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## Mining Linked Open Data: a Case Study with Genes Responsible for Intellectual Disability

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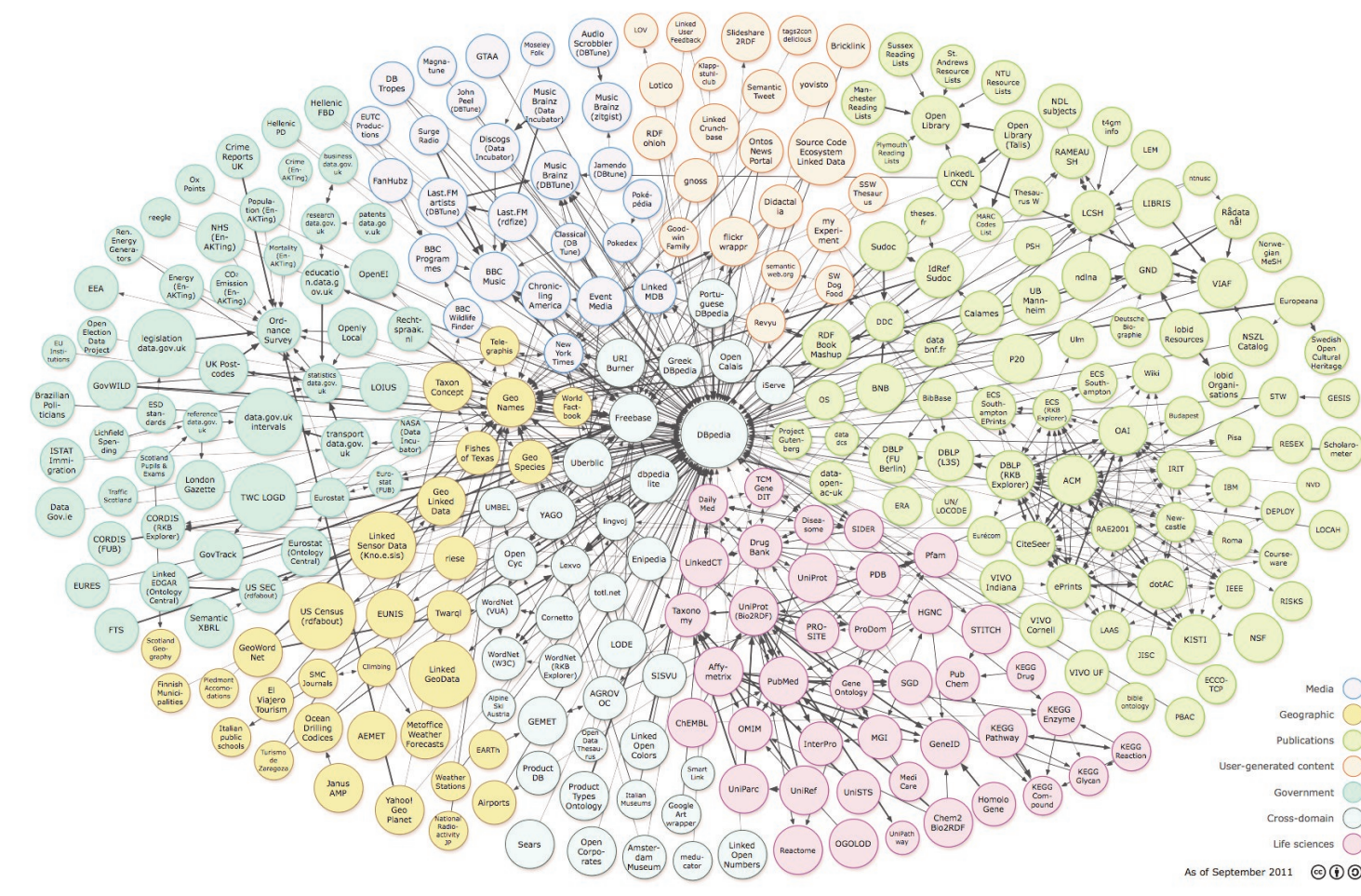
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## Motivation

Increasing amounts of life sciences data are made available through the **Linked Open Data** (Bio2RDF, EMBL-EBI RDF platforms).  
Challenge: use Linked Open Data to answer a biological question.

Approach:

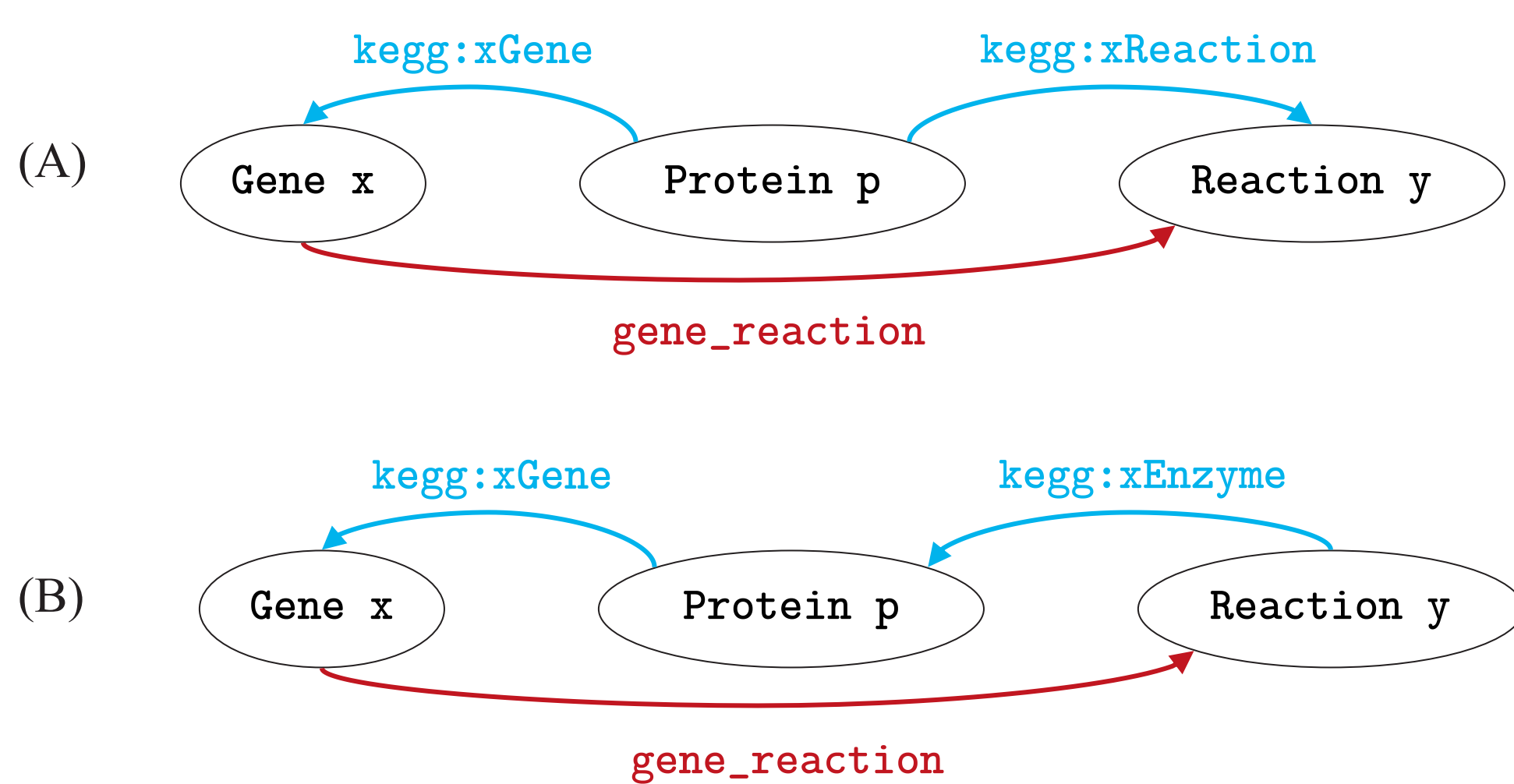
1. query and integrate Linked Open Data,
2. mine the collected data using **Inductive Logic Programming**, a relational data mining method.
3. assess the contribution of domain knowledge available in the Linked Open Data to the quality of both characterization and prediction.

Application: characterize **genes responsible for Intellectual Disability** and build a model predicting whether a gene is responsible for Intellectual Disability or not.

Characterization of genes responsible for Intellectual Disability (ID).

Input :

- list of 282 genes responsible for ID (Inlow and Restifo, 2004).
- list of 267 genes responsible for other phenotypes according to OMIM.
- data on these genes available in the Linked Open Data (LOD).



Mapping of the gene\_reaction relationship.

-Blue: RDF properties. Red: E/R relationship definition.

A gene *x* is **related** to a reaction *y* if there is a protein *p* whose coding gene (**kegg:xGene** property) is *x* and either:

- (A) *p* is involved in *y* (**kegg:xReaction** property),
- (B) *y* has *p* for an enzyme (**kegg:xEnzyme** property)

Relationship	Triples	Relationship	Triples	Entity	Instances
subClass	12779	pathway_protein	767	GOterm	7770
protein_BP	10242	pp_interaction	742	Protein	1257
protein_CC	4358	gene_reaction	500	Family	781
protein_MF	4063	protein_domain	262	Compound	628
domain_family	1238			Pathway	580
product	960			Gene	549
substrate	938			Reaction	433
gene_protein	819			Domain	262

Amounts of collected data per relationship and entity

Relational Data Mining with Inductive Logic Programming (ILP) using the Aleph program

**Principles:** generalization of a positive example (gene responsible for ID) to build a rule covering the most positive examples, and the least negative examples

**Advantages:** ILP natively supports the relational format of the LOD data, and can perform inference on domain knowledge (GO *is-a* hierarchy)

**Experiments:**

- no-GO*: all data except GO annotation data
- GO1*: all data including GO annotations, no inference on the GO *is-a* hierarchy (only one level is used)
- GO2*, *GO3* and *GO4*: all data including GO annotations, inferences over 2, 3, and 4 levels of the GO *is-a* hierarchy, respectively

Rule	Covered positive, negative examples
<code>is_responsible(A):-gene_in_reaction(A,B), gene_ch(A,x).</code>	15 2
<code>is_responsible(A):-gene_in_reaction(A,B), gene_ch(A,'1').</code>	14 0
<code>is_responsible(A):-gene_in_pathway(A,'Valine, leucine and isoleucine degradation').</code>	11 1
<code>is_responsible(A):-gene_in_pathway(A,'N-Glycan biosynthesis').</code>	8 0
<code>is_responsible(A):-gene_in_pathway(A,'Glycosaminoglycan degradation').</code>	8 0
<code>is_responsible(A):-gene_in_reaction(A,'Ubiquinol + Acceptor &lt;=&gt; Ubiquinone + Reduced acceptor').</code>	7 0
<code>is_responsible(A):-gene_in_reaction(A,B), gene_protein(A,C), pp_interaction(C,P30480).</code>	7 0
<code>is_responsible(A):-gene_chromosome_band(A,'22q13').</code>	6 0
<code>is_responsible(A):-gene_in_reaction(A,B), gene_protein(A,C), pp_interaction(C,D), pp_interaction(D,C).</code>	6 0
<code>is_responsible(A):-gene_in_pathway(A,'Alanine and aspartate metabolism').</code>	6 1
<code>is_responsible(A):-gene_in_pathway(A,'Formation of transcription-coupled NER (TC-NER) repair complex').</code>	5 0

### no-GO theory

Rule	Covered positive, negative examples
<code>is_responsible(A):-gene_in_reaction(A,B), gene_protein(A,C), protein_bp(C,D), subClass(D,'organonitrogen compound catabolic process').</code>	42 2
<code>is_responsible(A):-gene_protein(A,B), protein_bp(B,C), subClass(C,'cellular amino acid metabolic process'), subClass(C,'cellular metabolic process').</code>	32 3
<code>is_responsible(A):-gene_in_reaction(A,B), gene_protein(A,C), protein_bp(C,'small molecule metabolic process'), protein_cc(C,'mitochondrial inner membrane').</code>	23 1

Best 3 rules out of 16 from the GO4 theory

## Biological Question

Concept to learn

## Formalization

## Data Model

Entities and relationships

## Mappings to the Linked Open Data

## SPARQL Queries

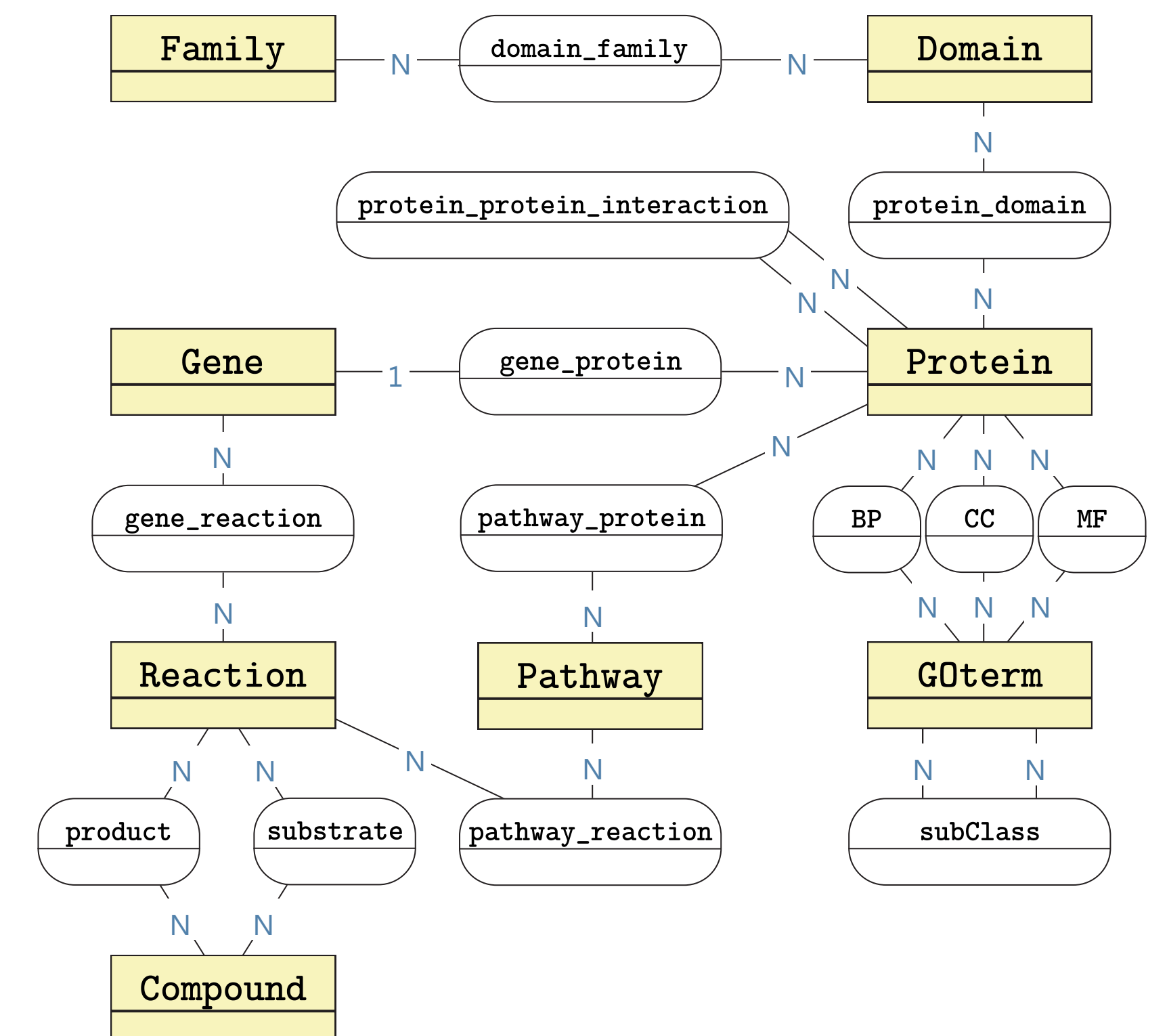
## Data Integration

## Triple Store

## Data Mining

## Theory

First-order logic rules



### Entity-Relationship Model covering the data related to the biological question

-Restricted to binary relationships to fit the LOD

-Domain knowledge in the form of the Gene Ontology *is-a* hierarchy

```

PREFIX kegg:<http://bio2rdf.org/kegg_vocabulary>
PREFIX geneid:<http://bio2rdf.org/geneid_vocabulary:>
SELECT ?x ?y
WHERE
{
  {?x rdf:type geneid:Gene}
  UNION
  {?x rdf:type kegg:Gene}
  } Mapping of Gene
  {?y rdf:type kegg:Reaction}
  } Mapping of Reaction
  ?p kegg:xGene ?x.
  {?y kegg:xEnzyme ?p}
  UNION
  {?p kegg:xReaction ?y}
  } Mapping of gene_reaction
  
```

### One query per relationship: example with the gene\_reaction relationship

-Query for relationship *R* retrieves couples (*x,y*) such that *R(x,y)*

-Involves the mapping of the relationship, plus the mapping of its domain and range

-Apply restrictions, for instance, domain restriction on our list of genes

### Characterization:

-*no-GO* theory is highly specific: points to individual reactions and pathways, low amount of false positives, but low coverage of positive examples

-*GO1-4* theories rarely use other data than GO annotations, but better coverage of positive examples

### Prediction evaluation:

-Scores computed using leave-one-out cross-validation (KNIME workflows)

-Sensitivity and accuracy improves with each additional inference level

Experiment	Sensitivity (%) TP/P	Specificity (%) TN/N	Accuracy (%) (TP+TN)/(P+N)
<i>no-GO</i>	26.6	94.4	59.6
<i>GO1</i>	47.9	81.3	64.1
<i>GO2</i>	55.7	80.5	67.8
<i>GO3</i>	55.7	81.7	68.3
<i>GO4</i>	57.1	83.1	69.8

Leave-one-out cross-validation evaluation for each experiment

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