Part 1: Ontologies and semantic similarity

Robert Hoehndorf

Before the tutorial

See `https://github.com/bio-ontology-research-group/ai-biomed-summer-school/`:

- install Docker (e.g.: `apt-get install docker`)
- `docker run -i -t -p 8888:8888 leechuck/ai-biomed-summer-school`
- in your browser, connect to `localhost:8888`

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

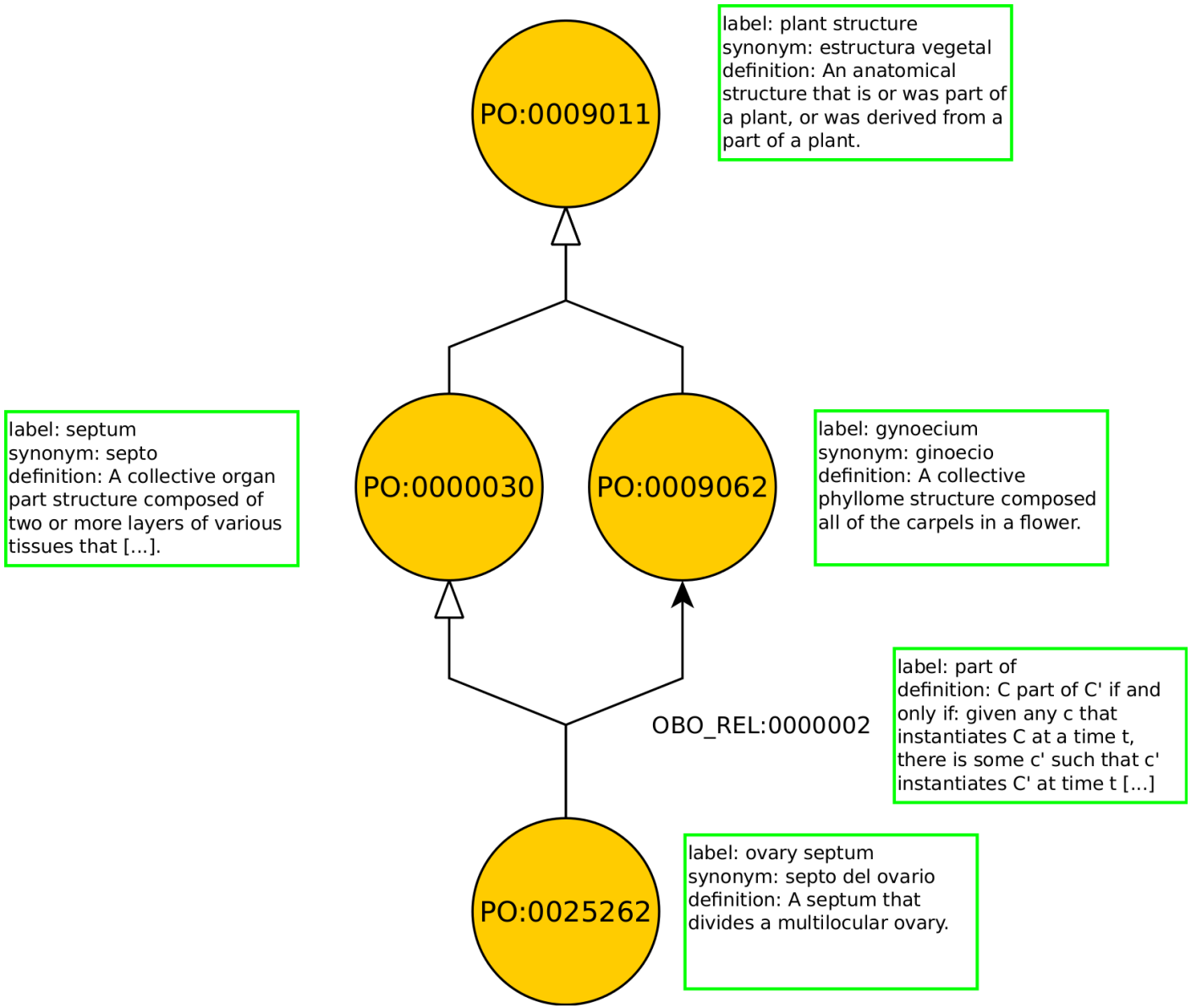
Agenda

- 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


PO:0009011
label: plant structure
synonym: estructura vegetal
definition: An anatomical structure that is or was part of a plant, or was derived from a part of a plant.
PO:0000030
label: septum
synonym: septo
definition: A collective organ part structure composed of two or more layers of various tissues that [...].
PO:0009062
label: gynoecium
synonym: ginoecio
definition: A collective phyllome structure composed all of the carpels in a flower.
OBO_REL:0000002
label: part of
definition: C part of C' if and only if: given any c that instantiates C at a time t, there is some c' such that c' instantiates C' at time t [...]
PO:0025262
label: ovary septum
synonym: septo del ovario
definition: A septum that divides a multilocular ovary.

Ontologies for data integration

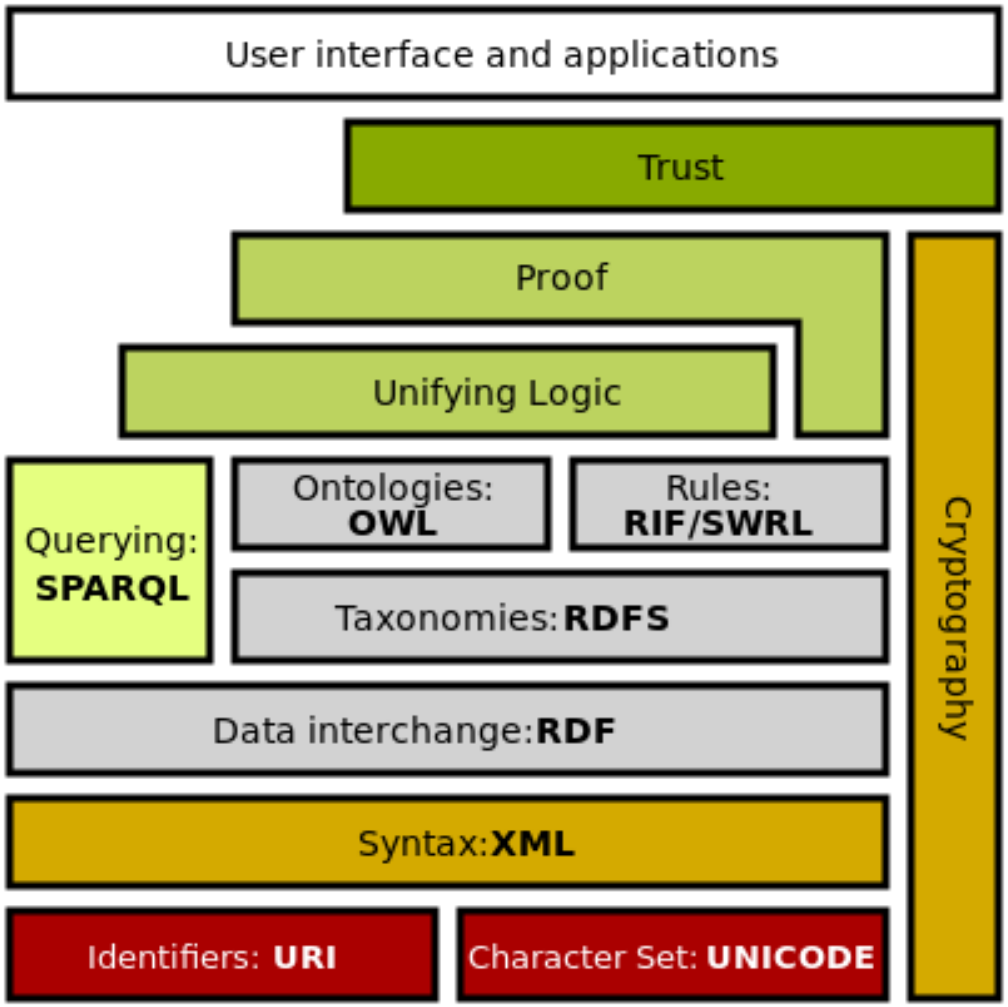
- standard identifiers (IRIs)
- labels of classes and relations
- human-readable descriptions
- axioms

Ontologies provide domain knowledge

Overview | Browse | DLQuery | Download

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

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`

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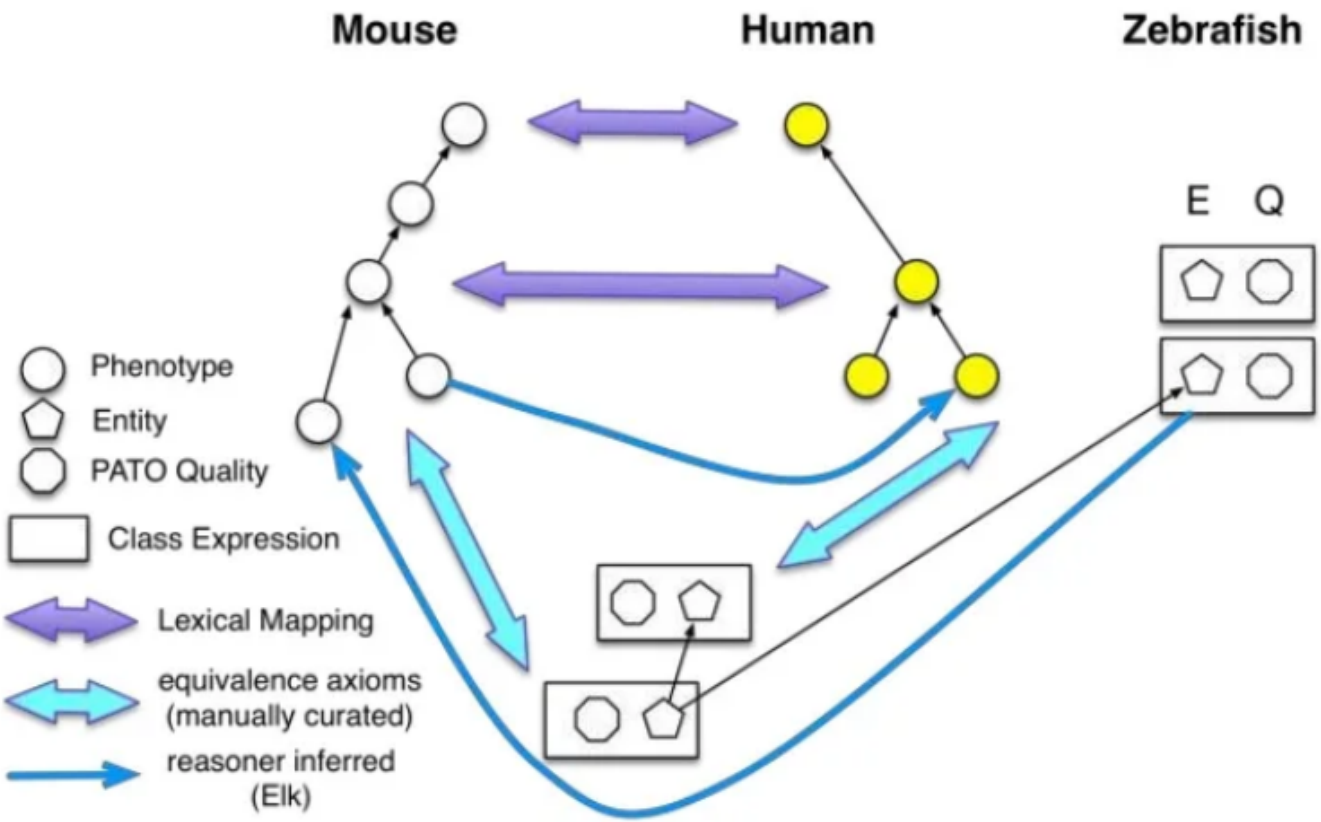
- `'B cell apoptosis' SubClassOf: 'lymphocyte apoptosis'`
  - generates a *taxonomy* from axioms

Reasoning with phenotype ontologies

Phenotype ontology:

- A phenotype is a quality that inheres in its bearer:
  - Enlarged heart: $\mathit{Enlarged}(x) \wedge \exists y(\mathit{inheresIn}(x, y) \wedge \mathit{Heart}(y))$
  - in DL: $\mathit{Enlarged} \sqcap \exists \mathit{inheresIn}.\mathit{Heart}$
  - 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
   - $\Rightarrow$ ontologies
2. integrate/compare phenotypes *within and between species* (to overcome limitations in phenotype data)
   - homologous organ structures
   - related/identical function
   - $\Rightarrow$ ontologies and automated reasoning
3. measure phenotypic similarity
   - use morphological or functional similarity
   - similarity in attribute values
   - $\Rightarrow$ semantic similarity, machine learning

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- 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?

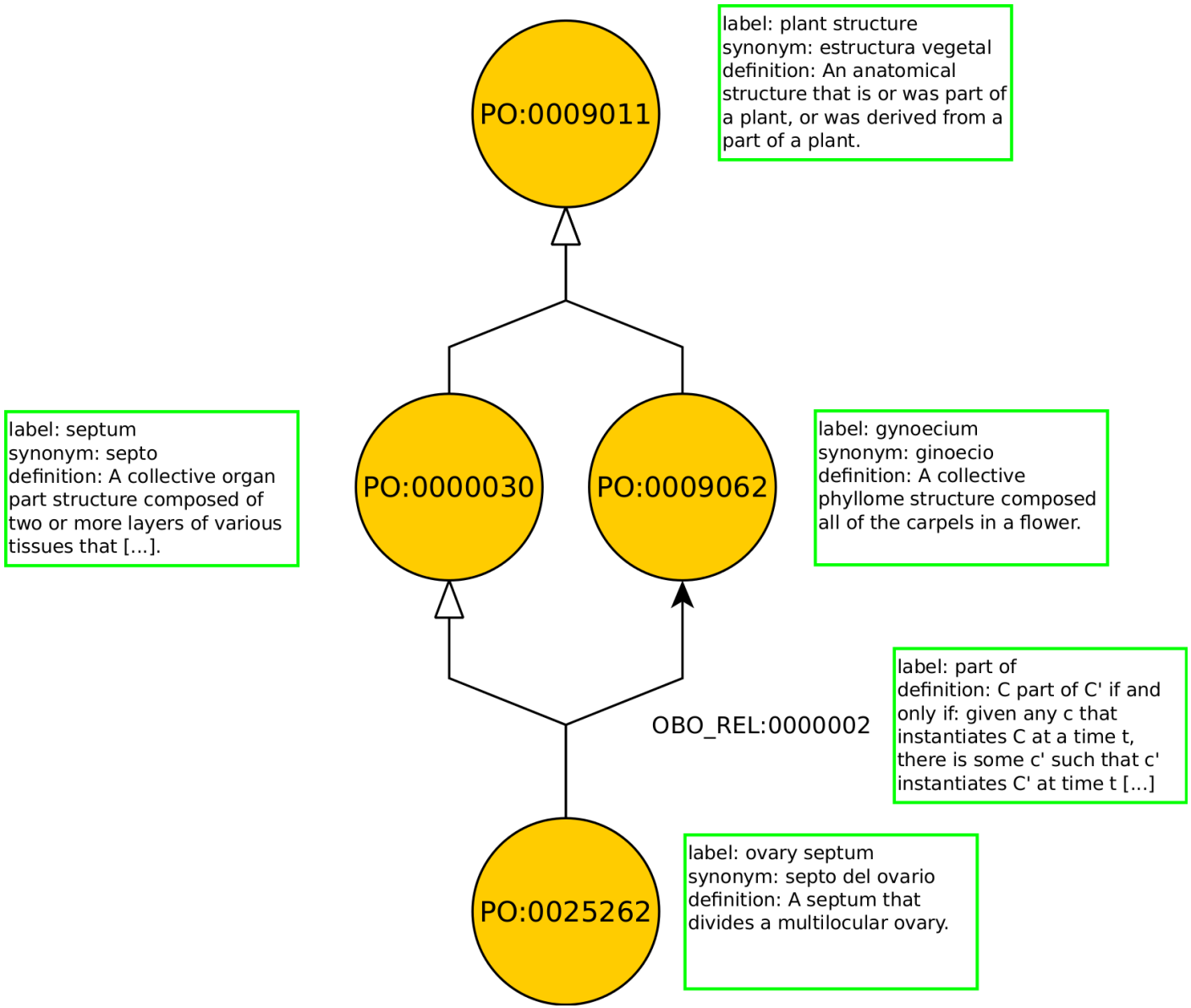
Ontologies and graphs

- semantic similarity measures can be graph-based, feature-based, or model-based
- we may need to generate graphs from ontologies
  - 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:` $X \overset{\equiv}{\leftrightarrow} Y, \{X, Y\}$

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

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What properties do we want in a similarity measure?
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- sim is a *normalized* similarity measure if it has values in $[0, 1]$

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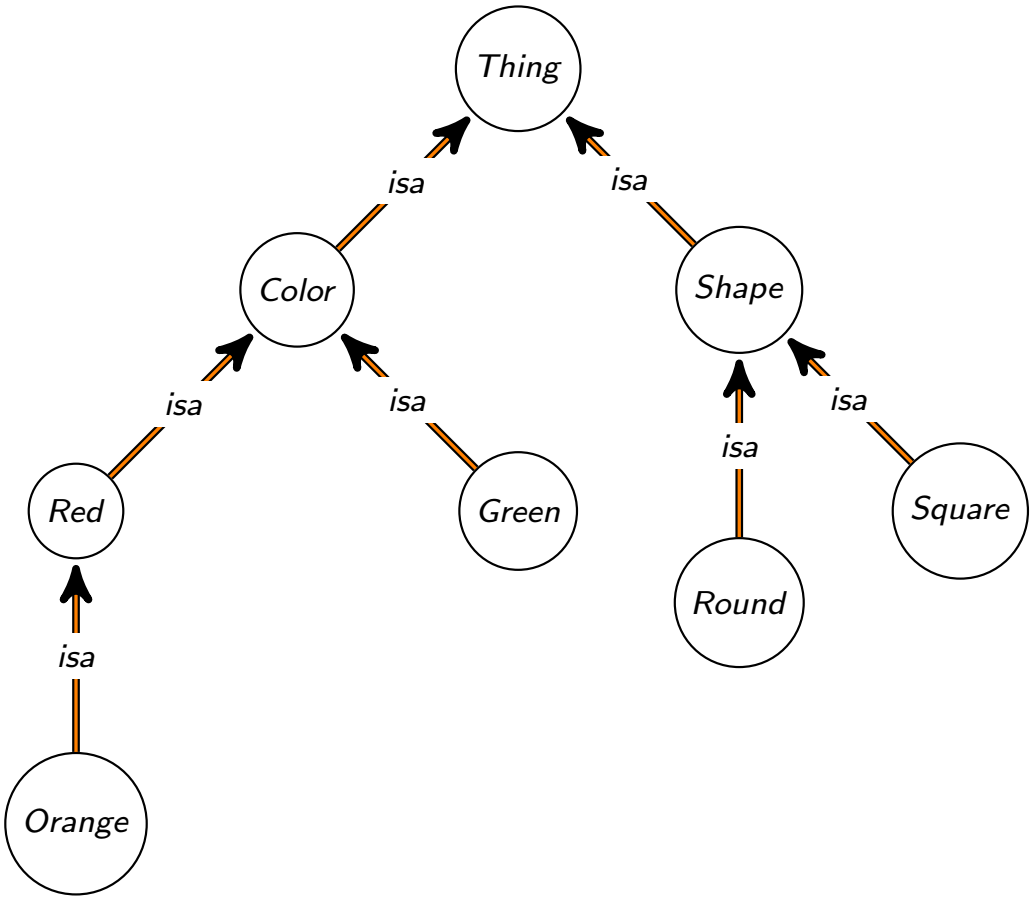

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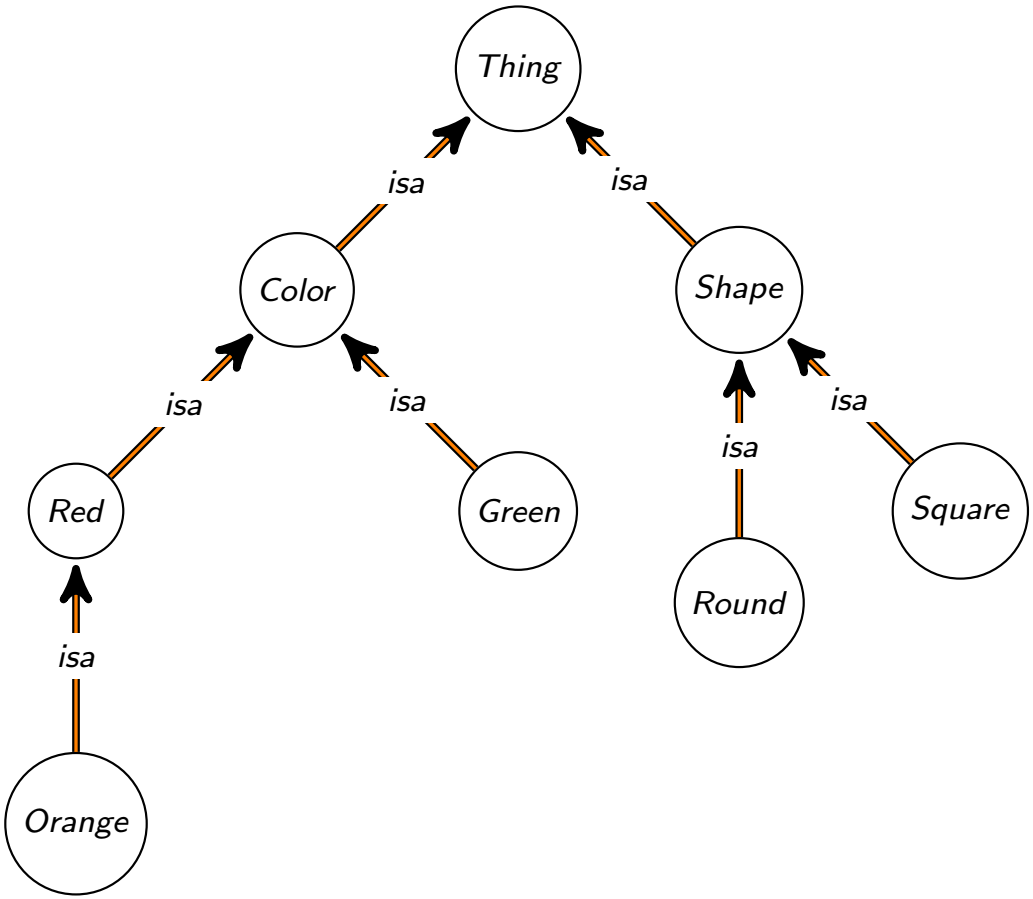

- distance on shortest path (Rada *et al.*, 1989)

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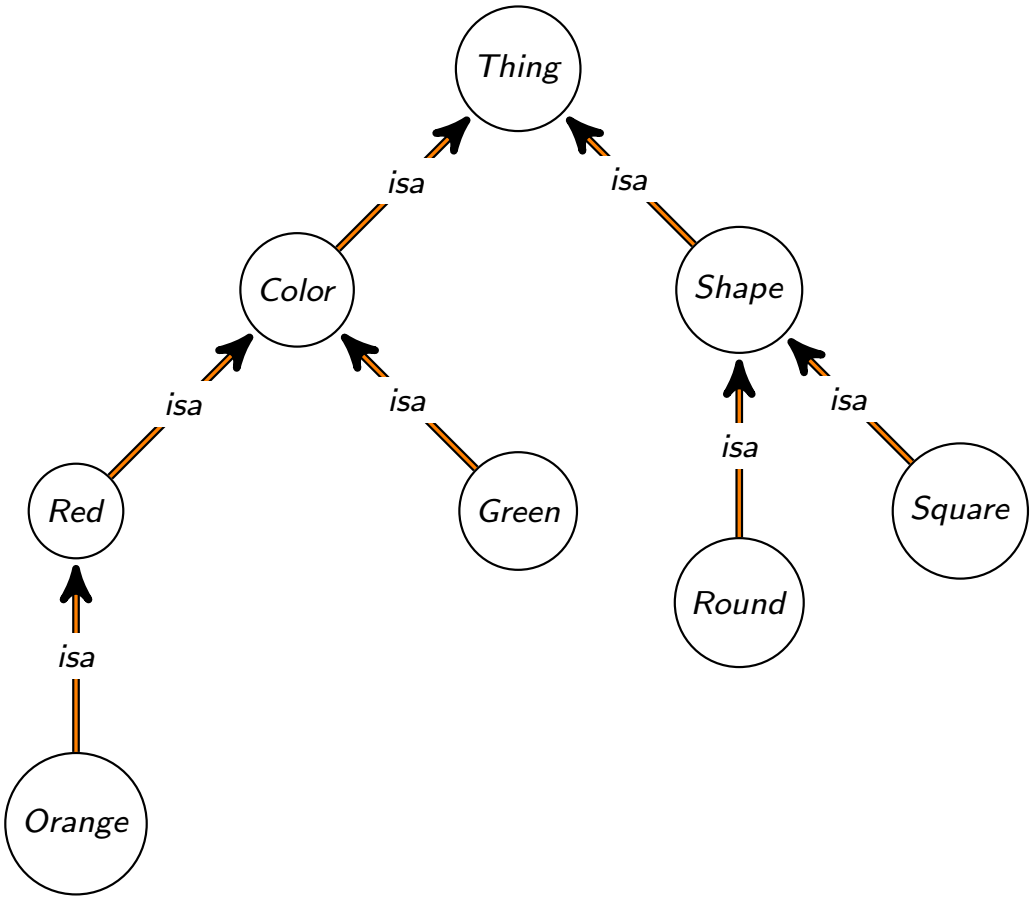

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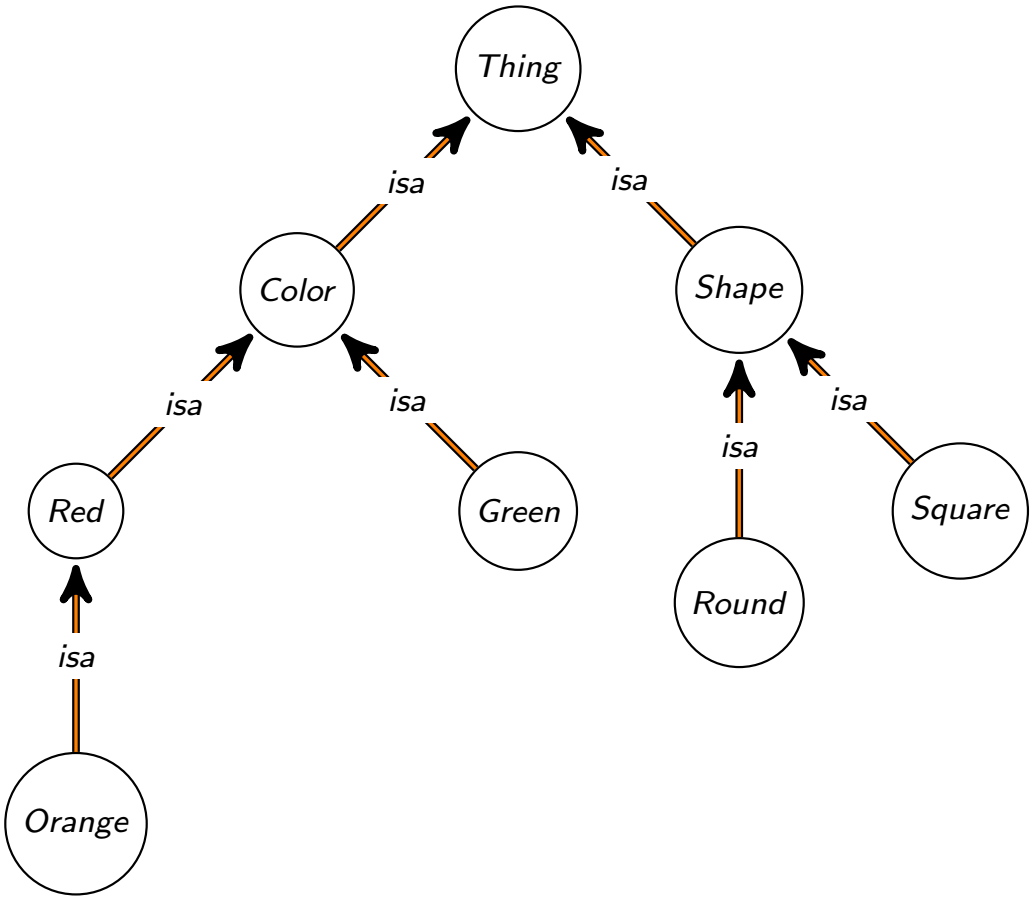

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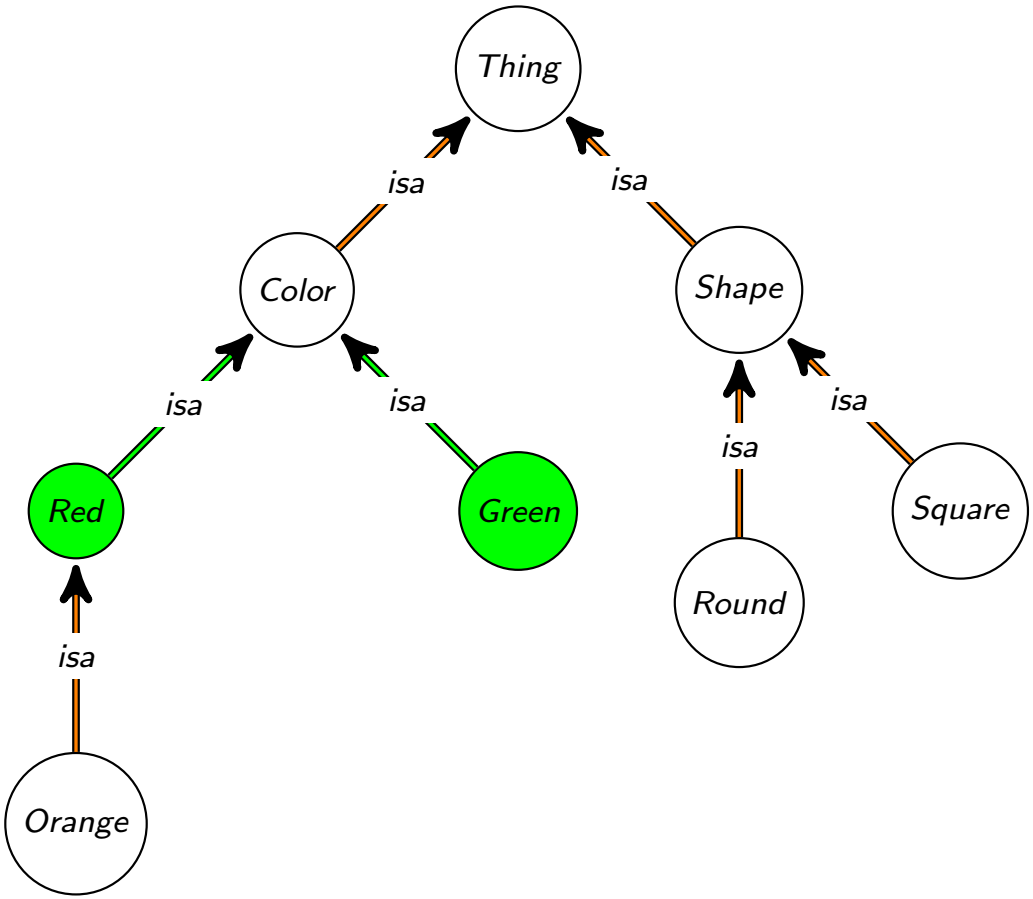

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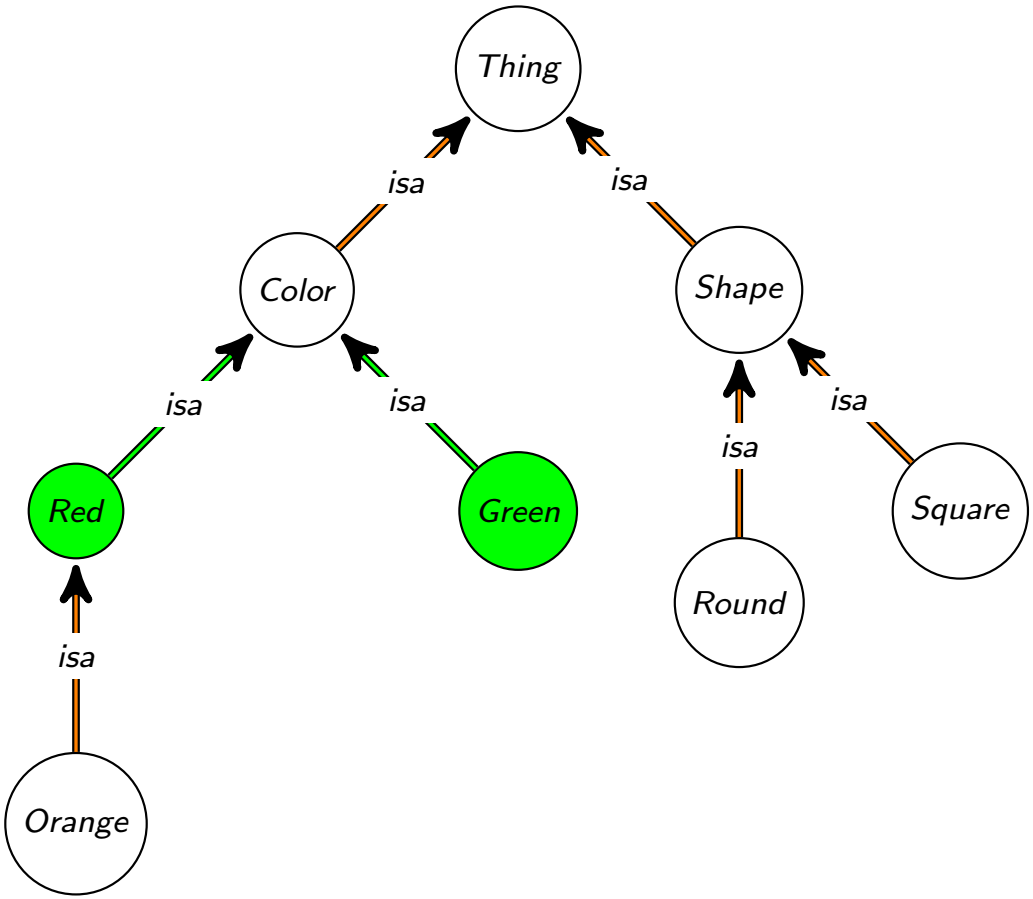

- distance on shortest path
- distance(green, red) $= 2$
- $sim_{Rada}(green, red) = \frac{1}{3}$

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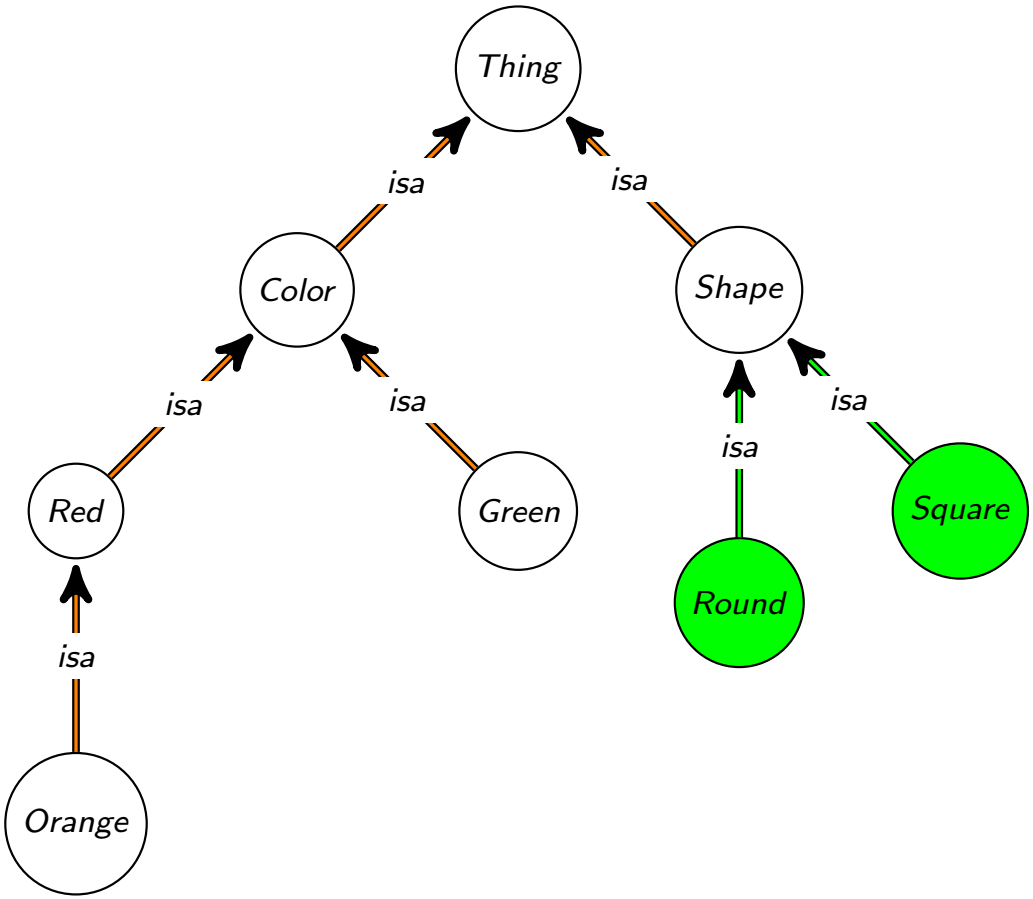

- distance on shortest path
- distance(square, round) $= 2$
- $sim_{Rada}(square, round) = \frac{1}{3}$

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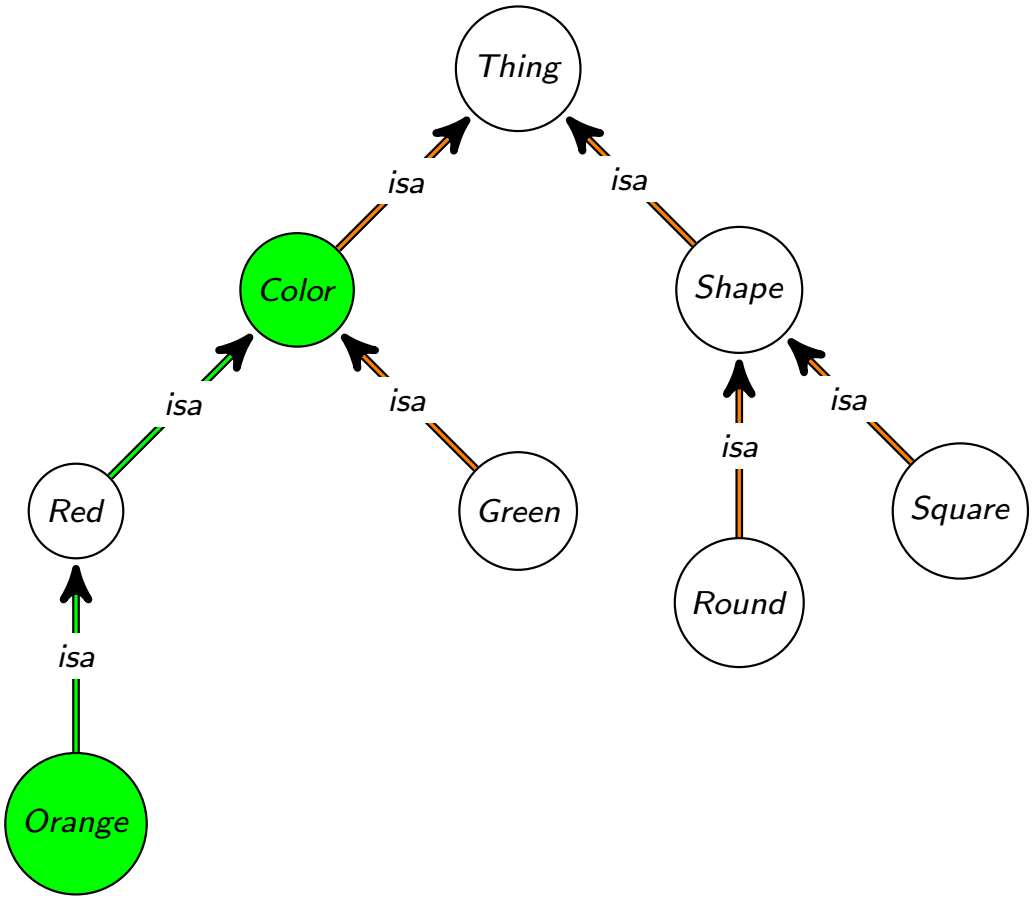

- distance on shortest path
- distance(orange, color) $= 2$
- $sim_{Rada}(orange, color) = \frac{1}{3}$

How to measure similarity?

- shortest path is not always intuitive

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  - number of ancestors
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- account for different edge types
  - non-uniform edge weighting

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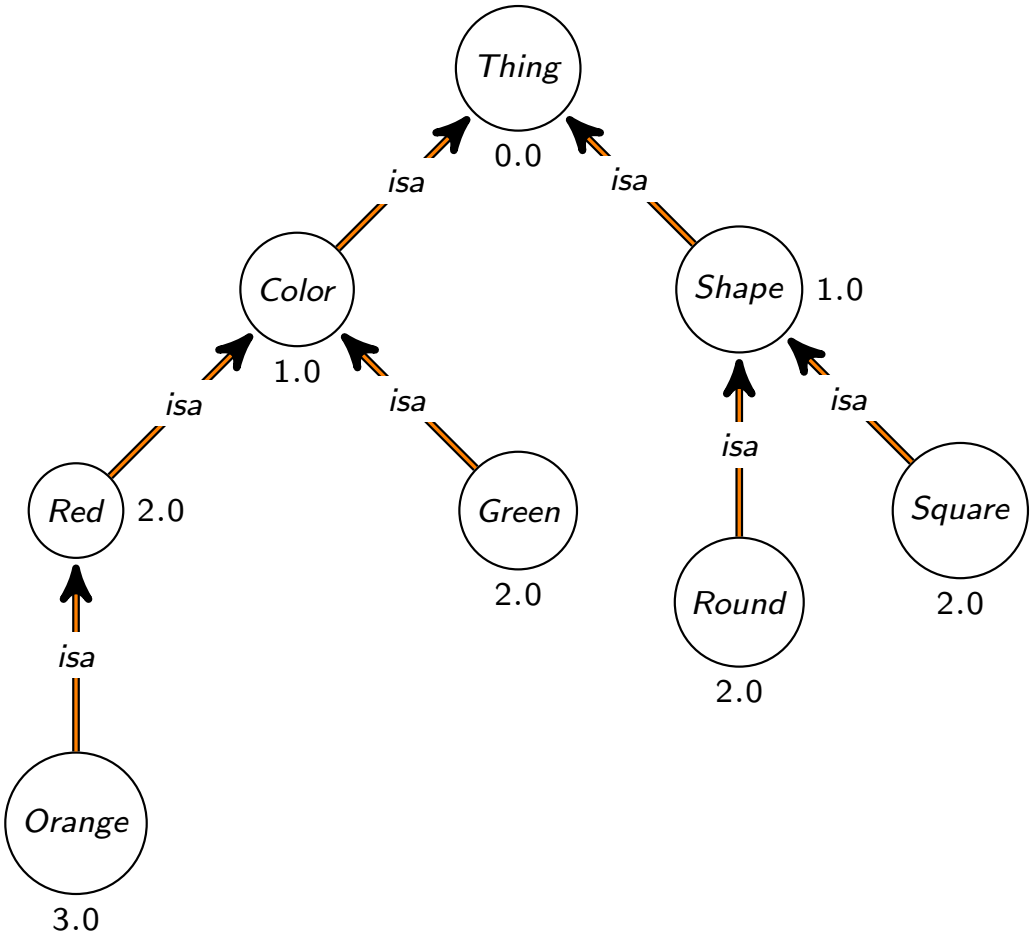
- extrinsic:
  - $\sigma(x)$ defined as a function of instances (or annotations) I
    - note: the number of instances monotonically decreases with increasing depth in taxonomies
  - Resnik 1995: $eIC_{Resnik}(x) = -\log p(x)$ (with $p(x) = \frac{|I(x)|}{|I|}$)
    - in biology, one of the most popular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

How to measure similarity?



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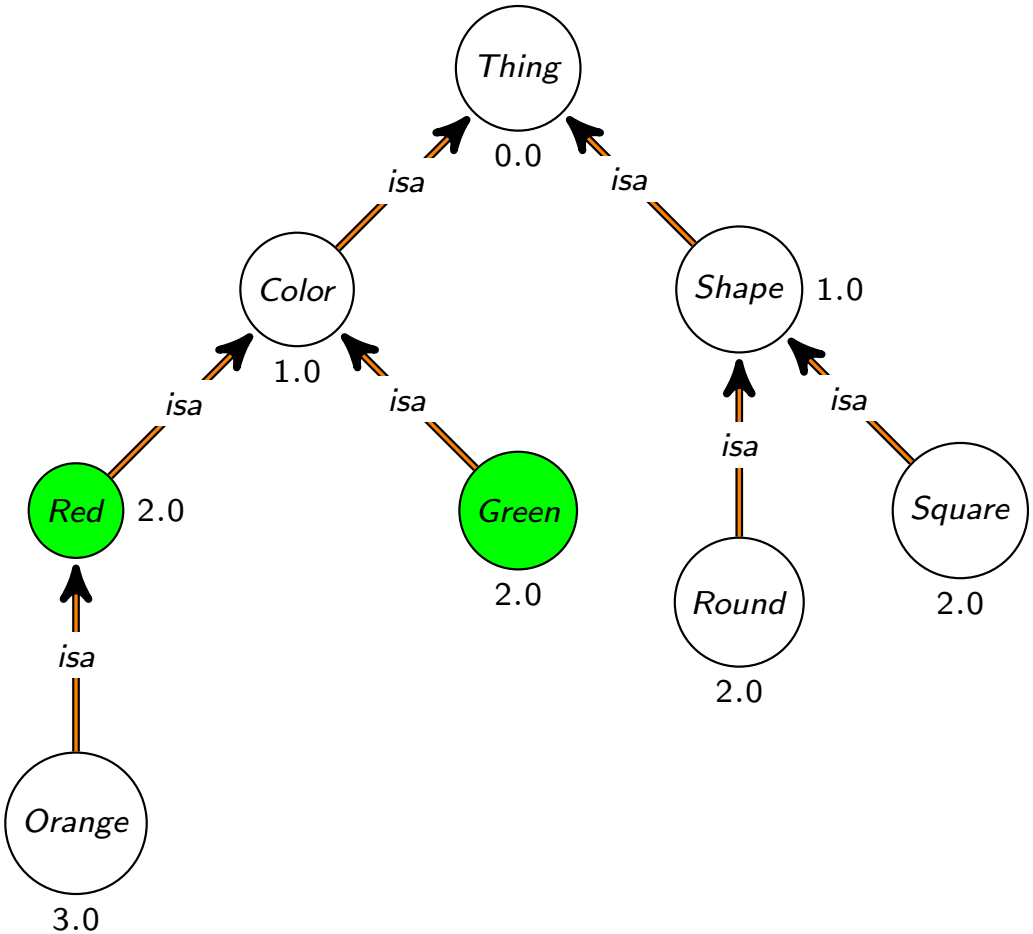

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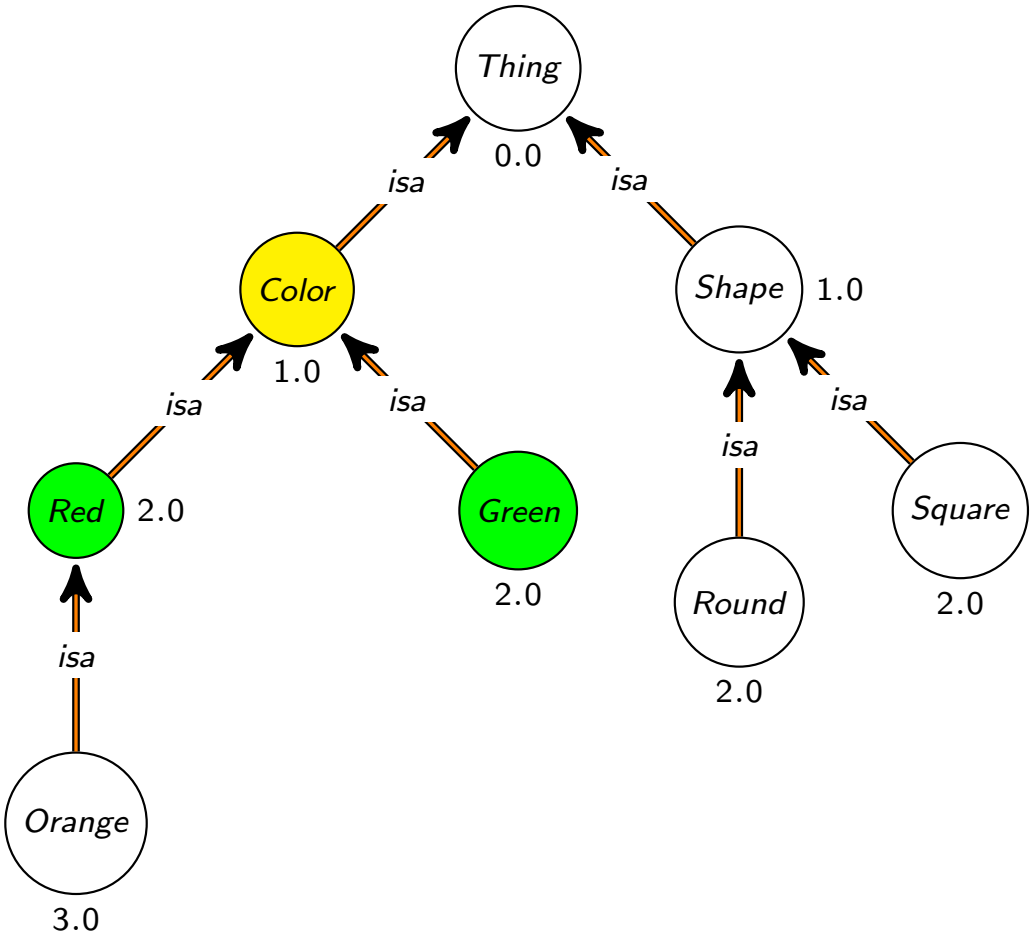

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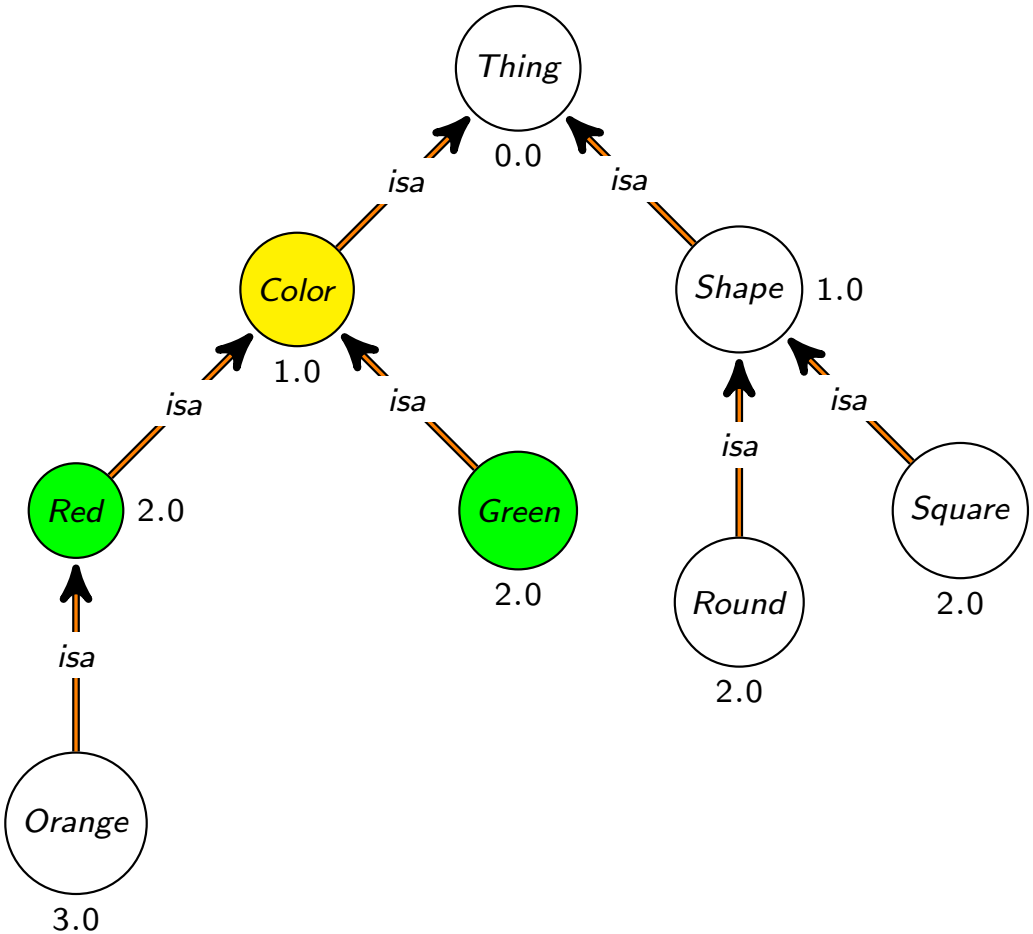

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- $sim_{Resnik}(Green, Red) = 1.0$

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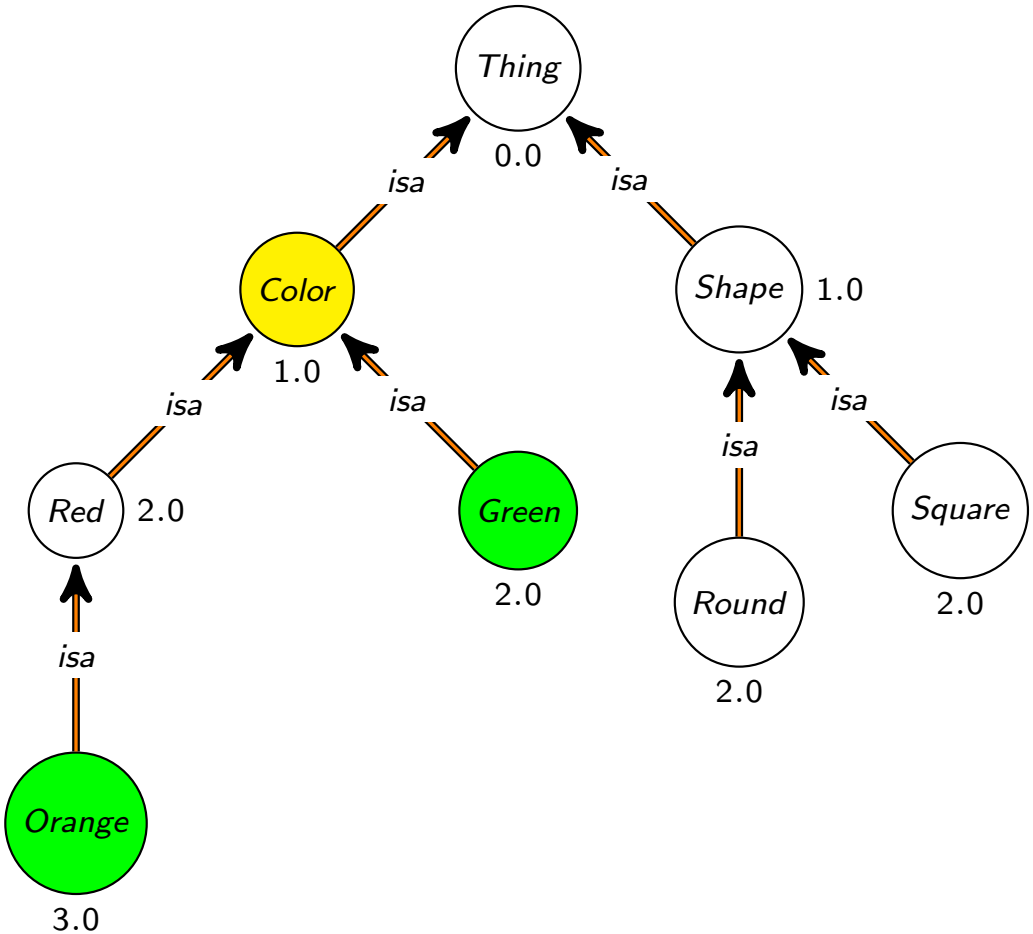

- Resnik 1995: similarity between x and y is the information content of the *most informative common ancestor*
- $sim_{Resnik}(Green, Orange) =$ 1.0

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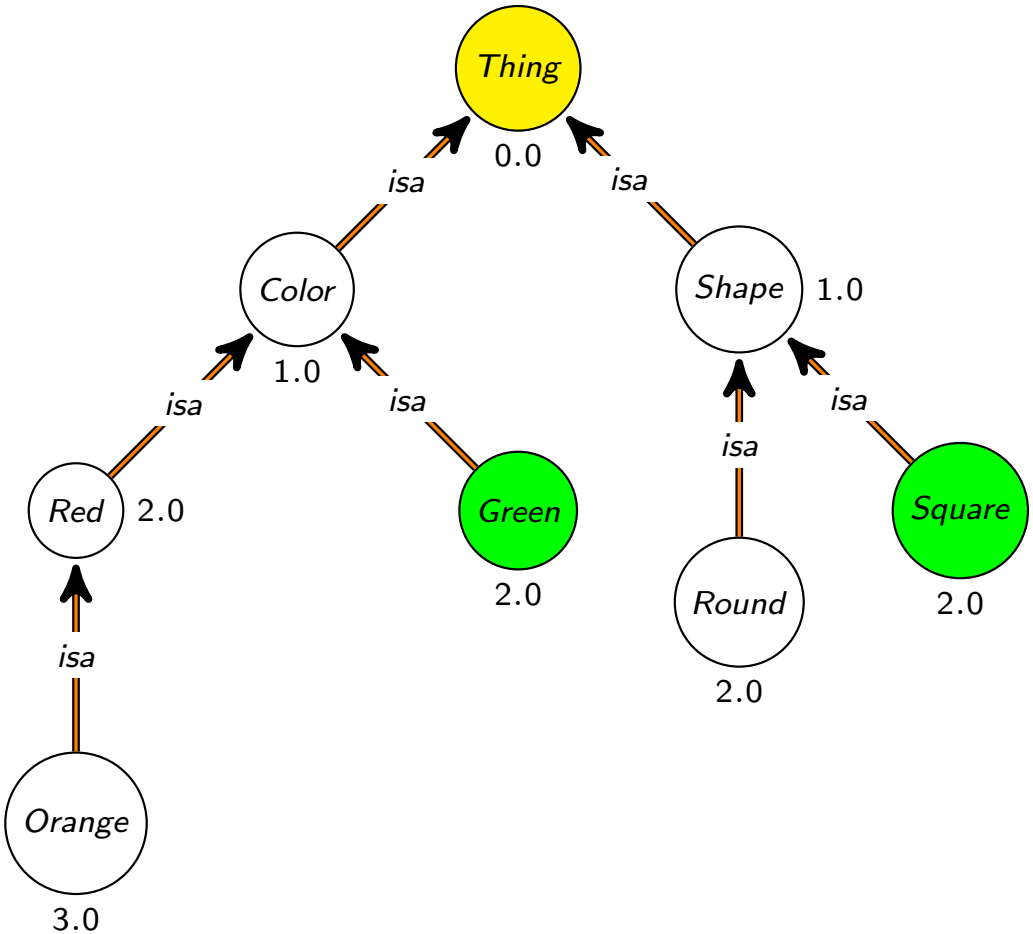

- Resnik 1995: similarity between x and y is the information content of the *most informative common ancestor*
- $sim_{Resnik}(Square, Orange)$ 0.0

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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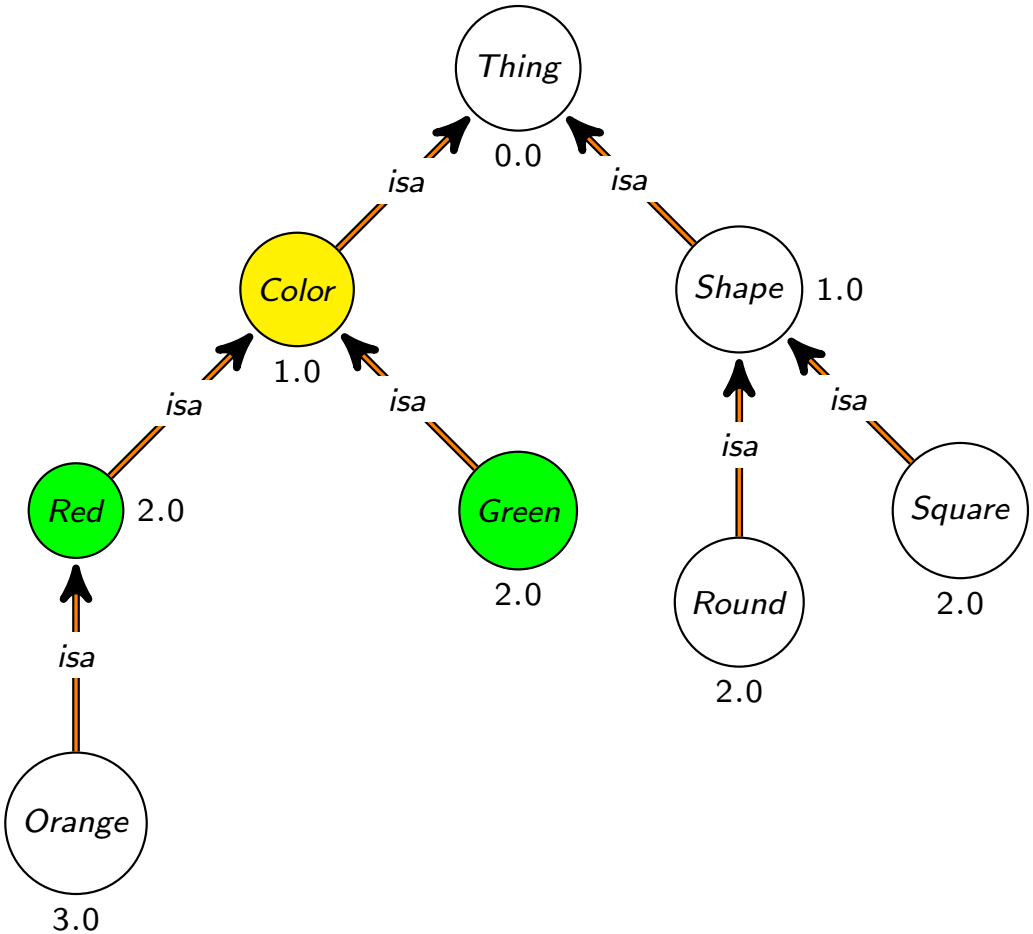

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  $sim_{Lin}(x, y) = \frac{2 \cdot IC(MICA(x,y))}{IC(x)+IC(y)}$

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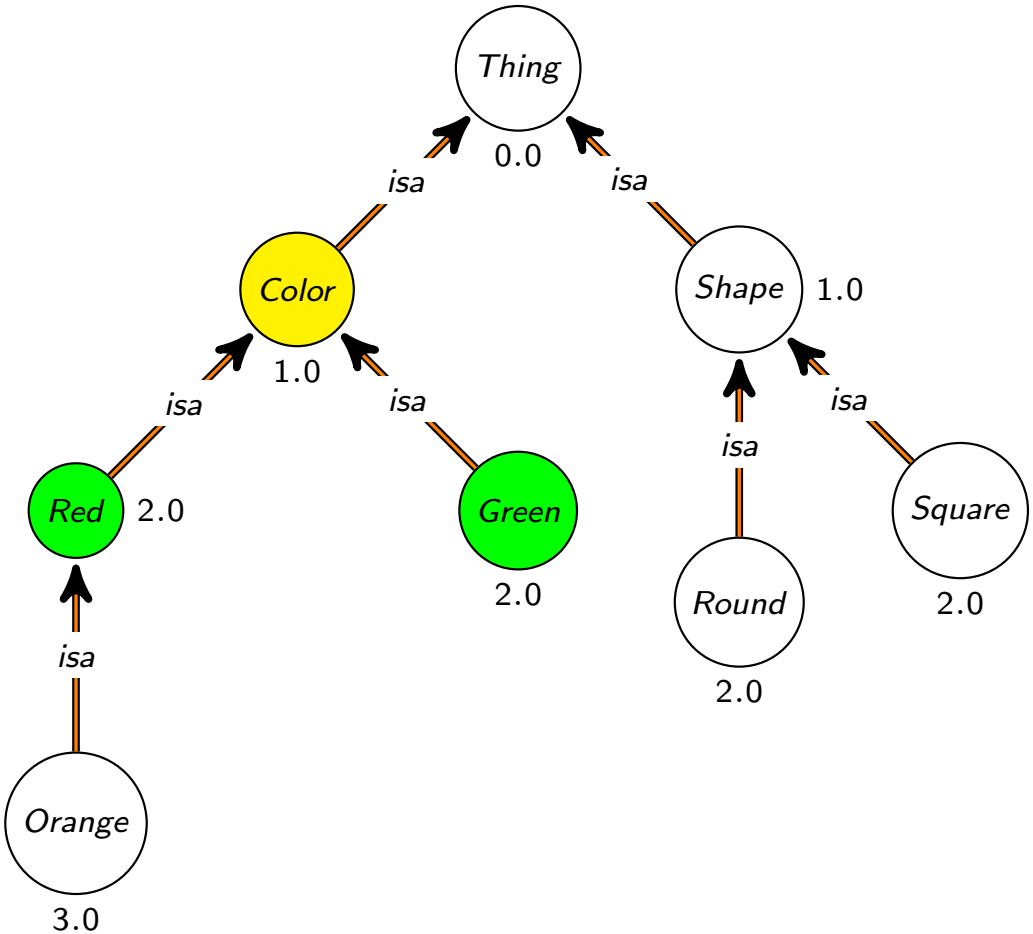

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- $sim_{Lin}(Green, Red) = 0.5$

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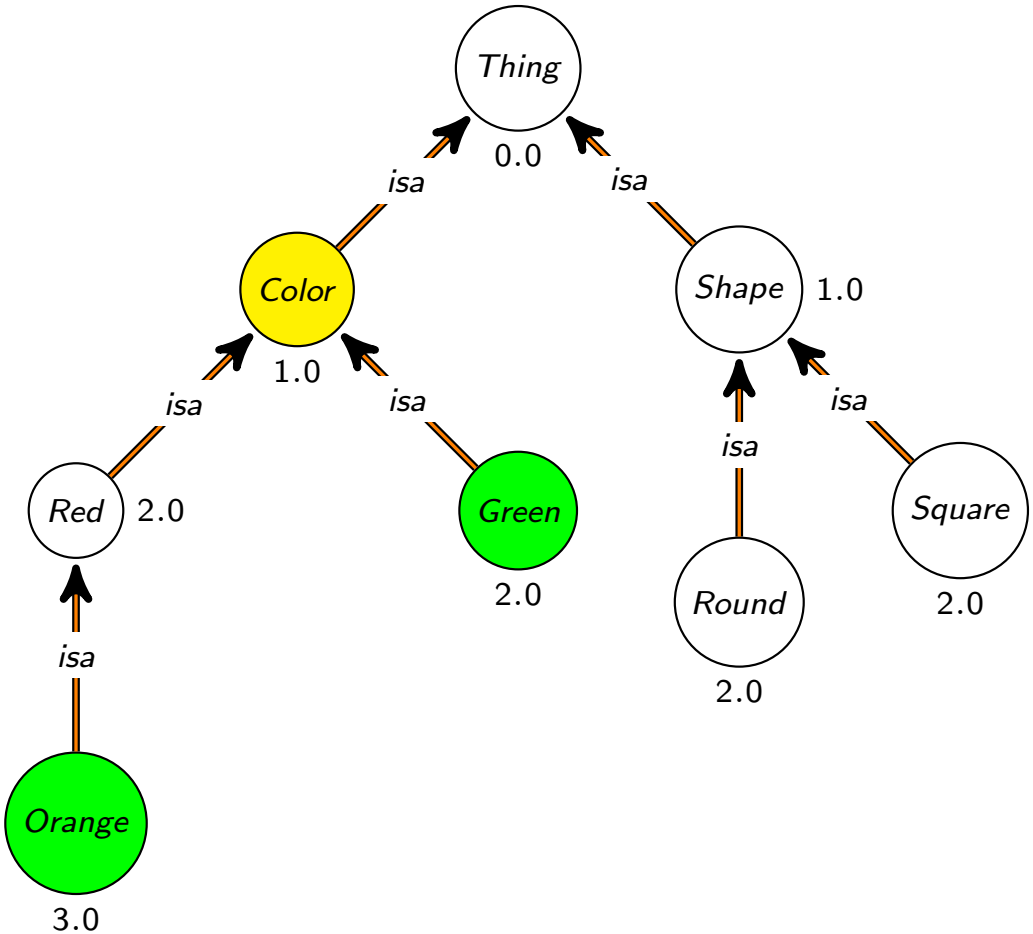


- Lin 1998:
  $sim_{Lin}(x, y) = \frac{2 \cdot IC(MICA(x,y))}{IC(x)+IC(y)}$
- $sim_{Lin}(Green, Orange) = 0.4$

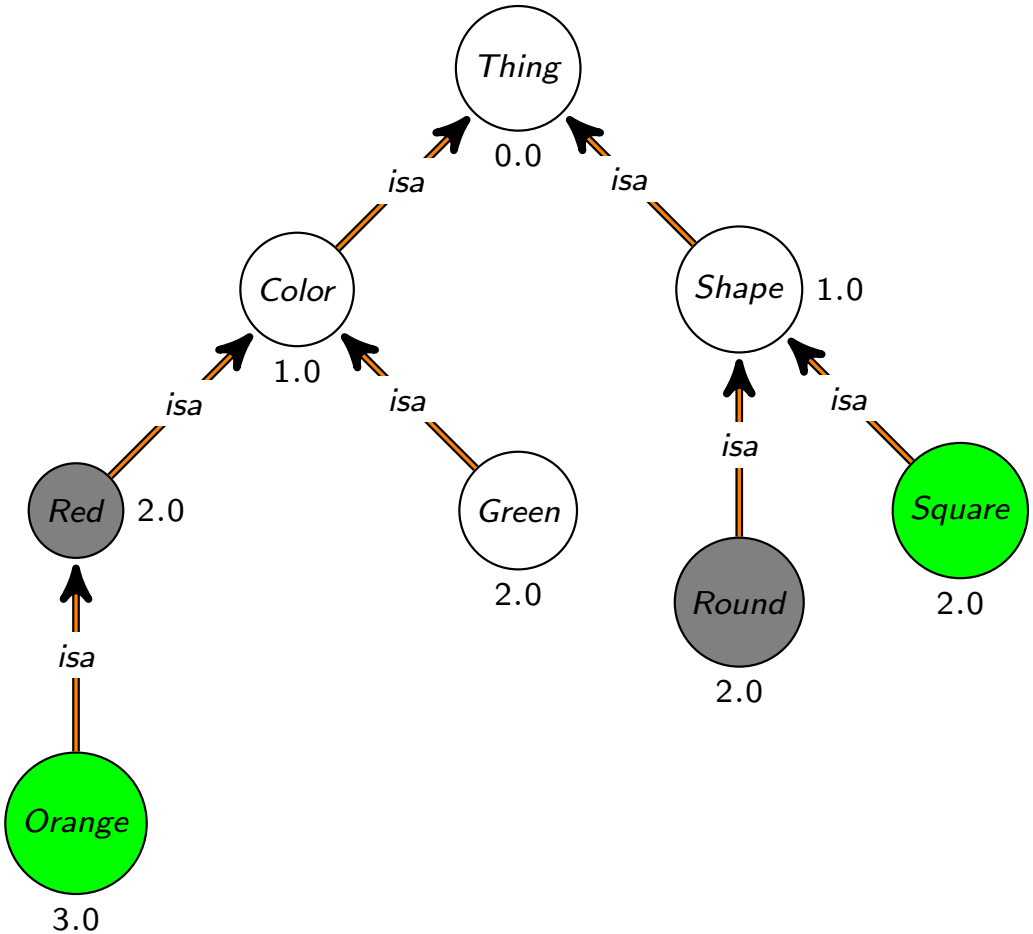
How to measure similarity?

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

How to measure similarity?

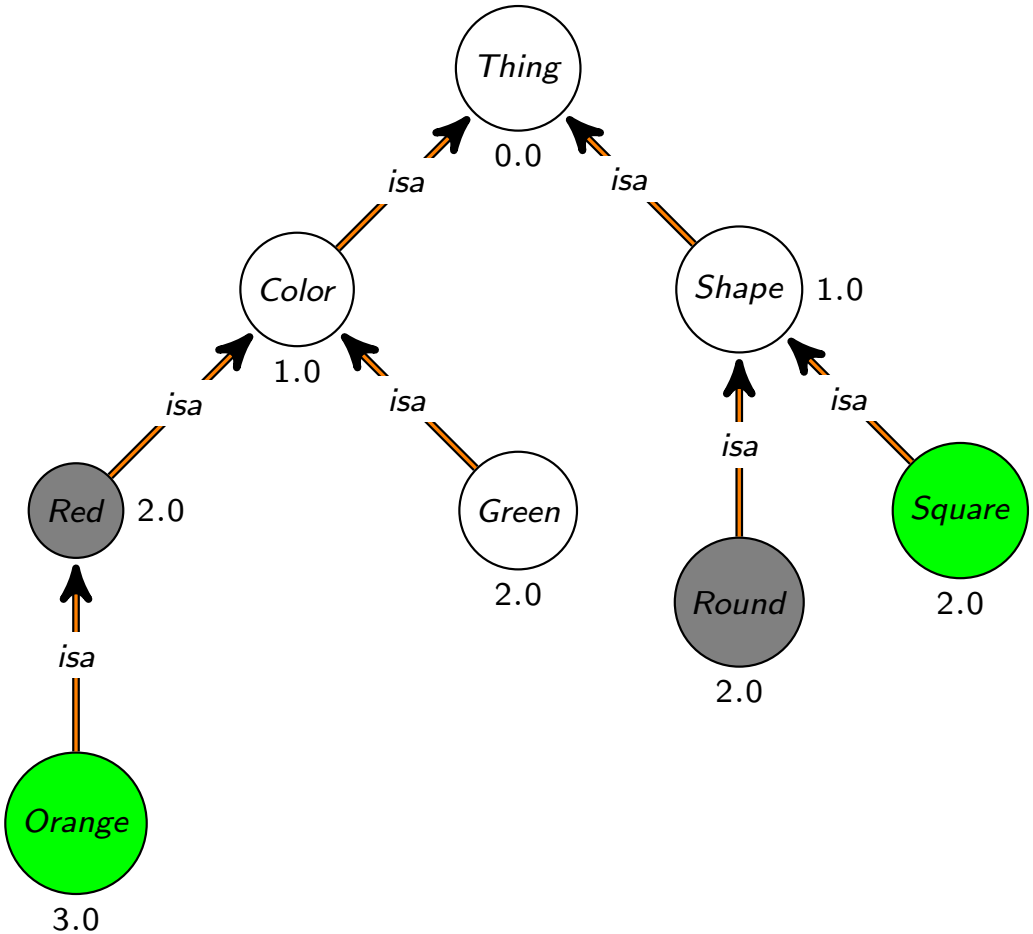
- we only looked at comparing pairs of classes
- mostly, we want to compare *sets* of classes
  - set of GO annotations
  - set of signs and symptoms
  - set of phenotypes
- two approaches:
  - compare each class individually, then merge
  - directly set-based similarity measures

How to measure similarity?



- similarity between a square-and-orange thing and a round-and-red thing

How to measure similarity?



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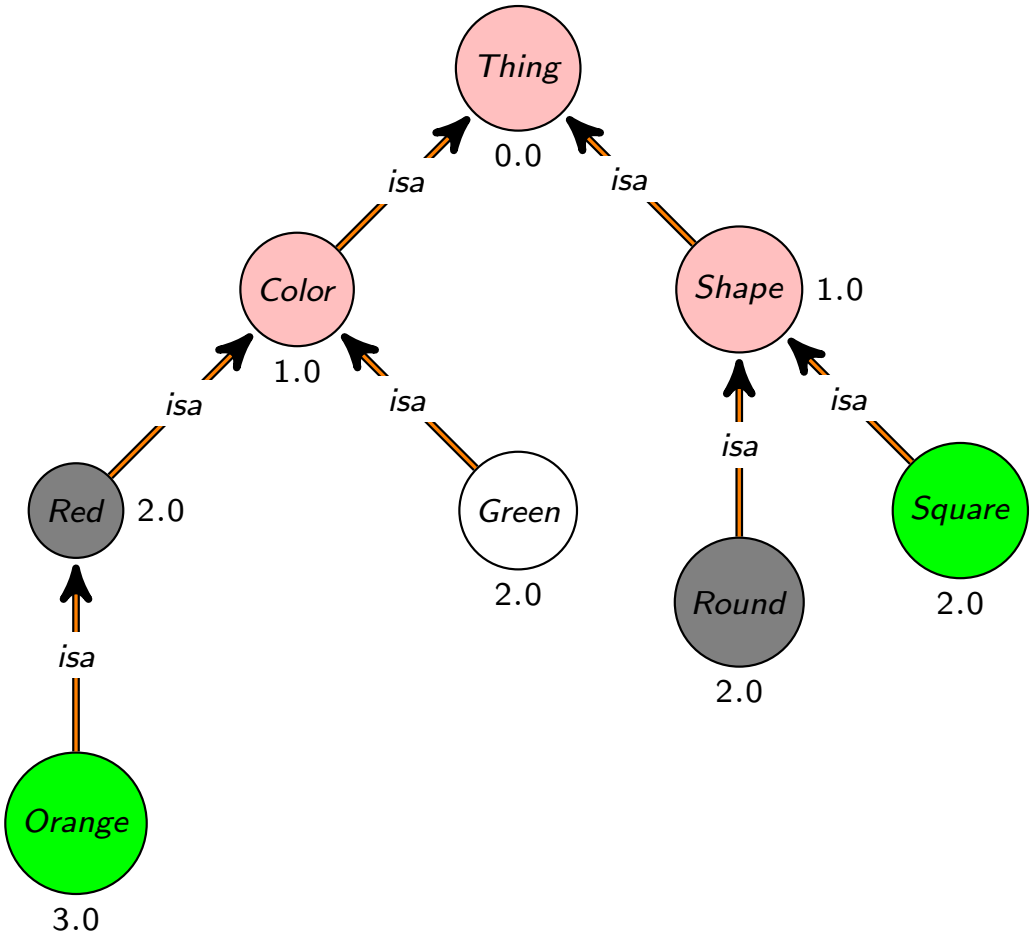

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- $simGIC(so, rr) = \frac{2}{11}$

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)

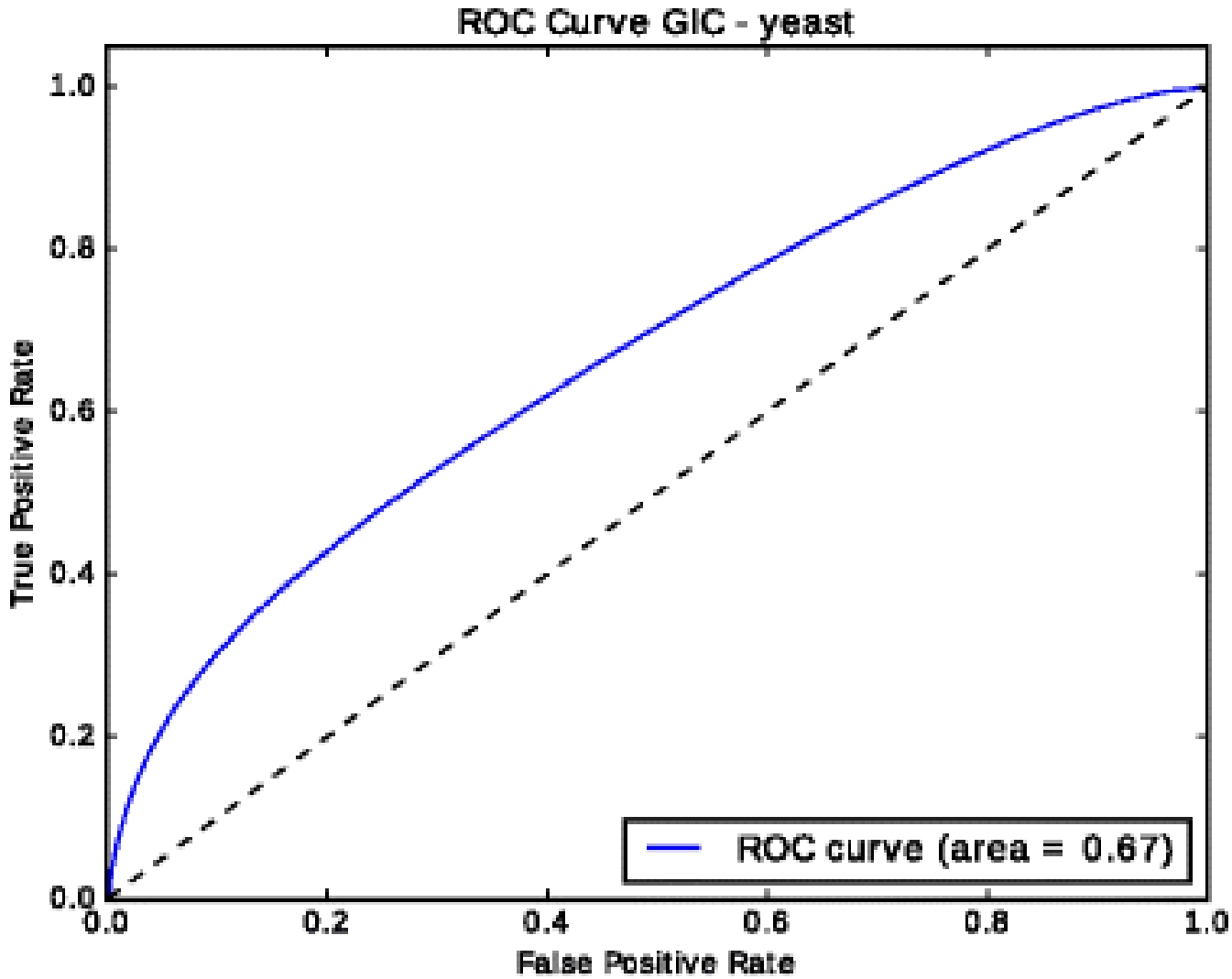
Applications of semantic similarity

Hypothesis

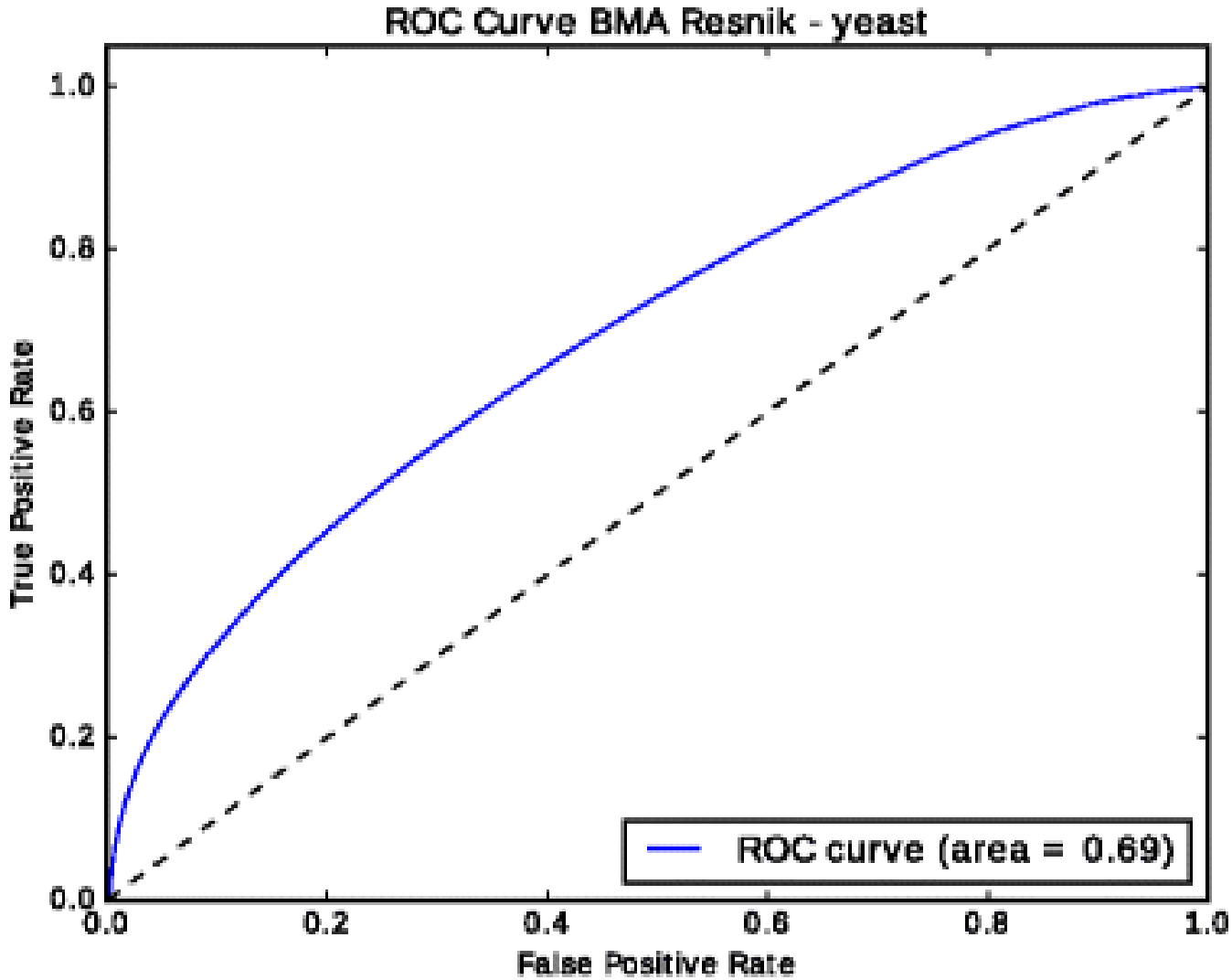
Proteins with similar functions are more likely to interact.

- 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?

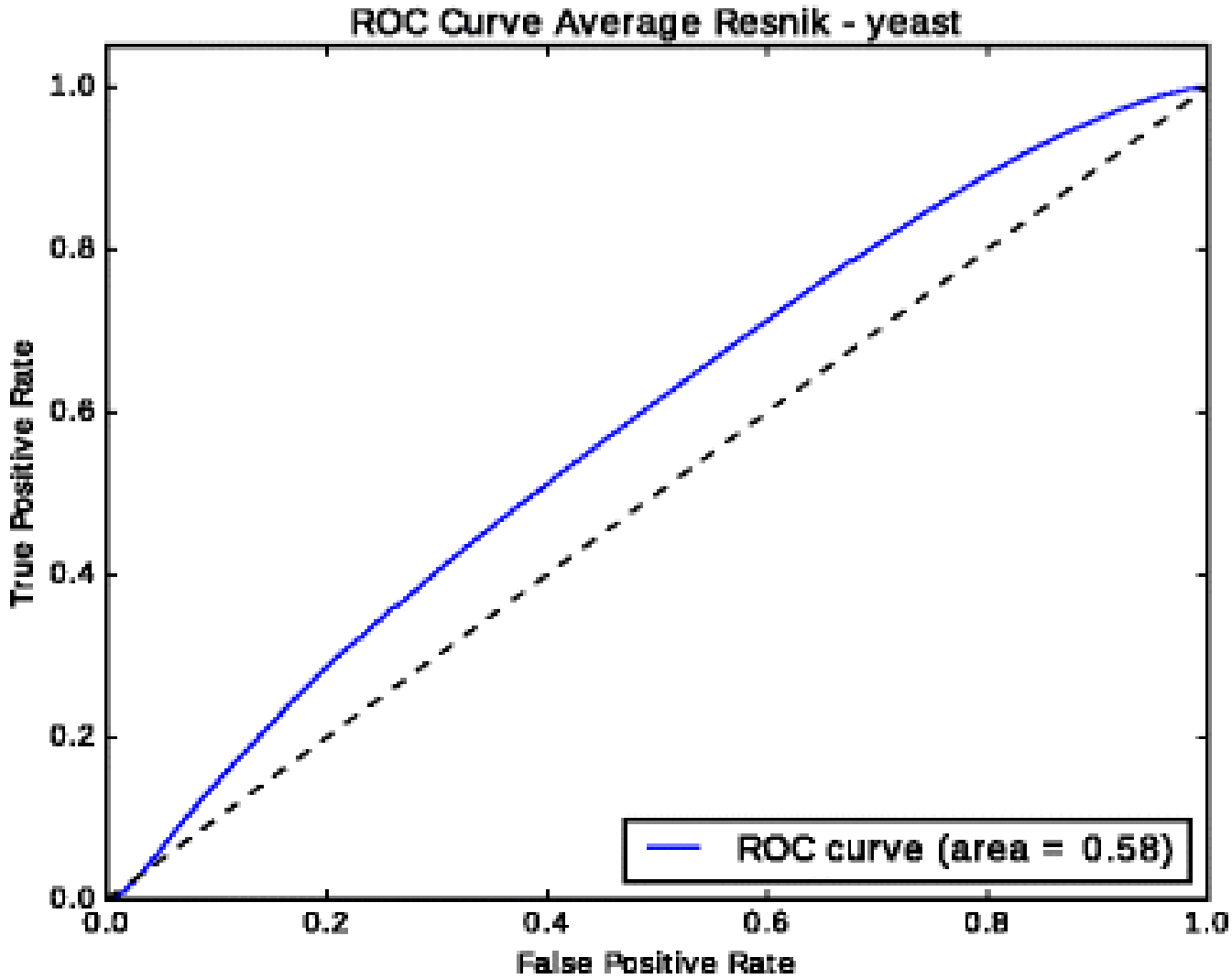
Applications of semantic similarity



Applications of semantic similarity



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 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)