# A Formal Ontology for the Cell-Cycle Domain

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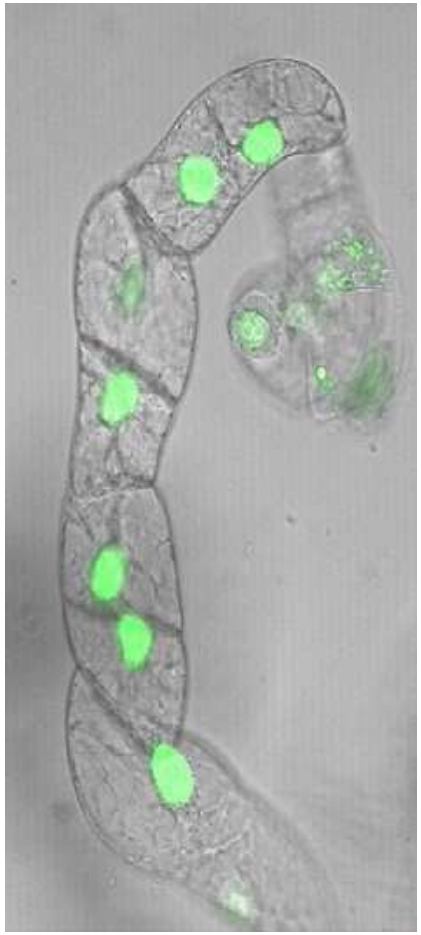
# Overview

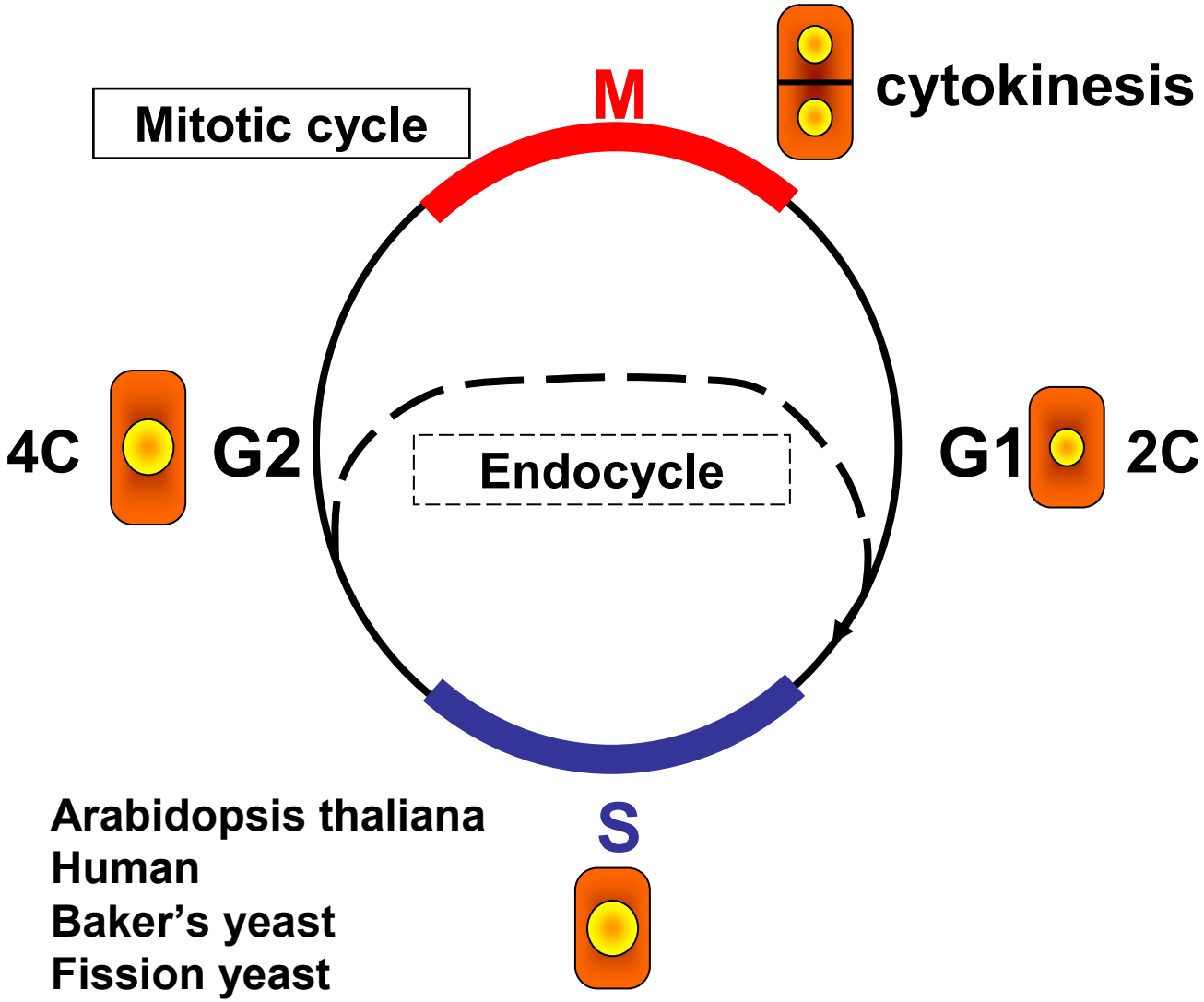
- Introduction
- Aim
- Data integration pipeline
- Format mapping
- CCO engineering
- A CCO sample
- Exploiting reasoning services
- Conclusions
- Future work

# Motivating scenarios

- I'm working with **AT5g35520**, in which interactions this gene play a role?
- From my microarray experiment I've got this gene **X**, is this gene involved in the cell cycle?
- Verify my models of genetic, metabolic and product interaction networks
- …

# Mitotic Cell Cycle and Endocycle





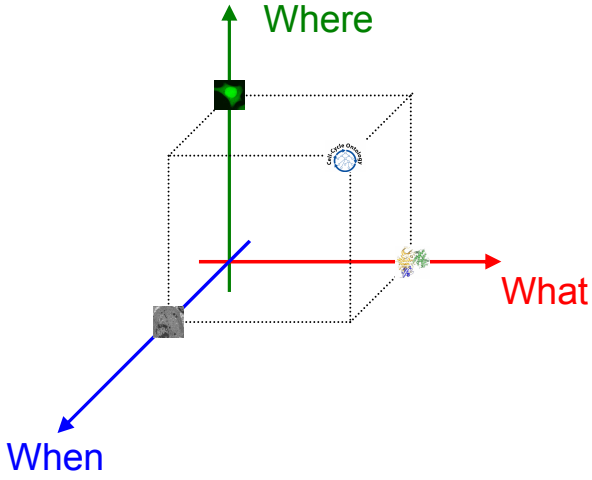

Arabidopsis thaliana
Human
Baker's yeast
Fission yeast

# Introduction

- Amount of data generated in biological experiments continues to grow exponentially
- Shortage of proper approaches or tools for analyzing this data has created a gap between raw data and knowledge
- Lack of a structured documentation of knowledge leaves much of the data extracted from these raw data unused
- Differences in the technical languages used (synonymy and polysemy) have complicated the analysis and interpretation of the data

# Objective

- Capture the knowledge of the CC process
- dynamic aspects of terms and their interrelations*
- promote sharing, reuse and enable better computational integration with existing resources
- Issues: *synonymy*, *polysemy*

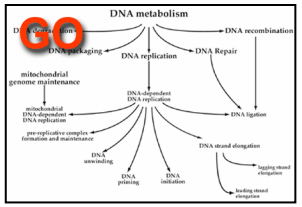



*"Cyclin B (what) is located in Cytoplasm (where) during Interphase (when)"*

* **Dynactome**: http://dynactome.mshri.on.ca/

# CCO architecture

- Core ontology:
  - Gene Ontology (GO)
  - Relationships Ontology (RO)
  - Dublin Core (DC)
  - Upper level ontology
- Data sources
  - GOA files
  - PPI: BIND, IntAct
  - Cell-cycle functional data
  - Data obtained using bioinformatics

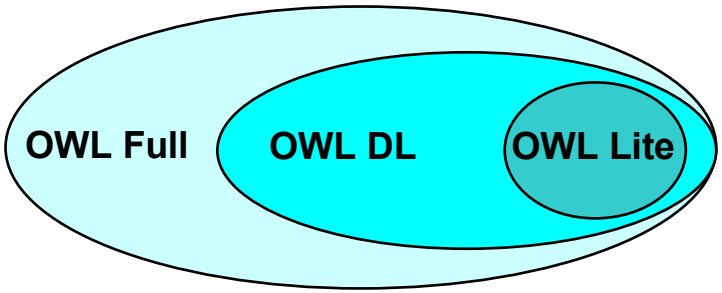







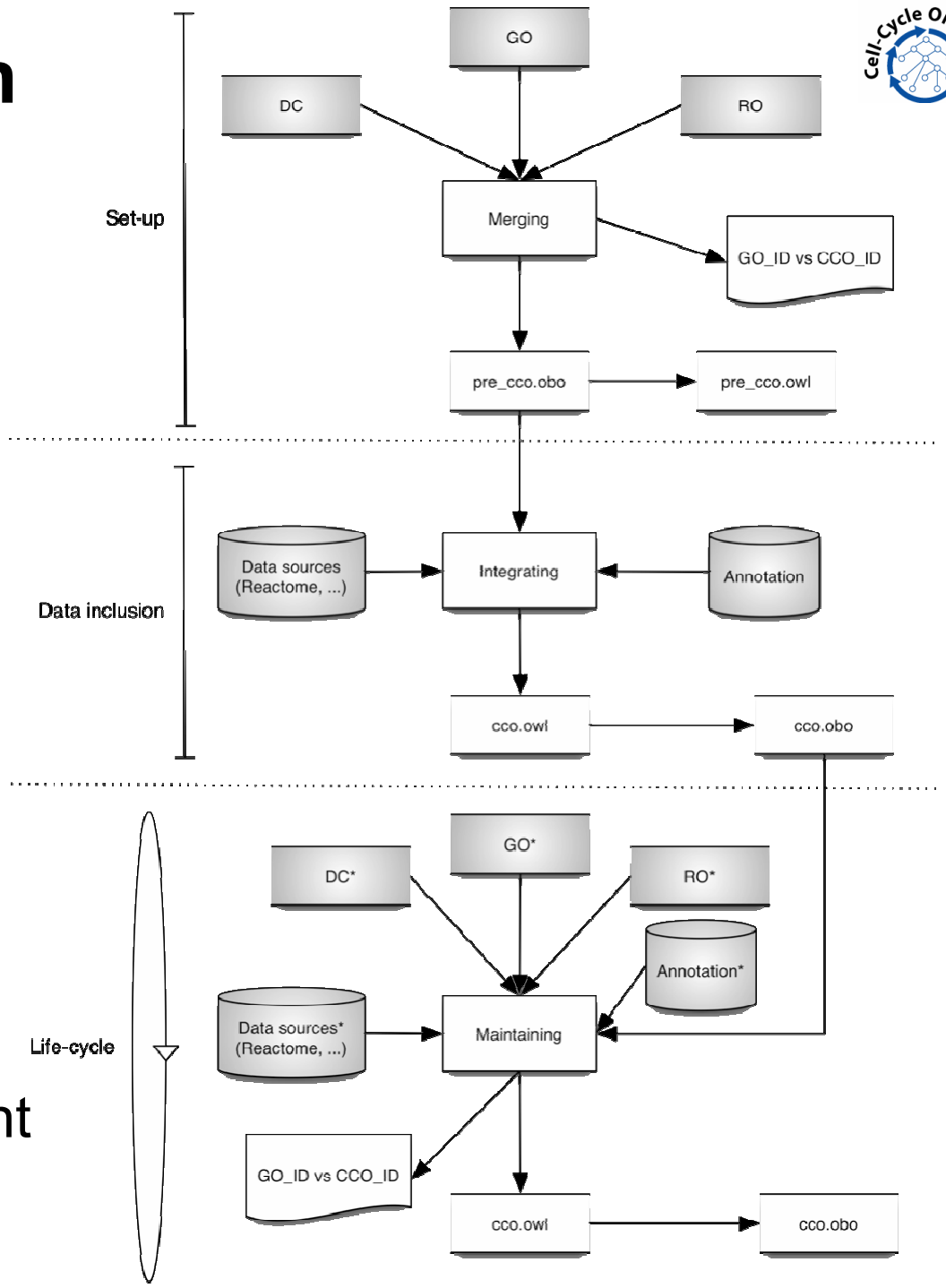
# Knowledge Formalization

- Why OBO?
  - "Human readable"
  - Standard
  - Tools (e.g. OBOEdit)
  - http://obo.sourceforge.net
- Why OWL?
  - "Computer readable"
  - Reasoning capabilities vs. computational cost rat
  - Formal foundation (Description Logics: http://dl.kr.org/)
  - http://www.w3c.org/TR/2004/REC-owl-features-20040210
  - Reasoning: RACER, Pellet, FaCT++



# Data integration

- ontology integration
- format mapping
- data integration
- data annotation
- consistency checking
- maintenance
- data annotation
- semantic improvement



# Format mapping: OBO⇔OWL

- Mapping not totally biunivocal; however, all the data has been preserved.
- Missing properties in OWL relations:
  - reflexivity,
  - asymmetry,
  - Intransitivity, and
  - partonomic relationships.
- Existential and universal restrictions cannot be explicitly represented in OBO => Consider all as existential.
- Mapping efforts:
  - http://spreadsheets.google.com/ccc?key=pWN_4sBrd9l1Umn1LN8WuQQ
  - http://www.psb.ugent.be/cbd/cco/OBO2OWL%20Mappings.pdf

# Mapping: oboInOwl

| OWL keyword | OWL element type |
|---|---|
| oboInOwl:has_definition | owl:AnnotationProperty |
| oboInOwl:Definition | owl:Class |
| oboInOwl:Synonym | owl:Class |
| oboInOwl:IDSpace | owl:Class |
| oboInOwl:has_dbxref | owl:ObjectProperty |
| oboInOwl:DbXref | owl:Class |
| oboInOwl:acc | owl:DatatypeProperty |
| oboInOwl:dbname | owl:DatatypeProperty |
| | |

# Mapping: header

| HEADER (owl:Ontology) | | |
|---|---|---|
| OBO keyword | OWL keyword | OWL element type |
| data-version | owl:versionInfo | rdf:datatype="http://www.w3.org/2001/XMLSchema#string" |
| date | hasDate | AnnotationProperty => rdf:datatype="http://www.w3.org/2001/XMLSchema#xsd:dateTime |
| saved-by | savedBy | AnnotationProperty => rdf:datatype="http://www.w3.org/2001/XMLSchema#string |
| auto-generated-by | autoGeneratedBy | AnnotationProperty => rdf:datatype="http://www.w3.org/2001/XMLSchema#string |
| subsetdef | NDY | |
| import | owl:imports | |
| synonymtypedef | NDY | |
| idspace | NDY | |
| default-relationship-id-prefix | NDY | |
| id-mapping | NDY | |
| default-namespace | NDY | |
| remark | rdfs:comment | rdf:datatype="http://www.w3.org/2001/XMLSchema#string" |
| | | |

# Mapping: terms

| TERMS | | |
|---|---|---|
| OBO keyword | OWL keyword | OWL element type |
| **[Term]** | **owl:Class** | **Class description** |
| id | rdf:ID | Class description |
| name | rdfs:label | rdf:Property |
| namespace | NDY | |
| is anonymous | NDY | NDY |
| alt id | hasAlternativeId | AnnotationProperty => rdf:datatype="http://www.w3.org/2001/XMLSchema#string |
| def | hasDefinition | owl:AnnotationProperty => oboInOwl:Definition |
| comment | rdfs:comment | NDY |
| subset | NDY | NDY |
| synonym | synonym | owl:DataTypeProperty, owl:AnnotationProperty |
| xref | xref | owl:DataTypeProperty, owl:AnnotationProperty |
| is_a | rdfs:subClassOf | owl:ObjectProperty |
| intersection_of | owl:intersectionOf | Class description |
| union _of | owl:unionOf | Class description |
| disjoint_of | owl:disjointWith | Class axiom |
| relationship | NDY | NDY |
| is_obsolete | owl:DeprecatedClass | Version information |
| replaced_by | NDY | NDY |
| consider | owl:equivalentClass | Class axiom |

# Mapping: relationships

| OBO keyword | OWL keyword |
|---|---|
| **[Typedef]** | **owl:ObjectProperty** |
| builtin | NDY |
| comment | NDY |
| def | rdfs:comment |
| exact_synonym | synonym (workaround) |
| narrow_synonym | synonym (workaround) |
| broad_synonym | synonym (workaround) |
| id | rdf:id |
| inverse_of | owl:inverseOf |
| is_a | rdfs:subClassOf |
| is_anti_symmetric | is_anti_symmetric (workaround) |
| is_reflexive | is_reflexive (workaround) |
| is_transitive | rdf:type (TransitiveProperty) |
| NDY | rdf:type (SymmetricProperty) |
| name | rdfs:label (string) |
| xref_analog | NDY |

# Reusing ontologies

- GO only considers subsumption (is_a) and partonomic inclusion (part_of).
- Maintainability issues in GO.
- GO and the RO: core ontologies in CCO
- All the processes from GO under the cell-cycle (GO:0007049) term were taken into account, while RO was completely imported.
- 304 terms adopted from GO
- 15 relationships from RO.
- The CCO is updated daily and checked using data from GO.

# Motivating scenarios

- Molecular biologist: interacting components, events, roles that each component play. Hypothesis evaluation.
- Bioinformatician: data integration, annotation, modeling and simulation.
- General audience: educational purposes.

# Competency questions*

- What is a X-type CDK?
- What is Y-type cyclin?
- In what events is CDK Z involved?
- In what events does Rb participate?
- Which CDKs are involved in the endoreduplication process?
- Which proteins are phosphorylated by kinase X?
- Which CDK pertains to [G1 | S | G2 | M] phase?

* How can I validate my ontology?

# CCO accession number

CCO:[CPFRTIBU]nnnnnnn

namespace

sub-namespace

7 digits

```
C: cellular component
P: biological process
F: molecular function
R: reference
T: taxon
I: interaction
B: bio-molecule
U: upper-level term
```

- **Examples in CCO:**
  - CCO: P0000056 ⟷ "*cell cycle*"
  - CCO: B0000046 ⟷ "CYCA3;2"
- **In other ontologies:**
  - OBO_REL: has_participant
  - GO:0007049 ⟷ "*cell cycle*"

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id: CCO:P0000016
name: M phase of mitotic cell
cycle
def: "Progression through M
phase, the part of the mitotic
cell cycle during which
mitosis and cytokinesis take
place." [GOC:mah,
ISBN:0815316194]
is_a: CCO:P0000038 ! M phase
relationship: part_of
CCO:P0000037 ! mitotic cell
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synonym: "M-phase of mitotic
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xref: GO:0000087
xref: Reactome:68886
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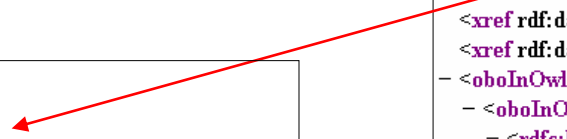

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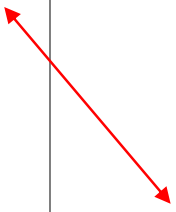

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place." [GOC:mah,
ISBN:0815316194]
is_a: CCO:P0000038 ! M phase
relationship: part_of
CCO:P0000037 ! mitotic cell
cycle
synonym: "M-phase of mitotic
cell cycle" EXACT []
xref: GO:0000087
xref: Reactome:68886
```

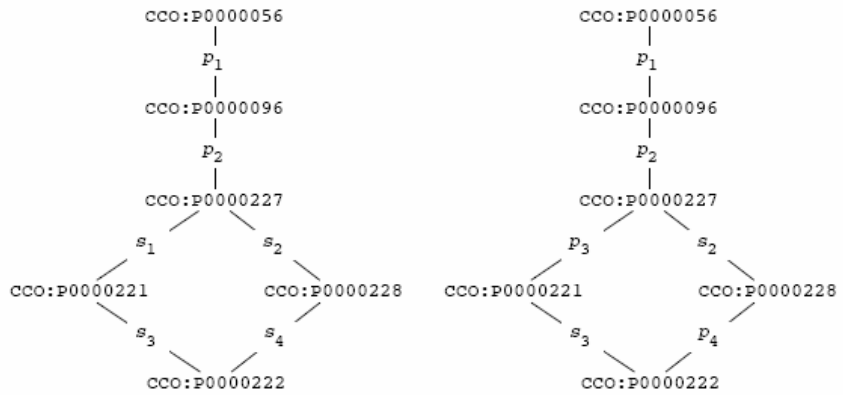
```
<owl:Class rdf:ID="CCO_P0000016">
  <rdfs:label xml:lang="en">M phase of mitotic cell cycle</rdfs:label>
  <xref rdf:datatype="http://www.w3.org/2001/XMLSchema#string">GO:0000087</xref>
  <xref rdf:datatype="http://www.w3.org/2001/XMLSchema#string">Reactome:68886</xref>
- <oboInOwl:has_definition>
  - <oboInOwl:Definition>
    - <rdfs:label xml:lang="en">
        Progression through M phase, the part of the mitotic cell cycle during which mitosis and cytokinesis take place.
      </rdfs:label>
    - <oboInOwl:has_dbxref>
      - <oboInOwl:DbXref rdf:about="xref/GOC#mah">
          <oboInOwl:acc>mah</oboInOwl:acc>
          <oboInOwl:dbname>GOC</oboInOwl:dbname>
        </oboInOwl:DbXref>
      </oboInOwl:has_dbxref>
    - <oboInOwl:has_dbxref>
      - <oboInOwl:DbXref rdf:about="xref/ISBN#0815316194">
          <oboInOwl:acc>0815316194</oboInOwl:acc>
          <oboInOwl:dbname>ISBN</oboInOwl:dbname>
        </oboInOwl:DbXref>
      </oboInOwl:has_dbxref>
    </oboInOwl:Definition>
  </oboInOwl:has_definition>
  <synonym rdf:datatype="http://www.w3.org/2001/XMLSchema#string">M-phase of mitotic cell cycle</synonym>
  <rdfs:subClassOf rdf:resource="#CCO_P0000038"/>
- <rdfs:subClassOf>
  - <owl:Restriction>
      <owl:onProperty rdf:resource="#part_of"/>
      <owl:someValuesFrom rdf:resource="#CCO_P0000037"/>
    </owl:Restriction>
  </rdfs:subClassOf>
</owl:Class>
```

# Single inheritance principle

- Principle: *"No class in a classification should have more than one is_a parent on the immediate higher level" (Smith B. et al.)*
- Detect the relationships which violate that rule using a reasoner (RACER*)
- Solution: disjoint among the terms at the same level of the structure
- 32 problems found:
  - 4: "part_of" instead of "is_a"
  - 18: should stay without any change (FP)
  - 10: not consistent (used terminology)

* http://www.racer-systems.com

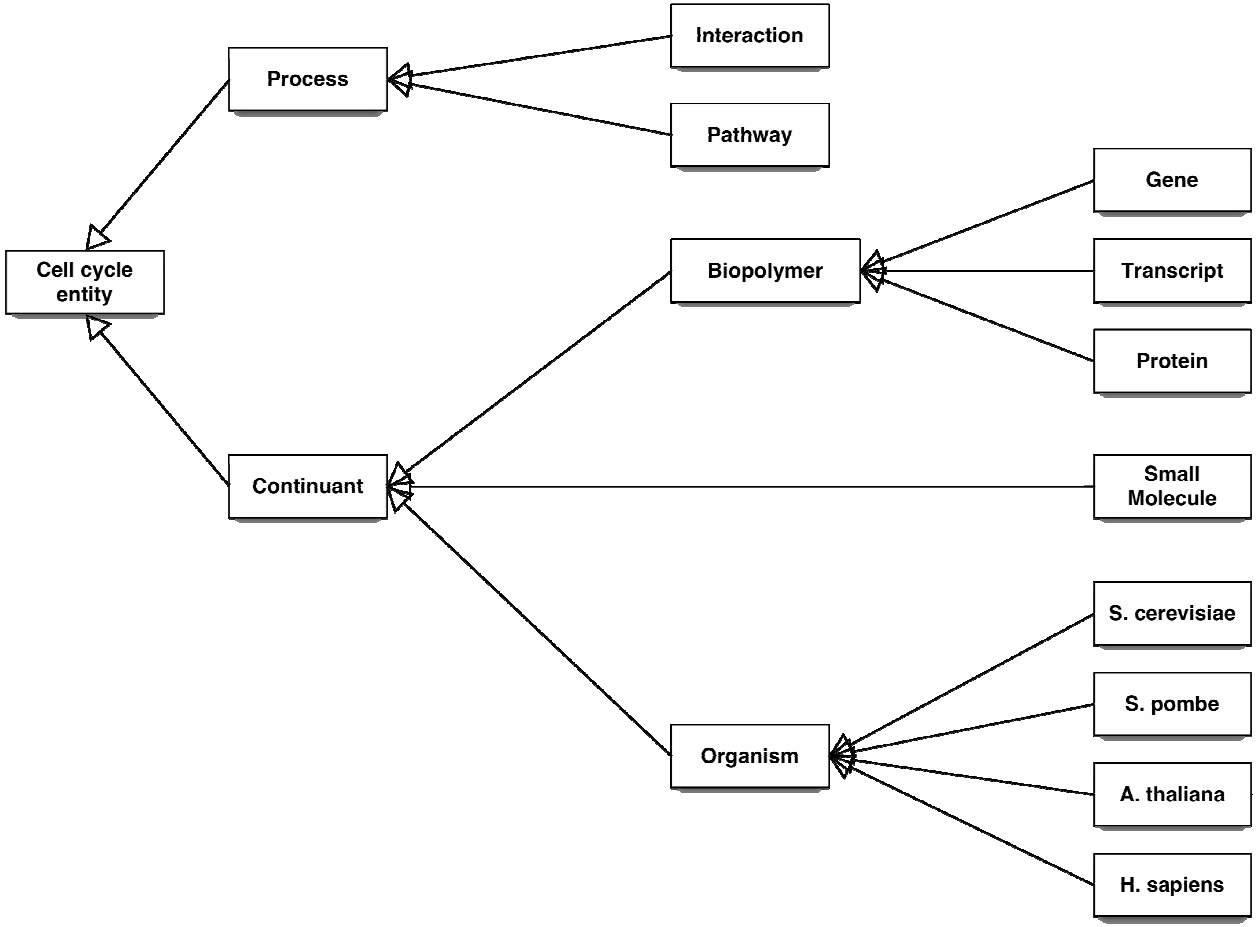
# ***part_of*** instead of ***is_a***




The sub-ontology on the left has inconsistent relation $s_4$ (is_a) which has been changed into part_of (right side) .

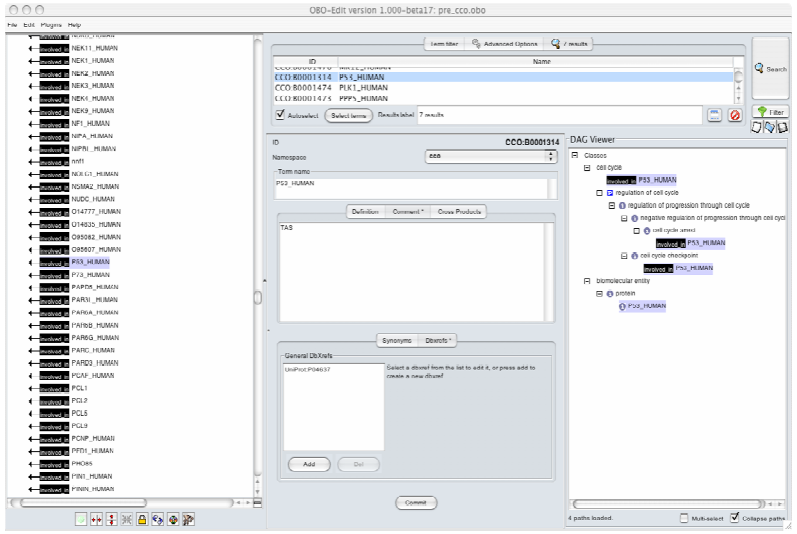
| CCO ID | Term |
|---|---|
| CCO:P0007049 | cell cycle |
| CCO:P0000096 | centrosome cycle |
| CCO:P0000227 | regulation of centrosome cycle |
| CCO:P0000221 | regulation of centriole replication |
| CCO:P0000228 | negative regulation of centrosome cycle |
| CCO:P0000222 | negative regulation of centriole replication |

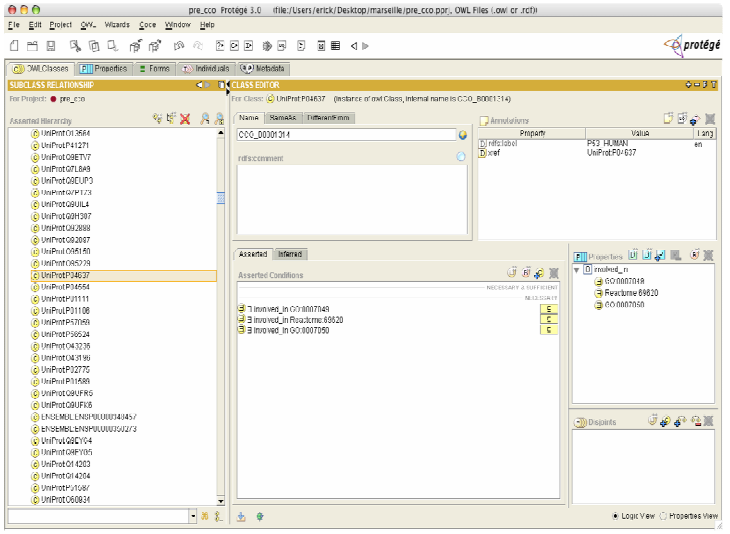
# Upper Level Ontology*

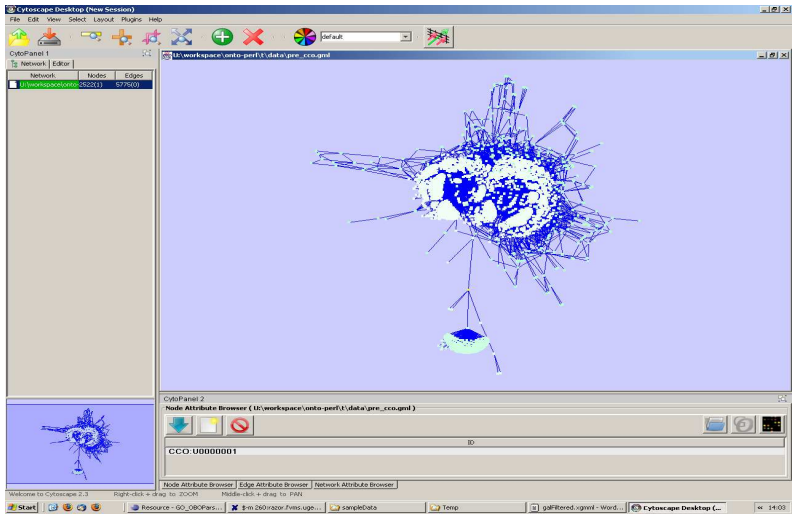


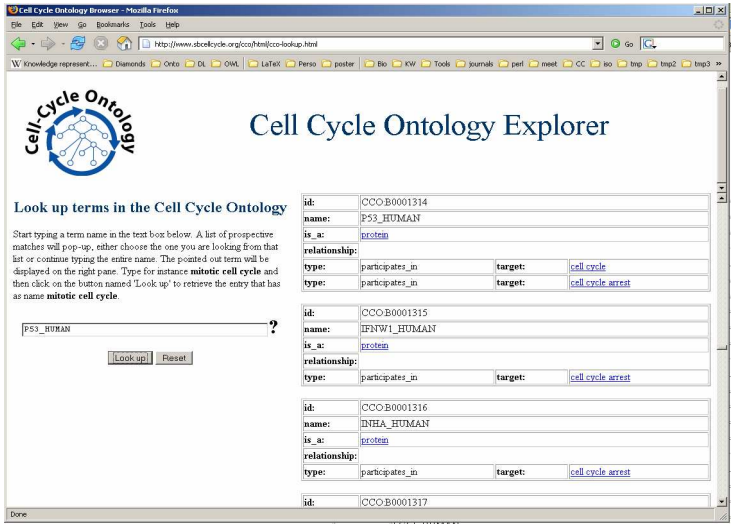

* Based on the concepts introduced by Smith et al.

# CCO in …

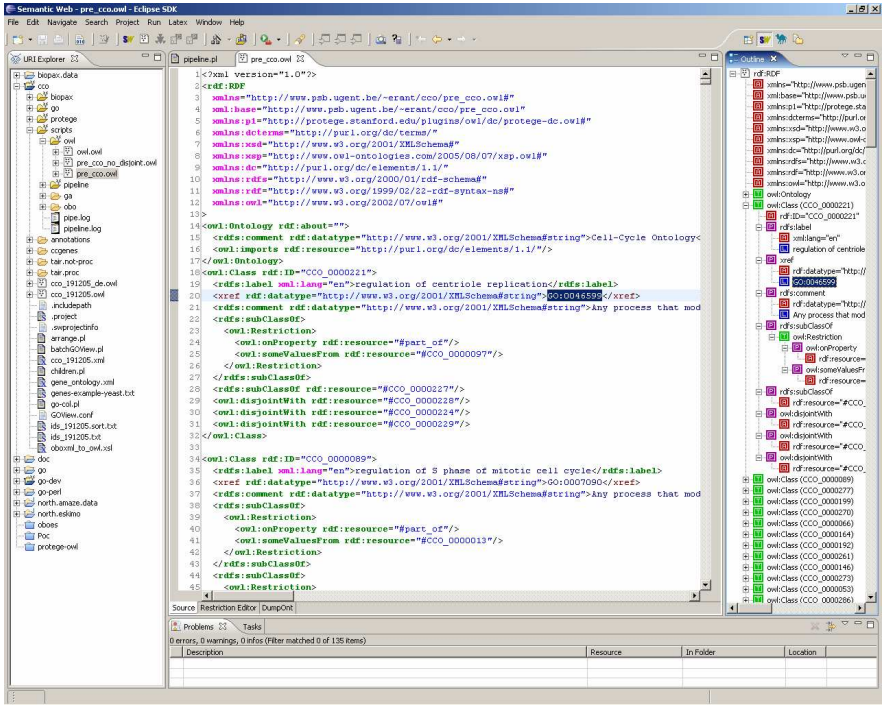

OBO-Edit version 1.000-beta17: pre_cco.obo
CCO:B0001314
DAG Viewer

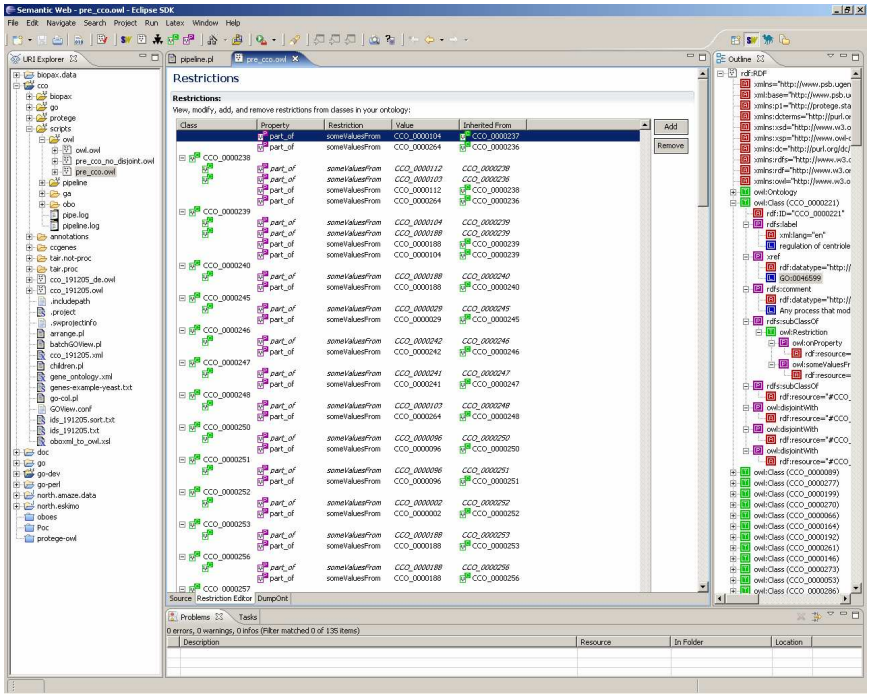

pre_cco Protégé 3.0
protégé
SUBCLASS RELATIONSHIP
CLASS EDITOR


Cytoscape Desktop (New Session)
CytoPanel 1
CytoPanel 2
Node Attribute Browser


Cell Cycle Ontology Browser - Mozilla Firefox
Cell Cycle Ontology Explorer
Look up terms in the Cell Cycle Ontology
Look up
Reset

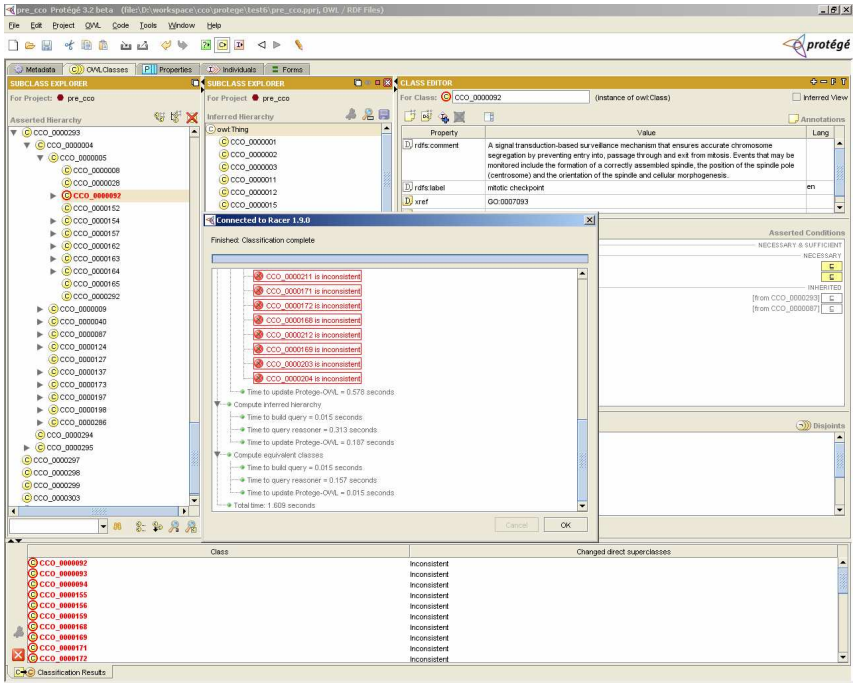
# CCO checked with…

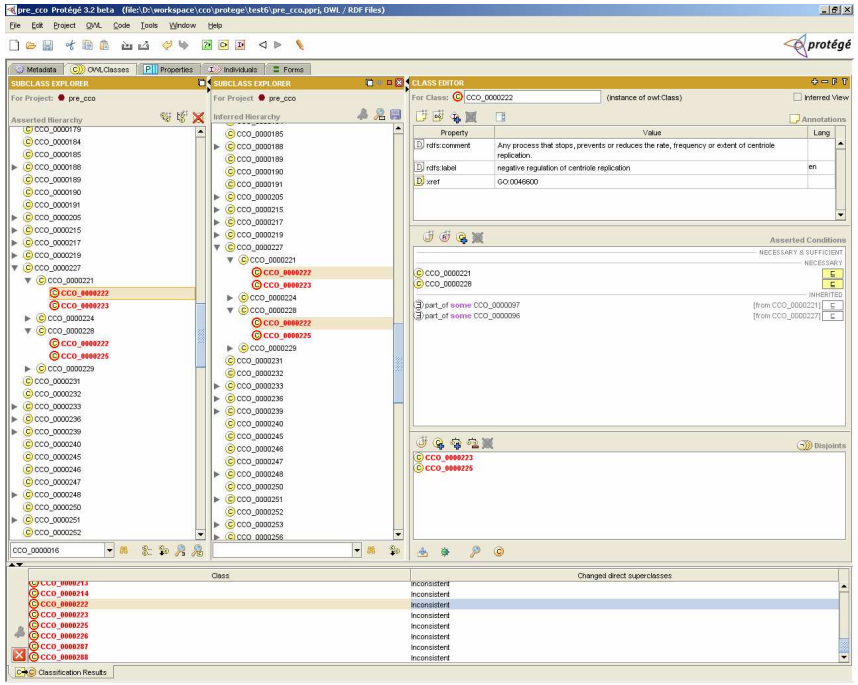




**SWeDE Eclipse plug-in:** http://owl-eclipse.projects.semwebcentral.org

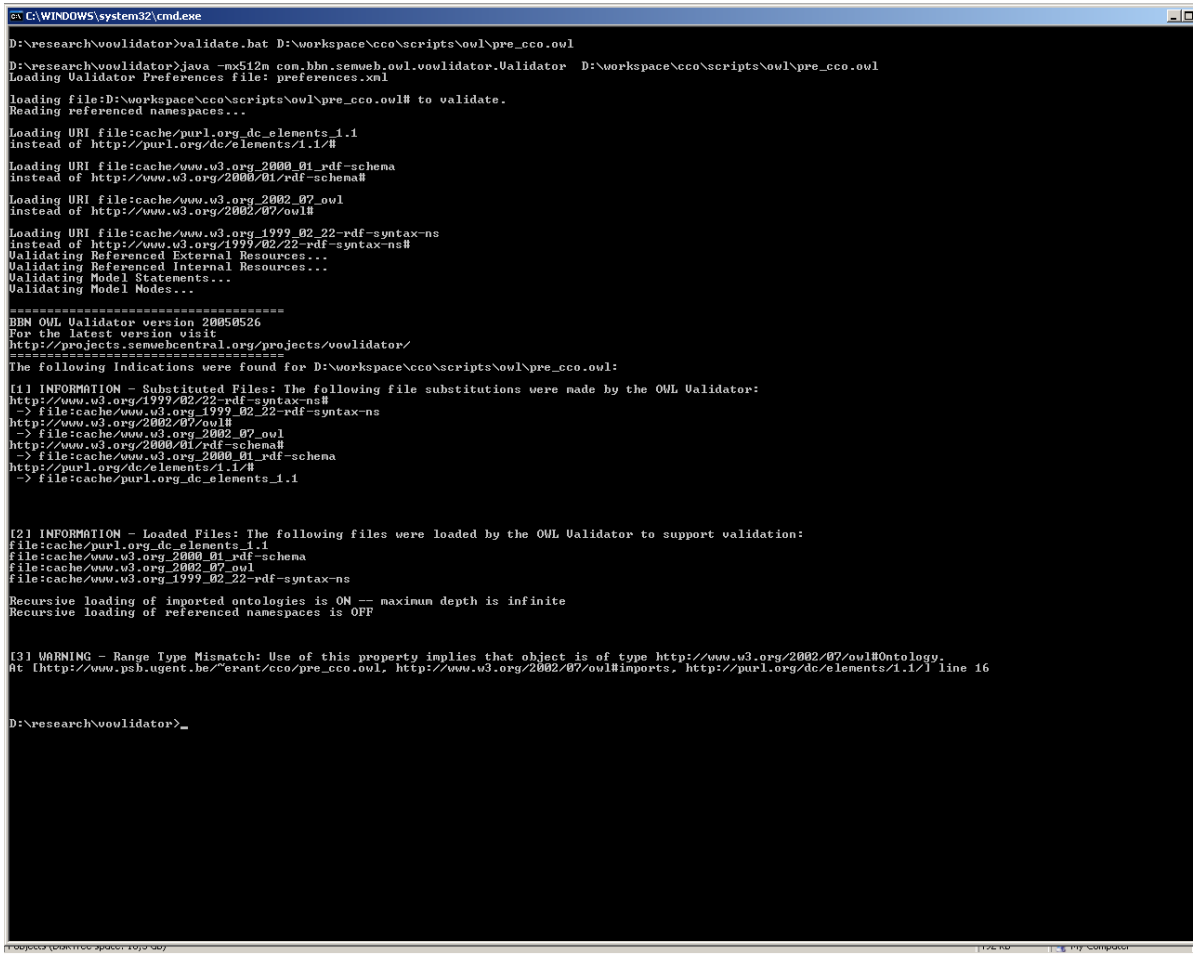
# Checked with…





**Protégé**: http://protege.stanford.edu/)

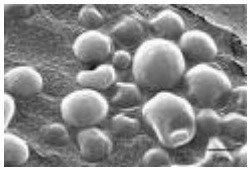
# and with…




**Vowlidator**: http://projects.semwebcentral.org/projects/vowlidator/)

# Availability

- At, Sc, Sp and Hu

- **CCO in OBO**: OBO-Edit
- **CCO in OWL**: Protégé, SWOOP, …
- Sourceforge: SVN (API)
- http://www.CellCycleOntology.org
- ***"A cell-cycle knowledge integration framework".*** Data Integration in Life Sciences, DILS 2006, LNBI 4075, pp. 19-34, 2006.
- Mailing list (low traffic):
  - **https://maillist.psb.ugent.be/mailman/listinfo/ccofriends**

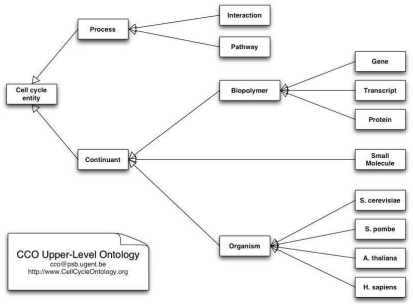
# Products

- API (Perl): OBO/OWL ontologies handling
- Exports:
  - OBO, OWL, DOT, GML, XGMML*, SBML*
- Conversion tools:
  - obo2owl
  - owl2obo*
- CCO explorer (online)
- Advanced query system*

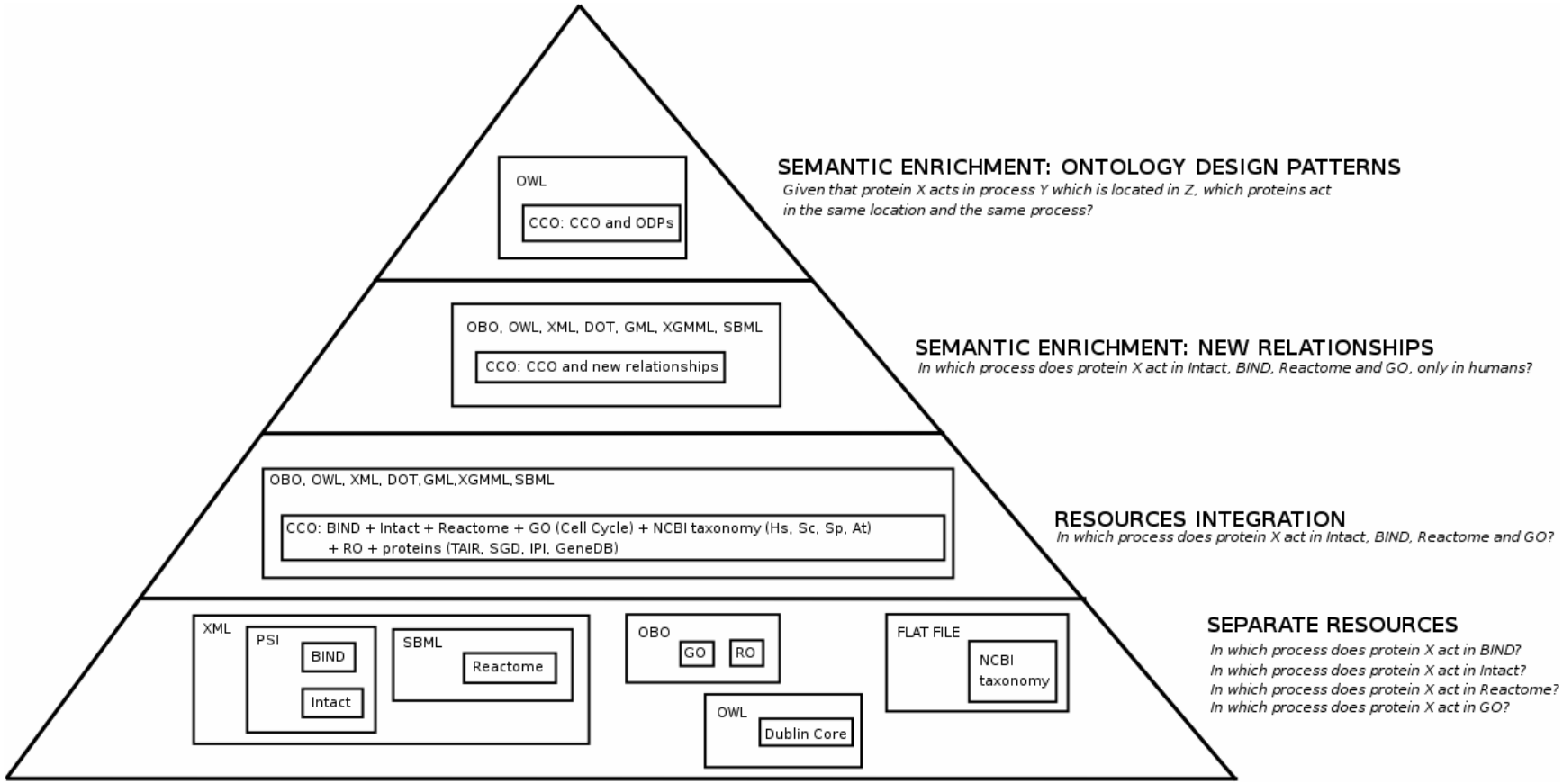
* Under development

# CCO Status

- #relationships = #RO + #CCO = 15 + 5 = 20
- #terms = 15 (ULO) + 306 (process branch) + 20 (xref, ref, etc)
  - #interactions = 194
  - #genes/proteins/transcripts = 1961
    - TAIR: 332
    - GeneDB_Spombe: 1064
    - GOA Human: 1354
    - SGD: 856



# Summary


OWL
CCO: CCO and ODPs
SEMANTIC ENRICHMENT: ONTOLOGY DESIGN PATTERNS
Given that protein X acts in process Y which is located in Z, which proteins act in the same location and the same process?
OBO, OWL, XML, DOT, GML, XGMML, SBML
CCO: CCO and new relationships
SEMANTIC ENRICHMENT: NEW RELATIONSHIPS
In which process does protein X act in Intact, BIND, Reactome and GO, only in humans?
OBO, OWL, XML, DOT, GML, XGMML, SBML
CCO: BIND + Intact + Reactome + GO (Cell Cycle) + NCBI taxonomy (Hs, Sc, Sp, At) + RO + proteins (TAIR, SGD, IPI, GeneDB)
RESOURCES INTEGRATION
In which process does protein X act in Intact, BIND, Reactome and GO?
XML
PSI
BIND
Intact
SBML
Reactome
OBO
GO
RO
OWL
Dublin Core
FLAT FILE
NCBI taxonomy
SEPARATE RESOURCES
In which process does protein X act in BIND?
In which process does protein X act in Intact?
In which process does protein X act in Reactome?
In which process does protein X act in GO?

# Conclusions

- Data integration pipeline prototype: life cycle of the KB
- Concrete problems and initial results: automatic format mappings and inconsistency checking issues
- Existing integration obstacles due to the diversity of data formats and lack of formalization approaches
- Common trade-offs in biological sciences

# Future developments

- Persistency: DB backend
- Ontology Design Patterns (U. Manchester)
- Weighted or scored knowledge: evidence codes expressing the support media similar to those implemented in GO (experimental, electronically inferred, and so forth) => Fuzzy relationships => More data...
- Advanced query system
- Web user interface
- The ultimate aim of the project is to support hypothesis evaluation about cell-cycle regulation issues.

# Acknowledgements


- Martin Kuiper (UGent/VIB)
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- Mikel Egaña (Manchester University)
- CBD group
- Users



http://www.CellCycleOntology.org