Block 3
Biological Knowledge Graphs: Examples and Construction Approaches

Tiffany J. Callahan MPH, PhD

Postdoctoral Research Fellow, Department of Biomedical Informatics

Constructing Knowledge Graphs for Advanced Biomedical Applications
April 26, 2023

COLUMBIA | COLUMBIA UNIVERSITY
DEPARTMENT OF
BIOMEDICAL INFORMATICS

@Tiff_callahan

Lecture Outline

Part 1 - Lecture

- Semantic Web Refresher
- Biological Knowledge Graphs
- Knowledge Graph Evaluation and Open Challenges

Part 2 - Activity

- Overview

Part 1 - Lecture

Semantic Web Refresher

Semantic Web

- The **World Wide Web** (WWW) was invented in 1989 by Tim Berners-Lee to enable rapid sharing of information between scientists across the world
- On the WWW, machines are content brokers storing, organizing, requesting, transmitting, receiving, and displaying content as documents[1]

Challenges

- Content is created for specific websites
- Licensing and technical issues cause fragmentation
- Limited reusability

W3C®

[1] DOI: 10.1201/b16859; https://home.cern/science/computing/birth-web/short-history-web

Semantic Web

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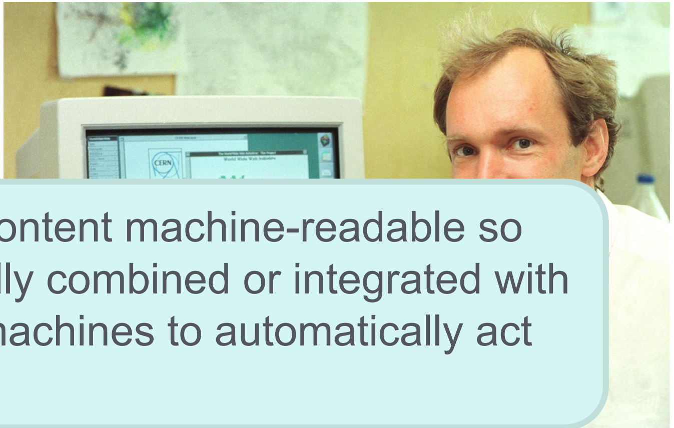

The goal of the **Semantic Web** is to make the Web's content machine-readable so that it can be reused (for any purpose) and automatically combined or integrated with other machine-readable content in order to enable to machines to automatically act upon it[1]

C

- Content is created for specific websites
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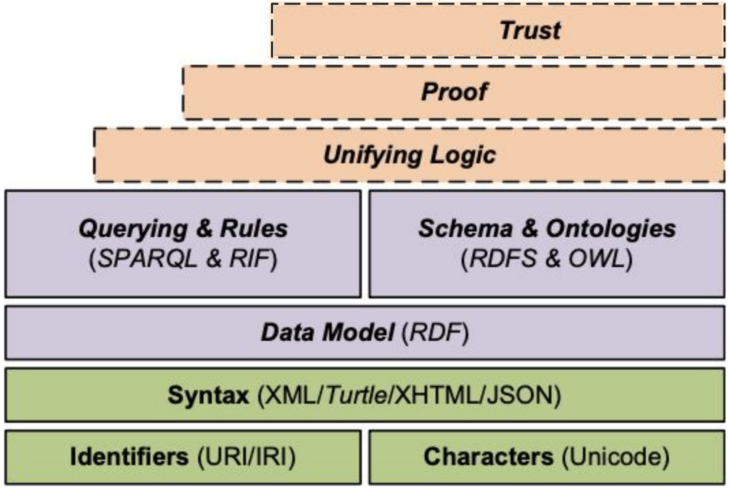
[1] DOI: 10.1201/b16859; https://home.cern/science/computing/birth-web/short-history-web

Semantic Web Standards



Trust

Proof

Unifying Logic

Querying & Rules
(SPARQL & RIF)

Schema & Ontologies
(RDFS & OWL)

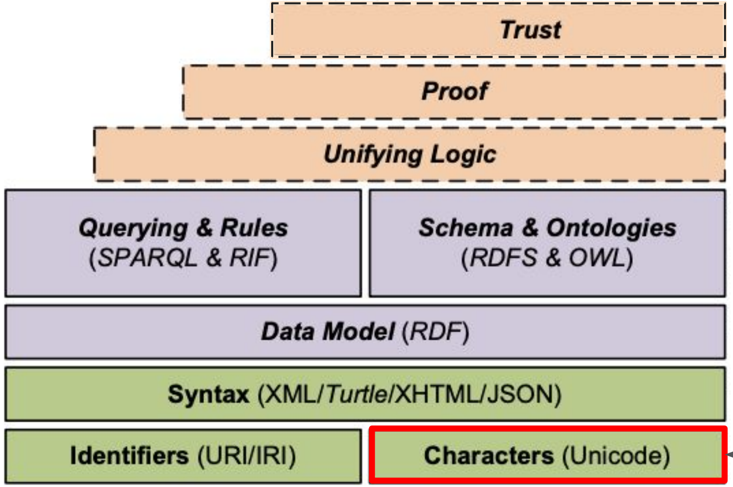
Data Model *(RDF)*

Syntax (XML/*Turtle*/XHTML/JSON)

Identifiers (URI/IRI)

Characters (Unicode)

Semantic Web Standards



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Semantic Web Stack

"Semantic Layer Cake"

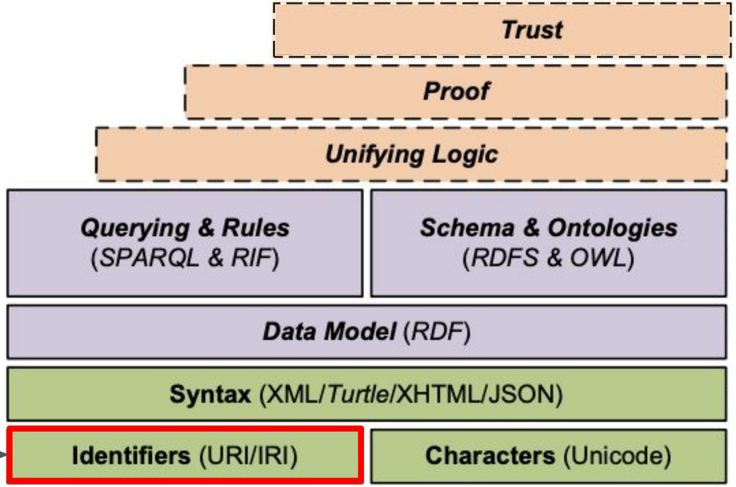
Characters: Unicode character-set used to map from binary streams to textual information

DOI: 10.1201/b16859

Semantic Web Standards

Identifiers: use globally agreed upon identifiers

Uniform Resource Identifier (**URI**)



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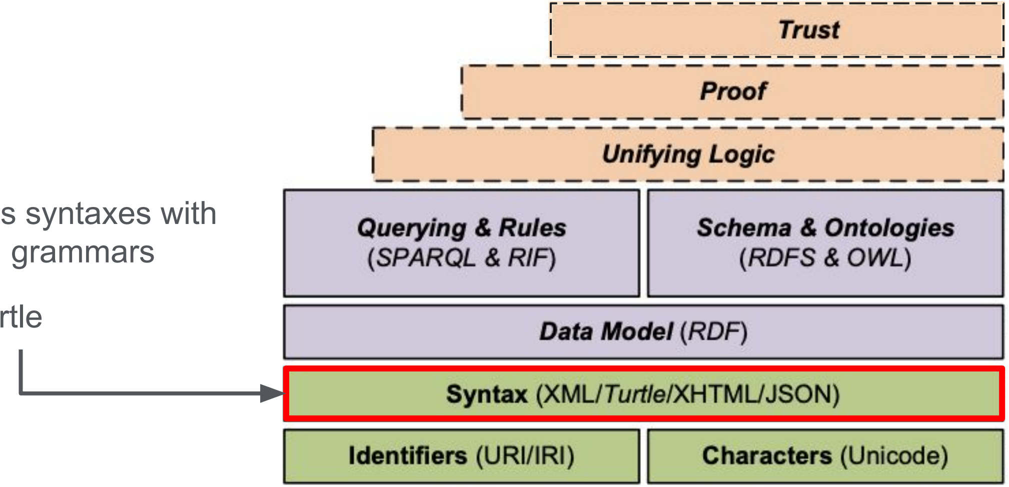
Semantic Web Stack

"Semantic Layer Cake"

Semantic Web Standards

Syntax: requires syntaxes with formally defined grammars

XML, JSON, Turtle



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Semantic Web Stack

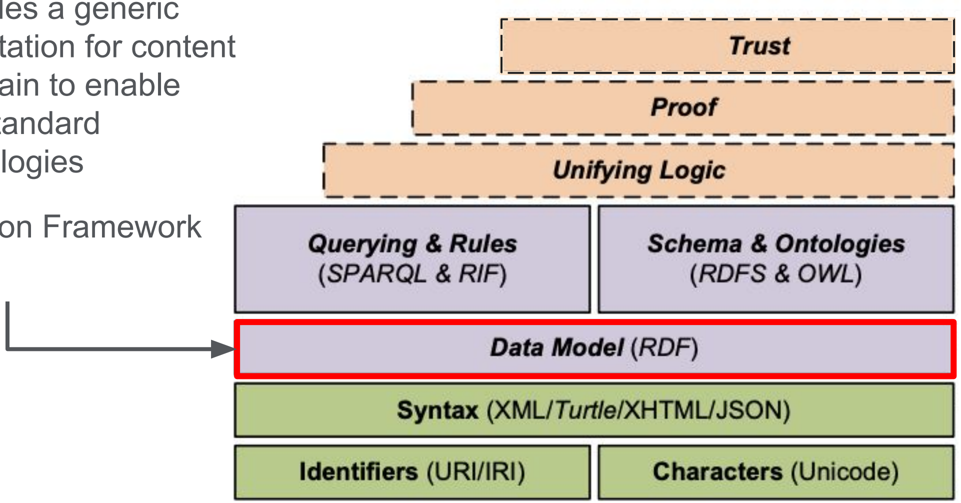
“Semantic Layer Cake”

DOI: 10.1201/b16859

Semantic Web Standards

Data Model: provides a generic canonical representation for content irrespective of domain to enable processing using standard off-the-shelf technologies

Resource Description Framework (**RDF**)



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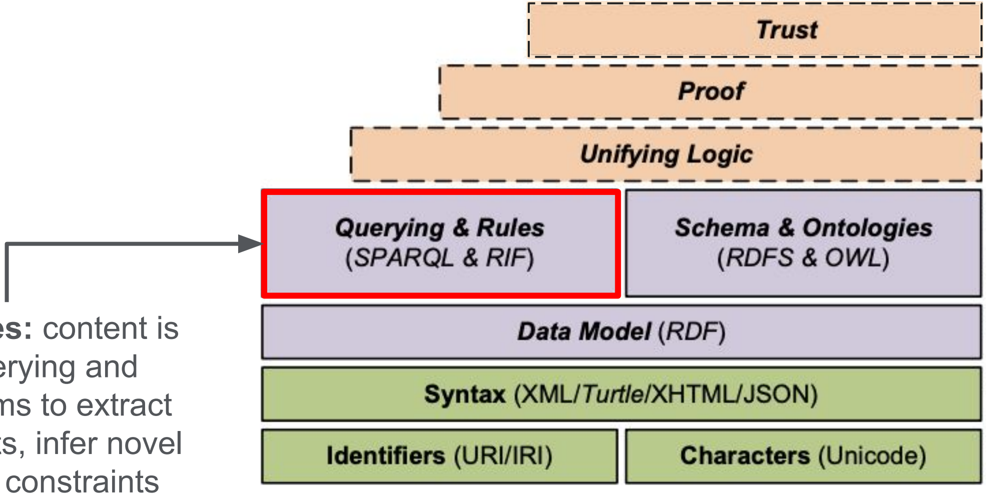
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Querying & Rules: content is processed by querying and rule-based systems to extract pertinent elements, infer novel data, and specify constraints

SPARQL Protocol and RDF Query Language (**SPARQL**)

Semantic Web Stack

"Semantic Layer Cake"

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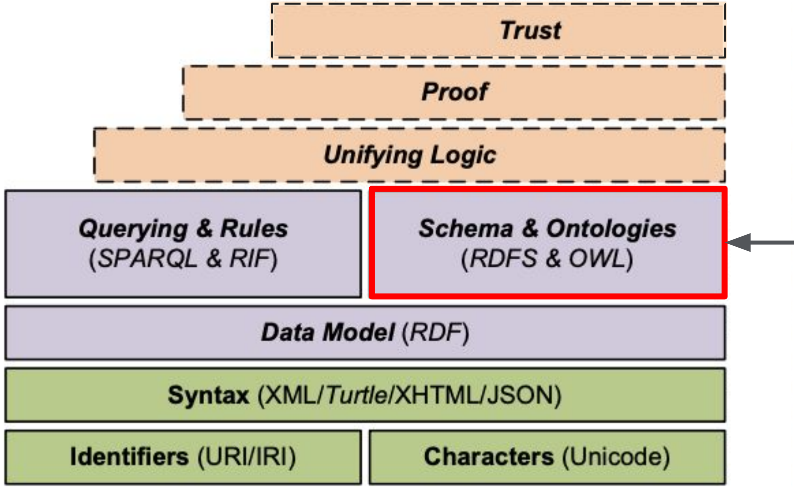
Semantic Web Standards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Semantic Web Stack
"Semantic Layer Cake"

Schema & Ontologies: formal languages that provide a meta-vocabulary with well-defined semantics that can be used in combination with the data model

RDF Schema (**RDFS**)
Web Ontology Language (**OWL**)

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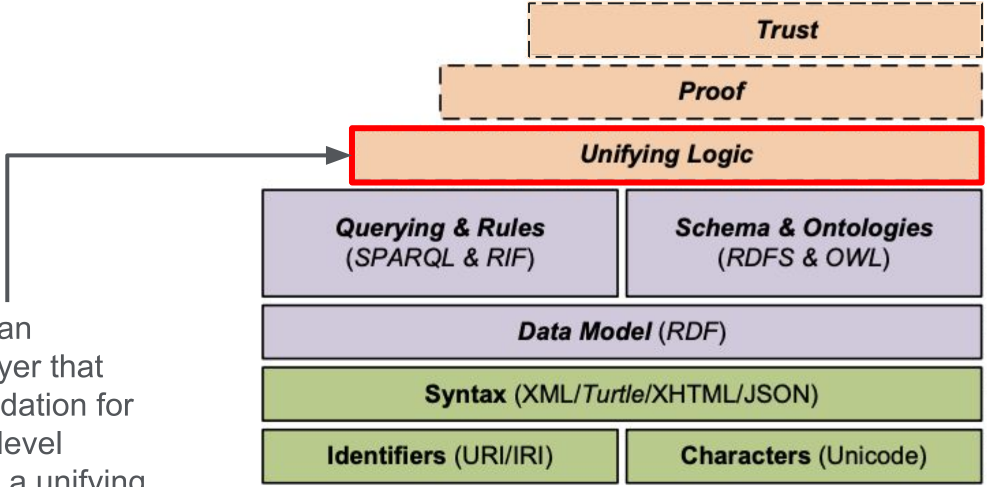
Semantic Web Standards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Semantic Web Stack
"Semantic Layer Cake"

Unifying Logic: an interoperability layer that provides the foundation for combining lower-level technologies with a unifying language to engage queries/rules over knowledge represented in RDF and associated ontologies/schemata

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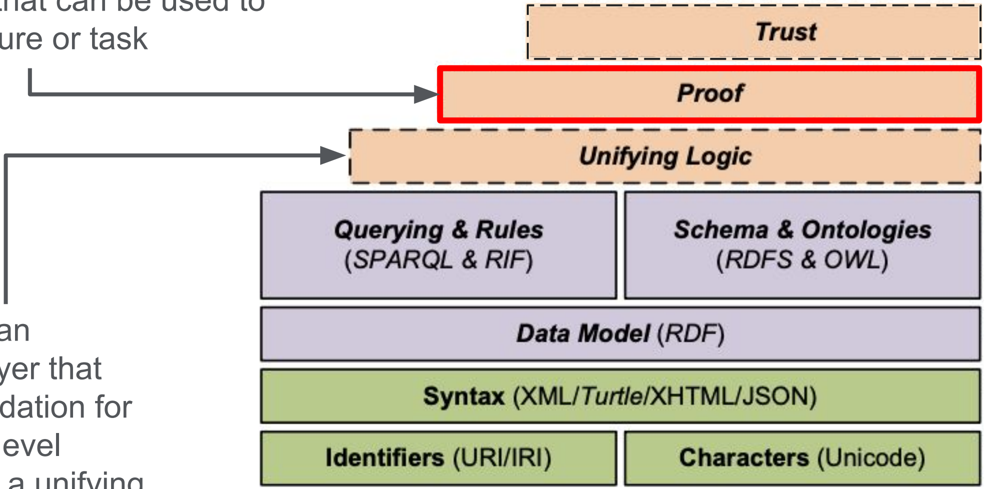
Semantic Web Standards

Proof: evidence that can be used to validate a procedure or task



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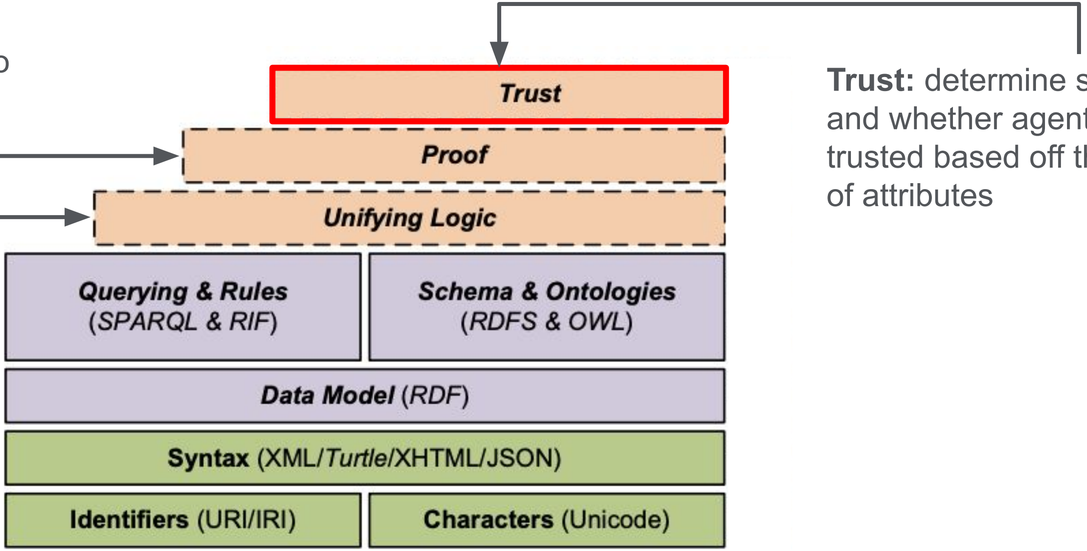
Semantic Web Standards

Proof: evidence that can be used to validate a procedure or task

Trust: determine source of *Proof* and whether agents can be trusted based off their unique set of attributes

Unifying Logic: an interoperability layer that provides the foundation for combining lower-level technologies with a unifying language to engage queries/rules over knowledge represented in RDF and associated ontologies/schemata



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Semantic Web Stack

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Semantic Web Standards - RDF

The **Resource Description Framework (RDF)** is the core data model for the Semantic Web[1]

RDF Terms

- **URIs**: universal resource identifiers that identify a resource and its publisher

  http://purl.obolibrary.org/obo/HP_0000726 (*dementia*)

- **Literals**: lexical values which can be plain or typed

  Plain: "dementia" @en
  Typed: "2" xsd:int (XML Schema definition used to specify variable type)

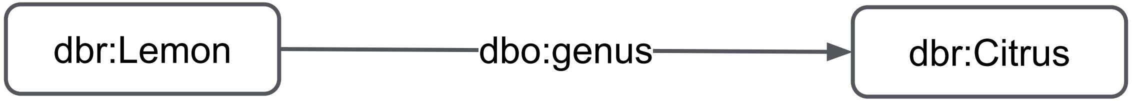
- **Blank Nodes**: "existential variables" that denote the existence of a resource without having to explicitly reference it with a URI or Literal (*example in 2 slides*)
  - Locally-scoped; usually referenced as a 32-digit hash

[1] http://www.w3.org/TR/rdf-primer/

Semantic Web Standards - **Triples**

RDF **Triples** are used to make statements about “things”

- **Subject:** RDF term (URI or blank node) that refers to the primary resource described by triple
- **Predicate:** RDF term (URI) that identifies the relation between the subject and the object
- **Object:** RDF term (URI, blank node or literal) that fills the value of the relation



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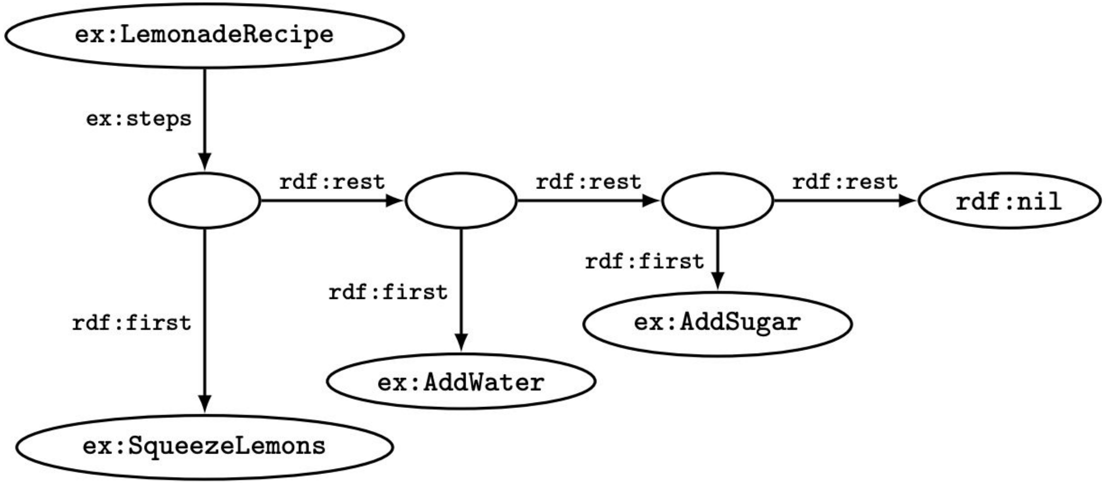
Semantic Web Standards - **Blank Nodes**

```
PREFIX rdf: <http://www.w3.org/1999/02/22-rdf-syntax-ns#>

ex:LemonadeRecipe ex:steps _:l1 .
_:l1 rdf:first ex:SqueezeLemons .
_:l1 rdf:rest _:l2 .
_:l2 rdf:first ex:AddWater .
_:l2 rdf:rest _:l3 .
_:l3 rdf:first ex:AddSugar .
_:l3 rdf:rest rdf:nil .
```



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Semantic Web Standards - RDF

The **semantics of RDF** are standardized in the form of a model theory

- RDF triples make claims about the nature or configuration of that world[1,2]

Objective: formalize claims in a manner that allows for evaluating the: (1) consistency of claims, (3) necessary entailments, and (3) the truth according to the theory

Given an RDF graph containing claims held as true, **entailments** are logical deductions implied by these claims

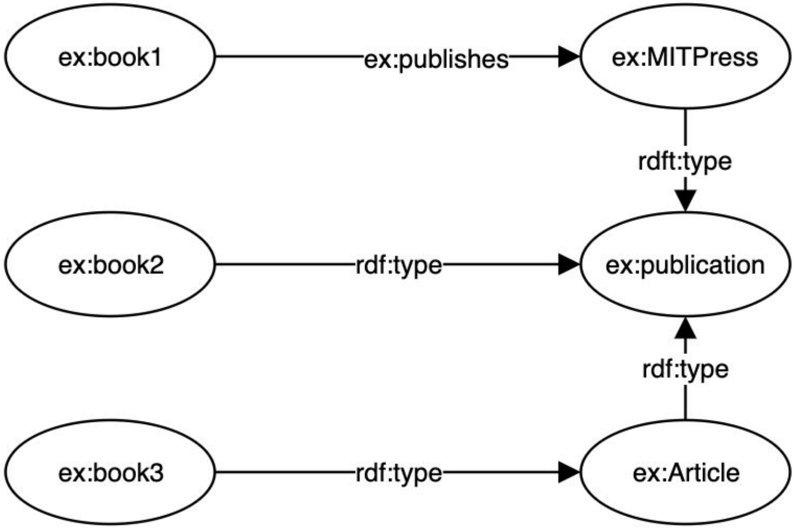
- Foundation for machine-readability
- Lets machines "connect the dots"

Example:

- "p53 is a tumor suppressor gene" entails "p53 is a gene" since p53 cannot be a tumor suppressing gene without also being a gene

[1] http://www.w3.org/TR/rdf-mt/; [2] DOI: 10.1201/b16859

Semantic Web Standards - **Entailment**



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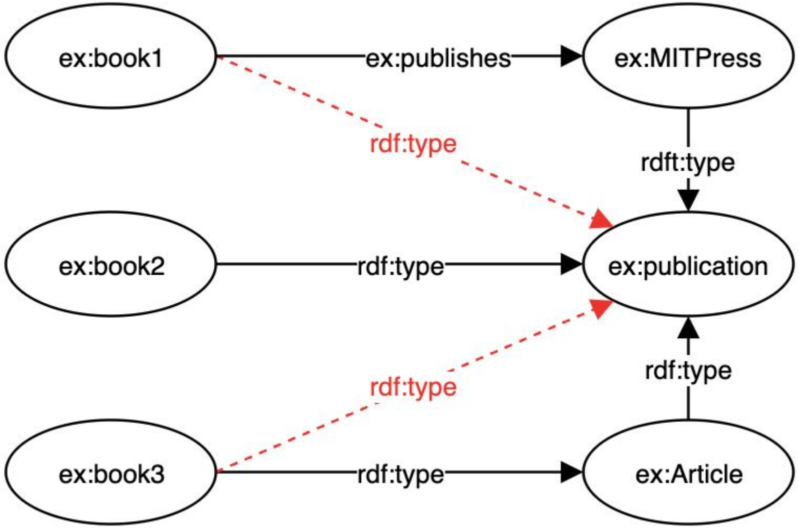


[1]http://www.w3.org/TR/rdf-mt/; [2]DOI: 10.1201/b16859

Semantic Web Standards - RDFS

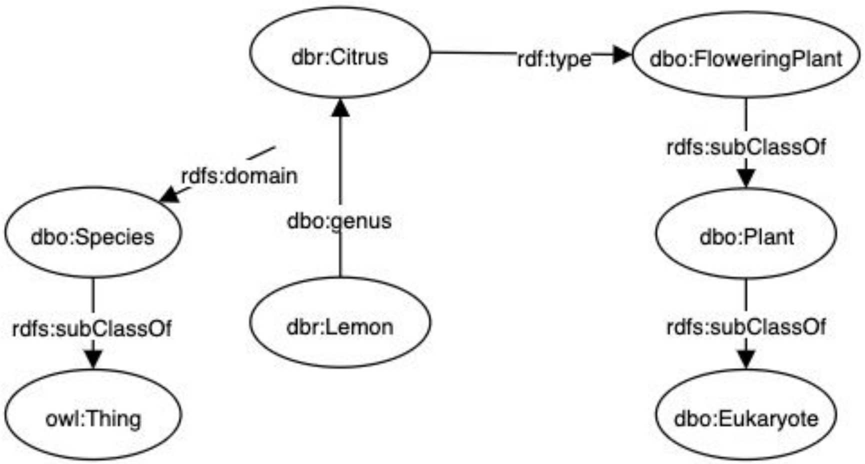
The **RDF Schema (RDFS)** attaches semantics to the RDF vocabulary.[1,2]

Extends the RDF Vocabulary in four key ways:

- rdfs:subClassOf: allows for stating that the extension of one class c1 (its set of members) is necessarily contained within the extension of another class c2
- rdfs:subPropertyOf: allows for stating that all things related by a given property p1 are also necessarily related by another property p2
- rdfs:domain: allows for stating that the subject of a relation with a given property p is a member of a given class c
- rdfs:range: analogously allows for stating that the object of a relation with a given property p is a member of a given class c

[1] http://www.w3.org/TR/rdf-schema/; [2] http://www.w3.org/TR/1999/REC-rdf-syntax-19990222/; DOI: 10.1201/b16859

Semantic Web Standards - **Entailment**



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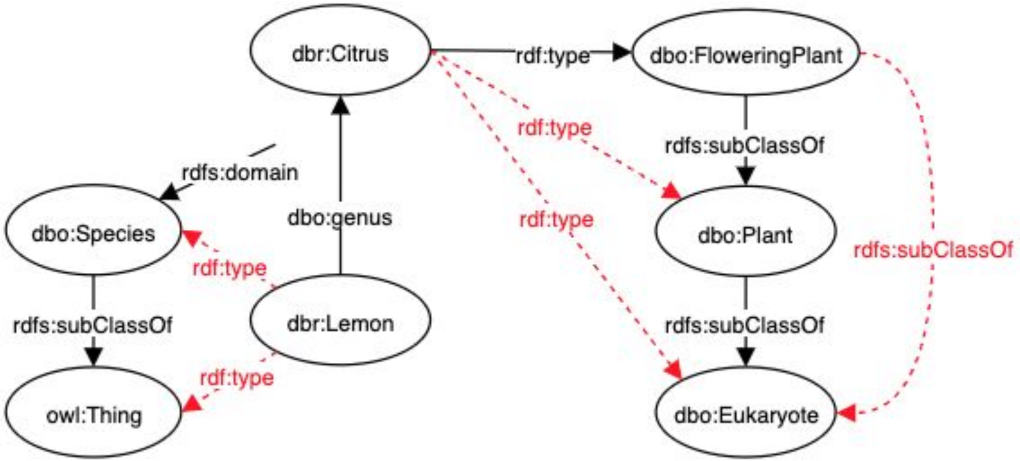

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Semantic Web Standards - OWL

The **Web Ontology Language (OWL)** enables more expressive semantics and richer entailment[1,2]

Extends the RDFS with things like:

- EquivalentClass/Property: allows for stating two classes/properties are the same
- disjointWith/disjointPropertyWith: allows for stating two classes/properties never the same
- TransitiveProperty: enables inference based on transitive law
- UnionOf/intersectionOf/ComplementOf: enables the application of set logic

[1] http://www.w3.org/TR/owl-features/; [2] DOI: 10.1201/b16859

Semantic Web Standards - OWL

OWL supports "RDF-based Semantics",

Supports "direct semantics" enabling ontologies to be translated into **axioms** compatible with a formalism called Description Logics[1]

Description Logics aim to define a subset of First Order Logic where the semantics of the language can be supported in a sound (correct) and complete manner using algorithms or reasoners[2]

Reasoners can verify:

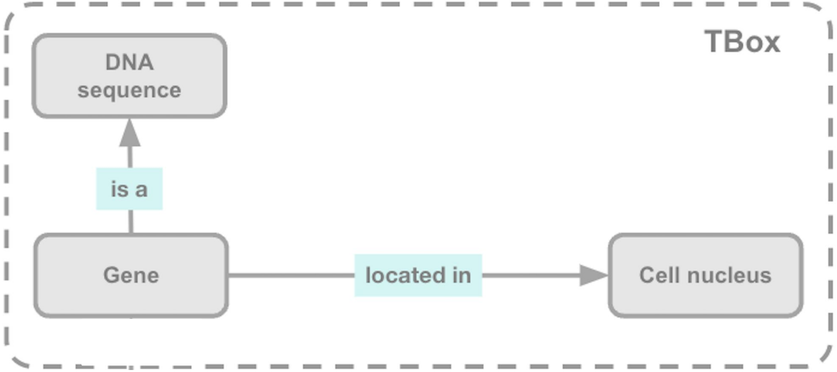
consistency, satisfiability (class membership does not cause logical contradictions), subsumption (a class is necessarily a subclass of another), instance (a resource is a member of a class) and conjunctive query answering (complex queries against the ontology and its entailments)[3]

[1] http://www.w3.org/TR/rdf-mt/; [2] DOI: 10.1201/b16859; [3] http://www.w3.org/TR/owl2-rdf-based-semantics/

Semantic Web Standards - Description Logics

Description logics splits concepts and their relationships from instances and their attributes/roles

TBox describes “classes” (i.e., types of objects), properties (i.e., relationships), and assertions (i.e., statements of facts) assumed to generally be true. The TBox is often formalized as an ontology



https://www.mkbergman.com/489/ontology-best-practices-for-data-driven-applications-part-2/
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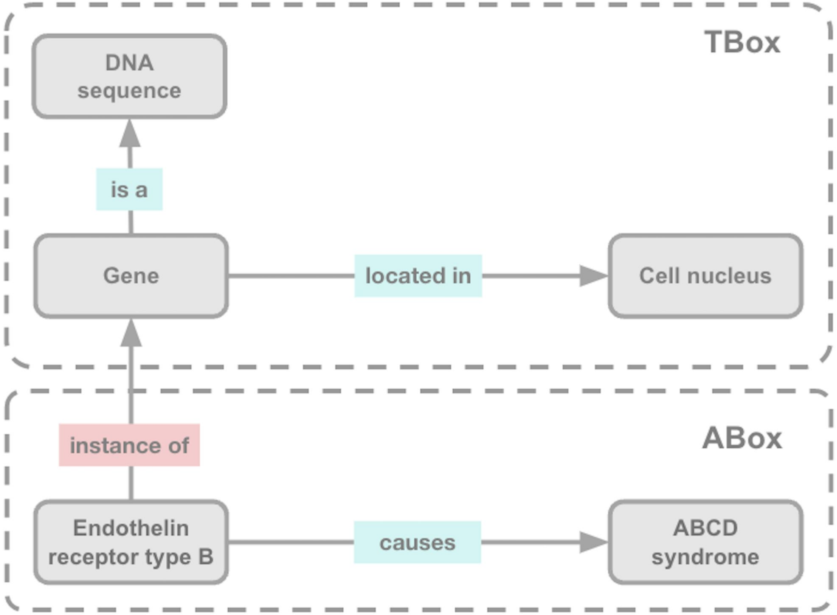
ABox describes “individuals” or instances of classes and assertions that are specific to an instance. The ABox models instances of ontology classes and properties



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Part 1 - Lecture

Biological Knowledge Graphs

Background

Construction

PheKnowLator

Knowledge-based Biomedical Data Science

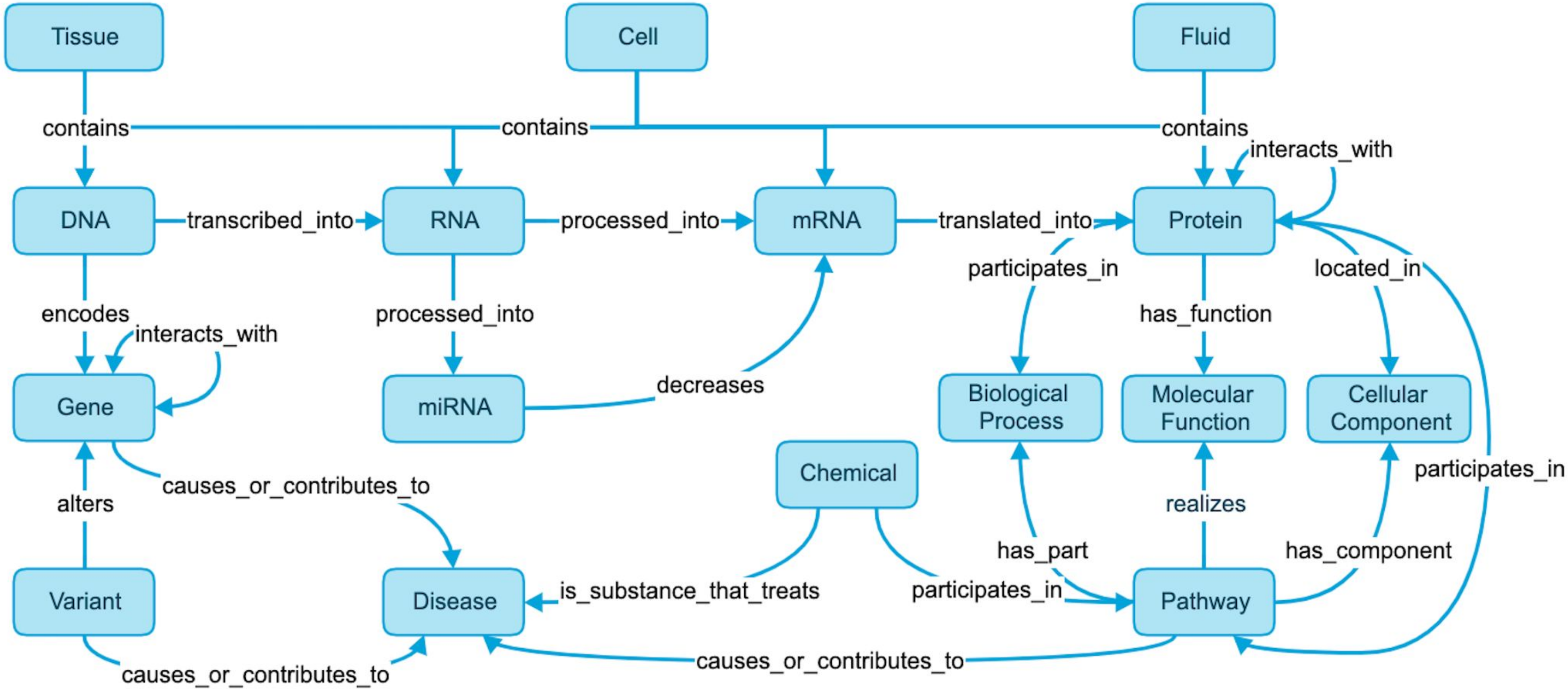
Knowledge-based biomedical data science involves designing computer systems to act as if they know about medicine and biology[1]

There are many ways in which a system might act as if it knows something:

- Use existing knowledge to generate, rank, or evaluate hypotheses about a dataset
- Answer a natural language question about a biomedical topic

Knowledge-based systems specify a knowledge representation—how a computer system represents knowledge internally—and one or more inference or reasoning methods—how computations over knowledge representations are used to produce output[2]

[1] PMID:30294517; [2] PMC:8095730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located_in
encodes
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processed_into
has_function
Gene
miRNA
decreases
Biological Process
Molecular Function
Cellular Component
participates_in
causes_or_contributes_to
Chemical
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realizes
has_part
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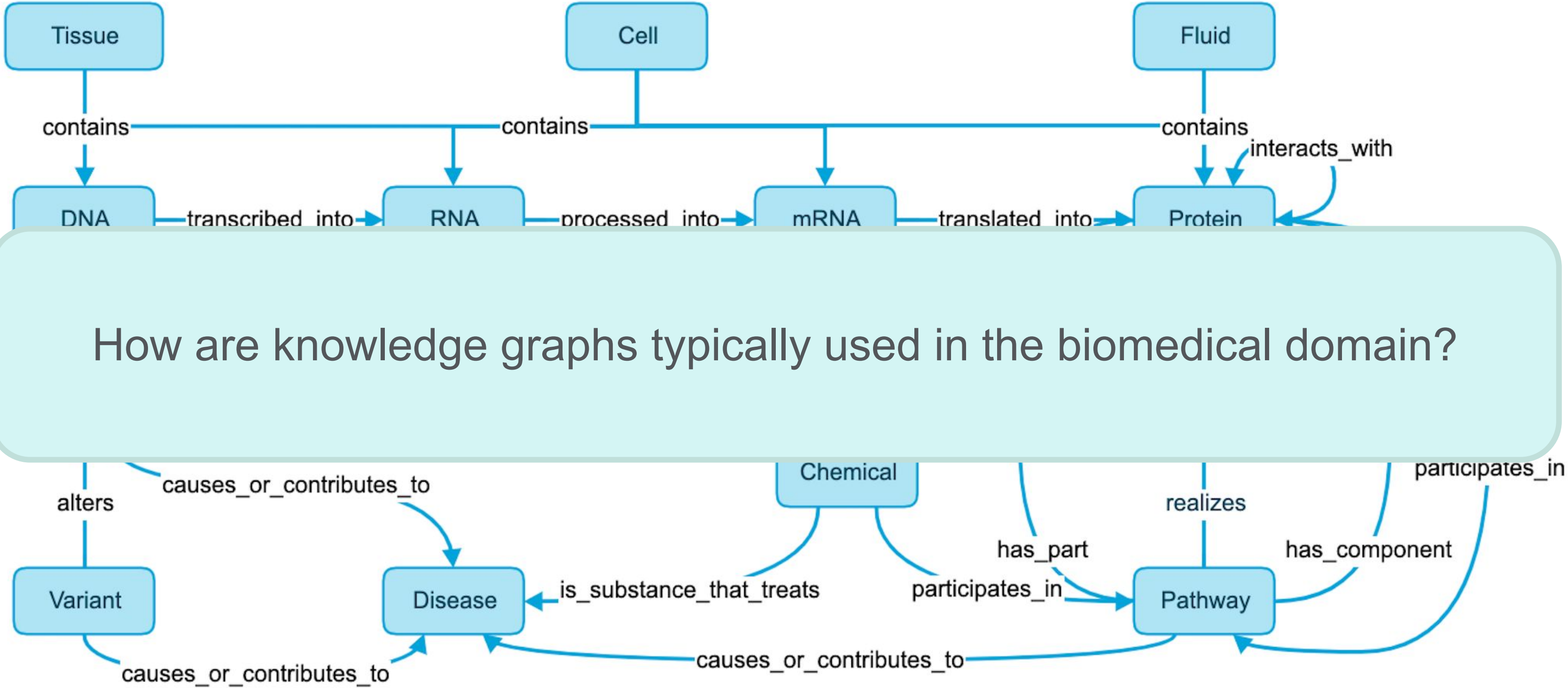
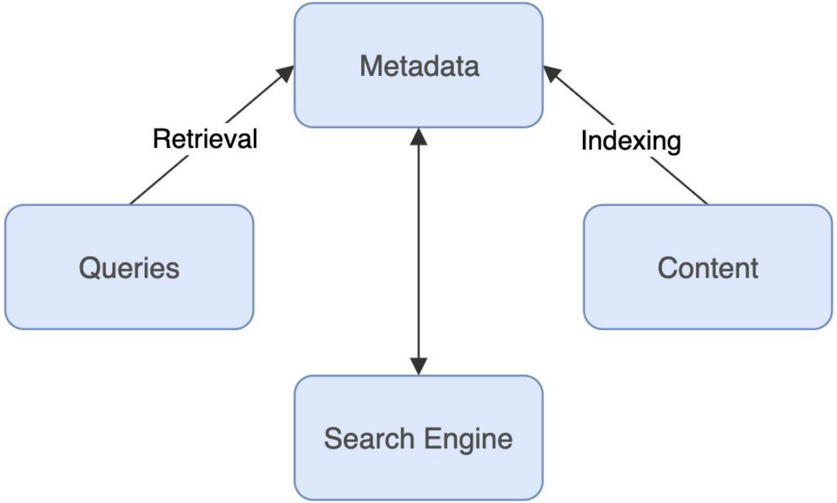


How are knowledge graphs typically used in the biomedical domain?

Biomedical Knowledge Graphs - **Applications**

Information Retrieval

- Knowledge graphs have been used to organize knowledge for information retrieval
- Designed to make it possible to find facts or evidence for a wide variety of topics



Biomedical Knowledge Graphs - **Applications**

Inferring New Knowledge

- Graph Algorithms
    - Edge (or link) prediction and community detection or clustering. These methods are a form of hypothesis generation and often include an estimate of confidence in the prediction

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Inferring New Knowledge

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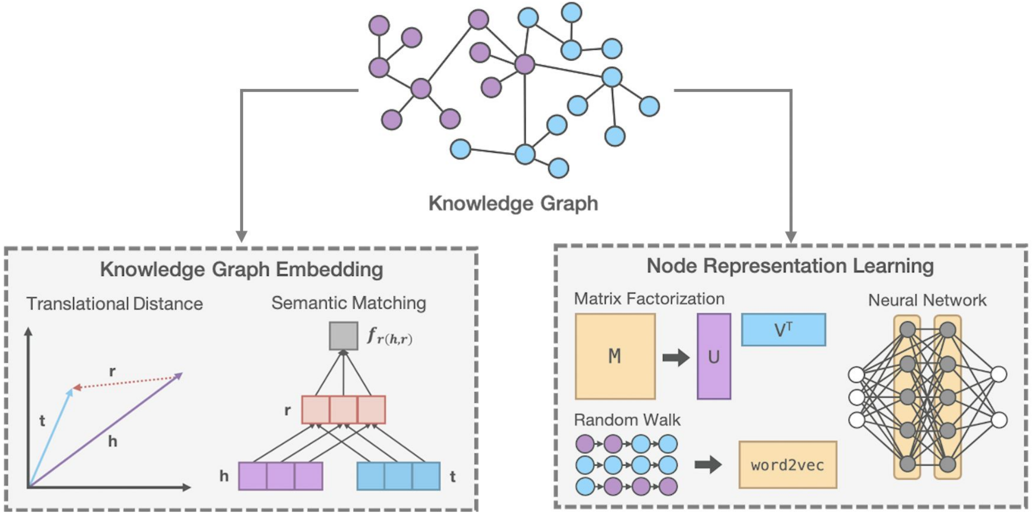
- Logical Reasoners
  - Satisfiability inference checks to see if a class definition is logically satisfiable
  - Subsumption inference uses class definitions to identify all classes that are fully contained within some other class. Particularly useful because it makes explicit many edges that are otherwise implicit, and therefore it can improve the results of other algorithms that depend on the structure of the graph, such as link prediction or embeddings

Biomedical Knowledge Graphs - **Applications**

Alternative Representations

- Neural networks are commonly applied to knowledge graphs to create embeddings which can be used as input for downstream learning and Q&A systems



PMC:8095730; image: 10.5281/zenodo.5716401

Biomedical Knowledge Graphs - **Clinical Applications**

Clinical

Using knowledge graphs with traditional rule-based approaches for information retrieval

- Graph-based patient representations to enable querying based on domain knowledge[1]
- Evidence for diagnostic assistance, clinical decision support machinery, or surveillance
  - Predict treatments for and causes of different diseases[2,3]
  - Pharmacovigilance and drug safety surveillance systems[4,5]

Discover missing knowledge or generate novel hypotheses

- Identify comorbid diseases[6,7] and drug repurposing candidates[8]

Capture complex patient information for further processing

- Create patient-specific KGs for analysis and visualization[9-11]
- Interactive tool to help users interact with complex data[12]

[1] arXiv:1812.09905; [2] PMID:29763706; [3] PMID:30441083; [4] DOI:hal-01976825; [5] arXiv:1905.11513
[6] PMID:31295118; [7] PMID:28449114; [8] PMID:29218876; [9] DOI:10.1109/HealthCom.2017.8210797
[10] DOI:10.1609/aaai.v33i01.33011126; [11] PMID:29218916; [43] PMID:14597658

Biomedical Knowledge Graphs - **Biological Applications**

Biological

Applying node embedding techniques to knowledge graphs

- For prediction or visualization of complex biological systems in low-dimensional spaces[15,45,46]
- To convert knowledge graphs into low-dimensional spaces in order to visualize clusters in two- or three-dimensional projections to better display entities of interest[41]
- To leverage semantic similarity-inspired hypotheses and identify valuable drug–drug[40,47,51], drug-target[51], or protein–protein interactions[46,48]
- To perform link prediction methods in order to test hypothesize previously hypothesized and/or unobserved biological relationships for drug repurposing[36,40,45,47-56]
- To combine with gene expression time series data in order to create specific and detailed hypotheses regarding mechanisms of toxicity[45]

Review Article: PMID:33954284

Biomedical Knowledge Graphs - **NLP**

Natural Language Processing (NLP)

Knowledge graphs have been used to improve NLP performance

- Summarization or information extraction from EHRs and Q&A systems[15,26,27,29,40,60,61]
- Knowledge graph-derived embeddings used alone or in combination with other text-derived features[46] improved the performance of a variety of NLP tasks, including named entity recognition,[62] coreference resolution,[63] and relation extraction[64]

Knowledge graphs are important components of information extraction systems

- Ontologies can serve as formal dictionaries allowing for rapid indexing in named entity recognition and word sense disambiguation tasks[65, 66]
- Knowledge graphs offer richer semantic context than lexicons, identifying not only similar concepts but also rich collections of relationships that can be used to disambiguate or otherwise improve concept recognition in texts[65-68]

Biomedical Knowledge Graphs - **Organizational Efforts**

The US and European scientific institutions support knowledge graph efforts

- The National Institutes of Health's National Center for Advancing Translational Sciences' Biomedical Data Translator project (https://ncats.nih.gov/translator)
  - A computational system that integrates sources of existing biomedical knowledge in order to translate clinical inquiries into relevant research results that synthesize elements of the integrated knowledge to directly answer the inquiry or generate testable hypotheses
- Elixir Europe (https://elixir-europe.org/)
  - Managing and safeguarding data generated by publicly funded life science research and integrating bioinformatics resources. The Elixir Core Data Resources are leaders in the production of interoperable knowledge resources and are widely used components of biomedical knowledge graphs

PMID:33954284

Part 1 - Lecture

Biological Knowledge Graphs

Background

Construction

Constructing Knowledge Graphs

There are many ways to construct a biomedical knowledge graph and nearly all rely on Linked Open Data

Approaches

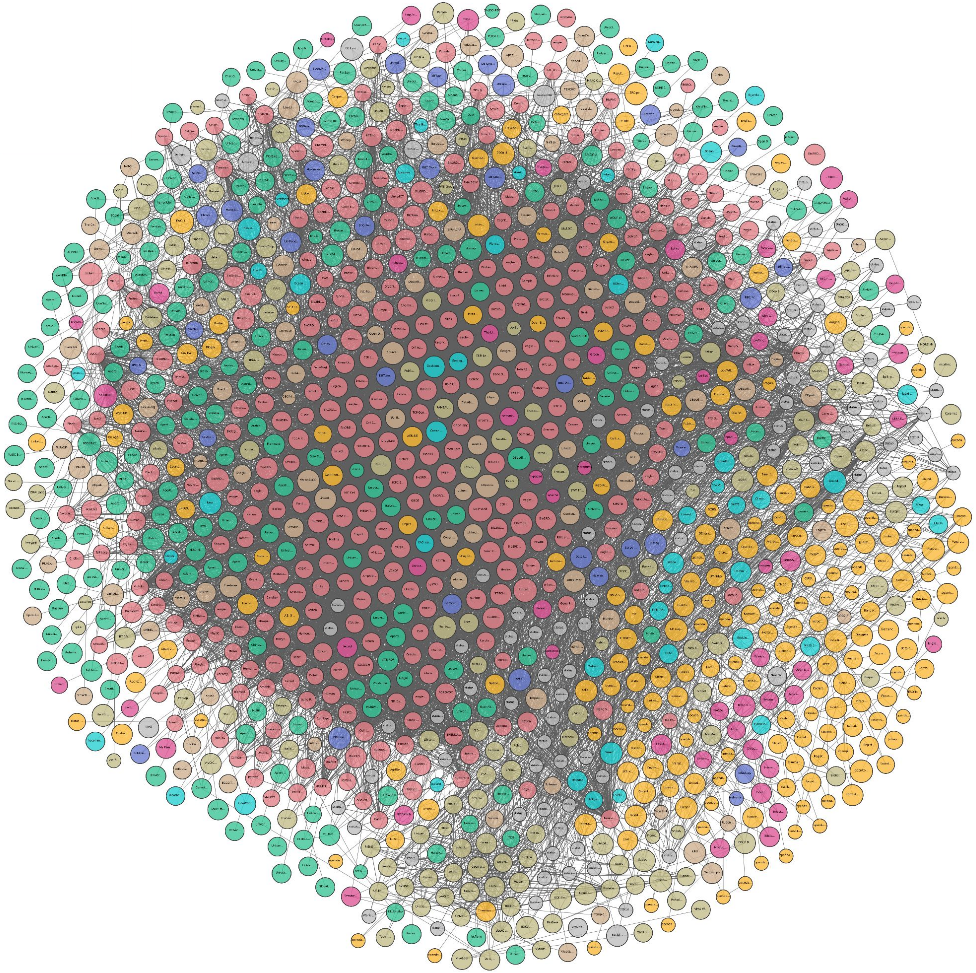
- Simple (Property Graphs): joining nodes as a series of edges
- Hybrid RDF Graphs: joining nodes as a series of edges to existing ontologies
- Complex (OWL Graphs): use of formal semantics with or without existing ontologies

General Build Workflow

- Download data
- Preprocess data (filtering, identifier mapping and cross-walking)
- Construct graph
- Prepare/incorporate node/edge metadata (if included)
- Serialize output

Legend

- Cross Domain
- Geography
- Government
- Life Sciences
- Linguistics
- Media
- Publications
- Social Networking
- User Generated



The Linked Open Data Cloud from lod-cloud.net

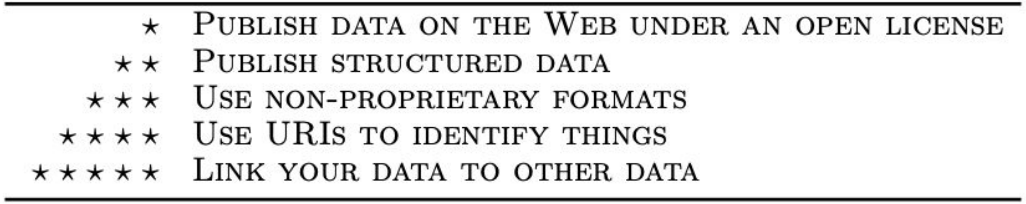
Constructing Knowledge Graphs- **Linked Open Data**

The core aim of **Linked Data** is to provide a set of principles by which the Semantic Web standards can be effectively deployed on the Web to facilitate discovery and interoperability of structured data[1]

Early RDF data were dumped into “silos”, which while the data within them were interoperable they were rarely interlinked, had inconsistent URI naming, and were often published using different conventions[1]

Linked Data Principles were created in 2006 to help address these limitations:

- Open Data “5 Star Scheme”, where each star increases the reusability and interopability[1,2]



★	Publish data on the Web under an open license
★★	Publish structured data
★★★	Use non-proprietary formats
★★★★	Use URIs to identify things
★★★★★	Link your data to other data

[1] DOI: 10.1201/b16859; [2] http://www.w3.org/DesignIssues/LinkedData.html

Constructing Knowledge Graphs - **Important Assumptions**

Open World Assumption

Given a knowledge base, a statement can be True, False, or Unknown

- True: a statement can always be derived from the knowledge base
- False: a statement can never be derived from the knowledge base
- Unknown: a statement can be derived by a version of the knowledge base

Assumption: knowledge base only covers key aspects of world

Closed World Assumption

Given a knowledge base, a statement can only be True or False

- True: a statement can always be derived from the knowledge base
- False: otherwise

Assumption: knowledge base has complete knowledge about part of the world

Constructing Knowledge Graphs - **Important Assumptions**

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True: a statement can always be derived from the knowledge base

False: otherwise

Assumption: knowledge base has complete knowledge about part of the world

DOI: 10.1201/b16859

Constructing Knowledge Graphs - **Simple**

Simple knowledge graphs aim to model entities and their relations using (basic) network science representations without formal semantics

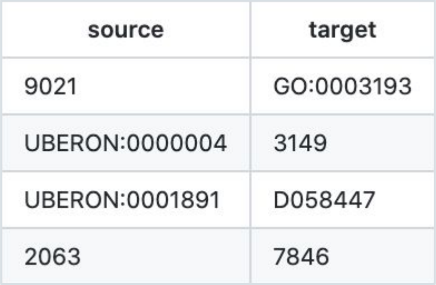
- One or more node types
- A single directed or undirected edge
- Associated node and edge metadata

Build Workflow: General

Output: flat-file (tabular) edge list and node data; adjacency matrix; metadata annotations

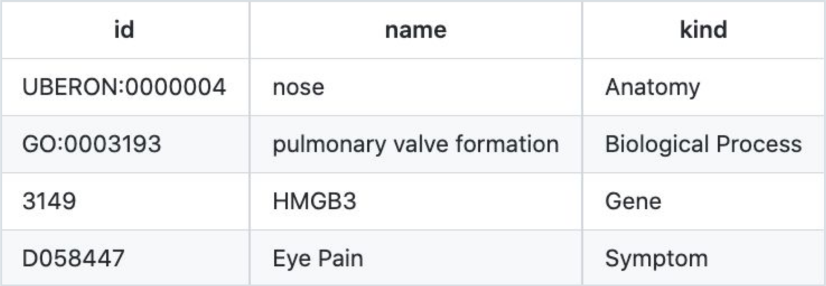
Constructing Knowledge Graphs - **Simple**

Edges

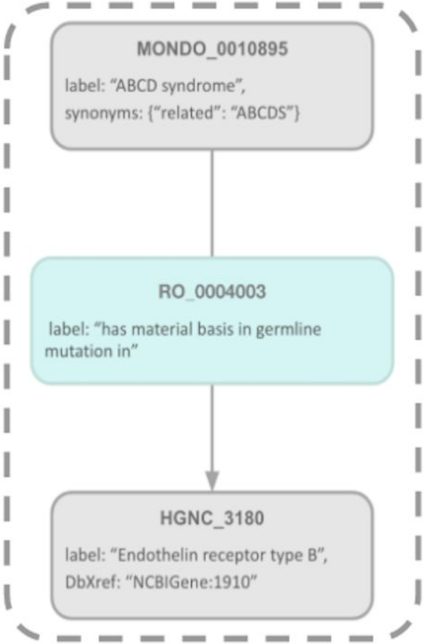


source	target
9021	GO:0003193
UBERON:0000004	3149
UBERON:0001891	D058447
2063	7846

Nodes



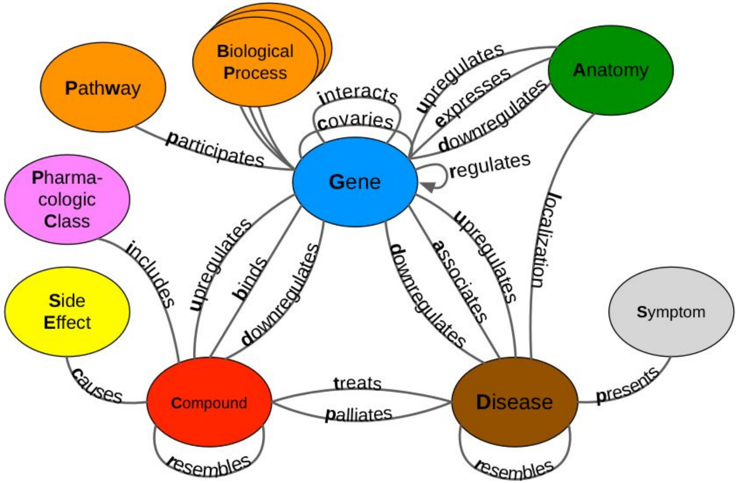
id	name	kind
UBERON:0000004	nose	Anatomy
GO:0003193	pulmonary valve formation	Biological Process
3149	HMGB3	Gene
D058447	Eye Pain	Symptom

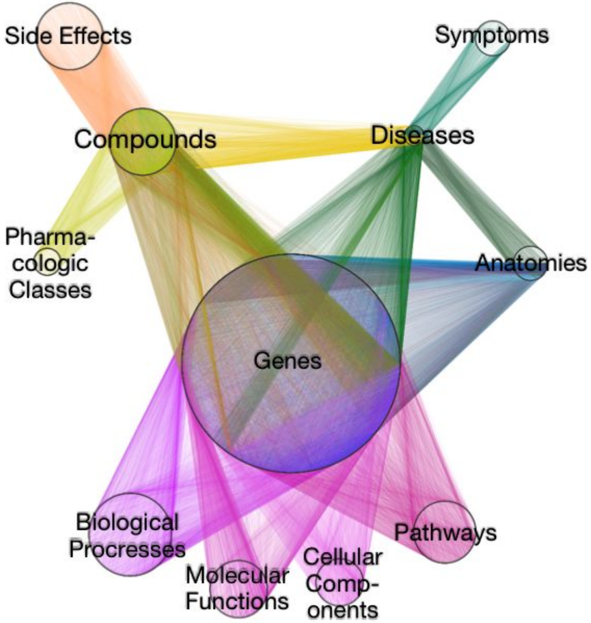

MONDO_0010895
label: "ABCD syndrome",
synonyms: {"related": "ABCDS"}
RO_0004003
label: "has material basis in germline mutation in"
HGNC_3180
label: "Endothelin receptor type B",
DbXref: "NCBIGene:1910"

Hetionet

Hetionet is a heterogeneous network with multiple node and edge (relationship) types. The hetnet was designed for Project Rephetio, which aims to systematically identify why drugs work and predict new therapies for drugs.

47,031 nodes (11 types) and 2,250,197 relationships (24 types)





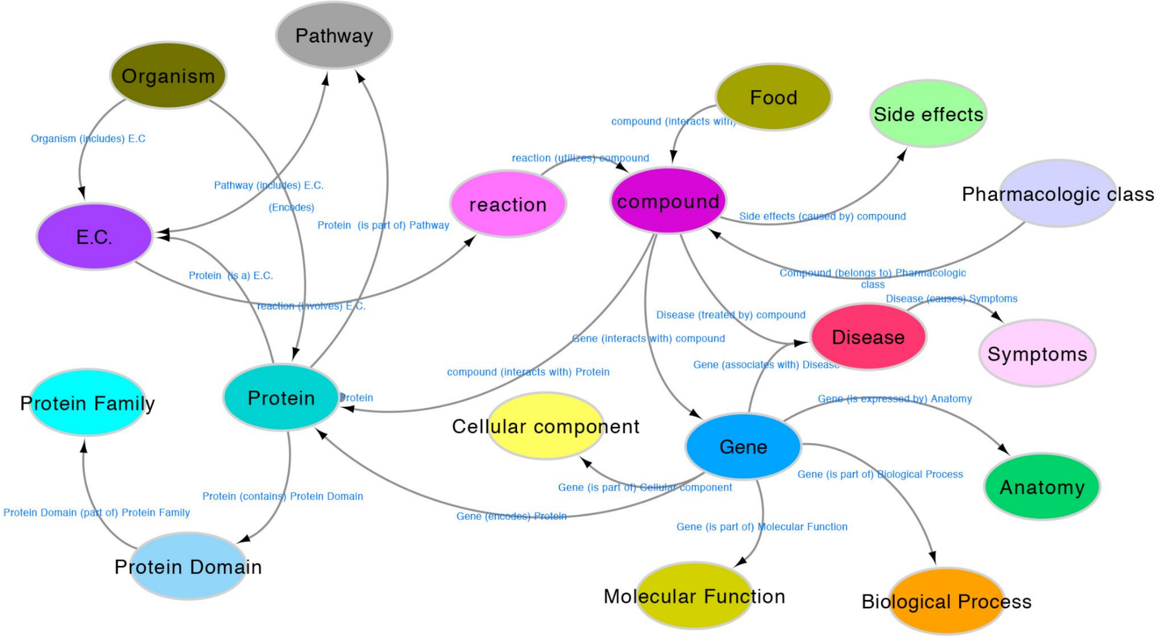
https://het.io/

DOI: 10.7554/eLife.26726

Scalable Precision Medicine Open Knowledge Engine

Scalable Precision Medicine Open Knowledge Engine (SPOKE) currently includes 19 databases such as LINCS, GWAS Catalog, ChemBL, DrugBank, SIDER and iRefIndex. The clinical insight sources include UCSF's large data store of de-identified patient clinical data. Designed to connect basic molecular data with clinical insights and environmental exposures.

47,000 nodes (11 types) and 2.25 million edges (24 types)



Pathway
Organism
Food
Side effects
compound (interacts with)
Organism (includes) E.C
reaction (utilizes) compound
Pathway (includes) E.C.
(Encodes)
reaction
compound
Pharmacologic class
Protein (is part of) Pathway
Side effects (caused by) compound
E.C.
Protein (is a) E.C.
Compound (belongs to) Pharmacologic class
reaction (involves) E.C.
Disease (causes) Symptoms
Disease (treated by) compound
Disease
Gene (interacts with) compound
Symptoms
Gene (associates with) Disease
compound (interacts with) Protein
Protein Family
Protein
Protein
Gene (is expressed by) Anatomy
Cellular component
Gene
Gene (is part of) Biological Process
Anatomy
Gene (is part of) Cellular component
Protein (contains) Protein Domain
Protein Domain (part of) Protein Family
Gene (encodes) Protein
Gene (is part of) Molecular Function
Protein Domain
Molecular Function
Biological Process

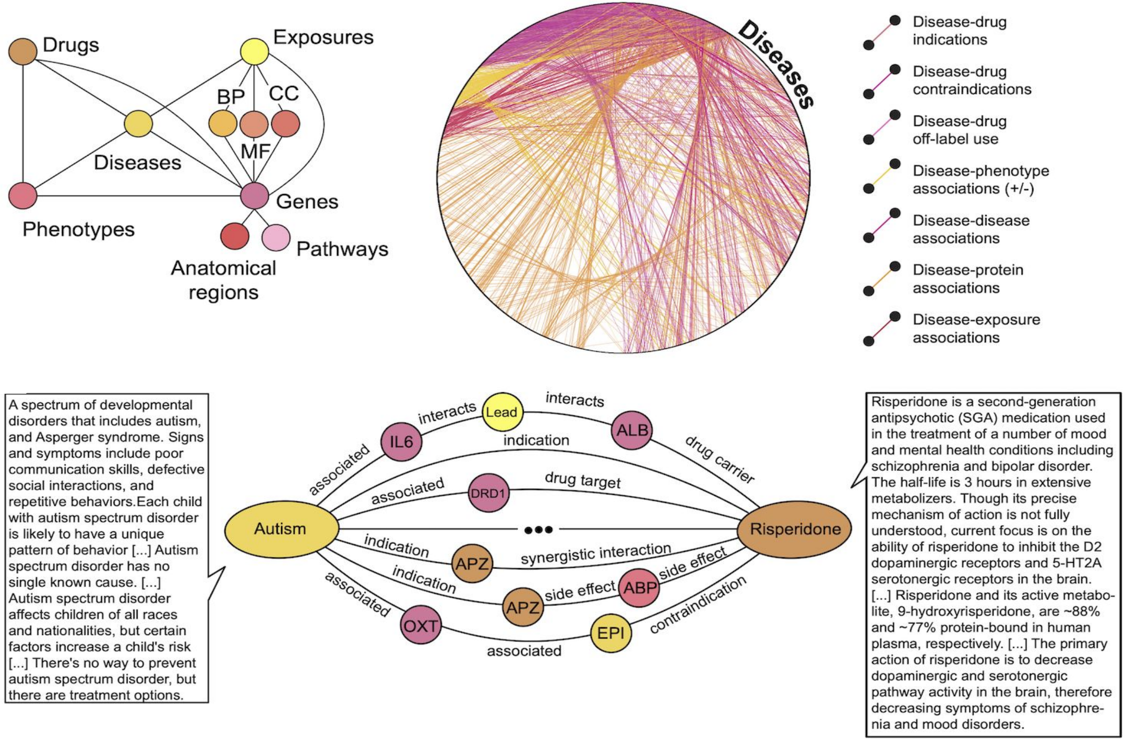
https://spoke.ucsf.edu/

PMID:31292438

PrimeKG

PrimeKG is a “a precision medicine-oriented knowledge graph that provides a holistic view of diseases”. The graph integrates 20 resources to describe diseases with relationships representing 10 major biological scales and all approved and experimental drugs.

129,375 nodes (10 types) and 8,100,498 edges (30 types)



A spectrum of developmental disorders that includes autism, and Asperger syndrome. Signs and symptoms include poor communication skills, defective social interactions, and repetitive behaviors.Each child with autism spectrum disorder is likely to have a unique pattern of behavior [...] Autism spectrum disorder has no single known cause. [...] Autism spectrum disorder affects children of all races and nationalities, but certain factors increase a child's risk [...] There's no way to prevent autism spectrum disorder, but there are treatment options.

Risperidone is a second-generation antipsychotic (SGA) medication used in the treatment of a number of mood and mental health conditions including schizophrenia and bipolar disorder. The half-life is 3 hours in extensive metabolizers. Though its precise mechanism of action is not fully understood, current focus is on the ability of risperidone to inhibit the D2 dopaminergic receptors and 5-HT2A serotonergic receptors in the brain. [...] Risperidone and its active metabolite, 9-hydroxyrisperidone, are ~88% and ~77% protein-bound in human plasma, respectively. [...] The primary action of risperidone is to decrease dopaminergic and serotonergic pathway activity in the brain, therefore decreasing symptoms of schizophrenia and mood disorders.

https://zitniklab.hms.harvard.edu/projects/PrimeKG/

DOI: 10.1101/2022.05.01.489928

Constructing Knowledge Graphs - **Hybrid**

Hybrid knowledge graphs aim to model entities and their relations using a mix of standard network representations and “some” formal semantics (usually RDF) borrowed from ontologies

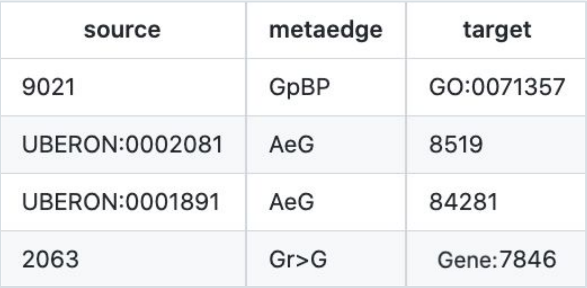
- One or more node types (typed)
- A single directed or undirected edge (typed)
- Associated node and edge metadata

Build Workflow: General

Output: flat-file (tabular) edge list and node data; adjacency matrix; metadata annotations

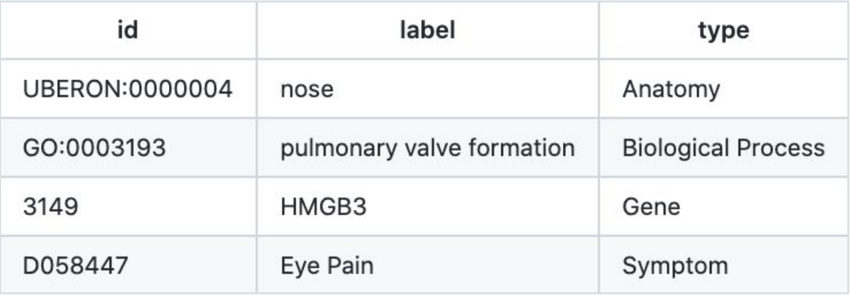
Constructing Knowledge Graphs - **Hybrid**

Edges



source	metaedge	target
9021	GpBP	GO:0071357
UBERON:0002081	AeG	8519
UBERON:0001891	AeG	84281
2063	Gr>G	Gene:7846

Nodes



id	label	type
UBERON:0000004	nose	Anatomy
GO:0003193	pulmonary valve formation	Biological Process
3149	HMGB3	Gene
D058447	Eye Pain	Symptom

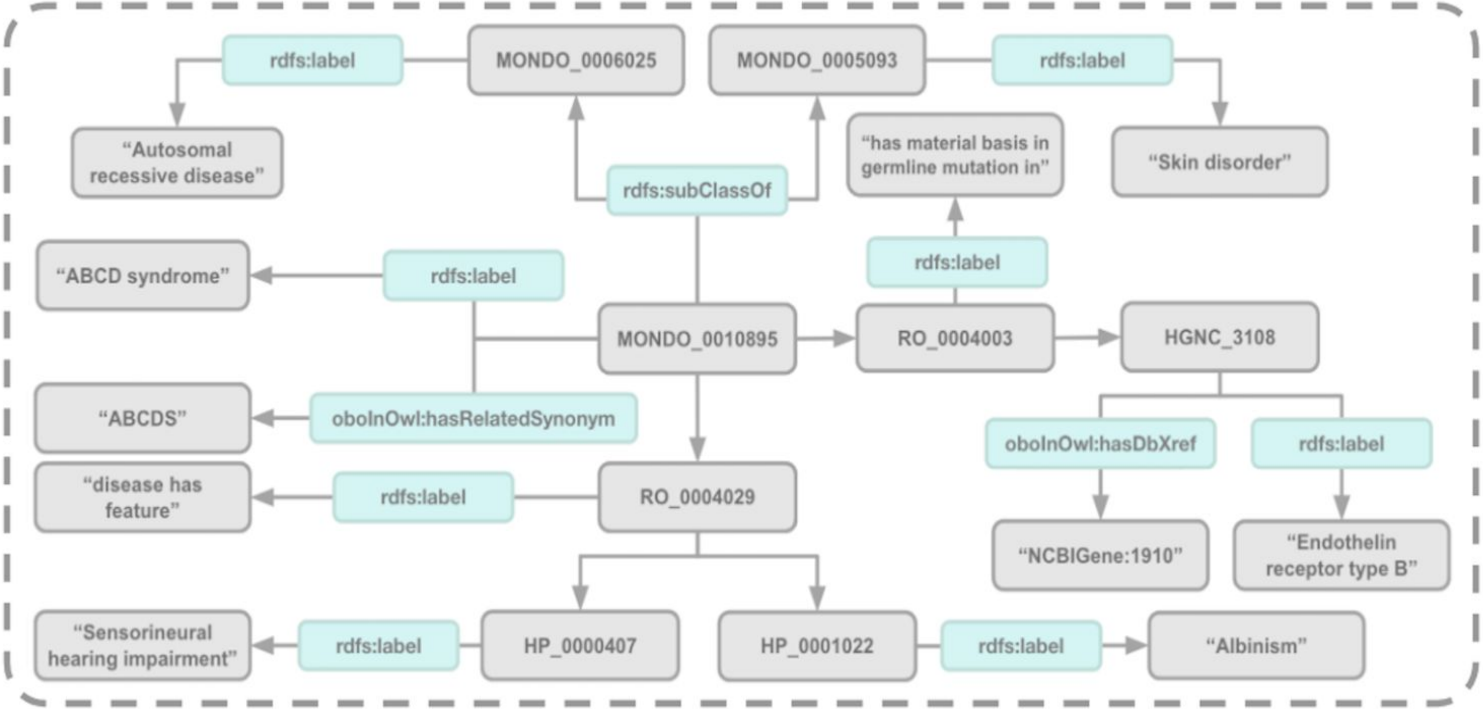
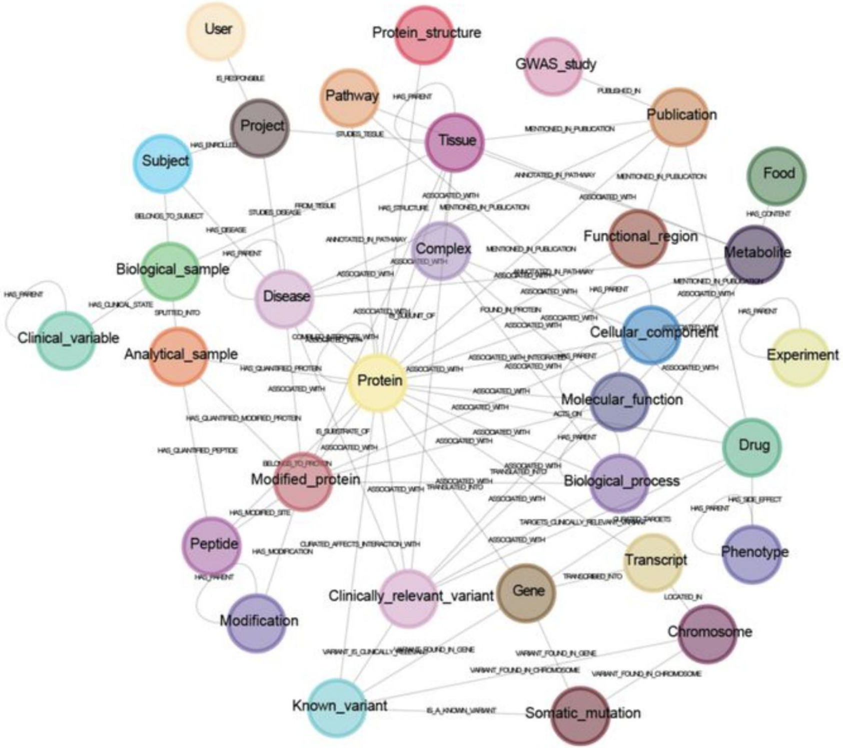


image: https://zenodo.org/record/5893789

Clinical Knowledge Graph (CKG)

The **Clinical Knowledge Graph (CKG)** is an open source platform designed for “integrating other types of omics data, like proteomics, into the clinical decision-making process”. The framework combines experimental data, public databases, and the literature. The Graph is constructed using data from 26 databases, 6 experiments, and 9 ontologies.

19,405,058 nodes (35 types) and 217,341,612 edges (57 types)



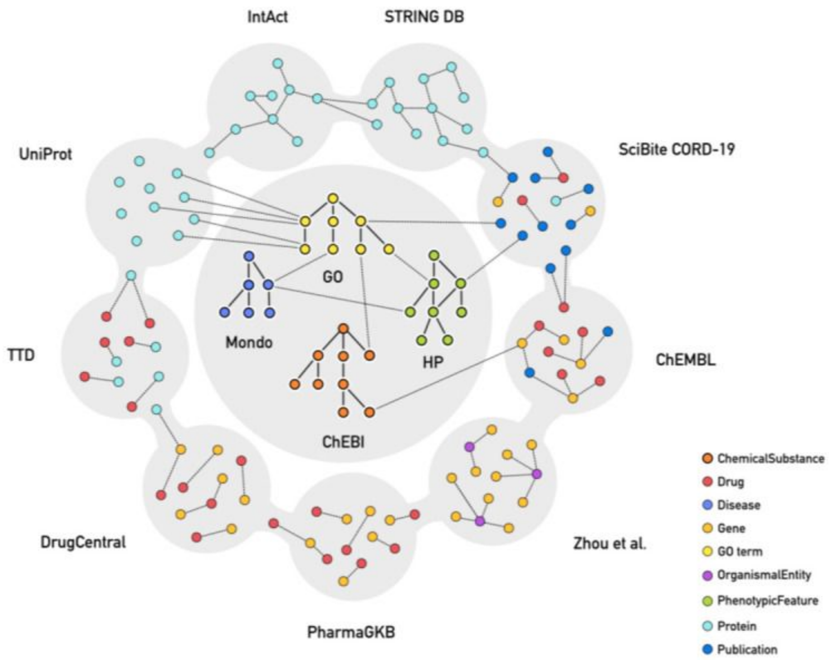
https://github.com/MannLabs/CKG

DOI:10.1101/2020.05.09.084897

KG-COVID-19

KG-COVID-19 is a framework developed and maintained by the Monarch Initiative that ingests and integrates different sources of biomedical data to produce knowledge graphs for COVID-19 response. "This framework can also be applied to other problems in which siloed biomedical data must be quickly integrated for different research applications, including future pandemics."

574,778 nodes (20 types) and 24,145,561 edges (561 types)



https://github.com/Knowledge-Graph-Hub/kg-covid-19/wiki

Constructing Knowledge Graphs - **Complex**

Complex knowledge graphs aim to model entities and their relations using formal semantics with explicit modifications to data not represented as an ontology

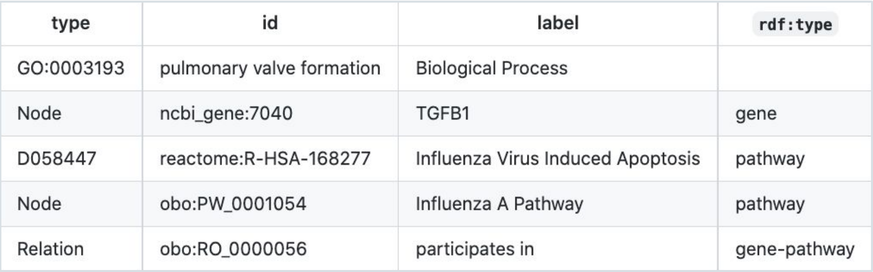
- One or more node types (RDF typed)
- Multiple directed edges (RDF typed)
- Associated node and edge metadata (integrated as annotation assertions or stored as named graphs)

Build Workflow: General + modifications to "ontologize" data not represented as an ontology

Output: Turtle, RDF/XML, OWL

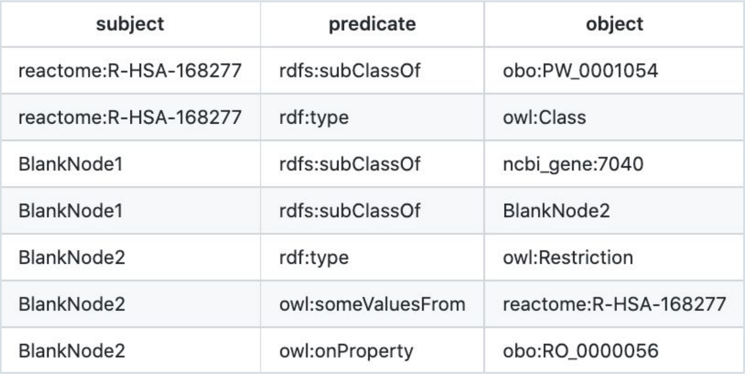
Constructing Knowledge Graphs - **Complex**

Nodes



type	id	label	`rdf:type`
GO:0003193	pulmonary valve formation	Biological Process	
Node	ncbi_gene:7040	TGFB1	gene
D058447	reactome:R-HSA-168277	Influenza Virus Induced Apoptosis	pathway
Node	obo:PW_0001054	Influenza A Pathway	pathway
Relation	obo:RO_0000056	participates in	gene-pathway

Edges



subject	predicate	object
reactome:R-HSA-168277	rdfs:subClassOf	obo:PW_0001054
reactome:R-HSA-168277	rdf:type	owl:Class
BlankNode1	rdfs:subClassOf	ncbi_gene:7040
BlankNode1	rdfs:subClassOf	BlankNode2
BlankNode2	rdf:type	owl:Restriction
BlankNode2	owl:someValuesFrom	reactome:R-HSA-168277
BlankNode2	owl:onProperty	obo:RO_0000056

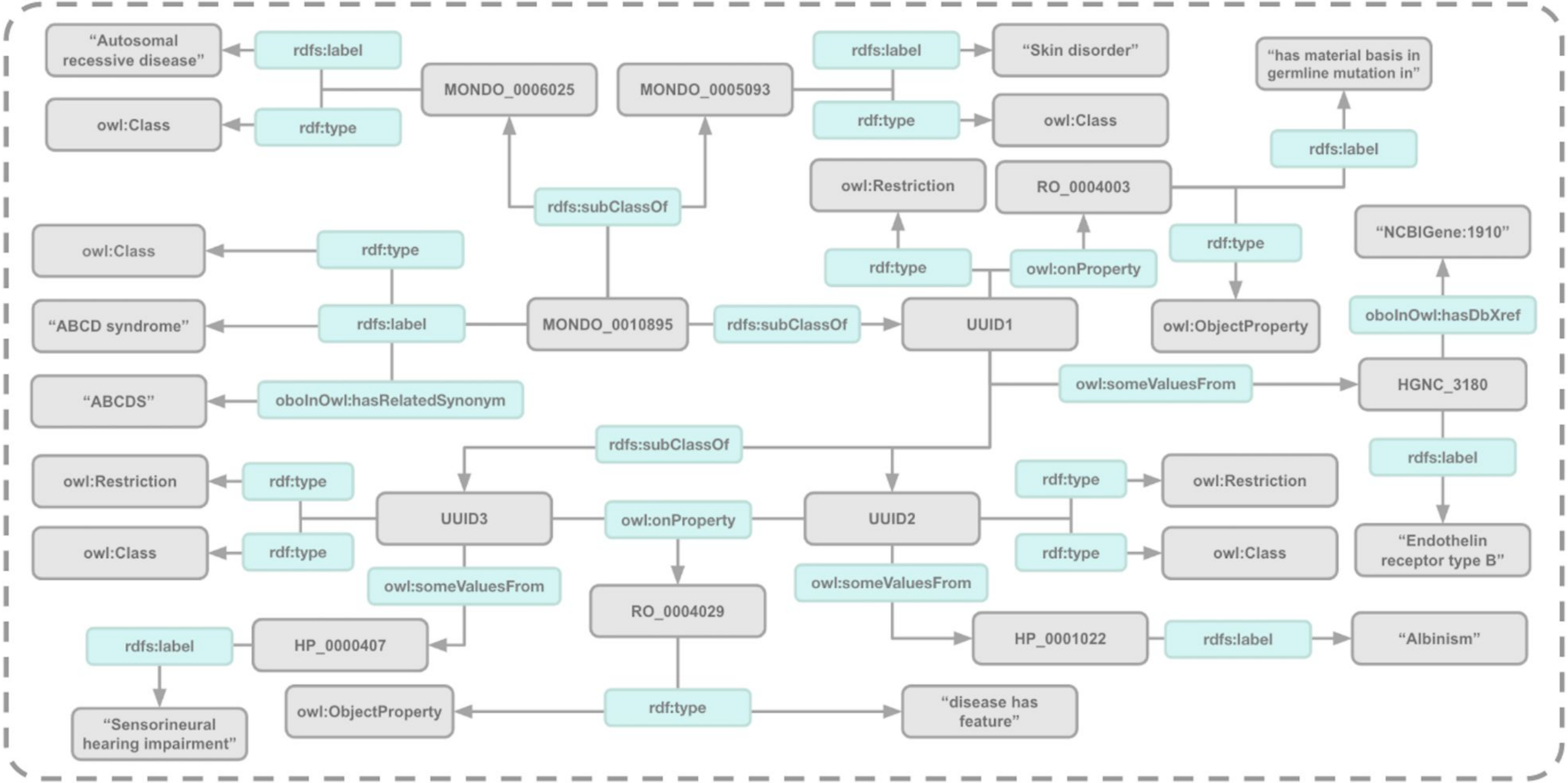
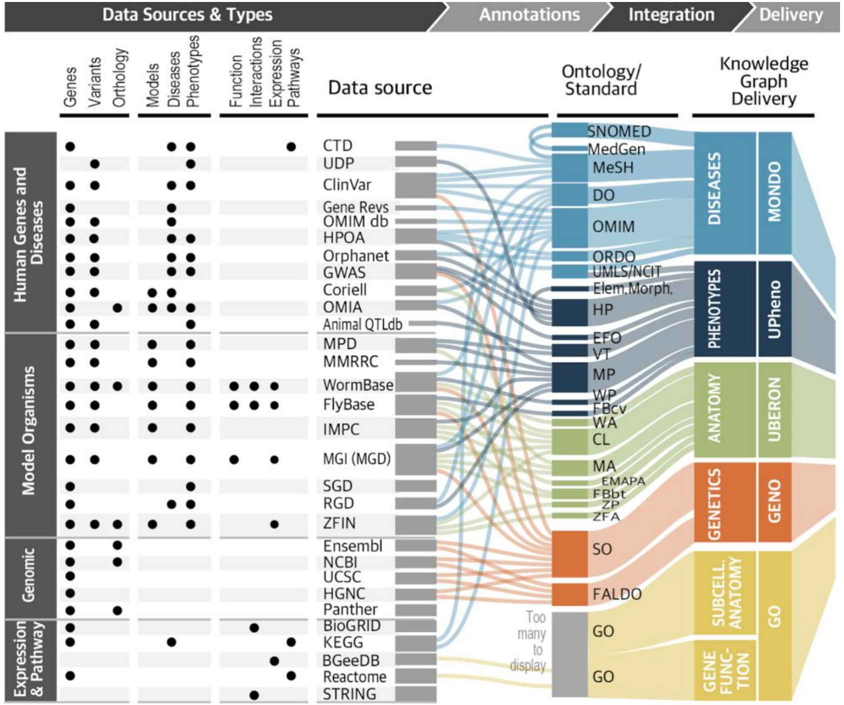


image: https://zenodo.org/record/5893789

Monarch Knowledge Graph

The **Monarch Knowledge Graph** is part of a large system designed and maintained by the Monarch Initiative with the goal of representing gene-to-phenotype relationships across multiple model organisms. The Monarch platform is used to construct this knowledge graph, which are used to construct several different ontologies, which can also be integrated with each other.

32.9 million nodes and 160,000,000 million edges



	Genes	Variants	Orthology	Models	Diseases	Phenotypes	Function	Interactions	Expression	Pathways	Data source
Human Genes and Diseases	●				●	●				●	CTD
		●				●					UDP
	●	●			●	●					ClinVar
	●				●						Gene Revs
	●	●			●						OMIM db
	●	●			●	●					HPOA
	●	●			●	●					Orphanet
	●	●			●	●					GWAS
	●	●		●	●						Coriell
	●		●	●	●	●					OMIA
	●	●				●					Animal QTLdb
Model Organisms	●	●		●		●					MPD
	●	●		●		●					MMRRC
	●	●	●	●		●	●	●	●		WormBase
	●	●		●		●	●	●	●		FlyBase
	●	●		●		●					IMPC
	●	●		●		●	●		●		MGI (MGD)
	●					●					SGD
	●				●	●					RGD
	●	●	●	●		●			●		ZFIN
Genomic	●		●								Ensembl
	●		●								NCBI
	●										UCSC
	●										HGNC
	●		●								Panther
Expression & Pathway	●							●			BioGRID
	●				●					●	KEGG
									●		BGeeDB
	●									●	Reactome
								●			STRING

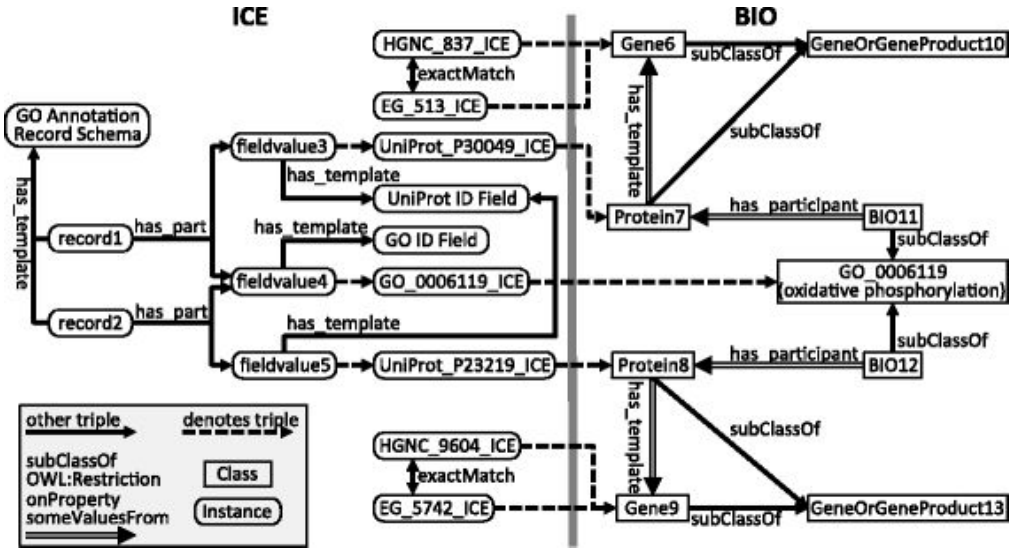
https://archive.monarchinitiative.org/latest

DOI: 10.1093/nar/gkz997

KaBOB

The **Knowledge Base of Biomedicine (KaBOB)** is a large-scale semantically rich representation of of important biomedica concepts and their relationships. KaBOB is grounded in the Open Biomedical and Biological Ontology Foundry Ontologies and represents data for seven model organisms.

~500 million triples (according to 2015 publication)



https://github.com/drlivingston/kabob

PMID:25903923

Simple

Hybrid

Complex

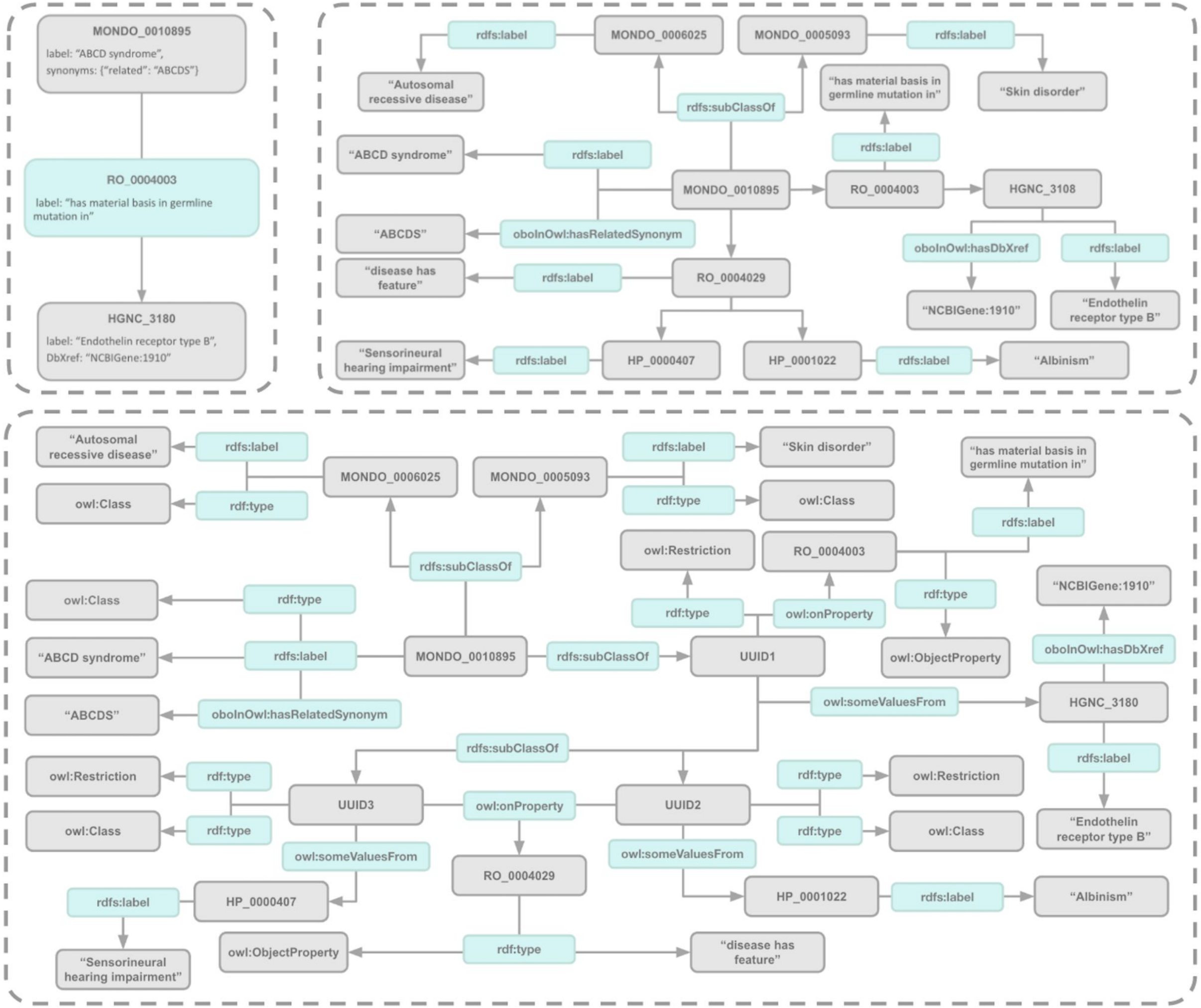


image: https://zenodo.org/record/5893789

Part 1 - Lecture

Biological Knowledge Graphs

Background

Construction

PheKnowLator

Motivation

Design Challenges

- Multiple approaches to modeling biomedical knowledge[1-3]
- No existing benchmarks for knowledges graphs built using different knowledge models

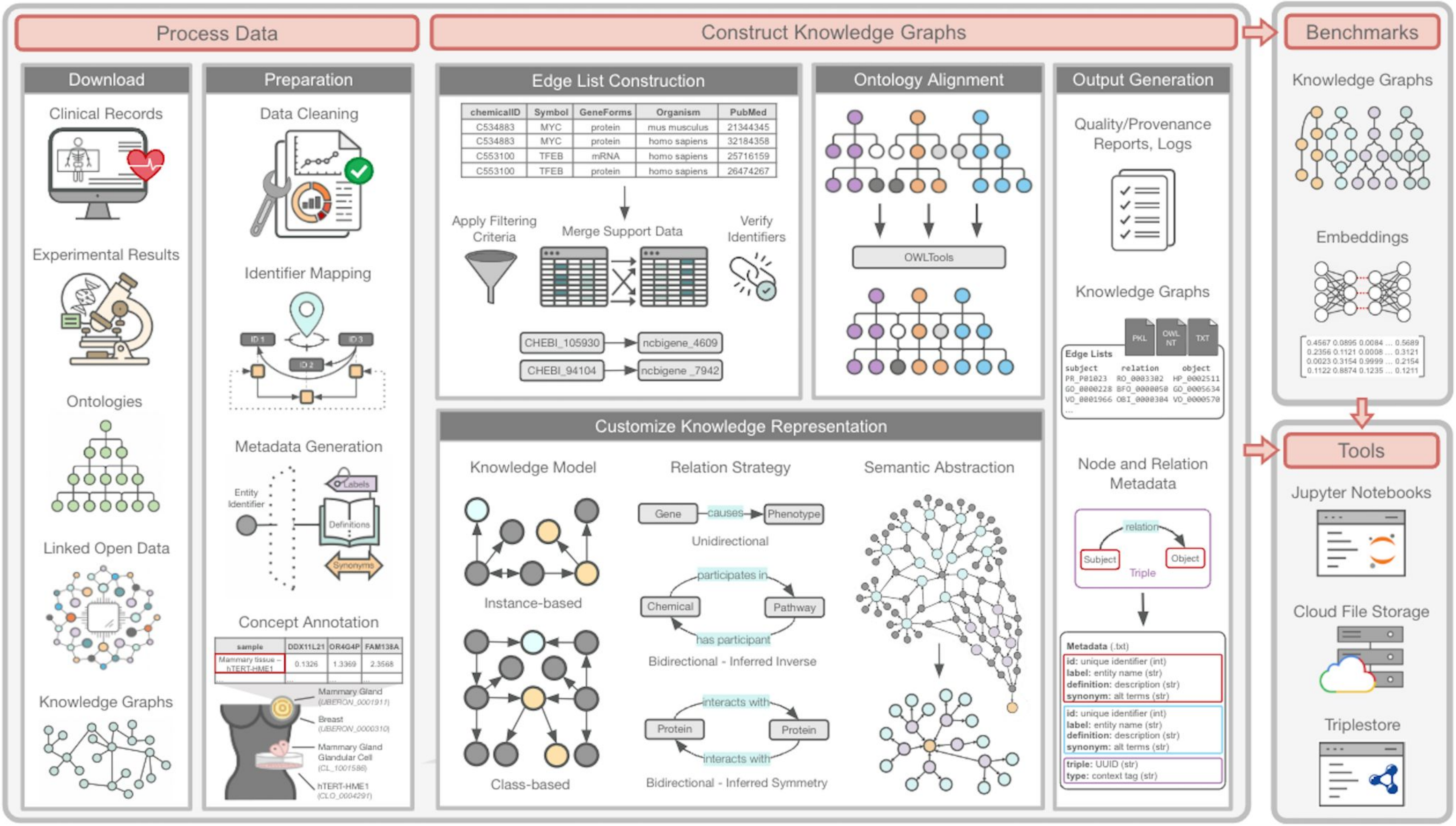
Implementation Challenges

- Methods may have varying functional, logical, and semantic consequences[1]
- Existing implementations are siloed and complicated
- Semantic Web standard is expressive, but unwieldy and of uncertain benefit[2]

PheKnowLator: A framework for building large-scale heterogeneous biomedical knowledge graphs under alternate knowledge models and hub for knowledge graph benchmarks

https://github.com/callahantiff/PheKnowLator

[1] PMID:30294517; [2] DOI: 10.1146/annurev-biodatasci-010820-091627; [3] DOI: 10.48550/arXiv.2002.0038



Process Data

Download

Clinical Records

Experimental Results

Ontologies

Linked Open Data

Knowledge Graphs

Preparation

Data Cleaning

Identifier Mapping

Metadata Generation

Concept Annotation

sample	DDX11L21	OR4G4P	FAM138A
Mammary tissue – hTERT-HME1	0.1326	1.3369	2.3568
...	...	...	...

Mammary Gland (UBERON_0001911)

Breast (UBERON_0000310)

Mammary Gland Glandular Cell (CL_1001586)

hTERT-HME1 (CLO_0004291)

Construct Knowledge Graphs

Edge List Construction

chemicalID	Symbol	GeneForms	Organism	PubMed
C534883	MYC	protein	mus musculus	21344345
C534883	MYC	protein	homo sapiens	32184358
C553100	TFEB	mRNA	homo sapiens	25716159
C553100	TFEB	protein	homo sapiens	26474267

Apply Filtering Criteria

Merge Support Data

Verify Identifiers

CHEBI_105930 → ncbigene_4609

CHEBI_94104 → ncbigene_7942

Ontology Alignment

OWLTools

Output Generation

Quality/Provenance Reports, Logs

Knowledge Graphs

```
Edge Lists
subject      relation      object
PR_P01023    RO_0003302    HP_0002511
GO_0000228   BFO_0000050   GO_0005634
VO_0001966   OBI_0000304   VO_0000570
...
```

Node and Relation Metadata

Metadata (.txt)

id: unique identifier (int)
label: entity name (str)
definition: description (str)
synonym: alt terms (str)

id: unique identifier (int)
label: entity name (str)
definition: description (str)
synonym: alt terms (str)

triple: UUID (str)
type: context tag (str)

Customize Knowledge Representation

Knowledge Model

Instance-based

Class-based

Relation Strategy

Gene → causes → Phenotype

Unidirectional

Chemical → participates in → Pathway

Pathway → has participant → Chemical

Bidirectional - Inferred Inverse

Protein → interacts with → Protein

Protein → interacts with → Protein

Bidirectional - Inferred Symmetry

Semantic Abstraction

Benchmarks

Knowledge Graphs

Embeddings

$$\begin{bmatrix} 0.4567 & 0.0896 & 0.0084 & \dots & 0.5689 \\ 0.2356 & 0.1121 & 0.0008 & \dots & 0.3121 \\ 0.0023 & 0.3154 & 0.9999 & \dots & 0.2154 \\ 0.1122 & 0.8874 & 0.1235 & \dots & 0.1211 \end{bmatrix}$$

Tools

Jupyter Notebooks

Cloud File Storage

Triplestore

image: https://zenodo.org/record/7035867

PheKnowLator Build Types

PheKnowLator is capable of building 12 different versions of the same knowledge graph by altering the following:

Knowledge Model: the approach used to convert a simple edge list into a rich OWL-based semantic representation.

Relation Strategy: the approach used when adding edges to the core set of ontologies.

Semantic Abstraction: a lossless compression algorithm that converts a rich OWL-based representation into a simple RDF property graph.

- With or without harmonizing the abstracted knowledge graph to be consistent with a class- or instance-based knowledge model

https://github.com/callahantiff/PheKnowLator

DOI: 10.5281/zenodo.5716383

Knowledge Modeling Approaches

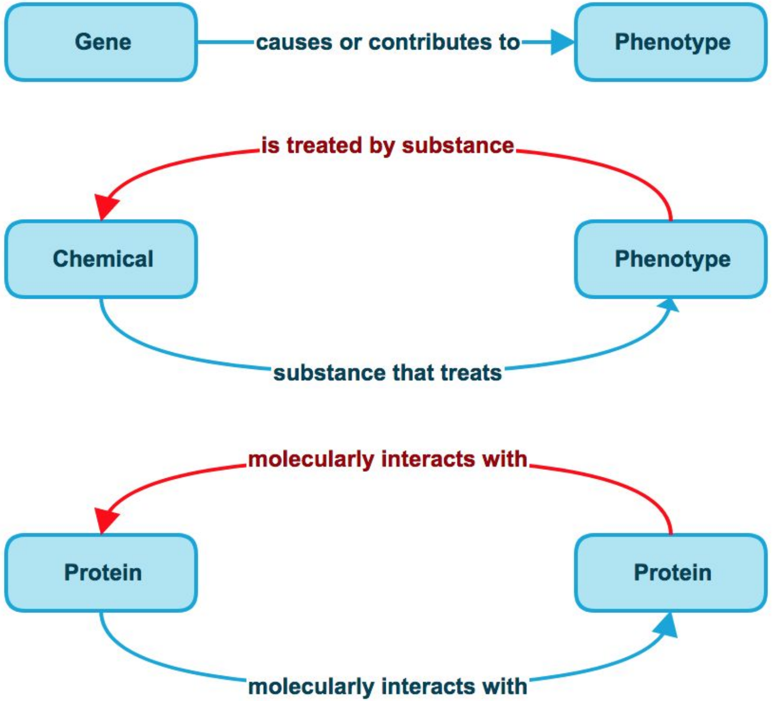
Example: Add <<EDNRB, Causes, ABCD syndrome>> to an ontologically-grounded knowledge graph.

Challenge: EDNRB is not currently represented in an ontology. ABCD syndrome is a class in the Human Phenotype Ontology, and is included in the knowledge graph.

Solution: Gene is a class in the Sequence Ontology and can be used to add EDNRB to the knowledge graph using two different strategies.

Instance-based Knowledge Model (ABox)	Class-based Knowledge Model (TBox)
EDNRB, rdfs:subClassOf, Gene EDNRB, rdf:type, owl:Class UUID1, rdf:type, EDNRB UUID1, rdf:type, owl:NamedIndividual UUID2, rdf:type,ABCD syndrome UUID2, rdf:type, owl:NamedIndividual UUID1, Causes, UUID2	EDNRB, rdfs:subClassOf, Gene EDNRB, rdf:type, owl:Class UUID1, rdfs:subClassOf, EDNRB UUID1, rdfs:subClassOf, UUID2 UUID2, rdf:type, owl:Restriction UUID2, owl:someValuesFrom, ABCD syndrome UUID2, owl:onProperty, Causes

Knowledge Modeling Approaches



DOI:10.5281/zenodo.5716383

Semantic Abstraction - OWL-NETS

OWL-NETS (NEtwork Transformation for Statistical learning) is a computational method that reversibly abstracts Web Ontology Language (OWL)-encoded biomedical knowledge into a more biologically meaningful network representation.

OWL-NETS generates semantically rich knowledge graphs that contain heterogeneous nodes and edges and can be used for tasks that do not require OWL semantics.

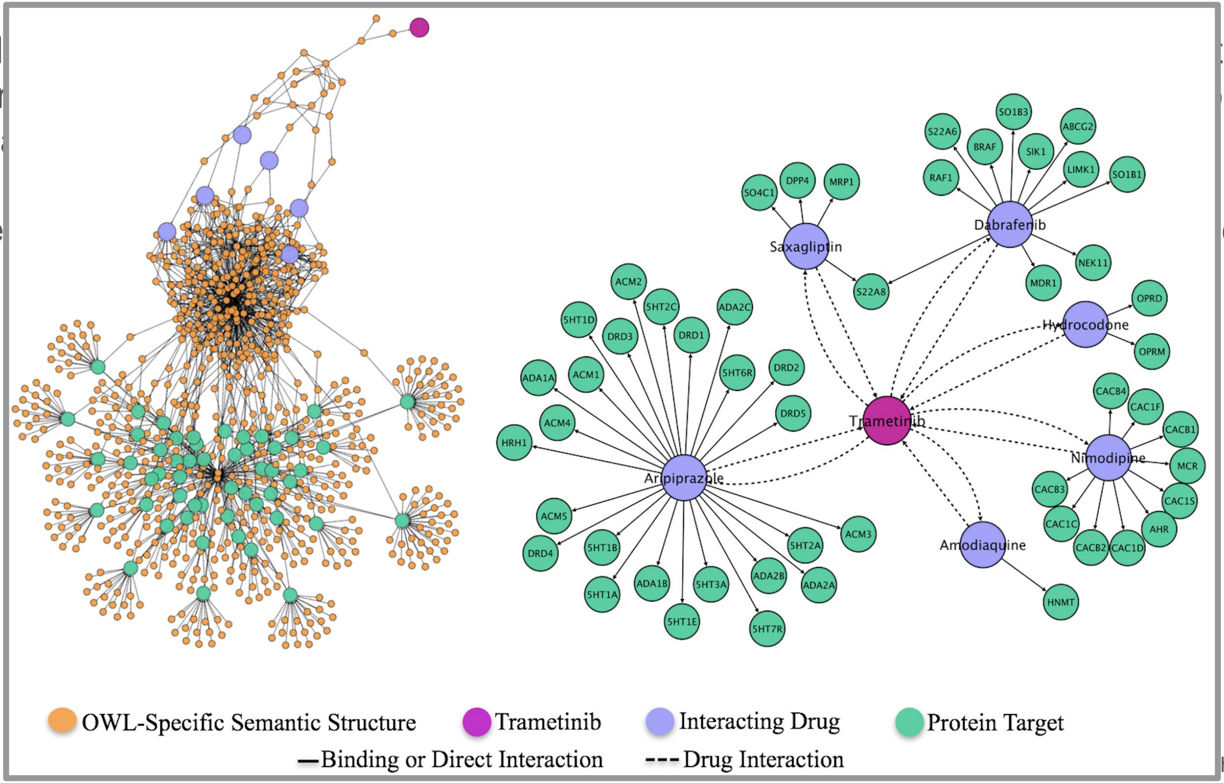
https://github.com/callahantiff/PheKnowLator/wiki/OWL-NETS-2.0

PMID:29218876

OWL-NETS

OWL-NETS (N … that
reversibly abstr … a more
biologically mea

OWL-NETS ge … odes and
edges and can



heKnowLator/wiki/OWL-NETS-2.0

PMID:29218876

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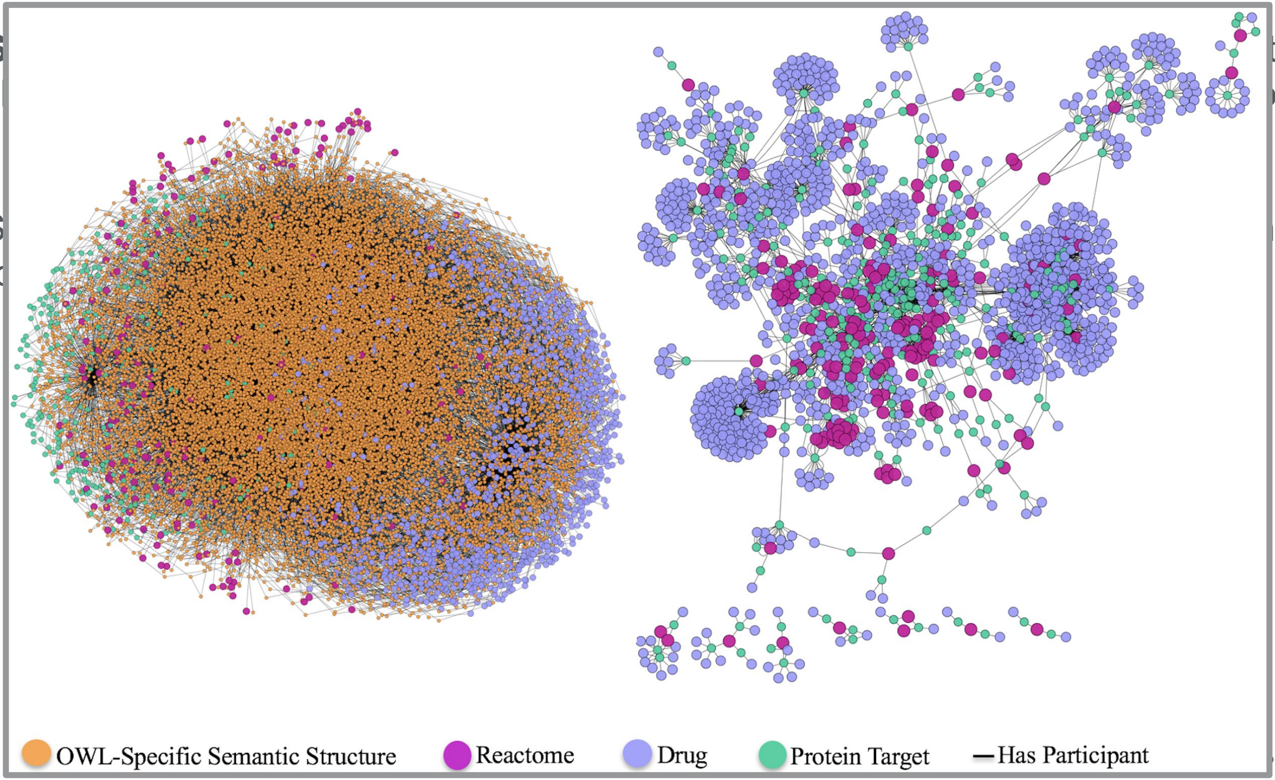
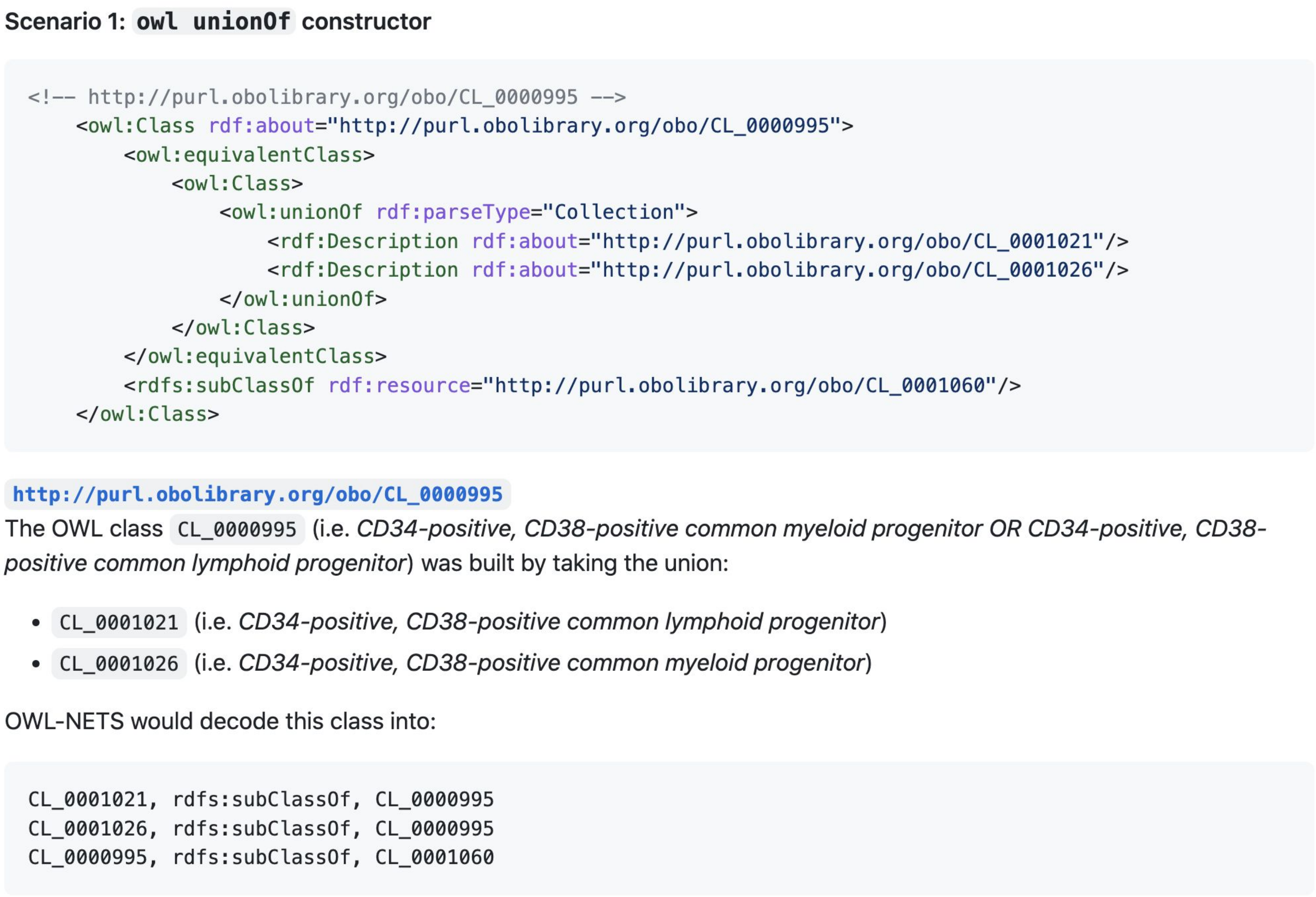
edges and



heKnowLator/wiki/OWL-NETS-2.0

PMID:29218876



Scenario 1: `owl unionOf` constructor

```
<!-- http://purl.obolibrary.org/obo/CL_0000995 -->
    <owl:Class rdf:about="http://purl.obolibrary.org/obo/CL_0000995">
        <owl:equivalentClass>
            <owl:Class>
                <owl:unionOf rdf:parseType="Collection">
                    <rdf:Description rdf:about="http://purl.obolibrary.org/obo/CL_0001021"/>
                    <rdf:Description rdf:about="http://purl.obolibrary.org/obo/CL_0001026"/>
                </owl:unionOf>
            </owl:Class>
        </owl:equivalentClass>
        <rdfs:subClassOf rdf:resource="http://purl.obolibrary.org/obo/CL_0001060"/>
    </owl:Class>
```

`http://purl.obolibrary.org/obo/CL_0000995`

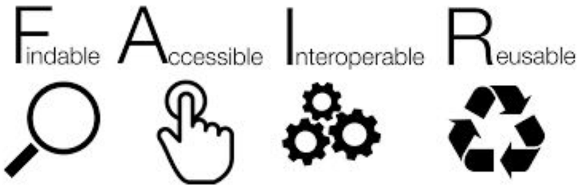
The OWL class `CL_0000995` (i.e. *CD34-positive, CD38-positive common myeloid progenitor OR CD34-positive, CD38-positive common lymphoid progenitor*) was built by taking the union:

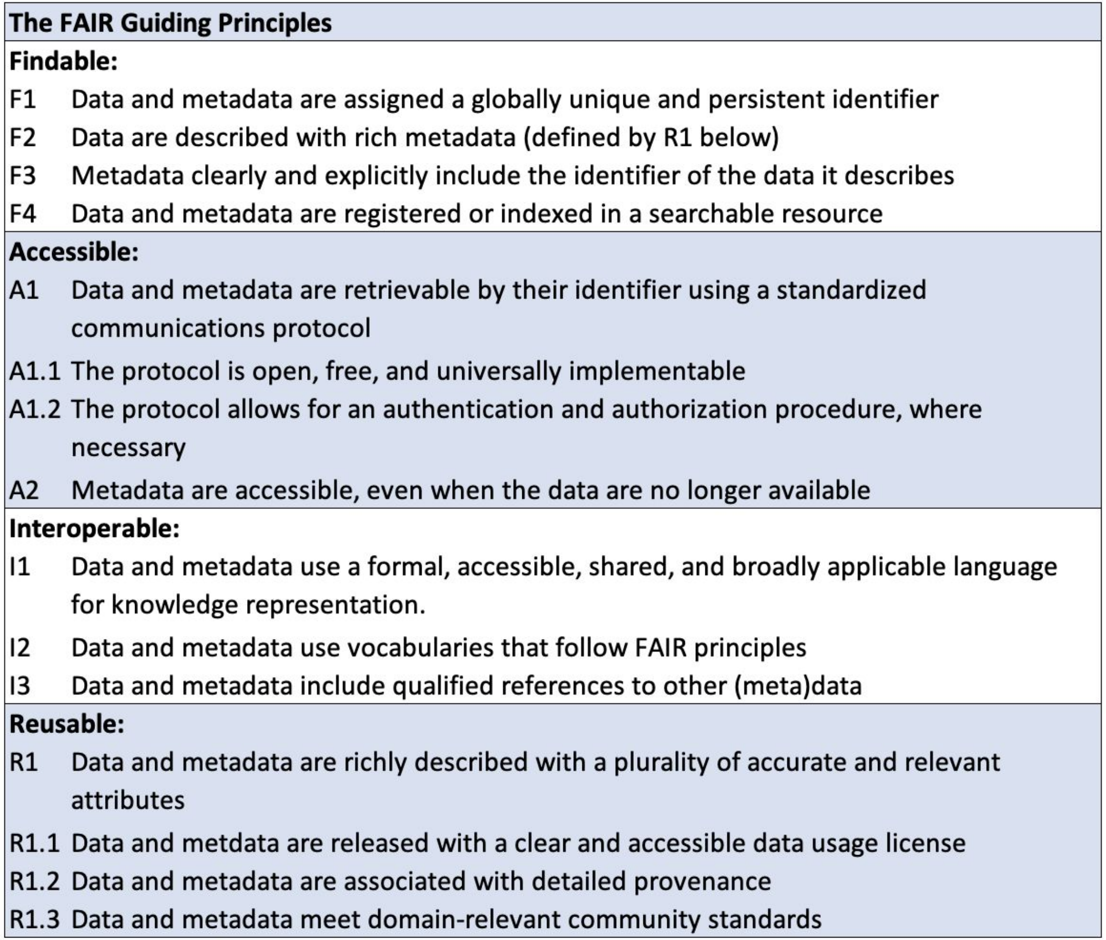
- `CL_0001021` (i.e. *CD34-positive, CD38-positive common lymphoid progenitor*)
- `CL_0001026` (i.e. *CD34-positive, CD38-positive common myeloid progenitor*)

OWL-NETS would decode this class into:

```
CL_0001021, rdfs:subClassOf, CL_0000995
CL_0001026, rdfs:subClassOf, CL_0000995
CL_0000995, rdfs:subClassOf, CL_0001060
```

https://github.com/callahantiff/PheKnowLator/wiki/OWL-NETS-2.0





The FAIR Guiding Principles	
Findable:	
F1	Data and metadata are assigned a globally unique and persistent identifier
F2	Data are described with rich metadata (defined by R1 below)
F3	Metadata clearly and explicitly include the identifier of the data it describes
F4	Data and metadata are registered or indexed in a searchable resource
Accessible:	
A1	Data and metadata are retrievable by their identifier using a standardized communications protocol
A1.1	The protocol is open, free, and universally implementable
A1.2	The protocol allows for an authentication and authorization procedure, where necessary
A2	Metadata are accessible, even when the data are no longer available
Interoperable:	
I1	Data and metadata use a formal, accessible, shared, and broadly applicable language for knowledge representation.
I2	Data and metadata use vocabularies that follow FAIR principles
I3	Data and metadata include qualified references to other (meta)data
Reusable:	
R1	Data and metadata are richly described with a plurality of accurate and relevant attributes
R1.1	Data and metdata are released with a clear and accessible data usage license
R1.2	Data and metadata are associated with detailed provenance
R1.3	Data and metadata meet domain-relevant community standards

PMID:26978244; https://fairtoolkit.pistoiaalliance.org/fair-guiding-principles/

Evaluation

To evaluate the knowledge graphs that PheKnowLator ecosystem, we conducted the following evaluation tasks:

Qualitative

- Compare existing open source biomedical knowledge graph construction methods

Quantitative

- Compare the performance when building the 12 different knowledge graphs designed to represent the molecular mechanisms underlying human disease

DOI:10.5281/zenodo.5716383

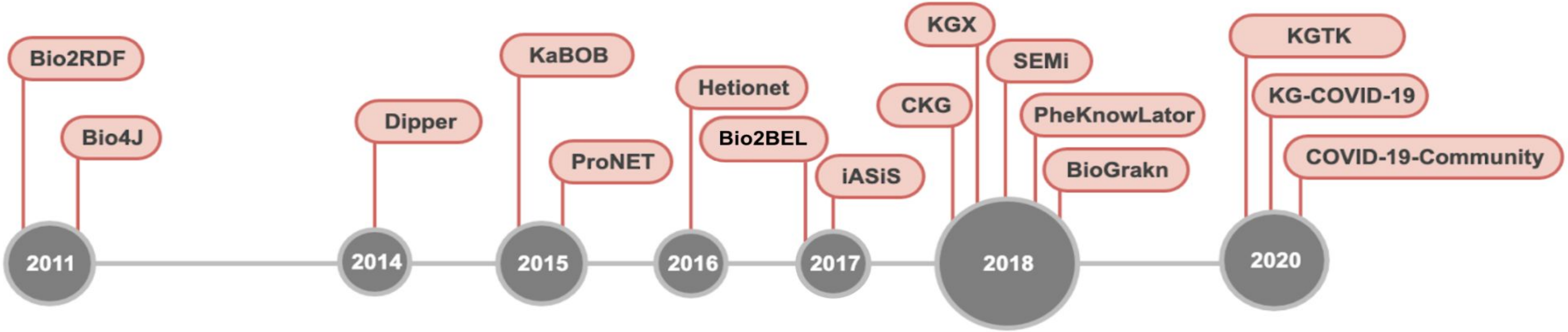
Evaluation - Comparison to Existing Methods

Goal: Compare PheKnowLator to existing open source knowledge graph construction methods

Identify Similar Methods

- GitHub API Query
- Recent review articles[1,2]

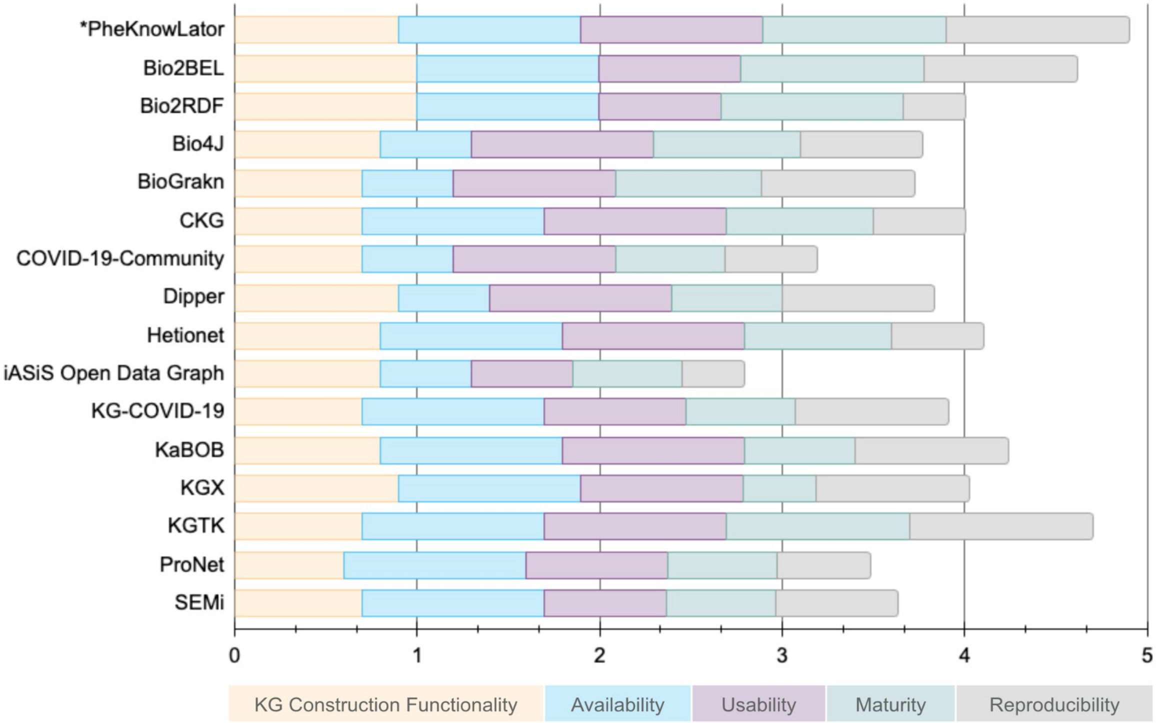
Survey: 5 criteria, 45 questions



DOI:10.5281/zenodo.5716383

Evaluation - Comparison to Existing Methods

Criteria	Description
Construction Functionality	The steps needed to construct a knowledge graph from downloading and processing data and building edge lists to generating and outputting a KG
Maturity	The level, stage or development phase of a method
Availability	The openness of a method and the ease of obtaining a copy of the method
Usability	Efforts put in place to ensure that a user, with reasonable technical skills, could use the method
Reproducibility	Whether or not the method provides tools or resources to help reproduce the KG construction process and maintain the code base



Evaluation - Human Disease Mechanism Graph

Goal: Construct 12 different builds of a knowledge graph designed to represent the molecular mechanisms of human disease and compare them on their build time and memory usage.

Knowledge Representation

- Designed with PhD molecular biologist
- Validated by wet lab experiments

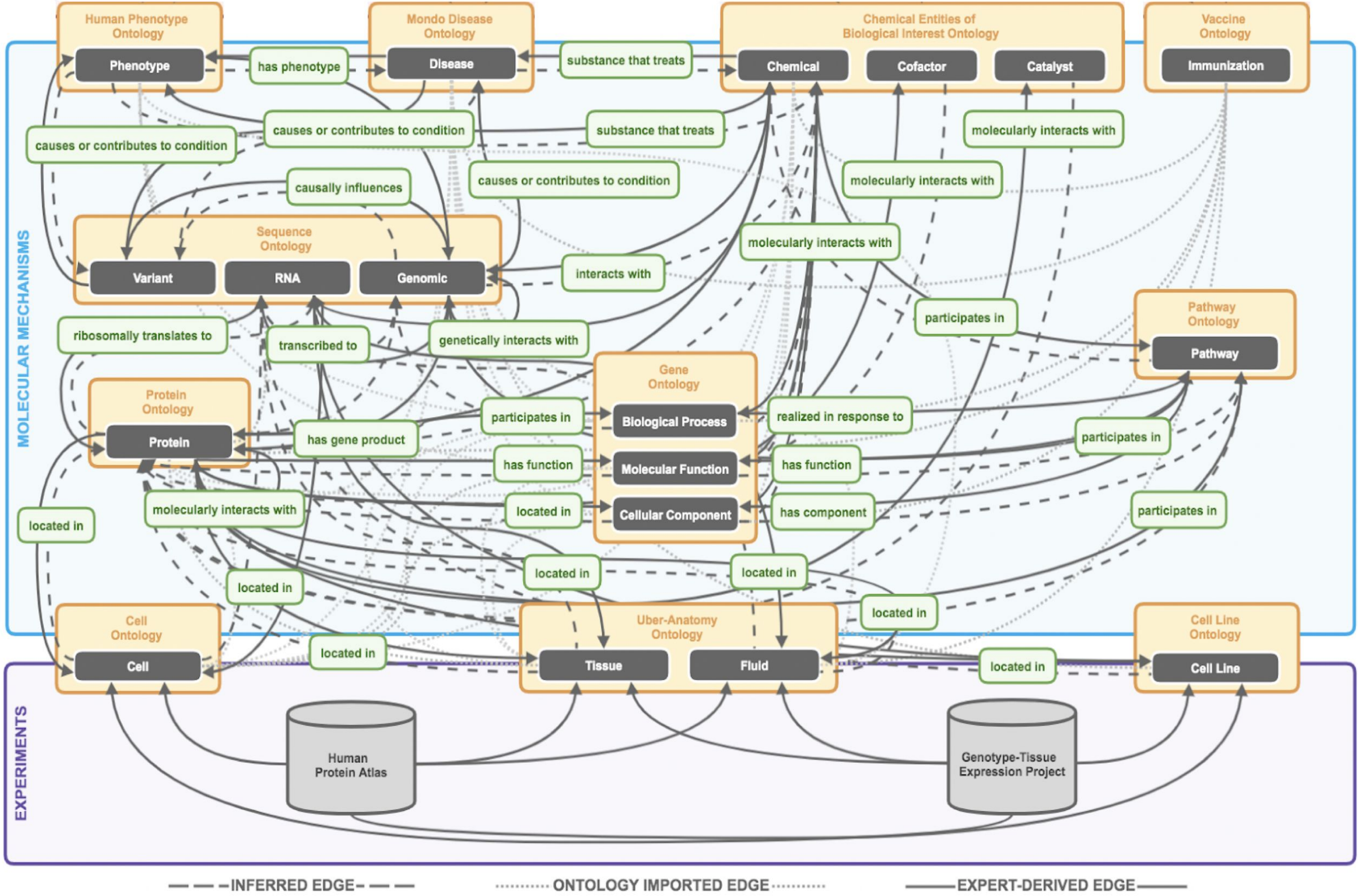
Build Data

- 12 Open Biological and Biomedical Ontologies Foundry ontologies
- 31 Linked Open Data
- 18 primary node types*
- 35 primary edge types*

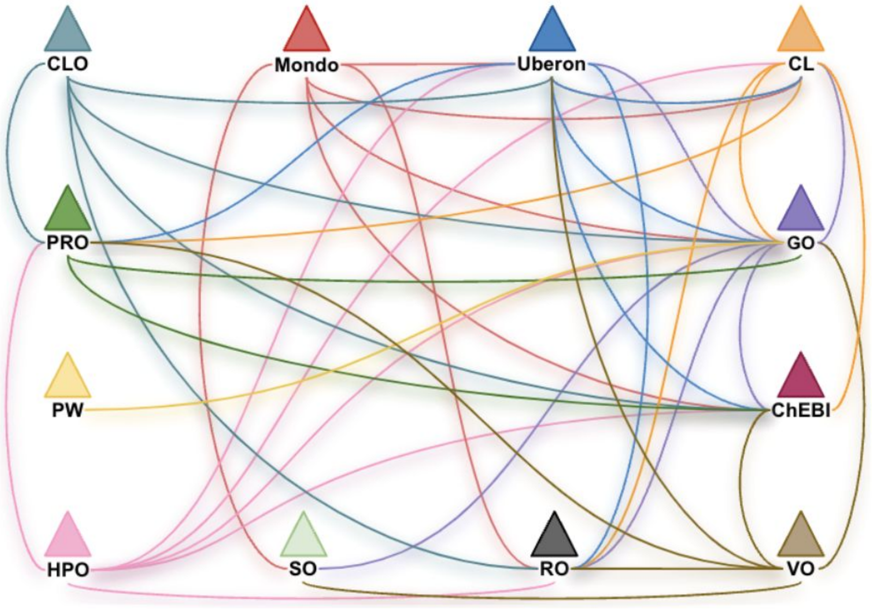
*Added to existing node and edge types present in the core set of ontologies

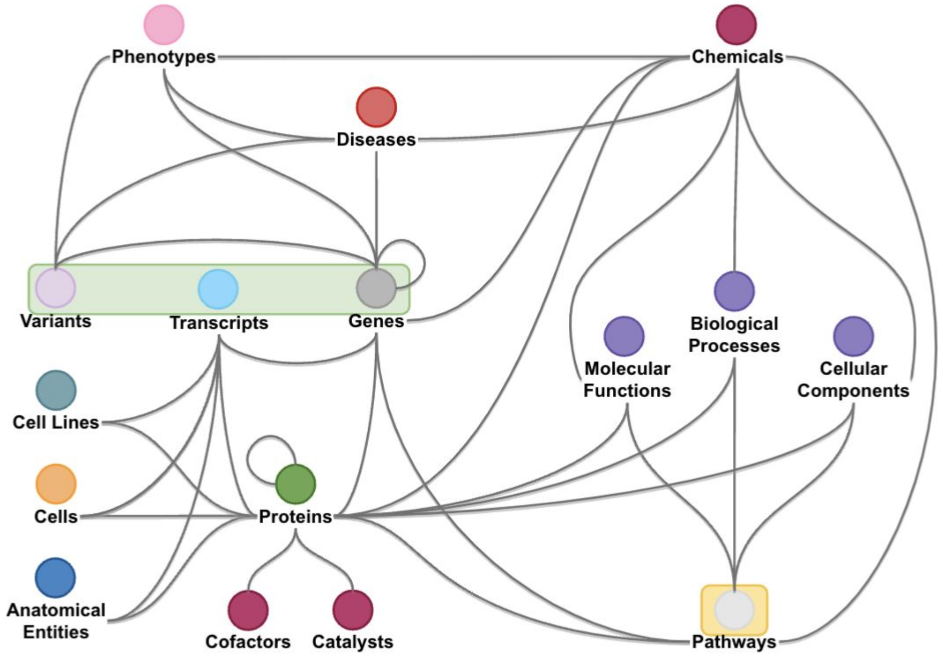
https://github.com/callahantiff/PheKnowLator

DOI:10.5281/zenodo.5716383


MOLECULAR MECHANISMS
EXPERIMENTS
Human Phenotype Ontology
Phenotype
Mondo Disease Ontology
Disease
Chemical Entities of Biological Interest Ontology
Chemical
Cofactor
Catalyst
Vaccine Ontology
Immunization
has phenotype
substance that treats
causes or contributes to condition
causes or contributes to condition
substance that treats
molecularly interacts with
causally influences
causes or contributes to condition
molecularly interacts with
Sequence Ontology
Variant
RNA
Genomic
molecularly interacts with
interacts with
participates in
Pathway Ontology
Pathway
ribosomally translates to
transcribed to
genetically interacts with
Gene Ontology
Biological Process
Molecular Function
Cellular Component
Protein Ontology
Protein
participates in
has gene product
realized in response to
participates in
has function
has function
molecularly interacts with
located in
has component
located in
participates in
located in
located in
located in
located in
located in
Cell Ontology
Cell
located in
Uber-Anatomy Ontology
Tissue
Fluid
located in
Cell Line Ontology
Cell Line
Human Protein Atlas
Genotype-Tissue Expression Project
INFERRED EDGE
ONTOLOGY IMPORTED EDGE
EXPERT-DERIVED EDGE

Evaluation - Human Disease Mechanism Graph





https://github.com/callahantiff/PheKnowLator

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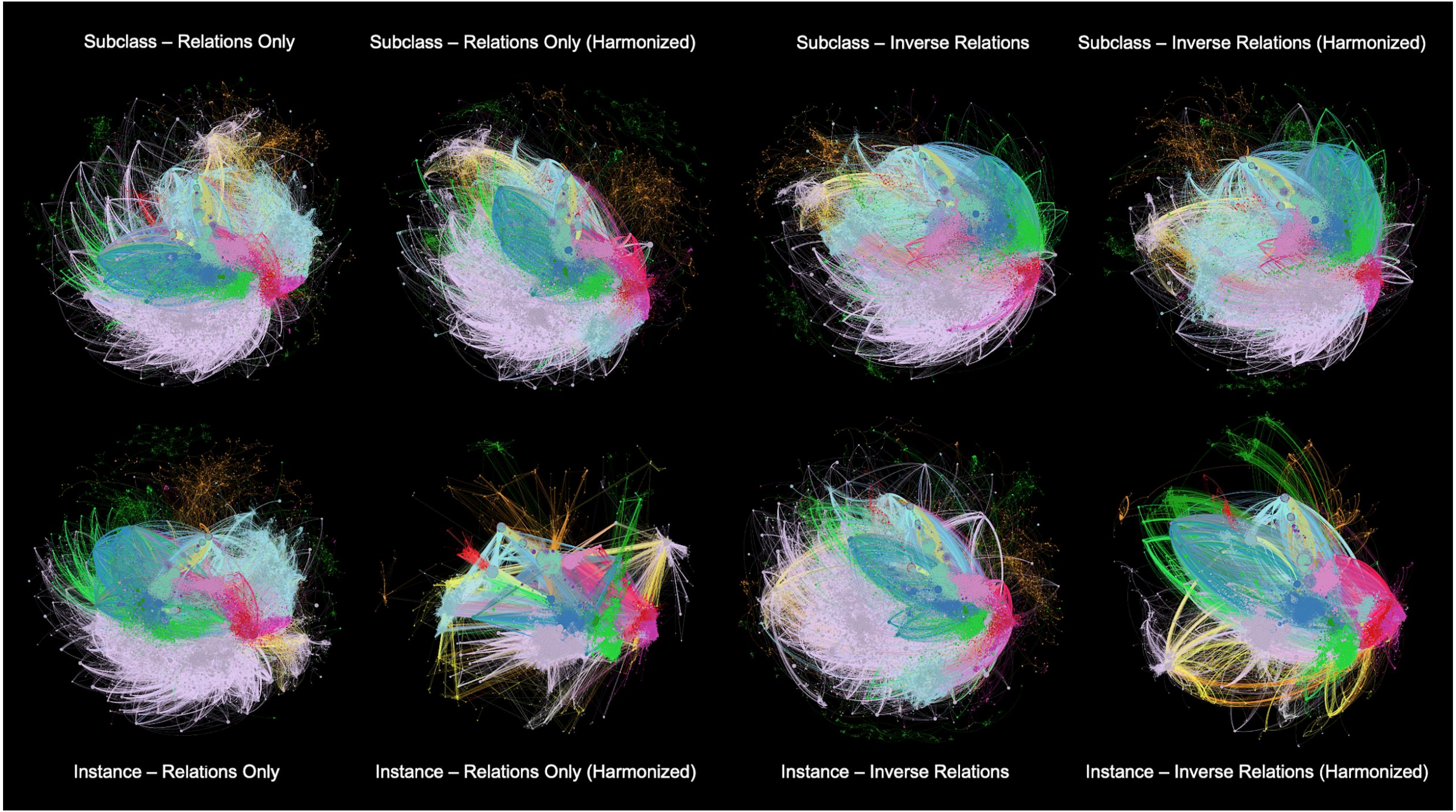
Evaluation - Human Disease Mechanism Graph

Knowledge Model	Relation Strategy	Semantic Abstraction	Edges	Nodes	Relations	Self-Loops	Average Degree
[a]Core OBO Foundry ontologies	N/A	N/A	4,044,658	1,399,756	847	3	2.89
Class	Standard Relations	None	25,143,729	8,479,167	847	3	2.97
		OWL-NETS Only	4,967,427	743,829	294	445	6.68
		OWL-NETS + Harmonization	4,967,429	743,829	293	445	6.68
	Inverse Relations	None	41,116,791	13,803,521	847	3	2.98
		OWL-NETS Only	7,629,597	743,829	301	445	10.26
		OWL-NETS + Harmonization	7,629,599	743,829	300	445	10.26
Instance	Standard Relations	None	21,770,455	8,479,167	847	3	2.57
		OWL-NETS Only	4,967,391	743,829	294	409	6.68
		OWL-NETS + Harmonization	7,285,496	743,829	293	649	9.79
	Inverse Relations	None	24,432,633	8,479,167	847	3	2.88
		OWL-NETS Only	7,629,594	743,829	301	409	10.26
		OWL-NETS + Harmonization	9,624,232	743,829	300	650	12.94



Subclass – Relations Only

Subclass – Relations Only (Harmonized)

Subclass – Inverse Relations

Subclass – Inverse Relations (Harmonized)

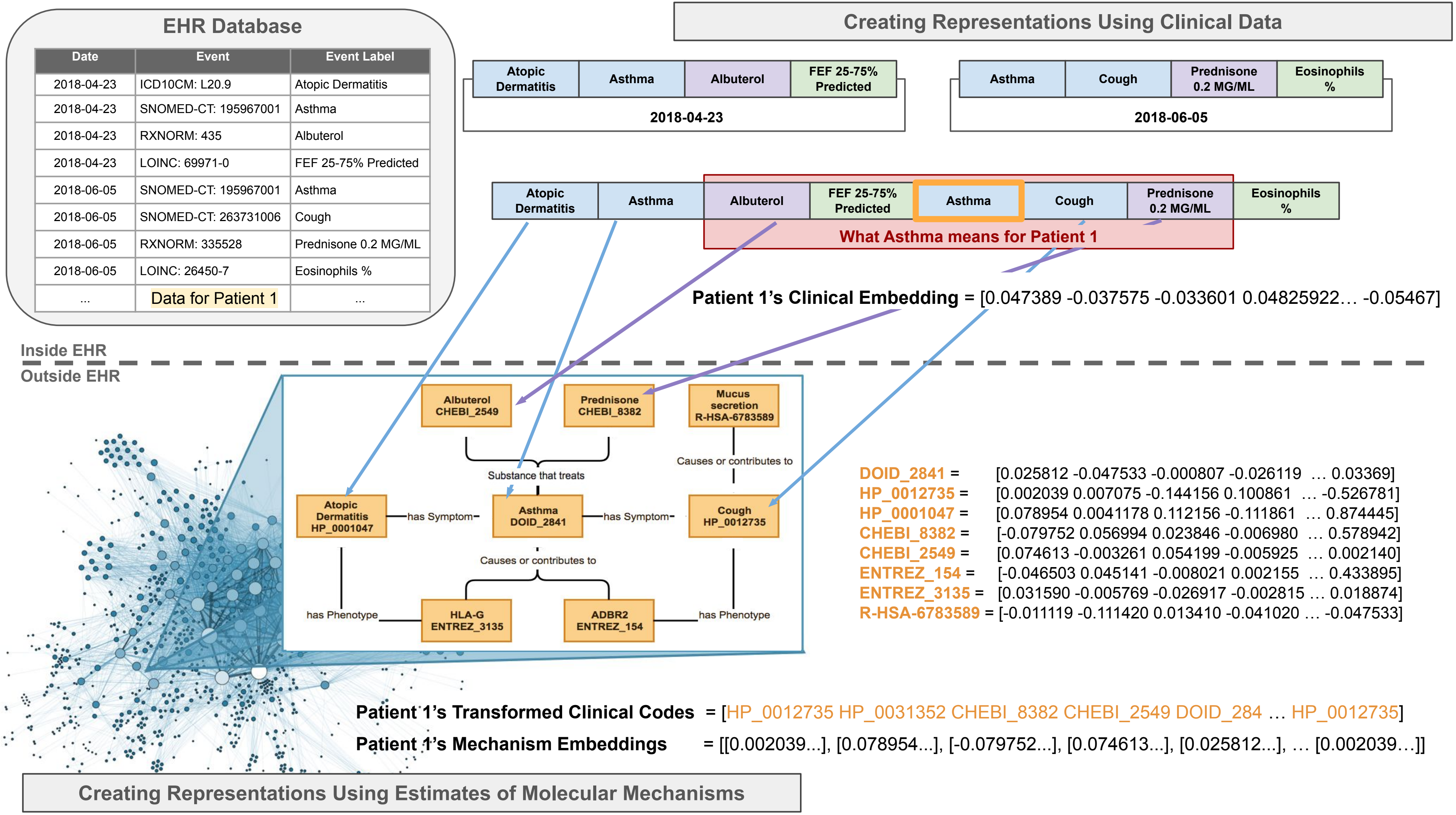
Instance – Relations Only

Instance – Relations Only (Harmonized)

Instance – Inverse Relations

Instance – Inverse Relations (Harmonized)

PheKnowLator Applications



Creating Representations Using Clinical Data

EHR Database

Date	Event	Event Label
2018-04-23	ICD10CM: L20.9	Atopic Dermatitis
2018-04-23	SNOMED-CT: 195967001	Asthma
2018-04-23	RXNORM: 435	Albuterol
2018-04-23	LOINC: 69971-0	FEF 25-75% Predicted
2018-06-05	SNOMED-CT: 195967001	Asthma
2018-06-05	SNOMED-CT: 263731006	Cough
2018-06-05	RXNORM: 335528	Prednisone 0.2 MG/ML
2018-06-05	LOINC: 26450-7	Eosinophils %
...	Data for Patient 1	...

Patient 1's Clinical Embedding = [0.047389 -0.037575 -0.033601 0.04825922… -0.05467]

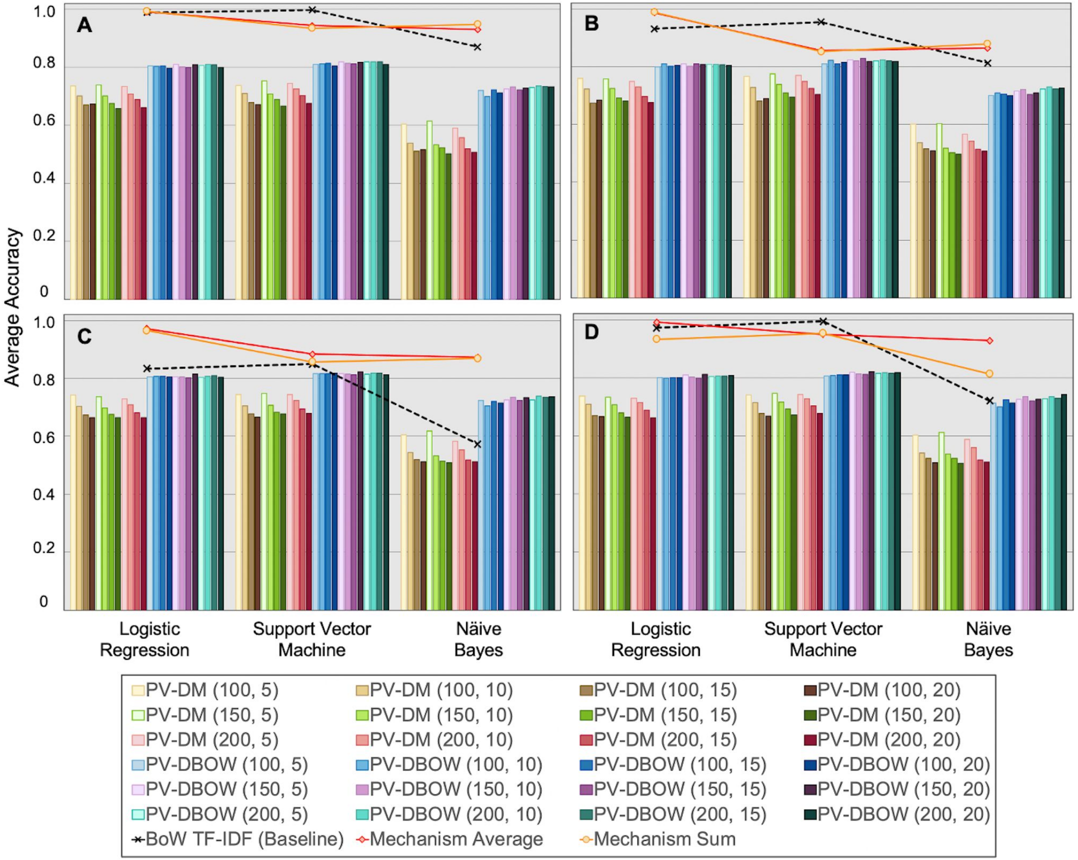
DOID_2841 = [0.025812 -0.047533 -0.000807 -0.026119 … 0.03369]
HP_0012735 = [0.002039 0.007075 -0.144156 0.100861 … -0.526781]
HP_0001047 = [0.078954 0.0041178 0.112156 -0.111861 … 0.874445]
CHEBI_8382 = [-0.079752 0.056994 0.023846 -0.006980 … 0.578942]
CHEBI_2549 = [0.074613 -0.003261 0.054199 -0.005925 … 0.002140]
ENTREZ_154 = [-0.046503 0.045141 -0.008021 0.002155 … 0.433895]
ENTREZ_3135 = [0.031590 -0.005769 -0.026917 -0.002815 … 0.018874]
R-HSA-6783589 = [-0.011119 -0.111420 0.013410 -0.041020 … -0.047533]

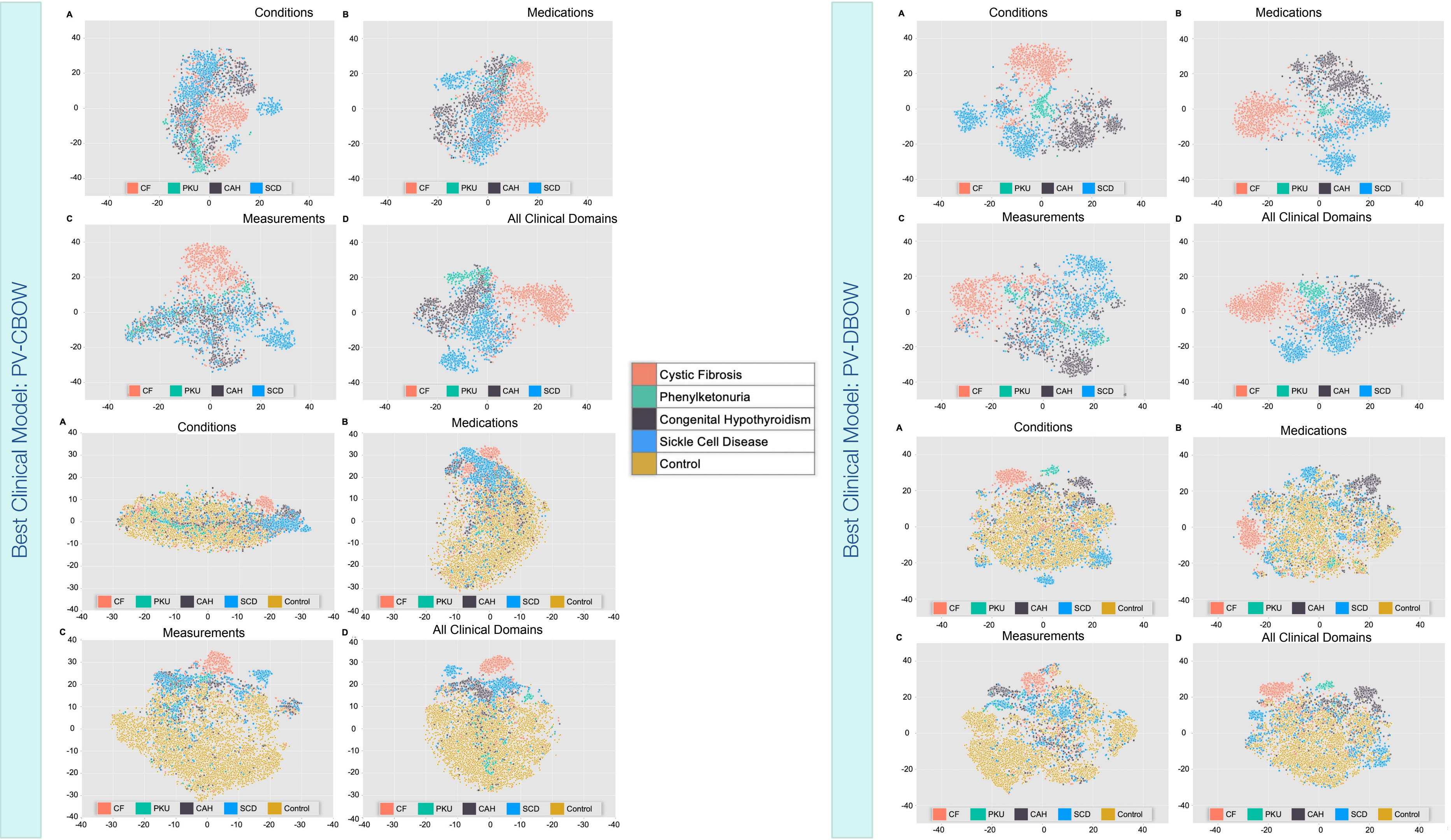
Patient 1's Transformed Clinical Codes = [HP_0012735 HP_0031352 CHEBI_8382 CHEBI_2549 DOID_284 … HP_0012735]

Patient 1's Mechanism Embeddings = [[0.002039…], [0.078954…], [-0.079752…], [0.074613…], [0.025812…], … [0.002039…]]

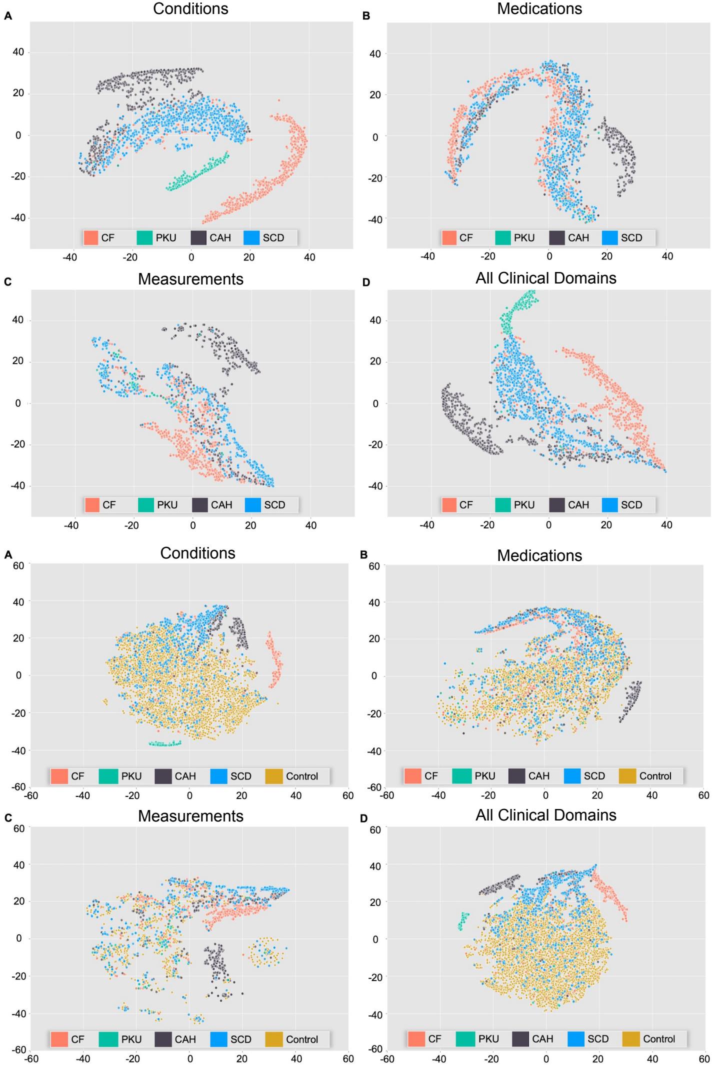
Creating Representations Using Estimates of Molecular Mechanisms

PheKnowLator Applications



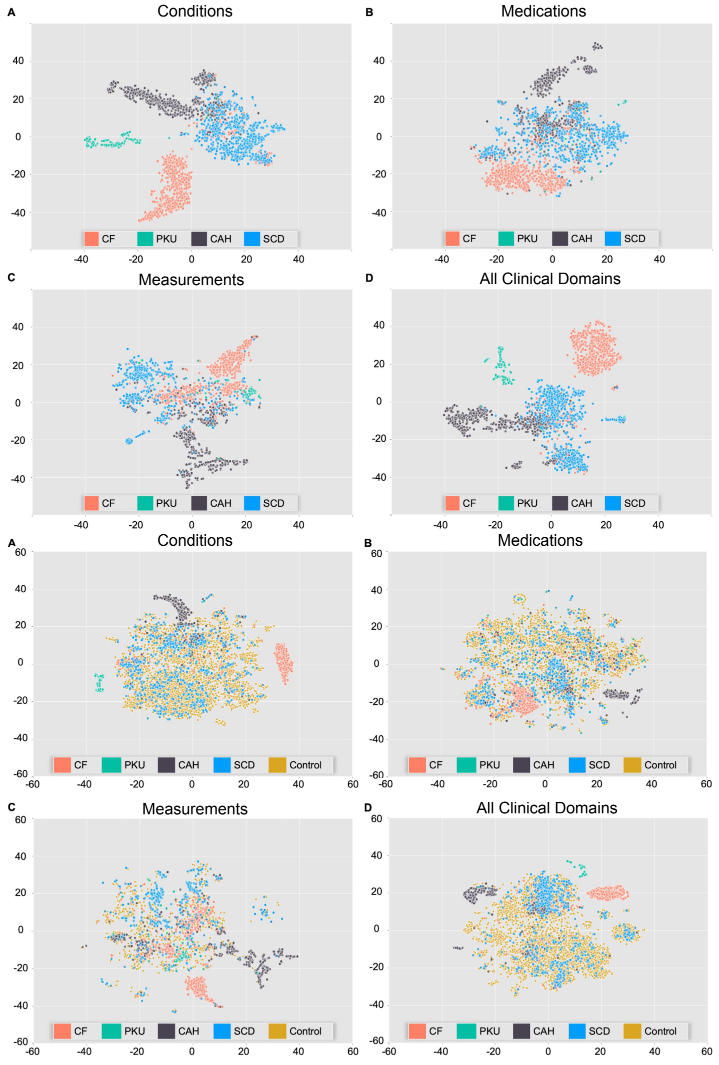

Best Clinical Model: PV-CBOW
A
Conditions
B
Medications
C
Measurements
D
All Clinical Domains
CF
PKU
CAH
SCD
Control
40
20
0
-20
-40
30
10
-10
-30
Cystic Fibrosis
Phenylketonuria
Congenital Hypothyroidism
Sickle Cell Disease
Control
Best Clinical Model: PV-DBOW
A
Conditions
B
Medications
C
Measurements
D
All Clinical Domains
CF
PKU
CAH
SCD
Control

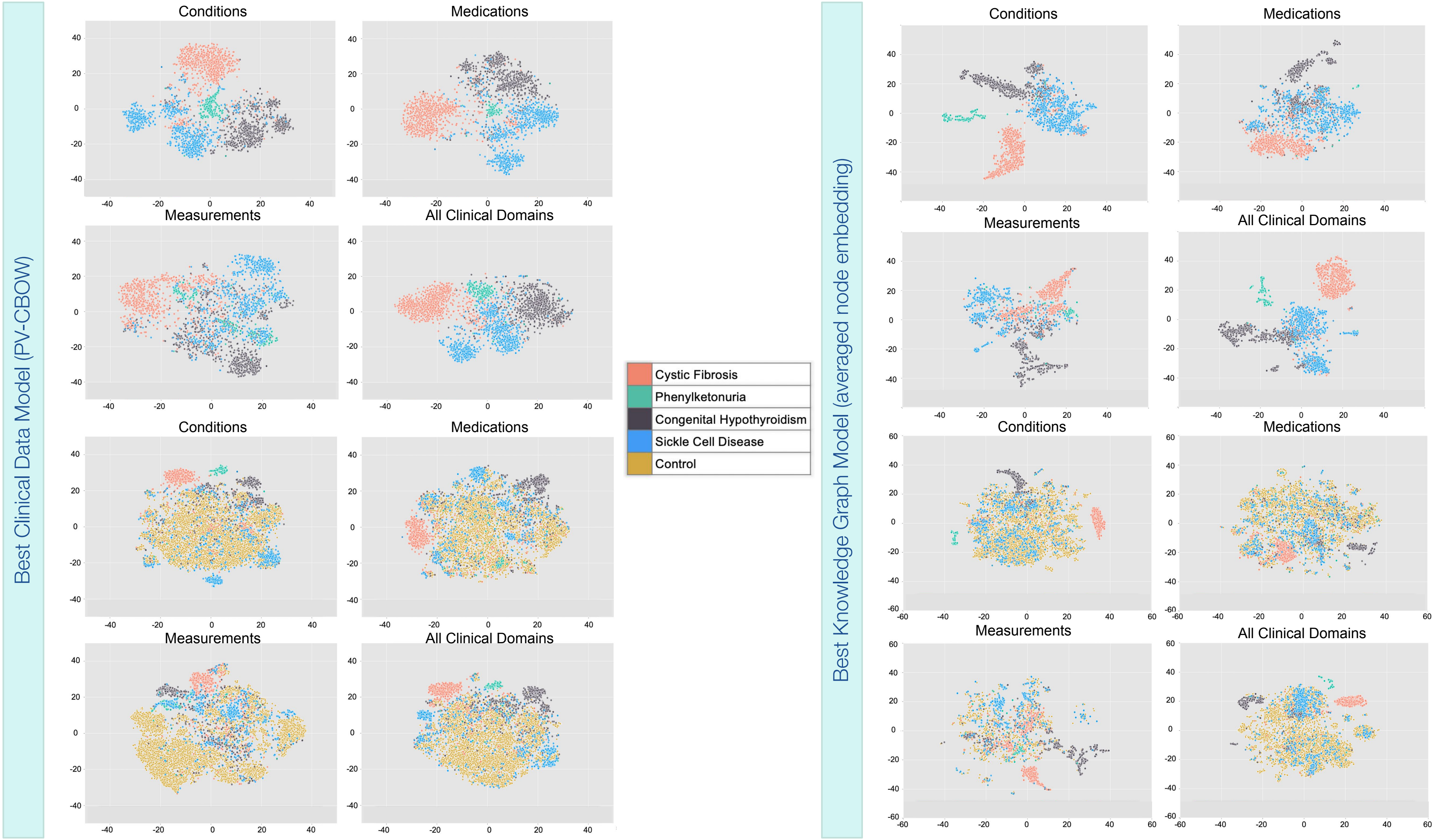
Best Knowledge Graph Model: Summed Node Embeddings



🟥	Cystic Fibrosis
🟩	Phenylketonuria
⬛	Congenital Hypothyroidism
🟦	Sickle Cell Disease
🟨	Control

Best Knowledge Graph Model: Averaged Node Embeddings




Best Clinical Data Model (PV-CBOW)
Conditions
Medications
Measurements
All Clinical Domains
Conditions
Medications
Measurements
All Clinical Domains
40
20
0
-20
-40
-40 -20 0 20 40
🟥 Cystic Fibrosis
🟩 Phenylketonuria
⬛ Congenital Hypothyroidism
🟦 Sickle Cell Disease
🟨 Control
Best Knowledge Graph Model (averaged node embedding)
Conditions
Medications
Measurements
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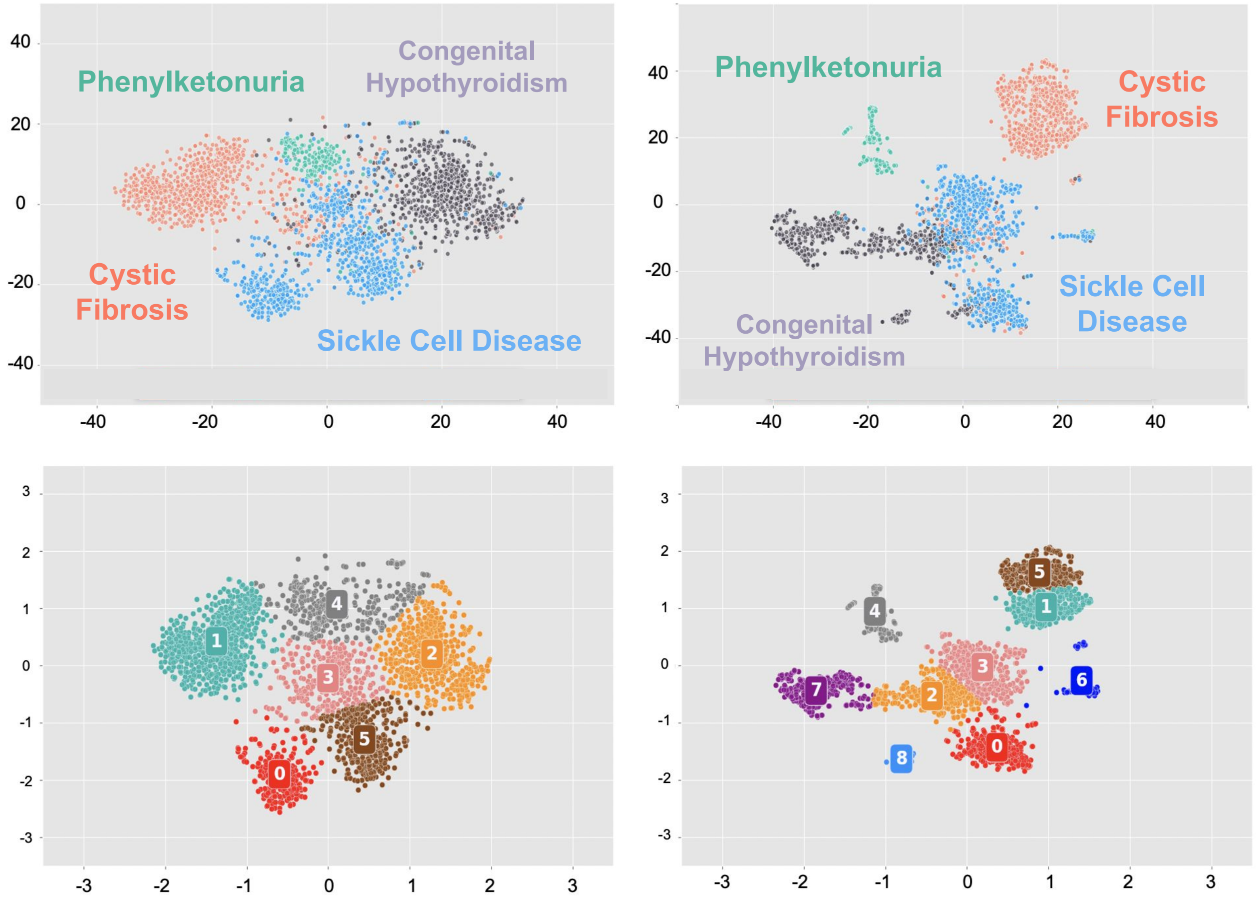
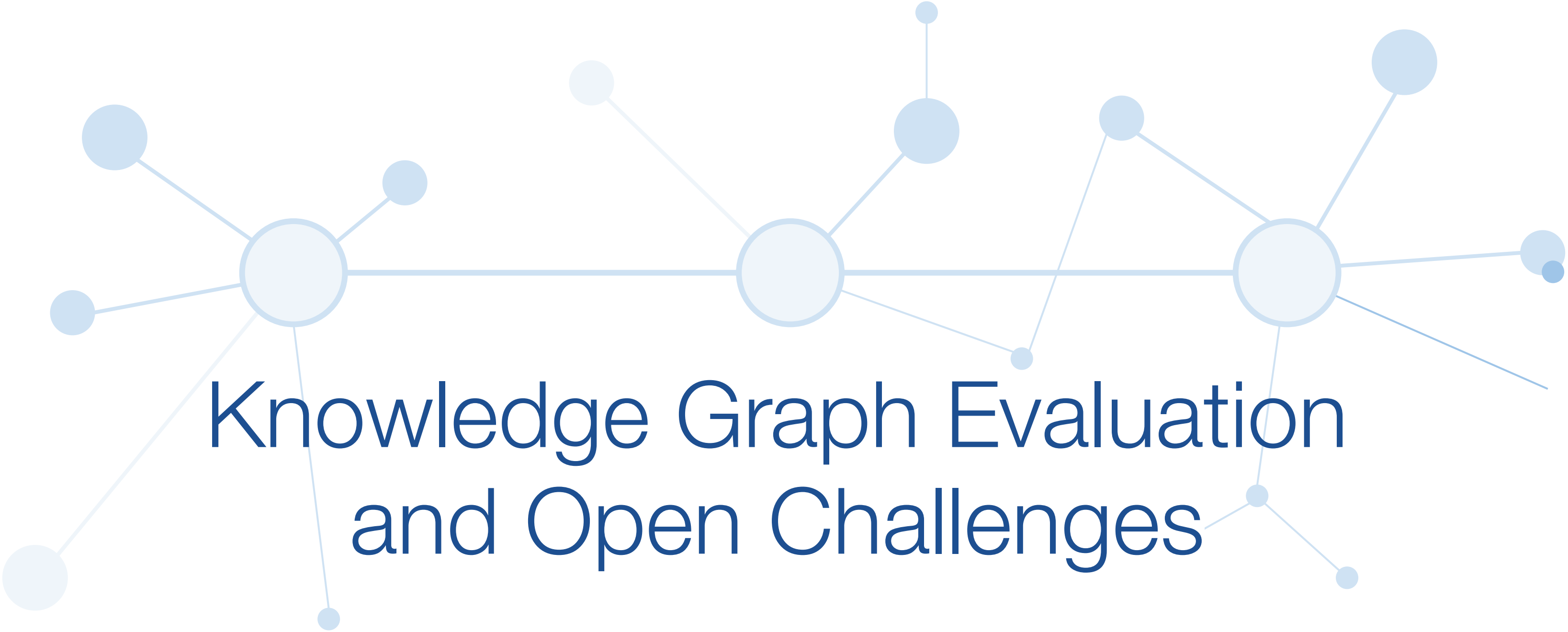
Conditions
Medications
Measurements
All Clinical Domains
60
40
20
0
-20
-40
-60
-60 -40 -20 0 20 40 60

Best Clinical Data Model

Best Knowledge Graph Model



Part 1 - Lecture



Knowledge Graph Evaluation and Open Challenges

Evaluating Biomedical Knowledge Graphs

Knowledge graph evaluation aims to prove that a resulting graph is ”good”. When using formal semantics, this can be done (mostly) with a description logics reasoner.

[1] arXiv:1907.09657; [2] DOI:10.1016/j.fmre.2021.08.018

Evaluating Biomedical Knowledge Graphs

Knowledge graph evaluation aims to demonstrate that a resulting graph is accurate. When using formal semantics, this can be done (mostly) with a description logics reasoner.

Evaluating a knowledge graph also includes verifying its data quality. This can be very challenging given the scope and heterogeneity of knowledge graphs. Although research is limited, existing work has used the following metrics:

- Percentage of triples in the knowledge graph that are correct[1]
  - Given a triple, the corresponding relationship is consistent with a real-life fact as judged by a human (randomly sampled)
- Accuracy, timeliness, trustworthiness, consistency, completeness, and availability[2]
- Precision/recall when using the knowledge graph to predict specific edge types that are known or domain expert validation of unknown or edge types or predictions

[1] arXiv:1907.09657; [2] DOI:10.1016/j.fmre.2021.08.018

Open Challenges - Part 1

Computational performance: biomedical knowledge is very extensive, which can result in biomedical knowledge graphs that contain billions of assertions

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Knowledge graph construction: a few knowledge graphs are constructed through intense expert curation. Automated approaches to knowledge graph construction fall into two broad classes:

- Data-driven knowledge graph construction can involve the integration of previously disparate resources or the direct analysis of large-scale datasets
- NLP methods are imperfect and often focused on assessing the reliability of extracted information or on techniques to manage missing or erroneous assertions and other noise

PMID:33954284

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Data integration: There are thousands of public, biomedically important databases; hence, integration approaches that support semantic compatibility are important but rarely out-of-the-box able to be integrated

PMID:33954284

Open Challenges - Part 2

The knowledge acquisition bottleneck: human curation is difficult to scale. Alternatives to manual curation, including applications of text mining and machine learning, have shown promise, but are still far short of human-like performance

PMID:30294517

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PMID:30294517

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Inference methods are lacking: existing inference methods are far short of the range and creativity of human experts in developing potential explanations, generating significant hypotheses, and generally interpreting results in light of previous knowledge. Promising inference methods scale poorly and are constrained in their ability to harness large knowledge-bases by the extremely large computational loads involved

PMID:30294517

Part 2 - Activity

Overview

Exercise Instructions

Set-up Environment

Clone the PheKnowLator GitHub: `git clone https://github.com/callahantiff/PheKnowLator.git`

Use the URL or QR code on the screen to download the zipped directory, which is called kg_course_block3_exercise, to the cloned PheKnowLator directory and unzip so its location is: `PheKnowLator/kg_course_block3_exercise` → https://ahahahahaha

Exercise Overview

The goal of this exercise is to provide exposure and experience with building and exploring different types of knowledge graphs. The notebook will give you experience with the following tasks:

1. Implementing different strategies for constructing knowledge graph edge lists
2. Exploring pre-built PheKnowLator knowledge graphs
3. Performing semantic abstraction on an ontology
4. Constructing a knowledge graph using functionality from the PheKnowLator Ecosystem