Characterization of colored Best Match Graphs

Manuela Geiß

Bioinformatics Group
University of Leipzig

TBI Winterseminar
Bled, 15th February 2018

Orthology Analysis

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

Two fundamentally different ways of orthology estimation:
1. Indirect approach: Infer orthology relation from a gene-tree/species-tree pair
2. Direct approach: Estimate orthology relation directly from data
$\rightarrow$ Best Match Heuristics

Best Match Heuristics

Assumption:
"The most closely related relative of a gene is the one that is most similar" (in terms of sequence distances)
$\rightarrow$ Molecular clock hypothesis (Zuckerkandl and Pauling)
$\rightarrow$ Often violated, still best match heuristics perform quite well on real data

Best Match Heuristics

Assumption:
"The most closely related relative of a gene is the one that is most similar" (in terms of sequence distances)
→ Molecular clock hypothesis (Zuckerkandl and Pauling)
→ Often violated, still best match heuristics perform quite well on real data

Software tools like `ProteinOrtho` give an approximate orthology graph
Workflow: Sequence data → `Proteinortho` → Cograph-editing → Orthology relation and representing tree

Assumption:
"The most closely related relative of a gene is the one that is most similar" (in terms of sequence distances)
→ Molecular clock hypothesis (Zuckerkandl and Pauling)
→ Often violated, still best match heuristics perform quite well on real data

Software tools like `ProteinOrtho` give an approximate orthology graph
Workflow: Sequence data → `Proteinortho` → Cograph-editing → Orthology relation and representing tree

Idea: Deeper understanding of Best Match Graphs to make the process more efficient

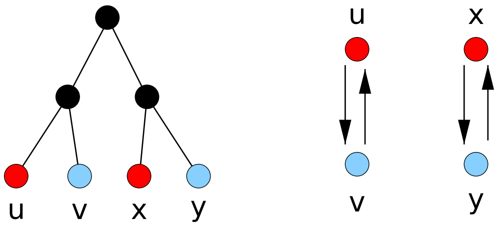
Evolutionary relatedness as phylogenetic property:

Definition

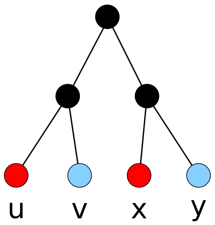
The leaf y is a best match of the leaf x in T if $\text{lca}(x,y) \preceq \text{lca}(x,y')$ for all leaves y' from species $\sigma(y') = \sigma(y)$. We write $x \rightarrow y$.

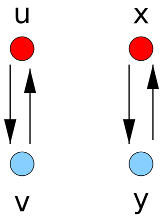
σ = colors (= species)

lca = last common ancestor



Best Match Graphs II

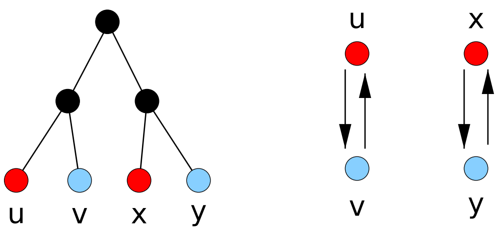




Definition

Given a tree T and a leaf-coloring σ, the colored best match graph $G(T, \sigma)$ has vertex set L and arcs $xy \in E(G)$ if $x \neq y$ and $x \rightarrow y$. Each vertex $x \in L$ obtains the color $\sigma(x)$.
The rooted tree T explains the vertex-colored graph (G, σ) if (G, σ) is the cBMG obtained from T.

σ = colors (= species)



Definition

Given a tree T and a leaf-coloring σ, the colored best match graph $G(T, \sigma)$ has vertex set L and arcs $xy \in E(G)$ if $x \neq y$ and $x \to y$.
Each vertex $x \in L$ obtains the color $\sigma(x)$.
The rooted tree T explains the vertex-colored graph (G, σ) if (G, σ) is the cBMG obtained from T.

σ = colors (= species)

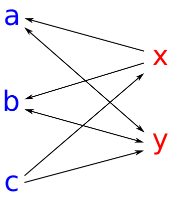
$\rightarrow$ Which directed graphs are Best Match Graphs?

Neighborhoods

In a colored di-graph, we define:

OUT-Neighborhood ("out-going edges"): $N(x) = \{z \mid xz \in E(G)\}$

IN-Neighborhood ("in-coming edges"): $N^{-}(x) = \{z \mid zx \in E(G)\}$



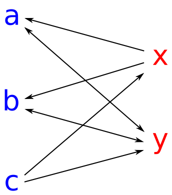
Example:

$$N(a) = N(b) = \{y\}$$
$$N^{-}(a) = N^{-}(b) = \{x, y\}$$
$$N(c) = \{x, y\}$$
$$N^{-}(c) = \emptyset$$

Thinness classes

Definition

Two vertices $x, y \in L$ are in relation $\overset{\bullet}{\sim}$ if $N(x) = N(y)$ and $N^{-}(x) = N^{-}(y)$.



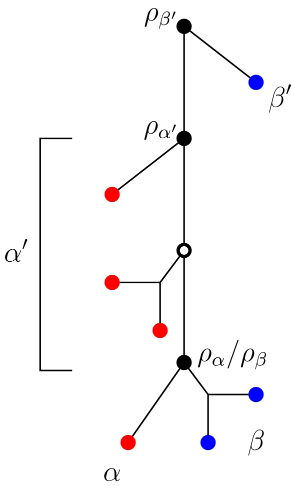
$\alpha = \{a, b\}, \beta = \{c\}, \gamma = \{x\}, \delta = \{y\}$

Observation: all vertices in a class are of the same color

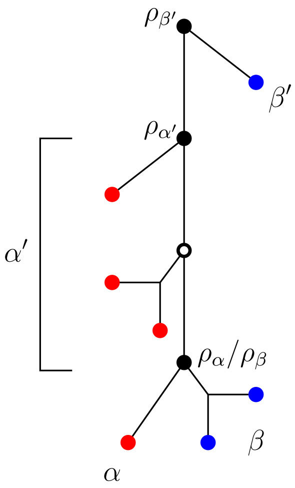
Monotonicity: $N(\alpha) \subseteq N(\beta) \Rightarrow N(N(\alpha)) \subseteq N(N(\beta))$

The case of two colors

Assumption: There is a tree that explains (G, σ).



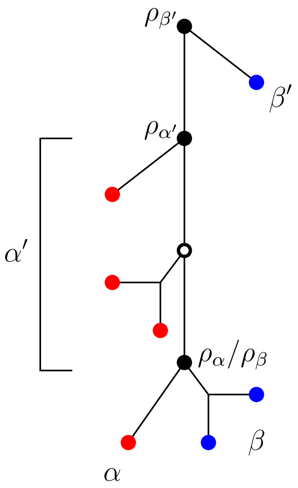
Assumption: There is a tree that explains (G, σ).



Some nice properties:

(N0) $\beta \subseteq N(\alpha)$ or $\beta \cap N(\alpha) = \emptyset$

Assumption: There is a tree that explains (G, σ).



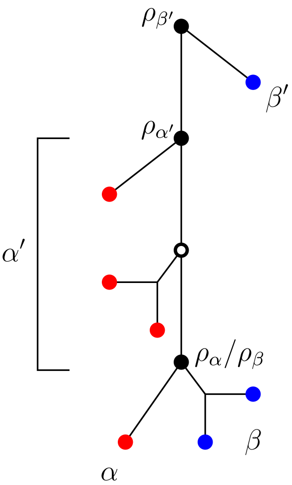
Some nice properties:

(N0) $\beta \subseteq N(\alpha)$ or $\beta \cap N(\alpha) = \emptyset$

(N2) $N(N(N(\alpha))) \subseteq N(\alpha)$

The case of two colors

Assumption: There is a tree that explains (G, σ).



Some nice properties:

(N0) $\beta \subseteq N(\alpha)$ or $\beta \cap N(\alpha) = \emptyset$

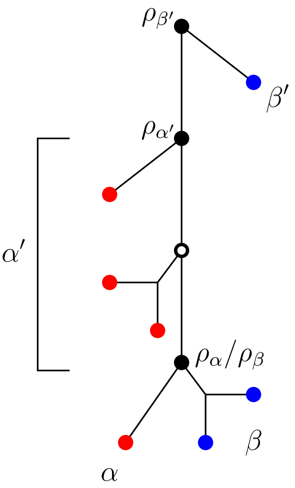
(N2) $N(N(N(\alpha))) \subseteq N(\alpha)$

Idea of hierarchy: for any class, one collects everything that is "below" this class and this gives the tree ($\rightarrow$ Hierarchy $\mathcal{H}$)

Intuition: The *reachable set* of α is

$$R(\alpha) = \alpha \cup N(\alpha) \cup N(N(\alpha))$$

Assumption: There is a tree that explains (G, σ).



Some nice properties:

(N0) $\beta \subseteq N(\alpha)$ or $\beta \cap N(\alpha) = \emptyset$

(N2) $N(N(N(\alpha))) \subseteq N(\alpha)$

Idea of hierarchy: for any class, one collects everything that is "below" this class and this gives the tree ($\rightarrow$ Hierarchy $\mathcal{H}$)

Intuition: The *reachable set* of α is

$$R(\alpha) = \alpha \cup N(\alpha) \cup N(N(\alpha))$$

$\rightarrow$ But when does such a tree exist for a 2-colored digraph?

The case of two colors: Characterization of a 2-cBMG

Augenkrätze-Theorem

Let (G, σ) be a 2-colored digraph. Then there exists a tree T explaining G if and only if G satisfies properties (N0), (N1), (N2), *and* (N3).

The case of two colors: Characterization of a 2-cBMG

Augenkrätze-Theorem

Let (G, σ) be a 2-colored digraph. Then there exists a tree T explaining G if and only if G satisfies properties (N0), (N1), (N2), *and* (N3).

(N0) $\beta \subseteq N(\alpha)$ or $\beta \cap N(\alpha) = \emptyset$

(N1) $\alpha \cap N(\beta) = \beta \cap N(\alpha) = \emptyset$ implies $N(\alpha) \cap N(N(\beta)) = N(\beta) \cap N(N(\alpha)) = \emptyset$.

(N2) $N(N(N(\alpha))) \subseteq N(\alpha)$

(N3) If $\alpha \neq \beta$ with $\alpha \cap N(N(\beta)) = \beta \cap N(N(\alpha)) = \emptyset$, then $N(\alpha) \cap N(\beta) \neq \emptyset$ if and only if $N(\alpha) \subseteq N(\beta)$ or $N(\beta) \subseteq N(\alpha)$, and $N^{-}(\alpha) = N^{-}(\beta)$.

Augenkrätze-Theorem

Let (G, σ) *be a 2-colored digraph. Then there exists a tree* T *explaining* G *if and only if* G *satisfies properties* (N0), (N1), (N2), *and* (N3).

(N0) $\beta \subseteq N(\alpha)$ or $\beta \cap N(\alpha) = \emptyset$

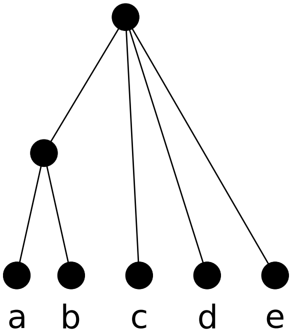
(N1) $\alpha \cap N(\beta) = \beta \cap N(\alpha) = \emptyset$ implies $N(\alpha) \cap N(N(\beta)) = N(\beta) \cap N(N(\alpha)) = \emptyset$.

(N2) $N(N(N(\alpha))) \subseteq N(\alpha)$

(N3) If $\alpha \neq \beta$ with $\alpha \cap N(N(\beta)) = \beta \cap N(N(\alpha)) = \emptyset$, then $N(\alpha) \cap N(\beta) \neq \emptyset$ if and only if $N(\alpha) \subseteq N(\beta)$ or $N(\beta) \subseteq N(\alpha)$, and $N^{-}(\alpha) = N^{-}(\beta)$.

$\rightarrow$ Before we extend these results to n colors, we need a little recap:

Rooted Tree T:



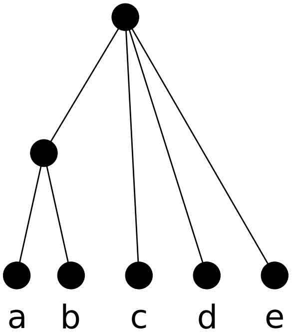
acyclic, connected graph

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.
- $\mathcal{R}(T) = \{ab|c, ab|d, ab|e\}$

Some basics: Rooted Trees and Triples

Rooted Tree T:



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 with $R \subseteq \mathcal{R}(T)$.

Generalization to n colors

All information that is needed, is contained in the 2-cBMG's:

Theorem

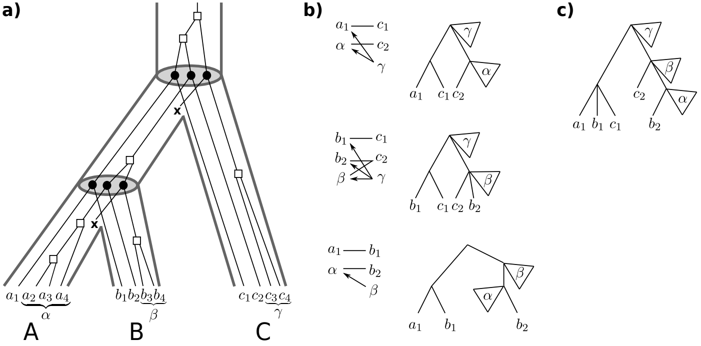
A colored digraph (G, σ) is a n-cBMG if and only if all induced subgraphs on two colors are 2-cBMG's and the union of the triples obtained from their least resolved trees forms a consistent set.

Generalization to n colors

All information that is needed, is contained in the 2-cBMG's:

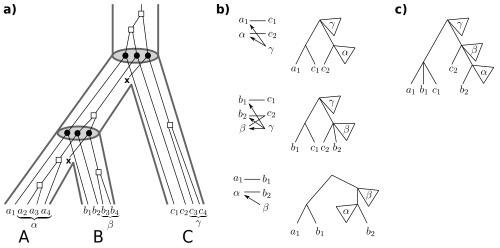
Theorem

A colored digraph (G, σ) 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.



a) Evolutionary scenario b) Induced subgraphs on two colors and least resolved trees. c) Least resolved tree for G

Algorithm for the tree-reconstruction of a *n*-cBMG



- For every induced subgraph on two colors: check (N0)-(N3) $\rightarrow$ if positive:
  - build the least-resolved tree using the hierarchy $\mathcal{H}$
  - collect all triples from this tree
- Use the set of all triples as input for `BUILD`: consistency check and tree construction

$\rightarrow$ The resulting tree is the least-resolved tree that explains the given graph

Summary & Outlook

What we did so far:

- Characterization of two-colored Best Match Graphs by properties (N0)-(N3) and extension to n colors
- Algorithm for the tree reconstruction of colored BMGs

Next steps:

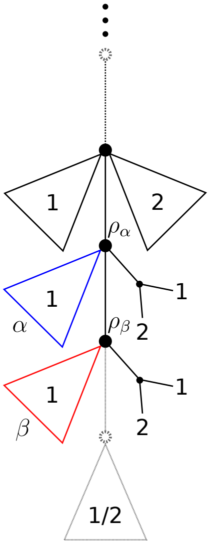
- What about *reciprocal* n-cBMG's?
- What can we say about Cographs?
- Optimization of data analysis in the context of `Proteinortho`

Special Thanks to:

Peter F. Stadler
Marc Hellmuth
Edgar Chávez
Marcos González
Maribel Hernández Rosales
Alitzel López
Dulce Valdivia

Thank you for your attention!

Appendix



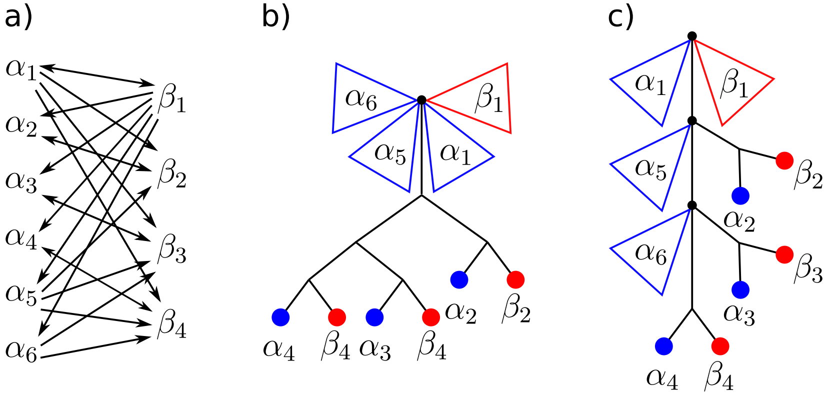
$$R(\alpha) = N(\alpha) \cup N(N(\alpha))$$

$$Q(\alpha) = \{\beta \mid N^-(\beta) = N^-(\alpha) \text{ and } N(\beta) \subseteq N(\alpha)\}$$

$$R'(\alpha) = R(\alpha) \cup Q(\alpha)$$

$$\mathcal{H} := \{R'(\alpha) \mid \alpha \in \mathcal{N}\}$$

Appendix


a)
α_1 α_2 α_3 α_4 α_5 α_6
β_1 β_2 β_3 β_4
b)
α_6 β_1 α_5 α_1
α_4 β_4 α_3 β_4 α_2 β_2
c)
α_1 β_1 α_5 β_2 α_2 α_6 β_3 α_3
α_4 β_4