Towards a Semantic Web application: Ontology-driven ortholog clustering analysis

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Outline

- Background of COG (Clusters of Orthologous Groups) database
- COG-based gene set enrichment analysis
- COG Analysis Ontology (CAO)
- OntoCOG, the semantic web application for COG enrichment analysis

Ortholog & COG database

- ortholog : Orthologs are genes in different species that have evolved from a common ancestral gene by speciation. Orthologs usually share the same functions in the course of evolution.

- COG database:
  1) collections of orthologs
  2) clusters orthologs to functional groups.
- Entry in COG has COG ID, or may have a functional category assignment.

COG vs. GO

- Same: Classified categories with gene product assigned, provide gene function annotation and classification.
- Different:
  - Categories
  - Species:
    GO: model animals; COG: 66 genomes.
    (COG covers more bacteria.)
  - Only Schizosaccharomyces *pombe* (fission yeast), *Saccharomyces cerevisiae* (baker's yeast) and *E. coli,* have both COG and GO annotations.
  - In *Brucella*, only one gene BMEI0467 in *B. melitensis* has been annotated both in GO and COG.
    GO:0042803 : protein homodimerization activity
    COG0408: Coproporphyrinogen III oxidase (Coenzyme transport and metabolism H)

COG enrichment analysis

Contingency table

	Given list	Not given list	Total
catA	*q*	*m-q*	M
Not catA	*k-q*	*t-m-(k-q)*	*t-m*
total	K	*t-k*	T

Given a list of *k* COG annotated proteins with a total of *t* proteins, for a given COG category A, there are *q* proteins within *k* and *m* proteins within *t* associated with it.

Fisher's Exact Test

$$P(X = x > q) = \sum_{x=q}^{m} \frac{\binom{m}{x}\binom{t-m}{k-x}}{\binom{t}{k}}$$

COG enrichment analysis is to find out the statistical significance of the distribution of the data, particularly, the p-value to test whether COG category *catA* annotated protein *q* is enriched (unevenly distributed) among the given protein list *t*.

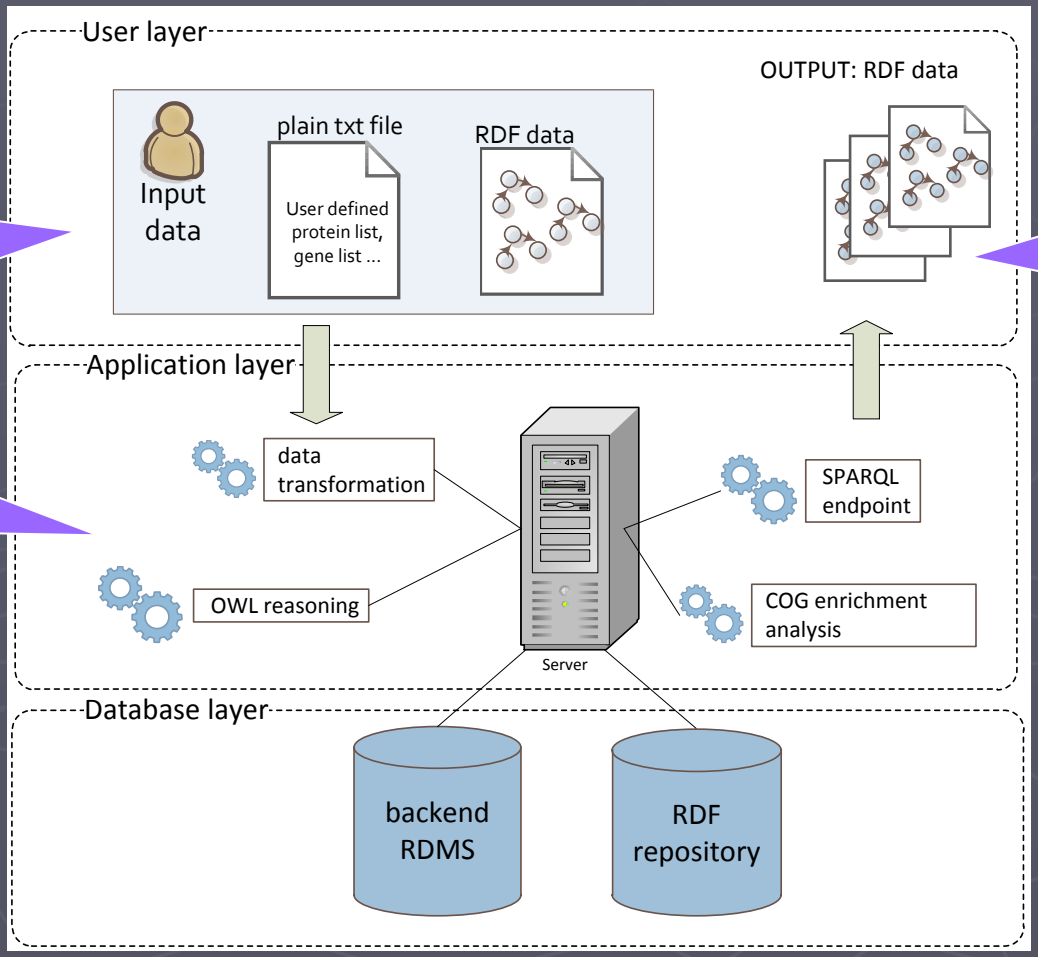
A lot of GO enrichment analysis services are available, but not the COG enrichment analysis service

Design of OntoCOG

OntoCOG : a Semantic Web service application for COG enrichment analysis.

Input data: a list of protein defined by user for COG enrichment analysis

CAO (COG Analysis Ontology) supported

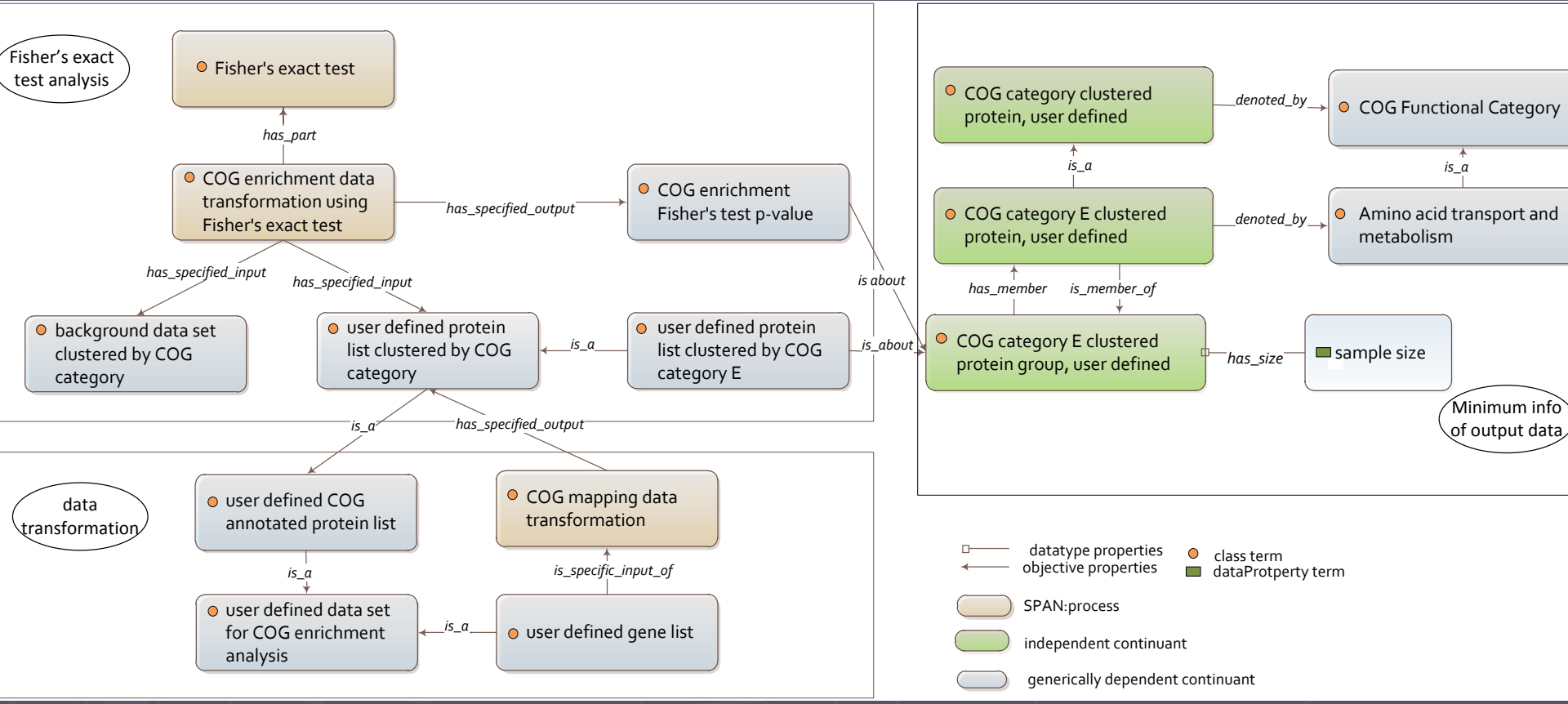


Output data: proteins grouped by COG category with a p-value in OWL format.

COG Analysis Ontology (CAO)

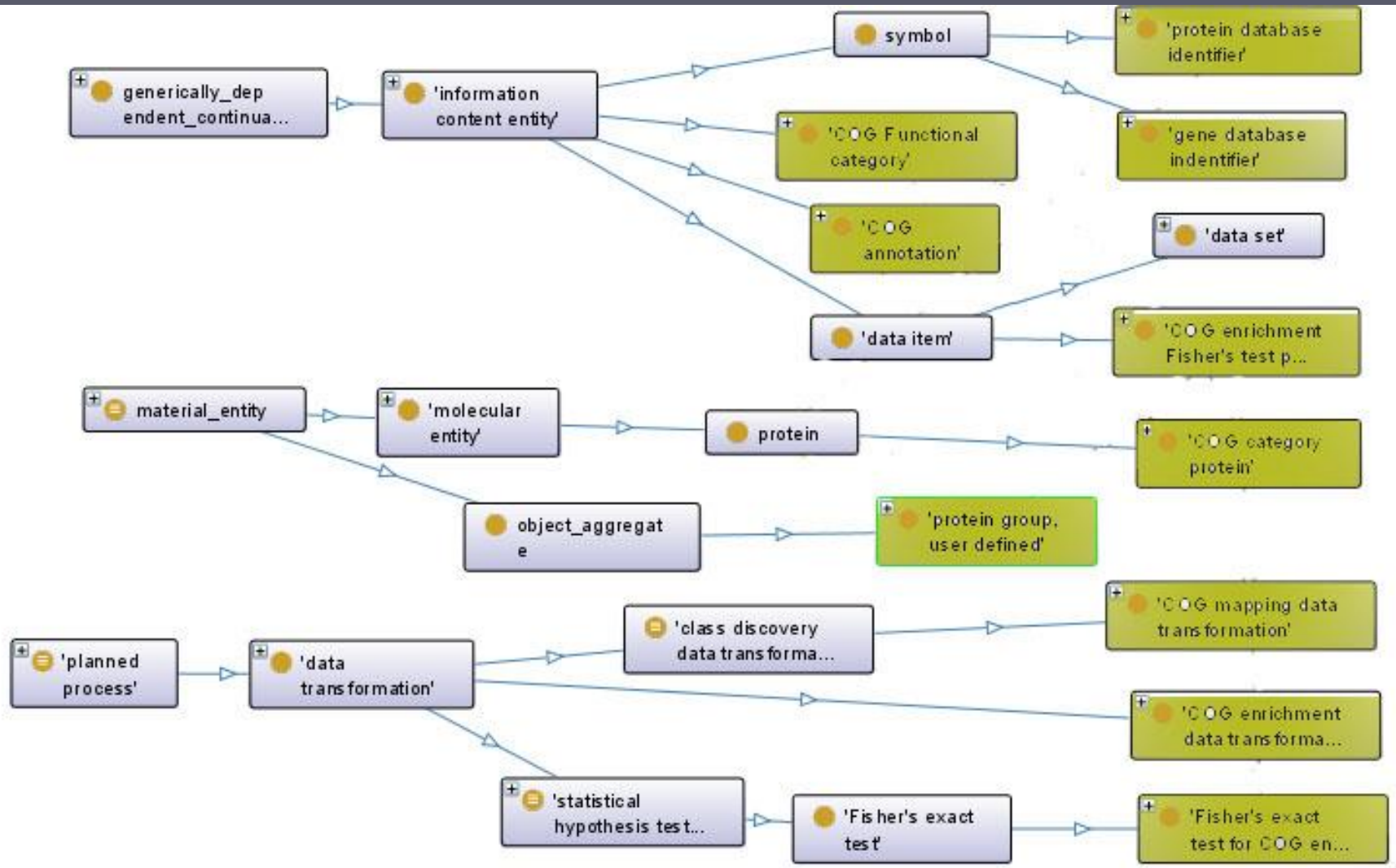
- Scope
  1) ontology-based software/service design;
  2) supporting data integration and exchange in OWL format.
- Domain
  statistical analysis
  protein's COG annotation

Design of CAO



CAO includes models for major components of the OntoCOG application: input data transformation, Fisher's exact test analysis, and minimum information of output data. Terms in yellow, light purple, and green boxes denote *processes*, *generically dependent continuants,* and *independent continuants,* respectively.

COG Analysis Ontology (CAO) : Core Terms



Information captured by CAO

- The given list
- The proteins grouped by COG categories
- The size of each category in the given list *
- The p-value of each category in the given list *

It captures more information than traditional COG enrichment analysis (non-SW technology supported)

Text output:
H: 1.49713616709924e-07; 35*
E: 7.45290117727196e-11; 72*
P: 0.0430093063719378; 7*
J: 6.95603641934163e-13; 52*
F: 1.32399203293874e-05; 21*
I: 0.00262575594696207; 1*
G: 1.00000000000047; 16
C: 0.221275273142313; 11
D: 1; 2
R: 5.22697546843457e-07; 7*
S: 8.81150233068625e-10; 1*
O: 0.0082668319976629; 3*
L: 0.0082668319976629; 3*
K: 3.25387512255916e-05; 2*
B: 0.162656083050577; 1
Q: 0.231179805591791; 2

The traditional output of COG enrichment analysis.

Format:
Category: p-value; size;
(* denotes p-value < 0.05 significant)

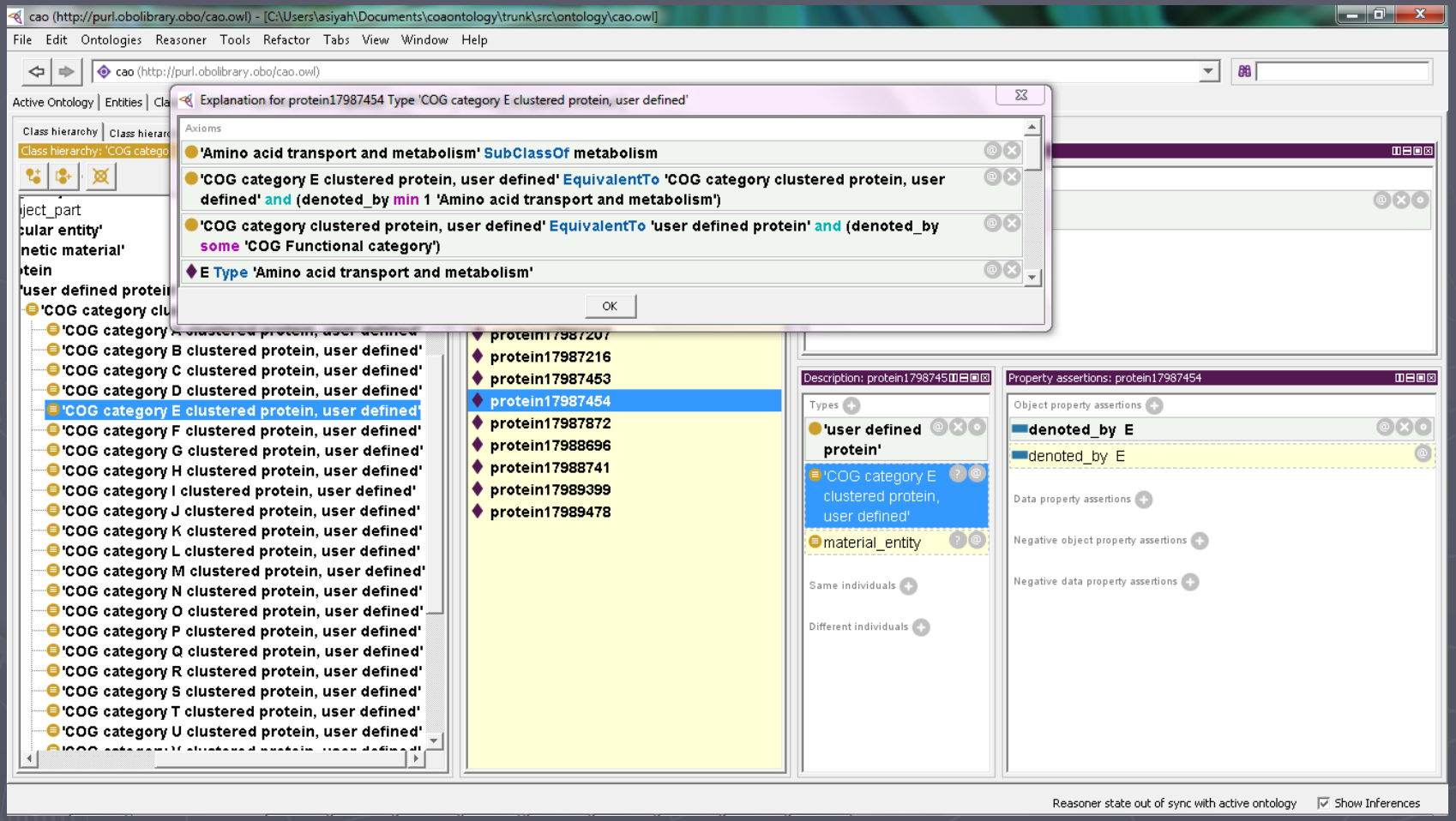
New relations in CAO

- denoted_by
  - describes a relation of an independent entity and a data item
    an independent entity "denoted_by" a data item
  - Not a reverse relation of "denotes"
- is_member_of
  has_member
  - Reverse relations
  - Describes relation of object and object aggregate

Axioms in CAO

- *COG category clustered protein, user defined ≡ user defined protein* and *(denoted_by* some *COG Functional category)*
- *COG category E clustered protein, user defined ≡ COG category protein and (denoted_by min 1 COG Amino acid transport and metabolism)*
- *COG category E clustered protein group, user defined ≡ protein group and (has_member only COG category E protein)*

Validation of CAO



Summaries on CAO

- An ontology to represent COG enrichment analysis
- An ontology to represent the COG enrichment analysis service : OntoCOG
- It is a use case of IAO (Information Artifact Ontology) and OBI (Ontology for Biomedical Investigation)
- It supports OntoCOG.

OntoCOG

http://ontobat.hegroup.org/ontocog/index.php

OntoCOG analysis of *Brucella* virulence factors

Ontobat

Home | SPARQL Query | OntoConvert | OntoCOG | Introduction | Tutorial

OntoCOG Query Result

OWL(RDF/XML) output file generated.

Text output:
E: 0.463287665317927; 32
I: 0.0829671299066097; 3
H: 0.323329281729191; 7
G: 0.0282030340169236; 24*
F: 0.00526801376681896; 14*
L: 0.236978256542513; 6
P: 0.455906297607988; 10
J: 0.0115540005944313; 5*
K: 0.162325010535853; 20
R: 0.00634131762994135; 14*
C: 0.394976297636098; 11
O: 0.324698940577407; 14
T: 0.111098524579059; 11
M: 1.00000000000005; 14
N: 0.0113452455156726; 8*
U: 0.0521202164142756; 9
V: 0.999999999999959; 3
Q: 0.12568302563995; 1
S: 7.7059734062508e-07; 3*

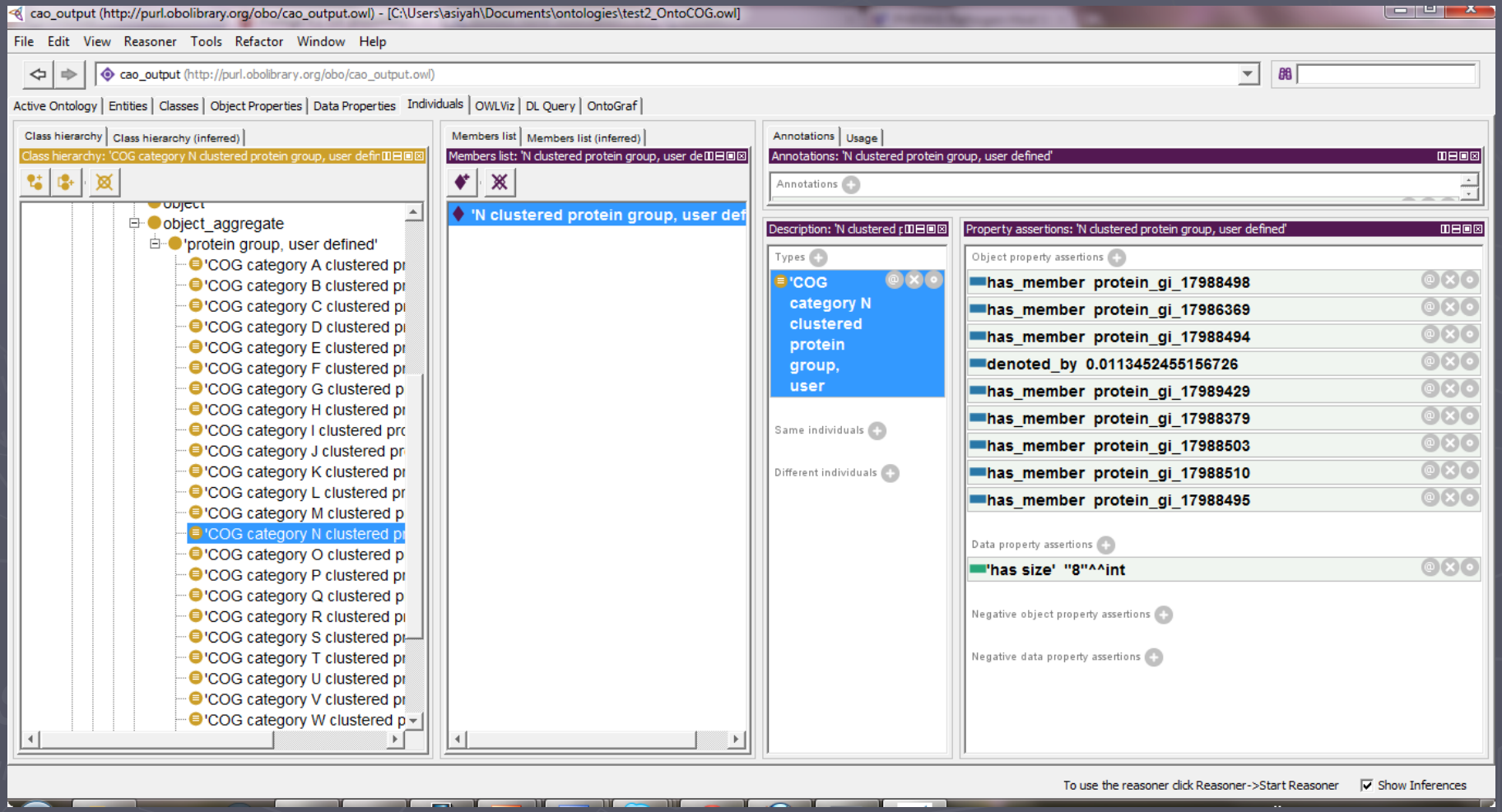
```
    <owl:NamedIndividual rdf:about="&obo;CAO_cog_group_N">
        <rdf:type rdf:resource="&obo;CAO_0000313"/>
        <rdfs:label>N clustered protein group, user defined</rdfs:label>
    <obo:CAO_0000051 rdf:datatype="&xsd;int">8</obo:CAO_0000051>
    <obo:CAO_0000052 rdf:resource="&obo;CAO_protein_17988379"/>
    <obo:CAO_0000052 rdf:resource="&obo;CAO_protein_17988510"/>
    <obo:CAO_0000052 rdf:resource="&obo;CAO_protein_17988494"/>
    <obo:CAO_0000052 rdf:resource="&obo;CAO_protein_17988498"/>
    <obo:CAO_0000052 rdf:resource="&obo;CAO_protein_17989429"/>
    <obo:CAO_0000052 rdf:resource="&obo;CAO_protein_17988503"/>
    <obo:CAO_0000052 rdf:resource="&obo;CAO_protein_17988495"/>
    <obo:CAO_0000052 rdf:resource="&obo;CAO_protein_17986369"/>
        <obo:CAO_0000117 rdf:resource="&obo;CAO_fisher_test_p_value_N"/>
    </owl:NamedIndividual>


    <owl:NamedIndividual rdf:about="&obo;CAO_fisher_test_p_value_N">
        <rdf:type rdf:resource="&obo;CAO_0000040"/>
        <rdfs:label>0.0113452455156726</rdfs:label>
    </owl:NamedIndividual>
```

Download CAO ontology.

FAQs | References | Links | Contact | Acknowledge

Result


cao_output (http://purl.obolibrary.org/obo/cao_output.owl) - [C:\Users\asiyah\Documents\ontologies\test2_OntoCOG.owl]
File Edit View Reasoner Tools Refactor Window Help
cao_output (http://purl.obolibrary.org/obo/cao_output.owl)
Active Ontology | Entities | Classes | Object Properties | Data Properties | Individuals | OWLViz | DL Query | OntoGraf
Class hierarchy | Class hierarchy (inferred)
Class hierarchy: 'COG category N clustered protein group, user defin
object_aggregate
'protein group, user defined'
'COG category A clustered pr
'COG category B clustered pr
'COG category C clustered pr
'COG category D clustered pr
'COG category E clustered pr
'COG category F clustered pr
'COG category G clustered p
'COG category H clustered pr
'COG category I clustered pro
'COG category J clustered pr
'COG category K clustered pr
'COG category L clustered pr
'COG category M clustered p
'COG category N clustered pr
'COG category O clustered p
'COG category P clustered pr
'COG category Q clustered p
'COG category R clustered pr
'COG category S clustered pr
'COG category T clustered pr
'COG category U clustered pr
'COG category V clustered pr
'COG category W clustered p
Members list | Members list (inferred)
Members list: 'N clustered protein group, user de
'N clustered protein group, user def
Annotations | Usage
Annotations: 'N clustered protein group, user defined'
Annotations
Description: 'N clustered p
Types
'COG category N clustered protein group, user
Same individuals
Different individuals
Property assertions: 'N clustered protein group, user defined'
Object property assertions
has_member protein_gi_17988498
has_member protein_gi_17986369
has_member protein_gi_17988494
denoted_by 0.0113452455156726
has_member protein_gi_17989429
has_member protein_gi_17988379
has_member protein_gi_17988503
has_member protein_gi_17988510
has_member protein_gi_17988495
Data property assertions
'has size' "8"^^int
Negative object property assertions
Negative data property assertions
To use the reasoner click Reasoner->Start Reasoner
Show Inferences

Final Conclusion

- OntoCOG provide a platform independent server for COG enrichment analysis
- CAO ontology supports the design and workflow of OntoCOG.
- OntoCOG is the first semantic web application used for such purpose.
- Future work: interface developing; expand to other statistical analysis; output data visualization.

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