MICAST, Minimum Information for Causality Statement

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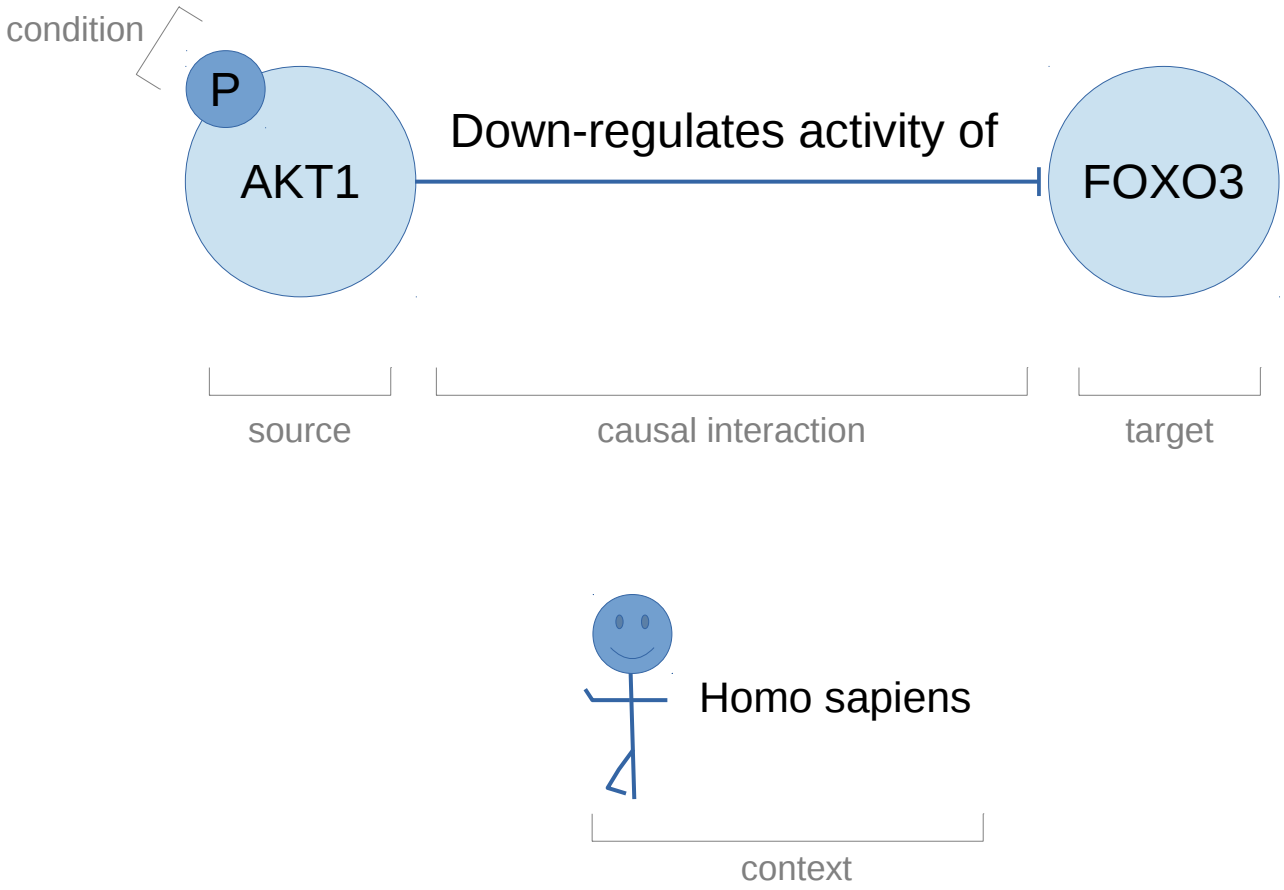
What is a causal statement?

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

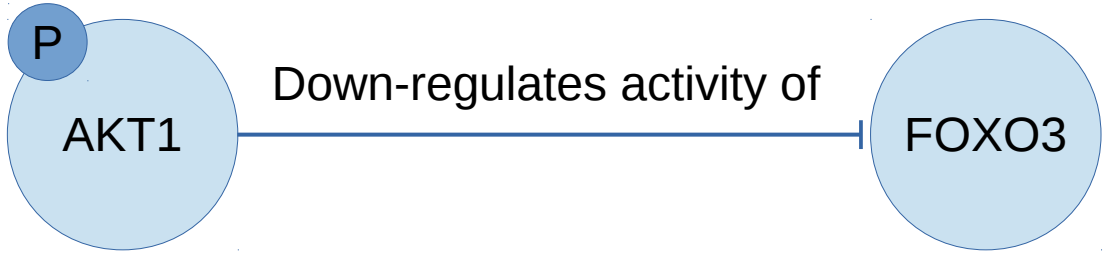


How to encode context and conditions in causal statements?

What is FOXO3's state?

When and where does this interaction occurs?

Which molecular function is down-regulated?



What is the regulation type?

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

Biological Effect 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

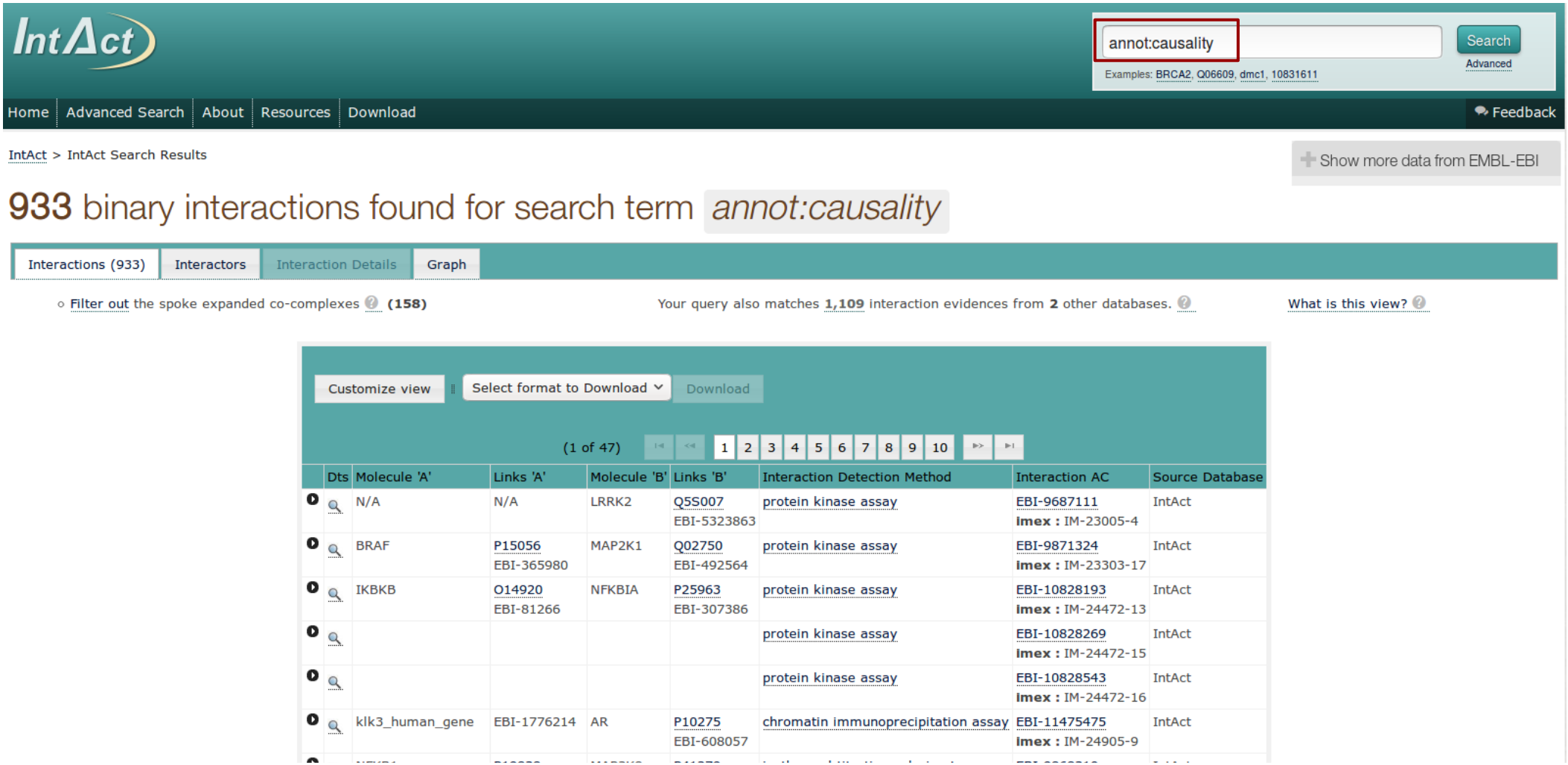
Update date

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



Overview: how is causality handled today?

CausalTAB format – extension of MITAB for causality representation

ID(s) interactor A

Alt. ID(s) interactor A

Alias(es) interactor A

~~Biological Effect 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)

\+

Causal statement

Causal regulatory mechanism

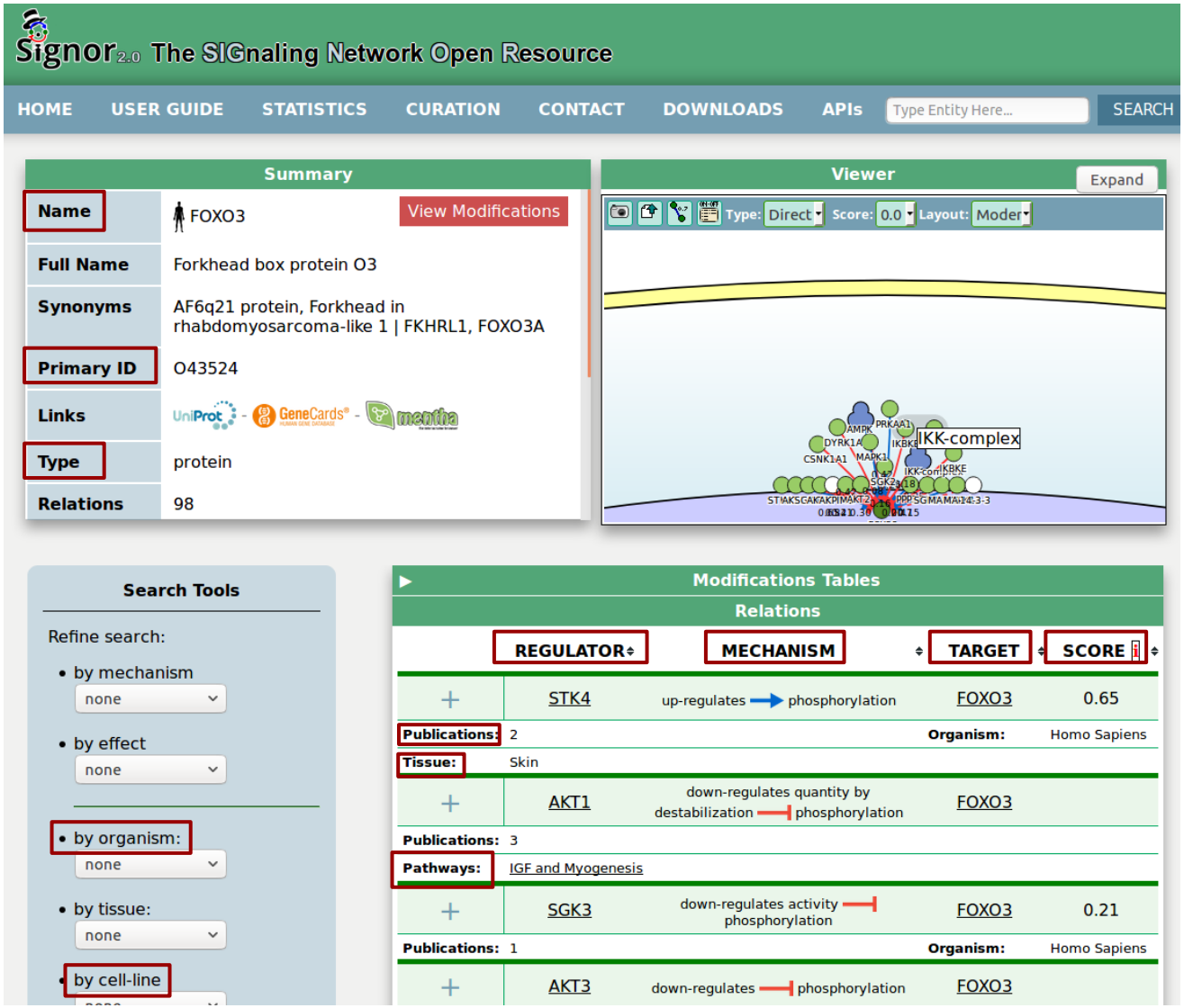
→ Directed interactions!

Overview: how is causality handled today?

Example of causalTAB support: Signor database

Name
Primary ID
Type

Tissue
Organism
Cell line



Regulator
Mechanism
Target
Score

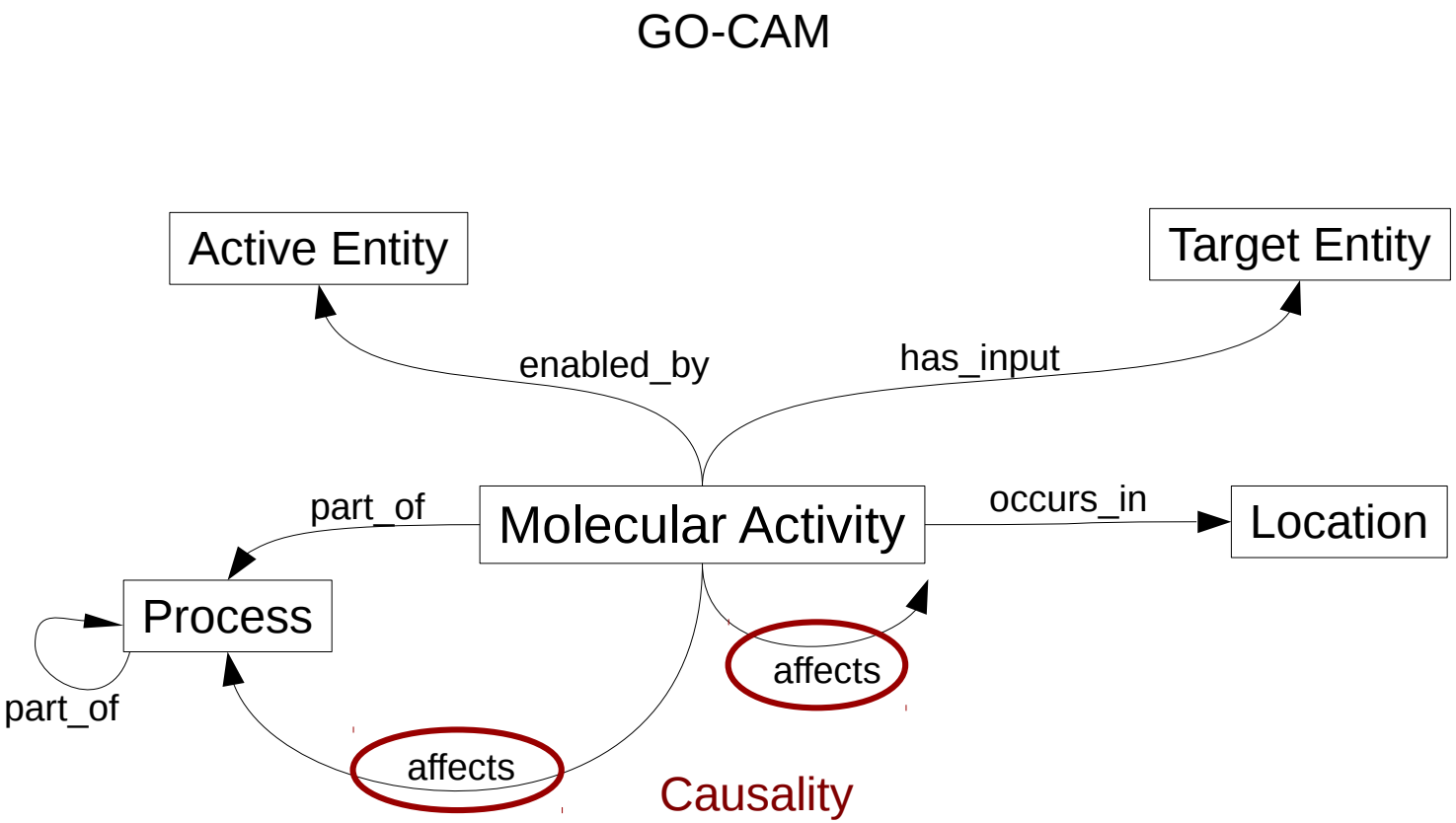
Publication

Overview: how is causality handled today?

GO-CAM

Gene Ontology - Causal Activity Model

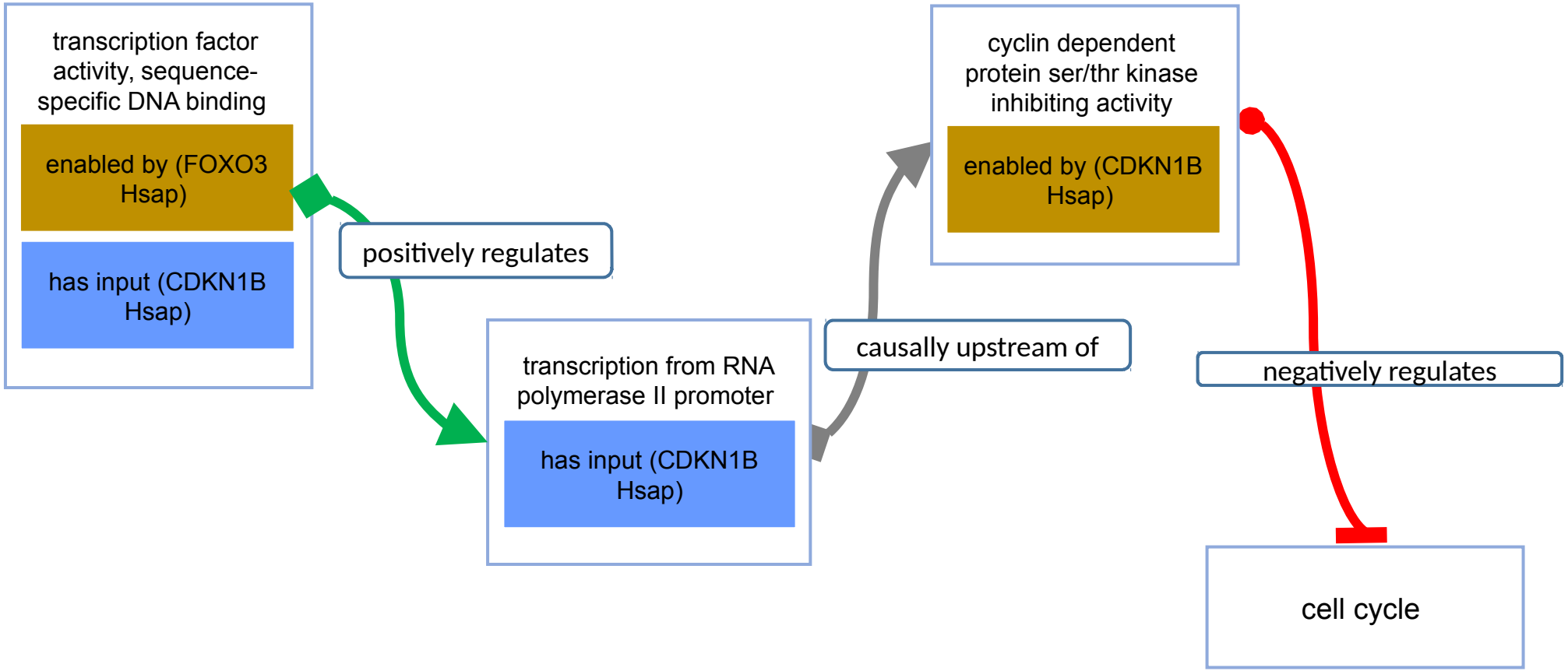
GO: Molecular Function (MF), Cellular Component (CC), Biological Process (BP)



LEGO (Logical Extension of the Gene Ontology) model

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

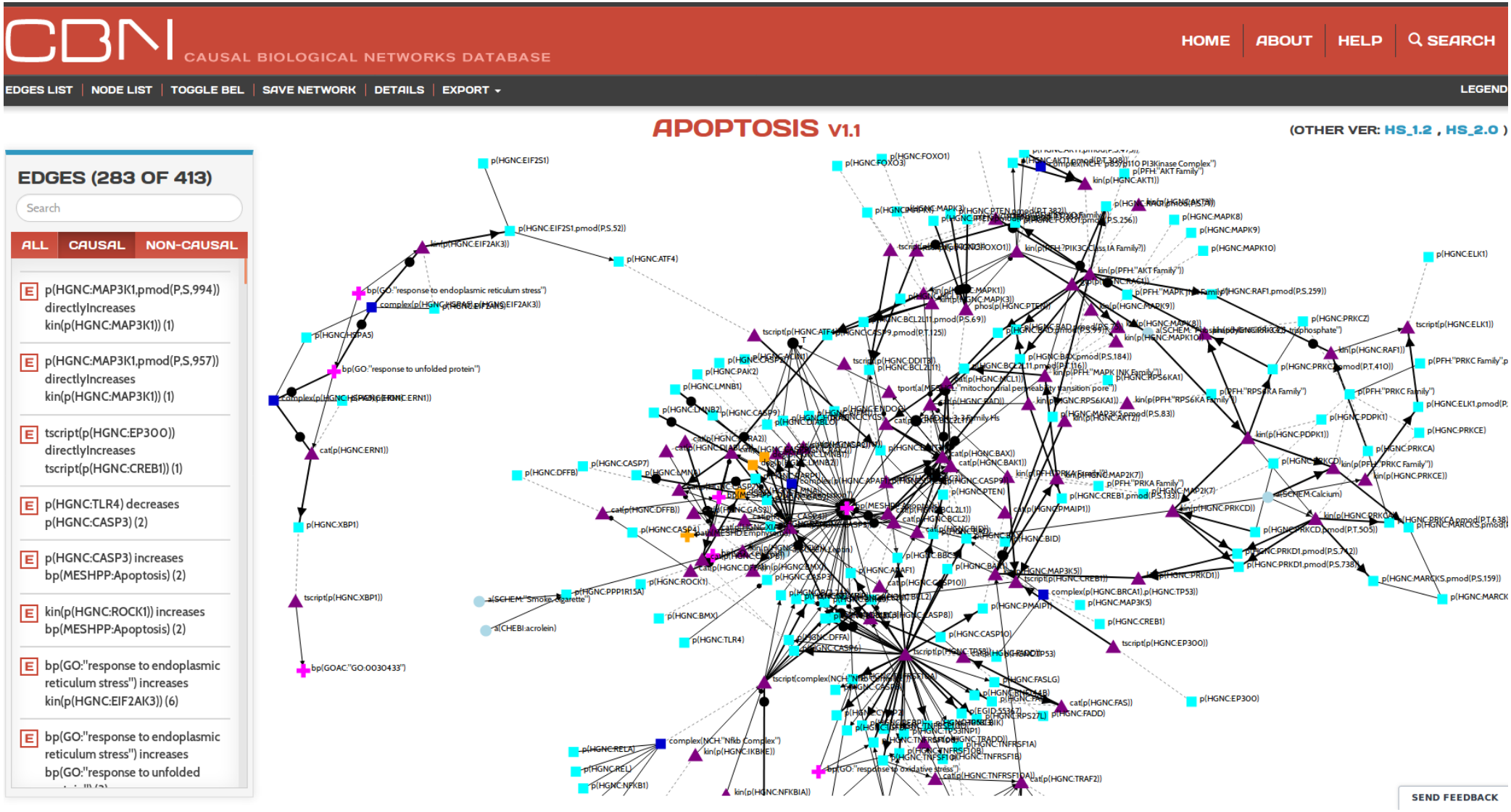
BEL annotations provide context:
Citation (Pubmed ID)
Evidence
Experimental context
Cell line, Species, Disease
Anatomy
etc…

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

Overview: how is causality handled today?

Causal Biological Networks

Example of BEL support: CBN database



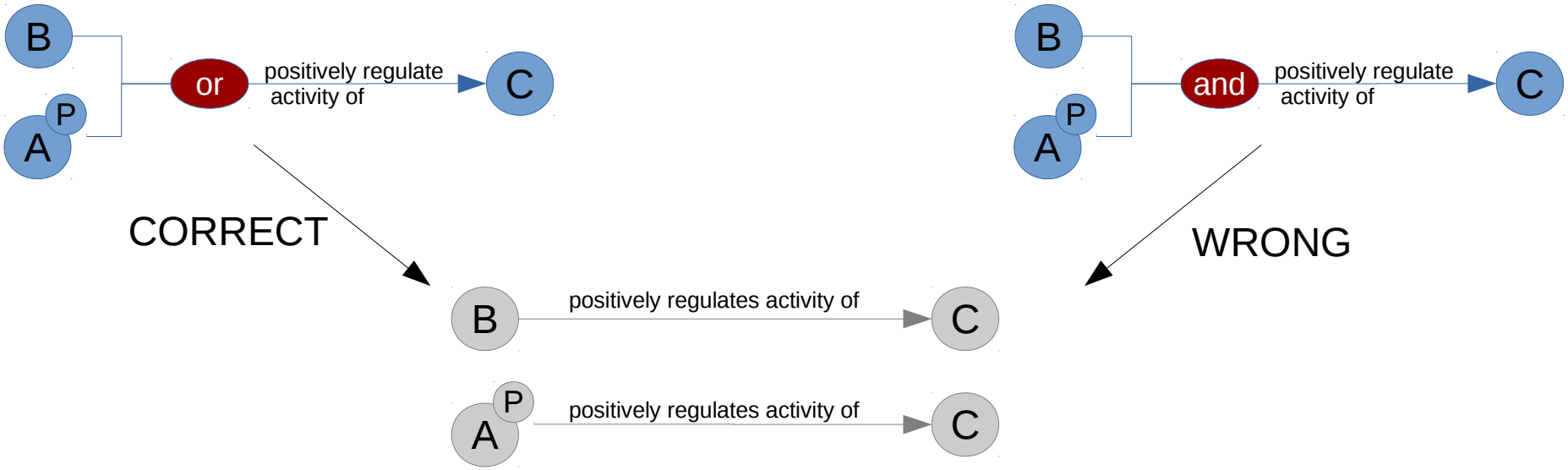
Summary: current state of causality

	Entities Identifiers	Directed	Causality annotation	Evidence	Format
MITAB2.7	Entrez gene/Ensembl embl/ddbj/genbank UniProtKB/RefSeq ChEBI	no	Free text: “causality statement:...”	PUBMED	tabular
Causaltab	Embl/ddbj/genbank UniprotKB/RefSeq ChEBI/PubChem ComplexPortal Signor_ID	yes	MI – causal interaction	PUBMED	tabular
GO-CAM	Gene symbols UniprotKB ChEBI	yes	Relation Ontology	PUBMED ECO	OWL
BEL	Mainly HGNC but flexible	yes	Own representation	Text with ontologies	BEL script, JSON

Necessity of unification or mapping

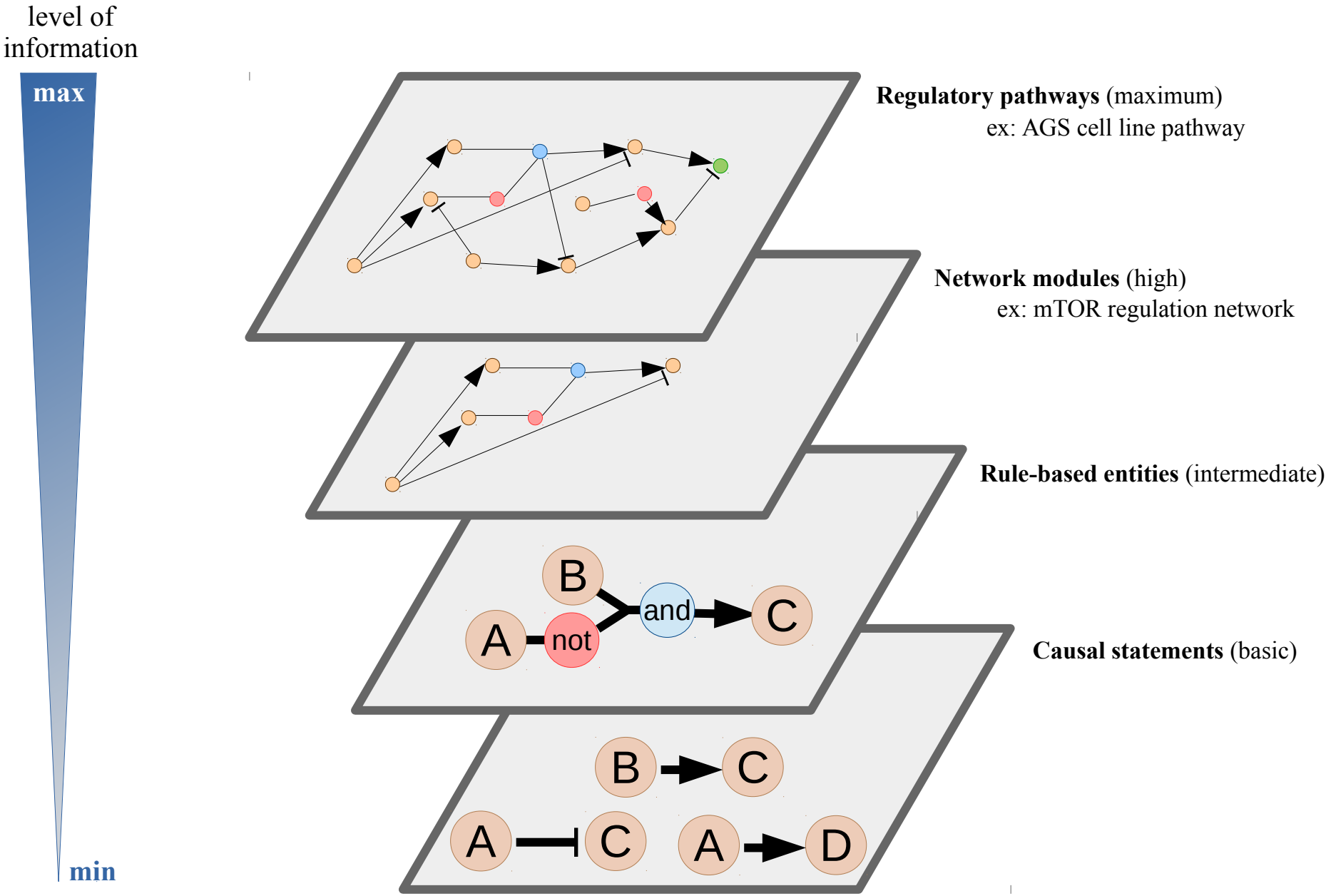
What is missing?

1) Multi-regulated causal interaction



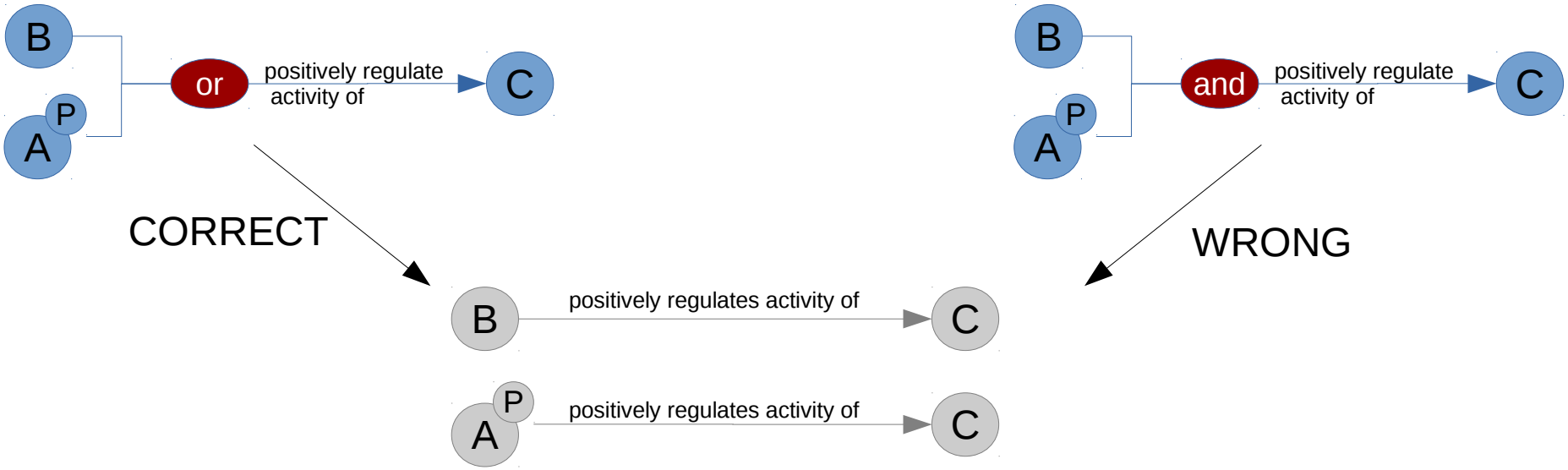
→ introduce logics in formats
→ define levels of abstraction

Defining levels of abstraction

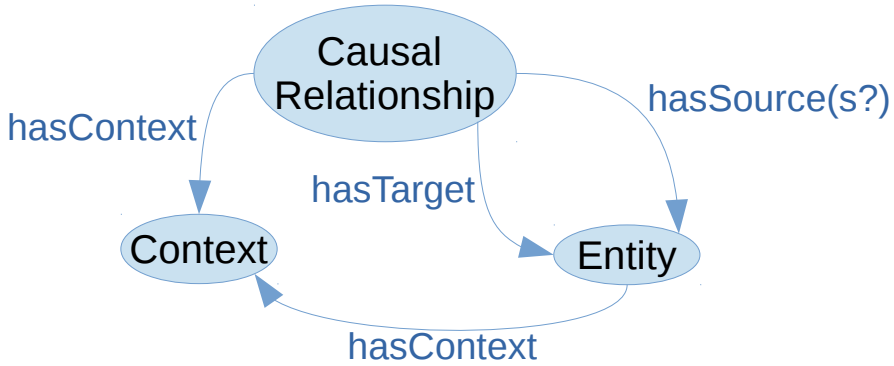


What is missing?

1) Multi-regulated causal interaction → introduce logics in formats



2) Common structure for representing causality
→ Guideline for representing causality
Frame for defining context
Ontologies recommendation



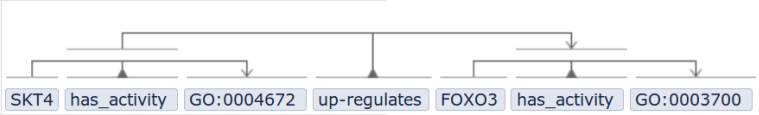
Minimum Information for Causality Statements

Mandatory

Example

Causal Relationship		
Regulation	RO? MI? BEL?	up-regulation
Mechanism	PSI-MOD	Phosphorylation, binding
Evidence	ECO	ECO:0000085: immuno-precipitation evidence
Reference	PubMed	22898666
Confidence	IntAct miscore	0.65
Text	Scicura http://scicura.org/info.html	

Entity		source	target
Identifiers	Follow MIMIx requests	Q13043	O43524
Type	SBO	0000245	0000245
Activity (MF involved)	GO:MF	0004672	0003700
Name	HGNC	STK4	FOXO3



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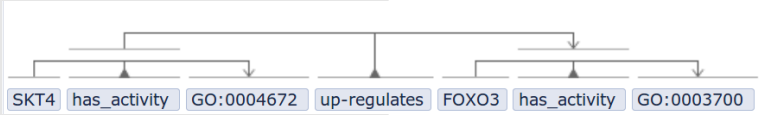

Context Causal Relationship			
Biological observation	Species	NCBI TaxID	9606
	Tissue type	BTO, Uberon	-
	Cell type	BTO, CLO	BTO_0000782
State	Tissue state	?	-
	Cell state	?	Apoptotic, s-phase
Experiment-al condition	?	?	?

Minimum Information for Causality Statements

Mandatory

Example

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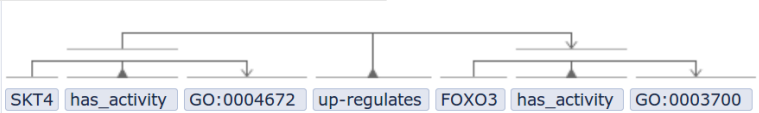

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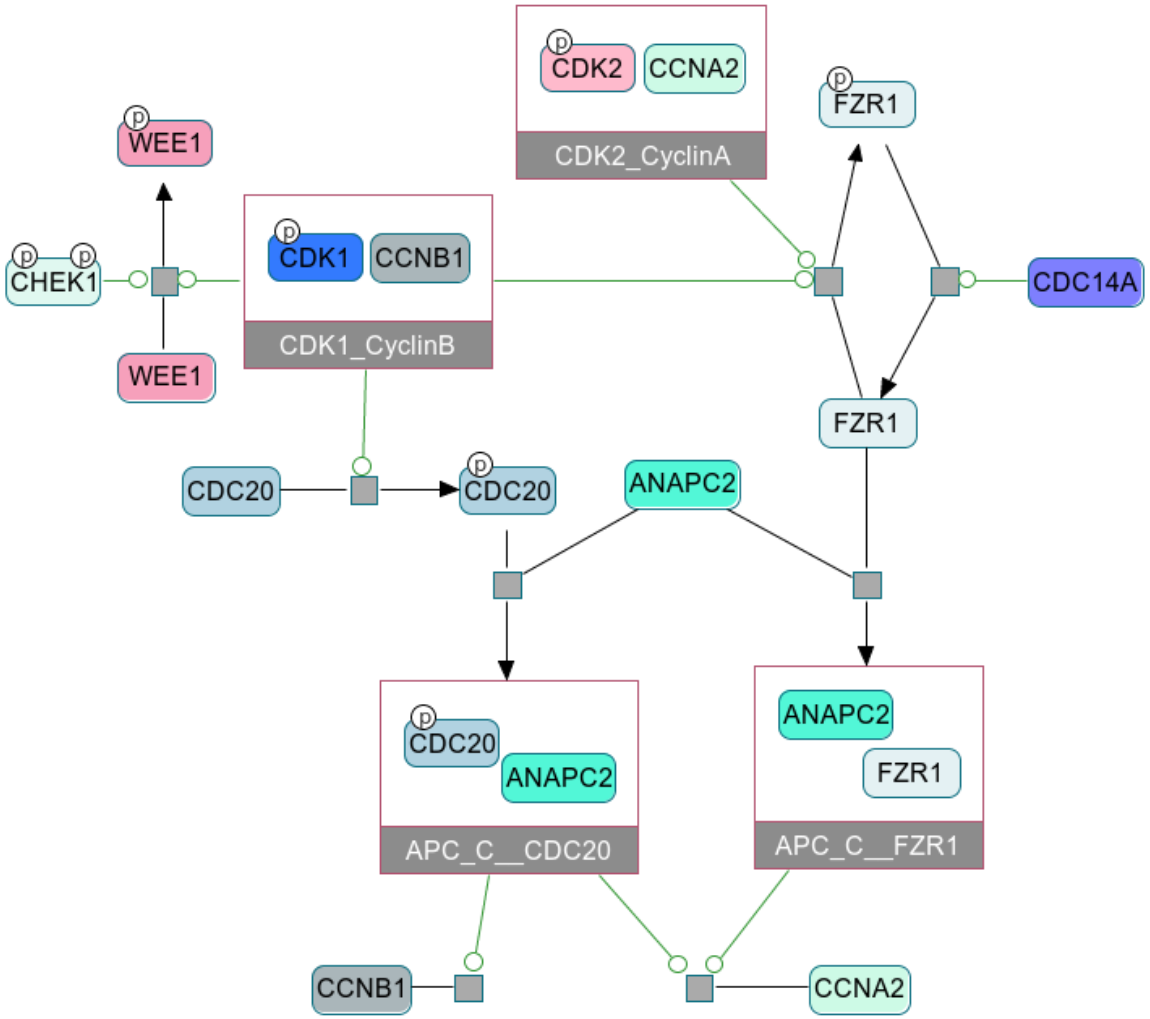
State	Tissue state	?	-
	Cell state	?	Apoptotic, s-phase
Experiment-al condition	?	?	?

Context Entity		source
Concentration/Level	Number or range	High, low
State	?	Active, phosphorylated
Compartment	GO	0005829

MICAST: example of use cases

Manual inference of causal interactions from the Cell Cycle – APC module in ACSN



List of causal interactions:

CDK2_CyclinA -| FZR1

CDK1_CyclinB -| FZR1

CDC14A -> FZR1

APC_C_CDC20 -| CCNA2

APC_C_FZR1 -| CCNA2

APC_C_CDC20 -| CCNB1

CDK1_CyclinB -> CDC20

Undefined causality:

CDK1_CyclinB regulates Wee1

CHEK1 regulates Wee1

Context depiction will depend on the DB's information availability

MICAST: example of use cases

Causal statement of CDC14A up-regulating the activity of FZR1

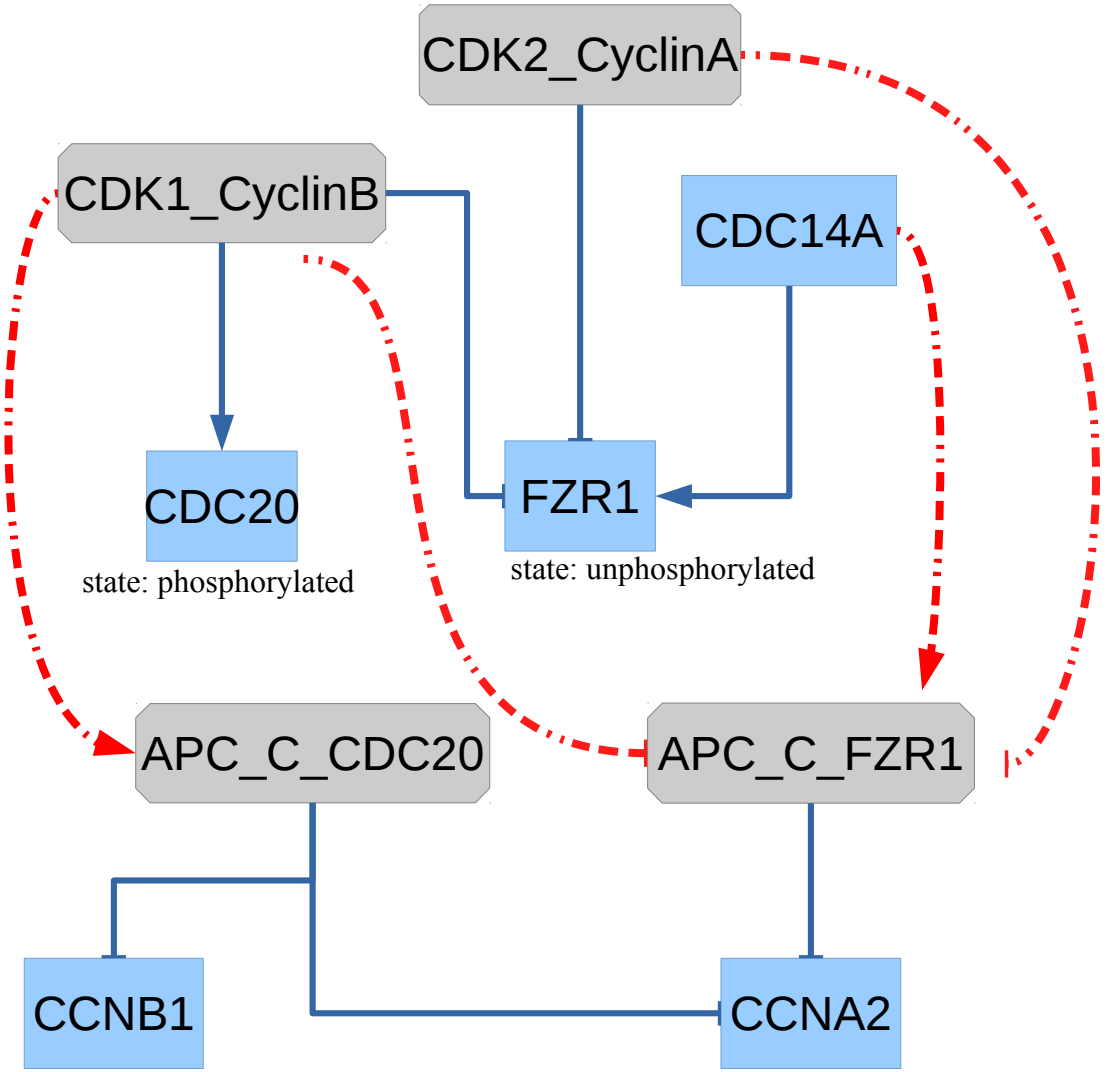
Type: SBO:0000245
Name: CDC14A
Activity: GO:0004721
Concentration: N/A
State: unphosphorylated
Compartment: Nucleus

Regulation: up-regulation
Mechanism: dephosphorylation
ECO: ECO:0000306
Reference: PMID:15840442, PMID:11598127
Confidence: -
Species: 9606

Type: SBO:0000245
Name: FZR1
Activity: GO:0010997
Concentration: N/A
State: unphosphorylated
Compartment: Nucleus

MICAST: example of use cases

Build influence network from causal interactions – **APC module** in ACSN



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CDC14A -> FZR1

APC_C_CDC20 -| CCNA2

APC_C_FZR1 -| CCNA2

APC_C_CDC20 -| CCNB1

CDK1_CyclinB -> CDC20

Inferred indirect regulations

Causality could help for reasoning on the data

Thank you for your attention!

The DrugLogics team

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Acknowledgments

Andrei Zinovyev
Inna Kuperstein
Emmanuel Barillot

Antonio Fabregat
Steve Jupe
Noemi Del Toro
Sandra Orchard
Henning Hermjakob

Aurélien Naldi
Denis Thieffry

institutCurie

EMBL-EBI

1794 ENS ÉCOLE NORMALE SUPÉRIEURE

Funding:

NTNU Helse

ERACOSYSMED