Norwegian University of Technology and Sciences

MICAST, Minimum Information about a Causal Statement

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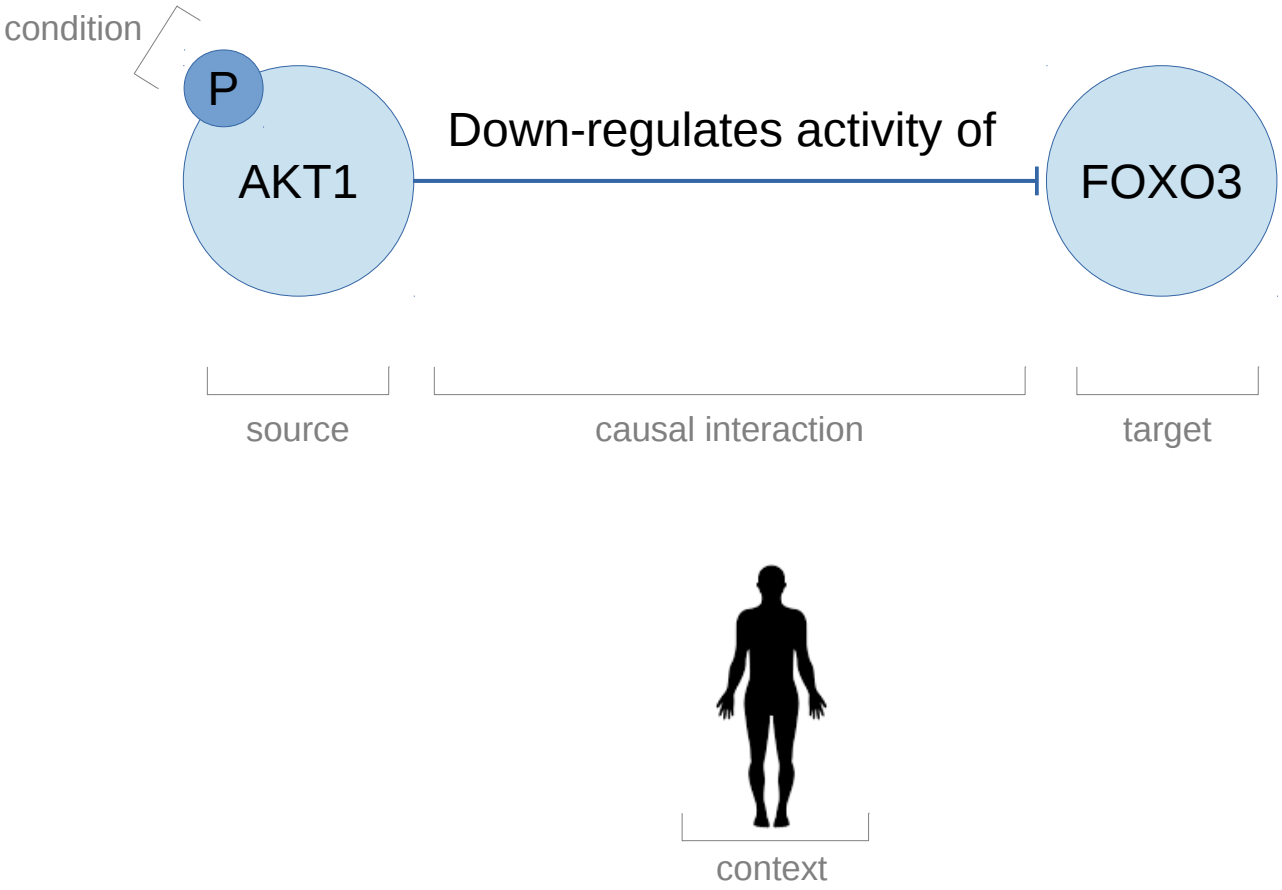
What is a causal statement?

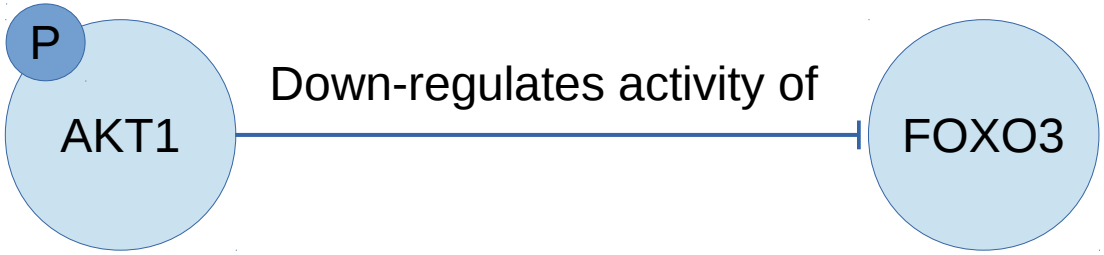
Causal interaction between biological entities (gene, RNA, protein, etc…)



How to encode context and conditions?

What is FOXO3's state?

Which function
is down-regulated?



When and where does
this interaction occurs?

Is it a direct or indirect
Interaction?

Overview: how is causality handled today?

MITAB2.7 format – with causality annotations

ID(s) interactor A

Alt. ID(s) interactor A

Alias(es) interactor A

Taxid interactor A

Biological role(s) interactor A

Experimental role(s) interactor A

Type(s) interactor A

Xref(s) interactor A

Annotation(s) interactor A

Feature(s) interactor A

Checksum(s) interactor A

Stoichiometry(s) interactor A

Identification method participant A

Note: Same columns for interactor B

Interaction type(s)

Interaction identifier(s)

Interaction annotation(s)

Interaction parameter(s)

Interaction Checksum(s)

Negative

Interaction Xref(s)

Interaction detection method(s)

Publication 1st author(s)

Publication Identifier(s)

Expansion method(s)

Confidence value(s)

Host organism(s)

Creation date

Update date

Source database(s)

causality statement:"\"CHEBI:16412 increases expression at protein level of Q9UNE7

Overview: how is causality handled today?

Example of MITAB support: IntAct database

Id molecule A	Id molecule B	Interaction Annotations
ENSG00000126581	P40763	**figure legend**:Fig. 3d; **agonist**:"Interleukin-6 (IL-6)"; **causality statement**:P40763 decreases expression at RNA level of ENSG00000126581; **causality statement**:P40763 decreases expression at protein level of ENSG00000126581; **comment**:"While this interaction involves human Stat3 protein, the causality between Stat3 and Beclin-1 gene expression is inferred from experiments in human cells using a constitutively active mouse Stat3 mutant, which is described in more detail in PMID:10458605 and PMID:19345327."; **dataset**:IBD - Inflammatory bowel disease; **full coverage**:Only protein-protein interactions; **curation depth**:imex curation [-]
ENSG00000112715	P16220	**figure legend**:5B; **causality statement**:P06850 increases the expression at protein level of ENSG00000112715; **causality statement**:Q969E3 increases the expression at protein level of ENSG00000112715; **causality statement**:CHEMBL296641 inhibits the Q969E3 and P06850 induced increase in expression at protein level of ENSG00000112715; **causality statement**:"CHEBI:90229 inhibits the Q969E3 and P06850 induced increase in expression at protein level of ENSG00000112715"; **causality statement**:P34998 increases the expression at RNA level of ENSG00000112715; **causality statement**:Q13324 increases the expression at RNA level of ENSG00000112715; **causality statement**:Q13324 increases the expression at protein level of ENSG00000112715; **causality statement**:P34998 increases the expression at protein level of ENSG00000112715; **causality statement**:"CHEBI:64211 increases the expression at protein level of ENSG00000112715"; **causality statement**:"CHEBI:90232 inhibits the Q969E3 and P06850 induced increase in expression at protein level of ENSG00000112715"; **causality statement**:"CHEBI:90232 inhibits the Q13324 induced increase in expression at protein level of ENSG00000112715"; **causality statement**:"CHEBI:90232 inhibits the P34998 induced increase in expression at protein level of ENSG00000112715"; **causality statement**:Q969E3 increased the expression at protein level of P16220; **causality statement**:P06850 increased the expression at protein level of P16220; **dataset**:IBD - Inflammatory bowel disease; **full coverage**:Only protein-protein interactions; **curation depth**:imex curation [-]

Currently 1,019 binary interactions

Overview: how is causality handled today?

CausalTAB format – extension as MITAB2.8 for causality representation

→ Directed interactions!

ID(s) interactor A

Alt. ID(s) interactor A

Alias(es) interactor A

Taxid interactor A

Biological role(s) interactor A

Experimental role(s) interactor A

Type(s) interactor A

Xref(s) interactor A

Annotation(s) interactor A

Feature(s) interactor A

Checksum(s) interactor A

Stoichiometry(s) interactor A

Identification method participant A

Note: Same columns for interactor B

Interaction type(s)

Interaction identifier(s)

Interaction annotation(s)

Interaction parameter(s)

Interaction Checksum(s)

Negative

Interaction Xref(s)

Interaction detection method(s)

Publication 1st author(s)

Publication Identifier(s)

Expansion method(s)

Confidence value(s)

Host organism(s)

Creation date

Update date

Source database(s)

Biological Effect interactor A

Biological Effect interactor B

Causal statement

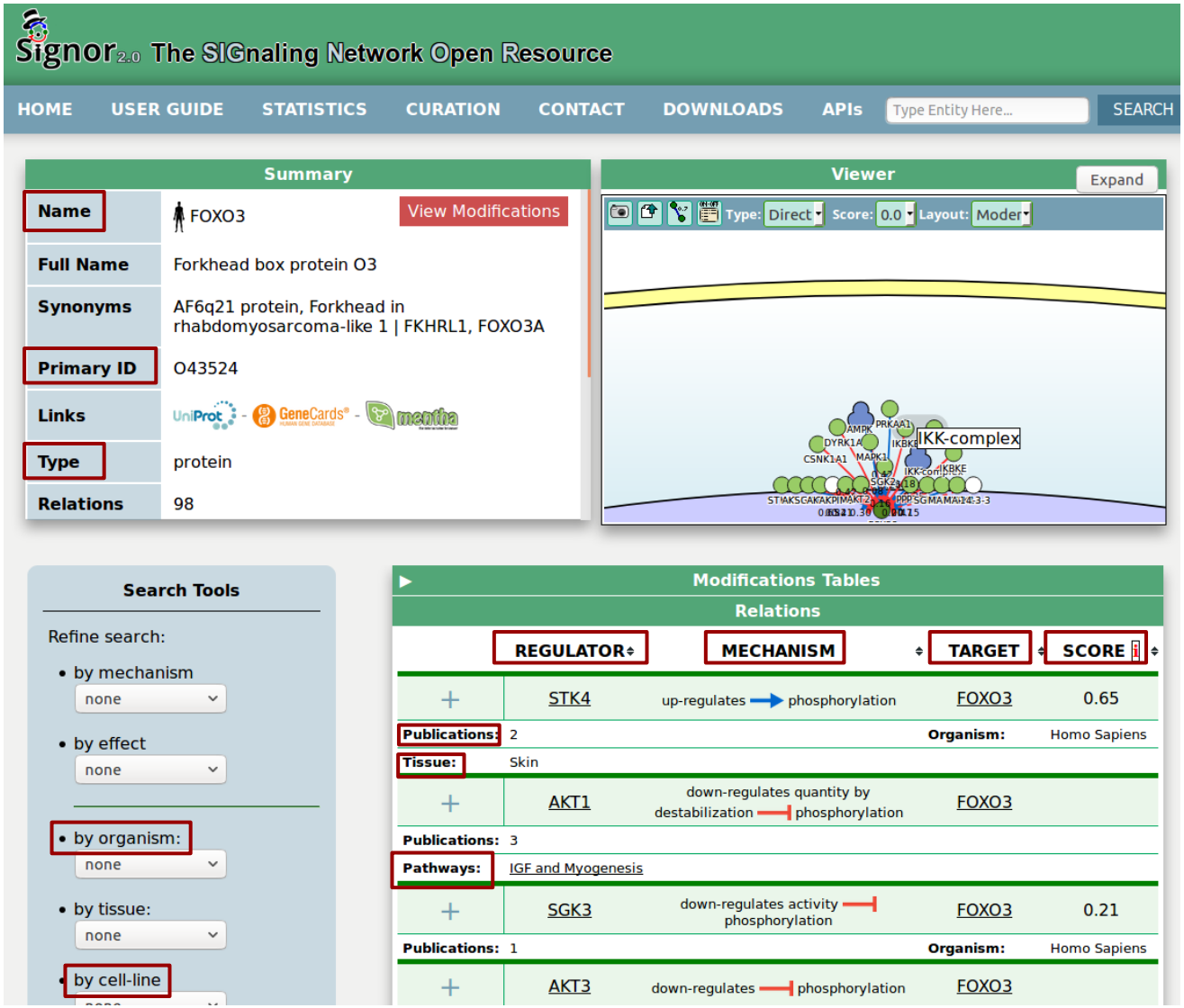
Causal regulatory mechanism

Overview: how is causality handled today?

Example of causalTAB support: Signor database

Name
Primary ID
Type

Tissue
Organism
Cell line



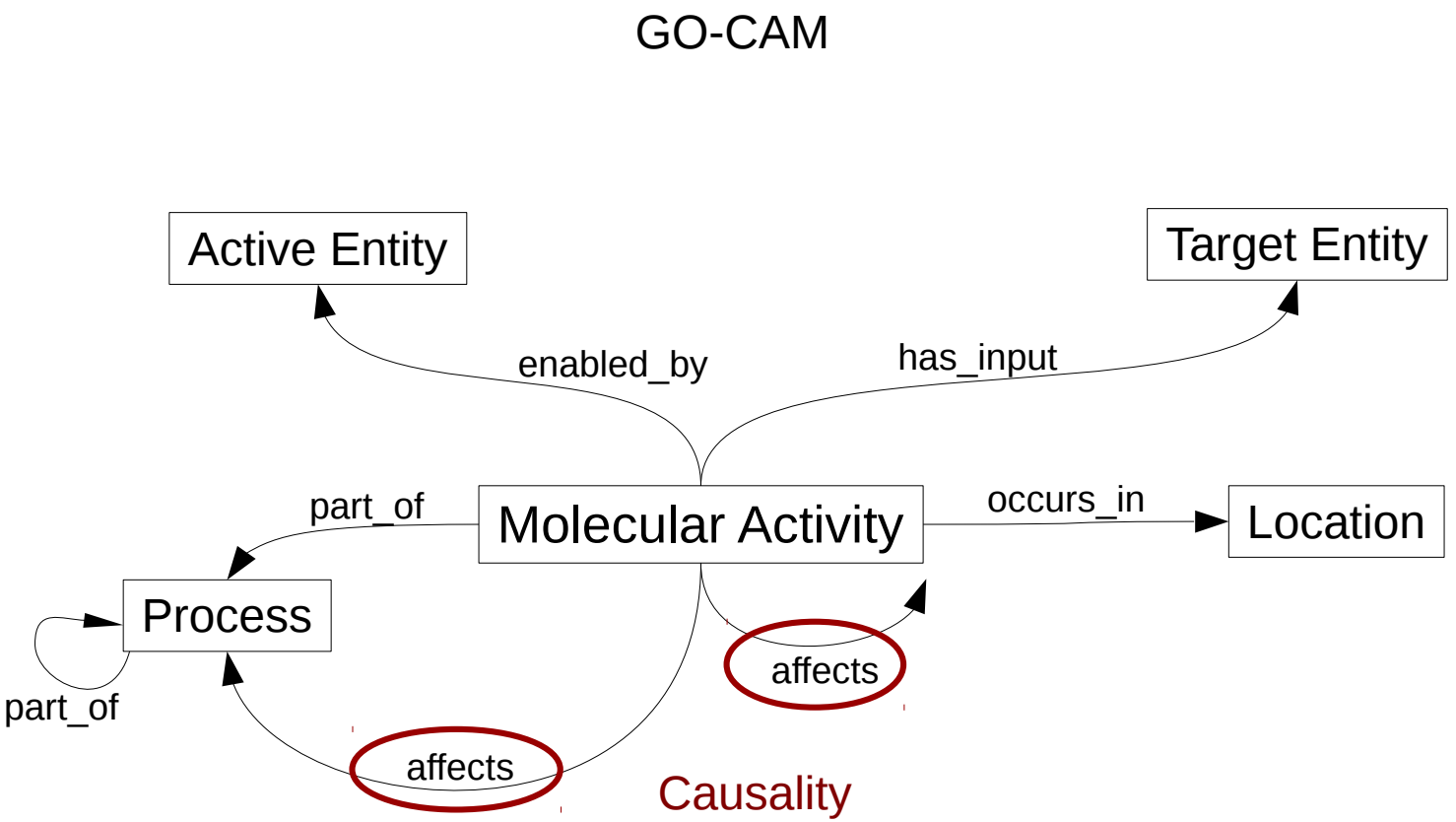
Regulator
Mechanism
Target
Score

Publication

Overview: how is causality handled today?

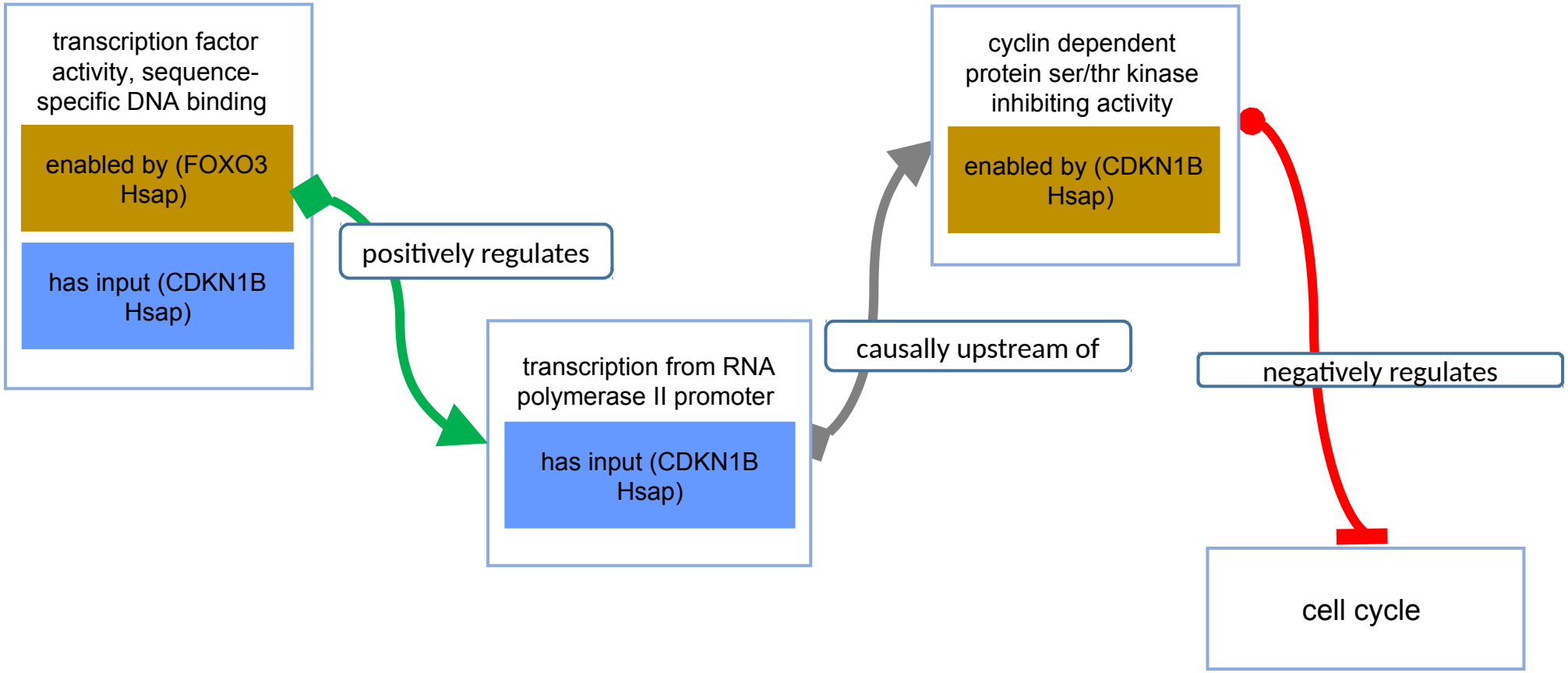
Gene Ontology - Causal Activity Model

GO: Molecular Function (MF), Cellular Component (CC), Biological Process (BP)



Overview: how is causality handled today?

Noctua



Overview: how is causality handled today?

BEL format – biological cause and effect relationships

BEL statement **p(HGNC:MAP3K1,pmod(P,S,994)) directlyIncreases kin(p(HGNC:MAP3K1))**

Subject

Predicate
= causal interaction

Object

BEL terms contains BEL functions

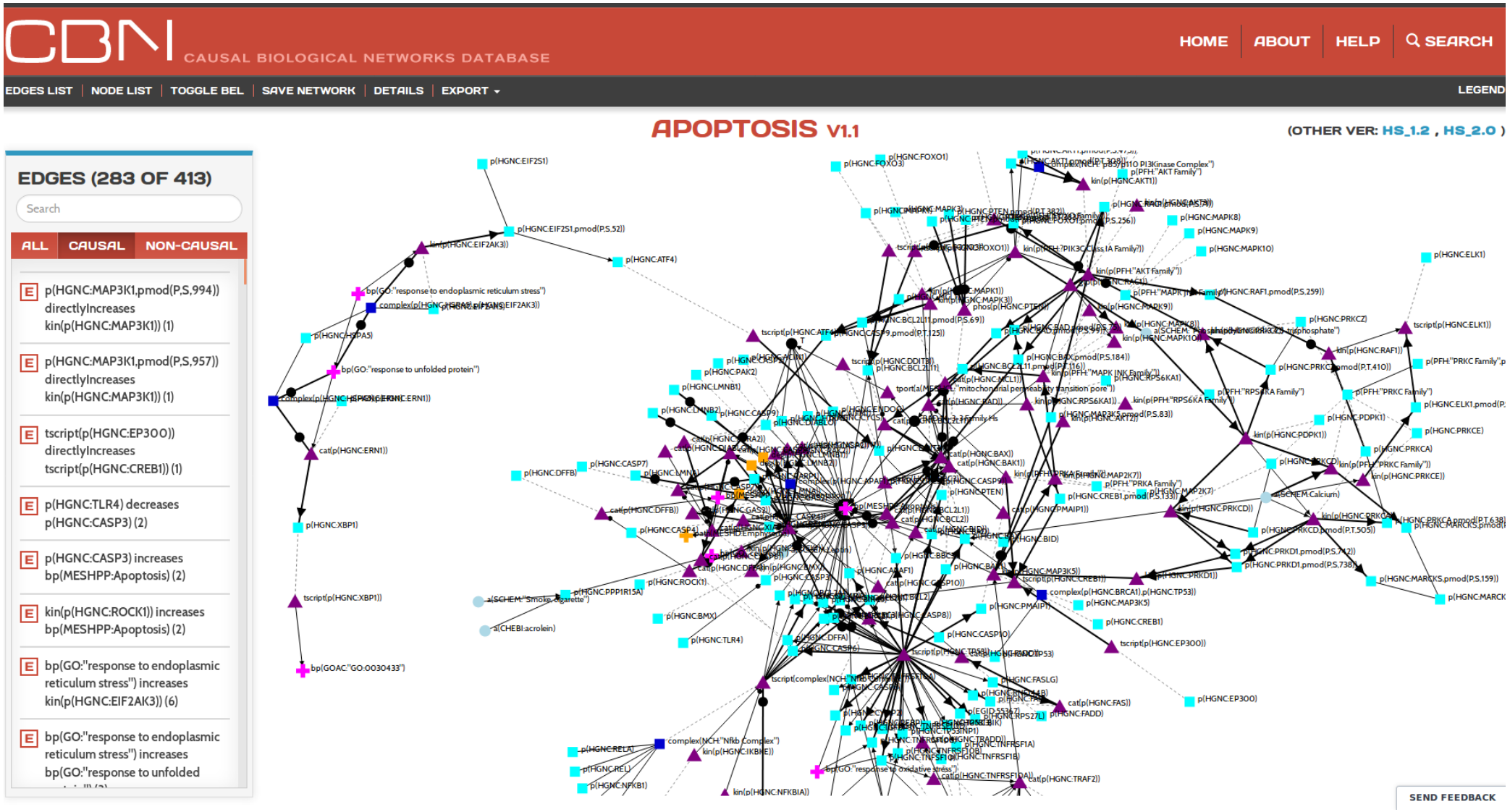
BEL annotations provide context:
Citation (Pubmed ID)
Evidence
Experimental context
Cell line, Species, Disease
etc…

pmod: protein modification
p: protein abundance
kin: kinase activity

Overview: how is causality handled today?

Causal Biological Networks

Example of BEL support: CBN database

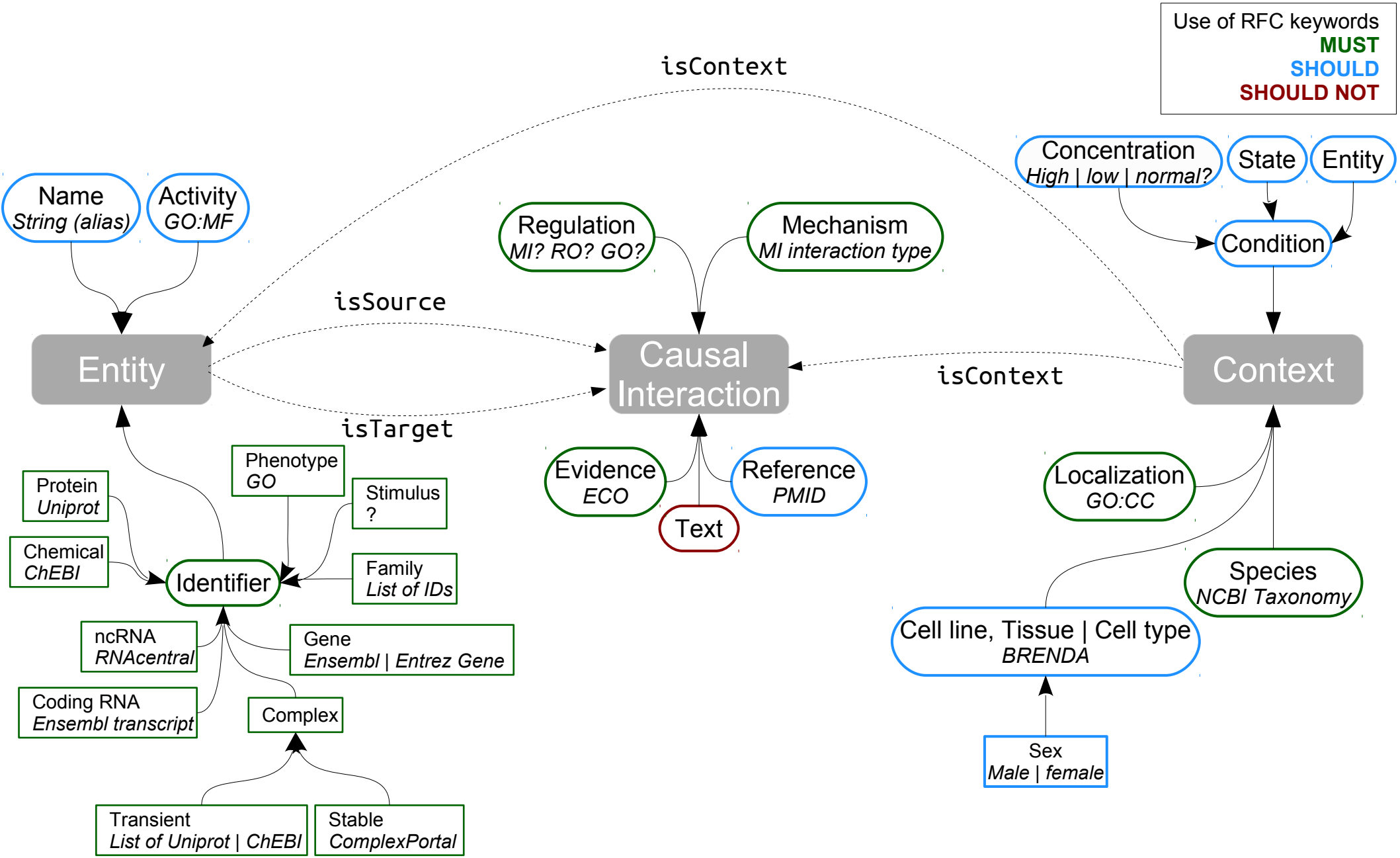


Summary: current state of causality

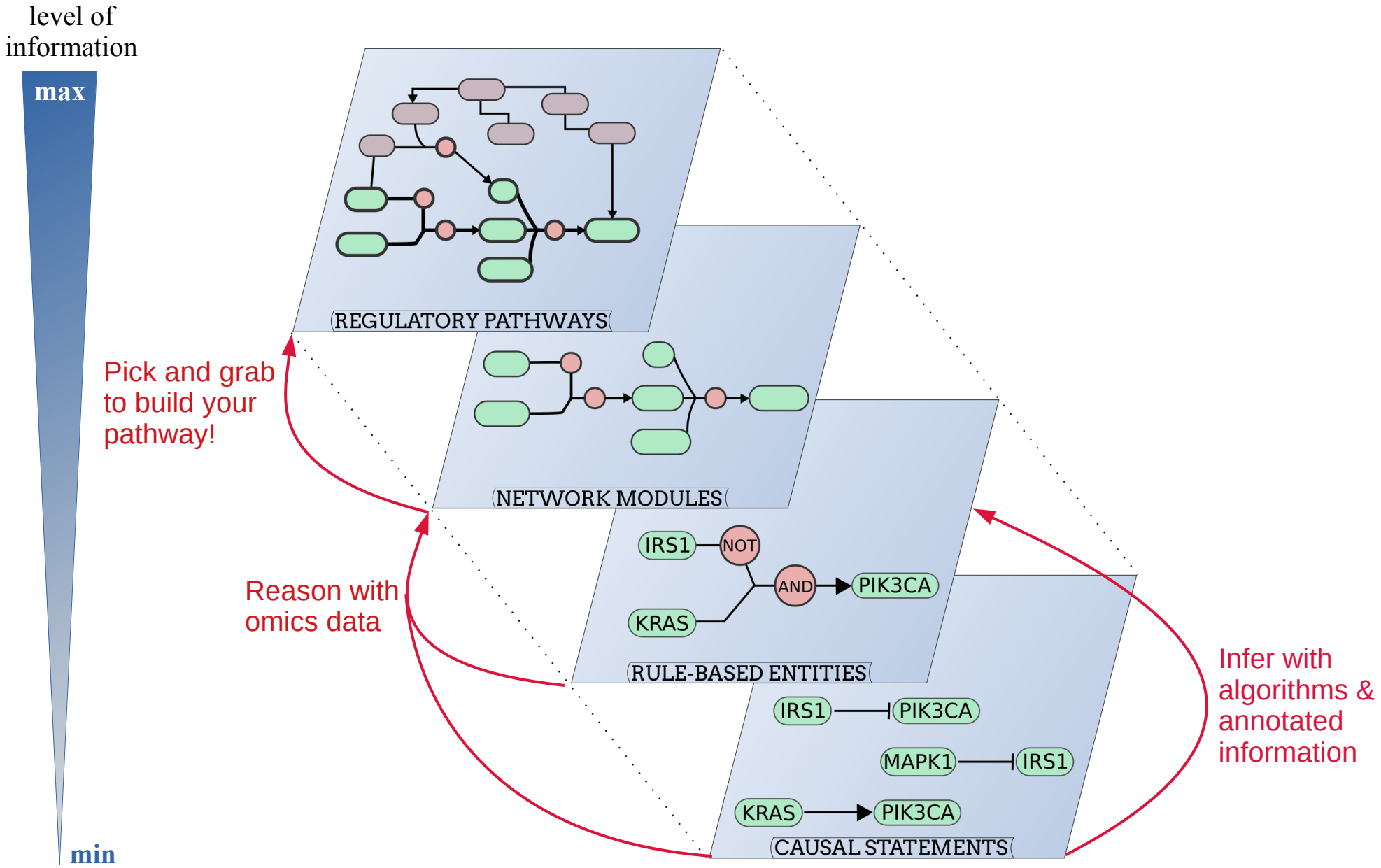
	Entities Identifiers	Causality annotation	Evidence	Format
MITAB2.7	Entrez gene/Ensembl embl/ddbj/genbank UniProtKB/RefSeq ChEBI	**Free text** "causality statement:..."	PUBMED	tabular
Causaltab	Embl/ddbj/genbank UniprotKB/RefSeq ChEBI/PubChem ComplexPortal Signor_ID	**MI – causal interaction** "up-regulates" "down-regulates"…	PUBMED	tabular
GO-CAM	Gene symbols UniprotKB ChEBI	**Relation Ontology** "activity directly positively regulates activity of"	PUBMED ECO	OWL
BEL	HGNC	"decreases", "increases"…	Text with ontologies	BEL script, JSON

Necessity of unification!

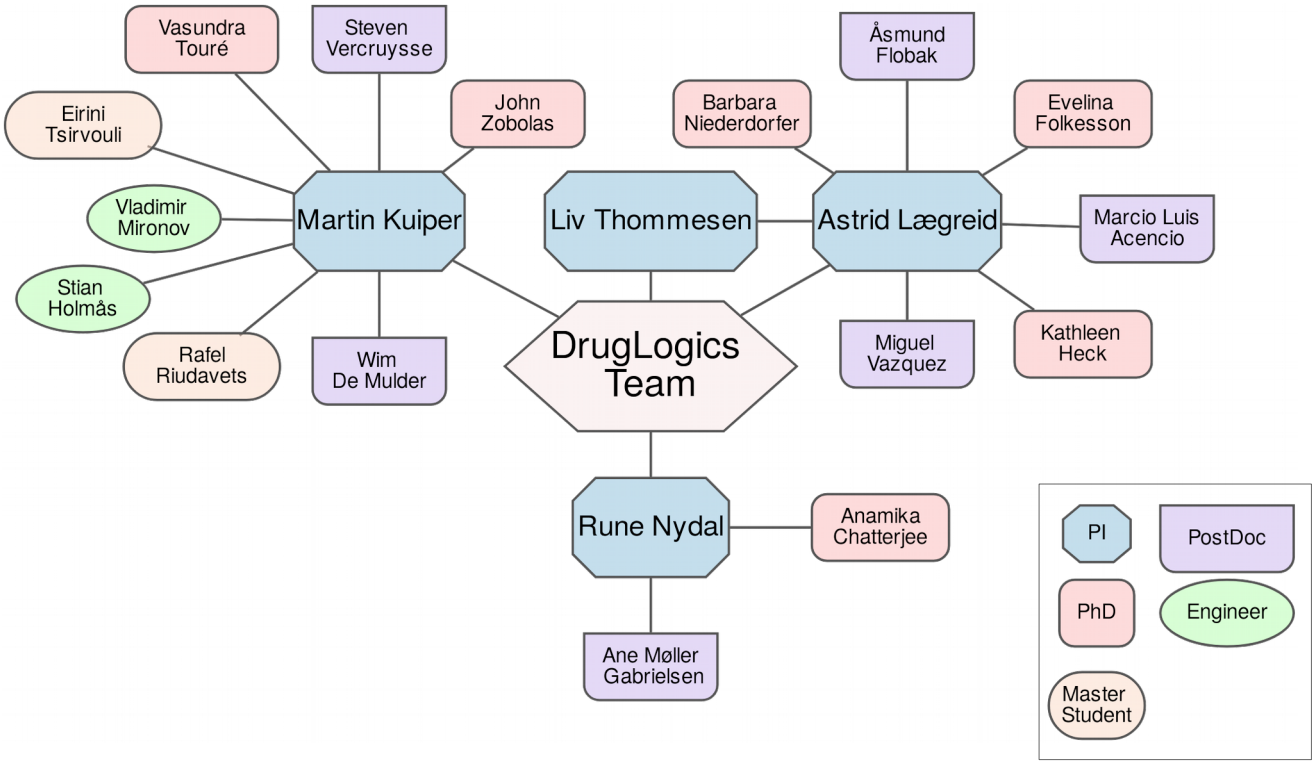
Minimum Information about a Causal Statement



Defining levels of abstraction



Thank you for your attention!



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