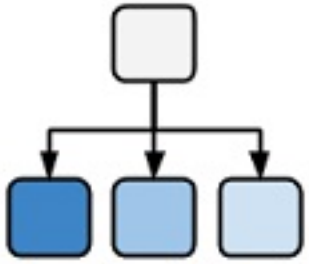
ONTOLOGIES



Michel Dumontier, Ph.D.

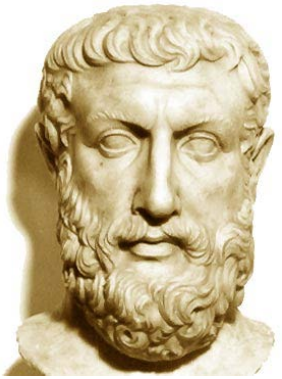
Associate Professor of Medicine (Biomedical Informatics)
Stanford University

Outline

- **What** and **why** of ontologies
- **Building and reasoning** over ontologies
- **Applications** in **biomedicine**

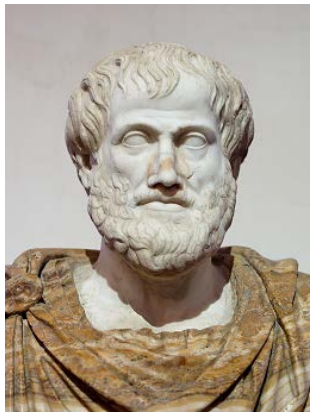
What is an ontology?

- Ontology stands for a ***logical discourse of existence***. It *aims to uncover and describe the nature and structure of things*.
- Predominantly the domain of philosophy known as ***metaphysics***, and associated with philosophers such as Plato (*forms*) and Aristotle (*empiricism*)
- Address **questions** such as
  - What does it mean *to be?*
  - What constitutes the *identity* of an object?
  - What *categories* can we sort existing things?
- Ontologies, when communicated to others, **foster a *shared* understanding of things.**



Greek philosopher Parmenides (515BC) proposed an ontological characterization of the fundamental nature of reality – akin to a grand unification theory

Early Bio-ontologists



Aristotle (384-322 BC)

- First systematic taxonomy of biology
- Classification of organisms by shared properties
- Used binomial *genus-differentia* nomenclature

Galen (130-210 AD)

- Systematic description of diseases, signs and symptoms.
- In *De Febrium Differentia* description of fever symptoms he uses the Aristotelian *genus-differentia* approach

genus–differentia definitions are *key* to good ontologies

A type of *intensional* definition - where necessary and sufficient conditions are specified - composed of two parts:

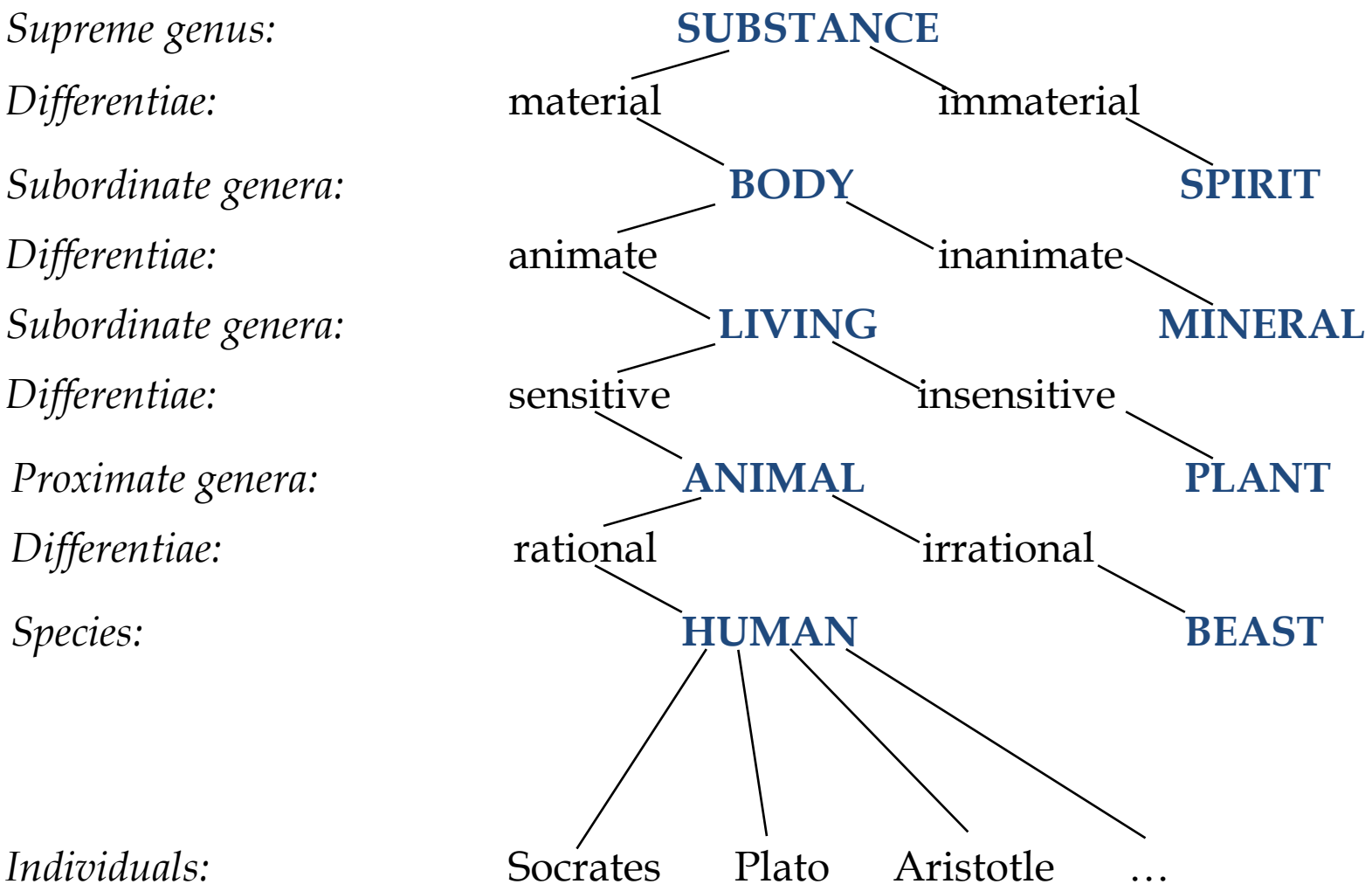
genus: Serves as the basis for a new definition; all definitions with the same genus are considered members of that genus.

differentia: The portion of the definition that is not provided by the genus.

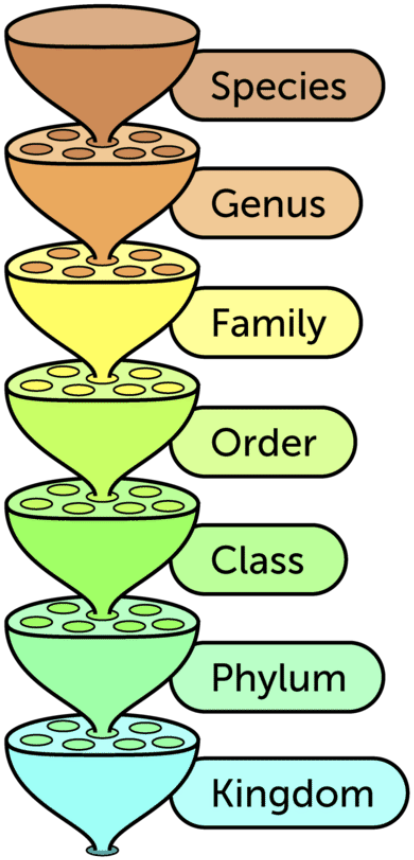
a **rhombus**: a **quadrilateral** that has bounding sides which all have the same length.

a **square**: a **rhombus** that has interior angles which are all right angles.

Porphyry's depiction of Aristotle's Categories



Biological Taxonomy



Rank: a classification Of taxonomic categories

Homo sapiens
Members of the genus Homo with a high forehead and thin skull bones.

Homo
Hominids with upright posture and large brains.

Hominids
Primates with relatively flat faces and three-dimensional vision.

Primates
Mammals with collar bones and grasping fingers.

Mammals
Chordates with fur or hair and milk glands.

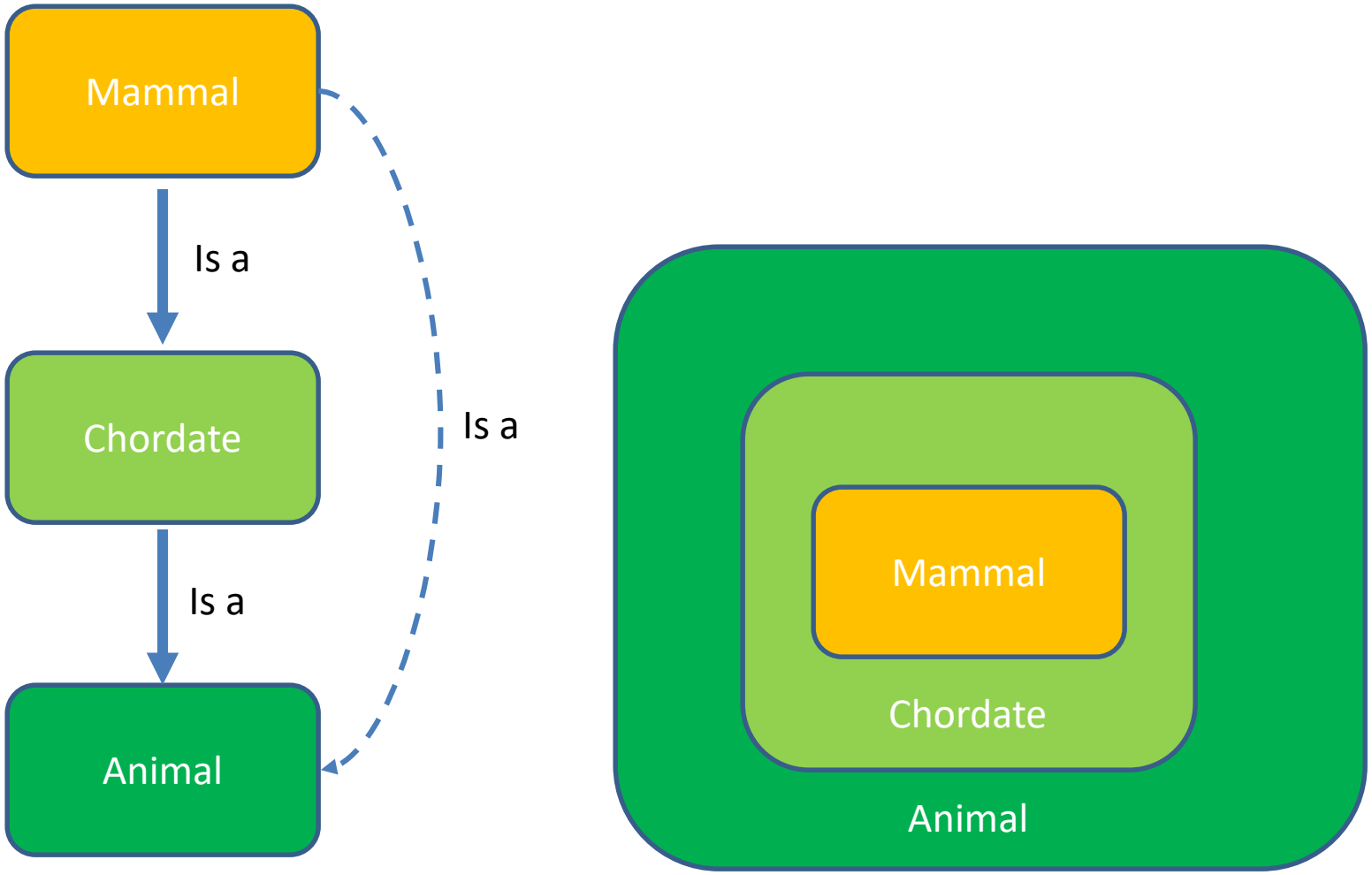
Chordates
Animals with a backbone.

Animals
Organisms able to move on their own.

Biological taxonomy: an is-a hierarchy of biological types

- A biological classification (taxonomy) by **Carl Linnaeus** in his Systema Naturae (1735)
- Three kingdoms, divided into classes, and they, in turn, into orders, families, genera, and species, with an additional rank lower than species.

Genus-differentia illustrates basic inference vis-à-vis the “is a” relationship



Development of an *increasingly* applied notion of ontology

An explicit specification of a conceptualization
- Thomas Robert Gruber, 1993 (inventor of Siri)

- A **conceptualization** is the way we think about a domain
- A **specification** provides a formal way of writing it down

*A **formal** specification of a **shared** conceptualization*
- Borst 1997

*An ontology specifies a **vocabulary** with which to make assertions, which may be inputs or outputs of knowledge agents (such as a software program). … **an ontology must be formulated in some representation language***
- Gruber (2007)

An ontology is defined by *axioms* in a **formal language** with the goal to provide an unbiased (domain- and application-independent) view on reality

How is an ontology different than a…

- **Folksonomy**
  - A collection of terms (tags) to enhance categorization.
- **Glossary**
  - List of terms with definitions and explanations in natural language
- **Controlled Vocabulary**
  - An enumeration of terms defined to be shared and reused.
- **Hierarchy**
  - A nested set of terms
- **Taxonomy**
  - A hierarchy that uses the “is a” relation.
- **Meronomy**
  - A hierarchy that uses the “part of” relation.
- **Classification**
  - A set of categories in which objects are grouped into

Why develop an ontology?

- To provide a **formal specification** of biomedical knowledge
- To provide a **classification** of biomedical entities
- To develop a **common understanding** of the entities in a given domain
- To enable **reuse** of **data** and **knowledge**
- To enable biomedical **discovery**

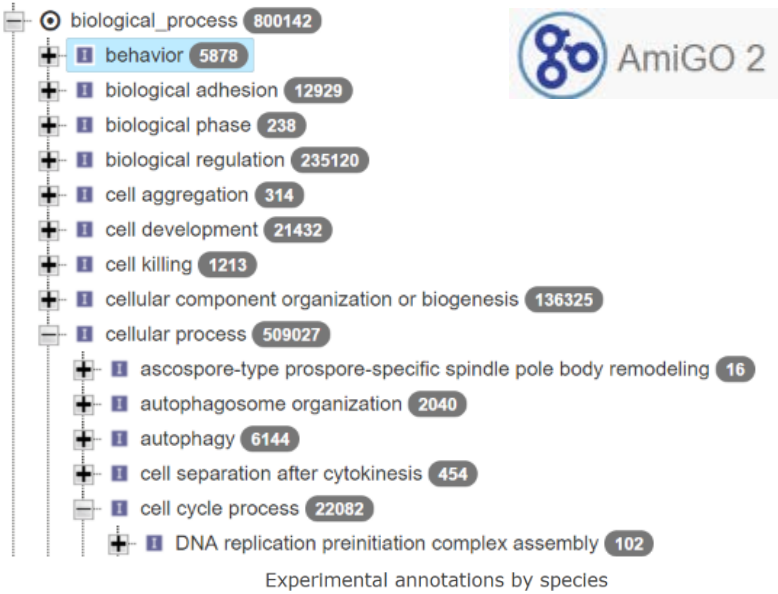
Gene Ontology

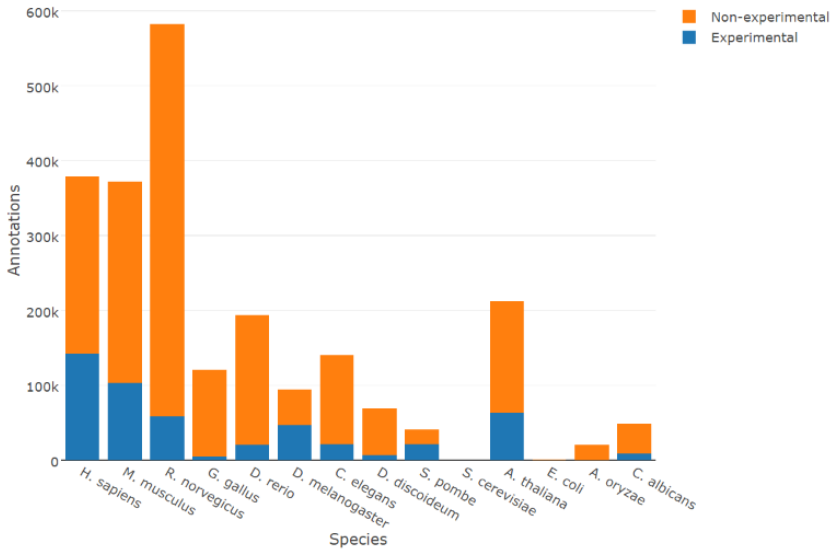
Arguably one of the most *successful* ontology projects in the life sciences.

Millions of annotations on hundreds of thousands of genes using GO terms.

The GO defines types used to describe gene function. It classifies functions along three aspects:

- **molecular function**
  - what gene products do
- **cellular component**
  - where gene products operate
- **biological process**
  - The pathways and processes that gene products participate in





UniProtKB - P34144 (RAC1A_DICDI)

Protein **Rho-related protein rac1A**

Gene **rac1A**

Organism *Dictyostelium discoideum (Slime mold)*

Status Reviewed - Annotation score: ●●●●● - Experimental evidence at protein level

Function

Overexpression promotes the formation of filopodia and membrane ruffles. 1 Publication

Manual assertion based on experiment in

"Rac1 GTPases control filopodia formation, cell motility, endocytosis, cytokinesis and development in Dictyostelium."
Dumontier M., Hoecht P., Mintert U., Faix J.
J. Cell Sci. 113:2253-2265(2000) [PubMed] [Europe PMC] [Abstract]
Cited for: INTERACTION WITH RGAA, FUNCTION.

Regions

Feature key	Position(s)	Length	Descrip
Nucleotide binding	10 – 17	8	GTP B
Nucleotide binding	57 – 61	5	GTP B
Nucleotide binding	115 – 118	4	GTP B

GO - Molecular function

- GTP binding Source: UniProtKB-KW
- protein kinase binding Source: dictyBase

GO - Biological process

- positive regulation of actin filament polymerization Source: dictyBase
- Rac protein signal transduction Source: dictyBase

Complete GO annotation...

Keywords - Ligand

GTP-binding, Nucleotide-binding

GO facilitates interoperability of function descriptions across species

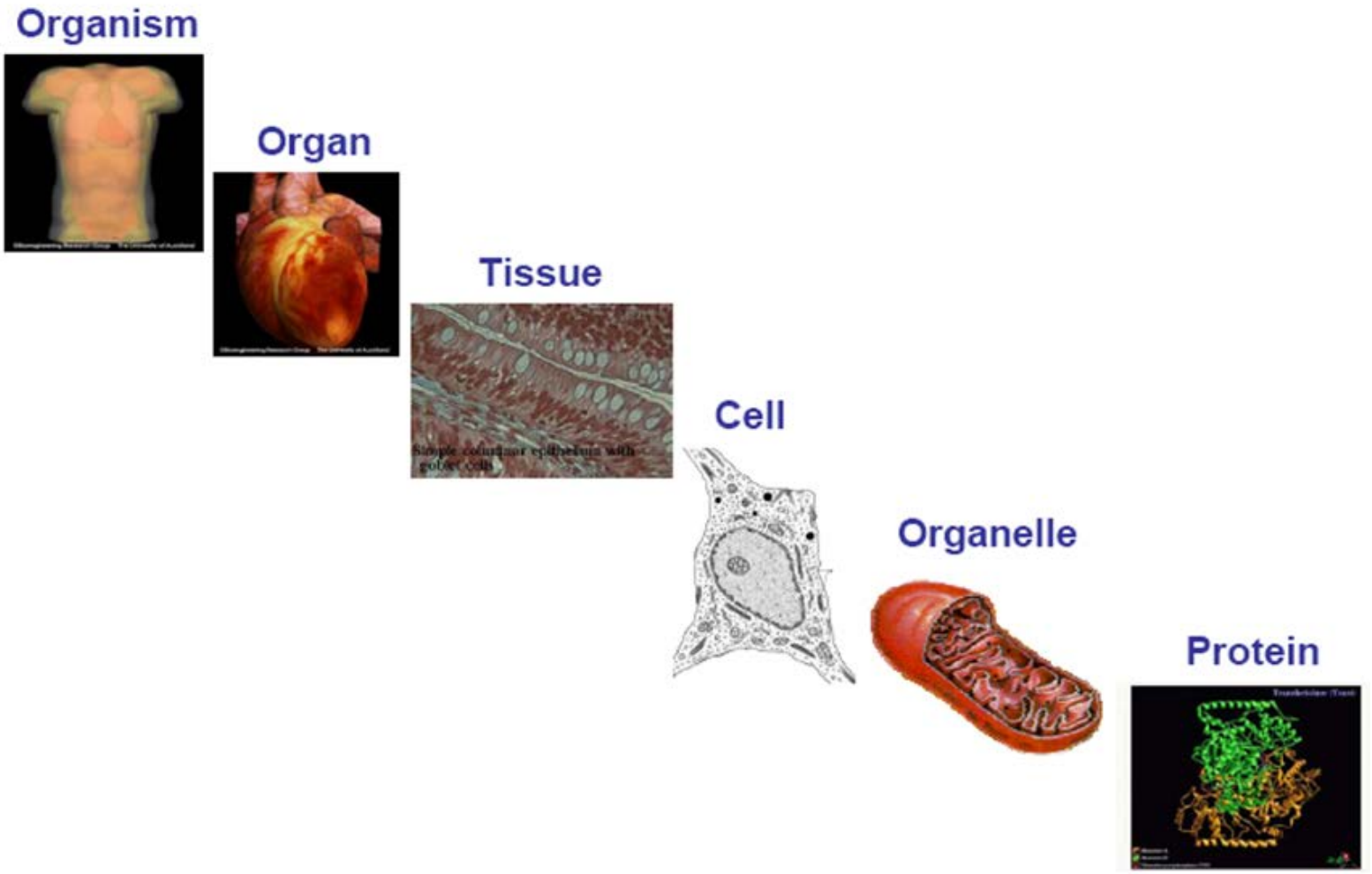
Term Information

Accession	GO:0005525
Name	GTP binding
Ontology	molecular_function
Synonyms	None
Alternate IDs	None
Definition	Interacting selectively and non-covalently with GTP, guanosine triphosphate. *Source:* GOC:ai
Comment	None
History	See term history for GO:0005525 at QuickGO
Subset	gosubset_prok
Related	Link to all **genes and gene products** annotated to GTP binding.
	Link to all direct and indirect **annotations** to GTP binding.
	Link to all direct and indirect **annotations download** (limited to first 10,000) for GTP binding.

Organism

(8780)	Eukaryota
(5564)	Metazoa
(4905)	Vertebrata
(3269)	Mammalia
(1661)	Fungi
(1268)	Danio rerio
(1013)	Rattus norvegicus
(848)	Viridiplantae
(590)	Bacteria
(569)	Mus musculus
(455)	Dictyostelium discoideum
(447)	Homo sapiens
(433)	Arabidopsis thaliana
(387)	Canis lupus familiaris
(376)	Bos taurus
(346)	Sus scrofa
(332)	Caenorhabditis elegans
(307)	Gallus gallus
(209)	Saccharomyces cerevisiae S288c
(165)	Drosophila melanogaster
(115)	Schizosaccharomyces pombe

Ontologies across scales



some disease and phenotype ontologies

- **Disease Ontology (DO)**
  - standardized ontology for human disease
  - Mapped to major terminologies, UMLS, MeSH, ICD10 etc.
  - 11,280 classes
- **Human Phenotype Ontology (HPO)**
  - phenotypic features encountered in human hereditary and other disease
  - 15,381 classes
- **Mammalian Phenotype Ontology (MP)**
  - Phenotypic features encountered in animal models
  - 12,805 classes
- **Experimental Factor ontology (EFO)**
  - application ontology
  - Imports classes from other phenotype and related ontologies (MIREOT)
  - 19,094 classes

- **Unified Medical Language System (UMLS)**
  - US National Library of Medicine
  - terminology, classification and coding standards
  - 8M normalized concepts
- **SNOMED-CT**
  - clinical terminology, diseases, diagnostics and procedures
  - 324,129 classes
- **NCI thesaurus**
  - vocabulary for clinical care, translational and basic research, and public information and administrative activities.
  - 118,941 classes
- **LOINC**
  - labs, vitals signs, clinical documents
  - 187,123 classes
- **ICD-10**
  - disease, epidemiology, billing
  - 12,450 classes

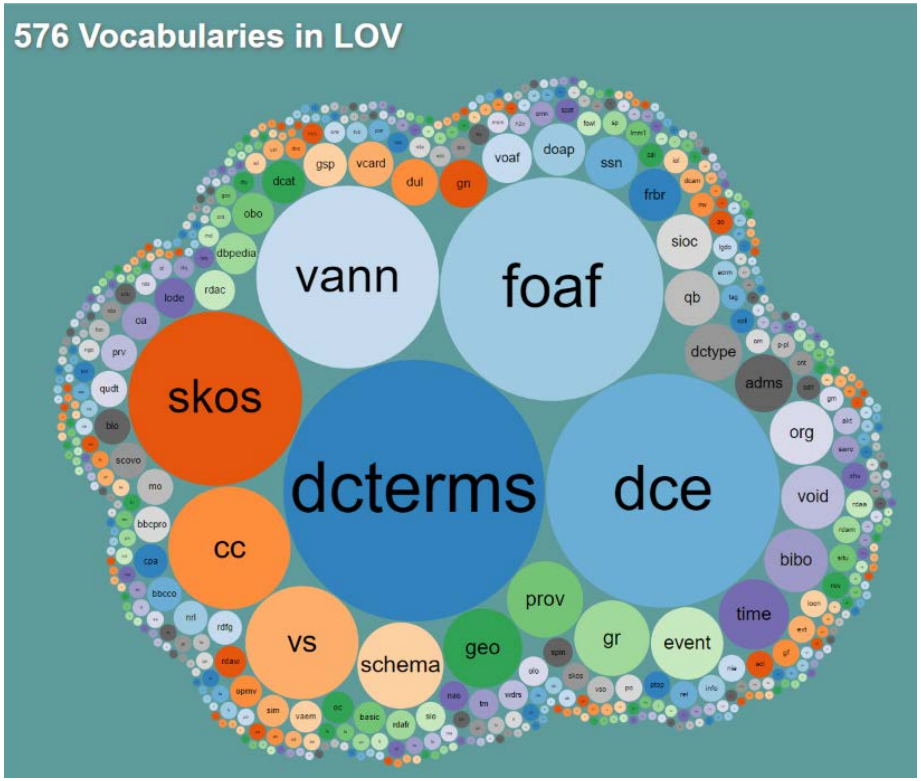
Where can we get ontologies?

BioPortal

Statistics

Ontologies	517
Classes	7,801,718
Resources Indexed	48
Indexed Records	39,359,542
Direct Annotations	95,468,433,792
Direct Plus Expanded Annotations	144,789,582,932

Linked Open Vocabularies (LOV)



Outline

- **What** and **why** of ontologies
- **Building and reasoning over ontologies**
- **Applications** in **biomedicine**

Formalization

- Formalization is the process by which we **map a conceptualization into a logical representation.**

- We *logically* combine the terms to form **expressions**, which have an *unambiguous* interpretation, and hence can be **automatically reasoned** about.

Logic-Based Ontologies
Can Be Constructed From *Concept and relation*
Lego

Description logics offer the building blocks for constructing *computable* ontologies

'transcription factor'
equivalentTo
'protein'
*that **'binds to'** some **DNA***
*and **'regulates'** some **'rate of transcription'***

molecule ontology

function ontology

Have you heard of OWL?

The Web Ontology Language (OWL) Has Explicit Semantics

It can be used to capture knowledge in a machine understandable way

OWL specifies a vocabulary and grammar to express more precisely what you mean

Enhanced vocabulary (strong axioms) to express knowledge relating to classes, properties, individuals and data values

- **Disjointness (sameAs, differnentFrom)**
- **Quantification (some, only, 0->n)**
  - existential, universal, cardinality restriction
- **Negation (not)**
- **Disjunction (or)**
- **property characteristics**
  - transitive, functional, inverse functional, symmetric, antisymmetric, reflexive, irreflexive
- **complex classes expressions** in domain and range restrictions
- **property chains**

Reasoning over OWL ontologies

- **Consistency:** determines whether the ontology contains **contradictions.**
- **Satisfiability**: determines whether classes can have **instances**.
- **Subsumption**: are **all instances** of one class **also instances** of another class?
- **Classification**: ***repetitive*** application of **subsumption** to discover implicit subclass links between named classes
- **Realization**: find the most **specific** class that an individual belongs to.

protégé

Protégé's plug-in architecture can be adapted to build both simple and complex ontology-based applications. Developers can integrate the output of Protégé with rule systems or other problem solvers to construct a wide range of intelligent systems. Most important, the Stanford team and the vast Protégé community are here to help.

ACTIVE COMMUNITY

Protégé is actively supported by a strong community of users and developers that field questions, write documentation, and contribute plug-ins.

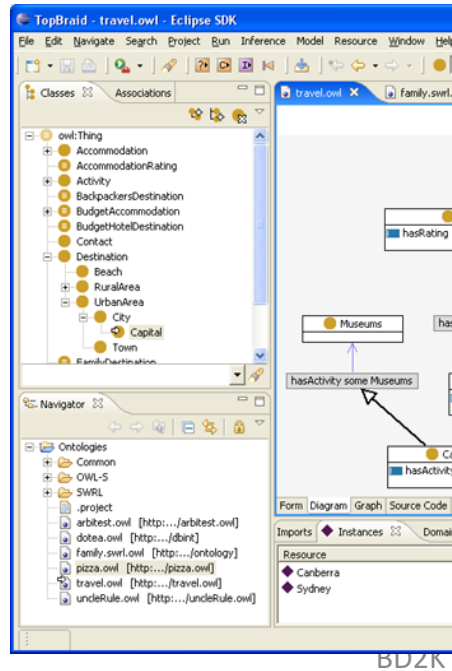
W3C STANDARDS SUPPORT

Protégé fully supports the latest OWL 2 Web Ontology Language and RDF specifications from the World Wide Web Consortium.

EXTENSIBLE OPEN SOURCE ENVIRONMENT

Protégé is based on Java, is extensible, and provides a plug-and-play environment that makes it a flexible base for rapid prototyping and application development.

DOWNLOAD NOW USE WEBPROTÉGÉ



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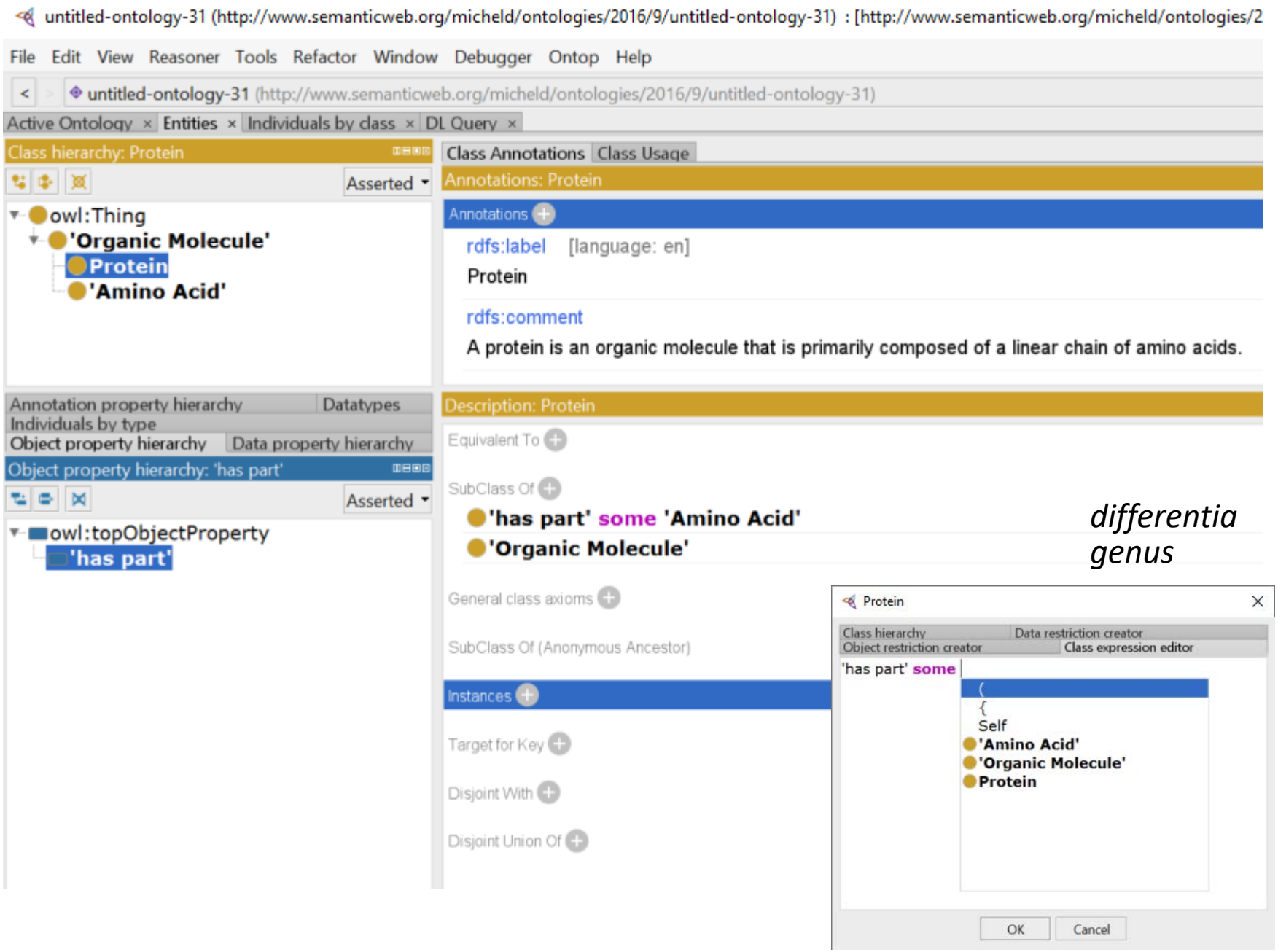
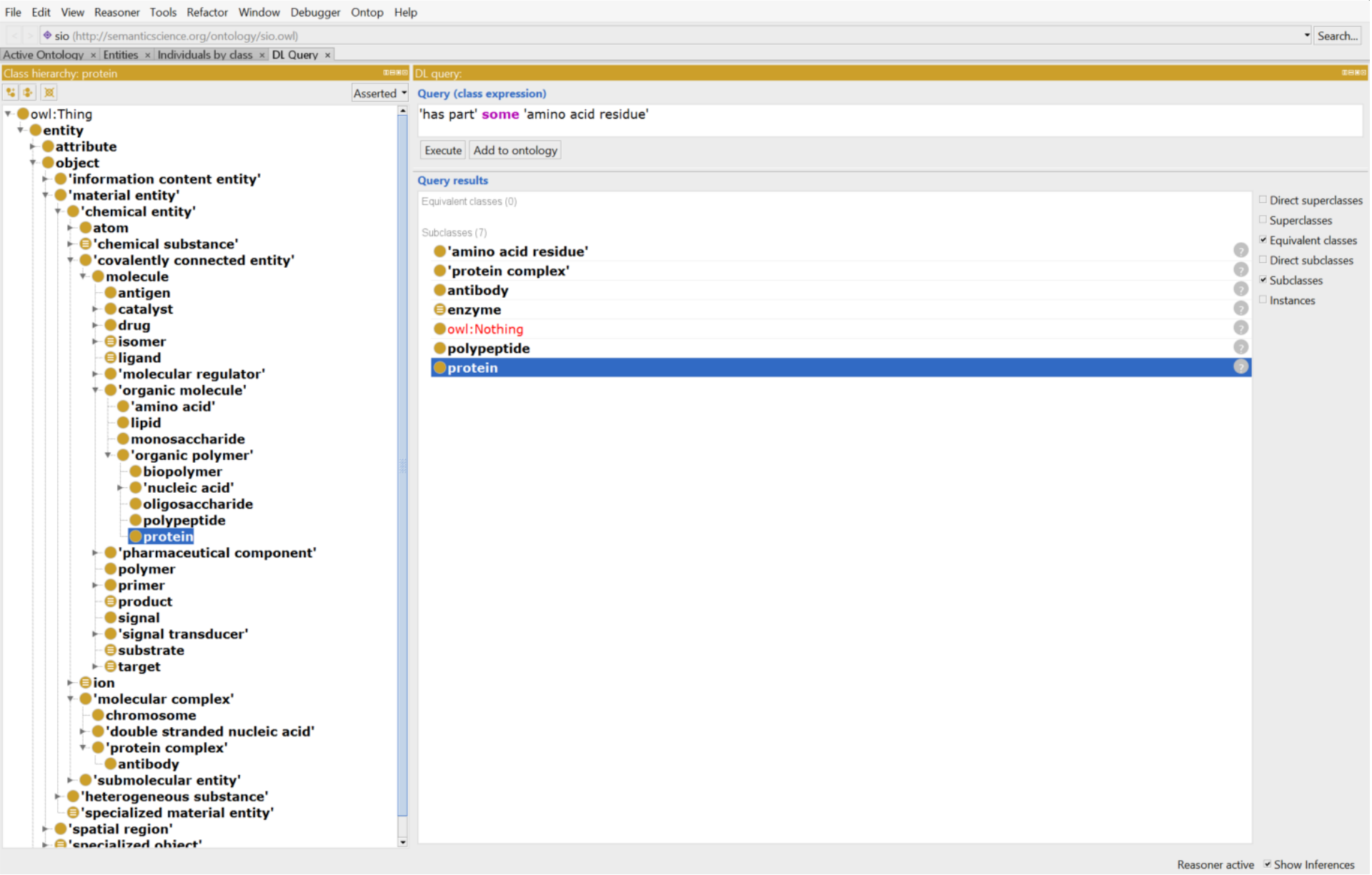

untitled-ontology-31 (http://www.semanticweb.org/micheld/ontologies/2016/9/untitled-ontology-31) : [http://www.semanticweb.org/micheld/ontologies/2
File Edit View Reasoner Tools Refactor Window Debugger Ontop Help
untitled-ontology-31 (http://www.semanticweb.org/micheld/ontologies/2016/9/untitled-ontology-31)
Active Ontology × Entities × Individuals by class × DL Query ×
Class hierarchy: Protein
Asserted
owl:Thing
'Organic Molecule'
Protein
'Amino Acid'
Class Annotations Class Usage
Annotations: Protein
Annotations
rdfs:label [language: en]
Protein
rdfs:comment
A protein is an organic molecule that is primarily composed of a linear chain of amino acids.
Annotation property hierarchy Datatypes
Individuals by type
Object property hierarchy Data property hierarchy
Object property hierarchy: 'has part'
Asserted
owl:topObjectProperty
'has part'
Description: Protein
Equivalent To
SubClass Of
'has part' some 'Amino Acid'
'Organic Molecule'
differentia
genus
General class axioms
SubClass Of (Anonymous Ancestor)
Instances
Target for Key
Disjoint With
Disjoint Union Of
Protein
Class hierarchy Data restriction creator
Object restriction creator Class expression editor
'has part' some
(
{
Self
'Amino Acid'
'Organic Molecule'
Protein
OK
Cancel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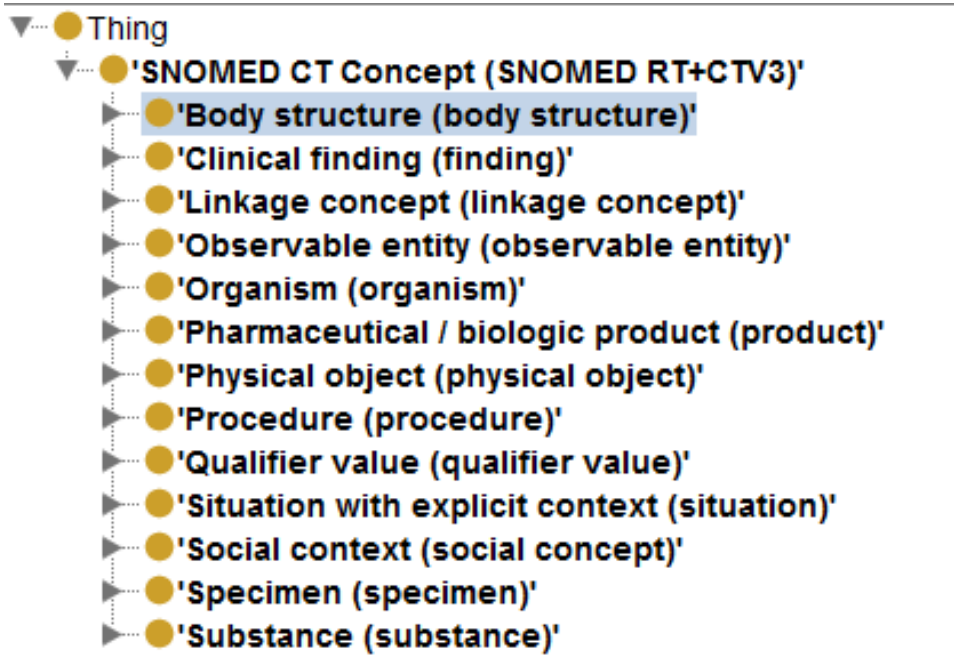
sio (http://semanticscience.org/ontology/sio.owl)
Search...
Active Ontology × Entities × Individuals by class × DL Query ×
Class hierarchy: protein
Asserted
owl:Thing
entity
attribute
object
'information content entity'
'material entity'
'chemical entity'
atom
'chemical substance'
'covalently connected entity'
molecule
antigen
catalyst
drug
isomer
ligand
'molecular regulator'
'organic molecule'
'amino acid'
lipid
monosaccharide
'organic polymer'
biopolymer
'nucleic acid'
oligosaccharide
polypeptide
protein
'pharmaceutical component'
polymer
primer
product
signal
'signal transducer'
substrate
target
ion
'molecular complex'
chromosome
'double stranded nucleic acid'
'protein complex'
antibody
'submolecular entity'
'heterogeneous substance'
'specialized material entity'
'spatial region'
DL query:
Query (class expression)
'has part' some 'amino acid residue'
Execute
Add to ontology
Query results
Equivalent classes (0)
Subclasses (7)
'amino acid residue'
'protein complex'
antibody
enzyme
owl:Nothing
polypeptide
protein
Direct superclasses
Superclasses
Equivalent classes
Direct subclasses
Subclasses
Instances
Reasoner active
Show Inferences

Outline

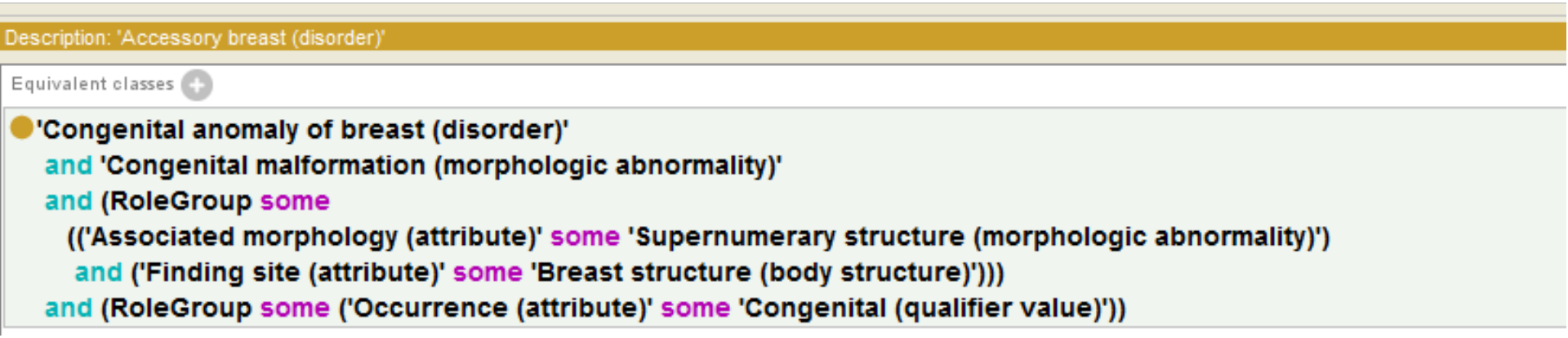
- **What** are ontologies and **why** are they useful?
- **Building and reasoning** over ontologies
- **Applications** in **biomedicine**

SNOMED-CT

- SNOMED-CT (Clinical Terms) ontology
- used in healthcare systems of more than 15 countries, including Australia, Canada, Denmark, Spain, Sweden and the UK
- used by major US providers
- ontology provides common vocabulary for recording clinical data
- 324,129 classes



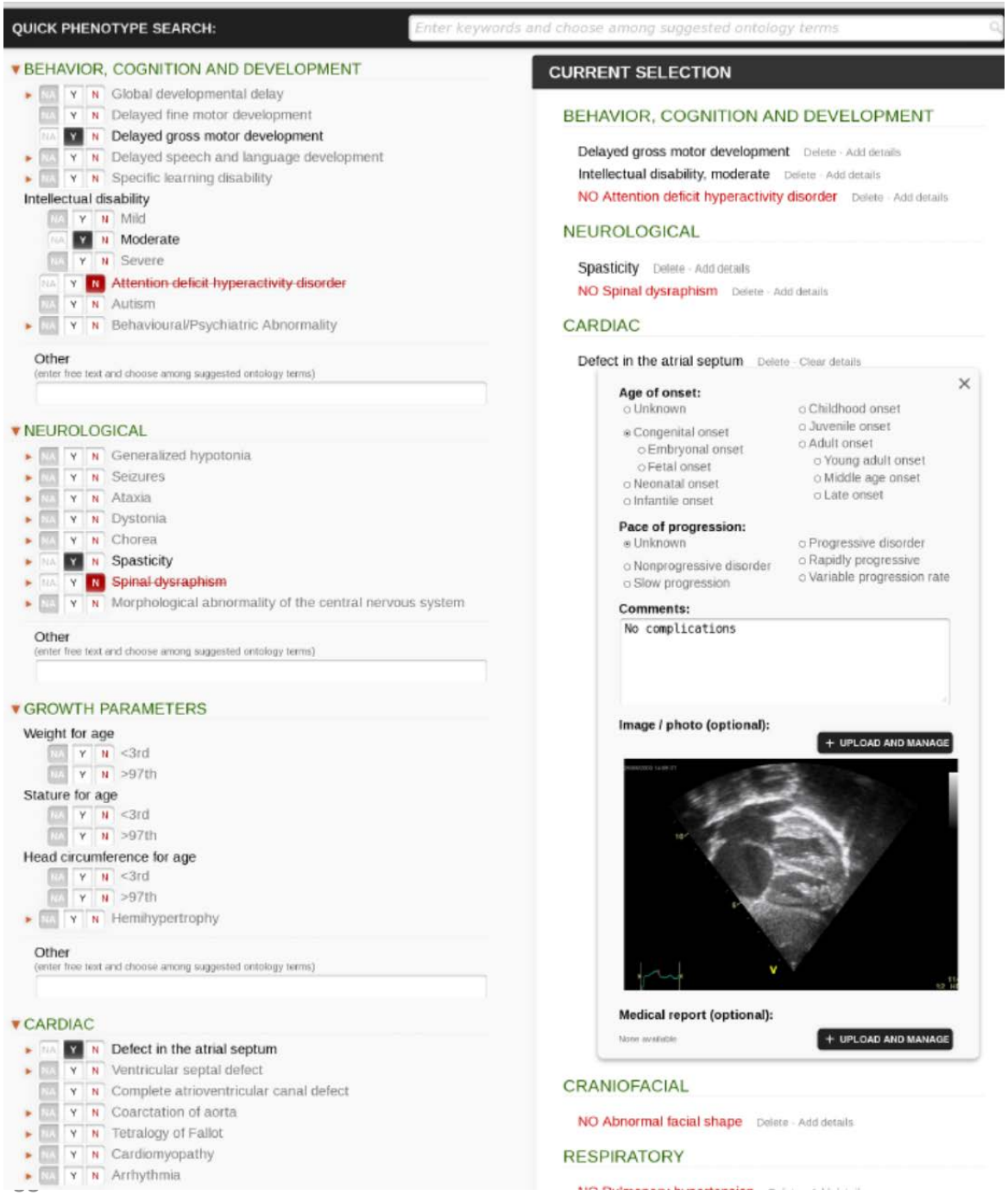
SNOMED-CT



- Pattern based knowledge capture
- Requires some training and an information system to implement

SNOMED - Verification

- **Kaiser Permanente** extended SNOMED to express, e.g.:
  - *non-viral pneumonia* (**negation**)
  - *infectious pneumonia* is caused by a *virus* or a *bacterium* (**disjunction**)
  - *double pneumonia* occurs in two *lungs* (**cardinalities**)
- This is easy in **SNOMED-OWL**
  - but reasoner failed to find expected **subsumptions**, e.g., that *bacterial pneumonia* is a kind of *non-viral pneumonia*
- Ontology **under-constrained**: need to add **disjointness** axioms
  - *virus* and *bacterium* must be disjoint
- Adding **disjointness** led to **surprising results**
  - many classes become inconsistent, e.g., *percutanious embolization of hepatic artery using fluoroscopy guidance*
- Cause of **inconsistencies** identified in the class *groin*
  - *groin* asserted to be subclass of both *abdomen* and *leg*
  - *abdomen and leg* are disjoint
  - modelling of *groin* (and other similar "junction" regions) identified as incorrect

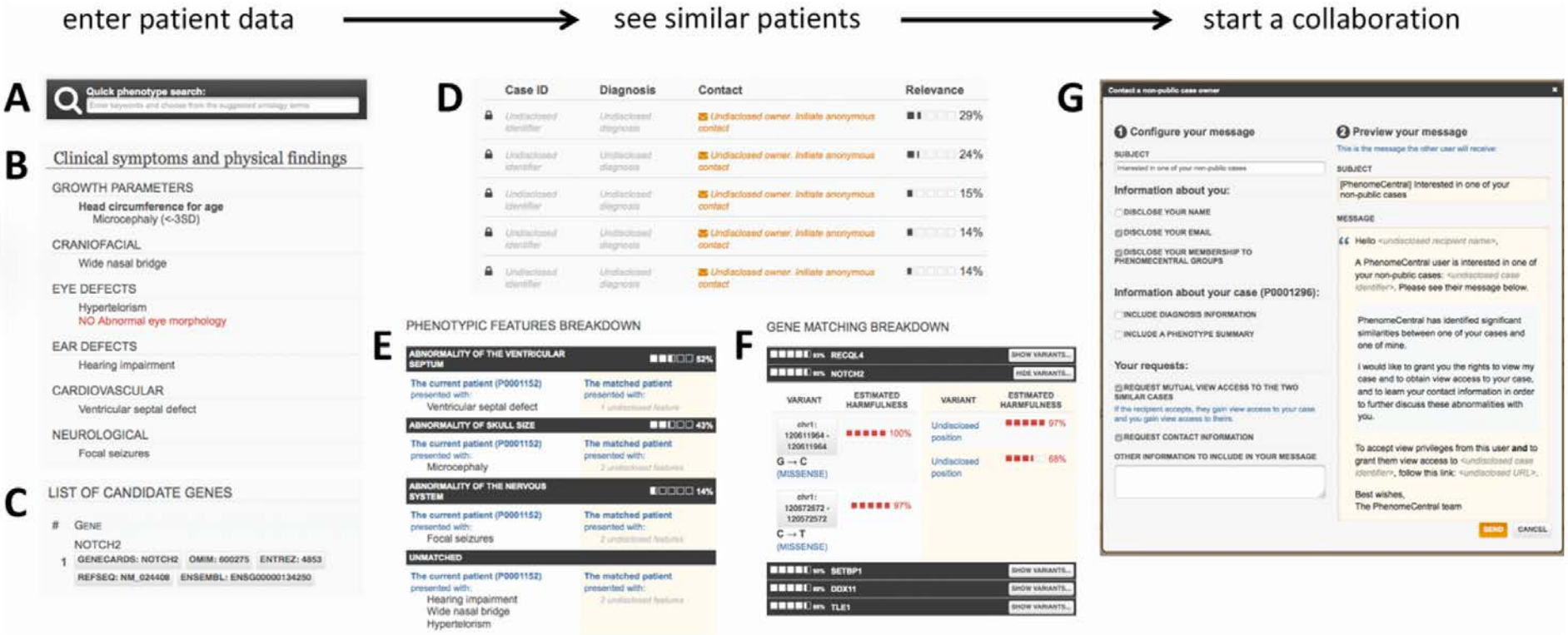


Phenotips

- Using controlled vocabulary (human phenotype ontology) for phenotyping
- Can collect demographics, medical history, family history, labs, findings

Girdea et al. (2013). Hum. Mutat., 34: 1057–1065. doi: 10.1002/humu.22347

PhenomeCentral: A Portal for Phenotypic and Genotypic Matchmaking of Patients with Rare Genetic Diseases

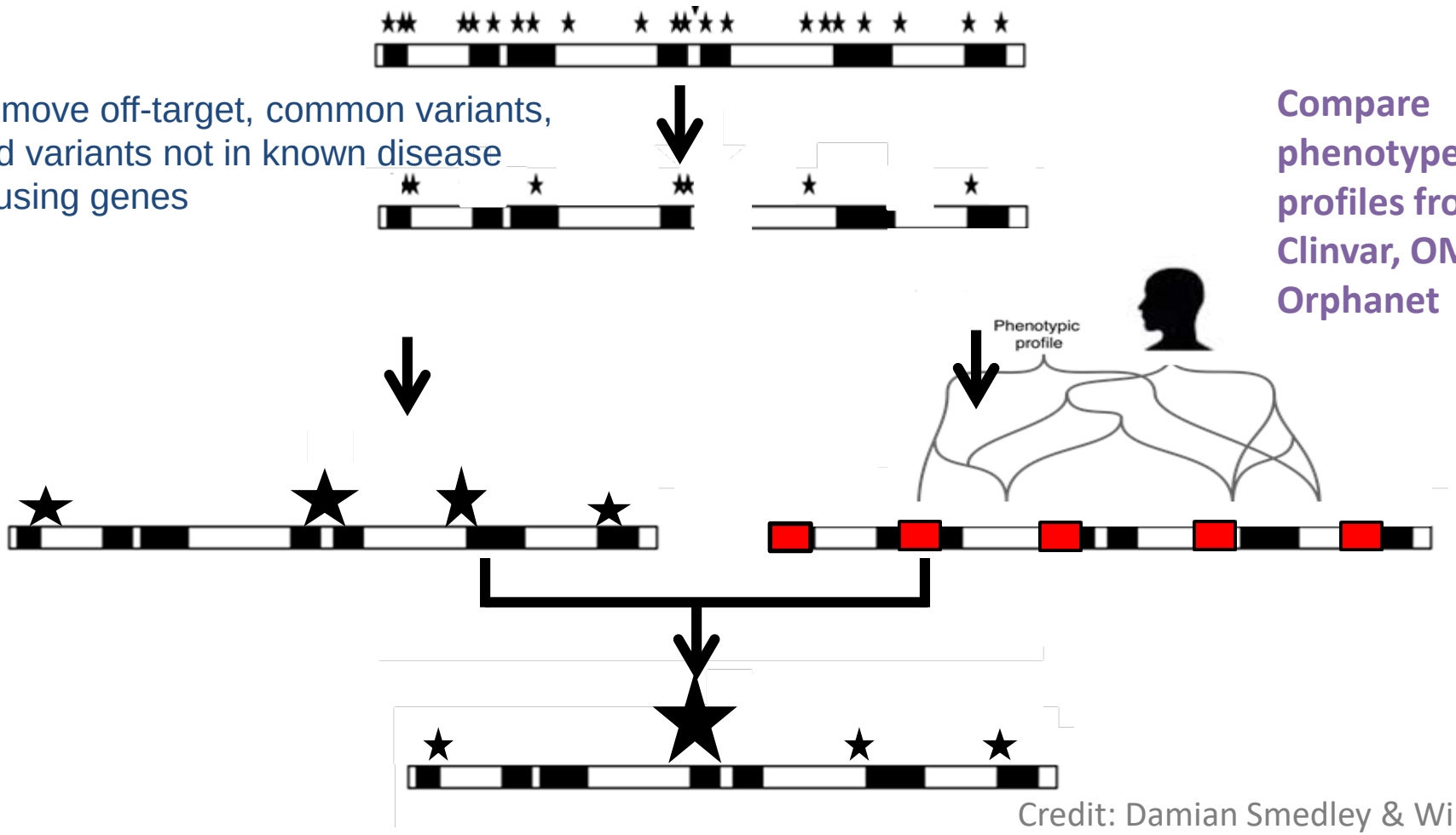


Human Mutation
Volume 36, Issue 10, pages 931-940, 31 AUG 2015 DOI: 10.1002/humu.22851
http://onlinelibrary.wiley.com/doi/10.1002/humu.22851/full#humu22851-fig-0001

Ontology-Aided Rare Disease Diagnosis

Remove off-target, common variants, and variants not in known disease causing genes

Compare phenotype profiles from: Clinvar, OMIM, Orphanet



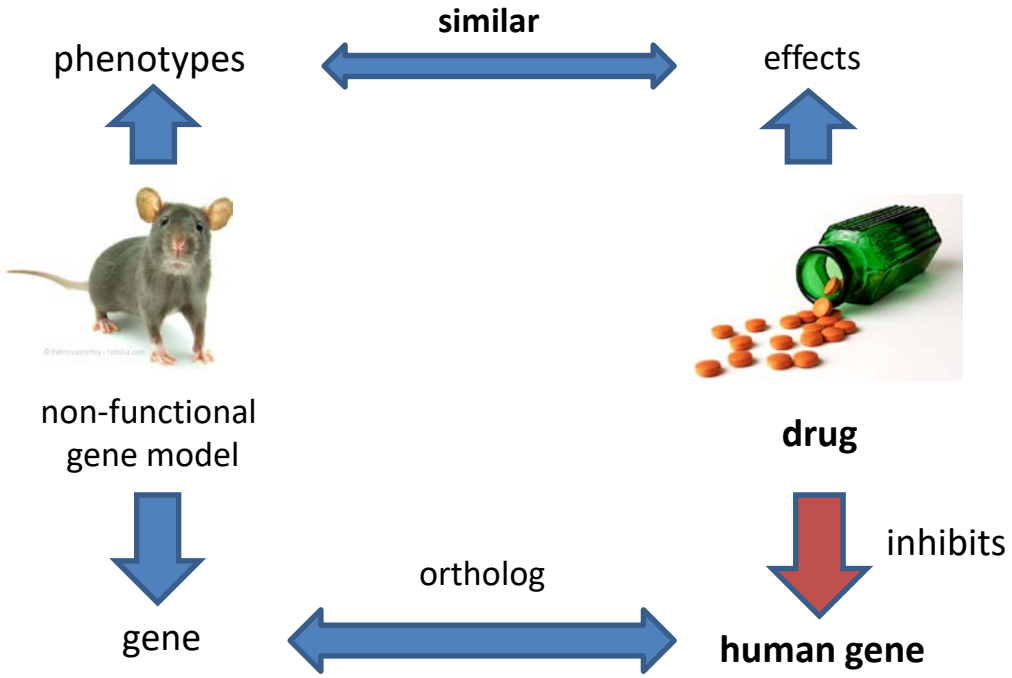
Credit: Damian Smedley & Will Bone

Zemojtel et al. Sci Transl Med. 2014. 6(252):252ra123

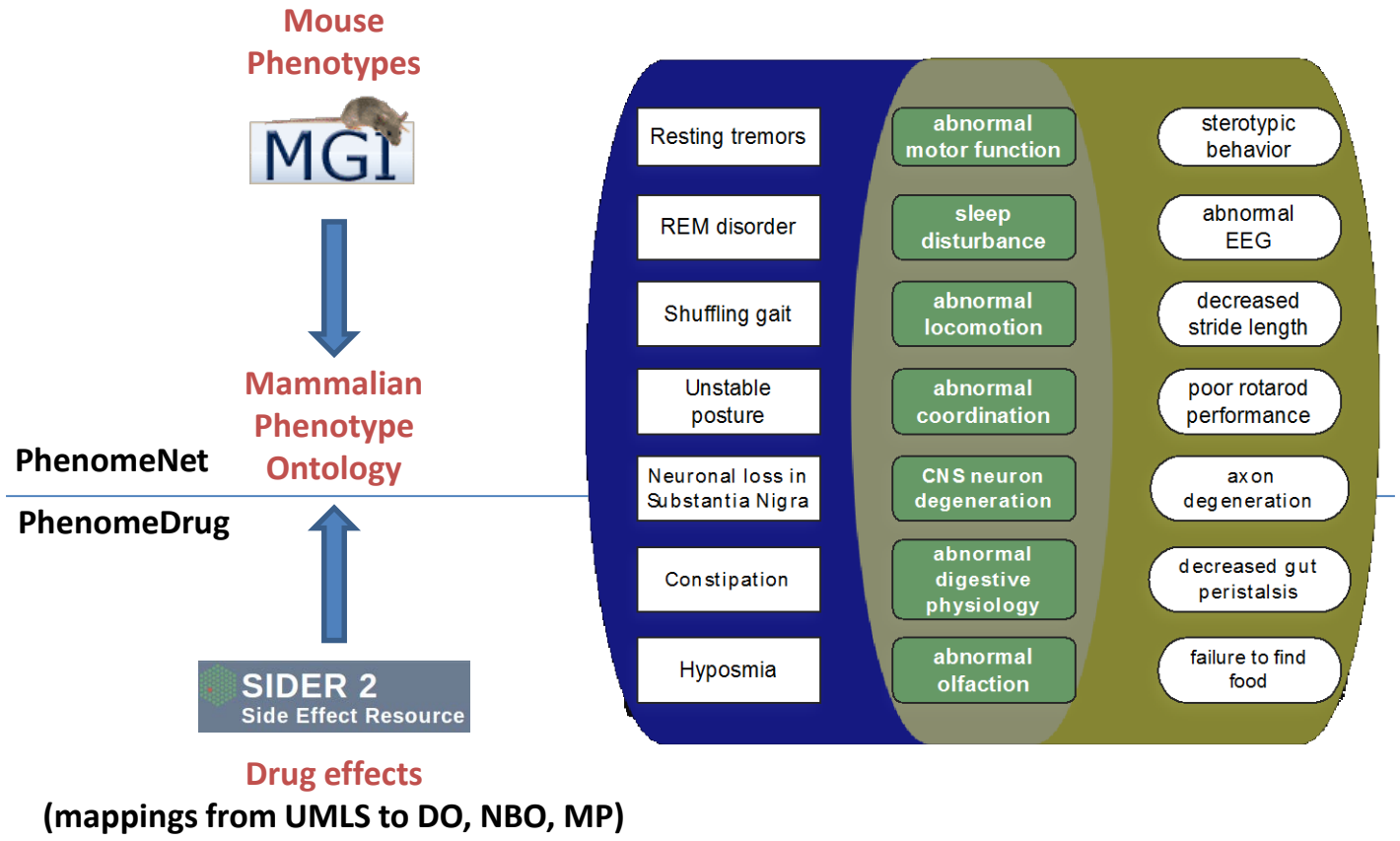
http://compbio.charite.de/PhenIX/

Identifying drug targets from mouse knock-out phenotypes

Main idea: we compare the phenotypes of knockout mouse models with the effects of drugs. When similar, we hypothesize that the drug acts as an inhibitor of the gene, thereby mimicking its phenotypic effect.



We use *mappings* to establish equivalences between human and mammalian phenotype ontologies



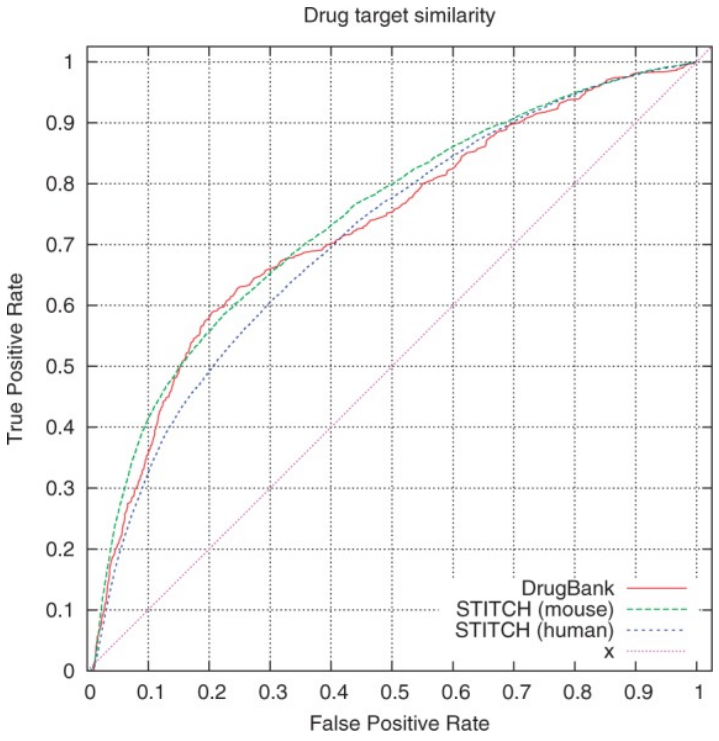
We use measures of semantic similarity to compare drugs to models

Given a drug effect profile D and a mouse model M, we compute the semantic similarity as an information weighted Jaccard metric.

$$sim(D,M) = \frac{\sum_{x \in Cl(D) \cap Cl(M)} IC(x)}{\sum_{y \in Cl(D)} IC(y)}$$

The similarity measure used is non-symmetrical and determines the amount of information about a drug effect profile D that is covered by a set of mouse model phenotypes M.

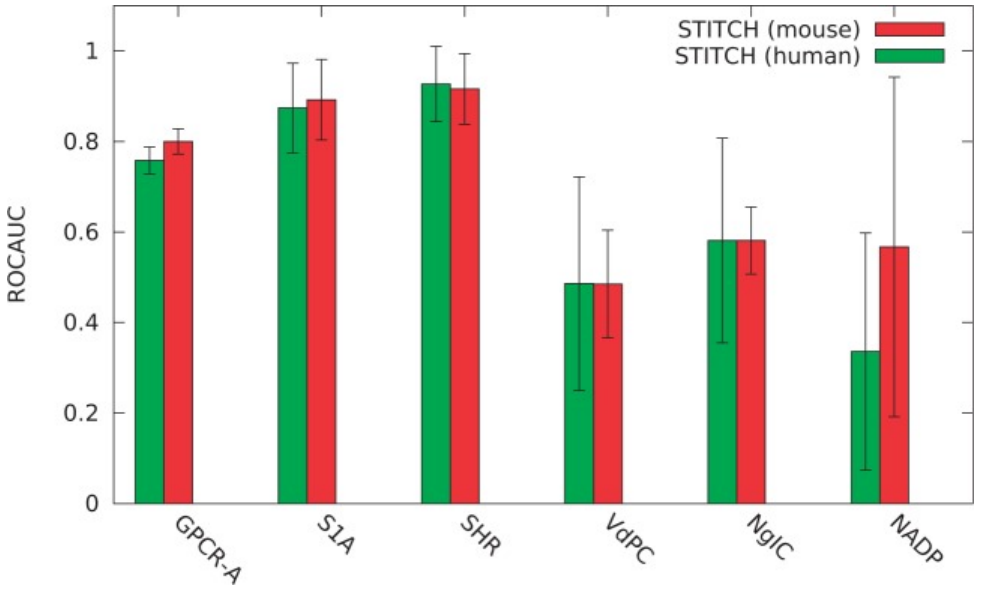
We find that phenotypic information alone can recover known drug targets (and predict new ones)



14,682 drugs; 7,255 mouse genotypes

Validation against known and predicted inhibitor-target pairs

- 0.82 ROC AUC for mouse targets (STITCH)
- 0.76 ROC AUC for human targets (STITCH)
- 0.72 ROC AUC for human targets (DrugBank)



Loss of function models provide information about the targets of inhibitor drugs

Diclofenac

- NSAID used to treat pain, osteoarthritis and rheumatoid arthritis
  - 46% drug effects explained by COX-2 knockout
    - inflammation, gastritis, constipation, upper GI tract pain
  - 49% drug effects explained by PPARg knockout
    - peroxisome proliferator activated receptor gamma (PPARg) regulates metabolism, proliferation, inflammation and differentiation,

Bioinformatics, 2013. doi:10.1093/bioinformatics/btt613

Summary

- Ontologies have a **rich history** in philosophy that has evolved to **modular and computable representation of human knowledge**
- **Description logics** (e.g. OWL) are the current favored formalism to build and test ontologies.
- Ontologies have a **variety of uses** from the answering questions to enabling sophisticated knowledge discovery.

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