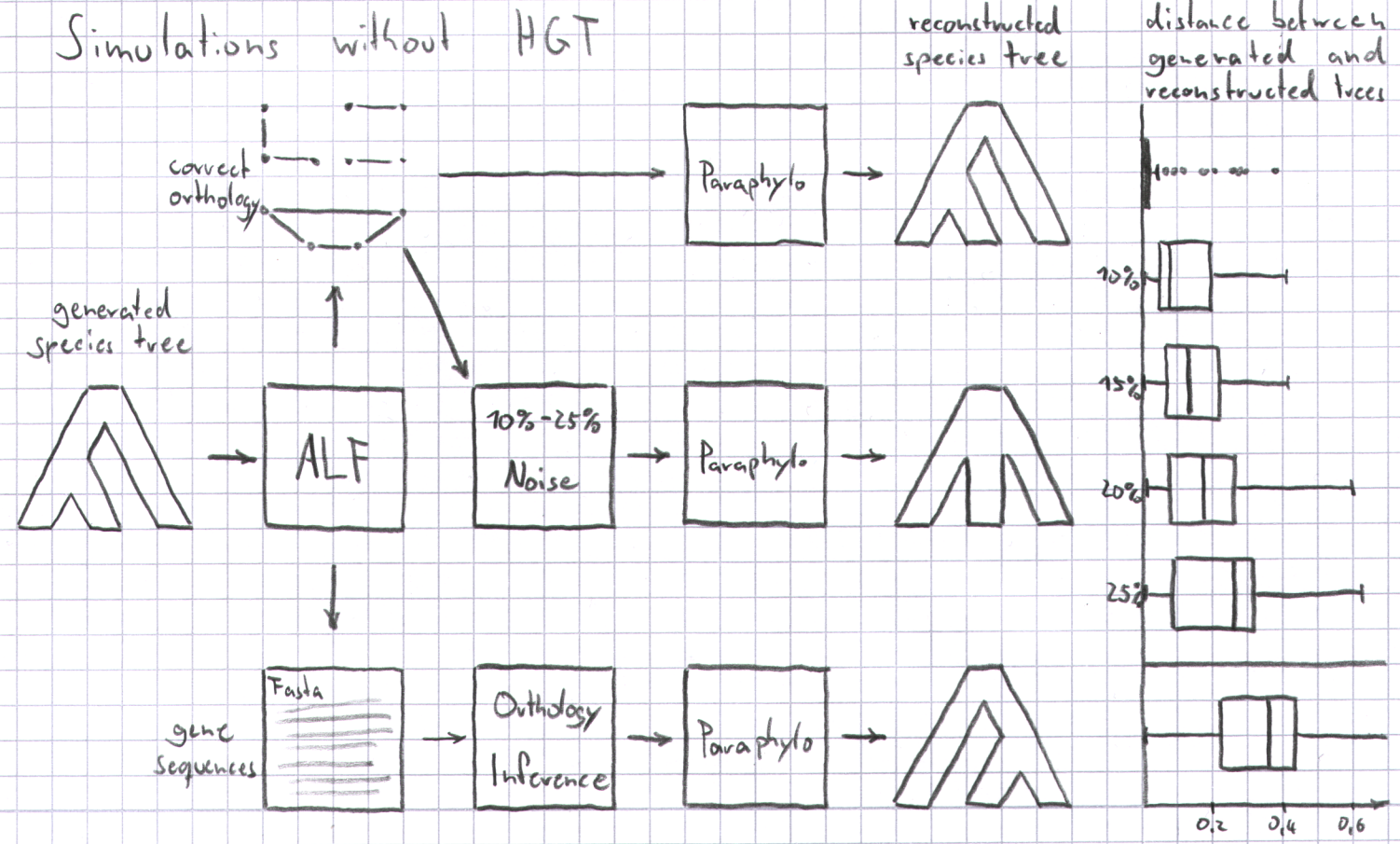

Orthology Inference - when does it go wrong

- ☐ no molecular clock-like data

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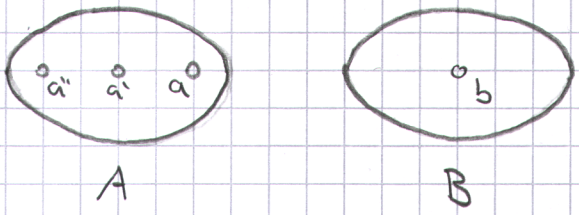
- ☐ no molecular clock-like data
- ☐ horizontal gene transfer
- ☐ gene losses

Orthology Inference - based on pairwise sequence comparisons

- compute evolutionary distance $d(a,b)$ between all genes a, b
- determine reciprocal best matches
  (a,b) is a RBM iff $\forall a' \in A, b' \in B$
  $d(a,b) \leq d(a',b)$ and $d(a,b) \leq d(a,b')$
- consider RBMs as orthologs



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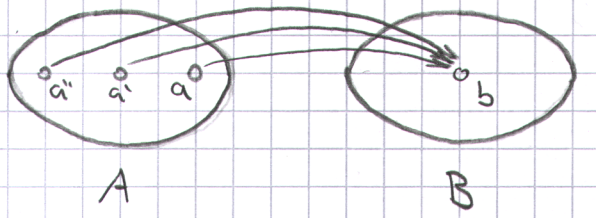

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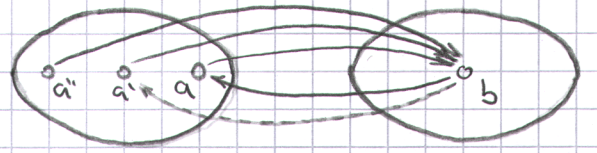

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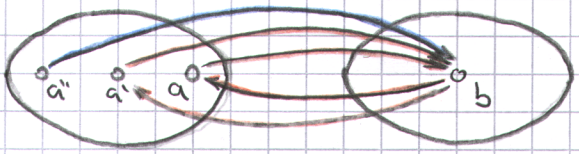

$d(a,b) \approx d(a',b) \ll d(a'',b)$

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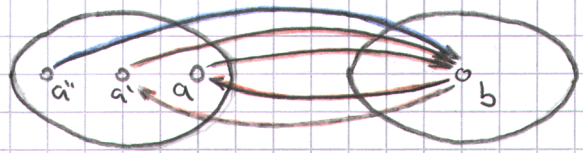

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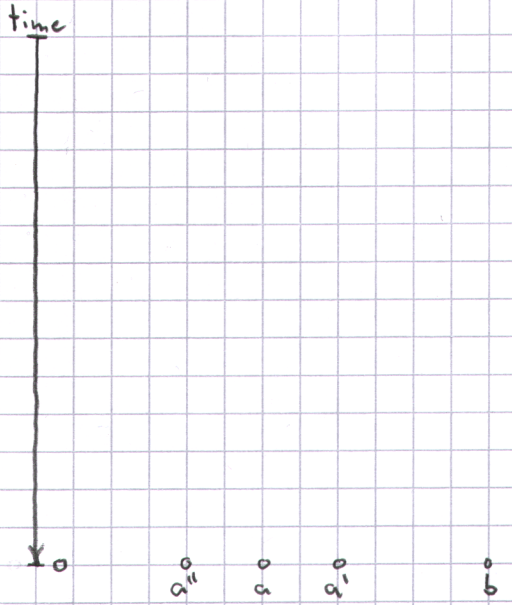

Orthology Inference – based on pairwise sequence comparisons

- ☐ compute evolutionary distance $d(a,b)$ between all genes a, b
- ☐ determine reciprocal best matches
  (a,b) is a RBM iff $\forall a' \in A, b' \in B$
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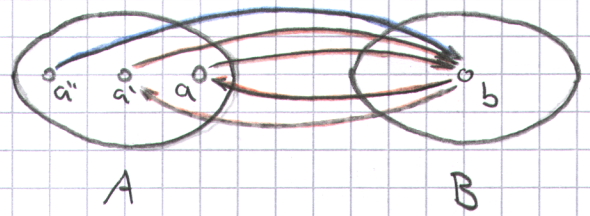
- ☐ consider RBMs as orthologs



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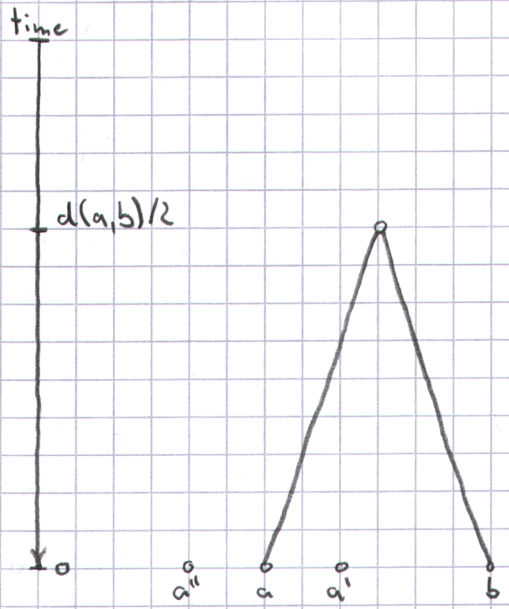

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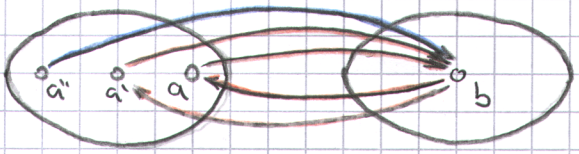

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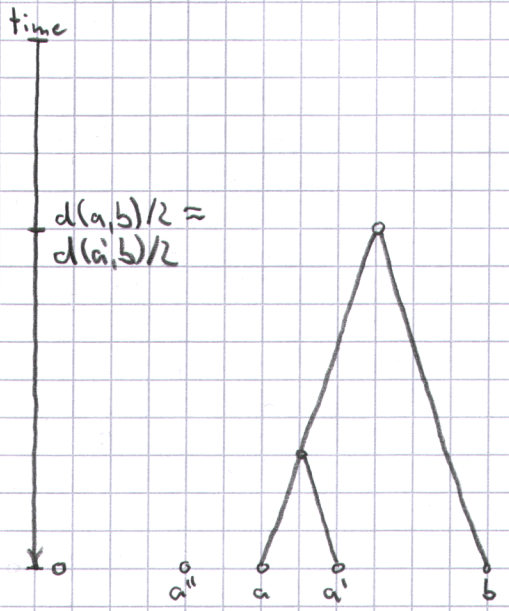

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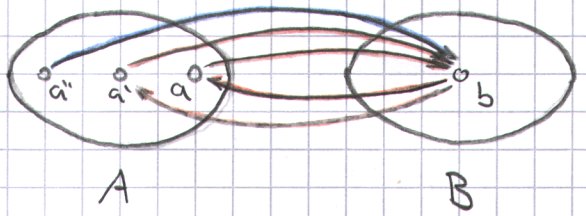

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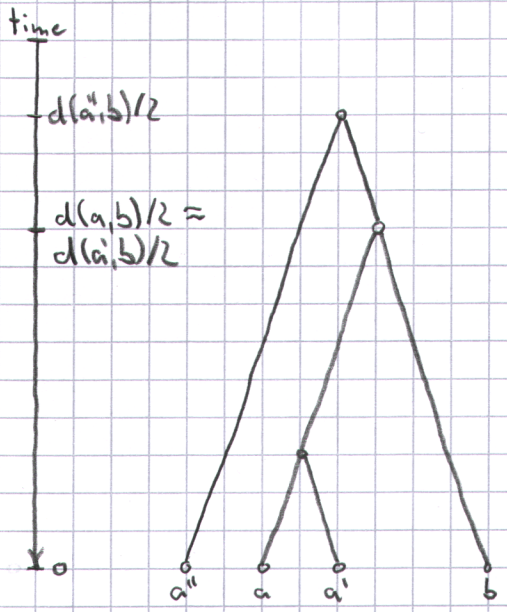

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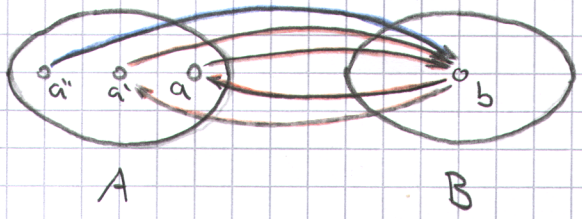

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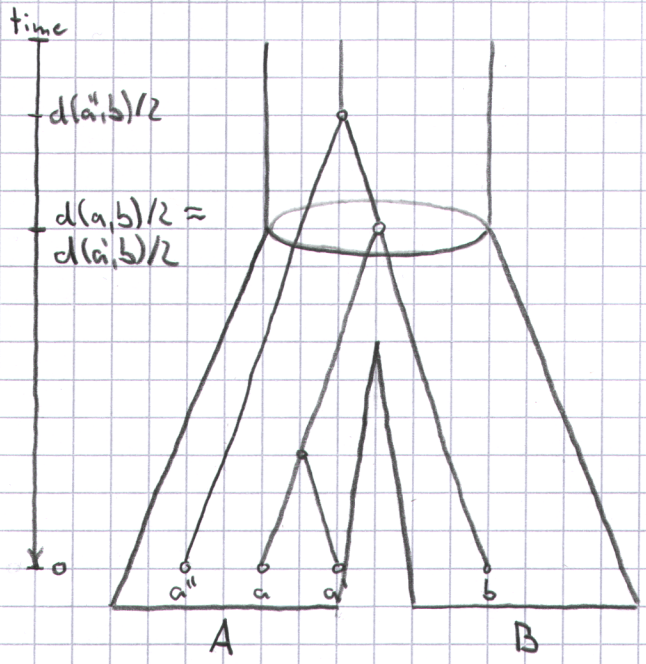

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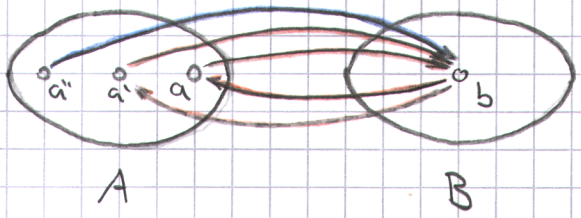

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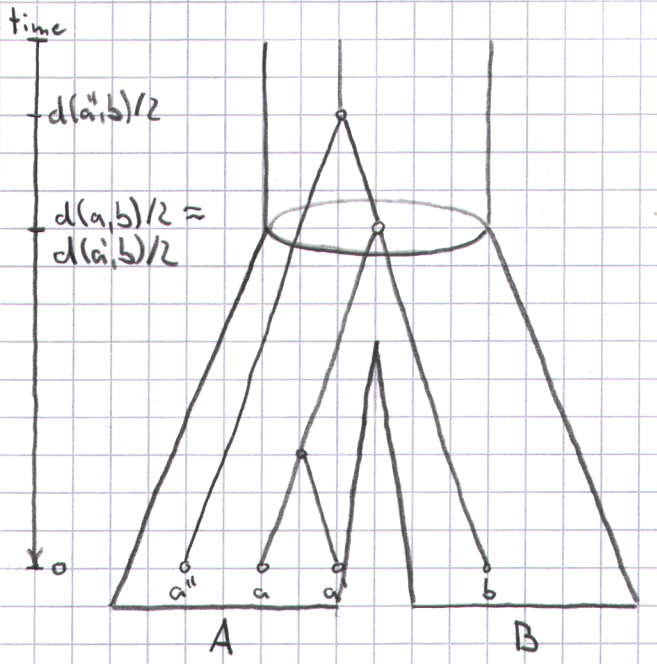


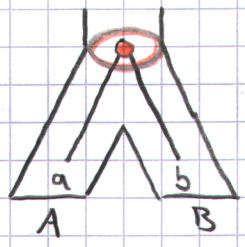
If (a,b) is a RBM then assume

$d(a,b) \triangleq d(A,B)$

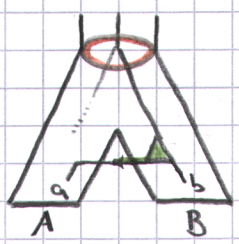
Orthology Inference - when does it go wrong

Let (a,b) be a RBM

- $d(a,b) \hat{=} d(A,B)$



- $d(a,b) \hat{<} d(A,B)$



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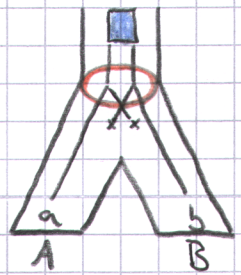

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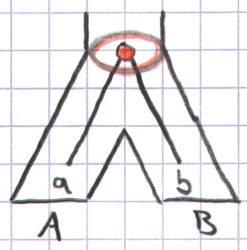

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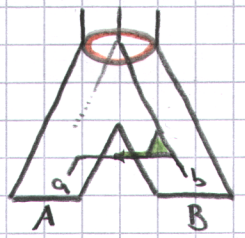

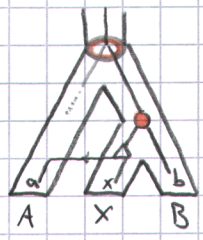

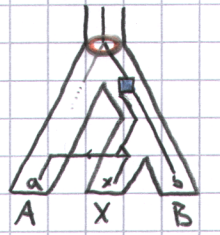

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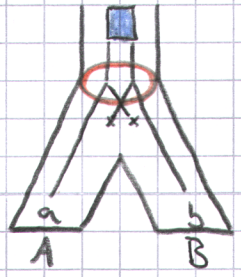
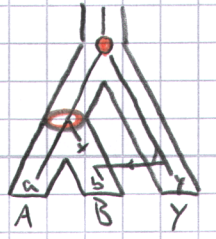
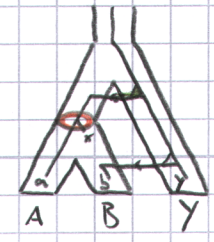
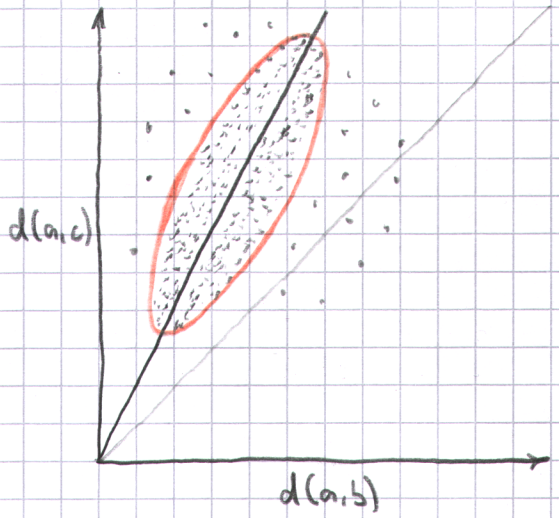


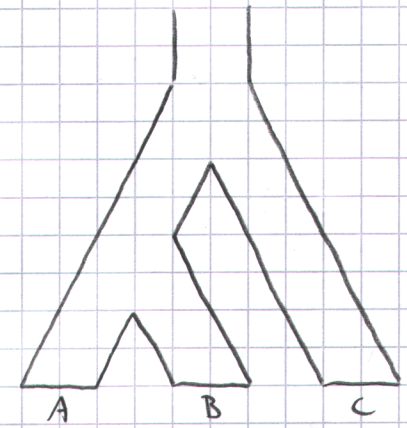




Improved Orthology Inference

- use RBM strategy to obtain an initial orthology estimation





- remove (a,b), (a,c) for all outliers $(d(a,b), d(a,c))$

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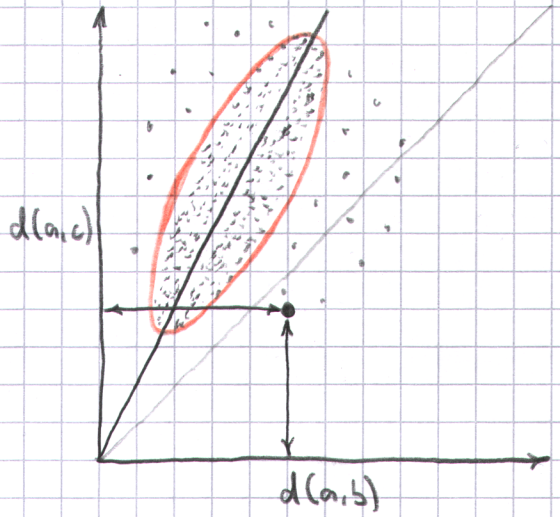

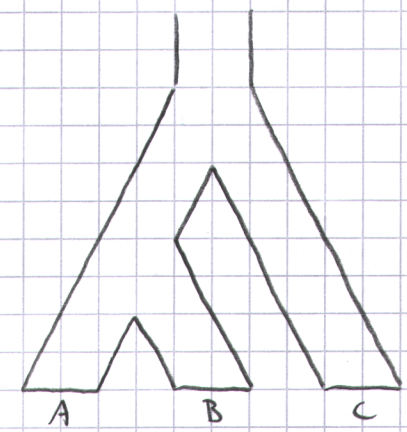

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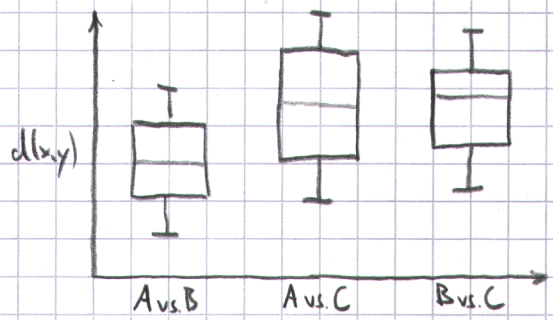
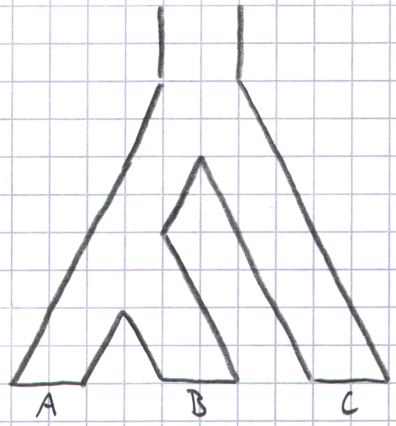
Improved Orthology Inference

- use filtered orthology estimates





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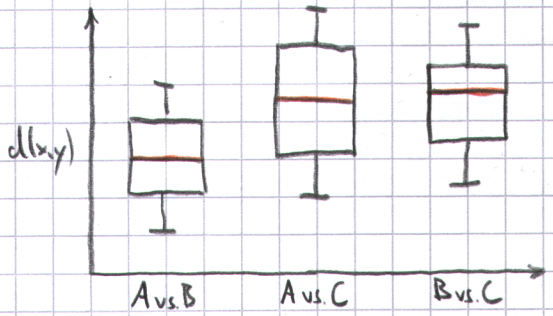
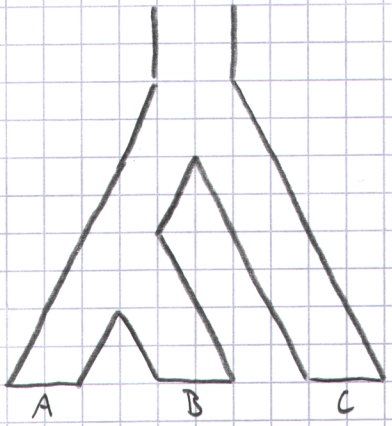


- define $d(X,Y) := \text{median}\left(d(x,y)\right)$



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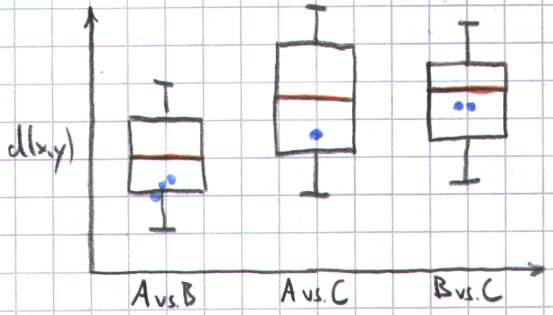

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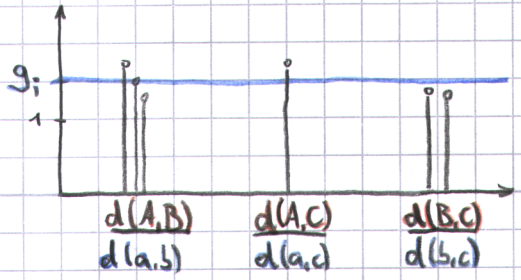
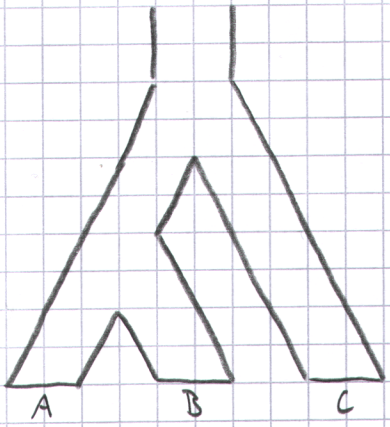


with a,b,c from gene family i



Improved Orthology Inference

- $d(a,b) \cong d(A,B)$ translates to $d(a,b) \cdot g_i \approx d(A,B)$
- $d(a,b) \hat{<} d(A,B)$ — " — $d(a,b) \cdot g_i \ll d(A,B)$
- $d(a,b) \hat{>} d(A,B)$ — " — $d(a,b) \cdot g_i \gg d(A,B)$

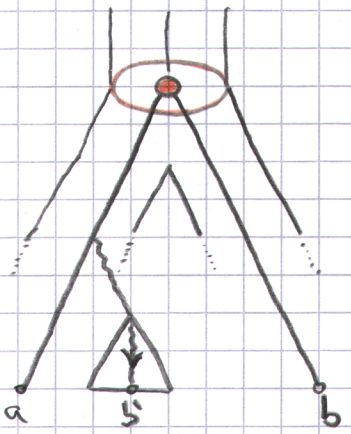
Infer Fitch Orthologs Θ_F

$$\Theta_F = \{(a,b) \mid d(a,b) \cdot g_i \approx d(A,B)\}$$

Fitch Xenology Inference

Idea: $(a,b') \in \chi^D_F$ if $\exists\, b$ s.t. $d(a,b') \cdot g_i \ll d(A,B) \approx d(a,b) \cdot g_i$

$$\chi^D_F = \{(x,b') \mid \exists\, a,b,\ a \in A, b,b' \in B,\ d(x,a) \lesssim d(x,b') \text{ and } d(a,b') \cdot g_i \ll d(A,B) \approx d(a,b) \cdot g_i\}$$



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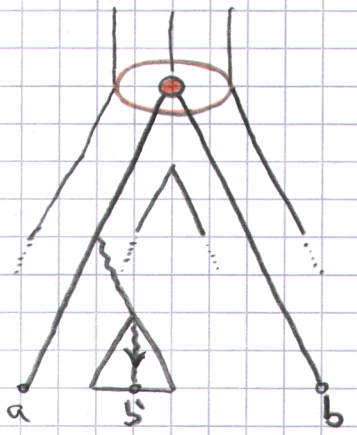
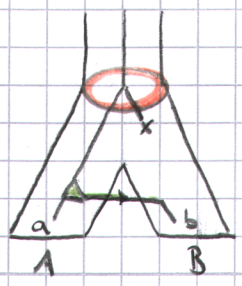
$\chi^{D}_{F} = \{(x,b') \mid \exists\, a,b,\ a \in A, b,b' \in B,\ d(x,a) \lesssim d(x,b')$ and $d(a,b') \cdot g_i \ll d(A,B) \approx d(a,b) \cdot g_i\}$

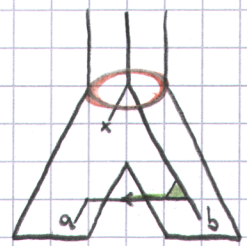


There is ambiguity!

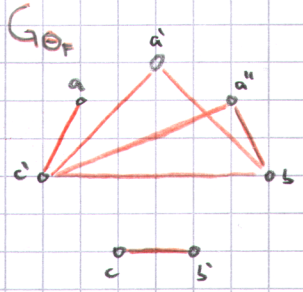
$(a,b) \in \chi^{D}_{F}$

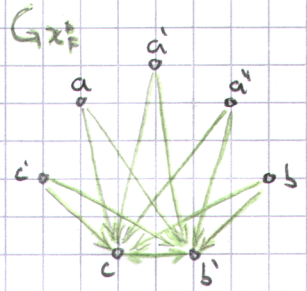


$(b,a) \in \chi^{D}_{F}$

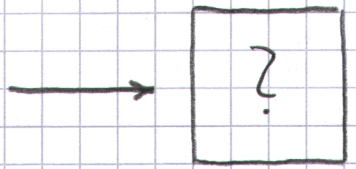


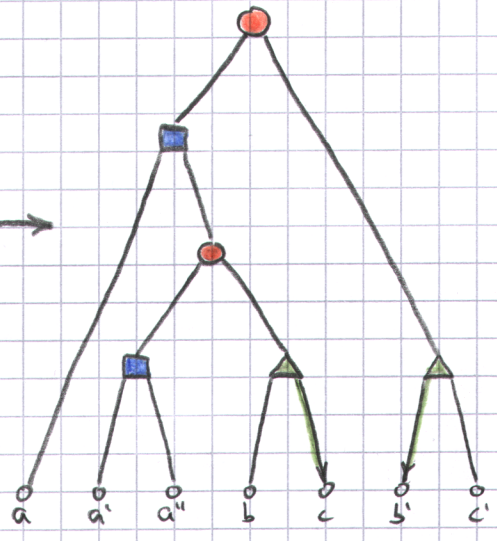
Reconstruction of event labeled gene trees





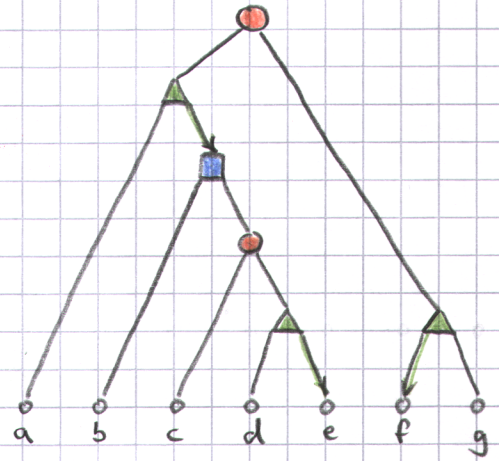
estimated Fitch Relations

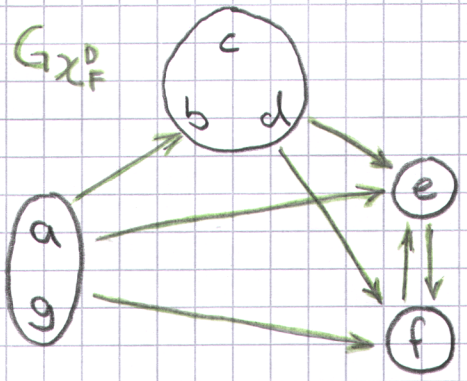




event labeled gene tree

Reconstruction of event labeled gene trees





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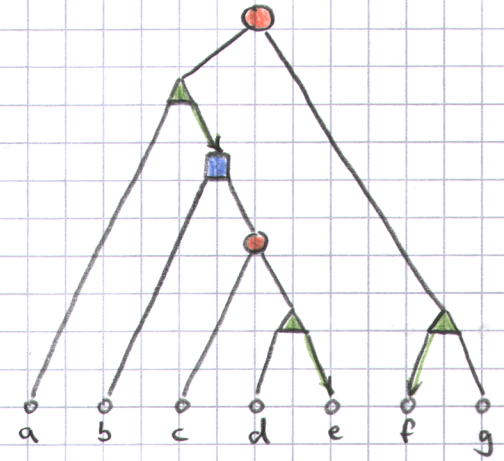

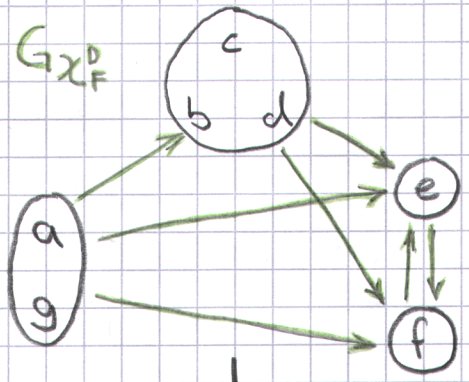

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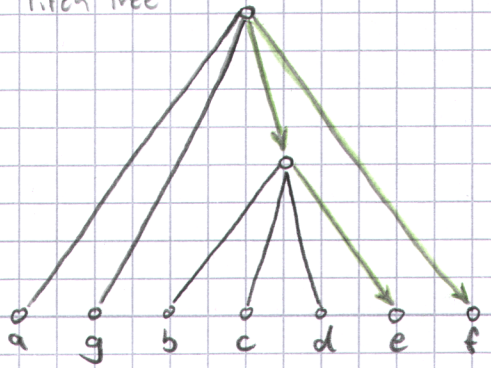

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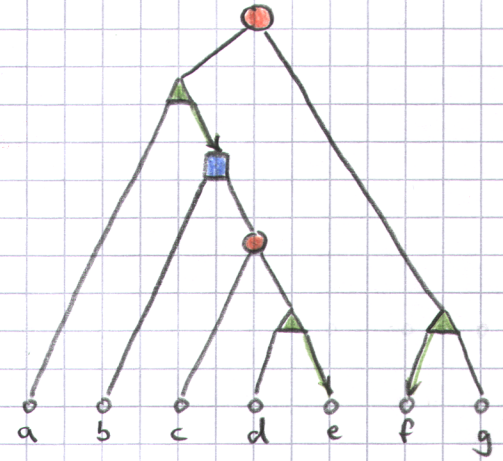
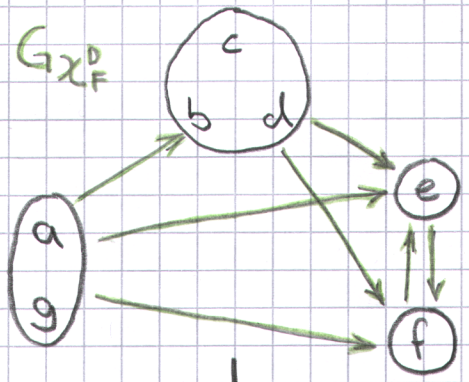
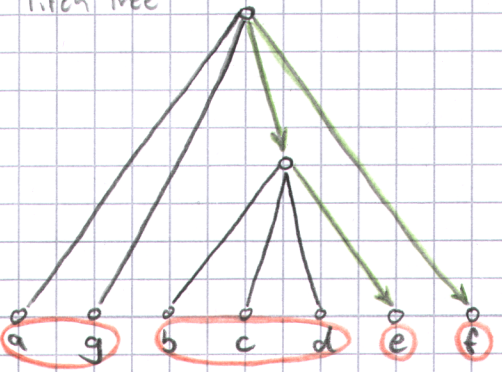
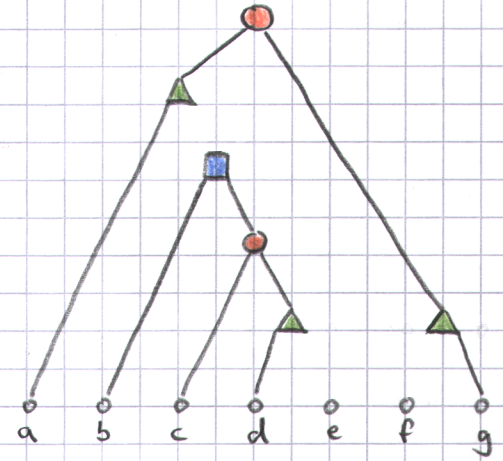
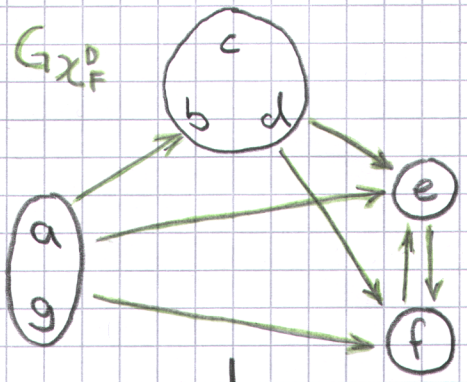


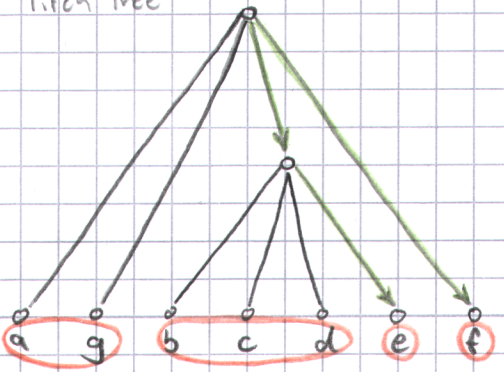




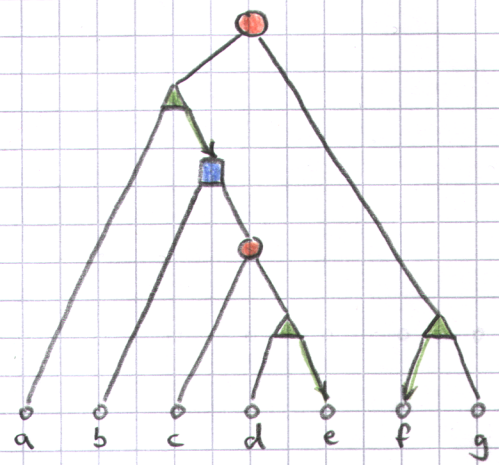
Reconstruction of event labeled gene trees



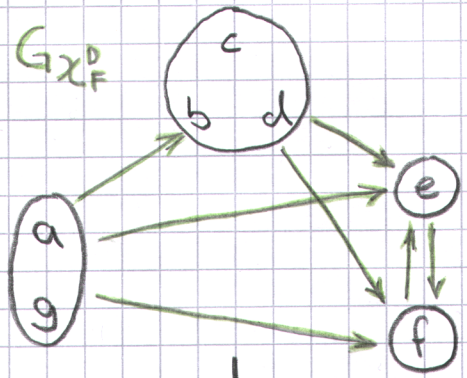




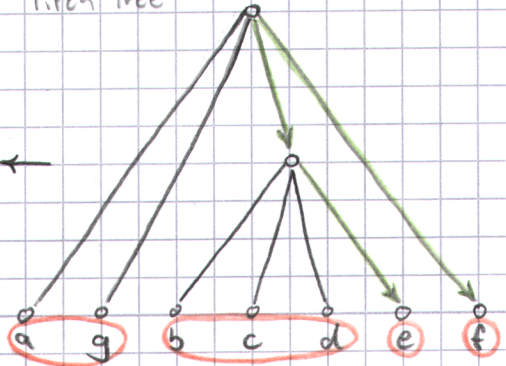
Reconstruction of event labeled gene trees

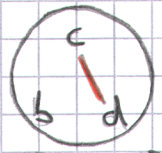


$G\chi_F^D$

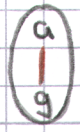


Fitch tree





$G_{O_F}[\{bucud\}]$

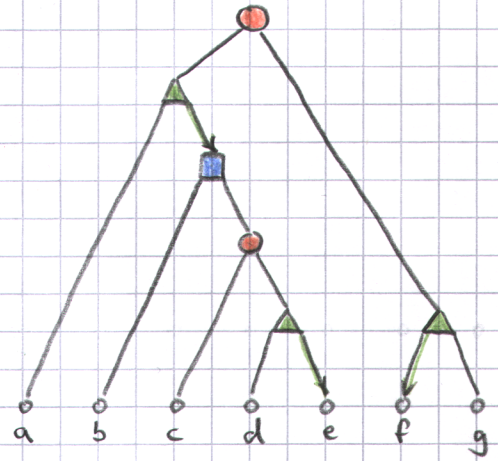


$G_{O_F}[\{aug\}]$

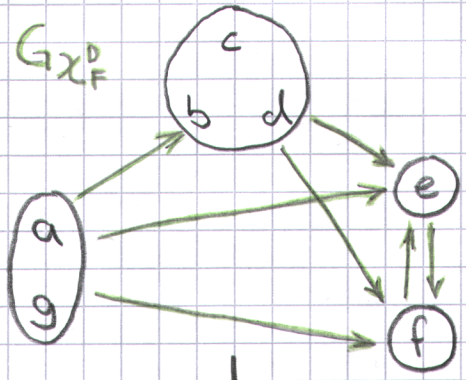
$G_{O_F}[\{e\}]$

$G_{O_F}[\{f\}]$

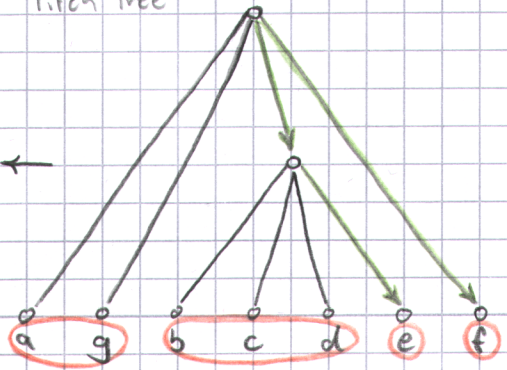
Reconstruction of event labeled gene trees

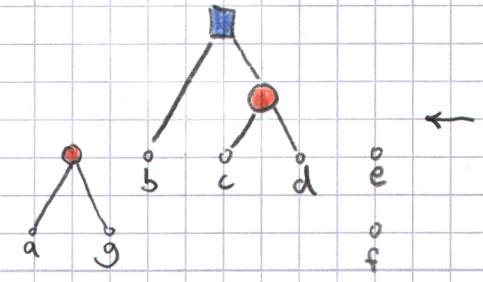


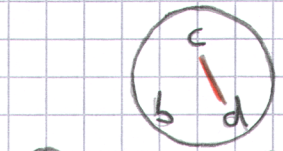
$G_{\chi_F^D}$



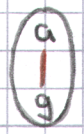
Fitch tree







$G_{\Theta_F}[\{bucud\}]$



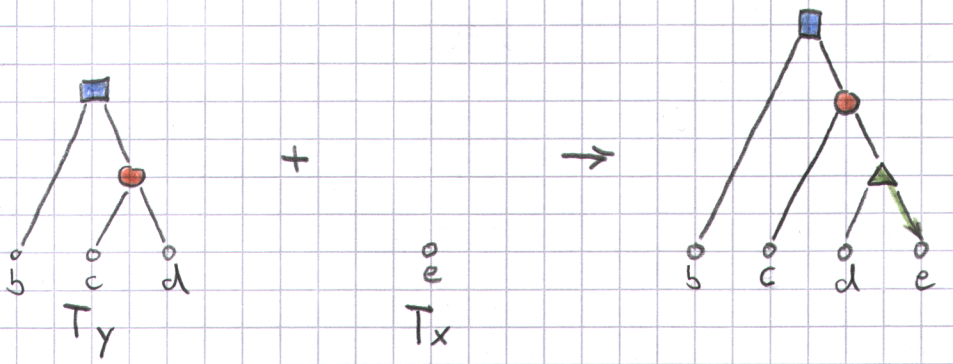
$G_{\Theta_F}[\{aug\}]$

$G_{\Theta_F}[\{e\}]$

$G_{\Theta_F}[\{f\}]$

Reconstruction of event labeled gene tree

How to append tree T_x to T_y



- find subtree $T_y(v)$ with $d(y,x) \ll d(y',x)$ for all $y \in L(T_y(v))$, $y' \in L(T_y) \setminus L(T_y(v))$ and $x \in L(T_x)$
- append T_x to T_y at edge (u,v) with HGT towards T_x

Summary

- improved orthology / xenology inference
- method for constructing event labeled gene trees from Fitch relations Θ_F, χ^D_F

Open Problems

- method relies on molecular clock-like data
- understand the connection between Θ_P, χ^D_F and species trees
- infer species trees
- construct time-consistent reconciliation map


Thank You...