Part 1: Ontologies and semantic similarity

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Before the tutorial

See https://github.com/bio-ontology-research-group/ontology-tutorial:

- ▶ install Docker (e.g.: apt-get install docker)
- ▶ docker pull coolmaksat/embeddings:latest
- ▶ docker run -i -t -p 8888:8888 coolmaksat/embeddings /bin/bash -c "jupyter notebook --notebook-dir=/home/borg/ontology-tutorial/ --ip='0.0.0.0' --port=8888 --no-browser --allow-root"

Learning goals

- ▶ brief overview of ontologies in biomedicine
- ▶ semantic similarity with ontologies
- ▶ machine learning with ontologies as *features* (or background knowledge)
- ▶ unsupervised or supervised:
  - ▶ here: mostly unsupervised *feature* learning
  - ▶ "deep" learning
- ▶ focus on existing tools and methods
  - ▶ Jupyter Notebooks and code examples
- ▶ not covered:
  - ▶ learning ontologies (axioms, definitions) from data
  - ▶ (most) natural language processing
  - ▶ reasoning with ontologies
  - ▶ learning on "knowledge graphs"
  - ▶ machine learning theory

Learning goals

Biomedical questions:

- ▶ diagnosing rare disease
- ▶ finding functionally similar proteins
- ▶ relying on heterogeneous data integration
 - ▶ from different databases
  - ▶ model organisms

Agenda

- ▶ Introduction: ontologies and graphs
- ▶ Semantic similarity
- ▶ Machine learning:
    - ▶ syntactic
    - ▶ graph-based
    - ▶ model-theoretic

Ontologies, machine learning, and AI

- ▶ ontologies are ubiquitous in biomedical research
- ▶ rich formal characterization (axioms)
- ▶ how can they be used for (predictive) data analysis?
    - ▶ "fuzzy", similarity-based search
    - ▶ background knowledge in machine learning

Ontologies
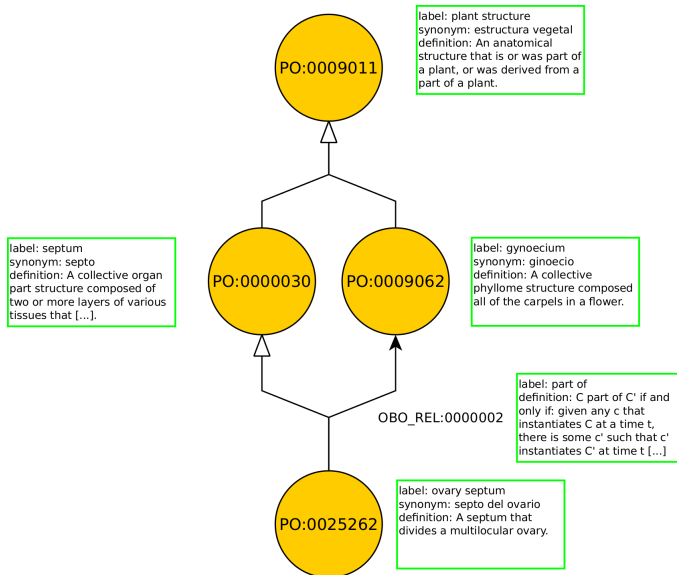
Ontologies for data integration

- ▶ standard identifiers (IRIs)
- ▶ labels of classes and relations
- ▶ human-readable descriptions
- ▶ axioms

Ontologies provide domain knowledge

Annotation	Value
label	B cell apoptotic process
definition	Any apoptotic process in a B cell, a lymphocyte of B lineage with the phenotype CD19-positive and capable of B cell mediated immunity.
class	http://purl.obolibrary.org/obo/GO_0001783
ontology	GO-PLUS
Equivalent	apoptotic process and (occurs in some B cell)
SubClassOf	occurs in some B cell, lymphocyte apoptotic process
id	GO:0001783
has_obo_namespace	biological_process

Overview | Browse | DLQuery | Download

The Semantic Web
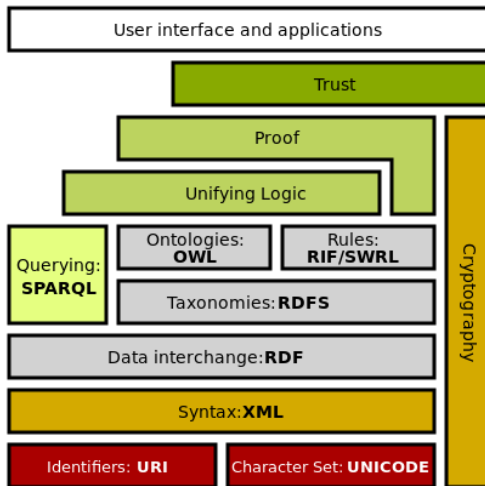
Manchester OWL Syntax

| DL Syntax	Manchester Syntax	Example
$C \sqcap D$	C and D	Human and Male
$C \sqcup D$	C or D	Male or Female
$\neg C$	not C	not Male
$\exists R.C$	R some C	hasChild some Human
$\forall R.C$	R only C	hasChild only Human
$(\geq nR.C)$	R min n C	hasChild min 1 Human
$(\leq nR.C)$	R max n C	hasChild max 1 Human
$(= nR.C)$	R exactly n C	hasChild exactly 1 Human
$\{a\} \sqcup \{b\} \sqcup ...$	{a b ...}	{John Robert Mary}

Reasoning with ontologies

- 'B cell apoptosis' EquivalentTo: apoptosis and
  'occurs in' some 'B cell'
- 'lymphocyte apoptosis' EquivalentTo: apoptosis
  and 'occurs in' some lymphocyte
- 'B cell' SubClassOf: lymphocyte

Reasoning with ontologies

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- 'B cell apoptosis' SubClassOf: 'lymphocyte apoptosis'

Reasoning with phenotype ontologies

Phenotype ontology:

- A phenotype is a quality that inheres in its bearer:
    - Enlarged heart: $Enlarged(x) \land \exists y(inheresIn(x, y) \land Heart(y))$
    - in DL: $Enlarged \sqcap \exists inheresIn.Heart$
    - Enlarged: reuse an ontology of qualities (PATO)
    - Heart: reuse ontology of (human, mammalian) anatomy

UberPheno, PhenomeNET
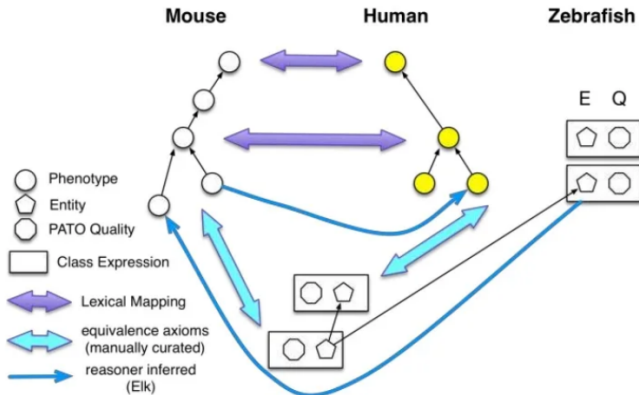
BLAST-like search over phenotypes

Using ontologies and reasoning, we can

1. describe phenotypes computationally
   - ▶ morphology
   - ▶ function
   - ▶ ⇒ ontologies

2. integrate/compare phenotypes *within and between species* (to overcome limitations in phenotype data)
   - ▶ homologous organ structures
   - ▶ related/identical function
   - ▶ ⇒ ontologies and automated reasoning

3. measure phenotypic similarity
   - ▶ use morphological or functional similarity
   - ▶ similarity in attribute values
   - ▶ ⇒ semantic similarity, machine learning

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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
  - ▶ remember: ontologies are sets of axioms
  - ▶ *subclass* axioms are easy
  - ▶ how about more complex axioms?
- ▶ solution: define relational patterns

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: $X \xleftrightarrow{\text{disjoint}} Y$
- X EquivalentTo: Y: $X \xleftrightarrow{\equiv} Y$, $\{X, Y\}$

Relations as patterns
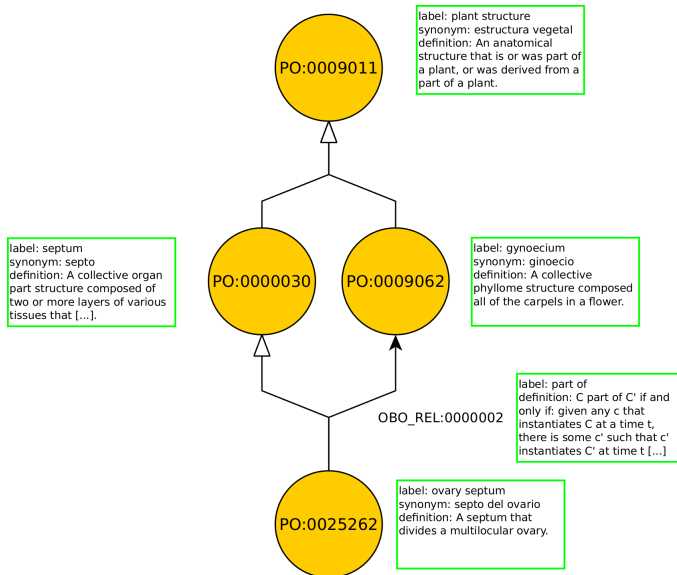
Semantic similarity

- ▶ We want to use *background knowledge* in ontologies to
  - ▶ determine similarity between classes,
  - ▶ instances,
  - ▶ and entities with ontology annotations

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
- $\Rightarrow$ reduce all of this to similarity between classes

How to measure similarity?

What properties do we want in a similarity measure?

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

How to measure similarity?
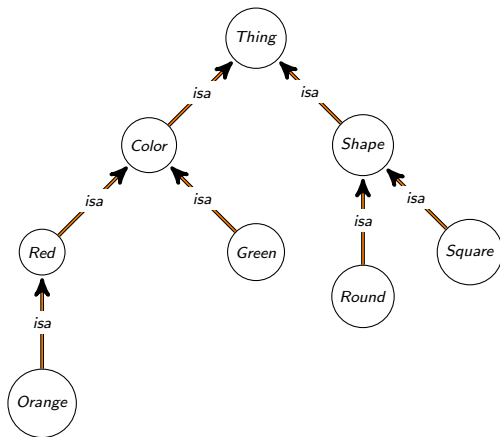
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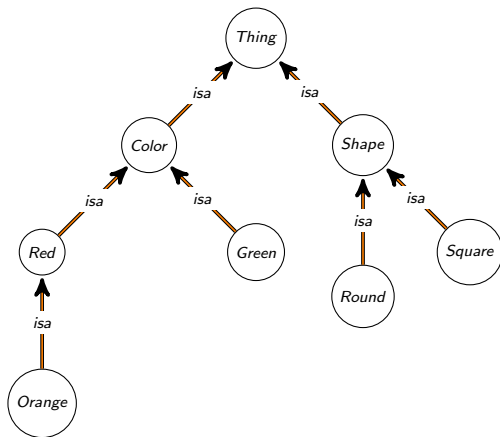
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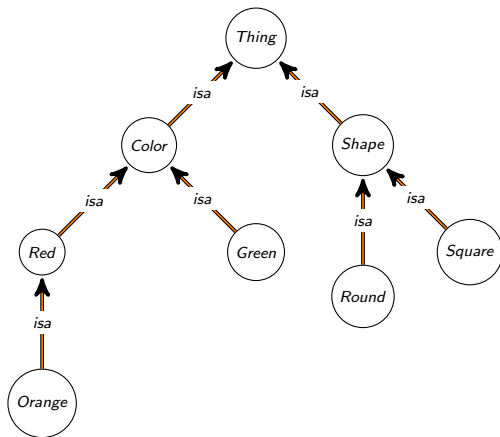
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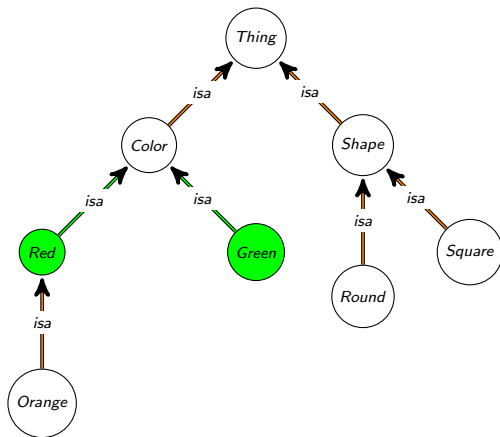- ▶ $dist_{Rada}(u, v) = sp(u, isa, v)$

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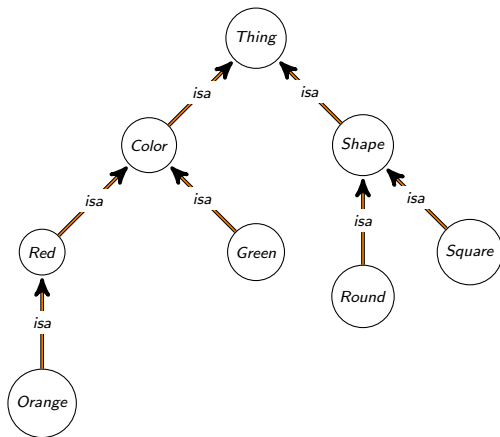
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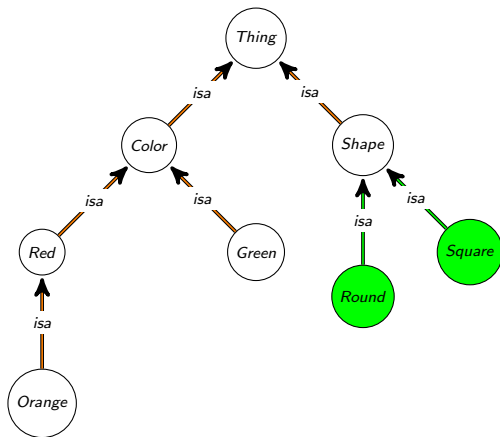- ▶ $sim_{Rada}(u, v) = \frac{1}{dist_{Rada}(u,v)+1}$

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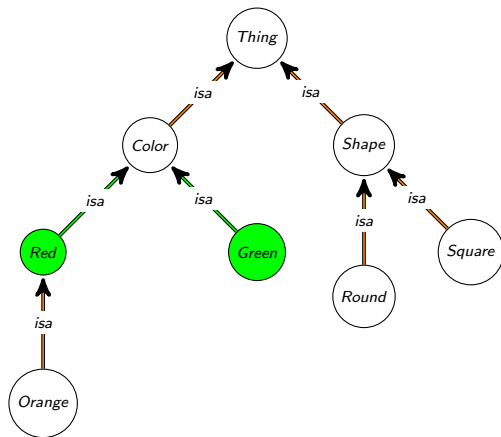
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How to measure similarity?

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

How to measure similarity?

- distance on shortest path
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- $sim_{Rada}(square, round) = \frac{1}{3}$

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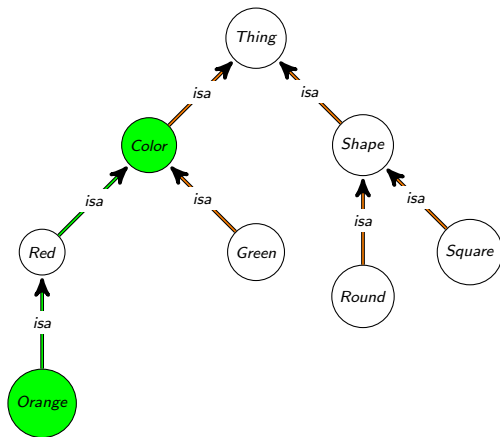
- distance on shortest path
- distance(orange, color) = 2
- $sim_{Rada}(orange, color) = \frac{1}{3}$

How to measure similarity?

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How to measure similarity?

- ▶ shortest path is not always intuitive
- ▶ we need a way to determine *specificity* of a class
  - ▶ number of ancestors
  - ▶ number of children
  - ▶ information content

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- ▶ *density* of a branch in the ontology
    - ▶ number of siblings
    - ▶ information content
- ▶ account for different edge types
    - ▶ non-uniform edge weighting

How to measure similarity

- ▶ term specificity measure $\sigma : C \mapsto \mathbb{R}$:
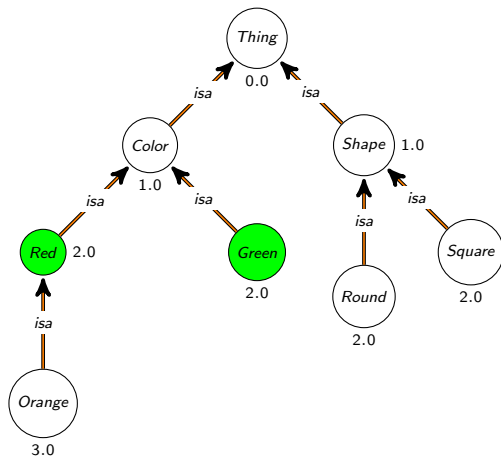 - ▶ $x \sqsubseteq y \rightarrow \sigma(x) \geq \sigma(y)$

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- ▶ intrinsic:
  - ▶ $\sigma(x) = f(depth(x))$
  - ▶ $\sigma(x) = f(A(x))$ (for ancestors $A(x)$)
  - ▶ $\sigma(x) = f(D(x))$ (for descendants $D(x)$)
  - ▶ many more, e.g., Zhou et al.:
    $\sigma(x) = k \cdot \left(1 - \frac{\log |D(x)|}{\log |C|} \right) + (1 - k) \frac{\log depth(x)}{\log depth(G_T)}$

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- extrinsic:
  - $\sigma(x)$ 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
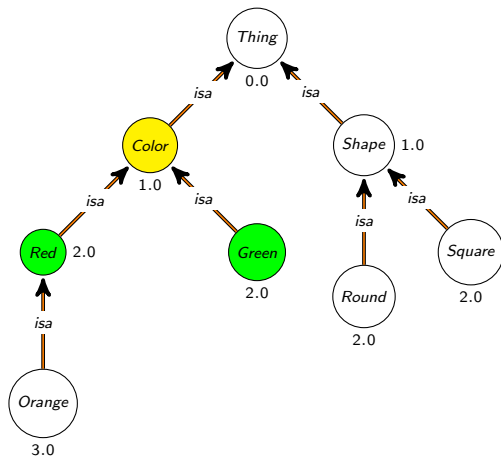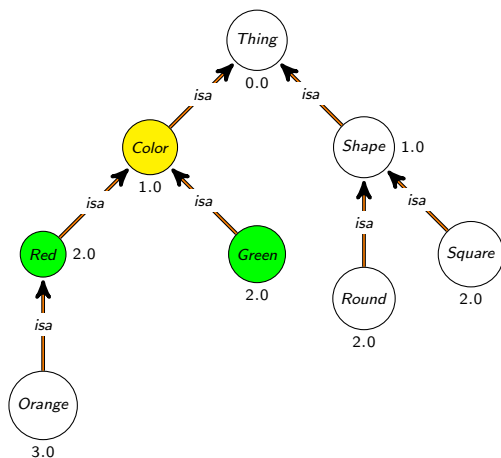
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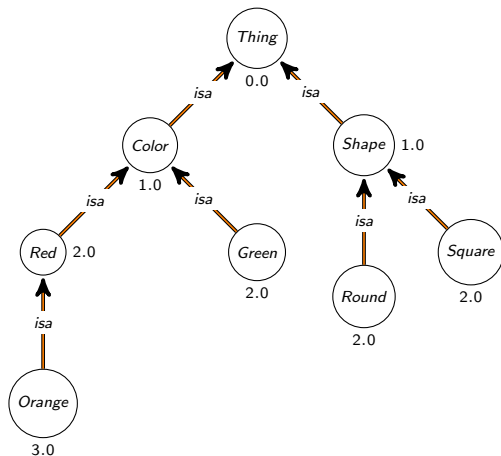
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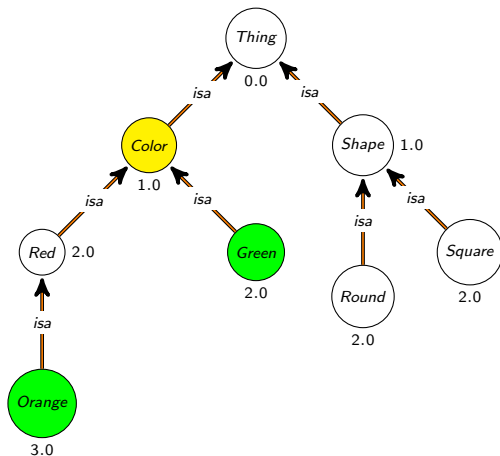- Resnik 1995: similarity between x and y is the information content of the *most informative common ancestor*

- $sim_{Resnik}(Green, Red) = 1.0$

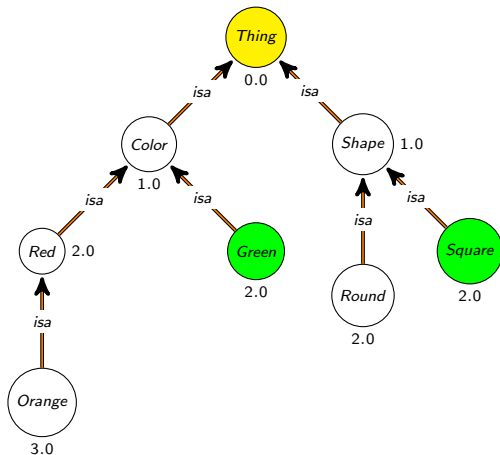# How to measure similarity?

- Resnik 1995: similarity between x and y is the information content of the *most informative common ancestor*

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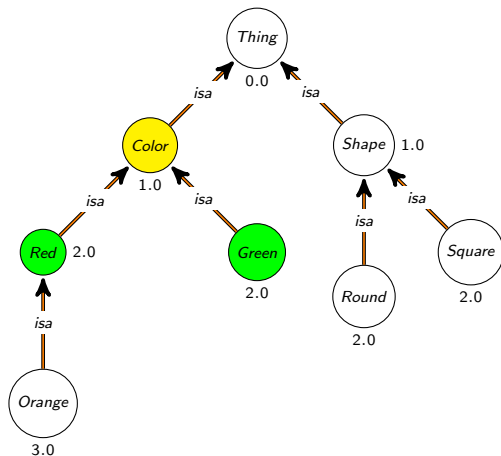
How to measure similarity?

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

How to measure similarity?

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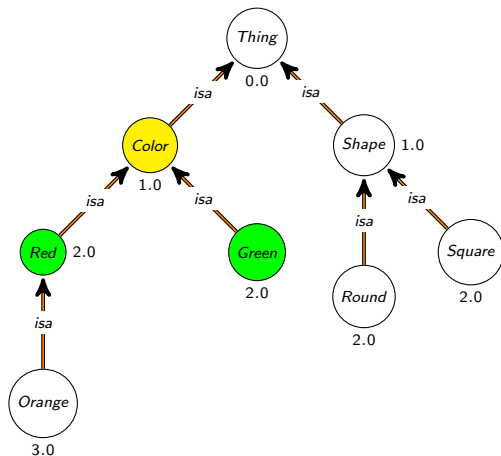- ▶ need to incorporate the specificity of the compared classes

How to measure similarity?

- Lin 1998:
  $$sim_{Lin}(x, y) = \frac{2 \cdot IC(MICA(x,y))}{IC(x)+IC(y)}$$
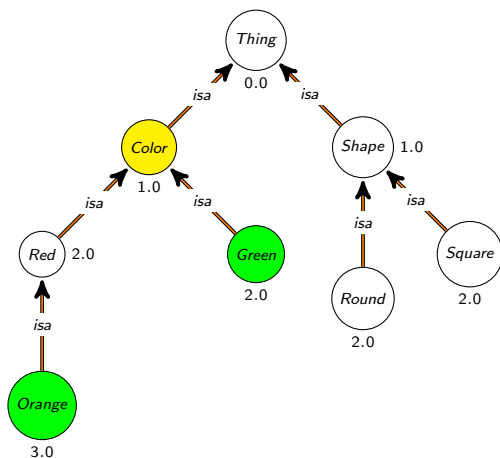
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-
  $sim_{Lin}(Green, Orange) = 0.4$

How to measure similarity?

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

How to measure similarity?

- 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

How to measure similarity?
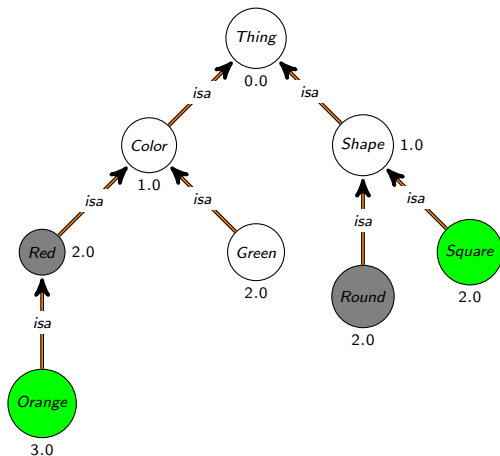
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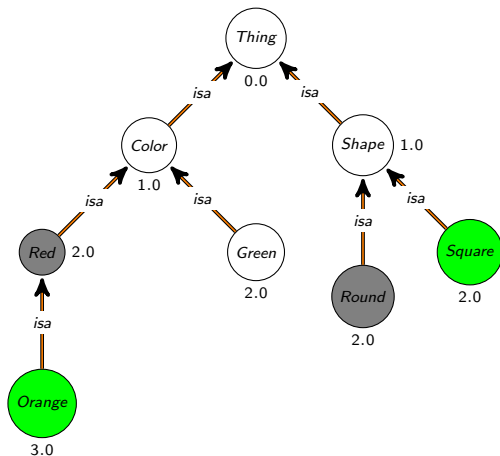
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- Pesquita et al., 2007:
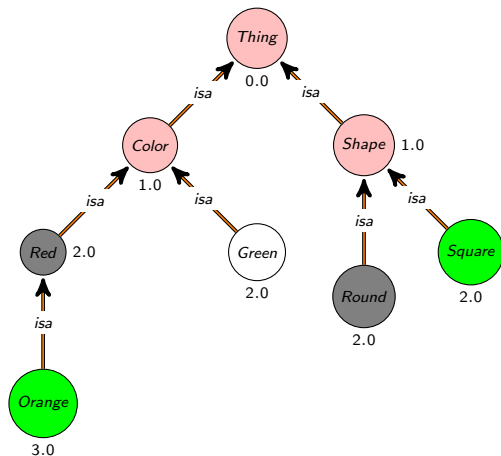 $$simGIC(X, Y) = \frac{\sum_{c \in A(X) \cap A(Y)} IC(c)}{\sum_{c \in A(X) \cup A(Y)} IC(c)}$$

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

How to measure similarity?

- 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)

Applications of semantic similarity

Hypothesis

Proteins with similar functions are more likely to interact.

- ▶ 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?
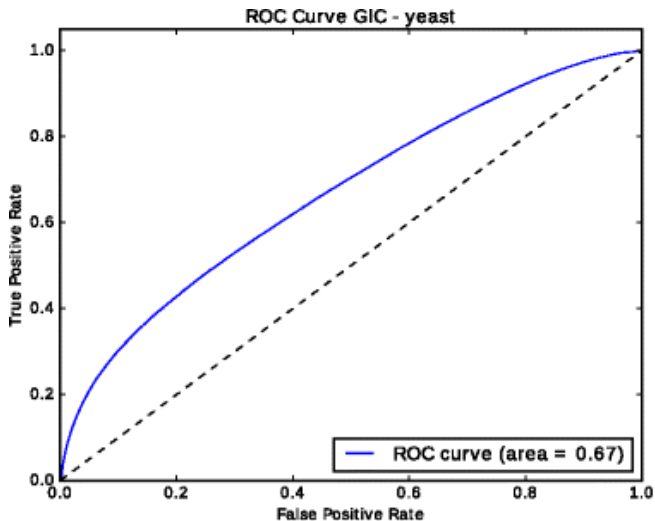
Applications of semantic similarity

Applications of semantic similarity

ROC Curve BMA Resnik - yeast

Applications of semantic similarity

ROC Curve Average Resnik - yeast
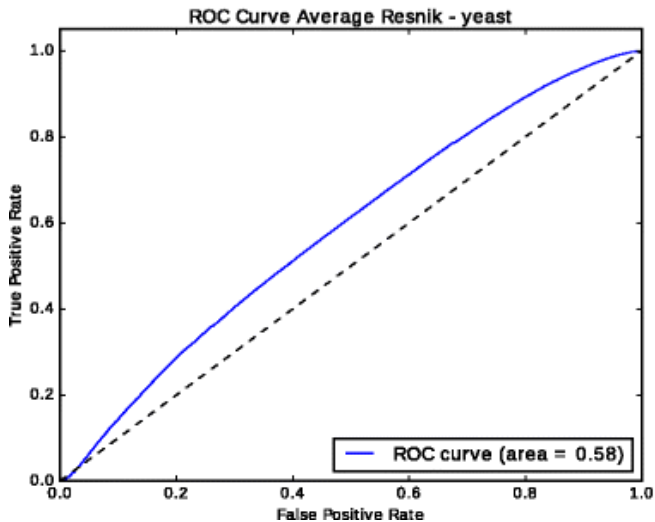
Applications of semantic similarity

- ▶ 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 for using semantic similarity::

- ▶ use Resnik's information content measure
- ▶ use Resnik's similarity
- ▶ use Best Match Average
- ▶ use the full ontology
- ▶ classify your ontology using a reasoner before applying semantic similarity
    - ▶ although many ontologies come pre-classified
- ▶ $\Rightarrow$ but there are many exceptions
    - ▶ similar location $\Rightarrow$ use location subset of GO
    - ▶ developmental phenotypes $\Rightarrow$ 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, e.g., 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

- 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, ...

Applications of semantic similarity

- ▶ 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/

Hands-on part: diagnosing rare disease using mouse phenotypes

- ▶ run the "Semantic Similarity" notebook
  - ▶ then find the mouse genotype with the most similar set of phenotypes to "Tetralogy of Fallot" (`OMIM:187500`)
  - ▶ or: use the data from `https://hpo.jax.org/app/download/annotation` to add more diseases and query by disease (hint: a disease is really just a set of phenotypes)