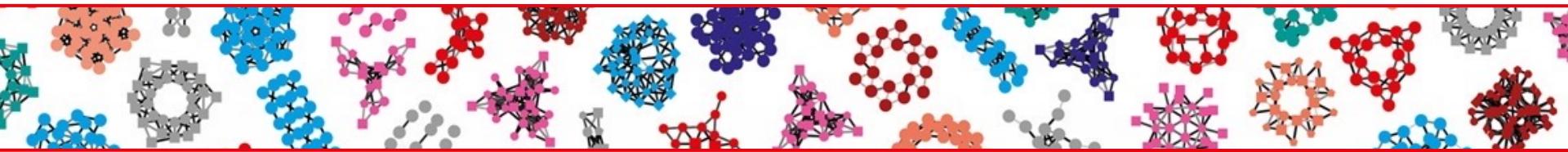


Swiss Institute
of
Bioinformatics

- Identifiers, cross-references and graphs
- MetaNetX
- Diffusion on graphs

Summer School in Aussois
6th of September 2023
Marco Pagni



Database structures

Source 1: Expert knowledge and literature

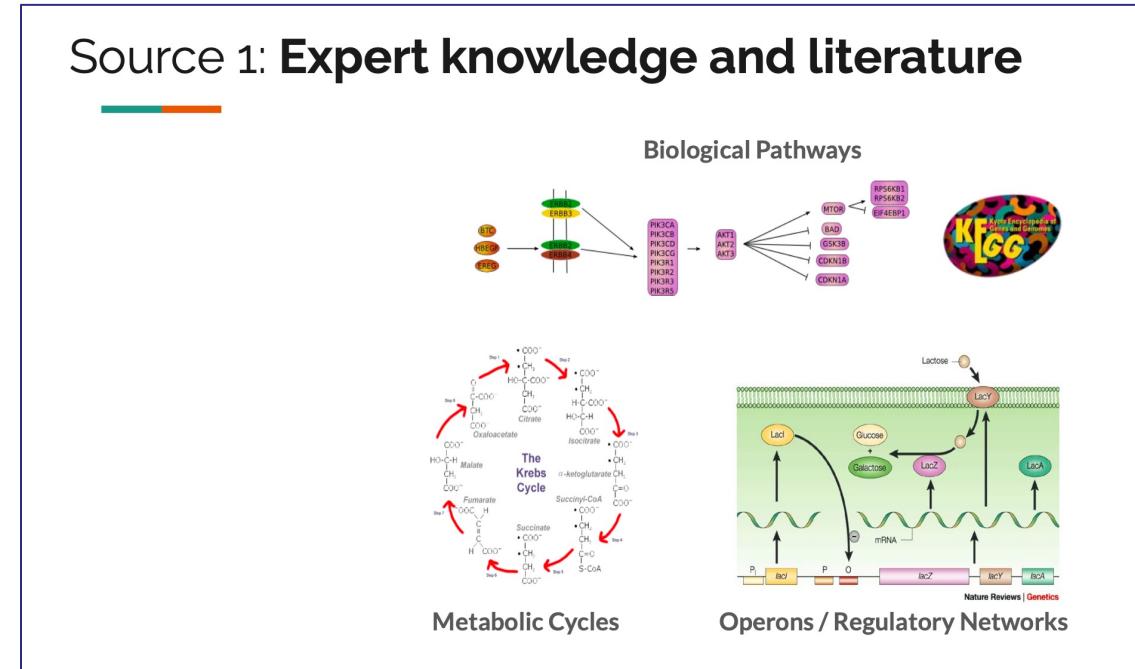


figure from Galadriel Briere presentation on Tuesday

A look back in time

- Database best practices have not really changed over the last 25 years
- User interfaces have dramatically improved

```
ID 1433B_BOVIN          Reviewed;      246 AA.
AC P68250; P29358; Q0VCL1;
DT 25-OCT-2004, integrated into UniProtKB/Swiss-Prot.
DT 23-JAN-2007, sequence version 2.
DT 22-FEB-2023, entry version 124.
DE RecName: Full=14-3-3 protein beta/alpha;
DE AltName: Full=Protein kinase C inhibitor protein 1;
DE Short=KCIP-1;
DE Contains:
DE   RecName: Full=14-3-3 protein beta/alpha, N-terminally processed;
GN Name=YWHAB;
OS Bos taurus (Bovine).
OC Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia;
OC Eutheria; Laurasiatheria; Artiodactyla; Ruminantia; Pecora; Bovidae;
OC Bovinae; Bos.
OX NCBI_TaxID=9913;
RN [1]
RP NUCLEOTIDE SEQUENCE [LARGE SCALE mRNA] (ISOFORM LONG).
RC STRAIN=Hereford; TISSUE=Fetal pons;
RG NIH - Mammalian Gene Collection (MGC) project;
RL Submitted (AUG-2006) to the EMBL/GenBank/DDBJ databases.
RN [2]
RP PROTEIN SEQUENCE OF 2-246.
RX PubMed=1671102; DOI=10.1016/0022-2836(91)90616-e;
RA Isobe T., Ichimura T., Sunaya T., Okuyama T., Takahashi N., Kuwano R.,
RA Takahashi Y.;
RT "Distinct forms of the protein kinase-dependent activator of tyrosine and
RT tryptophan hydroxylases.";
RL J. Mol. Biol. 217:125-132(1991).
RN [3]
RP NUCLEOTIDE SEQUENCE [mRNA] (ISOFORM SHORT).
RA Jones J.M., Niikura T., Pinke R.M., Guo W., Molday L., Leykam J.,
RA McConnell D.G. ;
RT "Expression of 14-3-3 proteins in bovine retinal photoreceptors.";
RL Submitted (JAN-1998) to the EMBL/GenBank/DDBJ databases.
RN [4]
RP FUNCTION.
RX PubMed=7931346; DOI=10.1046/j.1471-4159.1994.63051908.x;
RA Tanji M., Horwitz R., Rosenfeld G., Waymire J.C. ;
RT "Activation of protein kinase C by purified bovine brain 14-3-3: comparison
RT with tyrosine hydroxylase activation.";
RL J. Neurochem. 63:1908-1916(1994).
CC --!- FUNCTION: Adapter protein implicated in the regulation of a large
CC spectrum of both general and specialized signaling pathways. Binds to a
CC large number of partners, usually by recognition of a phosphoserine or
CC phosphothreonine motif. Binding generally results in the modulation of
CC the activity of the binding partner. Negative regulator of
CC osteogenesis. Blocks the nuclear translocation of the phosphorylated
CC form (by AKT1) of SRPK2 and antagonizes its stimulatory effect on
CC cyclin D1 expression resulting in blockage of neuronal apoptosis
CC elicited by SRPK2. Negative regulator of signaling cascades that
CC mediate activation of MAP kinases via AKAP13.
CC {ECO:0000250|UniProtKB:P31946, ECO:0000269|PubMed:7931346}.
```

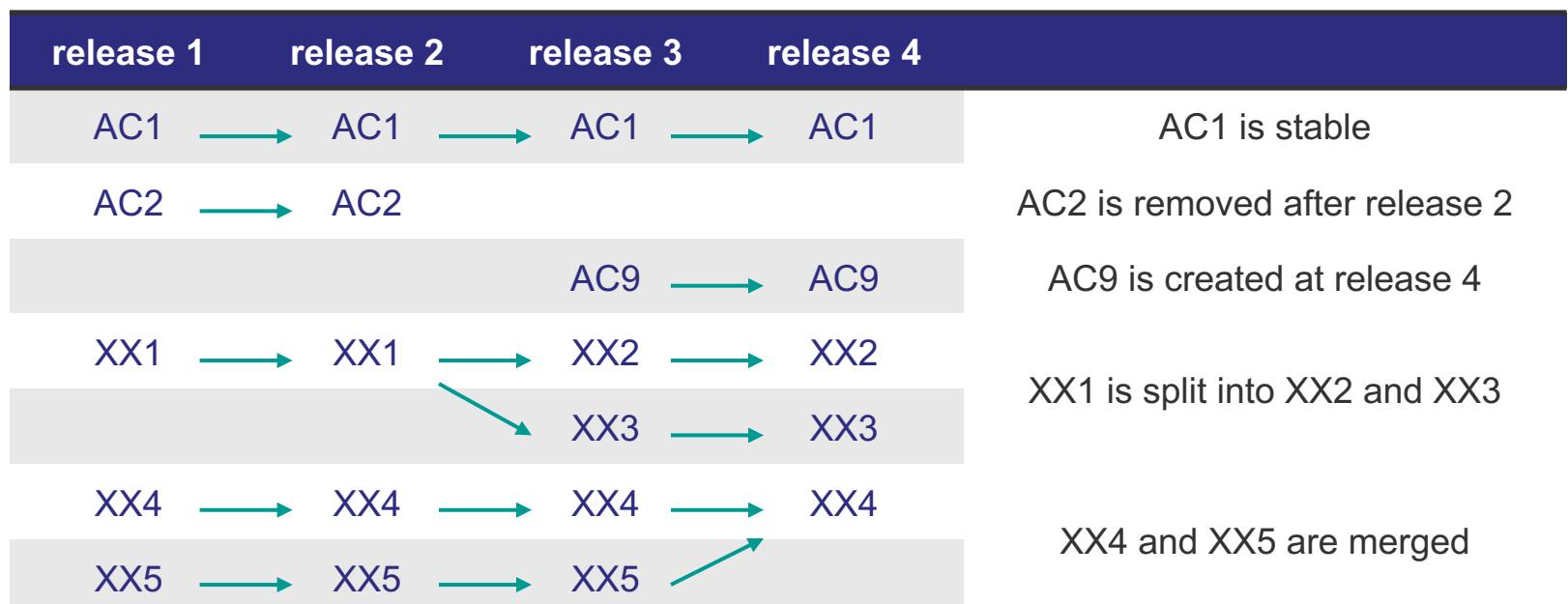
Database entry life cycle

An accession number:

- uniquely identify an "entry" across releases
- is a string, not a number
- is opaque
- is meant to be stable across releases
- must never be recycled

An entry:

- contains a core of information, secondary information and cross-references
- hopefully improves across releases
- typically contains more false negatives than false positives



→ forms a directed acyclic graph (DAG)

Mnemonic identifier

A mnemonic identifier:

- is meant to facilitate human life
- should not be used as a stable reference
- is not necessarily propagated across releases

- mnemonic
- primary accession number
- secondary (deprecated) accession numbers

ID	1433B_BOVIN	Reviewed;	246 AA.
AC	P68250; P29358; Q0VCL1;		
DT	25-OCT-2004, integrated into UniProtKB/Swiss-Prot.		
DT	23-JAN-2007, sequence version 2.		
DT	22-FEB-2023, entry version 124.		
DE	RecName: Full=14-3-3 protein beta/alpha;		
DE	AltName: Full=Protein kinase C inhibitor protein 1;		
DE	Short=KClP-1;		
DE	Contains:		
DE	RecName: Full=14-3-3 protein beta/alpha, N-terminally processed·		

Some resources have no mnemonic identifier. In ChEBI is found an accession number and a molecule name

Some resources do not distinguish accession number and mnemonic identifier. For example, this is found in some metabolic models

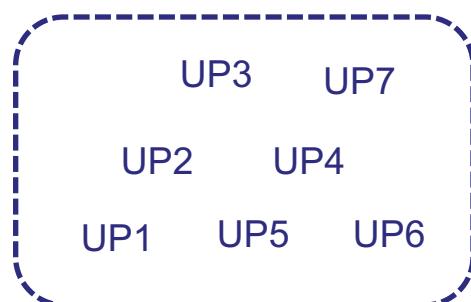
Gene names are rather on the "mnemonic side". ENSEMBL identifiers are accession number linked to a particular genome assembly.

Recommendations: work with mnemonic identifiers when available because they are more informative, but always keep track of the accession numbers.

Database structure

The overall database structure may consist in a set of independent entries. For example

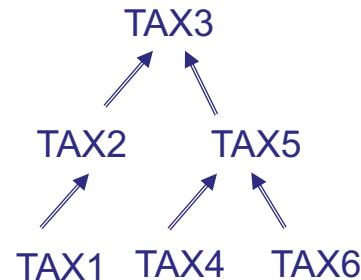
- **UniProt**
- **EMBL**



Database structure

In a tree structure, every entry (node) has zero or one parent entry.

- **The NCBI taxonomy is a single huge tree**
- **Medical Subject Headings (MeSH) are made of 16 trees.**



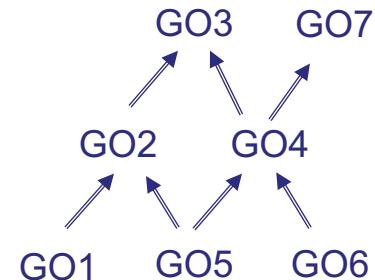
entry	parent
TAX1	TAX2
TAX2	TAX3
TAX3	
TAX4	TAX5
TAX5	TAX3
TAX6	TAX5

Database structure

In a directed acyclic graph (DAG) every entry (node) has zero, one or multiple parent entries.

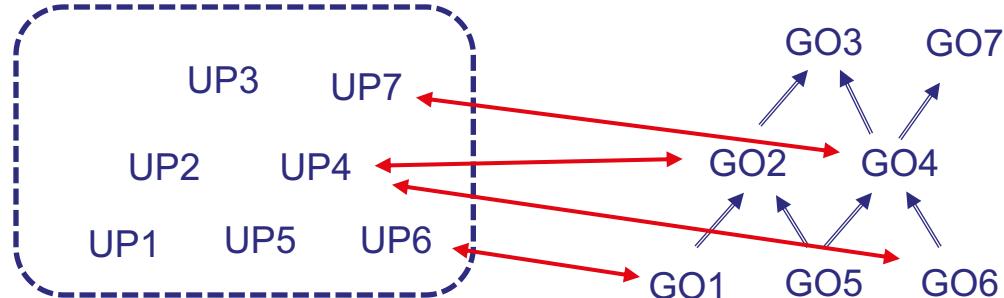
This can be referred to as an ontology, when the properties attributed to parents are inherited by their children

- **GENE Ontology (GO)**
- **ChEBI ontology**



entry	parent
GO1	GO2
GO2	GO3
GO3	
GO4	GO3, GO7
GO5	GO4
GO6	GO4
GO7	

About GO and GOA



The screenshot shows the GOA homepage with a navigation bar at the top featuring links to EMBL-EBI, Services, Research, Training, About us, a search bar, and the EMBL-EBI logo. Below the navigation is a large blue header with the word "GOA" and a network graph background. The main content area includes a red banner with the text: "The pre-release of the GO annotations for Coronavirus SARS-CoV-2 is available from the GOA FTP" and the URL "ftp://ftp.ebi.ac.uk/pub/databases/GO/goa/pre_release/". Below the banner is a section titled "Gene Ontology Annotation (GOA) Database" with descriptive text about the program's aims and the types of data it contains. At the bottom of the page are links for "Overview", "About", "Downloads", "FAQ", and "Contact Us".

Gene Ontology Annotation (GOA) Database

The GO annotation program aims to provide high-quality Gene Ontology (GO) annotations to proteins in the UniProt Knowledgebase (UniProtKB), RNA molecules from RNACentral and protein complexes from the Complex Portal. To search and view Gene Ontology terms and annotations, please use our QuickGO browser.

GOA files contain a mixture of manual annotation supplied by members of the Gene Ontology Consortium and computationally assigned GO terms describing gene products. Annotation type is clearly indicated by associated evidence codes and there are links to the source data.

Release cycle

All GOA files are released approximately every four weeks and can be accessed from our [Downloads](#) page.
We aim to coordinate our release with releases of UniProtKB.

Latest statistics

UniProt >	Human >
Mouse >	Rat >
Arabidopsis >	Zebrafish >
Chicken >	Cow >
Dicty >	Dog >
Pig >	Fly >
Worm >	Yeast >
Proteomes >	

The **GOA relationships** between UniProt and GO are most often many-to-many

They are readily available for model organisms

They can be computed for non-model organisms, using InterProScan for example. The resulting annotations are often too general to lead to interesting enrichment results.

ChEBI: Chemical Entities of Biological Interest

The parent structure
encompasses the child
structure

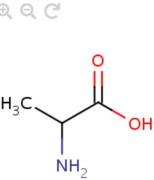
ChEBI

Home | Advanced Search | Browse | Documentation | Download | Tools | About ChEBI | Contact us | Submit

CheBI > Main

CHEBI:16449 - alanine

Main | ChEBI Ontology | Automatic Xrefs | Reactions | Pathways | Models



ChEBI Name: alanine
ChEBI ID: CHEBI:16449
Definition: An α -amino acid that consists of propionic acid bearing an amino substituent at position 2.
Stars: ★★★ This entity has been manually annotated by the ChEBI Team.
Secondary ChEBI IDs: CHEBI:2539, CHEBI:13748, CHEBI:22277
Supplier Information: ChemicalBook:CB9143191, eMolecules:476064, MolPort-001-573-589, MolPort-000-871-636
Download: Molfile XML SDF

- Find compounds which contain this structure
- Find compounds which resemble this structure
- Take structure to the Advanced Search

ChEBI Ontology

alanine (CHEBI:16449) has functional parent propionic acid (CHEBI:30768)

alanine (CHEBI:16449) has role fundamental metabolite (CHEBI:78675)

alanine (CHEBI:16449) is a α -amino acid (CHEBI:33704)

alanine (CHEBI:16449) is conjugate acid of alaninate (CHEBI:32439)

alanine (CHEBI:16449) is conjugate base of alaninium (CHEBI:32440)

alanine (CHEBI:16449) is tautomer of alanine zwitterion (CHEBI:66916)

Incoming

alanine derivative (CHEBI:22278) has functional parent alanine (CHEBI:16449)

D-alanine (CHEBI:15570) is a alanine (CHEBI:16449)

L-alanine (CHEBI:16977) is a alanine (CHEBI:16449)

L-alanine-2,3,3-d₃ (CHEBI:76050) is a alanine (CHEBI:16449)

alanine-2,3,3-d₃ (CHEBI:143534) is a alanine (CHEBI:16449)

alanine-d₃ (CHEBI:132498) is a alanine (CHEBI:16449)

alaninium (CHEBI:32440) is conjugate acid of alanine (CHEBI:16449)

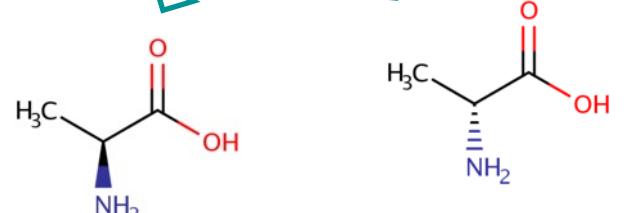
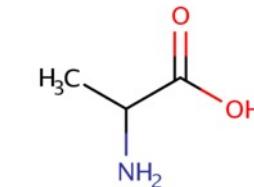
alaninate (CHEBI:32439) is conjugate base of alanine (CHEBI:16449)

alanine residue (CHEBI:32441) is substituent group from alanine (CHEBI:16449)

alanine group (CHEBI:22279) is substituent group from alanine (CHEBI:16449)

alanyl group (CHEBI:22280) is substituent group from alanine (CHEBI:16449)

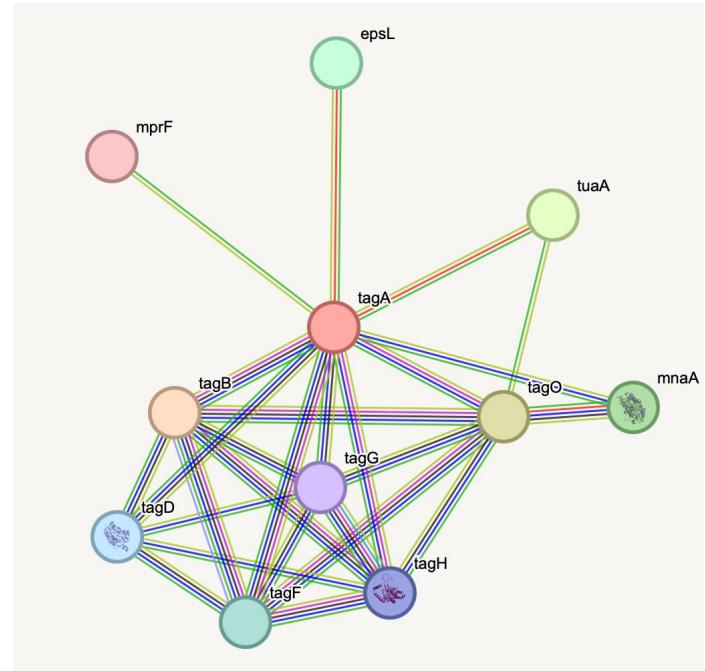
alanine zwitterion (CHEBI:66916) is tautomer of alanine (CHEBI:16449)



Many additional relationships
are defined among entries:
this is a knowledge graph

Database structure

STRINGdb is primarily an undirected graph with different types of relationships (different supporting evidences) among entries



Notations for external identifiers

The most commonly used compact notation nowadays is

prefix:accession-number

In the RDF world using Turtle syntax, given

```
PREFIX up: <http://purl.uniprot.org/uniprot/>
```

the identifier in short form

up:P29358

refers exactly to the same entity as the identifier in long form

```
<http://purl.uniprot.org/uniprot/P29358>
```

In RDF, the prefix definition is local, not public. Hence the stable public identifier is the long form.

Difficulties with prefix nomenclatures

Utilisation of prefixes is well codified in the RDF world. Less elsewhere!

`identifiers.org` is attempting to promote universal public prefixes. Unfortunately they have created new long forms, ignoring widely-used previous ones. This has introduced unnecessary communication difficulties between the Systems Biology and Bioinformatics communities.

Nota Bene: some identifiers were originally defined with a ":" as part of the accession numbers. In practice:

`CHEBI:16977`, `chebi:CHEBI:16977` and `chebi:CHEBI_16977` are very likely to refer to the same entry in ChEBI

Cross reference semantics

What does a cross reference means?

- Different identifiers for exactly the same entity
- Different identifiers for closely-related object, e.g. *in* two database of protein, one with the focus on protein structures, the other one on protein sequences
- Different identifiers for distinct but related object
 - gene \Leftrightarrow protein

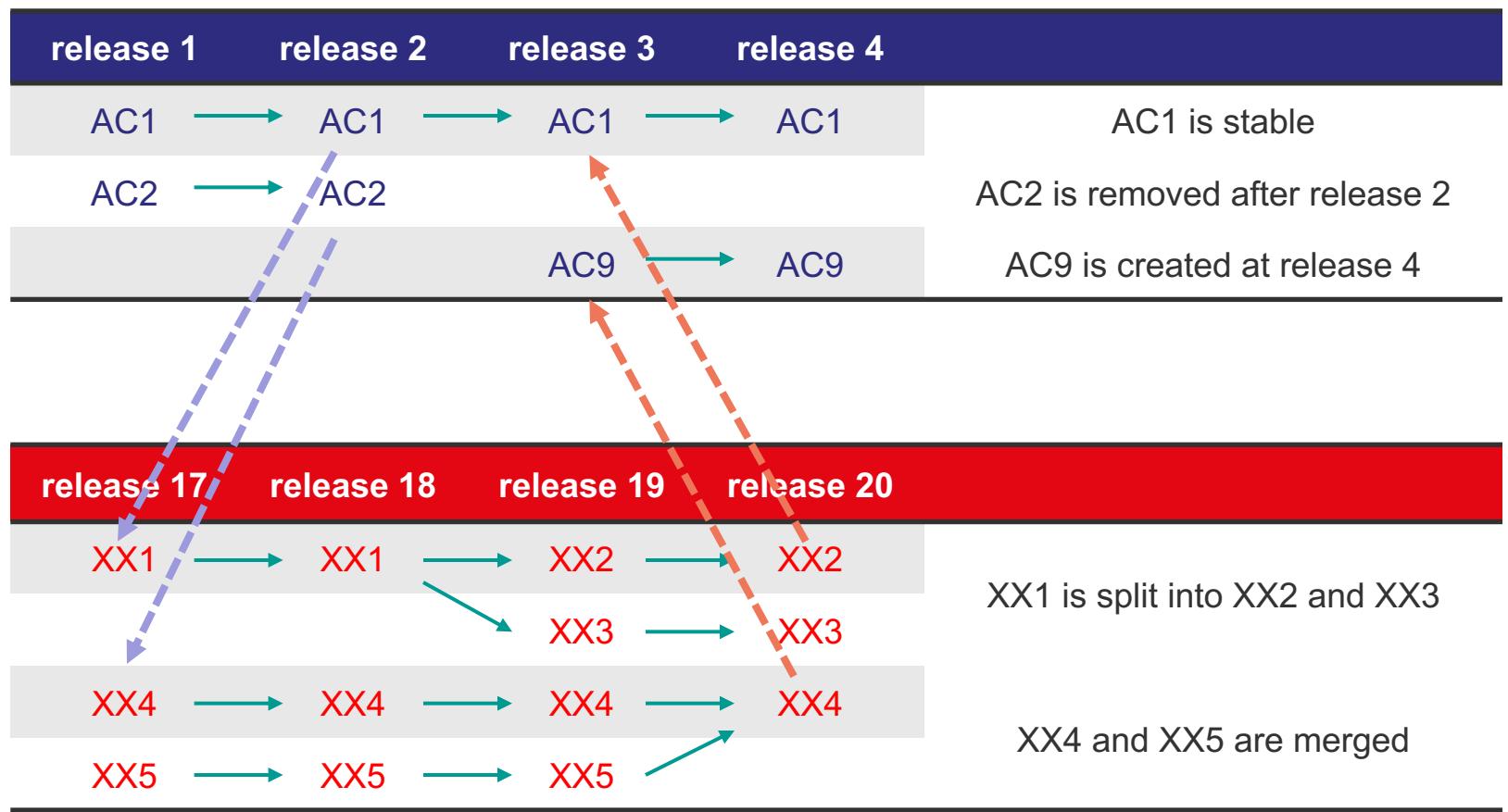
Cross references

A cross reference links an entry in a database to another entry in another database, *i.e.* using an external accession number

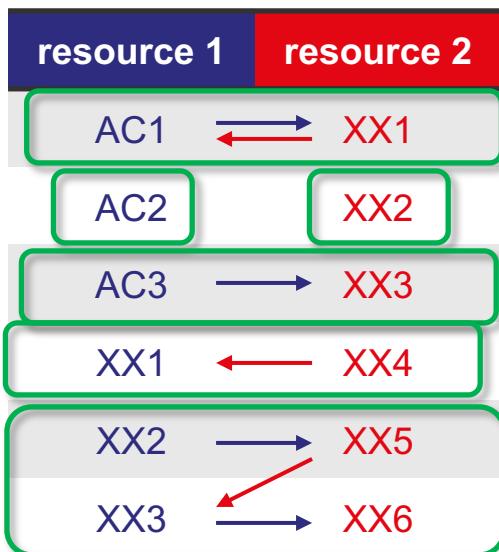
```
DR EMBL; BC120112; AAI20113.1; -; mRNA.  
DR EMBL; AF043736; AAC02090.1; -; mRNA.  
DR PIR; S13467; S13467.  
DR RefSeq; NP_777219.2; NM_174794.2.  
DR AlphaFoldDB; P68250; -.  
DR SMR; P68250; -.  
DR STRING; 9913.ENSBTAP00000022411; -.  
DR iPPTMnet; P68250; -.  
DR PaxDb; P68250; -.  
DR PeptideAtlas; P68250; -.  
DR GeneID; 286863; -.  
DR KEGG; bta:286863; -.  
DR GO; GO:0005737; C:cytoplasm; ISS:AgBase.  
DR GO; GO:0042470; C:melanosome; IEA:UniProtKB-SubCell.  
DR GO; GO:0048471; C:perinuclear region of cytoplasm; ISS:AgBase.  
DR GO; GO:0019904; F:protein domain specific binding; ISS:AgBase.  
DR InterPro; IPR000308; 14-3-3.  
DR InterPro; IPR023409; 14-3-3_CS.  
DR InterPro; IPR036815; 14-3-3_dom_sf.  
DR InterPro; IPR023410; 14-3-3_domain.  
DR PANTHER; PTHR18860; 14-3-3 PROTEIN; 1.  
DR PANTHER; PTHR18860:SF28; 14-3-3 PROTEIN BETA/ALPHA; 1.
```

Cross references across releases

For practical reason, cross-references usually refer to entries in previous release of the external databases !



Cross references



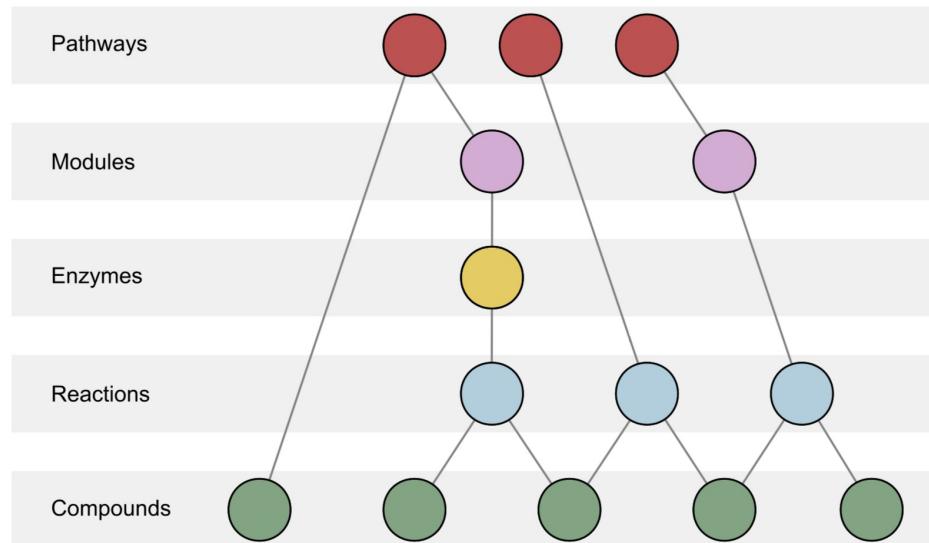
Computation of connected component helps to understand structure of cross references (available from `igraph`)

Database structure

KEGG is a DAG with a fixed depth.

It can also be viewed as a multipartite graph. Individual entries are assigned a type (compound, reaction ...) and relations are only considered between entries of different types.

The complete description of a biochemical pathways down to the metabolite level is the induced sub-graph starting from the pathway identifier.



RHEA

A database of biochemical reaction meant to annotate enzymes in UniProt

 ex:adenosine / CHEBI:29748 / RHEA:16505 / 4.1.3.40 / [Search](#)

[Examples](#) ▾ [Advanced search](#) [Browse](#)

[!\[\]\(3f8838d7e0a883aee88896beec531e3a_img.jpg\) Structure search](#) [!\[\]\(a1ee9bfb4a173ad3538d4ced1cc2067d_img.jpg\) Retrieve/ID mapping](#) [!\[\]\(9db8a0a2f8bc6ba7b48b09b6c779aced_img.jpg\) SPARQL](#) [!\[\]\(46a9da4e80960b218064a134fd098eb1_img.jpg\) Download](#) [!\[\]\(30b3510f6b04bcb01c1ecb2b08a6b894_img.jpg\) Help](#) [!\[\]\(3fcd2cf5f920c7c0c47db4cbbd1db4ea_img.jpg\) Feedback](#)

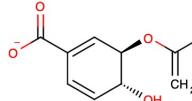
RHEA:16505 [!\[\]\(a03b456e5dc7ecff9132cc91a5934215_img.jpg\)](#)

[Reaction information](#) chorismate 4-hydroxybenzoate pyruvate

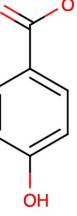
[Reaction participants](#)

[Cross-references](#)

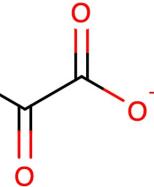
[Publications](#)


[zoom](#)

$=$


[zoom](#)

$+$


[zoom](#)

Enzymes

UniProtKB <small>(?)</small>	6,488 proteins
Enzyme class <small>(?)</small>	EC 4.1.3.40 chorismate lyase
GO Molecular Function <small>(?)</small>	GO:0008813 chorismate lyase activity

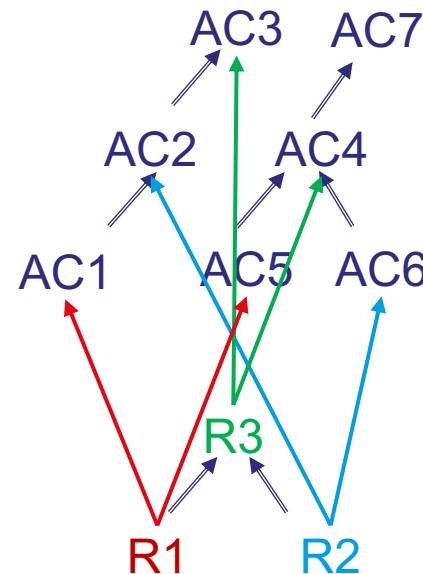
RHEA

RHEA is an ontology (a DAG) of biochemical reactions with reactants taken from the ChEBI ontology (another DAG)

R1: AC1 \leftrightarrow AC5

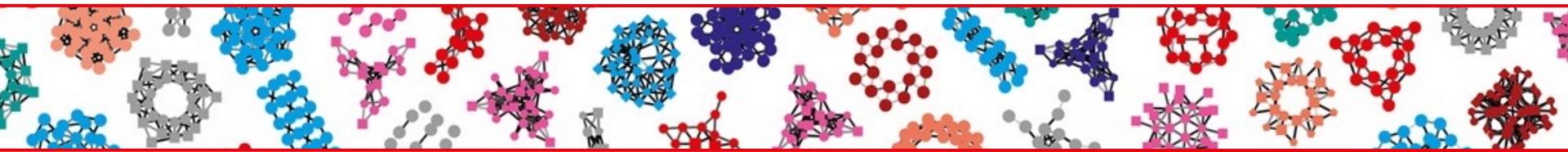
R2: AC2 \leftrightarrow AC6

R3: AC3 \leftrightarrow AC4



Reasoning with ontologies:

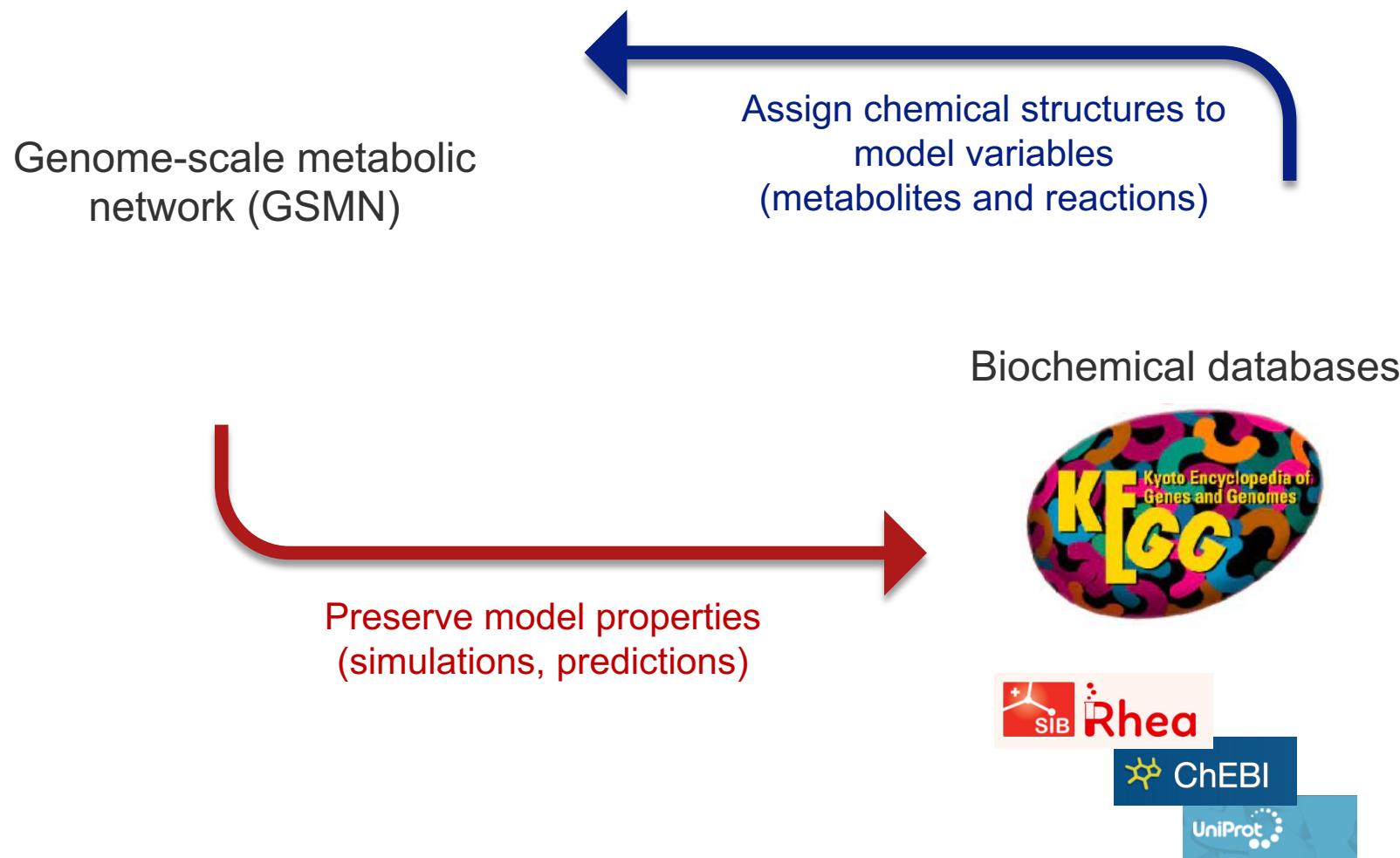
1. $AC1 \leftrightarrow AC6$ is implied by R3
2. reaction R1 is a child of R2



Adding molecular structures to stoichiometric models:

...where Systems Biology and Chemoinformatics meet

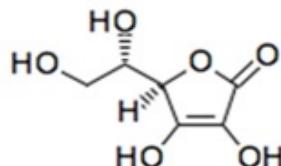
An old problem



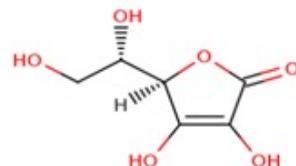
Merging chemicals / selecting representative

?

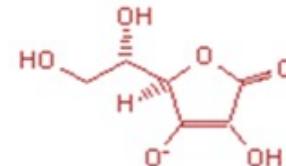
bigg:ascb_L
L-Ascorbate



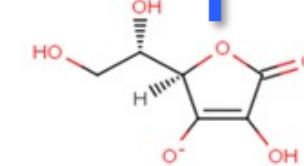
KEGG:C00072
ascorbate



CHEBI:29073
L-ascorbic acid



MetaCyc:ASCORBATE
L-ascorbate



CHEBI:38290
L-ascorbate



Evidences to group metabolites
(by decreasing importance):

1. Chemical records
2. Reaction contexts
3. Cross-references (with care)
4. Names



MNXM727871

The MNXref identifier
for this metabolite, *i.e.*
an identifier for the set
of molecules that are
grouped together



chebi:38290

The reference
(external) identifier
that "best" represents
this metabolite

Merging chemicals => merging reactions

rheAR:30243

The reference identifier
(external) that "best"
represents this reaction



Input reactions



MNXR191899

First step



MNXref identifier for this
set of reactions

Rewrite reactions



Second step



Rewrite reactions



reactions merged!

MNXref reconciliation in number (release 4.2)

metabolites

	all	in reac	in mnet*
CHEBI	116222	21196	5637
bigg	9130	9053	6541
envipath	12306	1580	591
hmdb	195008	9369	4500
keggC	18673	9899	2757
keggD	11147	650	250
keggE	864	0	0
keggG	11042	406	115
lipidmaps	43085	2832	929
metacyc	20296	16199	2505
reactome	5526	2031	1638
sabiork	8944	8899	1443
seed	33995	21634	3789
slm	777657	1831	524
MNXref	1043605	41584	9359
<i>ratio</i>	2.15	3.62	5.16

reactions

	all	in mnet
bigg	28167	40653
kegg	11160	2879
metacyc	17198	3262
rhea	12510	3101
sabiork	8118	1818
seed	43855	15958
MNXref	36944	13317
<i>ratio</i>	4.63	6.38



MetaNetX

Automated Model Construction
and Genome Annotation for
Large-Scale Metabolic Networks

The full dataset is distributed in
TAB-delimited and RDF/Turtle
formats under CC-BY license

*approx. 150 public GEMs from
different labs and different
organisms

Navigating MNXref at www.metanetx.org



MetaNetX

Automated Model Construction and Genome Annotation for Large-Scale Metabolic Networks

Search MNXref 

SystemsX.ch
The Swiss Initiative in Systems Biology

My Selection

- Summary
- Pick from repository
- Import model
- Upload reactions
- Delete models
- Upload genome
- New

Analyze

- Flux balance (FBA)
- Groups of coupled reactions (GCR)
- Blocked reactions (BLO)
- Reaction knockout (RKO)
- Gene/peptide knockout (PKO)

Create / Modify

- Combine logically
- Split and merge
- Growth recovery (GRE) New
- Build from a genome (BUILD) New

Utilities

- Search/Download MNXref namespace
- SPARQL query
- Reset session

Documents

- Getting started
- A short tutorial

	Mnet	#reac	#spec	#chem	#comp	#pept	Analysis
#1	bigg_e_coli_core	97	96	56	3	138	BC + Import
#3	bigg_e_coli_core_GRE	99	97	56	4	138	GRE + BC + FBA
Overall (non-redundant)		100	97	56	4	138	

All user data are removed after 24h

Reactions from bigg_e_coli_core_GRE

Search:	First	Previous	1	2	3	4	5	...	10	Next	Last	Show / hide columns
#3	Left	Rev	Right	MNXref ID	Enzy							
+	1 NH4(+) extracellular region	<=>	1 NH4(+) cytoplasm	MNXR101950	AMTB_ECOLI s0001 [LB;UB]							
+	1 L-glutamine + 1 ADP + 1 phosphate + 1 H(+) cytoplasm	<-->	1 ATP + 1 NH4(+) + 1 L-glutamate cytoplasm	MNXR100024	GLN1B_ECOLI PUUA_ECOLI [LB;0]							
+	1 L-glutamine extracellular region	-->	1 L-glutamine model boundary	MNXR100259	[0;UB]							
+	1 D-glucose extracellular region	<=>	1 D-glucose model boundary	MNXR145025	[-1.00e+01;UB]							
+	1 (2R)-2-phosphoglycerate cytoplasm	<=>	1 phosphoenolpyruvate + 1 H2O cytoplasm	MNXR97932	ENO_ECOLI [LB;UB]							
+	1 D-mannose 6-phosphate + 1 NADP(+) cytoplasm	<=>	1 6-phospho-D-glucono-1,5-lactone + 1 NADPH + 1 H(+) cytoplasm	MNXR190271	G6PD_ECOLI [LB;UB]							
+	1 (R)-lactate extracellular region	-->	1 (R)-lactate model boundary	MNXR97840	[0;UB]							

Navigating MNXref at www.metanetx.org

alpha-D-glucose 1-phosphate

Properties

MNX_ID	MNXM1102517
formula	C ₆ H ₁₁ O ₉ P
charge	-2
mass	258.119901
reference	chebi:58601

InChIKey: HXXFSFRBOHSIMQ-VFUOTHLC5A-L

InChI: InChI=1S/C6H13O9P/c7-1-2-3(8)4(9)5(10)6(14-2)15-16(11,12)13/h2-10H,1H2,(H2,11,12,13)/p-2/t2-,3-,4+,5-,6-/m1/s1

SMILES: OC[C@H]1O[C@H](OP([O-])[O-])[C@H](O)[C@@H](O)[C@H]1O

Occurrences in reactions

	#reac
Distinct reactions in my sandbox	0
Distinct generic reactions in MNXref	139
Distinct compartmentalized reactions in models	25

Similar chemical compounds in external resources	
Identifier	Description
chebi:58601 CHEBI:58601	alpha-D-glucose 1-phosphate alpha-D-glucopyranose 1-phosphate alpha-D-glucose 1-phosphate(2-)
biggM:gallp bigg.metabolite:gallp	Alpha-D-Galactose 1-phosphate
keggC:C00103 kegg.compound:C00103	D-Glucose 1-phosphate Cori ester D-Glucose alpha-1-phosphate alpha-D-Glucose 1-phosphate
seedM:cpd00089 seed.compound:cpd00089	Glucose-1-phosphate Cori ester D-Glucose 1-phosphate D-Glucose alpha-1-phosphate D-Glucose1-phosphate D-glucose 1-phosphate D-glucose-1-phosphate D-glucose-alpha-1-phosphate alpha-D-Glucose 1-phosphate alpha-D-Glucose-1-phosphate alpha-D-glucopyranose 1-phosphate alpha-D-glucose 1-phosphate alpha-D-glucose-1-P alpha-glucose-1-phosphate cori ester g1p glucose 1-phosphate glucose-1P
sabioRkM:1298 sabioRk.compound:1298	alpha-D-Glucose 1-phosphate D-Glucose alpha-1-phosphate alpha-D-Glucose-1-phosphate
metacycM:GLC-1-P metacyc.compound:GLC-1-P	alpha-D-glucopyranose 1-phosphate D-glucose 1-phosphate D-glucose-1-phosphate D-glucose-alpha-1-phosphate alpha-D-glucose 1-phosphate alpha-D-glucose-1-P alpha-glucose-1-phosphate cori ester glucose 1-phosphate glucose-1P

Diagnose metabolic networks

	Mnet	#reac	#spec	#chem	#comp	#pept	Analysis
#1	metatlas_HumanGEM	12888	9934	4054	10	3616	BC + Import
<i>Overall (non-redundant)</i>		12888	9934	4054	10	3616	



- ambiguous and conflicting mapping to MNXref
- duplicated reactions
- metabolites with isomeric parent/child relationships

source ID	mapped chem	MNXref ID	Comment
MAM02839c;MAM02839r;MAM02839s	3,3',5'-triiodothyronine	MNXM1102092	Ambiguous xrefs, parent MNXM1102092 selected: chebi:28774 => MNXM1102092; kegg:C07639 => MNXM1102093
MAM00078p	pristanoyl-CoA	MNXM1103831	Ambiguous xrefs, parent MNXM1103831 selected: bigg:pristocoa => MNXM1103831; chebi:64039 => MNXM733833
MAM03887c;MAM03887p	pristanoyl-CoA	MNXM1103831	Ambiguous xrefs, parent MNXM1103831 selected: bigg:pristocoa => MNXM1103831; chebi:64039 => MNXM733833
MAM00749m;MAM00749p	3alpha,7alpha,12alpha-trihydroxy-5beta-cholest-24-en-26-oyl-CoA	MNXM1103943	Ambiguous xrefs, parent MNXM1103943 selected: bigg:cholcoads,chebi:27505 => MNXM1103943; kegg:C05460 => MNXM2747
MAM00614c;MAM00614m;MAM00614p;MAM00614r	3alpha,7alpha-dihydroxy-5beta-cholestan-26-oyl-CoA	MNXM1104095	Ambiguous xrefs, parent MNXM1104095 selected: bigg:dholesterolcoa,chebi:15494 => MNXM1104095; kegg:C04644 => MNXM730494
MAM00614c	3alpha,7alpha-dihydroxy-5beta-cholestan-26-oyl-CoA	MNXM1104095	Isomeric parent/child relationship found in mnet
MAM00617p	(2S)-3alpha,7alpha-Dihydroxy-5beta-cholestanyl-CoA	MNXM737886	
MAM00614m	3alpha,7alpha-dihydroxy-5beta-cholestan-26-oyl-CoA	MNXM1104095	Isomeric parent/child relationship found in mnet
MAM00617p	(2S)-3alpha,7alpha-Dihydroxy-5beta-	MNXM737886	

RDF/Turtle distribution and SPARQL endpoint

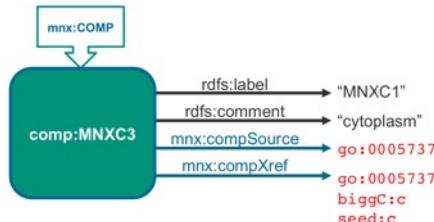
<https://rdf.metanetx.org>

Example of a compartment instance: Cytoplasm

```

@PREFIX mnx: <https://rdf.metanetx.org/schema/>
@PREFIX comp: <https://rdf.metanetx.org/comp/>
@PREFIX go: <http://purl.obolibrary.org/obo/GO_>
@PREFIX biggC: <https://identifiers.org/bigg.compartment/>
comp:mnxc3 a mnx:COMP ;
    rdfs:label 'MNXC1' ;
    rdfs:comment 'cytoplasm' ;
    mnx:compSource go:0005737 ;
    mnx:compXref go:0005737 , biggC:c , seed:c .

```



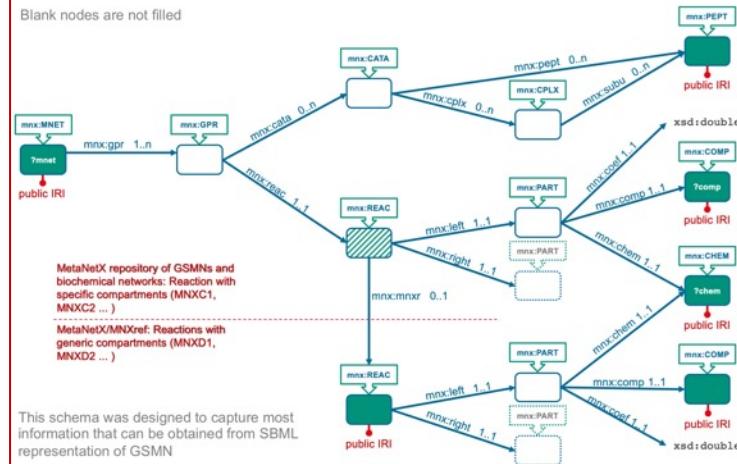
Schema overview

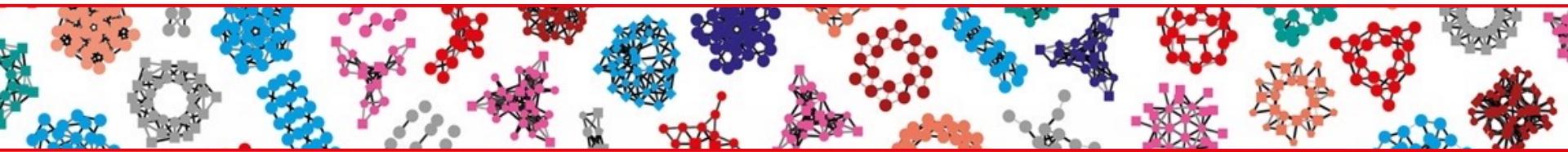
Blank nodes are not filled

MetaNetX repository of GSMNs and biochemical networks: Reaction with specific compartments (MNXC1, MNXC2 ...)

MetaNetX/MNXref: Reactions with generic compartments (MNXD1, MNXD2 ...)

This schema was designed to capture most information that can be obtained from SBML representation of GSMN





Graph diffusion

R packages from Bioconductor:

- FELLA
- diffuStats

Picart-Armada et al. *BMC Bioinformatics* (2018) 19:538
<https://doi.org/10.1186/s12859-018-2487-5>

BMC Bioinformatics

SOFTWARE

Open Access



FELLA: an R package to enrich metabolomics data

Sergio Picart-Armada^{1,2,*}, Francesc Fernández-Albert^{1,2,6}, Maria Vinaixa^{4,5}, Oscar Yanes^{4,5} and Alexandre Perera-Lluna^{1,2}

Abstract

Background: Pathway enrichment techniques are useful for understanding experimental metabolomics data. Their purpose is to give context to the affected metabolites in terms of the prior knowledge contained in metabolic pathways. However, the interpretation of a prioritized pathway list is still challenging, as pathways show overlap and cross talk effects.

Results: We introduce FELLA, an R package to perform a network-based enrichment of a list of affected metabolites. FELLA builds a hierarchical representation of an organism biochemistry from the Kyoto Encyclopedia of Genes and Genomes (KEGG), containing pathways, modules, enzymes, reactions and metabolites. In addition to providing a list of pathways, FELLA reports intermediate entities (modules, enzymes, reactions) that link the input metabolites to them. This sheds light on pathway cross talk and potential enzymes or metabolites as targets for the condition under study. FELLA has been applied to six public datasets –three from *Homo sapiens*, two from *Danio rerio* and one from *Mus musculus*– and has reproduced findings from the original studies and from independent literature.

Conclusions: The package FELLA offers an innovative enrichment concept starting from a list of metabolites, based on a knowledge graph representation of the KEGG database that focuses on interpretability. Besides reporting a list of pathways, FELLA suggests intermediate entities that are of interest per se. Its usefulness has been shown at several molecular levels on six public datasets, including human and animal models. The user can run the enrichment analysis through a simple interactive graphical interface or programmatically. FELLA is publicly available in Bioconductor under the GPL-3 license.

Keywords: Metabolomics, Pathways, Network analysis, Data mining, Knowledge representation

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Advance Access Publication Date: 5 October 2017

Applications Note

Data and text mining

diffuStats: an R package to compute diffusion-based scores on biological networks

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Original Paper

Data and text mining

The effect of statistical normalization on network propagation scores

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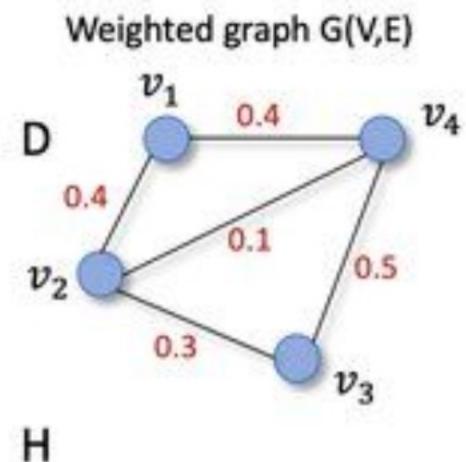
Heat diffusion on a network

v_i temperature of node i

$H_{i,j}$ thermal conductivity of edge i to j
(adjacency matrix)

l_i loss constant for node i

$$\frac{d\upsilon_i}{dt} = H_{i,j}(\upsilon_j - \upsilon_i) - l_i \upsilon_i$$



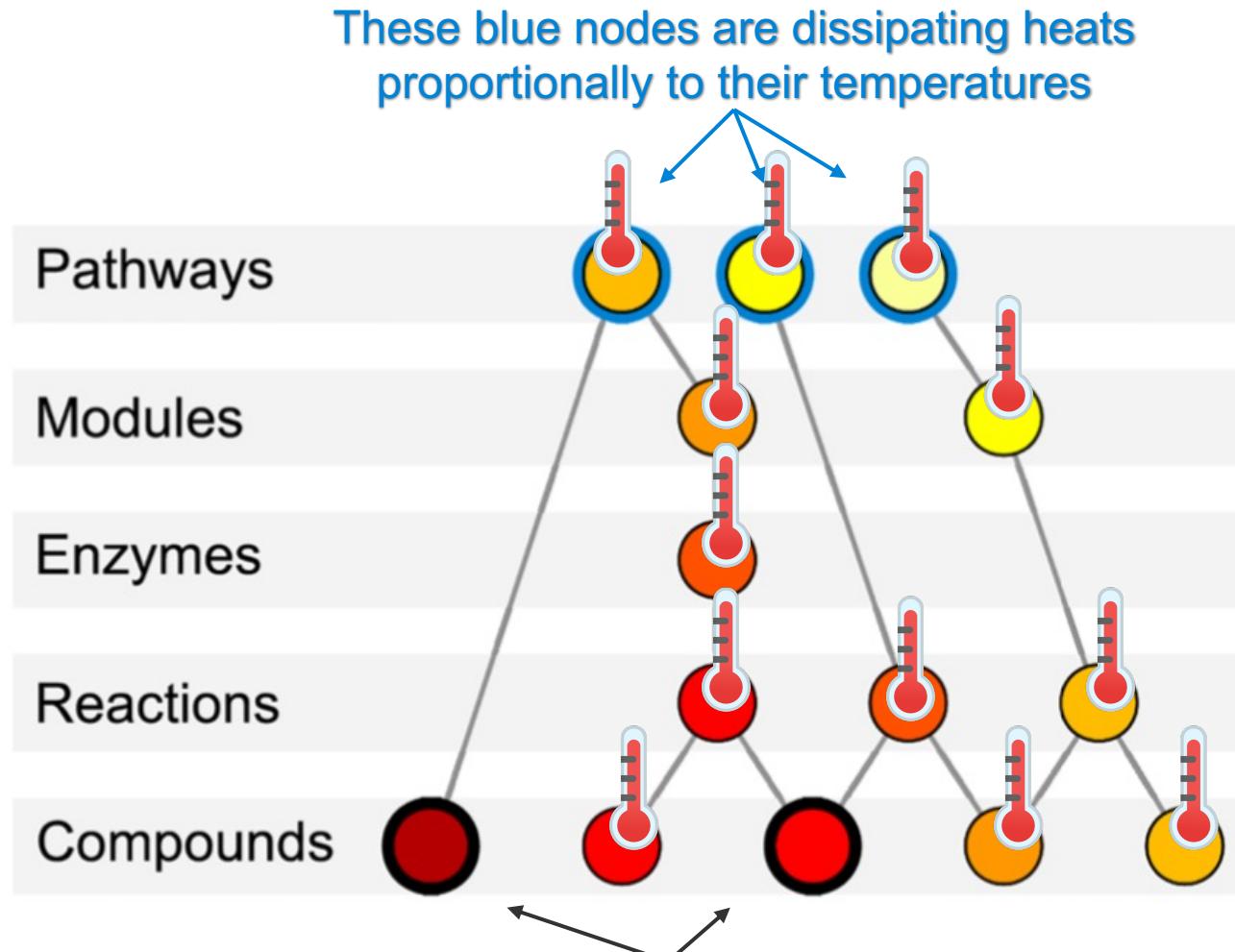
H

	v_1	v_2	v_3	v_4
v_1	0	0.4	0	0.4
v_2	0.4	0	0.3	0.1
v_3	0	0.3	0	0.5
v_4	0.4	0.1	0.5	0

More about the mathematics of diffusion on a graph,
including the definition of Laplacian at

<https://www.math.fsu.edu/~bertram/lectures/Diffusion.pdf>

FELLA principle



These black nodes belong to the observed metabolite universe . They are given a fixed temperature. For example, the metabolite that belong to a particular WGCNA module are given a temperature to 1° and all the others are set to 0°

Diffusion statistics principle

Random perturbations of the fixed input temperatures. Diffusion to steady state and estimation the mean and standard deviation of temperature for every node in the network

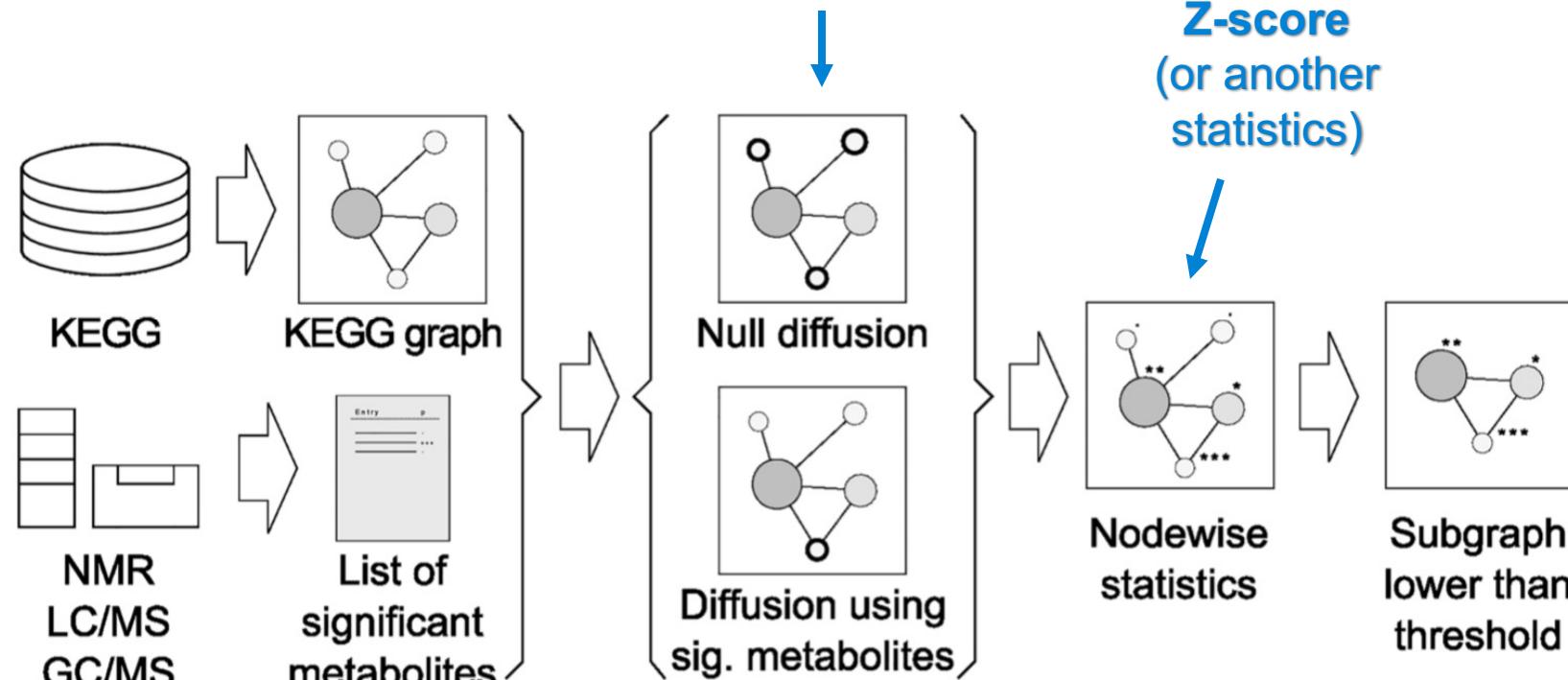


Fig 1. Workflow summary. Contextual knowledge is extracted from KEGG as a graph object while experimental data is introduced as a list of affected metabolites. A null diffusive model assesses, and reports in a subgraph, which part of the KEGG graph is relevant for the input metabolites.

FELLA / DiffusStats comes with a fast method to compute means and standard deviations, in addition to the standard permutation simulation

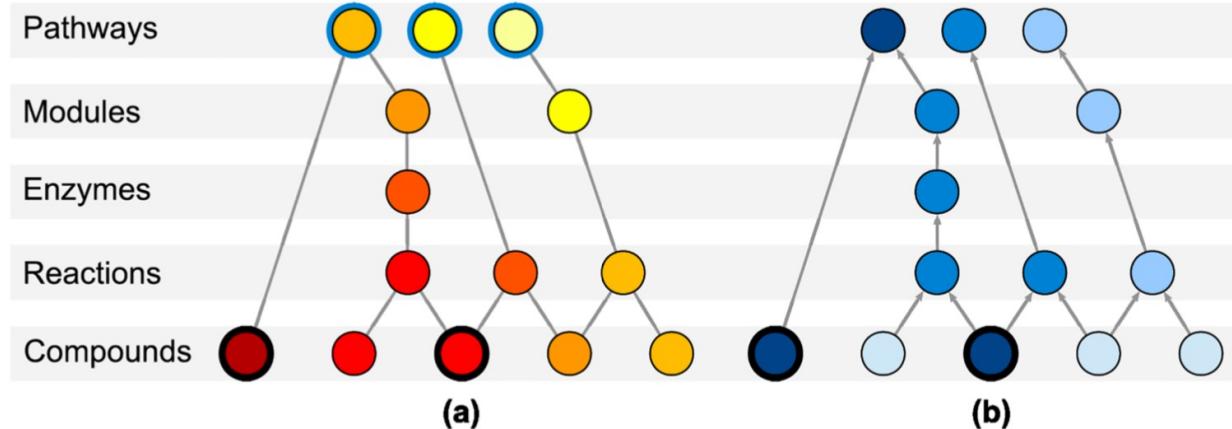


Fig 2. Nodes arrangement for (a) heat diffusion and (b) PageRank. The affected metabolites are highlighted with a black ring. For heat diffusion **(a)**, affected metabolites are forced to generate unitary flow. Every pathway is highlighted with a blue ring, representing its connection to a cool boundary node. In equilibrium, the highest temperature pathways (and nodes) will have the greatest heat flow, suggesting a relevant role in the experiment. For PageRank **(b)**, affected metabolites are the start of random walks. PageRank scores, represented by the intensity of the blue colour, will attain higher values in the frequently reached random walk nodes.

<https://doi.org/10.1371/journal.pone.0189012.g002>

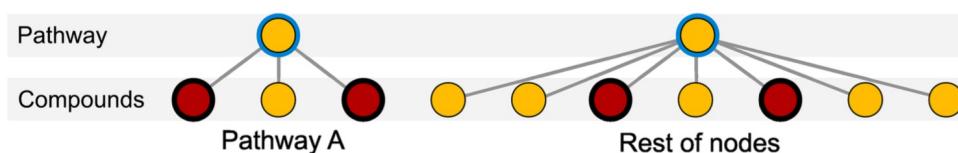


Fig 3. Toy example of an over-representation analysis of a hypothetical “pathway A” containing 3 metabolites out of a total of 10. The list to be enriched contains 4 metabolites, showing 2 hits in the pathway. The corresponding (Fisher’s exact test) over-representation can be understood as a diffusion process on the depicted network followed by a null model. The temperature of pathway A is always coincident with the number of hits in the pathway, implying that its null distribution is the hypergeometric distribution, to which a one-tailed temperature comparison is made.

<https://doi.org/10.1371/journal.pone.0189012.g003>

Applications / limitations

Diffusion statistics advantages:

- works on (weighted) undirected network of any topology
- scales easily up to 20'000 nodes and any number of edges
- diffuStats implementation of Z-score computation run fast with a single set of observations

Limitations:

- only one type of edge
- no directionality or logical constraint can be expressed
- multiple sets of observations can possibly be investigated with the much slower monte-Carlo algorithm (I have not yet tested it)