More ideas about new orthology inference methods

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Why Orthology Analysis?

Orthology analysis is an important part of data analysis in many areas such as comparative genomics and molecular phylogenetics.

Idea: There is only one true tree of life – we just need good methods to detect it!
Tree-based vs. graph-based methods

Tree-based:
- species tree must be known, gene tree via sequence alignments
- → tree reconciliation gives orthology relation
- accuracy highly depends on quality of trees
- high computational costs

Graph-based:
- construction of the trees from sequence data
- lower computational costs
- many tools restricted to small number of species (except ProteinOrtho)\(^1\)
- some tools even include manual correction

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→ Our overall-goal: improve orthology inference/develop new methods

What are best matches?

True divergence times of genes/species often not known → many tools use Best Match Heuristics
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**Definition**

The sequence $y$ of species $Y$ is a **best match** of the sequence $x$ of species $X$ if $y$ is "closest" to $x$ among all genes in species $Y$. 

→ Goal: Deeper understanding of (reciprocal) Best Match Graphs to make the process more efficient

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The sequences $x$ and $y$ are reciprocal best matches if $y$ is closest to $x$ and $x$ is closest to $y$. 
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→ Goal: Deeper understanding of (reciprocal) Best Match Graphs to make the process more efficient
Best Match Graphs (BMGs)

here: “closest” = closest last common ancestor (lca)

**Definition**

The leaf $y$ is a **best match** of the leaf $x$ in a tree $T$ if $\sigma(x) \neq \sigma(y)$, and

(i) $\text{lca}(x, y) \preceq \text{lca}(x, y')$ for all leaves $y'$ from species $\sigma(y') = \sigma(y)$.

We write $x \rightarrow y$.

$\sigma = \text{colors} (=\text{species})$
Reciprocal Best Match Graphs (RBMGs)

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Which (un-)directed graphs are (Reciprocal) Best Match Graphs, i.e., have a tree representation?

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→ **Which (un-)directed graphs are (Reciprocal) Best Match Graphs, i.e., have a tree representation?**
Mathematical Results about (Reciprocal) Best Match Graphs

BMGs\(^1\)

- Two characterizations for 2-cBMGs via triples and neighborhoods → Recognition in polynomial time
- Characterization for \(n\)-cBMGs via Aho-Tree from 2-cBMGs → Recognition and tree reconstruction in polynomial time
- Unique least resolved tree

2. M. Geiß, Marc Hellmuth, P.F. Stadler, 2019, Reciprocal Best Match Graphs \(\text{manuscript in preparation}\)
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**RBMGs**

- Classification of three distinct groups of 3-cRBMGs → Recognition in polynomial time
- Characterization for $n$-cRBMGs via supertree from 3-cRBMGs → Recognition and tree reconstruction presumably *not* in polynomial time
- No unique least resolved tree

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**RBMGs**

- Classification of three distinct groups of 3-cRBMGs → Recognition in polynomial time
- Characterization for n-cRBMGs via supertree from 3-cRBMGs → Recognition and tree reconstruction presumably **not** in polynomial time
- No unique least resolved tree → Much information lost by only looking at RBMGs!

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How can we use all this?

Theorem 1

In pure DL scenarios (i.e. in the absence of HGT events) the reciprocal best match graph can only produce false positive but not false negative orthology assignments.

⇒ The true orthology relation has to be contained in the RBMG.

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In pure DL scenarios (i.e. in the absence of HGT events) the reciprocal best match graph can only produce false positive but not false negative orthology assignments.

⇒ The true orthology relation has to be contained in the RBMG.

→ Some false positive edges can be identified using best match graphs


Remove middle edge: $P_4$-Editing (P4E)
Simulation results with 0 HGT events

Number of Duplications

Number of Losses

5

10

15

20

25

10 20 30 40

0.0

0.1

0.2

0.3

0.4

0.5

FPR before vs. after P4E

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Simulation results with 0 HGT events

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<tr>
<th>Number of Duplications</th>
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- **FPR before vs. after P4E**
- **FNR before vs. after P4E**

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Simulation results with 1 HGT event

FPR before vs. after P4E

Number of Duplications

Number of Losses

0
2
4
6
5 10 15
0.0
0.2
0.4
0.6
0.8
1.0

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Simulation results with 1 HGT event

Number of Duplications vs. Number of Losses

FPR before vs. after P4E

FNR before vs. after P4E

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Simulation results with 4 HGT events

FPR before vs. after P4E

FNR before vs. after P4E
Results so far:

- Characterization and tree reconstruction algorithms for BMGs and RBMGs
- RBMG contains no false positive orthologs in the absence of HGT
- $P_4$-Editing in the absence of HGT
- RBMG contains false negative orthologs in the presence of HGT

→ RBMG loses much information that is still contained in the BMG!
Summary & Outlook

Results so far:

- Characterization and tree reconstruction algorithms for BMGs and RBMGs
- RBMG contains no false positive orthologs in the absence of HGT
- $P_4$-Editing in the absence of HGT
- RBMG contains false negative orthologs in the presence of HGT

→ RBMG loses much information that is still contained in the BMG!

Next steps:

- BMGs might help to detect HGT events
- Improved graph editing based on characterization of BMGs and RBMGs
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Dulce Valdivia

Thank you for your attention!

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Some basics: Rooted Trees and Triples

Rooted Tree $T$:

```
    a
   /|
  b c
 / | /
| d e|
```

acyclic, connected graph

Triples:

- $T$ displays a triple $ab|c$ if the path from $c$ to the root is not intersected by the path from $a$ to $b$.
- $\mathcal{R}(T) = \{ab|c, ab|d, ab|e\}$
- A set of triples $R$ is said to be consistent if there is a tree $T$ with $R \subseteq \mathcal{R}(T)$.
- Consistency-check via BUILD-algorithm in polynomial time. In case of consistency, it returns a tree $T$ (the "Aho Tree") with $R \subseteq \mathcal{R}(T)$.
How do $n$-cBMGs look like?

**Theorem**

A colored digraph $(G, \sigma)$ is a $n$-cBMG if and only if all induced subgraphs on two colors are 2-cBMG’s and the union of the triples obtained from their least resolved trees forms a consistent set.

least resolved $= $ ”lowest possible resolution”

→ The unique least resolved tree for $(G, \sigma)$ can be reconstructed in cubic time

→ All information that is needed, is contained in the 2-colored best match graphs!
The case of two colors: Characterization via triples

Some 2-colored subgraphs on 3 vertices give us constraints on the tree topology:

\[
\begin{align*}
X_1, X_2, X_3, \text{ and } X_4 \text{ all give the informative triple } ab|c.
\end{align*}
\]

**Theorem**

A connected 2-colored digraph \((G, \sigma)\) is a 2-cBMG if and only if \((G, \sigma) = G(\text{Aho}(\mathcal{R}(G, \sigma)), \sigma)\), where \(\mathcal{R}(G, \sigma)\) is the set of all informative triples of \((G, \sigma)\).
The case of two colors: Characterization via out-neighborhoods

Augenkrätze-Theorem

A connected 2-colored digraph \((G, \sigma)\) is a 2-cBMG if and only if \((G, \sigma)\) satisfies properties (N0), (N1), (N2), and (N3). Moreover, the tree \(T\) defined by the \(\mathcal{H}' := \{R'(\alpha) \mid \alpha \in N\}\) is the unique least resolved tree that explains \((G, \sigma)\).

\[
\begin{align*}
(N0) & \quad \beta \subseteq N(\alpha) \text{ or } \beta \cap N(\alpha) = \emptyset \\
(N1) & \quad \alpha \cap N(\beta) = \beta \cap N(\alpha) = \emptyset \text{ implies } N(\alpha) \cap N(N(\beta)) = N(\beta) \cap N(N(\alpha)) = \emptyset. \\
(N2) & \quad N(N(N(\alpha))) \subseteq N(\alpha) \\
(N3) & \quad \alpha \cap N(N(\beta)) = \beta \cap N(N(\alpha)) = \emptyset \text{ and } N(\alpha) \cap N(\beta) \neq \emptyset \text{ implies } N^-(\alpha) = N^-(\beta) \text{ and } N(\alpha) \subseteq N(\beta) \text{ or } N(\beta) \subseteq N(\alpha)
\end{align*}
\]

properties can be nicely checked by an algorithm.
The three classes of 3-cRBMGs

There are exactly three classes of 3-cRBMGs:

(A)  

(B)  

(C)  

Theorem

A graph \((G, \sigma)\) is a 3-cRBMG if and only if the construction algorithm returns a tree that explains \((G, \sigma)\).
The three classes of 3-cRBMGs

There are exactly three classes of 3-cRBMGs:

(A)

(B)

(C)

Theorem

A graph \((G, \sigma)\) is a 3-cRBMG if and only if the construction algorithm returns a tree that explains \((G, \sigma)\).
What can we say so far about $n$-cRBMGs?

Idea: Similarly to the case of BMGs, all information needed is contained in the 3-colored induced subgraphs of $(G, \sigma)$

Conjecture

An undirected colored graph $(G, \sigma)$ is an $n$-cRBMG if and only if for any $(G_{rst}, \sigma_{rst})$ there exists a tree $(T_{rst}, \sigma_{rst})$ that explains $(G_{rst}, \sigma_{rst})$, such that $\mathcal{P} := \bigcup_{r,s,t} T_{rst}$ is compatible.

$(G_{rst}, \sigma_{rst}) :=$ induced subgraph on colors $r, s, t$ of $(G, \sigma)$

→ It looks like there is no polynomial-time construction algorithm for $n$-cRBMGs