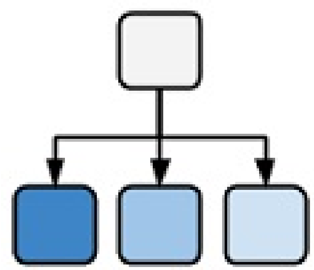
ONTOLOGIES
IN COMPUTATIONAL BIOLOGY



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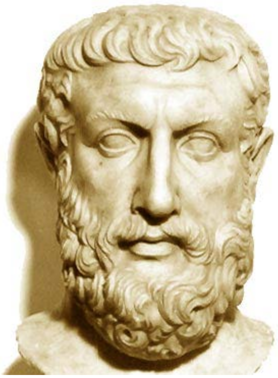
Director, Institute of Data Science
Maastricht University

Outline

- **What** are ontologies?
- **Why** are they important?
- **Reasoning** with 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 existence*.
- Predominantly the domain of philosophy known as ***metaphysics***
- Address **questions** such as
  - What does it mean *to be?*
  - What constitutes the *identity* of an object?
  - What *categories* of things exist?
- Ontologies, when communicated to others, **foster a *shared* understanding of things.**

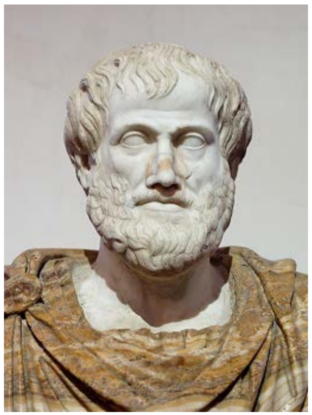


Greek philosopher Parmenides (515BC) proposed an ontological characterization of the fundamental nature of reality – akin to a grand unification theory

Why are ontologies important?

- To foster a **shared understanding** of entities, their attributes, and the relationships they hold
- To develop a **computer-accessible descriptions** of the entities and their relationships
- To enable **discovery, exchange, and reuse** of **data** and **knowledge**

Early 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 one way to specify ontologies

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

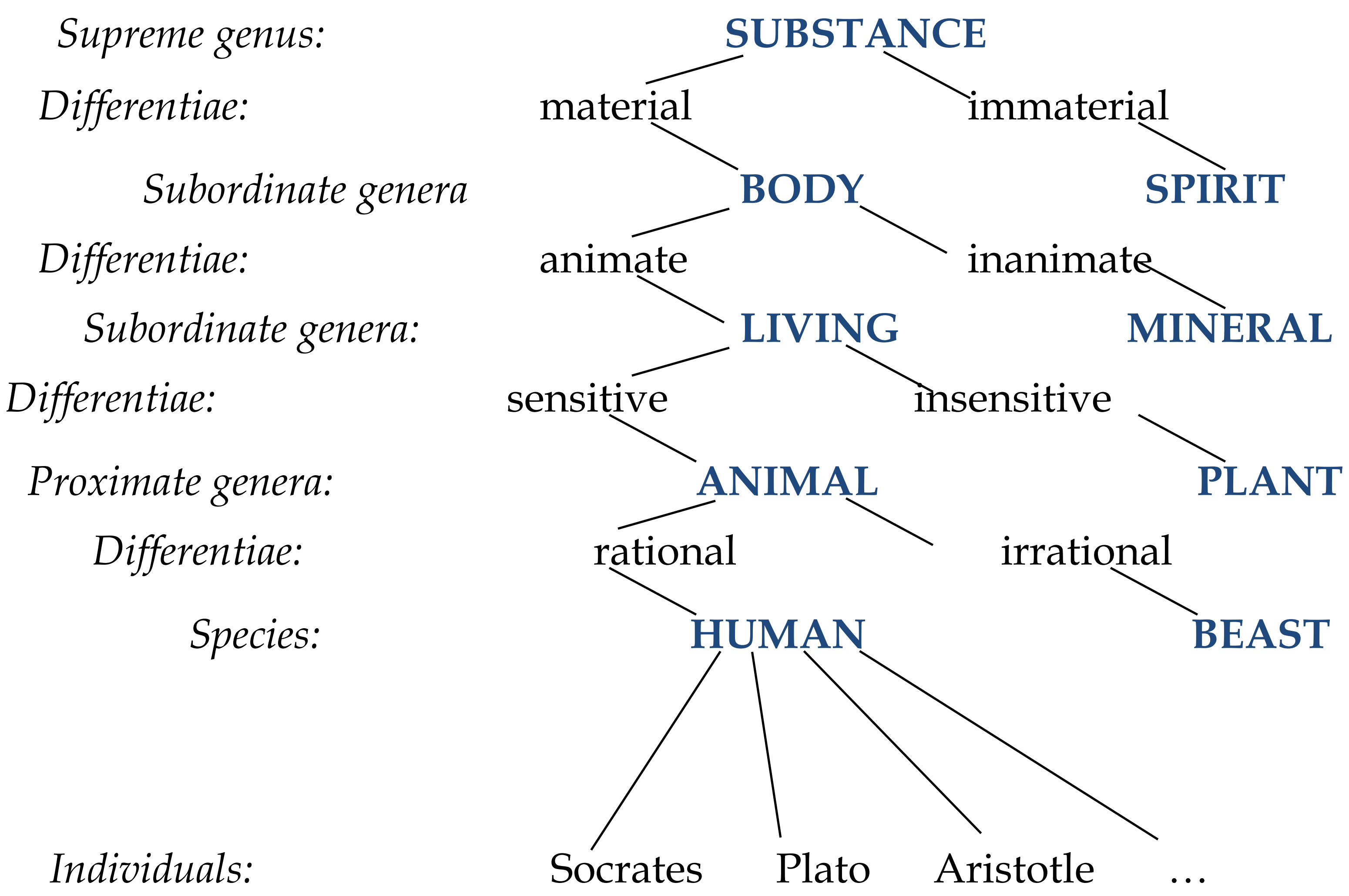
genus: Serves as the basis for a new definition; all definitions with the same genus are considered members of that genus.

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

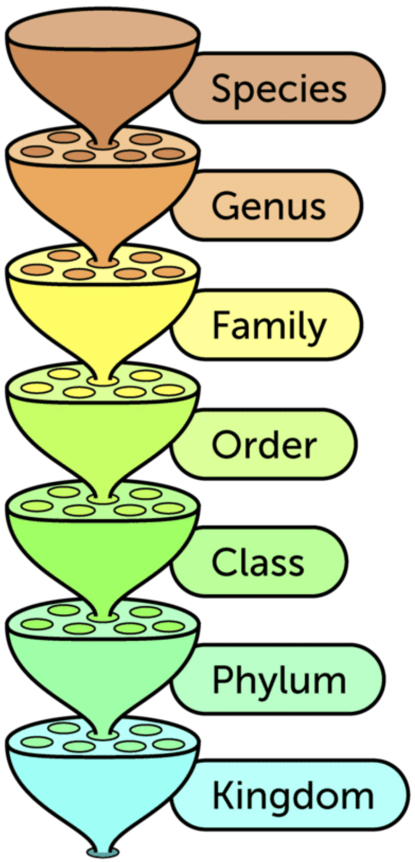
a **rhombus**: a **quadrilateral** that has bounding sides which all have the same length.

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

Porphyry's depiction of Aristotle's Categories



Biological Taxonomy



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.

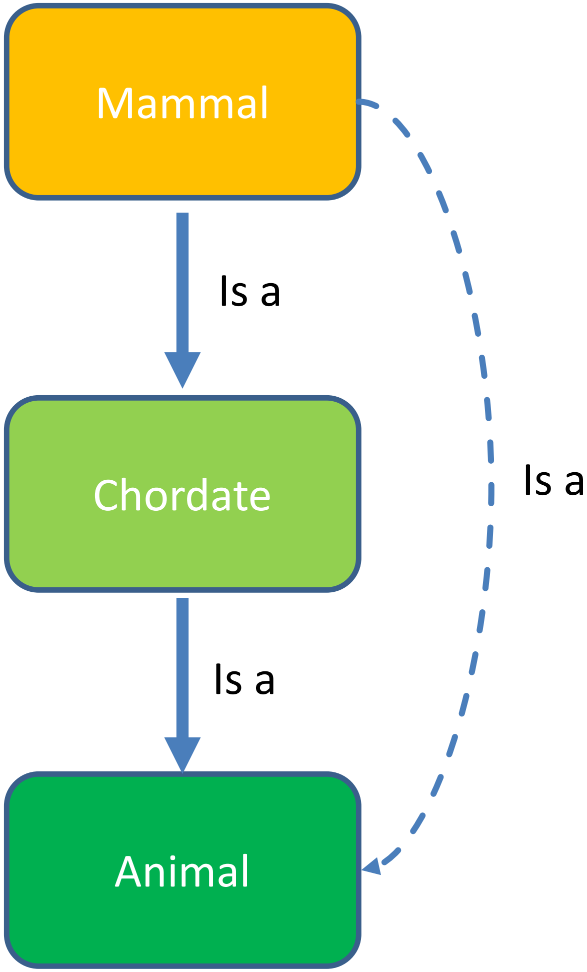
Animals
Organisms able to move on their own.

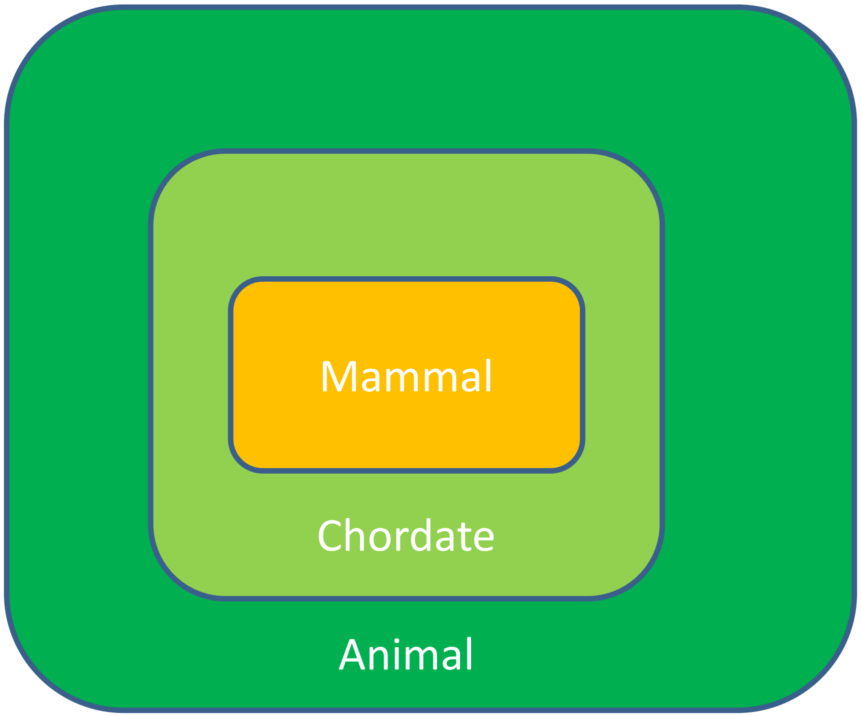
Rank: a classification
Of taxonomic categories

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 "system of categories accounting for a particular view on the world", i.e., a philosophical ontology)
- A **specification** provides a formal way of writing it down (and making it accessible to humans **and** machines)

*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 a hierarchy

Question

What is true about an **ontology** or a **classification**?

a) A classification focuses on grouping together relevant terms

b) A classification does not require a formal representation of the classes

c) An ontology is a formal representation that aims to accurately describe entities, their attributes, and their relationships

d) All of the above

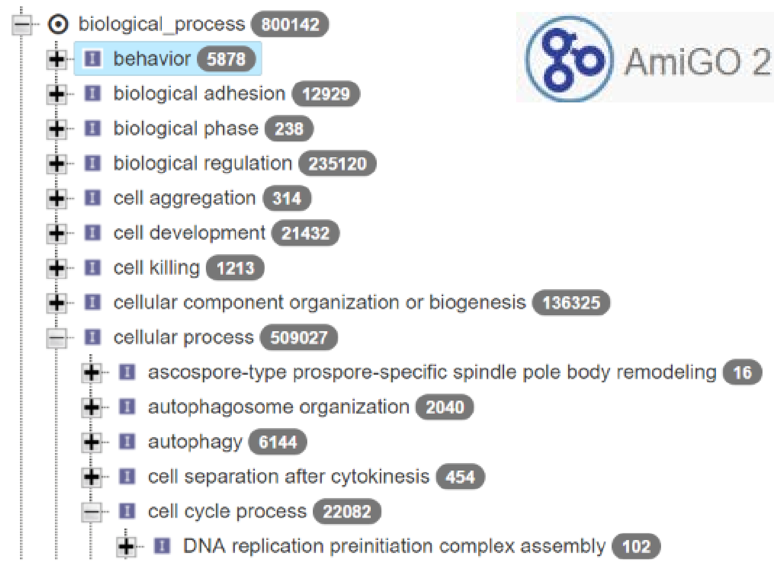
Gene Ontology

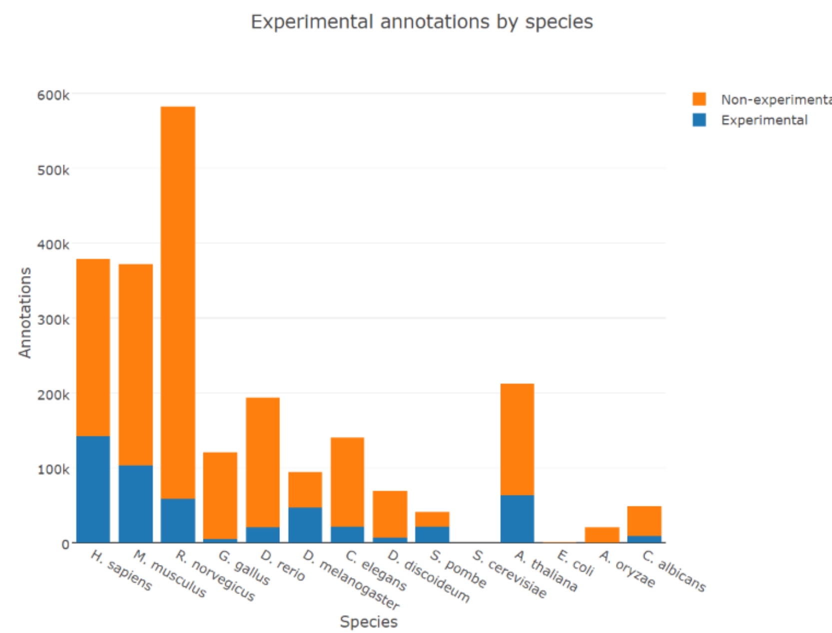
Arguably one of the most *successful* ontology projects in the life sciences.

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

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

- **cellular component**
  - where gene products operate
- **molecular function**
  - what gene products do
- **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[i]

Function[i]

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

Manual assertion based on experiment in[i]

"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[i]	10 – 17	8	GTP B
Nucleotide binding[i]	57 – 61	5	GTP B
Nucleotide binding[i]	115 – 118	4	GTP B

GO - Molecular function[i]

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

GO - Biological process[i]

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

Complete GO annotation...

Keywords - Ligand[i]

GTP-binding, Nucleotide-binding

GO enables interoperability of descriptions across species

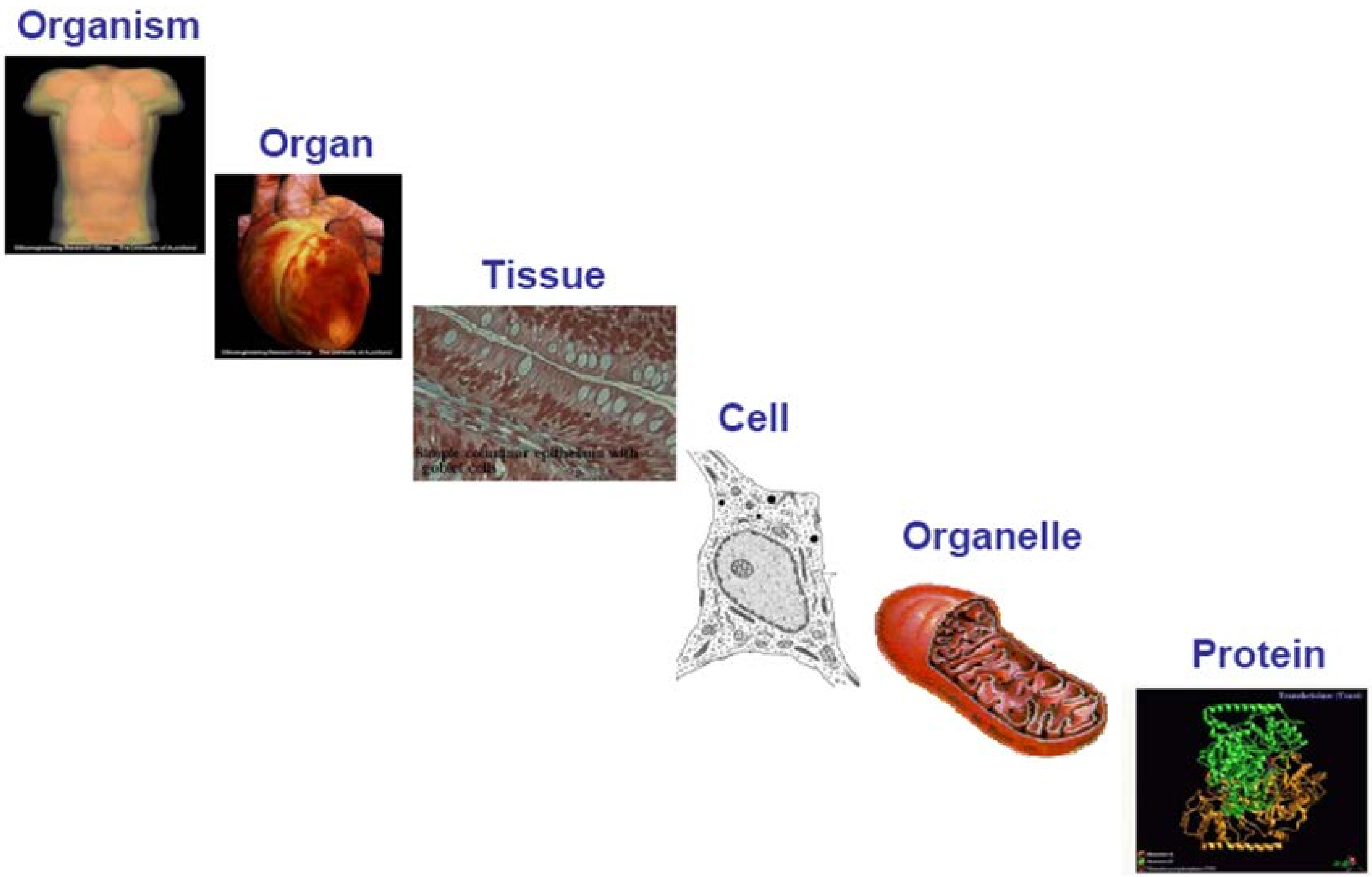
Term Information

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
- **SNOMED-CT**
  - clinical terminology, diseases, diagnostics and procedures
  - 324,129 classes
- **Unified Medical Language System (UMLS)**
  - US National Library of Medicine
  - terminology, classification and coding standards
  - 8M normalized concepts
- **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

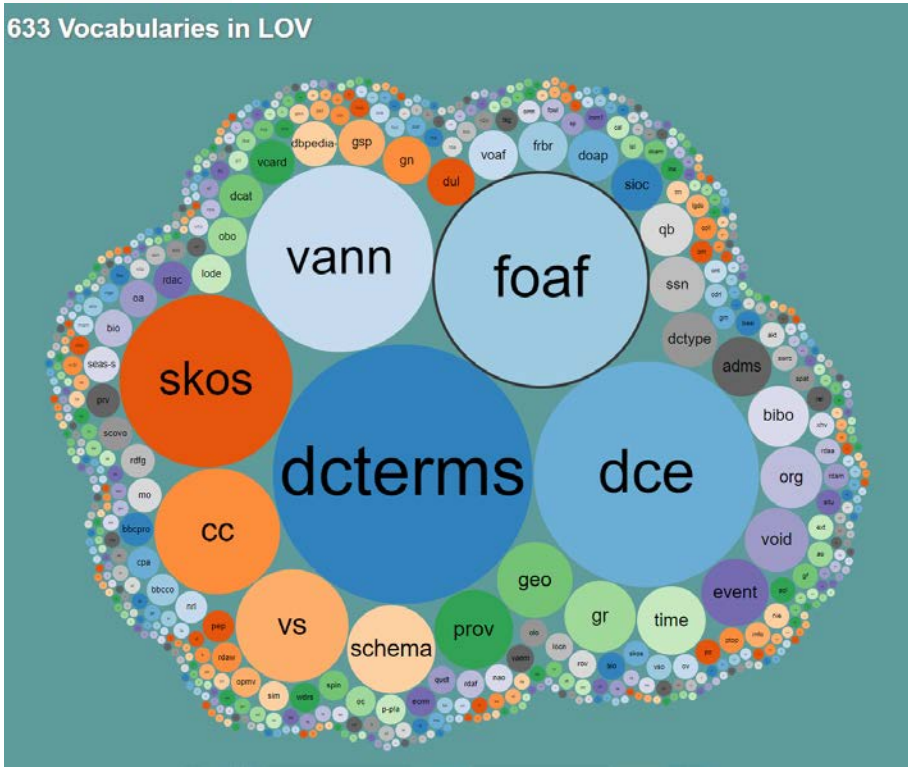
Where can we get ontologies?

BioPortal

BioPortal Statistics

Ontologies	707
Classes	8,820,000
Resources Indexed	48
Indexed Records	39,537,360
Direct Annotations	95,468,433,792
Direct Plus Expanded Annotations	144,789,582,932

Linked Open Vocabularies (LOV)



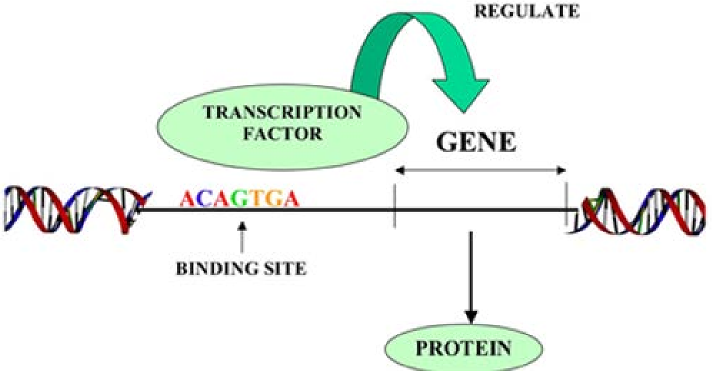
Formalization

- 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 to answer questions.

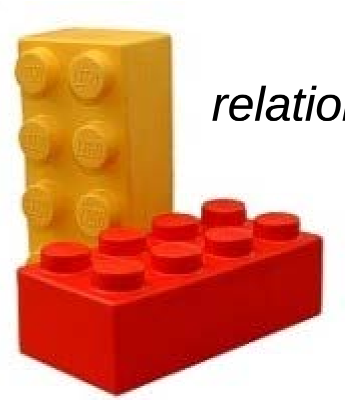
Logic-Based Ontologies Can Be constructed From *Concept and relation* Lego

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

A **transcription factor** *is a protein that binds to DNA and regulates the rate of transcription*



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



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 provides an extensive vocabulary to more precisely represent knowledge

- **Conjunction (and)**
- **Disjunction (or)**
- **Negation (not)**
- **Disjointness (sameAs, differentFrom)**
- **Quantification (some, only, 0->n)**
    - existential, universal, cardinality restriction

- **property characteristics**
    - transitive, functional, inverse functional, symmetric, antisymmetric, reflexive, irreflexive
- **complex classes expressions** in domain and range restrictions
- **property chains**

What is a class?

A **class** represents a **group of individuals** that share one or more things in common.

e.g. The class of “transcription factor” represents all entities that satisfy the criteria for class membership.

What is an instance?

An **instance** is an *individual* that is a member of a **class.**

e.g. An *individual* transcription molecule in the cell is an instance of the class “transcription factor”
e.g. Michel is an instance of Person

An individual can be a member of more than one class. For instance a transcription factor is also a member of the class Protein.

An individual may have properties

These properties can refer to attributes of the individual or relations to other **individuals.**

That individual transcription factor *is bound to* a single molecule of DNA

Robert *is a colleague of* Michel

subClass

A **subClass** is a class that minimally exhibits all the attributes of a parent class, and potentially more.

Transcription Factor **subClassOf** Protein

all transcription factors are also proteins -> each transcription factor shares all the attributes that proteins do.

However, the inverse, that all proteins are transcription factors is **not** implied.

Equivalent class

Two classes are **equivalent** when they are intensionally the same, and must therefore contain exactly the same individuals.

For example, we often use the term Protein and Polypeptide interchangeably, meaning that every instance of the class Protein is also an instance of class Polypeptide, and vice versa.

Disjoint classes

Two classes are **disjoint** when they cannot share the same instances. Membership in one class precludes membership in the other.

For example, no molecule can both be wholly a DNA molecule and also be a Protein molecule.

owl:disjointClasses (DNA, Protein)

Same and different individuals

OWL does not assume that two names imply two different individuals (Open World Assumption).
In fact, one individual may have two names – e.g. **P38398** and **Q7KYU9** are two names for **BRCA1** - so it would be wrong to assume/conclude that these refer to two different individuals (Closed World Assumption)

However, OWL provides a mechanism to explicitly indicate that individuals are the same as (owl:sameAs) or different from (owl:differentFrom) one another.

Same and different individuals

This has important implications when counting the number of entities in a knowledge base.

Individual: **P38398**

Individual: **Q7KYU9**

Individual: **Q16512**

-> how many individuals are there? At least 1

P38398 owl:sameAs **Q7KYU9**

-> how many individuals are there? At least 1

P38398 owl:differentFrom **Q16512**

-> how many individuals are there? At least 2

More complex class expressions

We can define more complex descriptions of a class by combining classes and properties together. The basic constructors are ‘and’/’that’, ‘or’, ‘not’, ‘some’, ‘only’, ‘min’, ‘max’.

‘transcription factor’
equivalentTo
‘protein’
that ***‘binds to’*** *some* ***DNA***
and ***‘regulates’*** *min 1* ***‘rate of transcription’***

Domain/Range Entailments

- We can set the domain and range of a relation in order to infer class membership for individuals involved in those relations

Michel hasColleague Robert

hasColleague:

Domain: Person ; Range: Person

-> Michel instanceOf Person

-> Robert instanceOf Person

Universal Quantification

Axioms involving universal quantification also generate an entailment for the object in a relation

Person subClassOf **hasColleague only Person**

Michel hasColleague Robert

-> Robert instanceOf Person

Reasoning over OWL ontologies

- **Consistency:** determines whether the ontology contains **contradictions.**
  (1) DNA disjointFrom Protein (2) myprotein instanceOf protein (3) myprotein instanceOf DNA

- **Satisfiability**: determines whether classes can have **instances**.
  (1) DNA disjointFrom Protein (2) DNA subClassOf Protein

- **Subsumption**: are **all instances** of one class **also instances** of another class?
  (1) Protein subClassOf Molecule

- **Classification**: ***repetitive*** application of **subsumption** to discover implicit subclass links between named classes
  (1) Transcription Factor equivalentTo Protein …
  -> (2) Transcription Factor subClassOf Protein

- **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.

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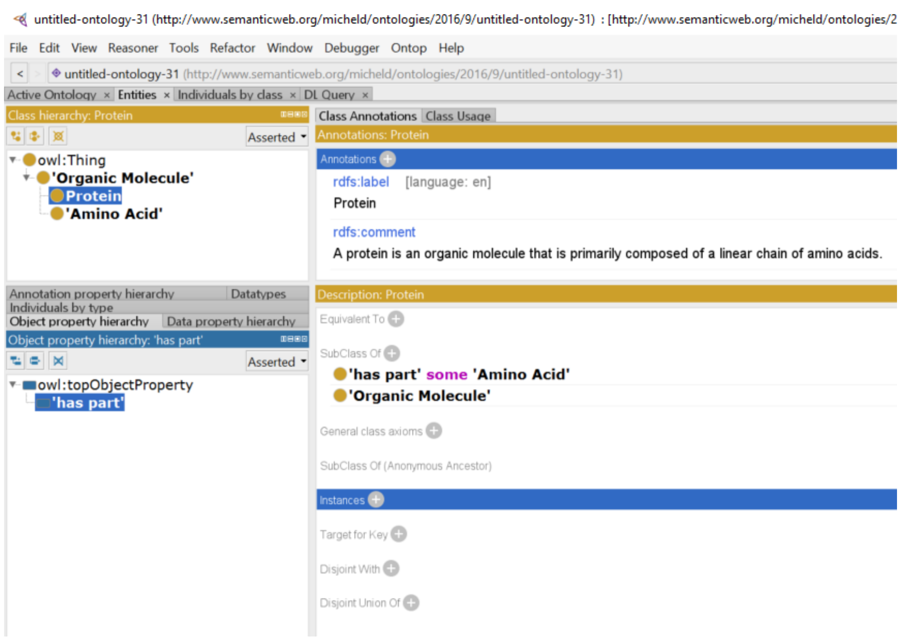
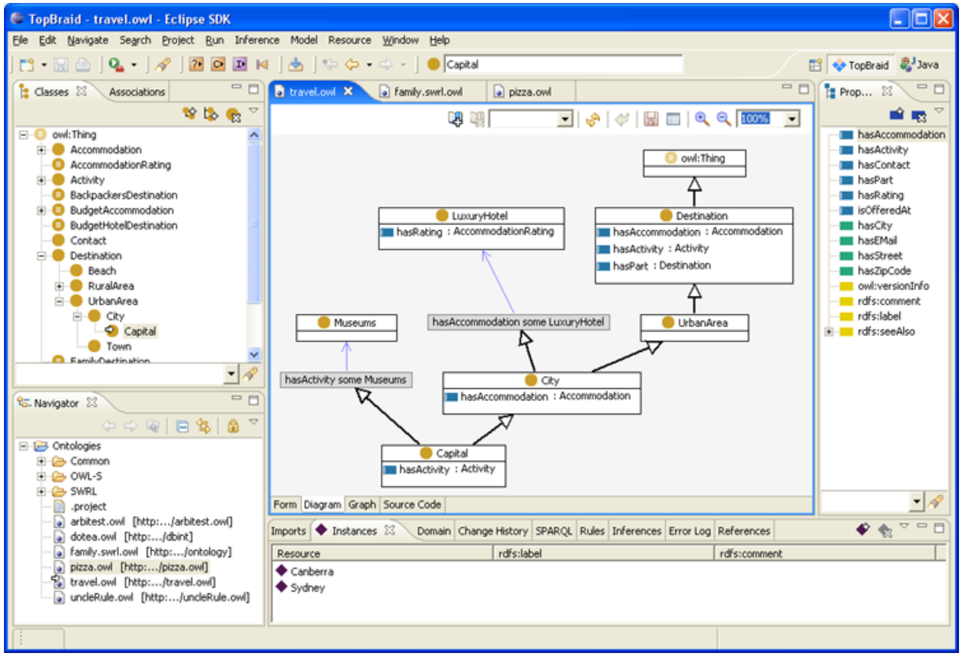
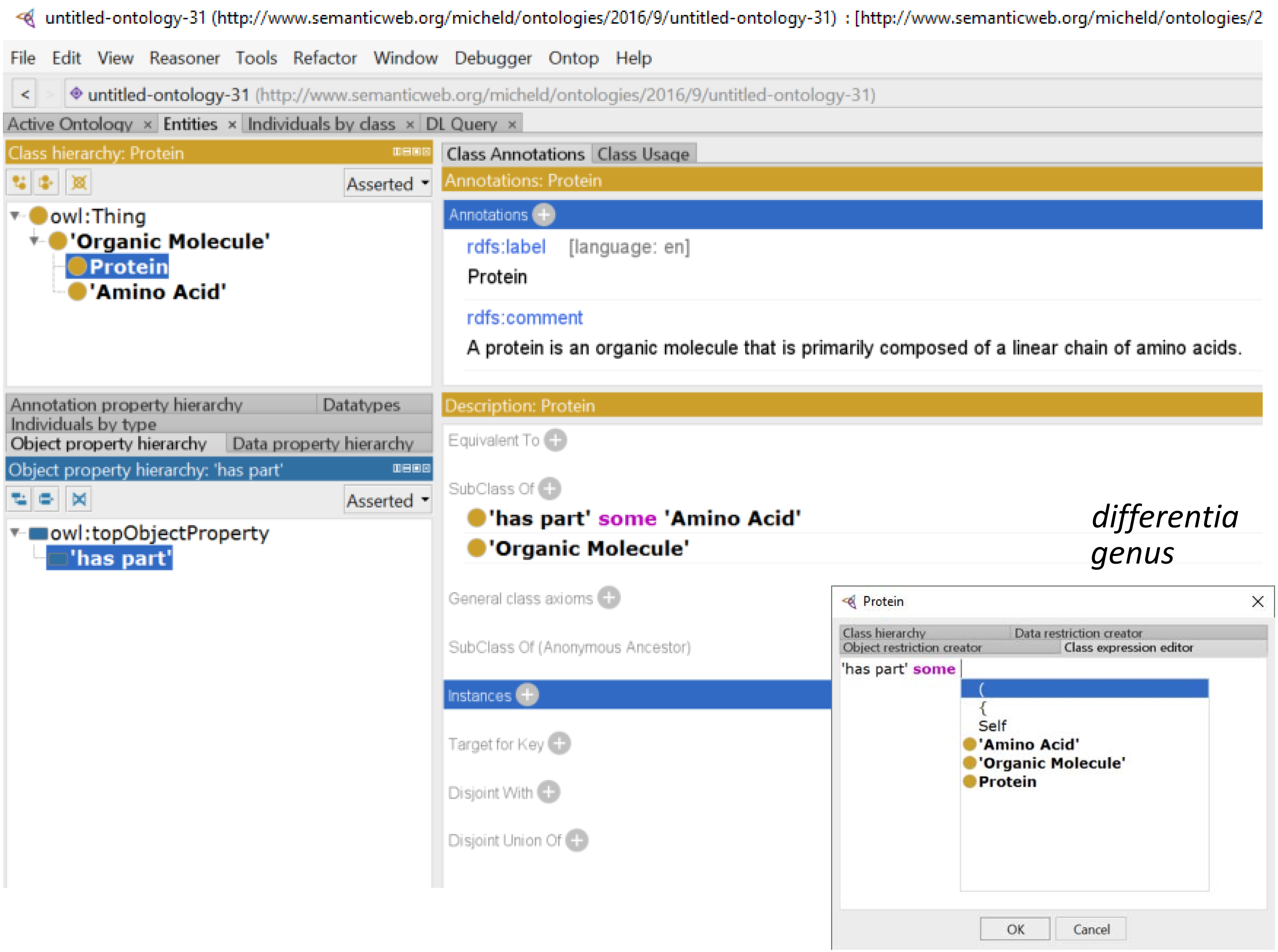
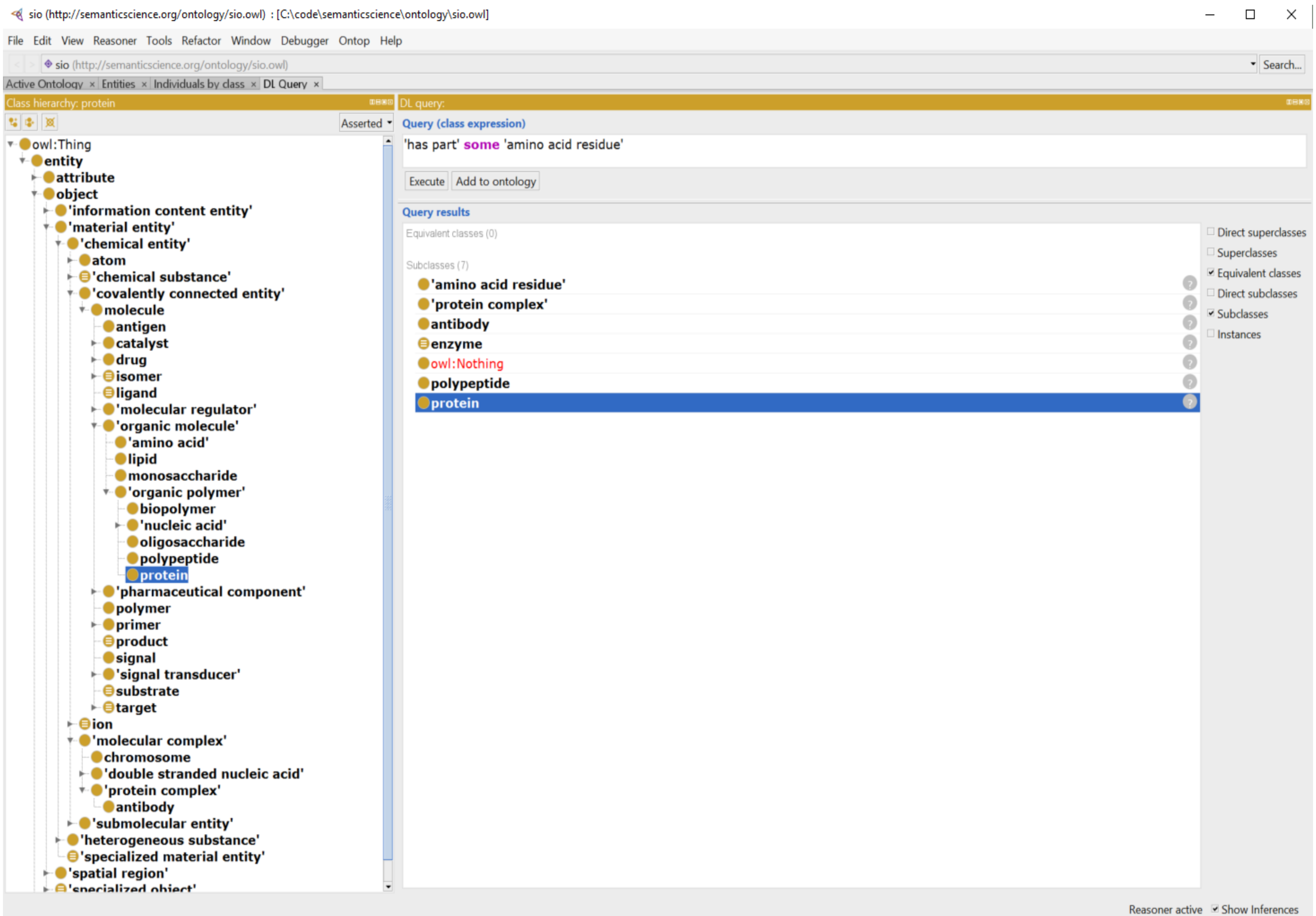
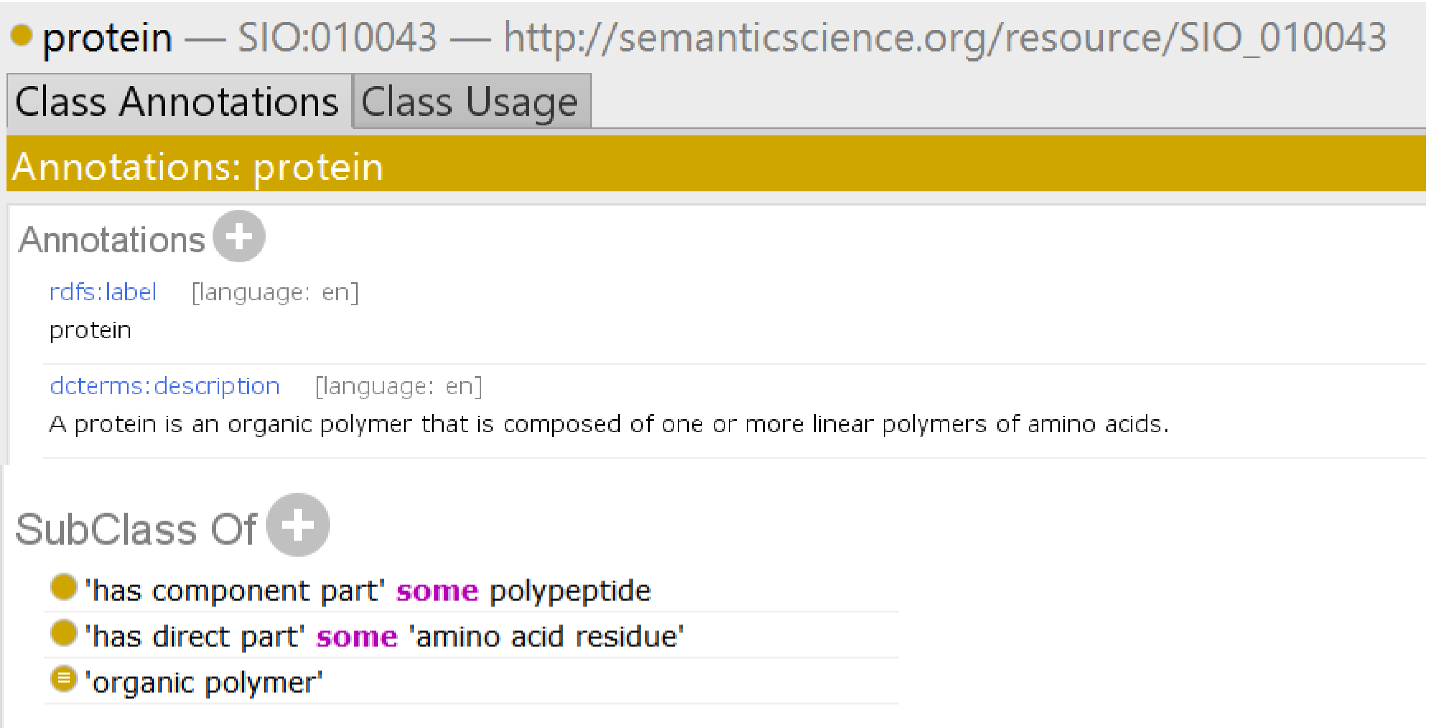




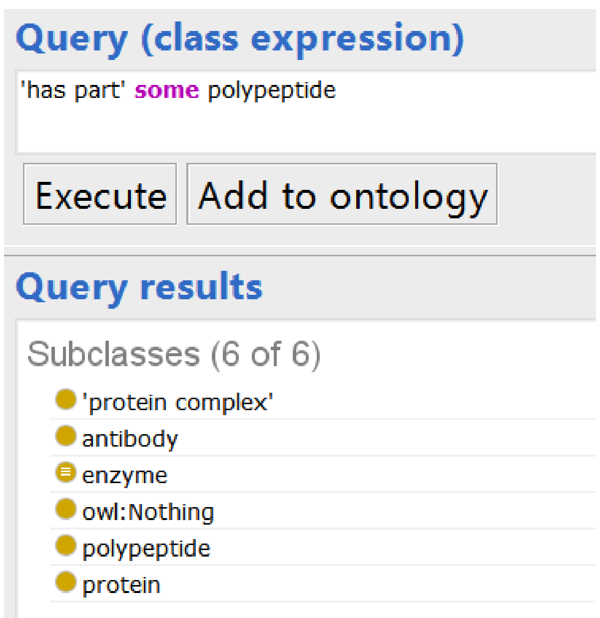

untitled-ontology-31 (http://www.semanticweb.org/micheld/ontologies/2016/9/untitled-ontology-31) : [http://www.semanticweb.org/micheld/ontologies/2
File Edit View Reasoner Tools Refactor Window Debugger Ontop Help
untitled-ontology-31 (http://www.semanticweb.org/micheld/ontologies/2016/9/untitled-ontology-31)
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

Query answering

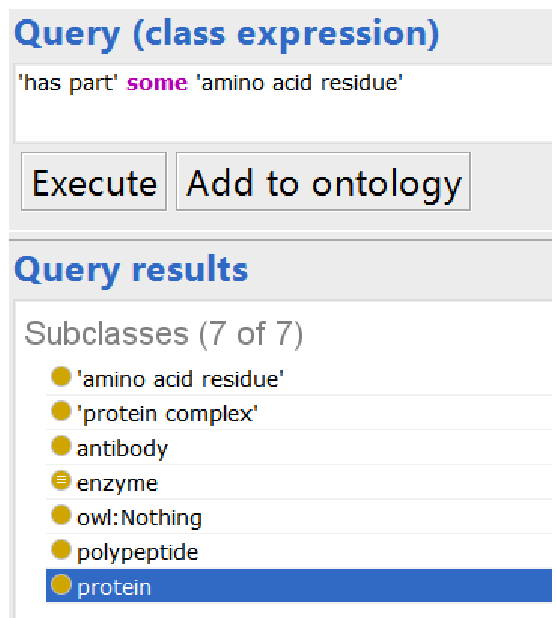




protein — SIO:010043 — http://semanticscience.org/resource/SIO_010043
Class Annotations
Class Usage
Annotations: protein
Annotations
rdfs:label [language: en]
protein
dcterms:description [language: en]
A protein is an organic polymer that is composed of one or more linear polymers of amino acids.
SubClass Of
'has component part' some polypeptide
'has direct part' some 'amino acid residue'
'organic polymer'



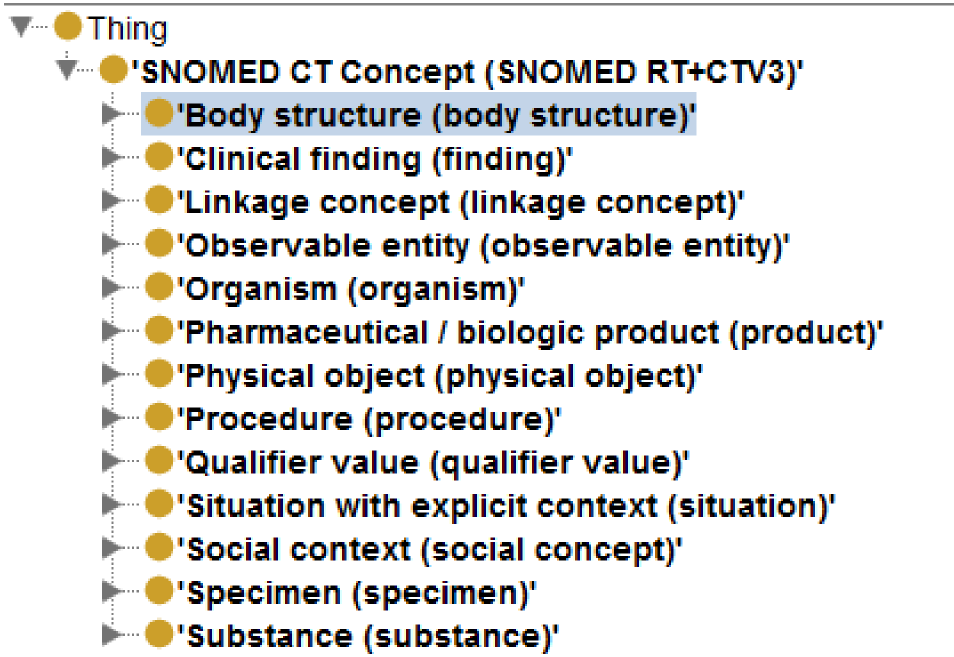
Query (class expression)
'has part' some polypeptide
Execute
Add to ontology
Query results
Subclasses (6 of 6)
'protein complex'
antibody
enzyme
owl:Nothing
polypeptide
protein



Query (class expression)
'has part' some 'amino acid residue'
Execute
Add to ontology
Query results
Subclasses (7 of 7)
'amino acid residue'
'protein complex'
antibody
enzyme
owl:Nothing
polypeptide
protein

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

Description: 'Accessory breast (disorder)'

Equivalent classes

```
'Congenital anomaly of breast (disorder)'
  and 'Congenital malformation (morphologic abnormality)'
  and (RoleGroup some
    (('Associated morphology (attribute)' some 'Supernumerary structure (morphologic abnormality)')
     and ('Finding site (attribute)' some 'Breast structure (body structure)')))
  and (RoleGroup some ('Occurrence (attribute)' some 'Congenital (qualifier value)'))
```

- 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

Reasoning with Ontologies

hasPet some owl:Thing subClassOf Human

Phoenix subClassOf petOf only Wizard

HarryPotter instanceOf Wizard

DracoMalfoy instanceOf Wizard

HarryPotter hasFriend RonWeasly

HarryPotter hasFriend HermioneGranger

HarryPotter hasPet Hedwig

Is DracoMalfoy a friend of HarryPotter?

Reasoning with Ontologies

hasPet some owl:Thing subClassOf :Human

Phoenix subClassOf: petOf only Wizard

HarryPotter instanceOf Wizard

DracoMalfoy instanceOf Wizard

HarryPotter hasFriend RonWeasly

HarryPotter hasFriend HermioneGranger

HarryPotter hasPet Hedwig

Is Draco a friend of Harry Potter?

-> we do not know. No -> DB closed reasoning

Reasoning with Ontologies

hasPet some owl:Thing **subClassOf** Human

Phoenix **subClassOf** petOf only Wizard

isPetOf **inverseOf** hasPet

facts:

Fawkes instanceOf Phoenix

Fawkes isPetOf DumbleDore

What new facts do we entail?

Reasoning with Ontologies

Fawkes isPetOf DumbleDore

isPetOf inverseOf hasPet

-> **DumbleDore hasPet Fawkes**

hasPet some owl:Thing subClassOf Human

-> **DumbleDore instanceOf Human**

Fawkes instanceOf Phoenix

Phoenix subClassOf petOf only Wizard

-> **Dumbledore instanceOf Wizard**

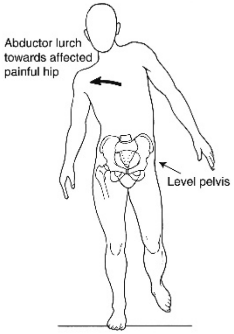
Applications in Biomedicine

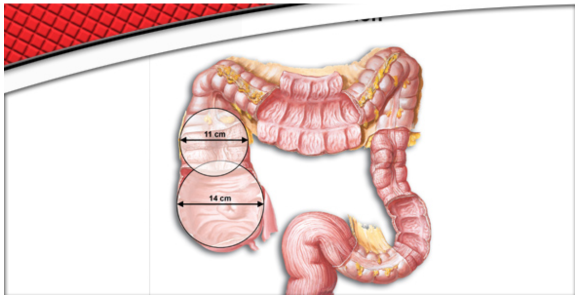
Use of ontologies for the diagnosis of rare diseases

Phenotypes

A phenotype is an observable characteristic of an individual and typically pertains to its morphology, function, and behavior.

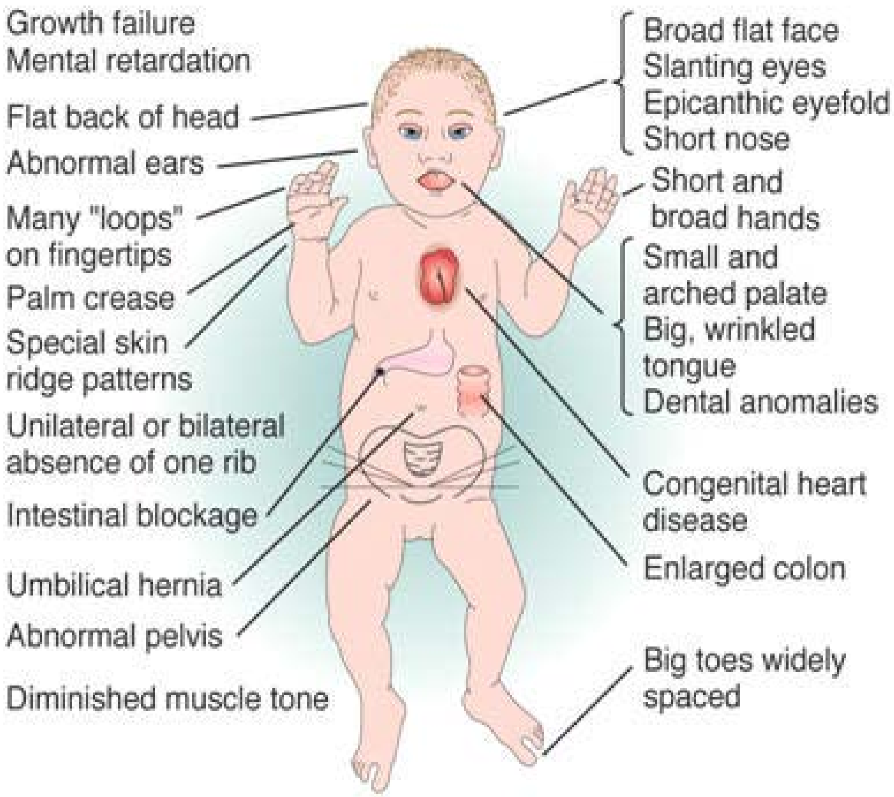
- qualitative, normal and abnormal phenoytpes





- red eye color, abnormal gait, enlarged colon

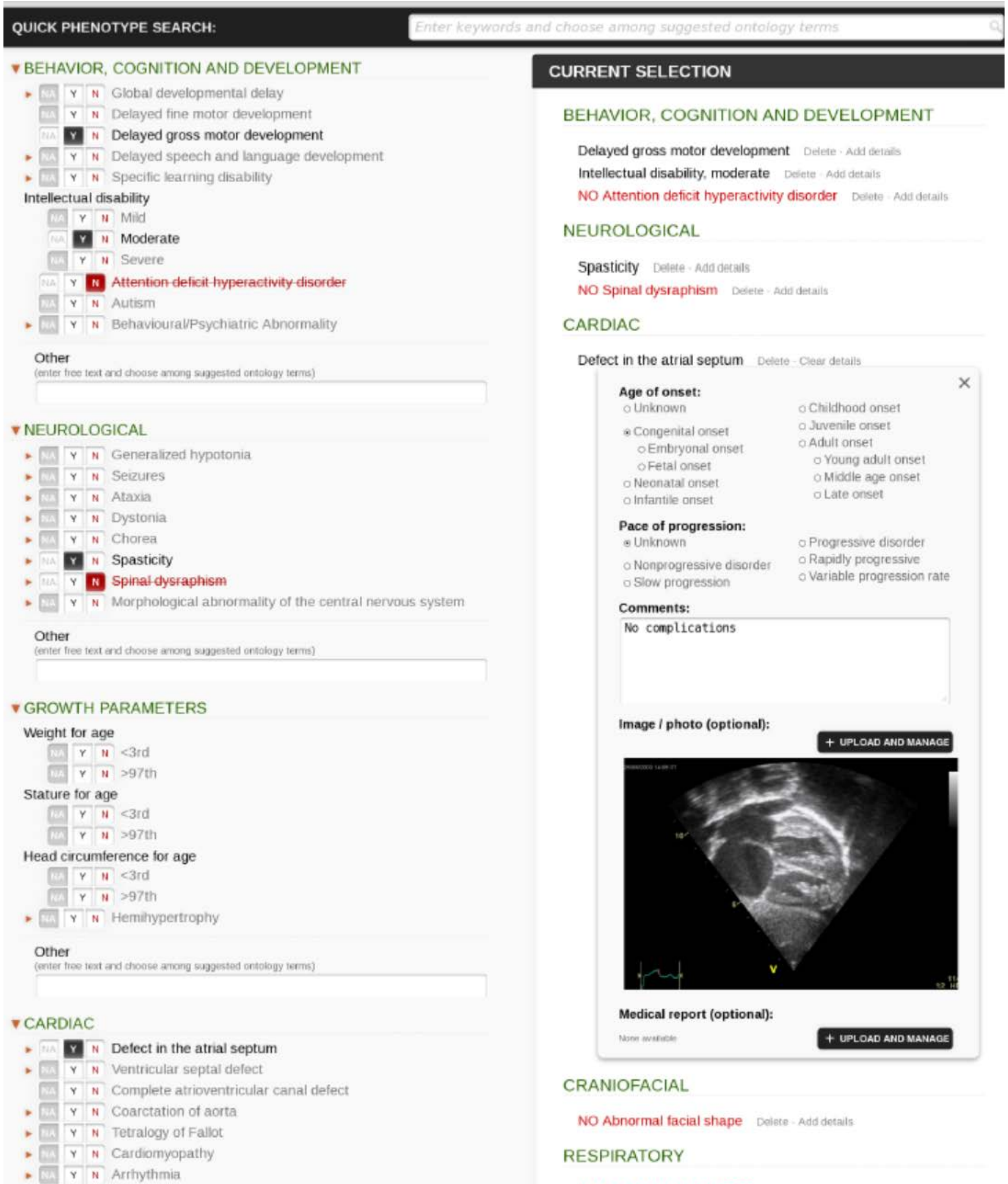
Diagnosis
uses observable/measured phenotypes



"Phenotypic Profile"

monarch INITIATIVE

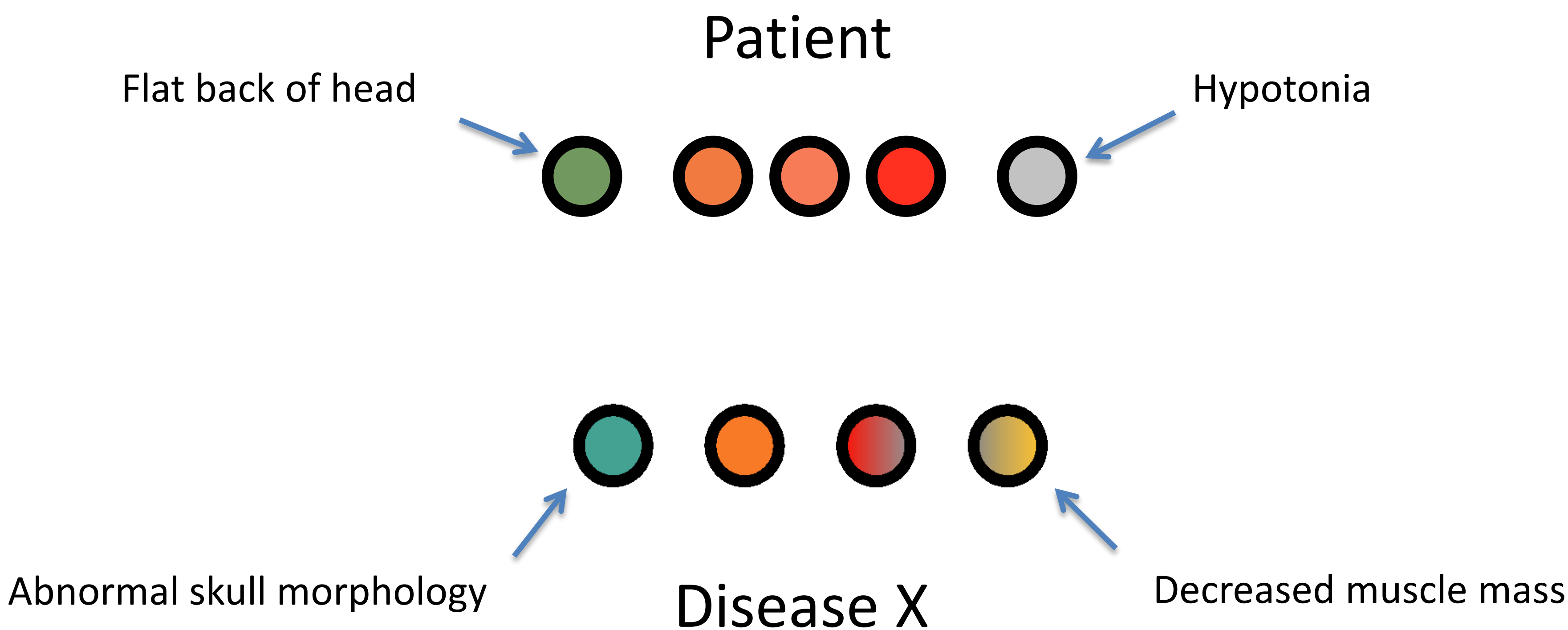
Phenotips



- 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

Matching patients to diseases



Differential diagnosis with similar but non-matching phenotypes is difficult

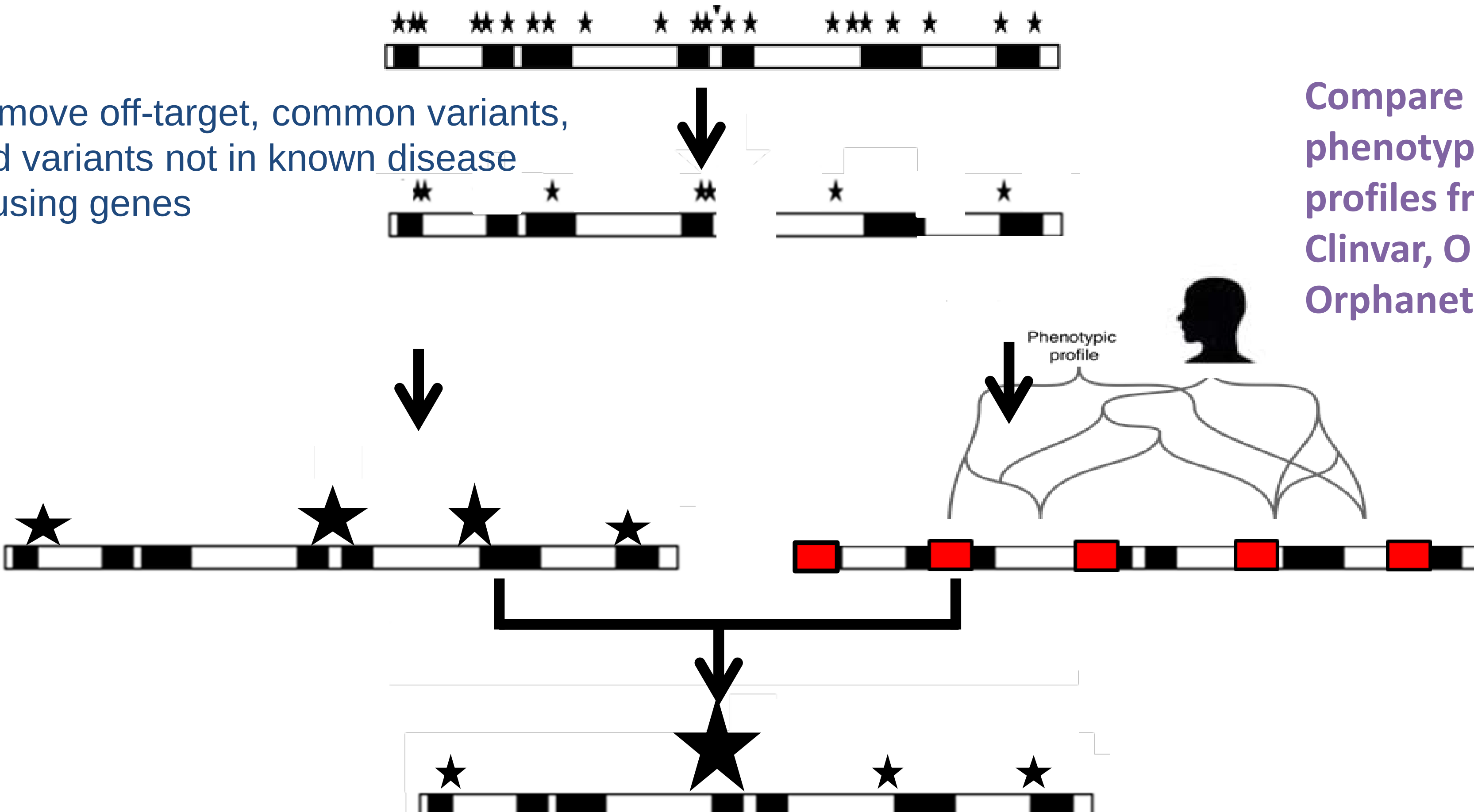
PhenIX

Genotypes + Phenotypes Improves Diagnosis

Target panel of 2741 known Mendelian disease genes

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

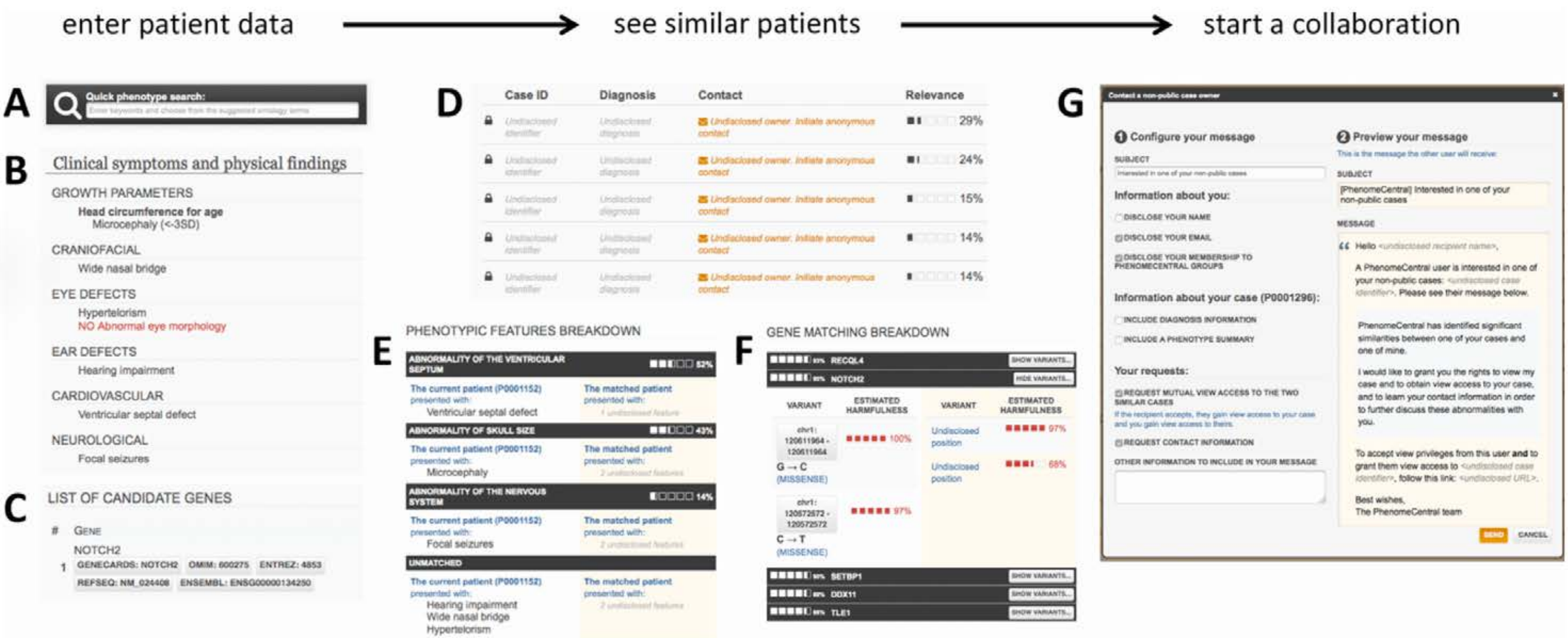
Zemojtel et al. Sci Transl Med. 2014. 6(252):252ra123

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

PhenIX helped diagnose 11/40 patients

ID	Age, Sex	Presentation	Gene	Rank	Diagnosis
P1	3y (f)	Intellectual disability + multiple congenital anomalies	*MLL*	2	Wiedemann-Steiner syndrome (*39*)
P2	5y (f)	Intellectual disability + multiple congenital anomalies	*SYNGAP1*	4	Mental retardation, MRD5 (*40*)
P3	6y (f)	Skeletal phenotype	*FGFR2*	1	Pfeiffer syndrome (*41*)
P4	Death at 5.5m (f)	Multiple congenital anomalieswithout intellectual disability	*SH3PXD2B*	6	Frank-ter Haar syndrome (*42*)
P5	6m (f)	Intellectual disability + neurological abnormalities	*SLC6A3*	1	Parkinsonism-dystonia (*43*)
P6	Fetus (m) Death at 22w of gestation	Skeletal phenotype	*ALPL*	2	Infantile hypophosphatasia (*44*)
P7	7y (m)	Eye phenotype	*NHS*	2	Nance-Horan Syndrome / Cataract 40, X-linked (*45*)
P8	14y (m)	Intellectual disability + multiple congenital anomalies	*MLL*	1	Wiedemann-Steiner syndrome (*39*)
P9	6y (f)	Intellectual disability + multiple congenital anomalies	*DYRK1A*	4	Mental retardation, MRD7 (*46*)
P10	4 children between 1 ½ and 7y	Intellectual disability + multiple congenital anomalies	*MCOLN1*	1	Type IV mucolipidosis (*47*)
P11	3y (m)	Intellectual disability + multiple congenital anomalies	*RBM10*	3	TARP syndrome

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

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.