Informatics of phenotype ontologies

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Anatomy and Physiology

- anatomy ontologies:
  - species-specific: FMA, MA, ZFA, ...
  - cross-species: UBERON, GO-CC
    - with mappings to species-specific ontologies
- physiology ontologies: GO-BP, GO-MF

Structure of anatomy ontologies

- part-of relations
  - `finger part-of hand`
  - `finger SubClassof:  part-of some hand`
- no (or rarely) has-part relations
  - `hand has-part finger?`
  - `hand SubClassOf:  has-part some finger`
    - adactylia, accidents

Structure of physiology ontologies (GO)

- part-of and has-part
- regulates
- molecular functions as processes

Phenotype ontologies

Principles

Phenotype ontologies should resemble anatomy and physiology ontologies.
Usually, this means using the anatomy/physiology ontologies to build the phenotype ontologies.

Please open `http://purl.obolibrary.org/obo/flopo.owl` in Protege now.

Patterns

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- or: `phenotype-of some (has-part some (E and has-quality some (Q and [refine])))`

A deeper look into PATO

PATO distinctions:

- quality and quantity
  - color vs mass
  - use OBO slims

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- normal and abnormal
  - use axioms, and the classes
  - `increase-relative-to`, `decreased-relative-to`

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  - `increase-relative-to`, `decreased-relative-to`
- unary and n-ary (n$\geq$ 2) qualities
  - OBO slim (relational_slim)
  - n-ary qualities are really just reified relations:
    - left-side-of, anterior-to, compatible-with, response-to, ...
  - use "towards" (or any other relation) as general argument to add second filler

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- `phenotype-of some (has-part some (E and has-quality some (Q and towards some E2)))`

Expressing "abnormal"

- in many phenotype ontologies, there is one qualifier: `abnormal`
- used to designate an *abnormal* phenotype
- add the qualifier to the Q (`... and has-qualifier some abnormal`)
- if *all* classes are constrained that way, nothing happens
- only useful to distinguish between normal and abnormal if both are included
    - and even there, `abnormal` qualifiers are not very useful!

Normal and abnormal

Abnormal phenotypes

What is an “abnormal” phenotype?

Normal and abnormal

Abnormal phenotypes

What is an "abnormal" phenotype?

- we don't care about philosophy here
- fundamental distinction: abnormal/comparative/divergent, and "plain" phenotypes
  - the first needs **two** kinds of entity, the latter only **one**!
- interconversion between both:
  - two normal phenosets make one abnormal (and one reference)
  - find the difference/opposite using PATO
    - reference based on anatomy/physiology
    - PATO: identify trait (red, yellow $\rightarrow$ color)
    - PATO: identify disjointness (red disjoint from yellow)
    - PATO: identify directionality (increased/decreased relative to)

Absences and other abnormalities

- Some classes are weird and require special treatment:
  - absent appendix, absent tail (or “aplastic”)
- actually means: not having E as part!
- quiz: what is correct?
  - absent hand subclass of absent finger
  - absent finger subclass of absent hand

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  - increased rate of B cell apoptosis, increase rate of apoptosis
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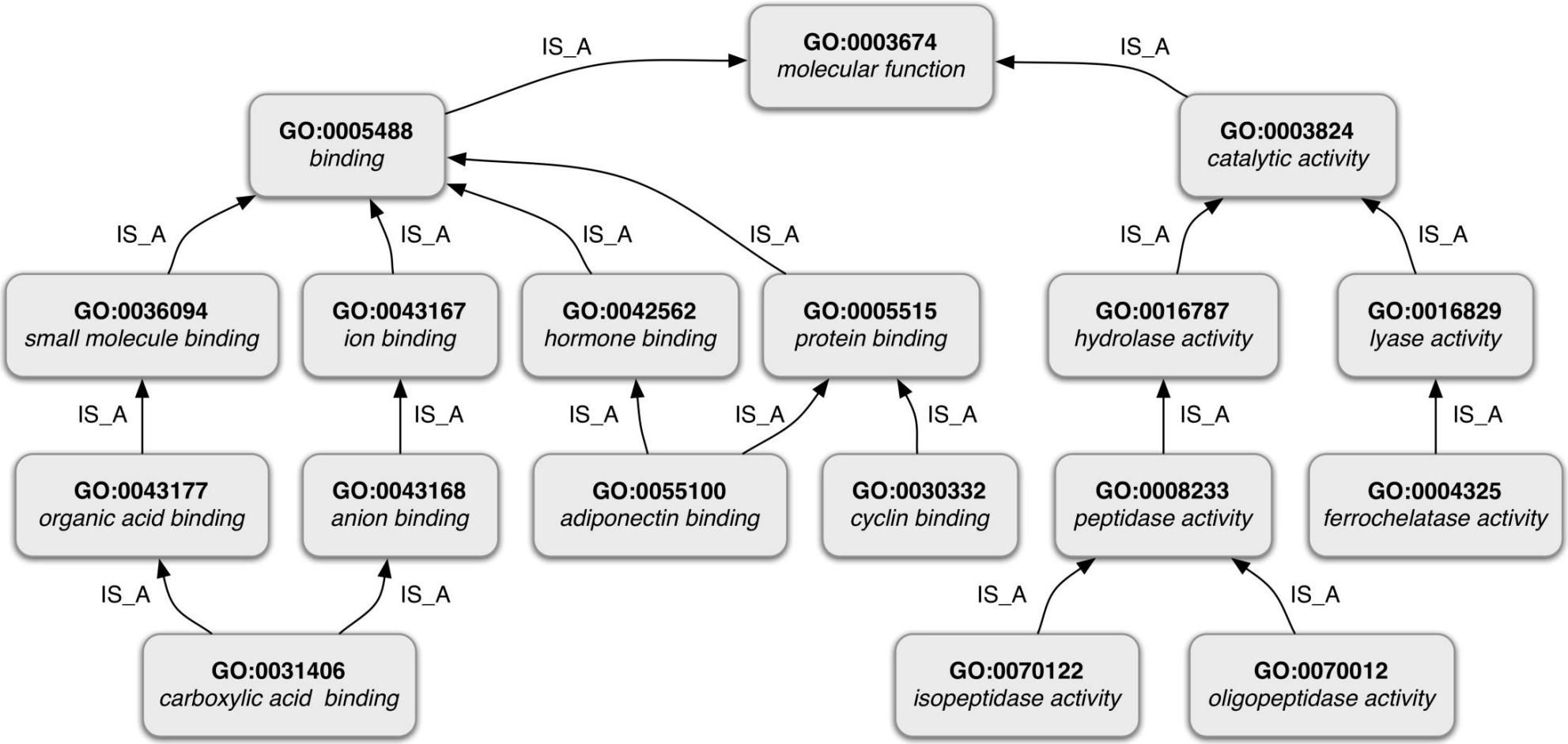
  - increased rate of apoptosis SubClassOf: increase rate of B cell apoptosis
- depends!
  - ALL apoptosis processes increased in rate?
  - SOME apoptosis processes increased in rate?

Why we care?

- taxonomic structure of ontologies is not merely a way of organizing classes
- ontology structure crucial for data analysis
  - semantic similarity
  - enrichment analysis

Gene Ontology (GO)

Example from Molecular Function ontology

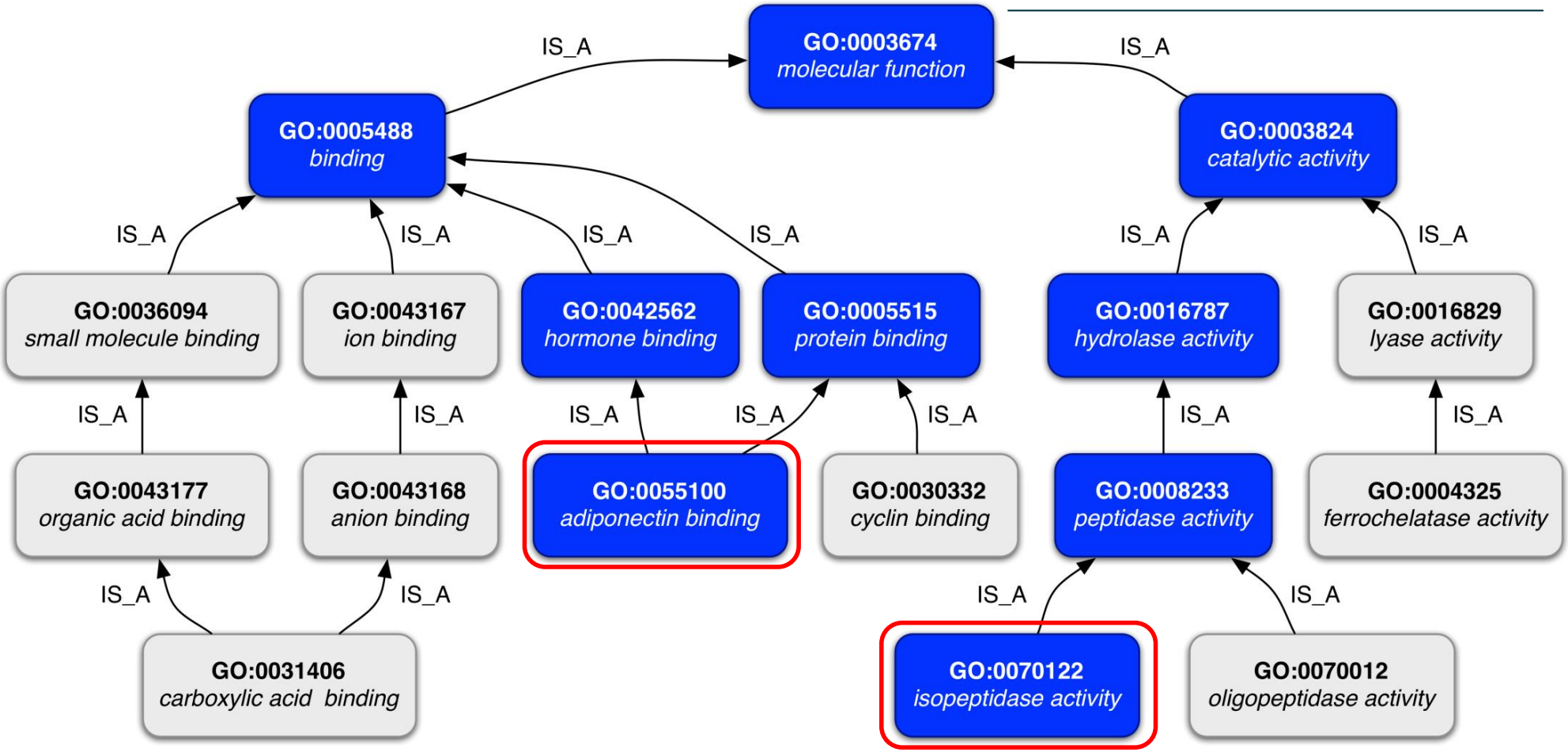


GO Annotations

$GOA(g_1)$ = {GO:0055100, GO:0070122}

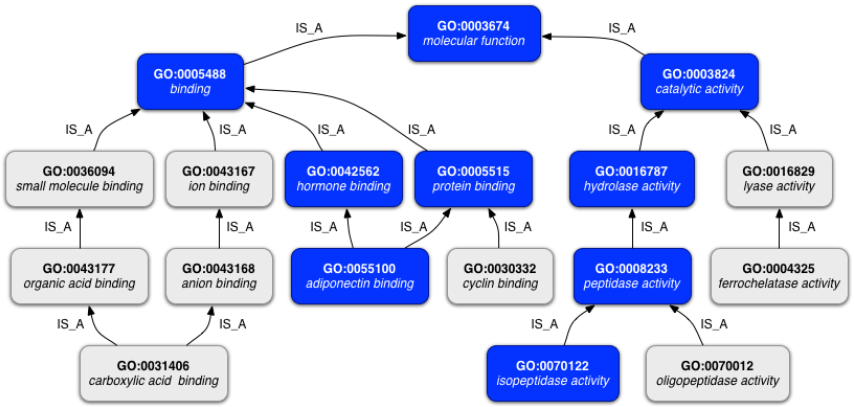
True Path Rule

"[...] the pathway from a child term all the way up to its top-level parent(s) must always be true".

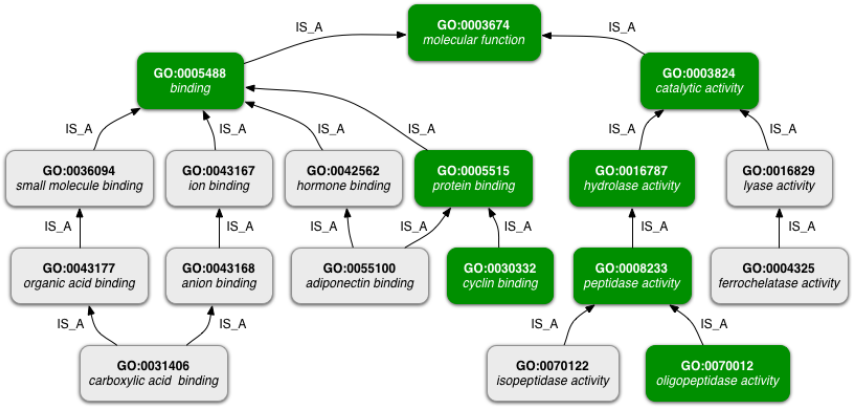


Semantic Similarity

$GOA(g_1)$ = {GO:0055100, GO:0070122}



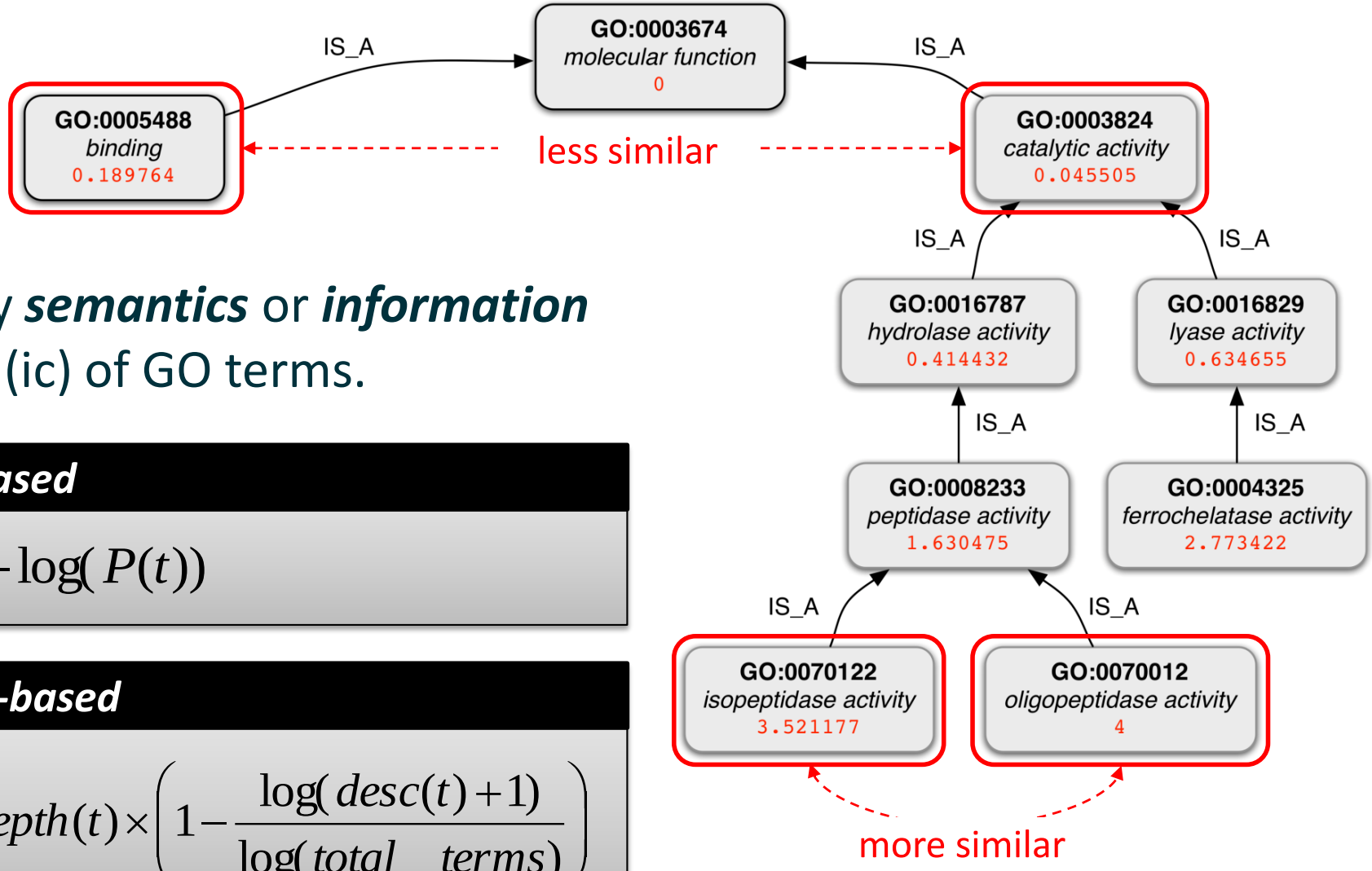
$GOA(g_2)$ = {GO:0030332, GO:0070012}



- Annotations provide an objective representation to compare genes on functional aspects.
- Semantic similarity measure quantifies relationships between (sets of) GO terms.

$$sim(g_1, g_2) = ?$$

Term Specificity



Quantify ***semantics*** or ***information content*** (ic) of GO terms.

Corpus-based

$$ic(t) = -\log(P(t))$$

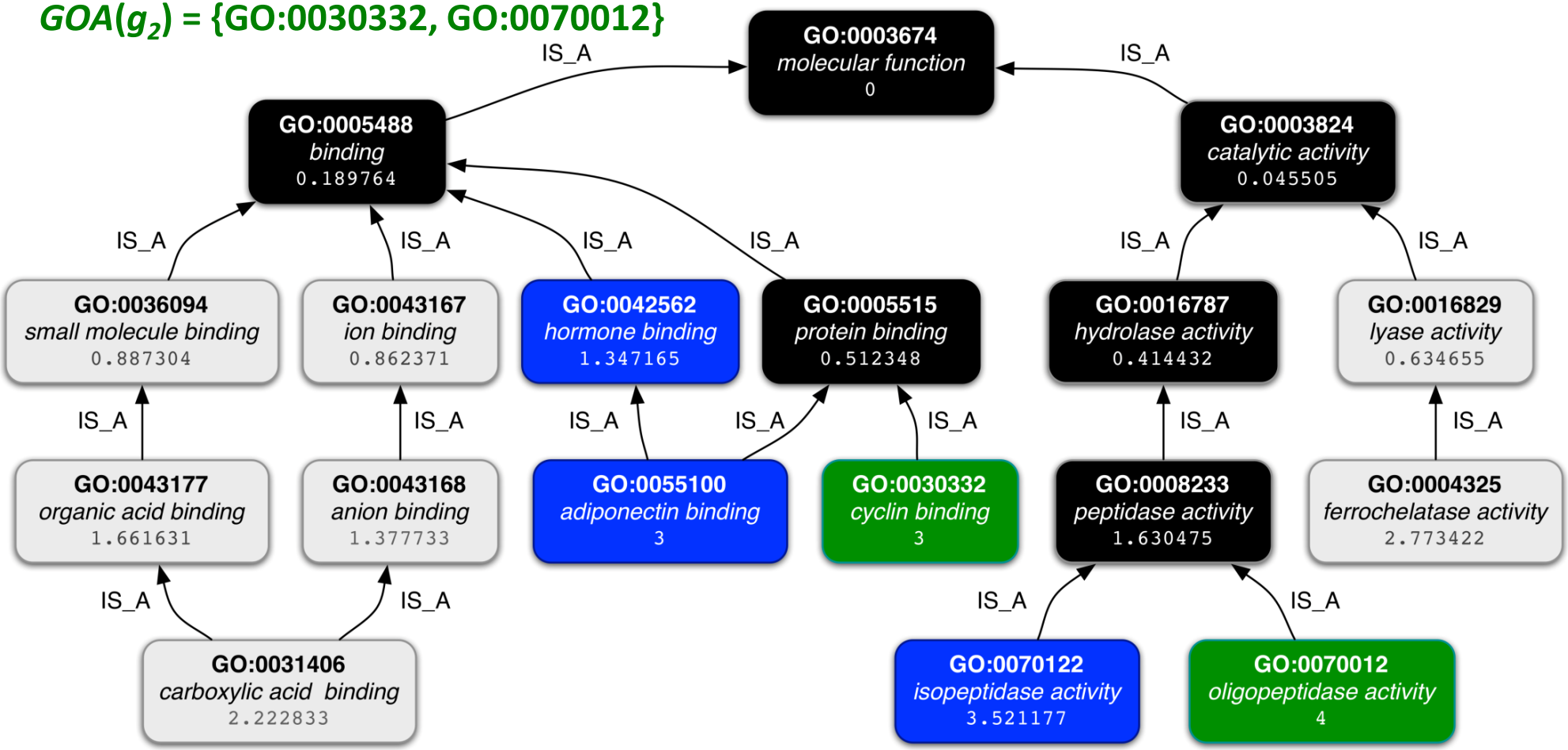
Structure-based

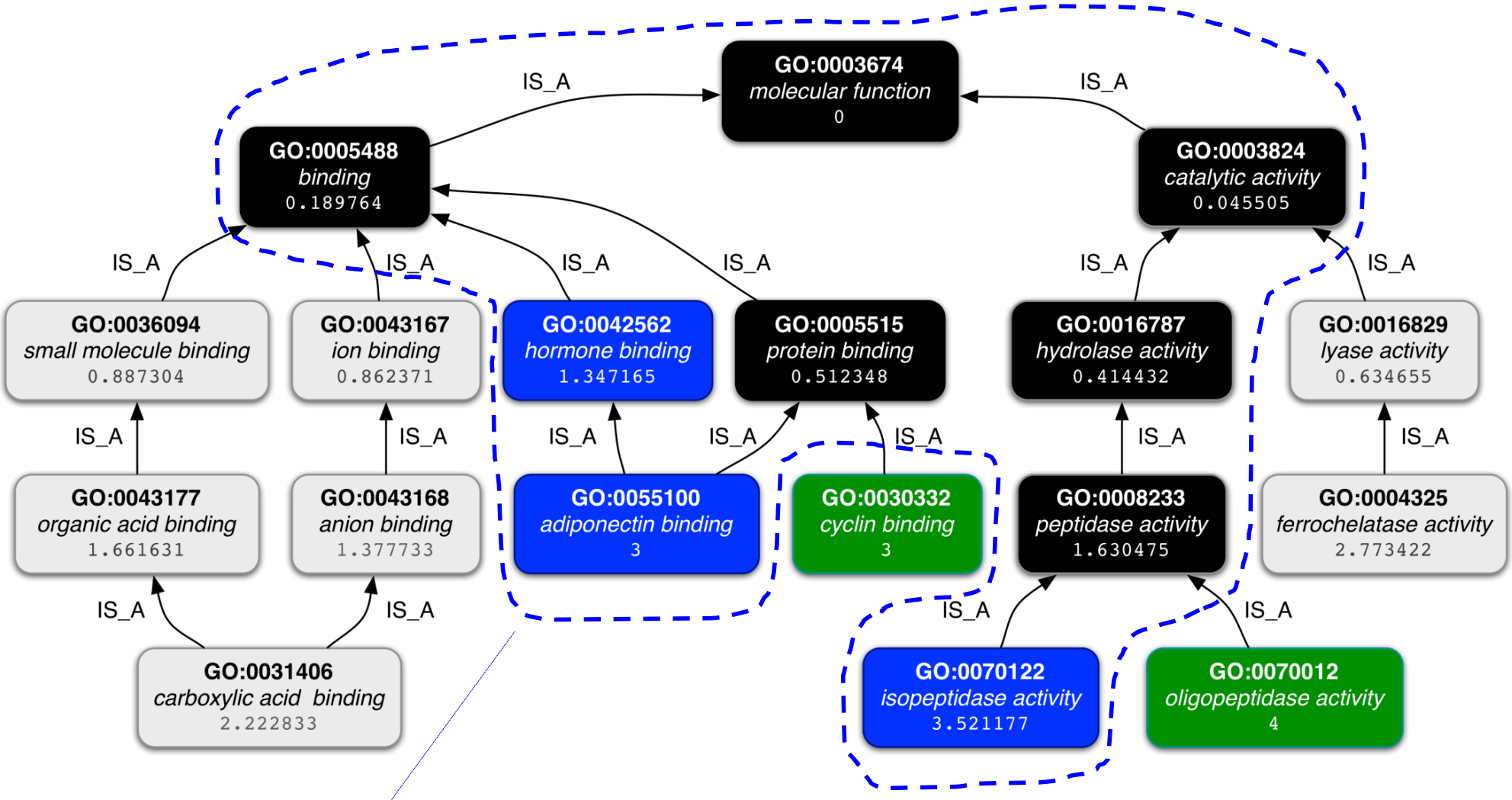
$$ic(t) = depth(t) \times \left(1 - \frac{\log(desc(t)+1)}{\log(total\_terms)}\right)$$

Group-wise Semantic Similarity

$GOA(g_1)$ = {GO:0055100, GO:0070122}

$GOA(g_2)$ = {GO:0030332, GO:0070012}





$IC(g_1) = 10.6609$

$IC(g_2) = 9.7925$

$IC(g_1 \oplus g_2) = 2.7925$

$sim(g_1, g_2) = 0.2736$

Group-wise Similarity

$$sim(g_1, g_2) = \frac{1}{2}\left(\frac{IC(g_1 \oplus g_2)}{IC(g_1)} + \frac{IC(g_1 \oplus g_2)}{IC(g_2)} \right)$$

X. Chen et al., Gene, 509 (2012)

Can we use this for comparing phenotypes?

We want to:

1. describe phenotypes formally
   - morphology
   - function
   - $\Rightarrow$ formal ontology

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2. integrate phenotypes within and between species
   - homologous organ structures (UBERON)
   - related/identical function (GO)
   - similar modifiers (ChEBI, CL, ...)
   - $\Rightarrow$ ontologies and automated reasoning

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   - $\Rightarrow$ ontologies and automated reasoning
3. find genotype-phenotype (and genotype-disease) relations
   - use phenotype similarity
   - $\Rightarrow$ semantic similarity

Properties
Taxonomy of properties

Top-level ontology of properties based on defining class Y:

- Structural: having parts, lacking parts, being part of, not being part of
  - $\exists pheneOf.(Mouse \sqcap \exists hasPart.Tail)$
- Qualitative: having qualities, lacking qualities, having quality-values, not having quality-values
  - $\exists pheneOf.(Flower \sqcap \exists hasQuality.Red)$
- Functional: being capable to do X, not being capable to do X, being dysfunctional w.r.t. F
  - $\exists pheneOf.(Heart \sqcap \exists hasFunction.PB)$
- Participatory: pumping blood, being a catalyst
  - $\exists pheneOf.(Heart \sqcap \exists participatesIn.PB)$

Phenotype representation

Apply this method to

- Arabidopsis Information Resource
- Gramene
- WormBase
- FlyBase
- Saccharomyces Genome Database
- Mouse Genome Informatics database
- Zebrafish Model Organism Database
- OMIM
- OrphaNet
- ...

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... but all of them have different anatomy and physiology.

Crossspecies integration

Can we use this framework for data integration *across* species?

Crossspecies integration

- UBERON ontology of homologous organ structures
  - *Heart (human)* homologous to *Heart (mouse)*

Crossspecies integration

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  - *Tail (mouse)* homologous to... ?

Crossspecies integration

- UBERON ontology of homologous organ structures
  - *Heart (human)* homologous to *Heart (mouse)*
  - *Tail (mouse)* homologous to... ?
  - *Tail (mouse)* SubClassOf: part-of some *Trunk (mouse)*
  - *Trunk (mouse)* homologous to *Trunk (human)*

  What if we treat homologous organ structures as *equivalent* (for this purpose)?

Crossspecies integration

- Human absent appendix:
  $\exists pheneOf.(Human \sqcap \neg\exists hasPart.HumanAppendix)$
- Mouse absent appendix:
  $\exists pheneOf.(Mouse \sqcap \neg\exists hasPart.MouseAppendix)$
- Mouse homologous to (equivalent to) Human
- MouseAppendix homologous to (equivalent to) HumanAppendix
- $\Rightarrow$ Human absent appendix equivalent to Mouse absent appendix

Crossspecies integration

- Mouse absent tail:
  $\exists pheneOf.(Mouse \sqcap \neg \exists hasPart.MouseTail)$
- MouseTail homologous to (equivalent to) ???

Crossspecies integration

- Mouse absent tail:
  $\exists pheneOf.(Mouse \sqcap \neg \exists hasPart.MouseTail)$
- MouseTail homologous to (equivalent to) ???
- Infer using mouse anatomy

Crossspecies integration

Starting with a pair of Entity and Quality, generate the following classes:

- $EPhenotype \equiv \exists pheneOf.(\exists partOf.E \sqcap \exists hasQuality.\top)$
- 'E Q' $\equiv \exists pheneOf.(E \sqcap \exists hasQuality.Q)$
  - or any of the other structural forms, depending on Q
- assert equivalence between Es in different species (based on homology)
- then, include anatomy ontologies

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- AbsentTail (mouse) will become a subclass of TrunkPhenotype (mouse, human)

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- more than 250,000 formal phenotype descriptions
- $>$ 2,000,000 axioms

Crossspecies integration

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Crossspecies integration

- Classify the resulting ontology using a OWL (EL) reasoner
- 70% of classes are unsatisfiable... why?
- it's not so easy to combine different anatomy ontologies; different conceptualizations!
  - Anus (human) is an orifice which is a kind of *immaterial anatomical entity*; Anus (mouse) is a *material entity*
  - *immaterial anatomical entity* and *material anatomical entity* are disjoint in human anatomy
- a (lossy) solution: get rid of all the disjointness axioms

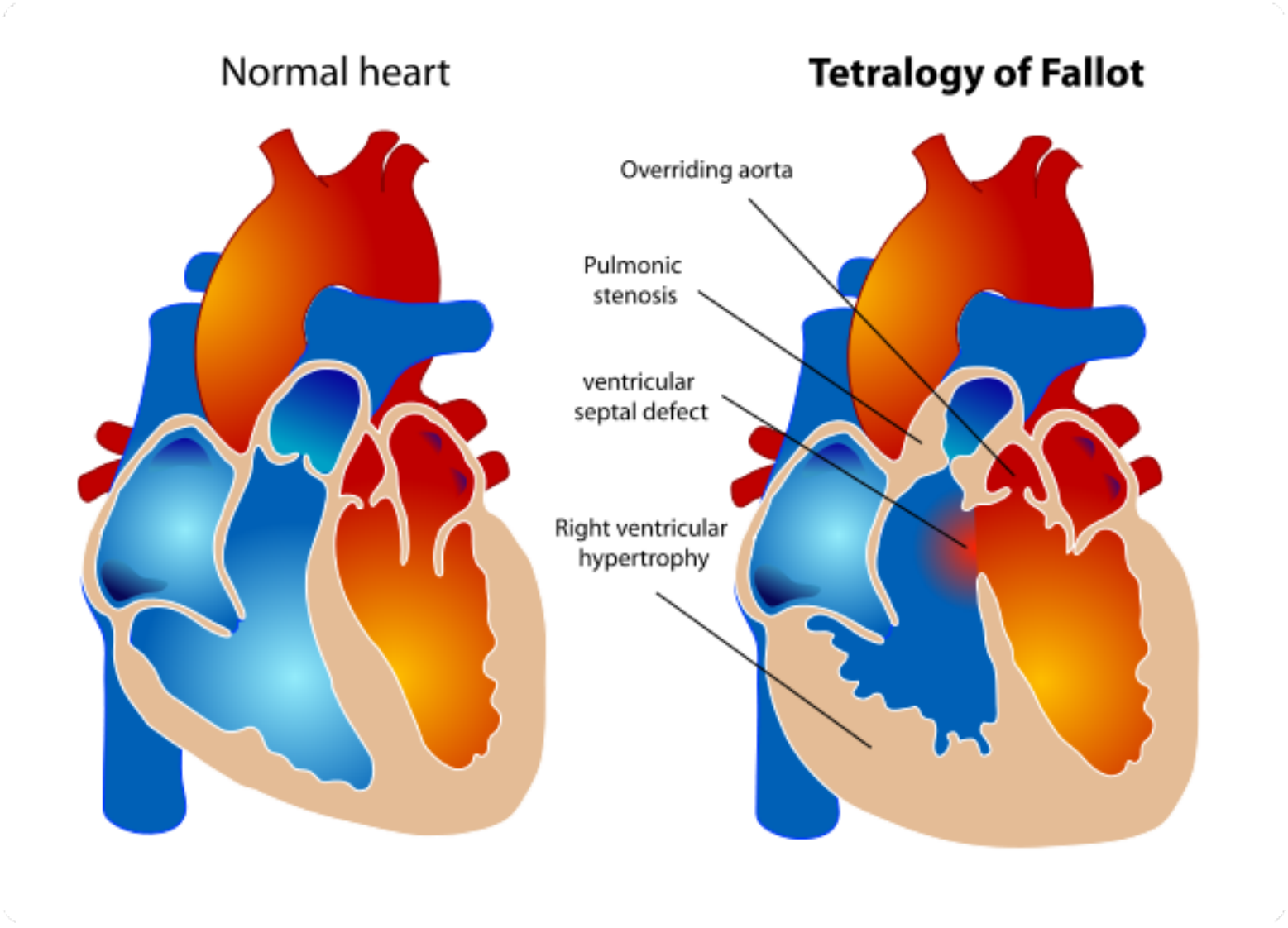
Crossspecies integration

We can now

- formally describe phenotypes
- integrate phenotype with anatomy and physiology ontologies
- integrate phenotypes across species (with some losses)
- integrate **disease and model organism phenotypes**

We can now compare *human* phenotypes (in diseases, drug effects) with *animal model* phenotypes!

Integration



Integration
Human phenotypes

- Overriding aorta (HP:0002623)
- Ventricular septal defect (HP:0001629)
- Pulmonic stenosis (HP:0001642)
- Right ventricular hypertrophy (HP:0001667)

Application
Comparison of phenotypes

phenotype of mutations subclass of disease phenotype allows inference of gene-disease association if

- disease phenotypes *sufficient* for having the disease
- mutation phenotypes *necessary* for having a specific genotype

Analyzing phenotypes

Phc1 knockout mice

Affected Systems	Genotypes: hm1	hm2
cardiovascular system		√
pulmonary trunk hypoplasia		√
abnormal cardiovascular development		√
abnormal heart looping		√
abnormal bulbus cordis morphology		√
abnormal outflow tract development		√
abnormal heart morphology		√
overriding aorta		√
ventricular septal defect		√
heart right ventricle hypertrophy		√
abnormal semilunar valve morphology		√
aortic valve stenosis		√
pulmonary valve stenosis		√
abnormal heart right ventricle outflow tract morphology		√
dilated heart ventricle		√
thin ventricular wall		√

Analyzing phenotypes

Integration of phenotype ontologies enables identification of disease phenotypes in mice.

Affected Systems	Genotypes:	hm1	hm2
cardiovascular system			√
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dilated heart ventricle			√
thin ventricular wall			√

Analyzing phenotypes

- Overriding aorta (`MP:0000273`)
- Ventricular septal defect (`MP:0010402`)
- Pulmonary valve stenosis (`MP:0006128`)
- Heart right ventricle hypertrophy (`MP:0000276`)
- ...

Analyzing phenotypes

4,000 genetic diseases in OMIM, 6,000 in OrphaNet, have an unknown molecular basis

OMIM®

Online Mendelian Inheritance in Man®

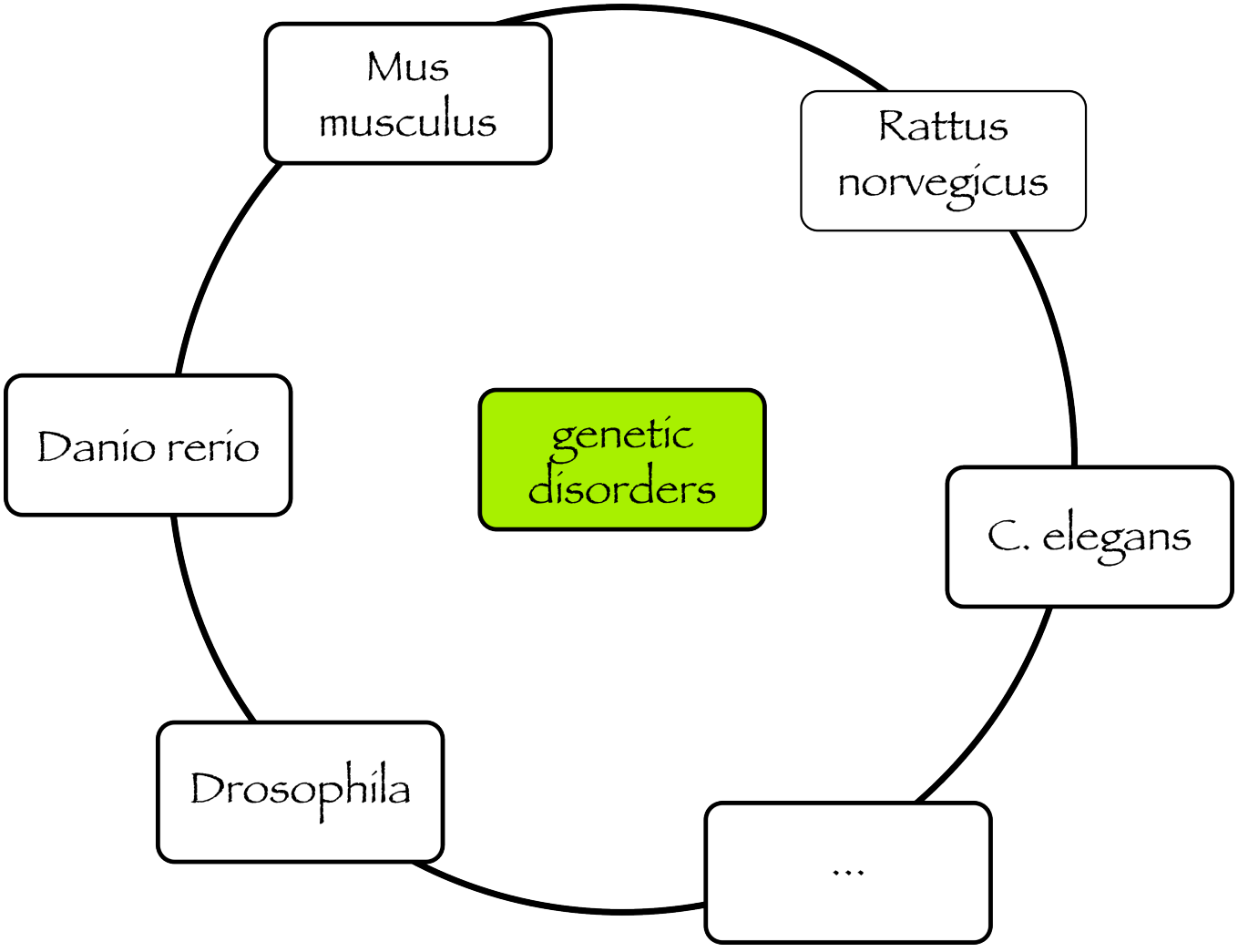
An Online Catalog of Human Genes and Genetic Disorders

Number of Entries:

Prefix	Autosomal	X Linked	Y Linked	Mitochondrial	Totals
* Gene description	12,750	627	48	35	13,460
+ Gene and phenotype, combined	250	14	0	2	266
# Phenotype description, molecular basis known	2,836	240	4	28	3,108
% Phenotype description or locus, molecular basis unknown	1,628	135	5	0	1,768
Other, mainly phenotypes with suspected mendelian basis	1,819	130	2	0	1,951
Totals	19,283	1,146	59	65	20,553

orphanet

Analyzing phenotypes



Analyzing phenotypes

Semantic similarity over phenotype ontologies measures phenotypic similarity

- $\Rightarrow$ phenotypic similarity combines similarity between anatomy, function, and quality
  - ... because this is how we built our phenotype ontology!
  - anatomy: front limb – hind limb vs. front limb – eye
  - function: detection of salty taste – detection of sweet taste vs. detection of salty taste – apoptosis
  - quality: red – orange vs. red – green vs. red – round

Analyzing phenotypes

Information content of phenotype:

$$IC(x) = -\log(p(x))$$

Phenotype similarity:

$$sim(P, D) = \frac{\sum_{x \in CI(P) \cap CI(D)} IC(x)}{\sum_{y \in CI(P) \cup CI(D)} IC(y)}$$

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$\Rightarrow$ systematic, pairwise comparison of disease and model organism phenotypes

Analyzing phenotypes

disease id	rank 1	rank 2	rank 3	...
604290	rd14	nmf242	nmf127	...
100050	frg	Spry4<tm1Ayos>	Ryk<tm1Stac>	...
100070	Atp7a<Mo-to>	Slc2a10<S150F>	Pdgfrb<tm7Sor>	...

Analyzing phenotypes

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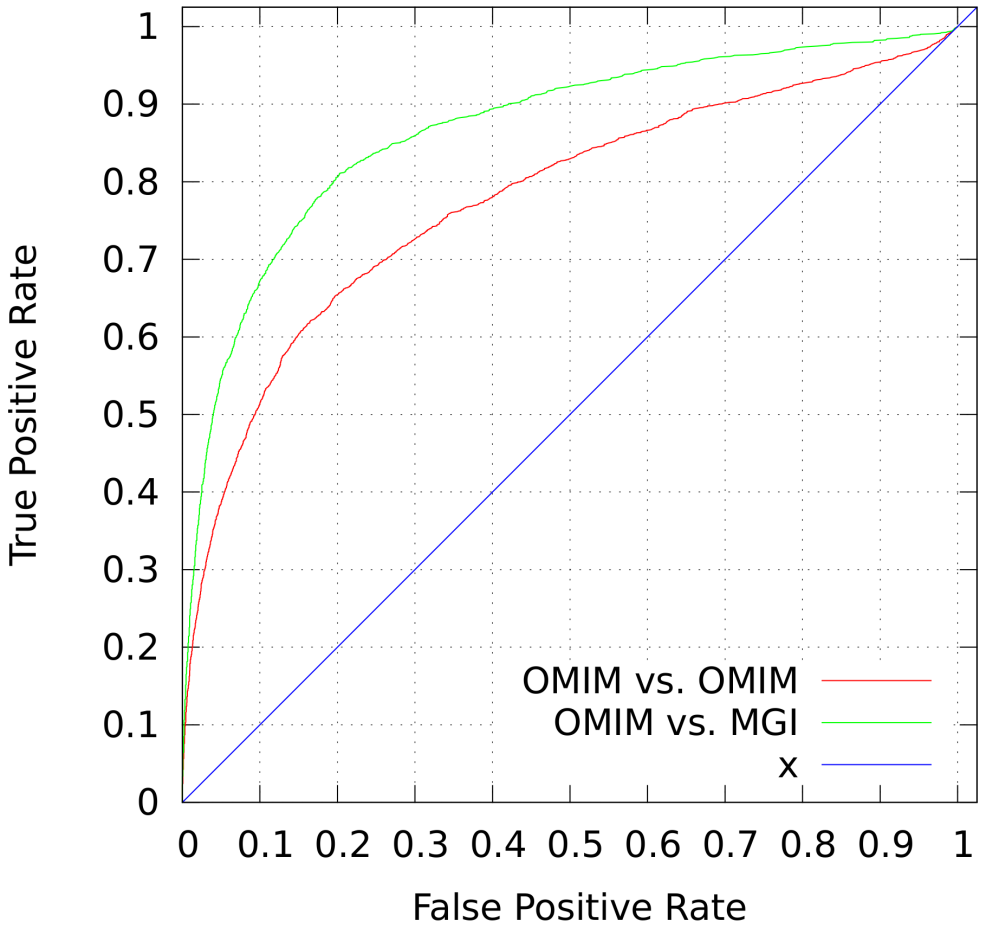
How well does this approach recover known disease genes?

Analyzing phenotypes



- AUC (OMIM): 0.84
- AUC (MGI): 0.91

Analyzing phenotypes

- *Adam19* and *Fgf15* in mice and (mammalian homologs of) *Cx36.7* and *Nkx2.5* in zebrafish are candidates for Tetralogy of Fallot
- Gene disease associations for orphan diseases
  - *Slc34a1* (`MGI:1345284`) and Fanconi renotubular syndrome 1 (`OMIM:134600`)
  - *Hip1* and Bassoe syndrome
- Disease pathways
  - Cytokine-cytokine receptor interaction pathway (`ko04060`) is significantly correlated with Tetralogy of Fallot ($p = 5 \cdot 10^{-7}$, Wilcoxon signed-rank test)

Bassoe Syndrome

Signs and symptoms

- skeletal:
  - kyphosis, hypertensible joints, cubitus valgus
- muscular:
  - hypotonia, muscle hypotrophy, amyotrophy
- behavior:
  - abnormal gait, amimia
- visual:
  - cataract, strabismus
- reproductive:
  - hypogonadism, hypogenitalism, abnormal ovaries, hypoplastic testis, reduced fertility

Bassoe Syndrome

http://phenomebrowser.net

Related OrphaNet phenotypes for Hip1

Rank	Name (ID)	Similarity		
1	Hypomyelination - hypogonadotropic hypogonadism - hypodontia (ORPHANET:88637)	0.3064	Show	explore
2	46,XX testicular disorder of sex development (ORPHANET:393)	0.3027	Show	explore
3	Intellectual deficit, X-linked - hypogonadism - ichthyosis - obesity - short stature (ORPHANET:85331)	0.2999	Show	explore
4	46,XY complete gonadal dysgenesis (ORPHANET:242)	0.2891	Show	explore
5	Bilateral anorchia (ORPHANET:983)	0.2801	Show	explore
6	Hypergonadotropic hypogonadism - cataract syndrome (ORPHANET:2410)	0.2792	Show	explore
7	Hypogonadotropic hypogonadism - frontoparietal alopecia (ORPHANET:2230)	0.2745	Show	explore
8	Camurati-Engelmann disease (ORPHANET:1328)	0.2722	Show	explore
9	Neurosensory deafness - pituitary dwarfism (ORPHANET:3228)	0.2706	Show	explore
10	Hydrocephalus - obesity - hypogonadism (ORPHANET:2183)	0.2689	Show	explore
11	Alopecia - intellectual deficit - hypergonadotropic hypogonadism (ORPHANET:1014)	0.268	Show	explore
12	46,XY disorder of sex development due to 5-alpha-reductase 2 deficiency (ORPHANET:753)	0.2654	Show	explore
13	46,XY disorder of sex development due to 17-beta-hydroxysteroid dehydrogenase 3 deficiency (ORPHANET:752)	0.2623	Show	explore
14	Androgen insensitivity syndrome (ORPHANET:754)	0.2555	Show	explore
15	Woodhouse-Sakati syndrome (ORPHANET:3464)	0.253	Show	explore
16	XK aprosencephaly (ORPHANET:3469)	0.2529	Show	explore
17	Intellectual deficit, X-linked, Miles-Carpenter type (ORPHANET:85283)	0.2527	Show	explore

Bassoe Syndrome

HIP1 knockout mice

Allele Symbol Gene; Allele Name	Chr	Synonyms	Category	Observed Phenotypes in Mouse		Allelic Composition (Genetic Background)
				Affected Anatomical Systems	Similar Human Diseases	
Hip1^{tm1Hay} huntingtin interacting protein 1; targeted mutation 1, Michael Hayden	5	HIP1-	Targeted (Reporter)	mortality/aging, behavior, growth/size, skeleton, muscle		Hip1^{tm1Hay}/Hip1^{tm1Hay} (involves: 129S1/Sv * 129X1/SvJ * C57BL/6)
Hip1^{tm1Tsr} huntingtin interacting protein 1; targeted mutation 1, Theodora S Ross	5	HIP1-	Targeted (knock-out)	mortality/aging, reproductive, endocrine/exocrine, hematopoietic, cellular		Hip1^{tm1Tsr}/Hip1^{tm1Tsr} (involves: 129X1/SvJ * C57BL/6)
				reproductive, endocrine/exocrine		Hip1^{tm1Tsr}/Hip1+ (involves: 129X1/SvJ * C57BL/6)
				growth/size, skeleton		Hip1^{tm1Tsr}/Hip1^{tm1Tsr} Hip1r^{tm1Tsr}/Hip1r^{tm1Tsr} (involves: 129X1/SvJ * C57BL/6)
Hip1$^{tm2.1Tsr}$ huntingtin interacting protein 1; targeted mutation 2.1, Theodora S Ross	5	Hip1$^{delta3-5}$	Targeted (knock-out)	reproductive, skeleton		Hip1$^{tm2.1Tsr}$/Hip1$^{tm2.1Tsr}$ (involves: 129X1/SvJ)
Hip1^{tm2Tsr} huntingtin interacting protein 1; targeted mutation 2, Theodora S Ross	5	Hip1^{loxp}	Targeted (Floxed/Frt)	none		Hip1^{tm2Tsr}/Hip1^{tm2Tsr} (involves: 129X1/SvJ * C57BL/6)
Hip1^{tm3Tsr} huntingtin interacting protein 1; targeted mutation 3, Theodora S Ross	5	Hip1^{null}	Targeted (knock-out)	mortality/aging, growth/size, hematopoietic, reproductive, skeleton, vision/eye, endocrine/exocrine		Hip1^{tm3Tsr}/Hip1^{tm3Tsr} (involves: 129X1/SvJ * C57BL/6)
Hip1^{tm4Tsr} huntingtin interacting protein 1; targeted mutation 4, Theodora S Ross	5	Hip1$^{LSL-H/P}$	Targeted (Floxed/Frt)	vision/eye		Hip1^{tm4Tsr}/Hip1+ (involves: 129X1/SvJ * C57BL/6)
				mortality/aging, hematopoietic, tumorigenesis, immune, homeostasis		Hip1^{tm4Tsr}/Hip1+ Tg(Mx1-cre)1Cgn/0 (involves: 129X1/SvJ * C57BL/6 * CBA) *conditionally targeted*
				mortality/aging, hematopoietic, tumorigenesis, liver/biliary, respiratory, immune		Hip1^{tm4Tsr}/Hip1+ Runx1^{tm3Dow}/Runx1+ Tg(Mx1-cre)1Cgn/0 (involves: 129X1/SvJ * C57BL/6 * CBA)

Bassoe Syndrome

HIP1 mouse phenotypes

Bassoe Syndrome:

- kyphosis, hypertensible joints, cubitus valgus
- amyotrophy, hypotonia, muscle hypotrophy
- abnormal gait, amimia
- cataract, strabismus
- testicular atrophy, hypogonadism, hypogenitalism, abnormal ovaries, reduced fertility

Mouse phenotypes:

- kyphosis, abnormal spine curvature, lordosis
- abnormal muscle morphology
- abnormal gait, hypoactivity, tremors
- nuclear cataracts, microphthalmia
- testicular atrophy, male infertility

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HIP1 mouse phenotypes

Bassoe Syndrome:

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- amyotrophy, hypotonia, muscle hypotrophy
- abnormal gait, amimia
- cataract, strabismus
- testicular atrophy, hypogonadism, hypogenitalism, abnormal ovaries, reduced fertility

Mouse phenotypes:

- kyphosis, abnormal spine curvature, lordosis
- abnormal muscle morphology, muscle hypotrophy, muscle wasting
- abnormal gait, hypoactivity, tremors, failure to thrive, ataxia
- nuclear cataracts, microphthalmia
- testicular atrophy, male infertility, ovarian abnormalities, testicular degeneration, increased apoptosis of postmeiotic spermatids, oligospermia

Bassoe Syndrome

Computational analysis of mouse phenotypes provides an indication that HIP1 may be involved in Bassoe syndrome.

Drug target

Can a similar approach be used to identify drug targets and indications?

Hypothesis

A similarity between drug D's effects and phenotypes resulting from *knock-out/knock-down* of a gene/protein in an animal model may indicate that D *inhibits* the gene/protein (or its human ortholog).

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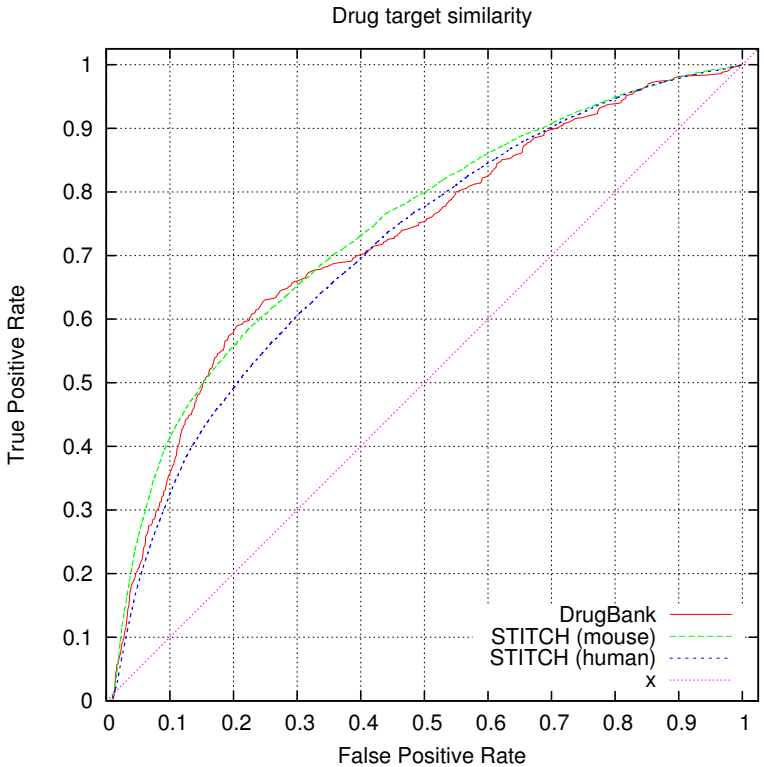
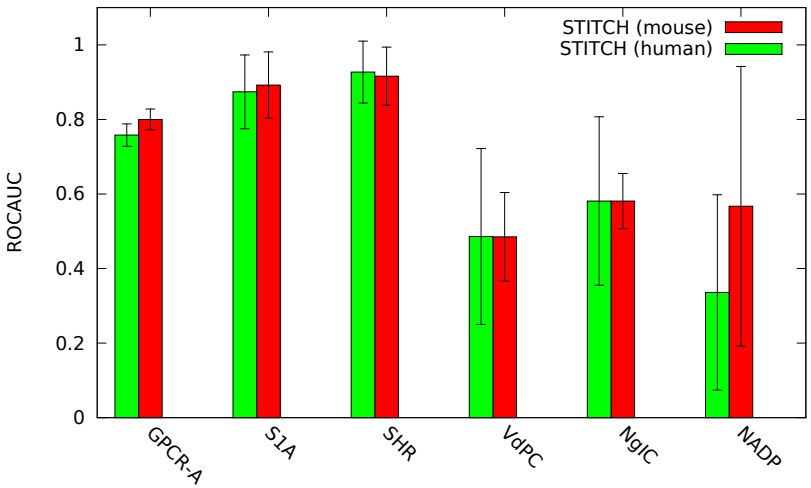
Evaluation using experimentally verified drug targets:

- DrugBank
- STITCH (human and mouse)

Drug target

Similarity between drug effects and mouse model phenotypes reveals drug targets.





- AUC: 0.76 (STITCH human)
- AUC: 0.80 (STITCH mouse)
- AUC: 0.72 (DrugBank)