

# Introduction to ontologies

## Semantic similarity

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# Overview

1. Ontologies and graphs
2. Semantic similarity
3. Applications
4. Hand-on session

## Some examples

- ▶ Are cyclin dependent kinases *functionally* more similar to lipid kinases or to riboflavin kinases? How about *phenotypically*?

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- ▶ Which genetic disease produces similar symptoms to ebola?
- ▶ Does functional similarity correlate with phenotypic similarity?

# Ontologies and graphs

- ▶ semantic similarity measures can be graph-based, feature-based, or model-based
- ▶ we may need to generate graphs from ontologies
  - ▶ *is-a* relations are easy
  - ▶ how about *part-of*, *regulates*, *precedes*, etc.?
- ▶ relational patterns are defined in OBO Relation Ontology
  - ▶ in first order logic
  - ▶ needs to translate them into OWL

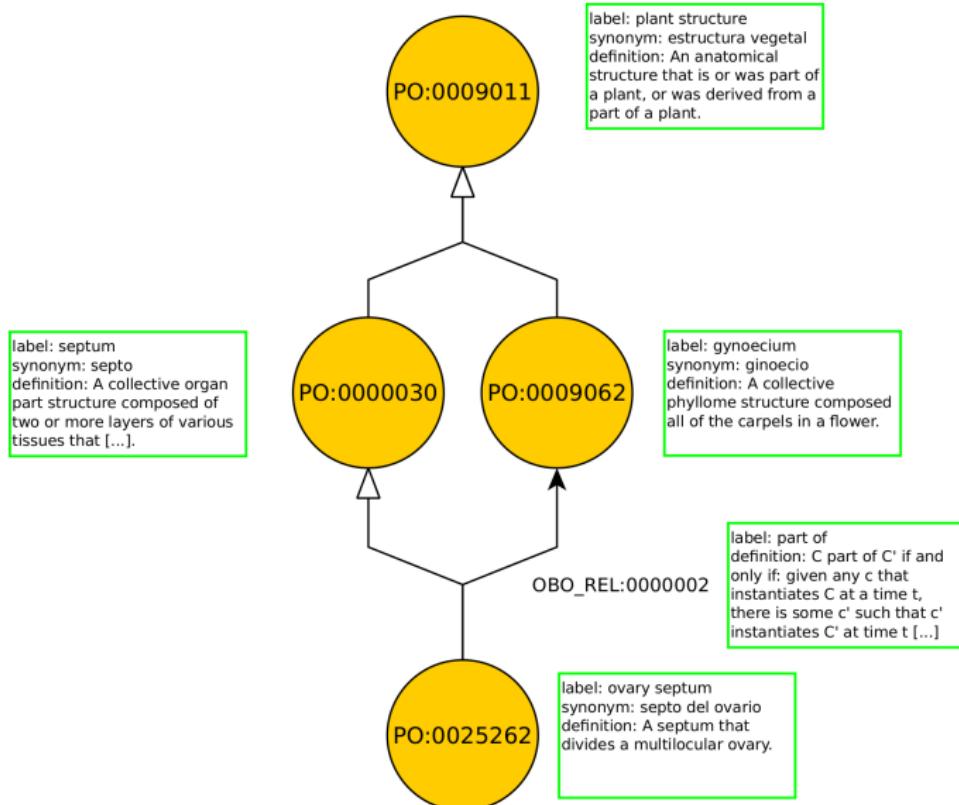
# Relations as patterns

- ▶ X SubClassOf: Y:  $X \xrightarrow{\text{is-a}} Y$
- ▶ X SubClassOf: part-of some Y:  $X \xrightarrow{\text{part-of}} Y$
- ▶ X SubClassOf: regulates some Y:  $X \xrightarrow{\text{regulates}} Y$
- ▶ X DisjointWith: Y:  $X \xleftarrow{\text{disjoint}} Y$
- ▶ X EquivalentTo: Y:  $X \xrightleftharpoons{\equiv} Y, \{X, Y\}$

# Relations as patterns

- ▶ OBO Relation Ontology (RO):
  - ▶ <https://github.com/oborel/obo-relations>
- ▶ Basic Formal Ontology (BFO):
  - ▶ provides top-level classes
    - ▶ Continuant, Process, Function, Material object, etc.
  - ▶ used for some OBO Foundry ontologies
- ▶ RO and BFO provide a top-level system of classes and relations shared across many biomedical ontologies
  - ▶ even GO, although somewhat hidden!

# Relations as patterns



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- ▶ *axioms* are
  - a specification of conditions that instances of classes must satisfy
  - b rules that can be executed to produce new knowledge
  - c statements that are considered to be true in a domain of knowledge

# How to measure similarity?

- ▶ semantic similarity measures similarity between classes
- ▶ semantic similarity measures similarity between instances of classes
- ▶ semantic similarity measures similarity between entities annotated with classes
- ▶ ⇒ reduce all of this to similarity between classes

# How to measure similarity?

What properties do we want in a similarity measure?

A function  $\text{sim} : D \times D$  is a similarity on  $D$  if, for all  $x, y \in D$ , the function  $\text{sim}$  is:

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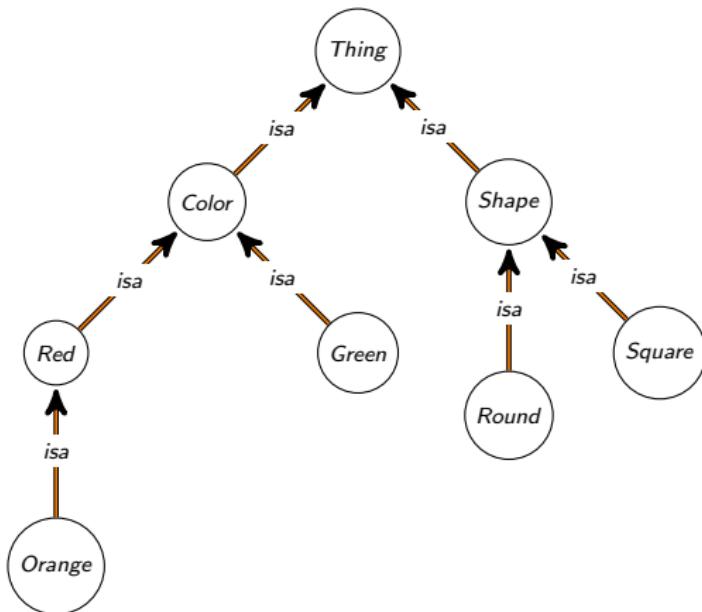
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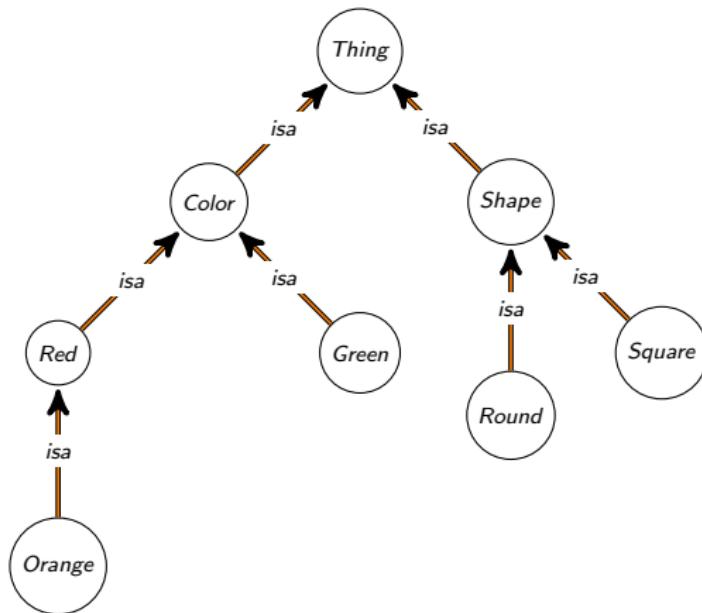
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- ▶  $\text{sim}(x, x) > \text{sim}(x, y)$  for  $x \neq y$
- ▶  $\text{sim}$  is a *normalized* similarity measure if it has values in  $[0, 1]$

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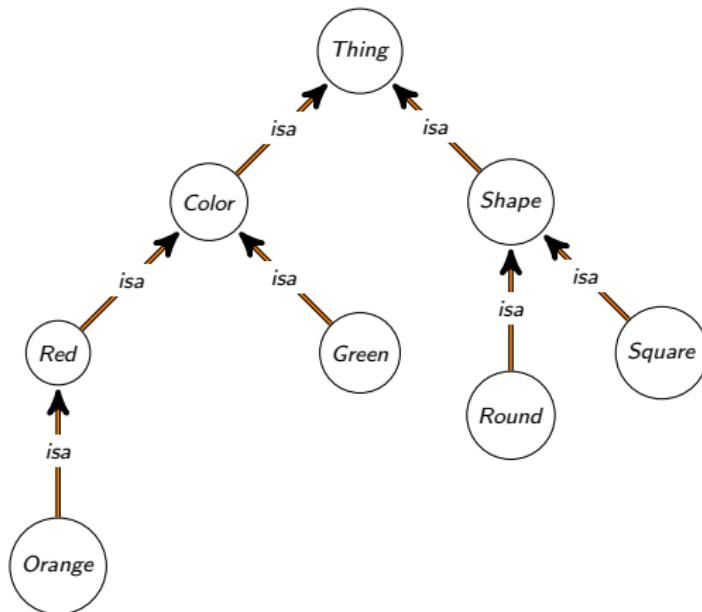


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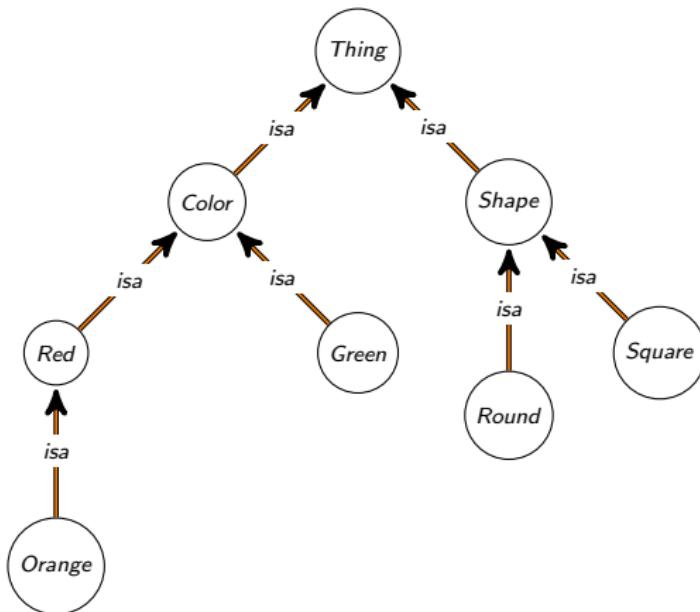
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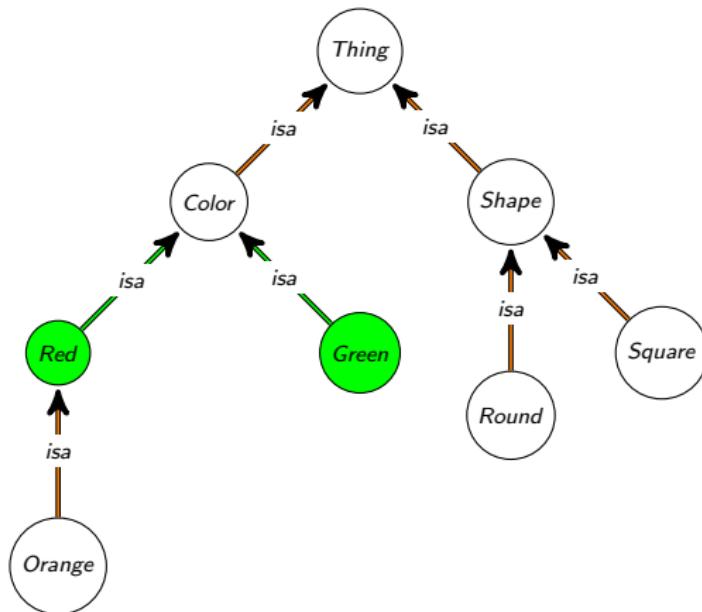
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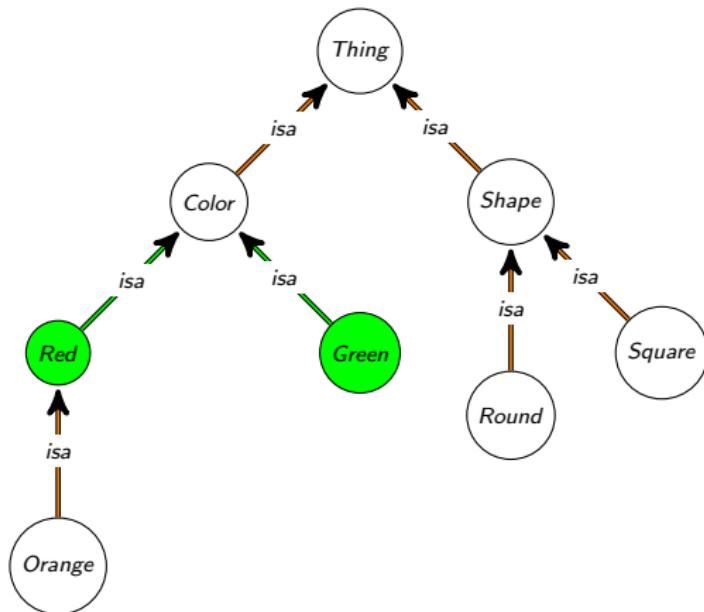
- distance on shortest path (Rada *et al.*, 1989)
- $dist_{Rada}(u, v) = sp(u, \text{isa}, v)$
- $sim_{Rada}(u, v) = \frac{1}{dist_{Rada}(u, v) + 1}$

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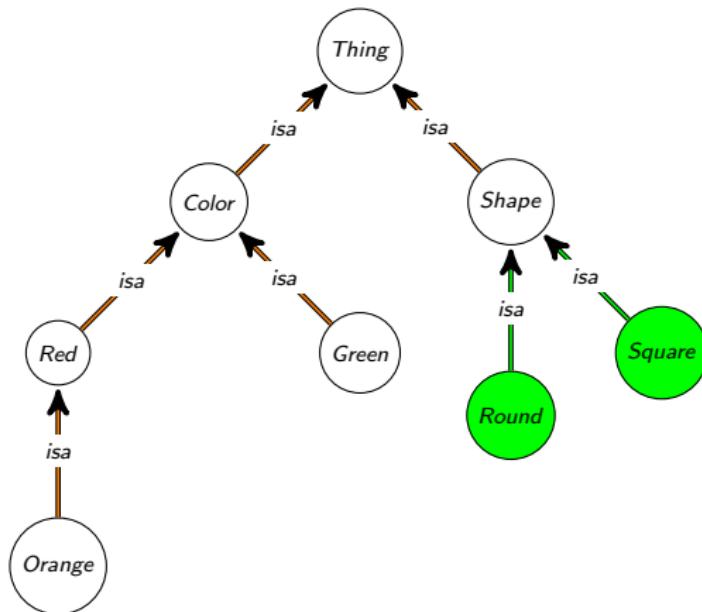
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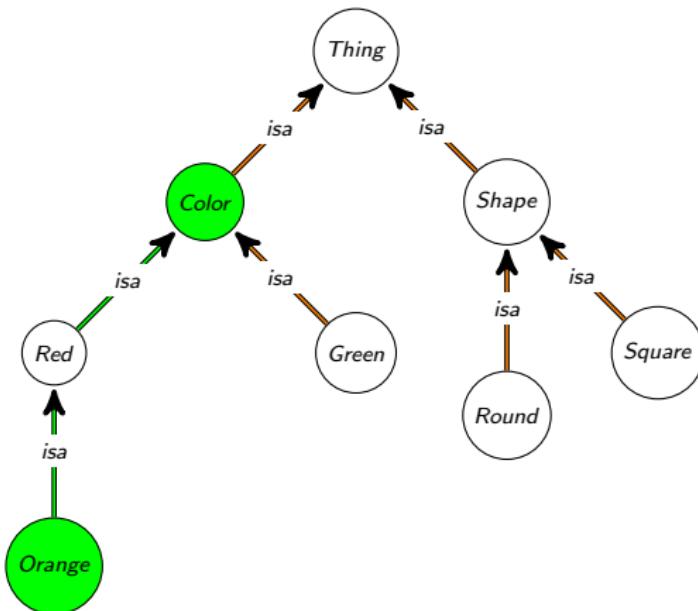
- ▶ distance on shortest path
- ▶  $\text{distance}(\text{green}, \text{red}) = 2$
- ▶  $\text{sim}_{\text{Rada}}(\text{green}, \text{red}) = \frac{1}{3}$

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- ▶ distance on shortest path
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- ▶ *density* of a branch in the ontology
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  - ▶ information content
- ▶ account for different edge types
  - ▶ non-uniform edge weighting

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- ▶  $\sigma(x) = f(A(x))$  (for ancestors  $A(x)$ )

- ▶  $\sigma(x) = f(D(x))$  (for descendants  $D(x)$ )

- ▶ many more, e.g., Zhou et al.:

$$\sigma(x) = k \cdot \left(1 - \frac{\log |D(x)|}{\log |C|}\right) + (1 - k) \frac{\log \text{depth}(x)}{\log \text{depth}(G_T)}$$

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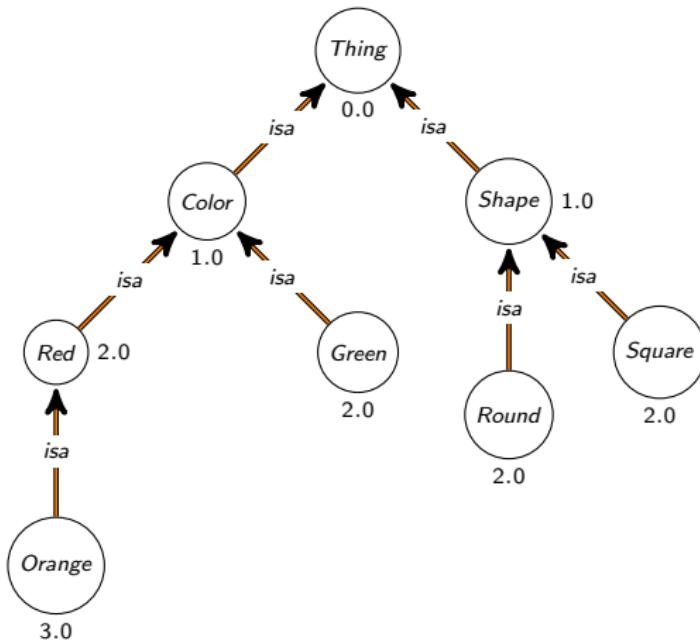
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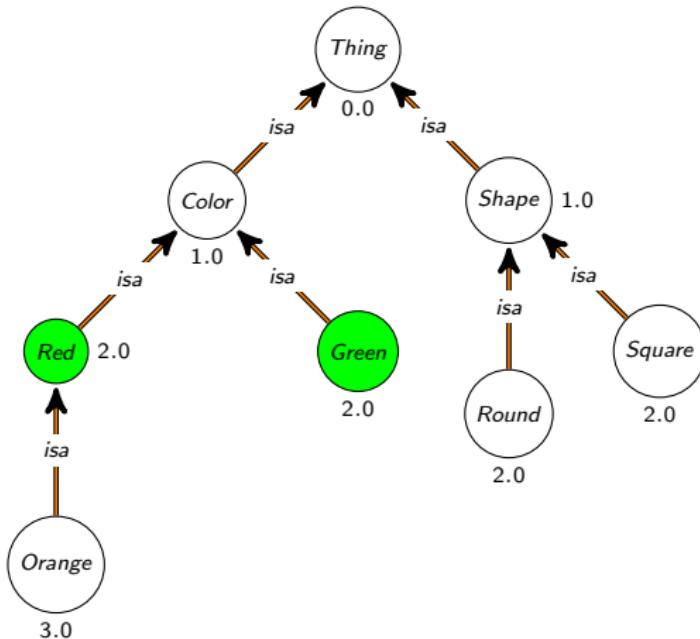
- ▶  $\sigma(x)$  defined as a function of instances (or annotations)  $I$ 
    - ▶ note: the number of instances monotonically decreases with increasing depth in taxonomies
  - ▶ Resnik 1995:  $eIC_{Resnik}(x) = -\log p(x)$  (with  $p(x) = \frac{|I(x)|}{|I|}$ )
    - ▶ in biology, one of the most popular specificity measure when annotations are present

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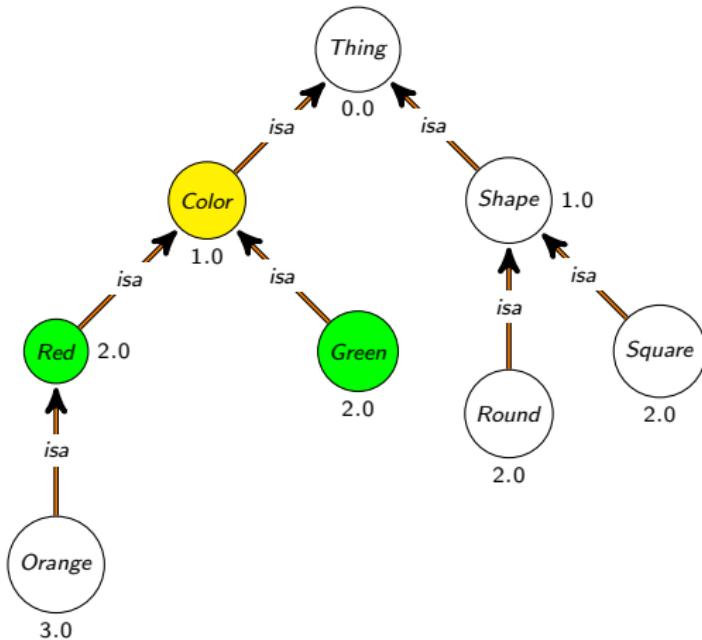
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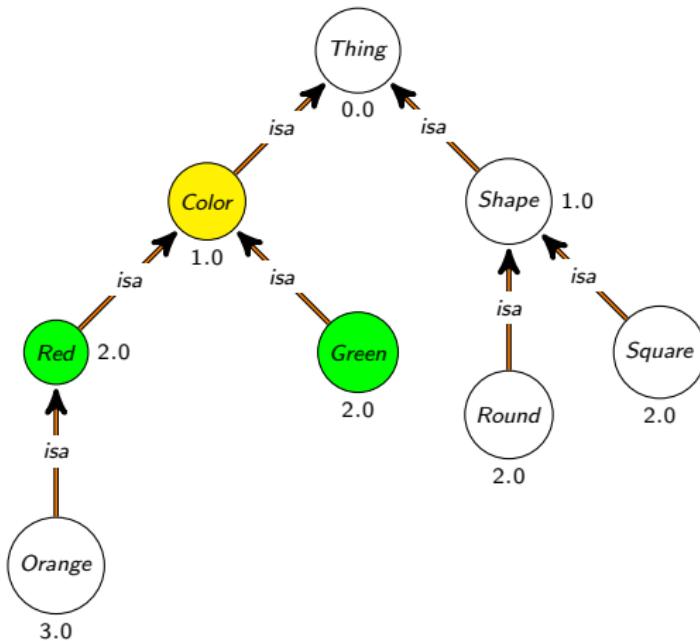
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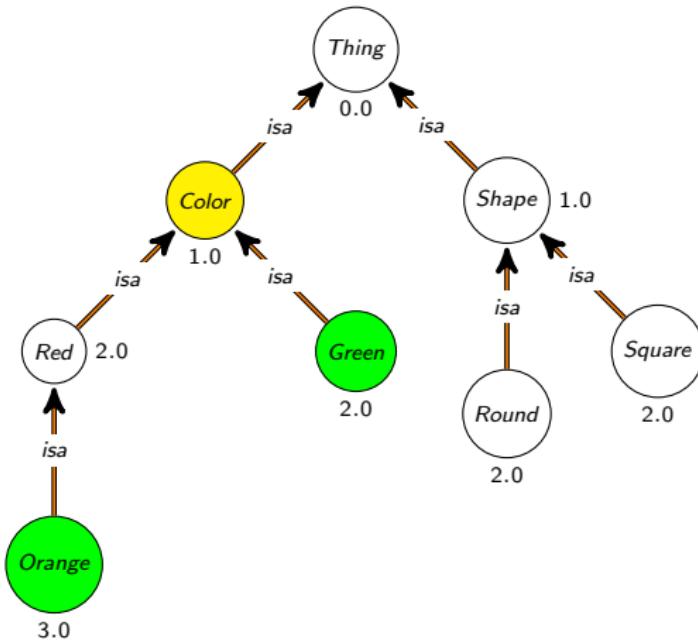


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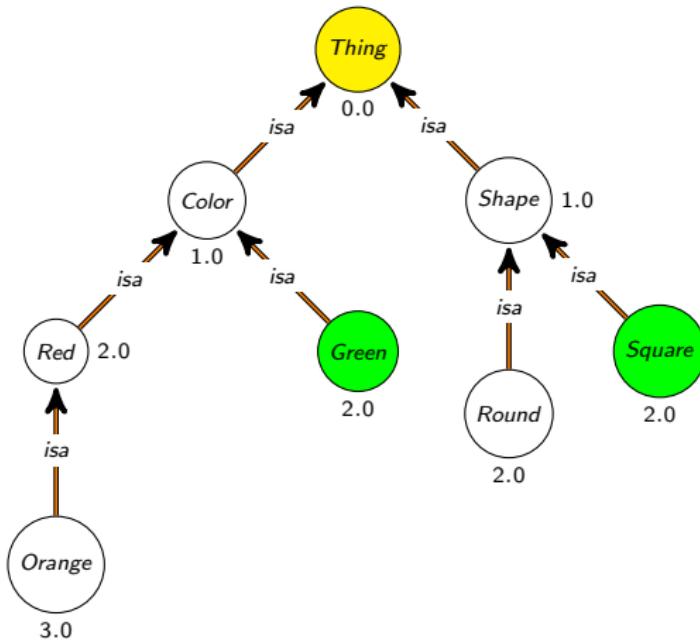


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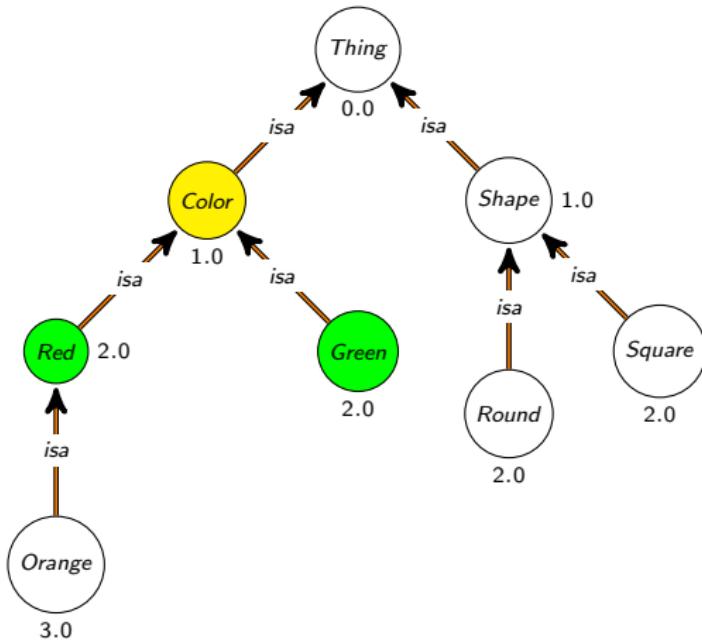


$sim_{Resnik}(Square, Orange)$   
0.0

## How to measure similarity?

- ▶ (Red, Green) and (Orange, Green) have the same similarity
- ▶ need to incorporate the specificity of the compared classes

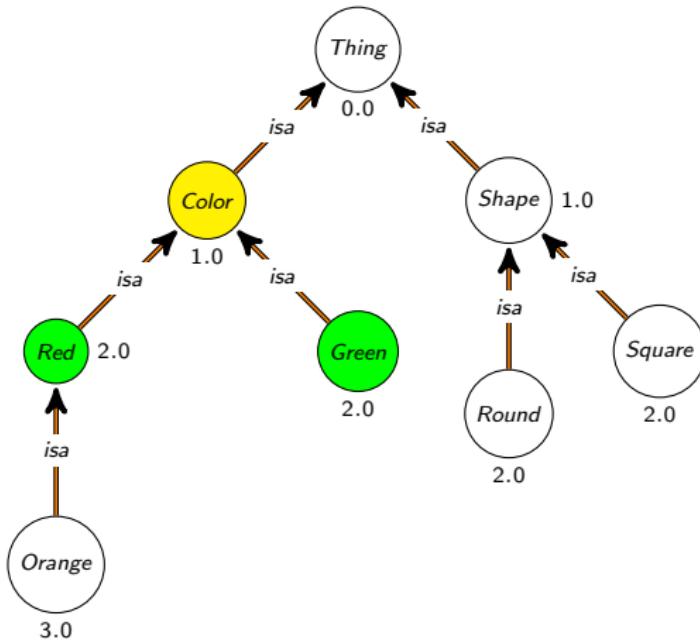
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► Lin 1998:

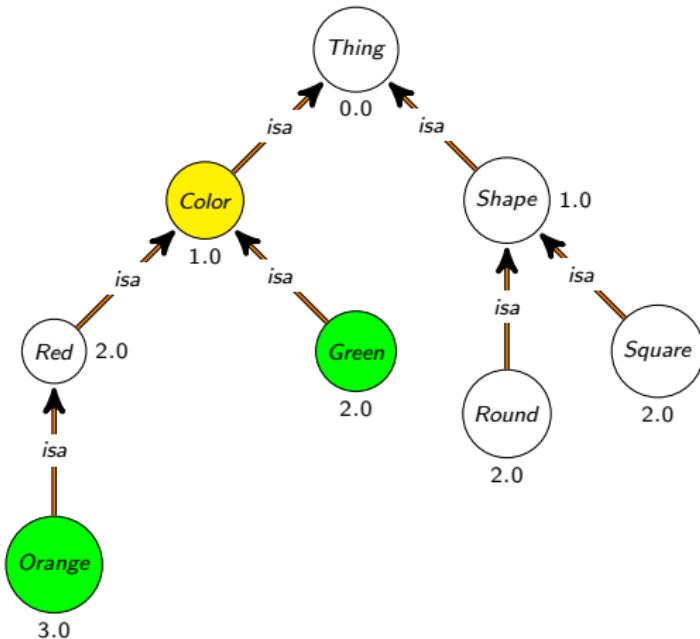
$$sim_{Lin}(x, y) = \frac{2 \cdot IC(MICA(x, y))}{IC(x) + IC(y)}$$

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- Lin 1998:  
$$sim_{Lin}(x, y) = \frac{2 \cdot IC(MICA(x, y))}{IC(x) + IC(y)}$$
- $sim_{Lin}(Green, Red) = 0.5$

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► Lin 1998:

$$sim_{Lin}(x, y) = \frac{2 \cdot IC(MICA(x, y))}{IC(x) + IC(y)}$$

►

$$sim_{Lin}(Green, Orange) = 0.4$$

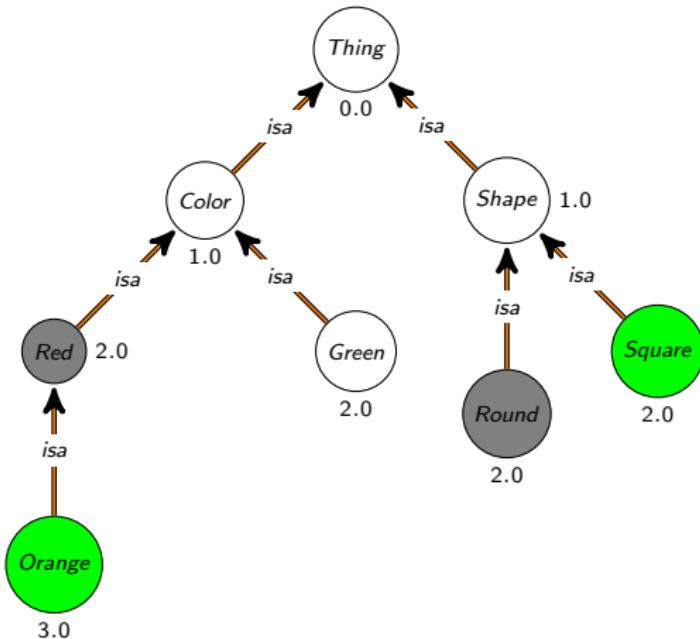
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- ▶ many(!) others:
  - ▶ Jiang & Conrath 1997
  - ▶ Mazandu & Mulder 2013
  - ▶ Schlicker et al. 2009
  - ▶ ...

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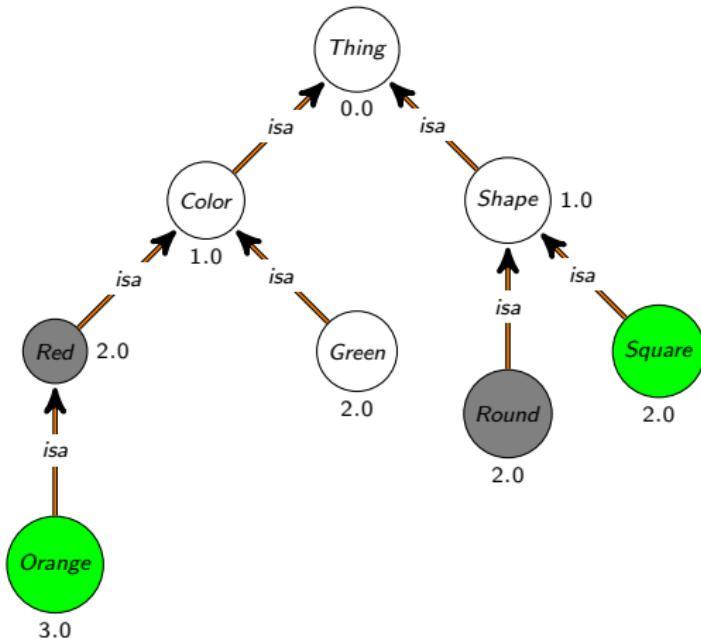
- ▶ we only looked at comparing pairs of classes
- ▶ mostly, we want to compare *sets* of classes
  - ▶ set of GO annotations
  - ▶ set of signs and symptoms
  - ▶ set of phenotypes
- ▶ two approaches:
  - ▶ compare each class individually, then merge
  - ▶ directly set-based similarity measures

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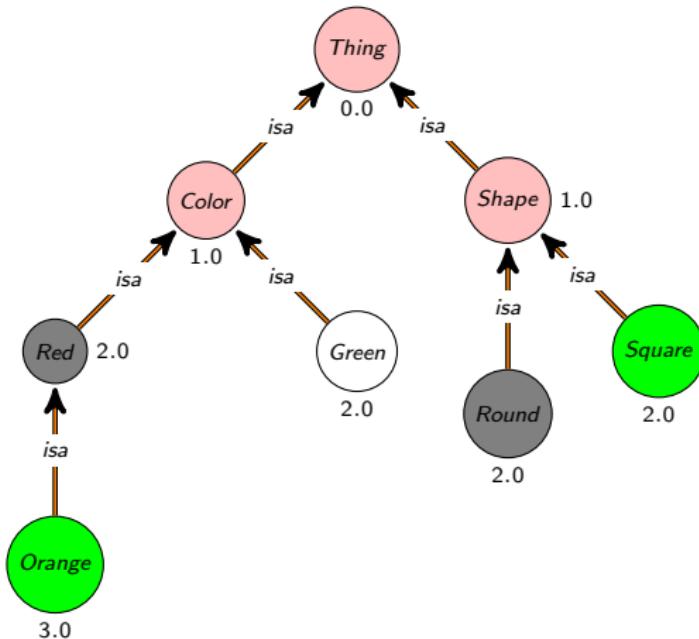
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- ▶  $\text{simGIC}(so, rr) = \frac{2}{11}$

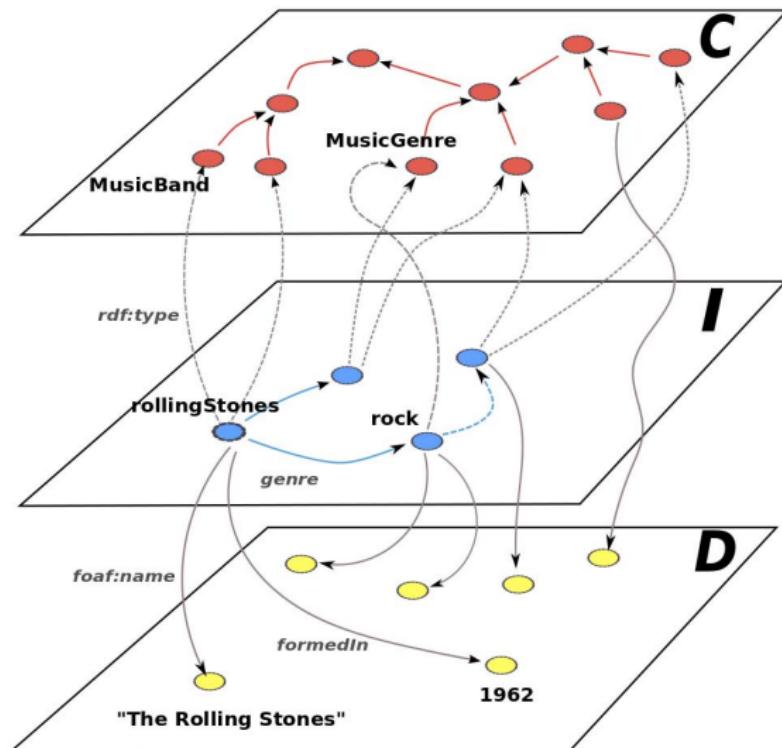
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- ▶ alternatively: use different merging strategies
- ▶ common: average, maximum, **best-matching average**
  - ▶ Average:  $sim_A(X, Y) = \frac{\sum_{x \in X} \sum_{y \in Y} sim(x, y)}{|X| \times |Y|}$
  - ▶ Max average:  $sim_{MA}(X, Y) = \frac{1}{|X|} \sum_{x \in X} \max_{y \in Y} sim(x, y)$
  - ▶ Best match average:  $sim_{BMA}(X, Y) = \frac{sim_{MA}(X, Y) + sim_{MA}(Y, X)}{2}$

# How to measure similarity?

- ▶ Semantic Measures Library:
  - ▶ comprehensive Java library
  - ▶ <http://www.semantic-measures-library.org/>
- ▶ R packages: GOSim, GOSemSim, HPOSim, LSAfun, ontologySimilarity,...
- ▶ Python: sematch, fastsemsim (GO only)

# How to measure similarity?



From Harispe et al., Semantic Similarity From Natural Language And Ontology Analysis, 2015.

# How to measure similarity?

- ▶ Shortest Path
  - ▶ applicable to arbitrary knowledge graphs
  - ▶ does not capture similarity well over all edge types, e.g., *disjointWith*, *differentFrom*, *opposite-of*, etc.
- ▶ Random Walk
  - ▶ with or without restart
  - ▶ iterated
  - ▶ does not consider edge labels ⇒ captures only adjacency of nodes
  - ▶ scores whole graph with *probability* of being in a state
  - ▶ can take multiple seed nodes
    - ▶ widely used to find disease genes

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- ▶ e.g., iterated, edge-labeled random walk
  - ▶ over instances and classes
  - ▶ walks form *sentences*
  - ▶ sentences form a *corpus*
  - ▶ feature learning on corpus through Word2Vec (or factorization of co-occurrence matrix)
  - ▶ RDF2Vec: <http://data.dws.informatik.uni-mannheim.de/rdf2vec/>

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<https://github.com/bio-ontology-research-group/walking-rdf-and-owl>
    - ▶ (self-promotion warning)

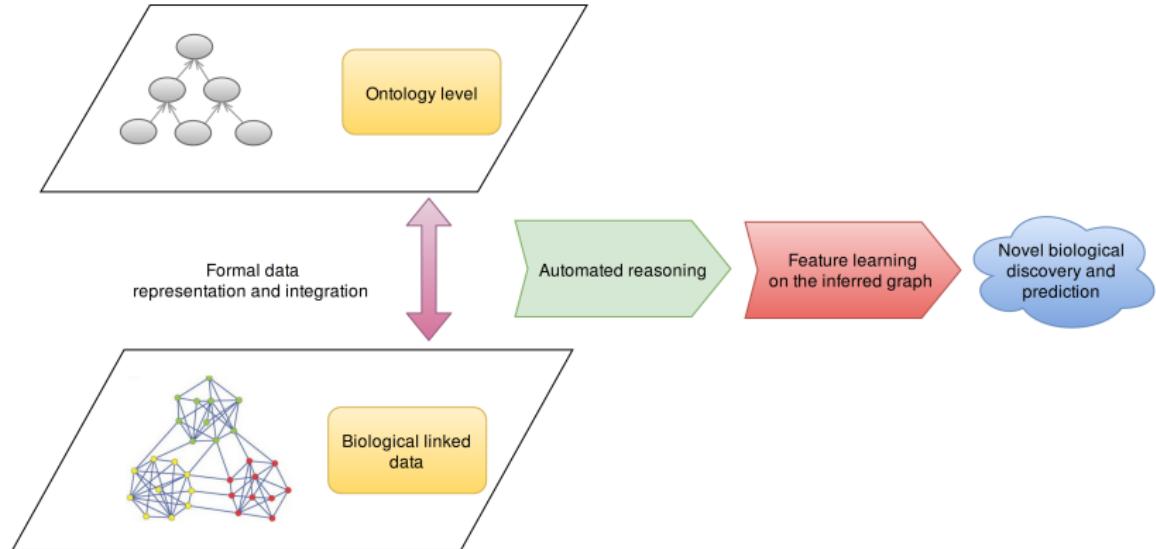
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<https://github.com/bio-ontology-research-group/walking-rdf-and-owl>
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- ▶ Translational knowledge graph embeddings: TransE, TransR, TransE, HolE, etc.
  - ▶ analogy-based
  - ▶ <https://github.com/thunlp/KB2E>

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  - ▶ walks form *sentences*
  - ▶ sentences form a *corpus*
  - ▶ feature learning on corpus through Word2Vec (or factorization of co-occurrence matrix)
  - ▶ RDF2Vec: <http://data.dws.informatik.uni-mannheim.de/rdf2vec/>
  - ▶ with support for reasoning over bio-ontologies:  
<https://github.com/bio-ontology-research-group/walking-rdf-and-owl>
    - ▶ (self-promotion warning)
- ▶ Translational knowledge graph embeddings: TransE, TransR, TransE, HolE, etc.
  - ▶ analogy-based
  - ▶ <https://github.com/thunlp/KB2E>
- ▶ generates (dense) feature vectors for nodes (classes, instances) and relations

# How to measure similarity?



# How to measure similarity?

- ▶ vector-based similarity measure
- ▶ cosine similarity:  $sim(X, Y) = \frac{\sum_{i=1}^n X_i Y_i}{\sqrt{\sum_{i=1}^n X_i^2} \sqrt{\sum_{i=1}^n Y_i^2}}$ 
  - ▶ bounded between  $[-1, 1]$
- ▶ Euclidean distance:  $sim(X, Y) = \sqrt{\sum_{i=1}^n (X_i - Y_i)^2}$ 
  - ▶ not bounded (and rarely used)

# How to measure similarity?

- ▶ many graph based semantic similarity measures for comparing two classes
- ▶ several set-based measures
  - ▶ directly set-based
  - ▶ merging pair-wise comparison
- ▶ most useful when comparing instances/annotations
- ▶ other approaches consider relations between instances:
  - ▶ path-based
  - ▶ random-walk
- ▶ very recent: knowledge graph embeddings
  - ▶ and any vector-based similarity measure

# How to measure similarity?

Recommended reading:

- ▶ recommended, comprehensive overview: Sebastian Harispe et al. Semantic Similarity from Natural Language and Ontology Analysis. Morgan & Claypool Publishers, 2015
- ▶ Catia Pesquita et al. Semantic Similarity in Biomedical Ontologies. PLoS CB, 2009.
- ▶ Maximilian Nickel et al. A Review of Relational Machine Learning for Knowledge Graphs, Proceedings of the IEEE, 2016.

## How to measure similarity: Quiz

- ▶ How many semantic similarity measures are there?
  - a One (and it is called The Semantic Similarity Measure)
  - b Three (graph-based, set-based, feature-based)
  - c Many (depending on context, many functions can determine similarity)

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  - a depends on the number of children and ancestors, and the depth
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  - c can improve similarity estimates significantly
- ▶ In the presence of (relations between) instances, semantic similarity
  - a cannot be computed, it only works with ontologies
  - b can be estimated using only class specificity measures
  - c can be computed using feature learning and knowledge graph embeddings

# Applications of semantic similarity

- ▶ ontologies are used *almost everywhere* in biology
- ▶ many applications of semantic similarity:
  - ▶ predicting interacting proteins
  - ▶ predict candidate genes
    - ▶ using the guilt-by-association principle, or without
  - ▶ predict drug targets and indications
  - ▶ as features in machine learning models

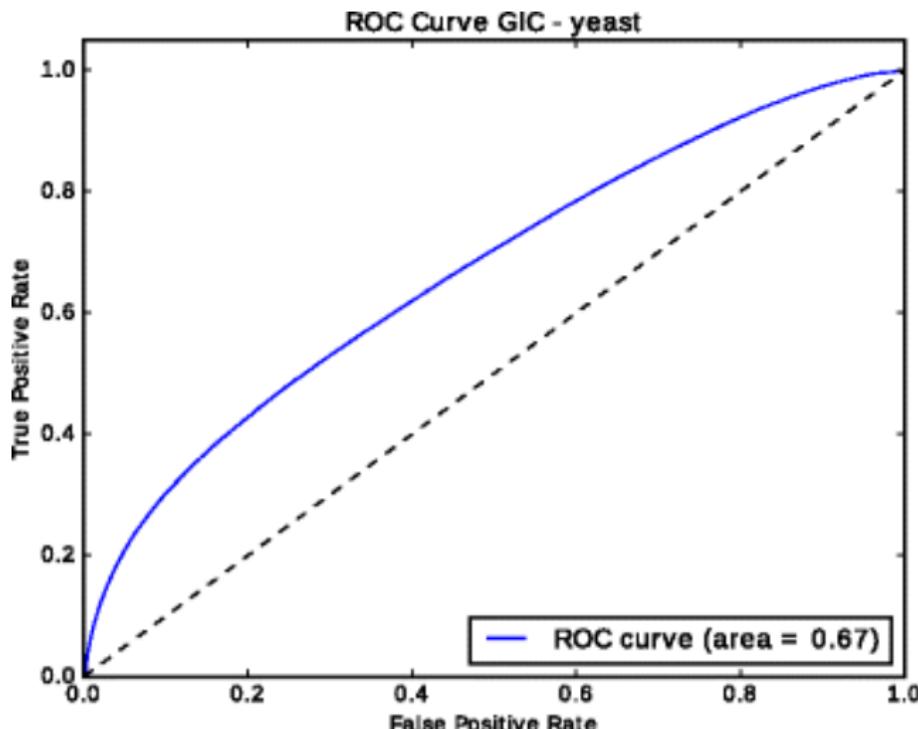
# Applications of semantic similarity

## Hypothesis

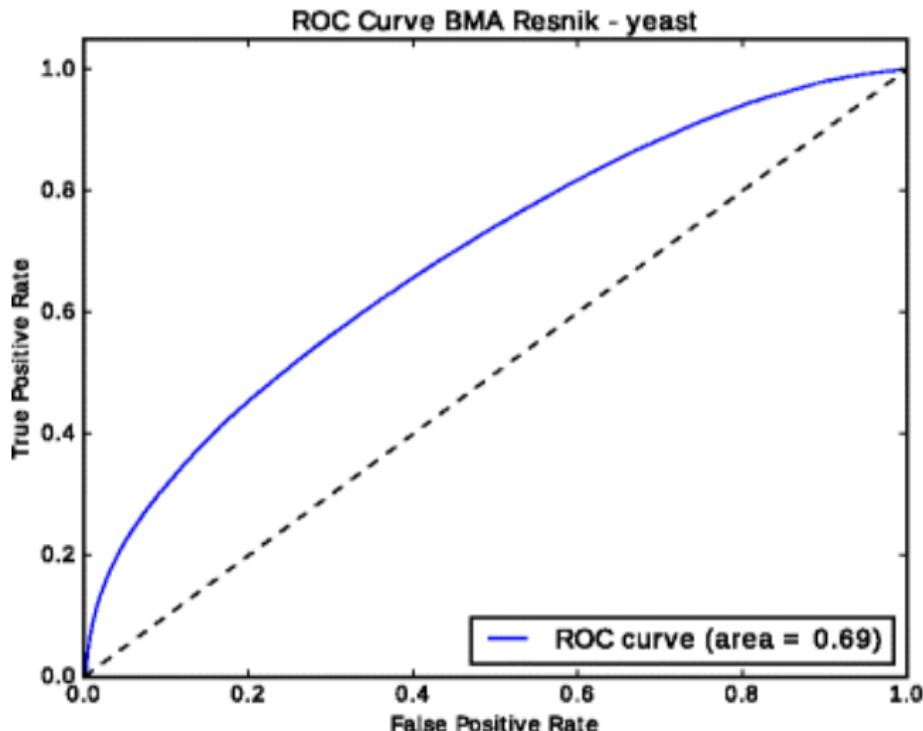
Interacting proteins have similar functions.

- ▶ relies on background knowledge about functions (encoded in GO)
- ▶ “similarity” can mean:
  - ▶ part of the same pathway
  - ▶ siblings of a common super-class
  - ▶ located in the same location
- ▶ set-based comparison of GO functions
  - ▶ single GO hierarchy or all?
  - ▶ which similarity measure?

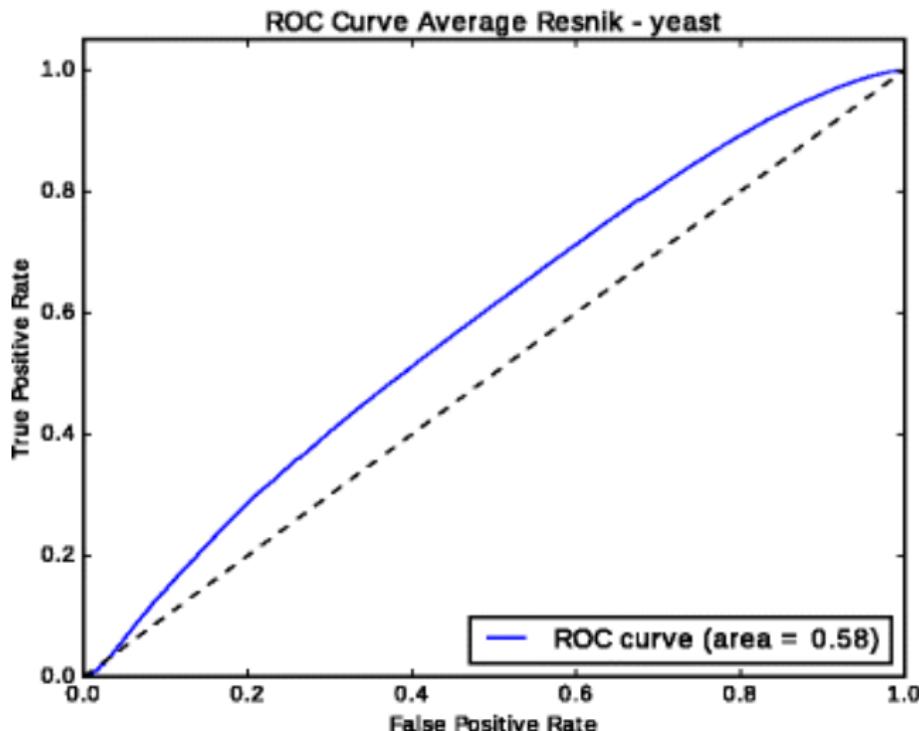
# Applications of semantic similarity



# Applications of semantic similarity



# Applications of semantic similarity



# Applications of semantic similarity

- ▶ no obvious choice of similarity measure
- ▶ depends on application
  - ▶ predicting PPIs in different organisms may benefit from a different similarity measure!
- ▶ different similarity measures may react differently to biases in data
- ▶ needs some testing and experience

# Applications of semantic similarity

Recommendations:

- ▶ use Resnik's information content measure
- ▶ use Resnik's similarity
- ▶ use Best Match Average
- ▶ use the full ontology
- ▶ classify your ontology using an automated reasoner before applying semantic similarity
  - ▶ although many ontologies come pre-classified
- ▶ ⇒ but there are many exceptions
  - ▶ similar location ⇒ use location subset of GO
  - ▶ developmental phenotypes ⇒ use developmental branch of phenotype ontology

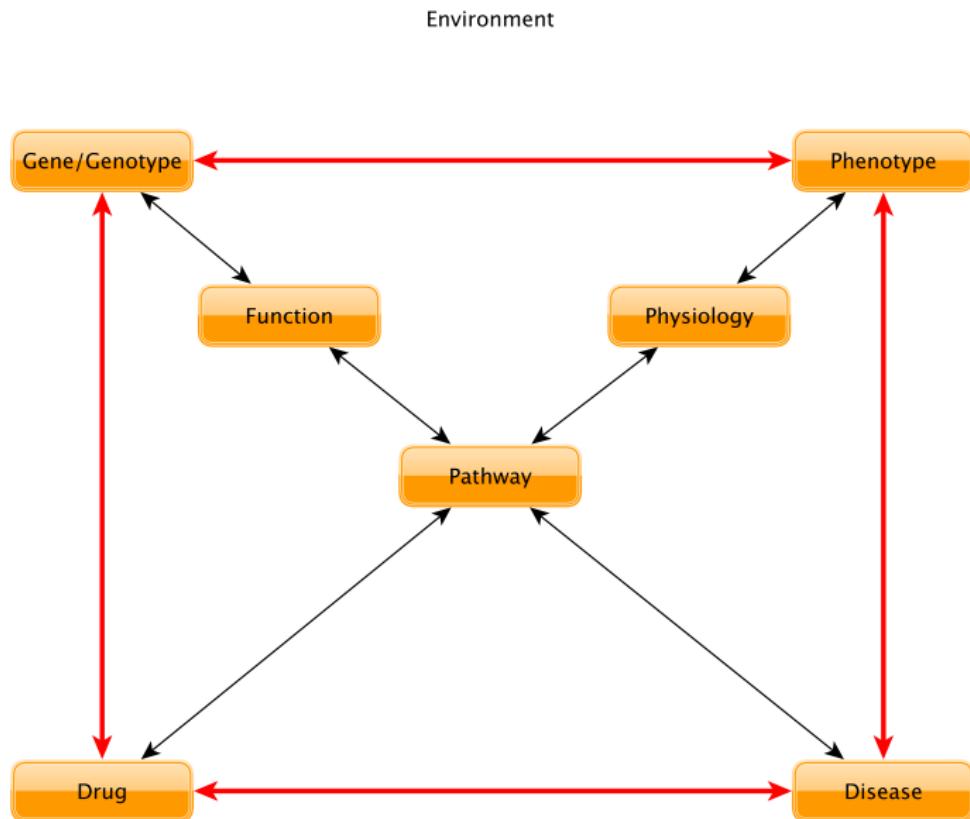
# Applications of semantic similarity

- ▶ choice of ontology determines the kind of similarity
- ▶ functional similarity: Gene Ontology
- ▶ anatomical, structural similarity: anatomy ontologies (Uberon, MA, FMA, etc.)
- ▶ phenotypic similarity: phenotype ontology (HPO, MP, etc.)
- ▶ chemical structural similarity: ChEBI

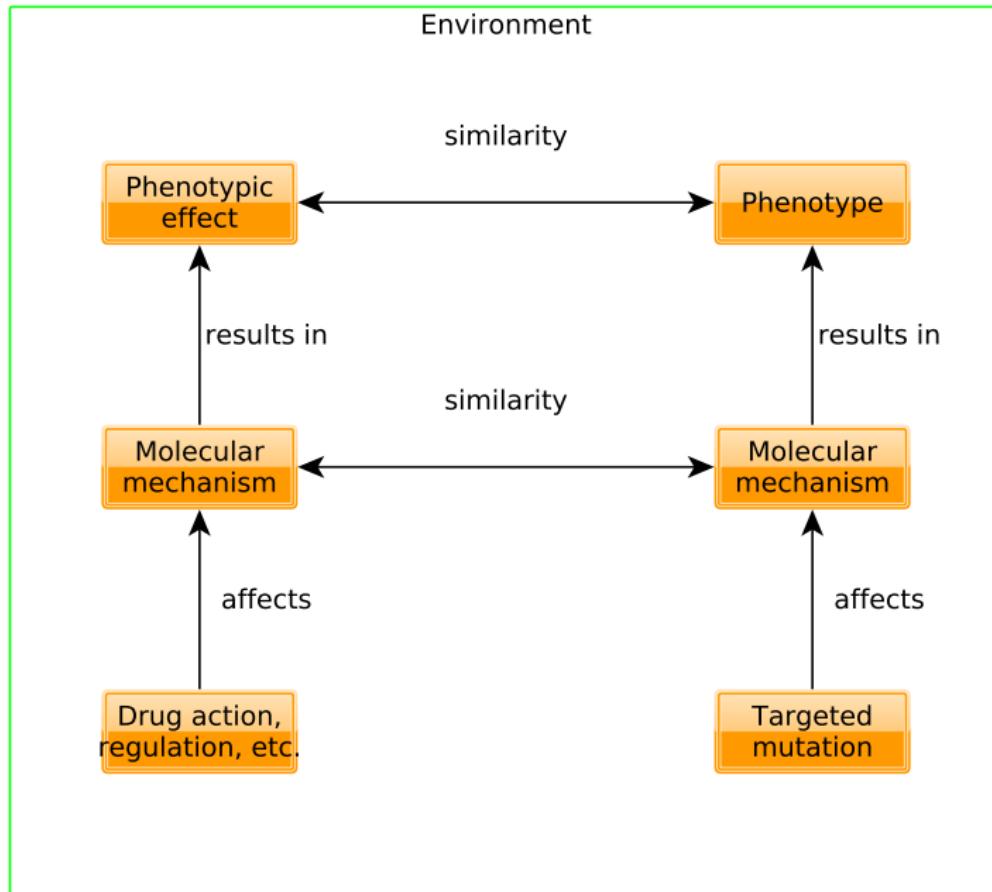
# Applications of semantic similarity

- ▶ phenotypic similarity used to:
  - ▶ diagnosis: similarity between patient phenotypes and disease phenotypes
    - ▶ also between patient phenotypes and gene–phenotype associations
    - ▶ Phenomizer: <http://compbio.charite.de/phenomizer/>
  - ▶ disease modules: similarity between disease and disease
  - ▶ clustering/stratification: similarity between patient and patient
  - ▶ disease gene discovery: similarity between patient/disease phenotypes and gene–phenotype associations
    - ▶ in humans
    - ▶ in model organisms
  - ▶ drug repurposing: side-effect similarity; similarity between side effect profile and gene–disease associations

# Applications of semantic similarity



# Applications of semantic similarity



# Applications of semantic similarity

- ▶ Guilt-by-association:
  - ▶  $x$  is associated with  $y$
  - ▶  $z$  is similar to  $x$
  - ▶ therefore:  $z$  may be associated with  $y$
- ▶ candidate genes (polygenic disease):
  - ▶ FunSimMat: similar function  $\Rightarrow$  similar/same disease
  - ▶ side effect similarity: similar side effects  $\Rightarrow$  similar targets/indications

# Applications of semantic similarity

- ▶ No guilt-by-association:
  - ▶  $x$  causes  $a$
  - ▶  $y$  has  $b$
  - ▶  $a$  similar to  $b$
  - ▶ therefore:  $b$  is caused by  $x$
- ▶ candidate genes (monogenic and polygenic disease):
  - ▶ Phenomizer: gene  $x$  causes phenotypes  $a$ ; patient  $y$  has symptoms  $b$ ;  $a$  is similar to  $b$ ; therefore: gene  $x$  causes the symptoms in  $b$
  - ▶ PhenomeNET: similar to Phenomizer but using model organism phenotypes (knockouts)
  - ▶ PhenomeDrug: knockout of gene  $x$  causes phenotypes  $a$ ; drug  $y$  causes side effects  $b$ ;  $a$  is similar to  $b$ ; therefore: drug  $y$  inhibits  $x$  (or: phenotypes  $b$  are caused by inhibition of  $x$ )
  - ▶ needs to compare model organism phenotypes and human phenotypes  $\Rightarrow$  ontology alignment/integration/mapping

# Applications of semantic similarity

- ▶ comparing entities annotated with *different* ontologies/vocabularies of the *same* (or related) domains
  - ▶ medical: UMLS, HPO, DO, ORDO, NCIT, ICD, SNOMED CT, MeSH, ...
  - ▶ phenotype: HPO, MP, CPO, WBPhenotype, FBCV, MeSH, ...
  - ▶ chemical: ChEBI, MeSH, DrOn, RXNorm, DrugBank, ...
- ▶ needs mapping, alignment, or integration
  - ▶ mapping: given a term  $t$ , find corresponding class in ontology  $O$ 
    - ▶ can be 1:1, 1:n, n:1, n:m
    - ▶  $t$  can be from ontology, vocabulary, database, or text
    - ▶ use  $O$  for analysis
  - ▶ alignment: given two ontologies or vocabularies  $O_1$  and  $O_2$ , find all mappings between classes/terms in  $O_1$  and  $O_2$ 
    - ▶ applicable to ontologies and vocabularies
    - ▶ use  $O_1$  or  $O_2$  for analysis
  - ▶ integration: given two ontologies  $O_1$  and  $O_2$ , combine both ontologies into a single ontology  $O$ 
    - ▶ maintain meaning of classes
    - ▶ use  $O$  for analysis

# Applications of semantic similarity

- ▶ lexical mappings: use class labels (and synonyms) to find matches
  - ▶ hypertension (HP:0000822) and hypertension (MP:0000231)
- ▶ semantic mappings: use class axioms to find matches
  - ▶ pulmonary valve stenosis (MP:0006182) and Pulmonic stenosis (HP:0001642)
  - ▶ both definitions based on constricted (PATO:0001847) and pulmonary valve (UBERON:0002146)
- ▶ hybrid: combine lexical and semantic mappings

# Applications of semantic similarity

tools for ontology mapping, matching, integration:

- ▶ AgreementMaker Light:  
<https://github.com/AgreementMakerLight/AML-Jar>
  - ▶ structural (semantic) and lexical matches
  - ▶ can use domain-specific background knowledge
- ▶ LogMap: <https://github.com/ernestojimenezruiz/logmap-matcher>
  - ▶ structural (semantic) and lexical matches
  - ▶ biology-themed versions
- ▶ NCBO Annotator:  
<https://bioportal.bioontology.org/annotator>
  - ▶ lexical matches only
  - ▶ can annotate full text
- ▶ recent tools and comprehensive ongoing evaluation:
  - ▶ OAEI: <http://oaei.ontologymatching.org/>

# Applications of semantic similarity

semantic similarity and text mining:

- ▶ find all occurrences of classes of one (or more) ontologies in text
  - ▶ using lexical matching or semantic annotations of text
  - ▶ TextPresso (<http://www.textpresso.org/>), NCBO Annotator (<https://bioportal.bioontology.org/annotator>), WhatIzIt (<http://www.ebi.ac.uk/webservices/whatizit/info.jsf>)
  - ▶ ontology-specific text normalization tools
    - ▶ DNorm (diseases), GNorm (gene names), OSCAR (chemicals), ...
- ▶ use for database construction (automatic annotation), relation extraction, network construction (co-occurrence network), etc.

# Applications of semantic similarity

<http://aber-owl.net/aber-owl/diseasephenotypes/>

- ▶ find phenotypes (signs and symptoms) associated with common diseases
  - ▶ no resource available for comparison
- ▶ pattern-based mining of literature with Aber-OWL: PubMed
- ▶ evaluation (of genetically based disease phenotypes) with experimentally validated disease genes

# Applications of semantic similarity

<http://aber-owl.net/aber-owl/diseasephenotypes/>

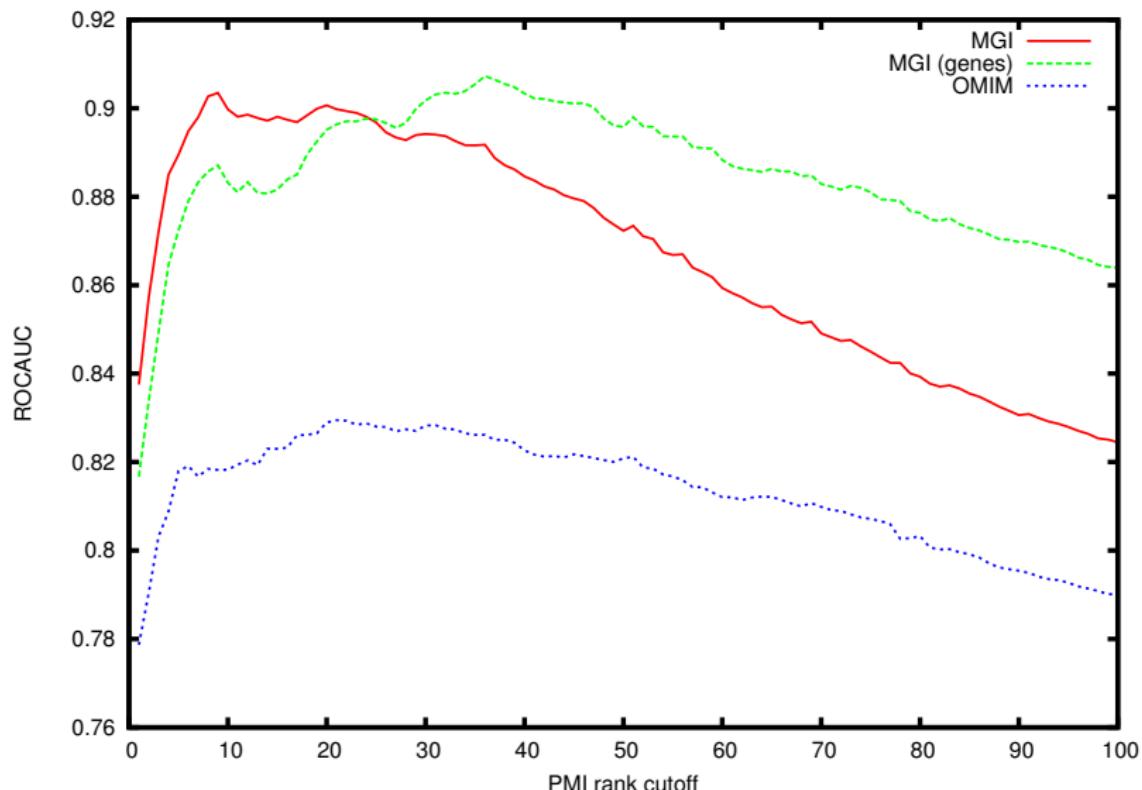
## Phenotypes for 'bubonic plague'

- [Mouse models](#)
- [Network](#)

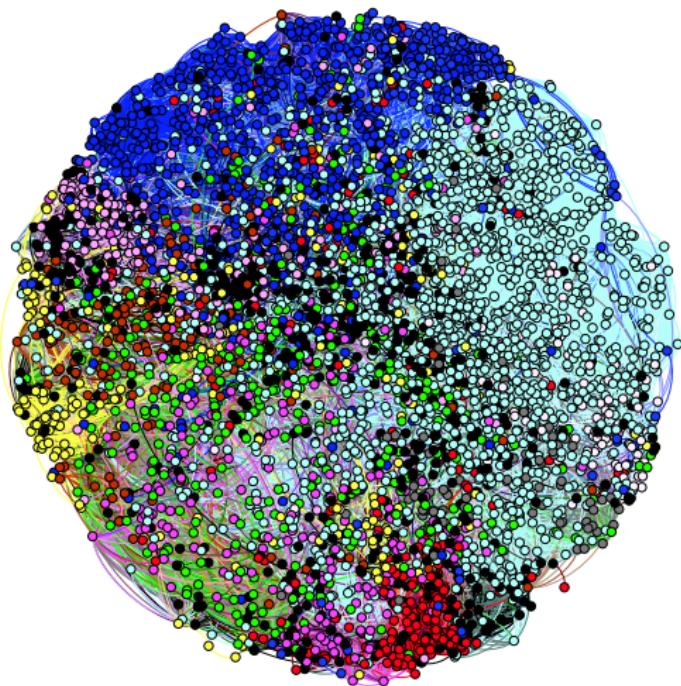
Show	100	entries	
	Phenotype	ID	Pointwise Mutual Information
death		MP:0001641	0.22837393990989352
Increased IgA level		HP:0003261	0.21745157416550895
eye lesions		MP:0013146	0.21110960811807034
Lymphadenitis		HP:0002840	0.20726444631165528
lymph node inflammation		MP:0003865	0.2070583004125834
Mediastinal lymphadenopathy		HP:0100721	0.16667331911036262
Abnormality of the lymph nodes		HP:0002733	0.14851361059698084
decreased susceptibility to infection		MP:0002409	0.1442019284611426
Pustule		HP:0200039	0.10968881998477503
tachypnea		MP:0005426	0.10850084511186676
Atrioventricular canal defect		HP:0006695	0.10364210532782134
Tachypnea		HP:0002789	0.10273022349597967
increased pulmonary respiratory rate		MP:0005573	0.09848893732226834

# Applications of semantic similarity

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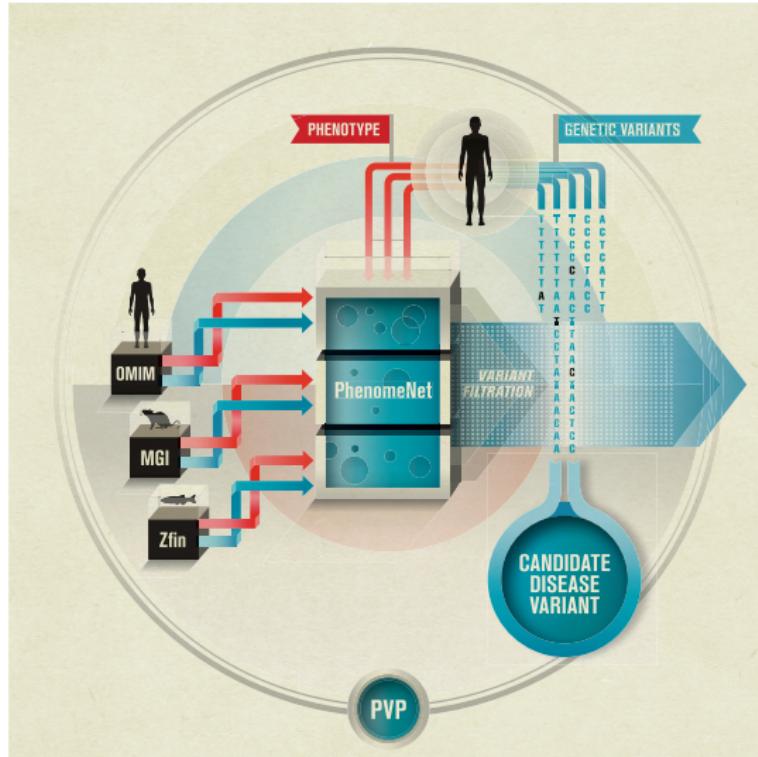
# Applications of semantic similarity



# Applications of semantic similarity

- ▶ semantic similarity can be used as features in machine learning models
  - ▶ when annotation space is too large
    - ▶ e.g., GO: 50,000 classes
    - ▶ replace binary representation
  - ▶ to incorporate background knowledge
    - ▶ semantic similarity encodes *implicitly* for ontology structure and axioms
    - ▶ encodes for *specificity* of classes
  - ▶ negative: reduce all annotations to single value
    - ▶ leads to loss of information
    - ▶ but is easier to use by many machine learning methods

# Applications of semantic similarity



# PVP Evaluation

- Synthetic data
  - 8,746 ClinVar pathogenic variants appended to WEX from 1000 Genome Project
  - 11,251 ClinVar pathogenic variants appended to WGS from 1000 Genome Project
- Real patient data
  - **19 exomes** from **UK10K\_RARE\_THYROID** study sample dataset.
  - 43 exomes from Addenbrooke's Hospital at Cambridge, UK with diseases of diverse phenotypes (e.g Bardett-Biedl Syndrome)
  - 1 patient's exome (Glutaric aciduria)
  - 5 genomes from Personal Genome Project

# Synthetic WEX patients

	Top Hit	Top 10	ROC AUC
GWAVA	1.41%	6.32%	0.711
DANN	6.06%	26.69%	0.928
eXtasy	14.85%	42.99%	0.782
CADD	15.15%	32.05%	0.946
Exomiser	24.65%	58.56%	0.89
Phevor	28.25%	64.70%	0.912
<b>PVP</b>	<b>78.80%</b>	<b>89.50%</b>	<b>0.978</b>

# Synthetic WGS patients

	Top Hit	Top 10	ROC AUC
GWAVA	0.46%	0.70%	0.949
DANN	4.95%	18.99%	0.99
CADD	5.76%	24.30%	0.962
Genomiser	31.35%	77.98%	0.948
<b>PVP</b>	<b>76.47%</b>	<b>88.61%</b>	<b>0.995</b>

# Summary

- ▶ many semantic similarity measures
  - ▶ graph-based
  - ▶ feature-based
- ▶ useful for similarity-based prediction
  - ▶ similar entities ⇒ guilt-by-association
  - ▶ different entities
- ▶ combine with data and text mining
- ▶ features in machine learning methods

## Acknowledgements

- ▶ Mona Alsharani
- ▶ Imene Boudellioua
- ▶ Maxat Kulmanov
- ▶ Sarah Alghamdi

# Hands-on: semantic similarity

- ▶ if you have not done so *before* the tutorial, don't start now
  - ▶ you need to download *a lot* of data
  - ▶ you can just follow our demonstration and try later
  - ▶ (unless Internet is exceptionally fast for a conference Wifi, then just go ahead and do everything now)
- ▶ Jupyter Notebook
  - ▶ notebooks consist of code and rich text fragments
  - ▶ human readable (with nice figures) *and* executable
  - ▶ need to install the SciJava kernel (default: iPython)
  - ▶ very widely used
- ▶ Beaker Notebook
  - ▶ like Jupyter notebook, with lots of kernels pre-installed
  - ▶ Python, Groovy, Javascript, ...
- ▶ <https://github.com/bio-ontology-research-group/ontology-tutorial>

# Hands-on: semantic similarity

In the tutorial, we will

- ▶ download an ontology
- ▶ explore the ontology with OWLAPI
- ▶ classify the ontology with an OWL reasoner
  - ▶ and query using an OWL reasoner
- ▶ store the inferred version locally
- ▶ use the Semantic Measures Library to:
  - ▶ explore the ontology as graph
  - ▶ compute similarity between classes
  - ▶ use different similarity measures
  - ▶ compare patients to mice
- ▶ you can build on this and extend for your own research!

## Hands-on: semantic similarity

Do the tutorial...

# Hands-on: semantic similarity

- ▶ now play with the Notebook:
  - ▶ look at the results list (check MGI)
  - ▶ try another disease (check OMIM)
  - ▶ or a drug effect (check SIDER)
- ▶ you can also test another ontology
  - ▶ GO for functional similarity
  - ▶ ChEBI for chemical (structural) similarity
  - ▶ or yeast phenotypes