FUZZY CLUSTERING IMPROVES PHYLOGENETIC RELATIONSHIPS RECONSTRUCTION FROM METABOLIC PATHWAYS

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Plan of the talk

- Motivation

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- Conclusion and future work

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The increasing amount of available information on metabolic pathways for several species motivates the use of similarities among such pathways to infer phylogenetic trees not based exclusively in sequence data.

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- KEGG (Kyoto Encyclopedia of Genes and Genomes): over 32 000 pathways, 382 species

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- Evolutionary relationships among several species believed to have a common ancestor
- Assumption: similar metabolic pathways can reflect similar evolutionary history
- Develop a measure of pathway similarity based on component chemical substances and enzymes
- Improve phylogenetic tree reconstruction methods using these similarities

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Structural similarity of metabolic pathways entails:

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- a hypergraph representation of a metabolic pathway
- a similarity measure between individual reactions, enzymes, and compounds

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  - Size of subtree rooted at least common ancestor of the enzymes in the hierarchy

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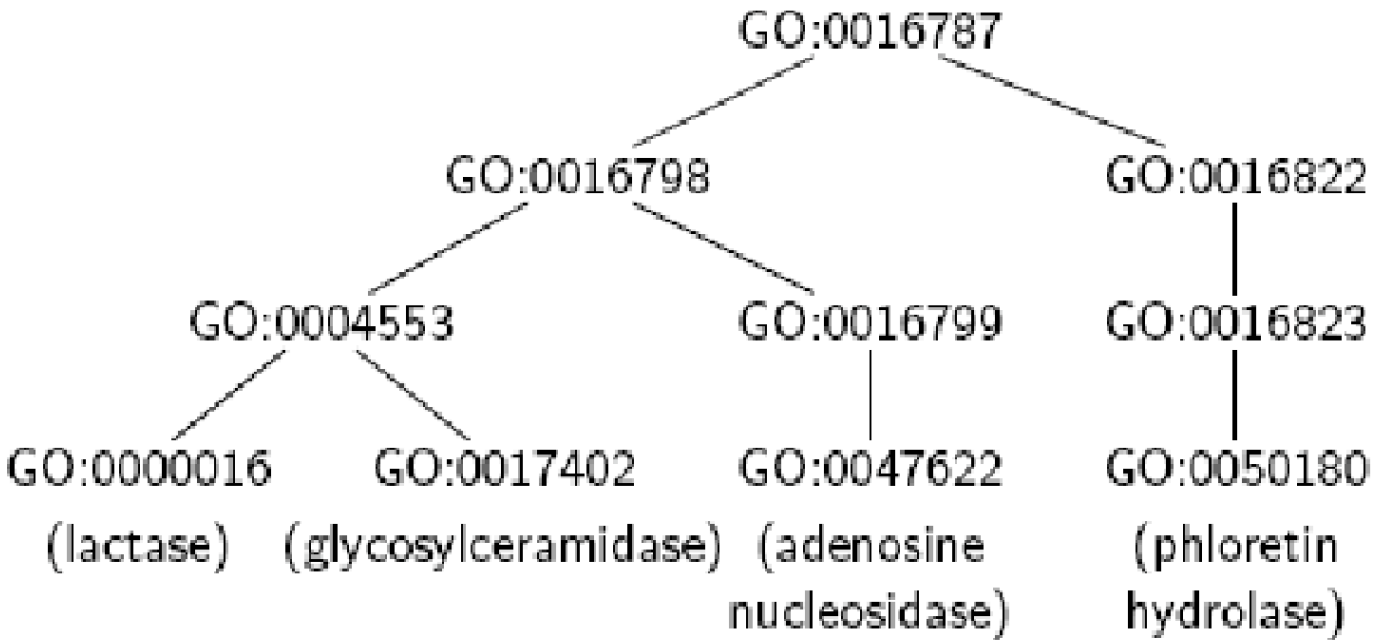
- Gene Ontology similarity, GO



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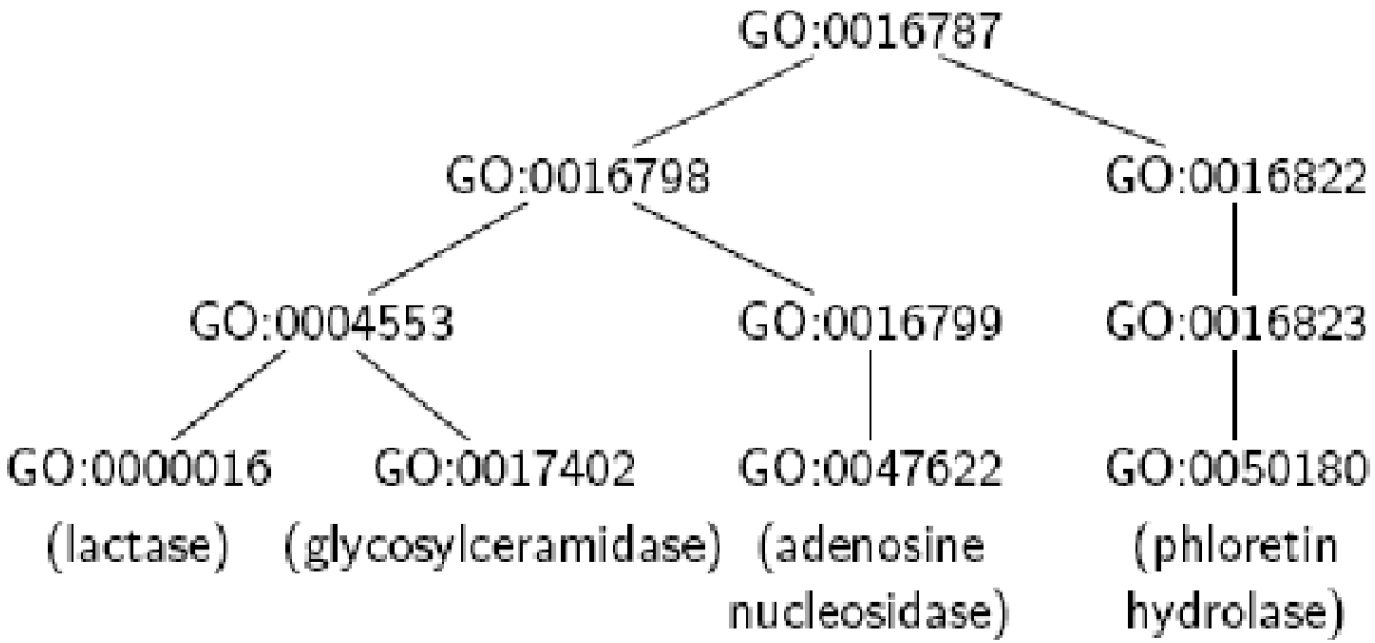

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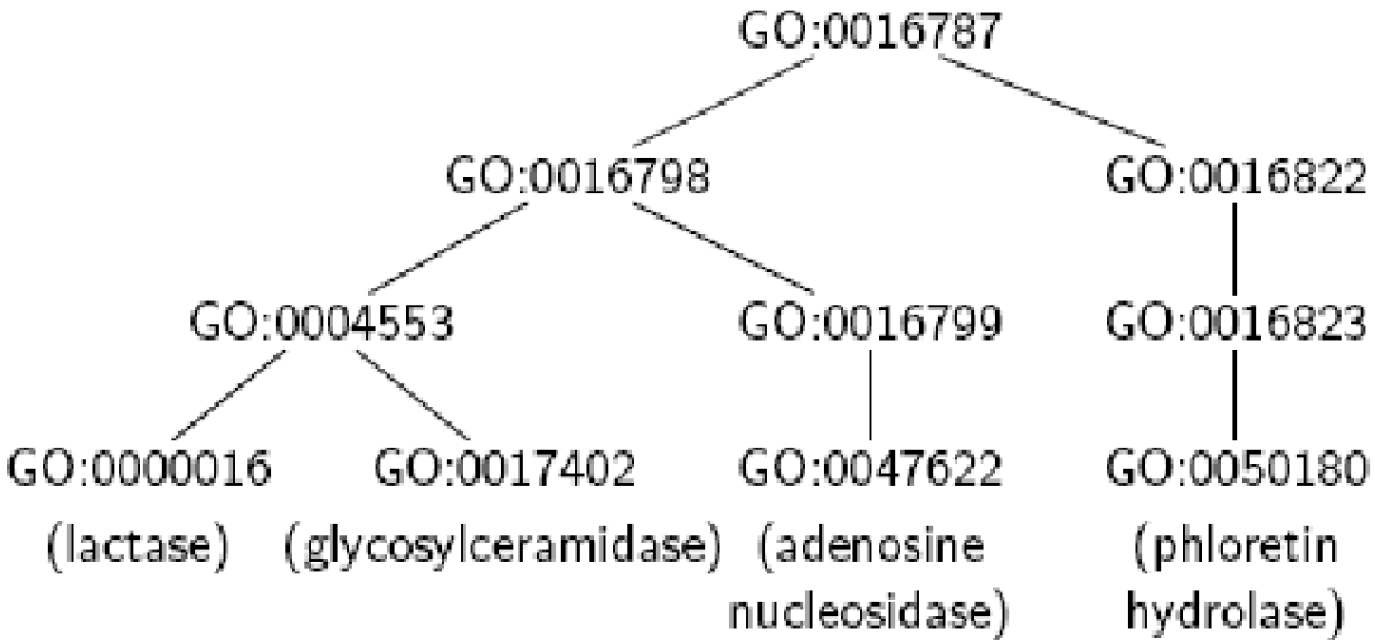
  - Shortest path distance in the GO molecular function ontology



Pathway Similarity

Similarity of pathways

- Let $P = (R)$, $Q = (S)$ be two pathways, with R, S the respective set of reactions:

$$sim(P,Q) = \frac{1}{|R \cup S|}\Big(\sum_{R \in \mathbf{R} \cap \mathbf{S}} \max_{S \in \mathbf{R} \cap \mathbf{S}} sim(R,S) + \sum_{R \in \mathbf{R} \setminus \mathbf{S}} \max_{S \in \mathbf{S}} sim(R,S) + \sum_{S \in \mathbf{S} \setminus \mathbf{R}} \max_{R \in \mathbf{R}} sim(R,S) \Big)$$

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Similarity of reactions

- Let $R = (C, E)$, $S = (D, F)$ be two reactions, with C, D the set of compounds and E, F the sets of enzymes involved

$$sim(R, S) = \frac{1 - \alpha}{|C \cup D|} cpdsim(R, S) + \frac{\alpha}{|E \cup F|} enzsim(R, S)$$

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- Reaction similarity is determined by calculating how similar the sets of compounds (*cpdsim*) and enzymes (*enzsim*) are
- The α parameter establishes relative weight of compounds and enzymes in the similarity of reactions

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Reconstruction and validation of phylogenetic relationships

- Create similarity matrix for n species from pathway similarity measure

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Clemente et al (2005) used standard Average Link Hierarchical (ALH) clustering (specifically, Perl `Bio::Tree::DistanceFactory` implementation of UPGMA)

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- Compute the fuzzy equivalence relation E generated by the similarity matrix
- For each t in E, take the partition induced by the t-cut equivalence relation, obtained by replacing in E every entry $< t$ by 0 and every entry $\geqslant t$ by 1
- These partitions, together with the hierarchy induced by the increasing order of t, yield a classification tree.

Phylogenetic Relationships

FER clustering: Example

Compute the similarity of the Glycolysis pathways of the organisms

AFU	*A.fulgidus*
MJA	*M.jannaschii*
MGE	*M.genitalum*
HIN	*H.influenzae*
MTU	*M.tuberculosis*
ECO	*E.coli*

using GO similarity and $\alpha = 0.8$.

The similarity matrix:

	MGE	HIN	MTU	MJA	ECO	AFU
MGE	1.00	0.33	0.07	0.02	0.17	0.22
HIN	0.33	1.00	0.33	0.32	0.34	0.27
MTU	0.07	0.33	1.00	0.09	0.20	0.20
MJA	0.02	0.32	0.09	1.00	0.18	0.24
ECO	0.17	0.34	0.20	0.18	1.00	0.32
AFU	0.22	0.27	0.20	0.24	0.32	1.00

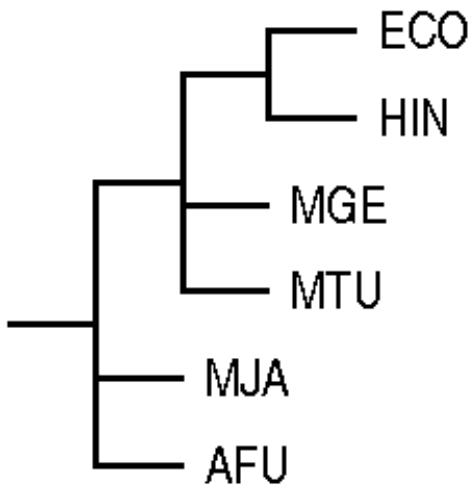
The fuzzy equivalence relation it generates (through max-min transitive closure) is:

	MGE	HIN	MTU	MJA	ECO	AFU
MGE	1.00	0.33	0.33	0.32	0.33	0.32
HIN	0.33	1.00	0.33	0.32	0.34	0.32
MTU	0.33	0.33	1.00	0.32	0.33	0.32
MJA	0.32	0.32	0.32	1.00	0.32	0.32
ECO	0.33	0.34	0.33	0.32	1.00	0.32
AFU	0.32	0.32	0.32	0.32	0.32	1.00

The hierarchy of partitions defined by the t-cuts is:

t	Partition corresponding to the t-cut
1.00	$\{MGE\}\{HIN\}\{MTU\}\{MJA\}\{ECO\}\{AFU\}$
0.34	$\{HIN, ECO\}\{MGE\}\{MTU\}\{MJA\}\{AFU\}$
0.33	$\{MGE, HIN, MTU, ECO\}\{MJA\}\{AFU\}$
0.32	$\{MGE, HIN, MTU, MJA, ECO, AFU\}$

This hierarchical clustering yields the classification tree



very close to the NCBI taxonomy.

Results

To compare the performance of FER clustering and ALH clustering:

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- We have computed the similarities of the Glycolysis pathways of a model set of 16 organisms, downloaded from the KEGG server
- We have computed the phylogenetic trees generated by these similarities by using both the ALH and the FER clustering
- We have compared the resulting trees to the NCBI taxonomy of the 16 organisms.

Results: cousins

The cousins tool measures the similarity of phylogenetic trees at the ground level (roughly, it compares sets of triples consisting of pairs of leaves and their distance, up to a certain distance:

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Probably because INFO is more "fine grained"

Results: F-measure

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FER always outperforms ALH:

F-measure for all ALH-trees is 0.88

F-measure for all FER-trees is 0.92

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  - Outperform previous best measure
- Fuzzy clustering
  - A test on 16 organisms shows FER outperforms ALH
  - Similar results for a larger (73) set of organisms (unpublished)
  - But we are still far from obtaining a fully correct taxonomy

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  - Larger sets of organisms

The organisms

Organisms studied, classified by domain (A: Archaea, B: Bacteria, E: Eukaryota), together with their identifier in the NCBI taxonomy

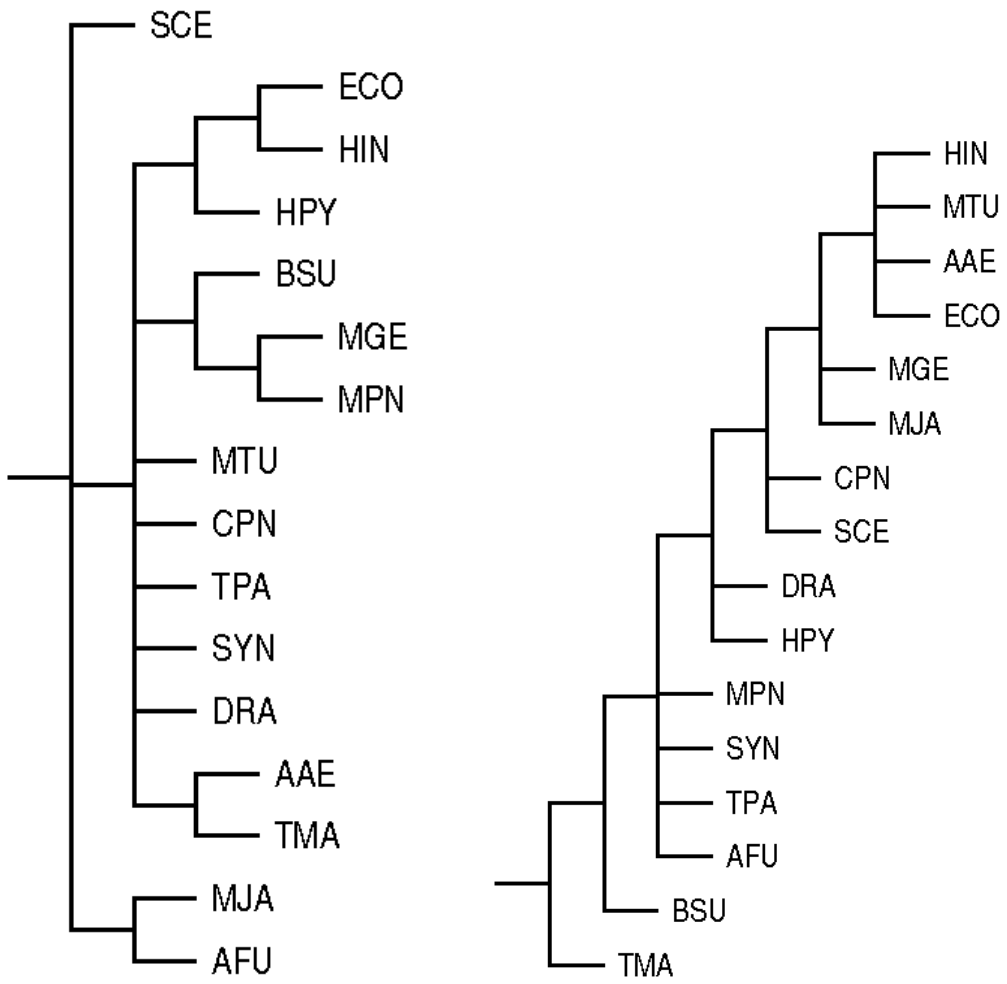
AFU	*A.fulgidus*	A	224325
MJA	*M.jannaschii*	A	243232
CPN	*C.pneumoniae*	B	115713
MGE	*M.genitalum*	B	243273
MPN	*M.pneumoniae*	B	272634
HIN	*H.influenzae*	B	71421
SYN	*Synechocystis*	B	1148
DRA	*D.radiodurans*	B	243230
MTU	*M.tuberculosis*	B	83332
TPA	*T.pallidum*	B	243276
BSU	*B.subtilis*	B	224308
AAE	*A.aeolicus*	B	224324
TMA	*T.maritima*	B	243274
ECO	*E.coli*	B	83333
HPY	*H.pylori*	B	85962
SCE	*S.cerevisiae*	E	4932

F-measure

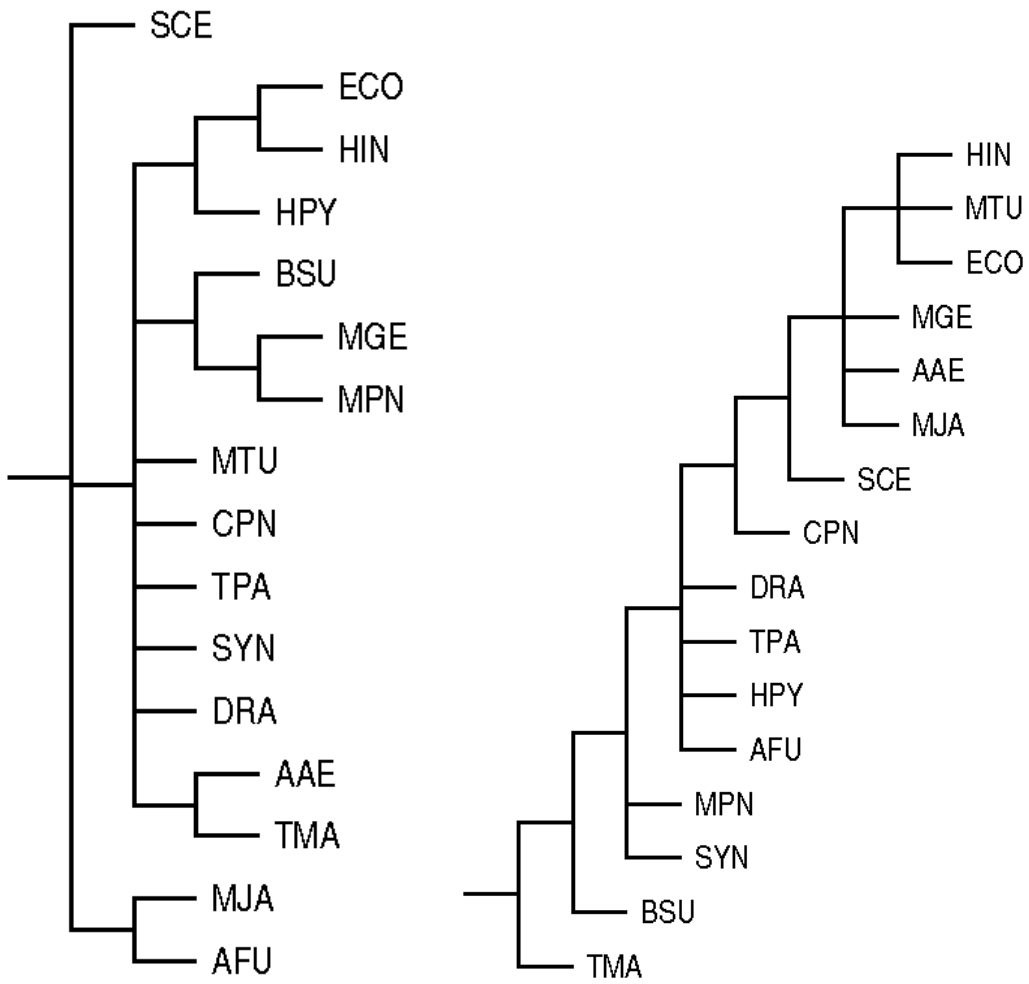
F-measure combines precision and recall
It is defined as

$$F(C) = \sum_{t \in T} \frac{N_t}{N} \max_{C_k \in C} \frac{2P_{tk}R_{tk}}{(P_{tk} + R_{tk})}$$

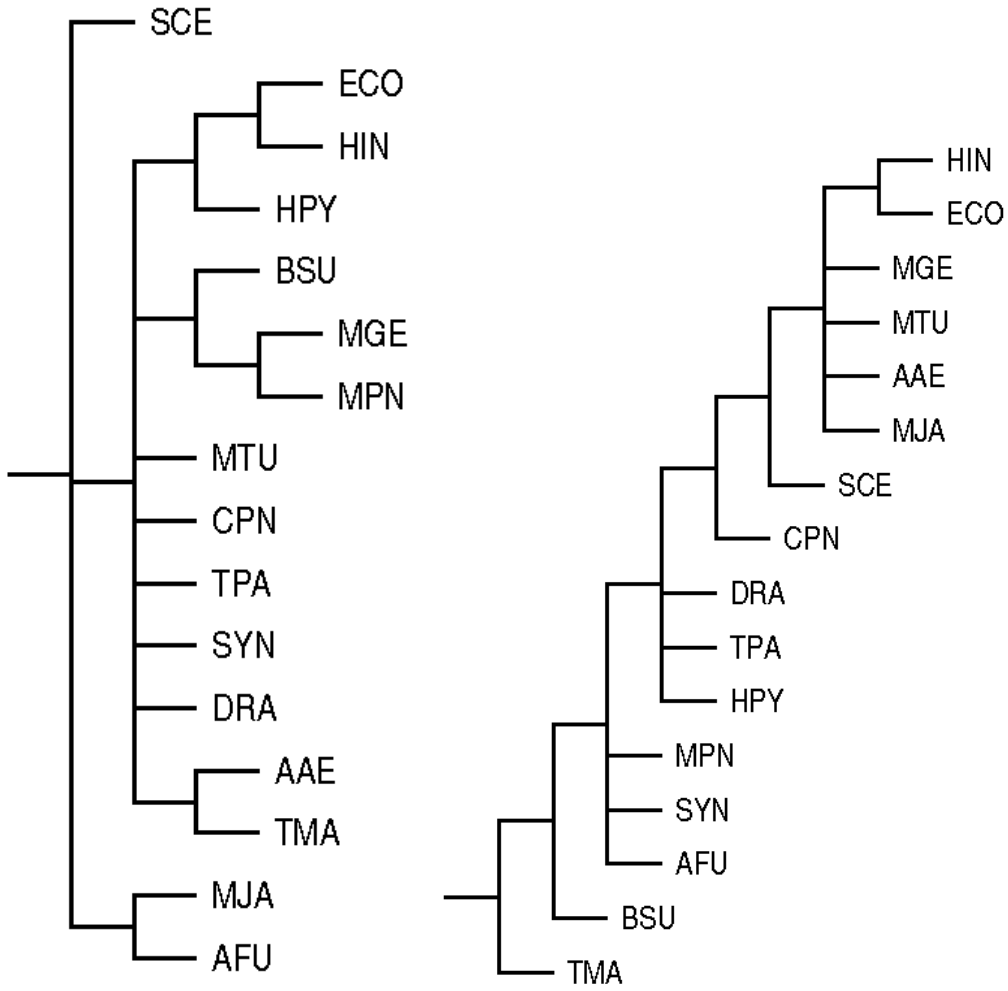
where N_{tk} is the number of elements of class t within cluster C_k, precision is defined as $P_{tk} = N_{tk}/N_k$, and recall is defined as $R_{tk} = N_{tk}/N_t$.



NCBI taxonomy (left) and best tree obtained with FER clustering and GO similarity ($\alpha = 0.2$) (right)



NCBI taxonomy (left) and best tree obtained with FER clustering and HIER similarity ($\alpha = 0.2$) (right)



NCBI taxonomy (left) and best tree obtained with FER clustering and INFO similarity ($\alpha = 0.1$) (right)