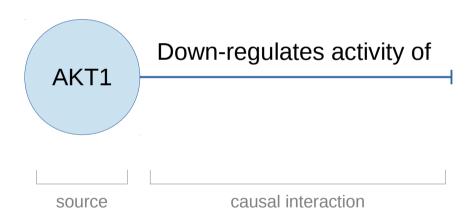
MICAST, Minimum Information for Causality Statement

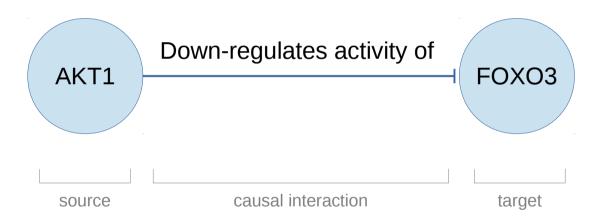
Vasundra Touré¹, Astrid Laegreid², Martin Kuiper¹

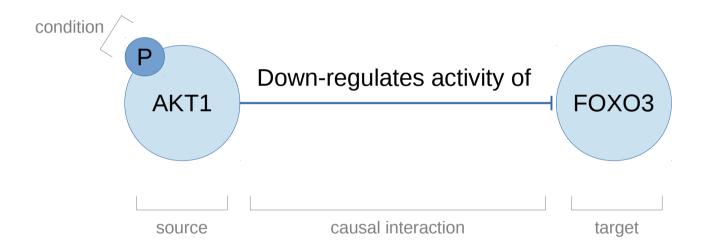
¹Department of Biology

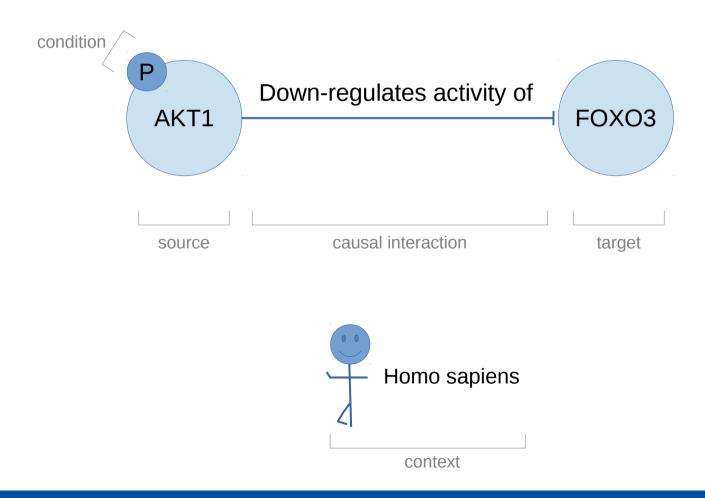
²Department of Clinical and Molecular Medicine









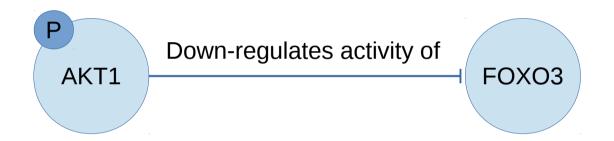


How to encode context and conditions in causal statements?

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?



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

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

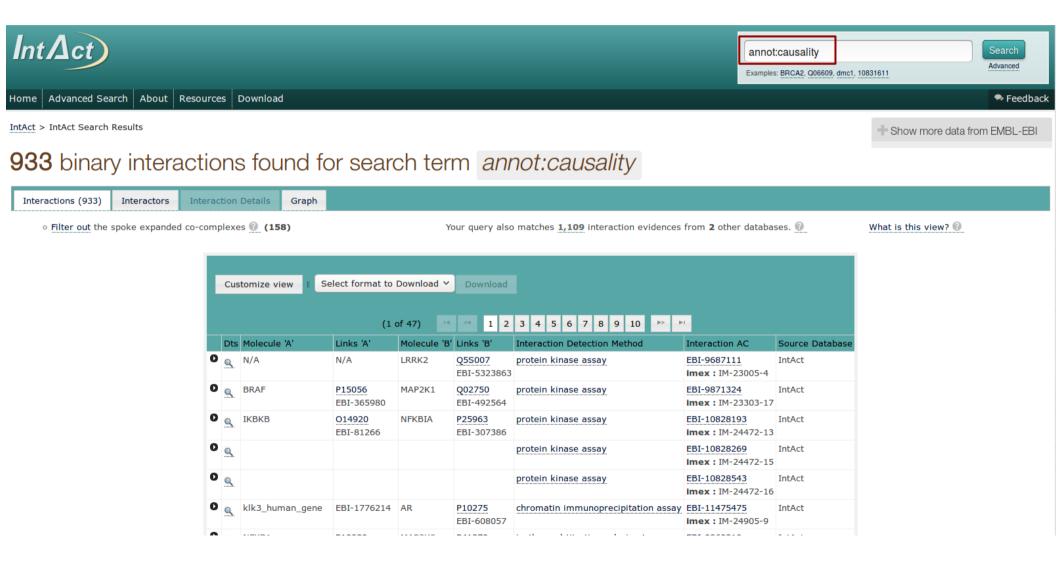
Source database(s)

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

Note: Same columns for interactor B



Example of MITAB support: IntAct database





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

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

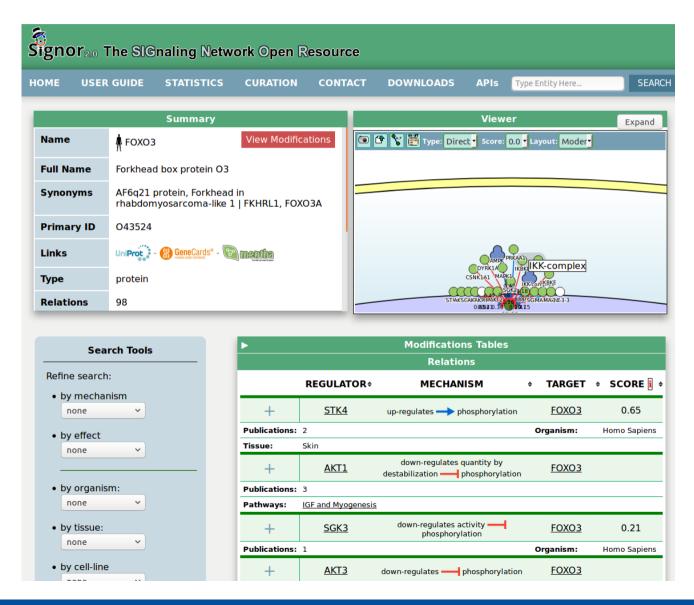
Note: Same columns for interactor B

→ Direct

Directed interactions!



Example of causalTAB support: Signor database



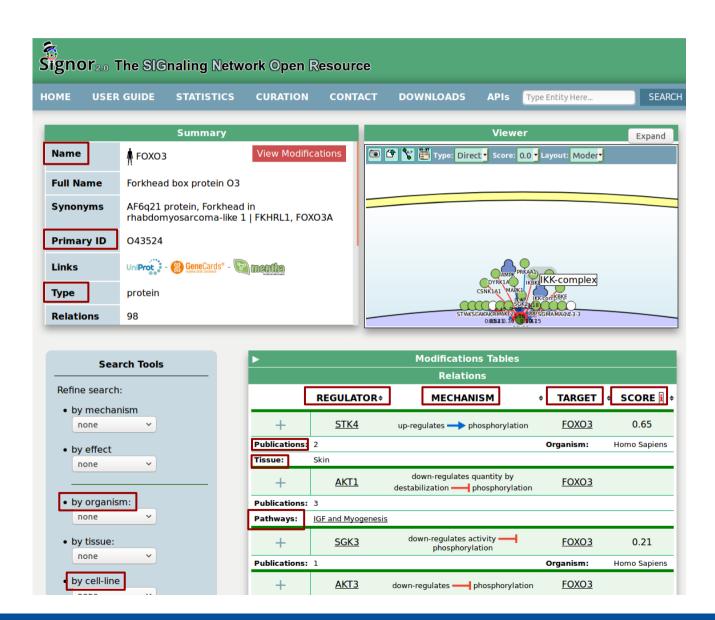
Website: http://signor.uniroma2.it/



Example of causalTAB support: Signor database

Name Primary ID Type

Tissue Organism Cell line



Regulator Mechanism Target Score

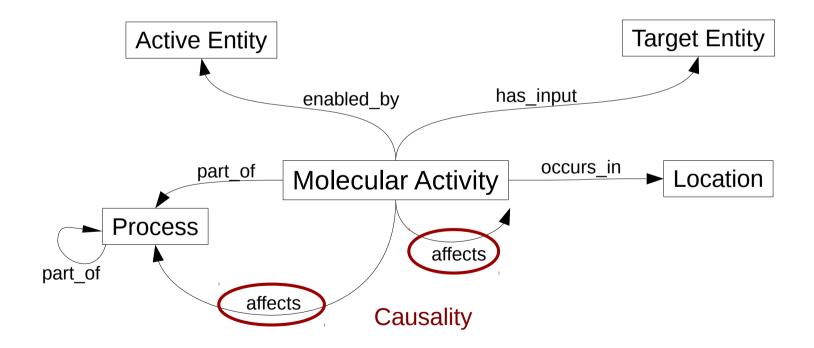
Publication

Website: http://signor.uniroma2.it/

Gene Ontology - Causal Activity Model

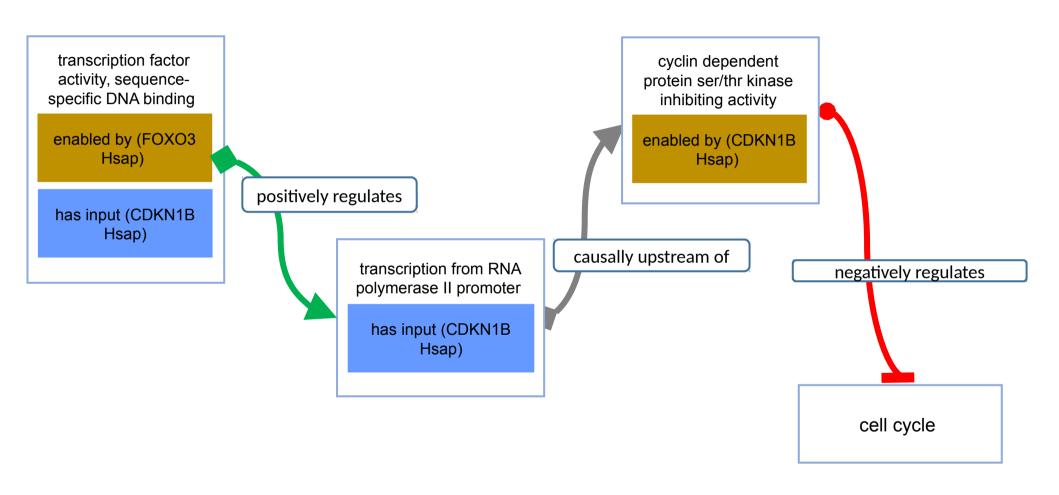
GO: Molecular Function (MF), Cellular Component (CC), Biological Process (BP)





LEGO (Logical Extension of the Gene Ontology) model

Noctua





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

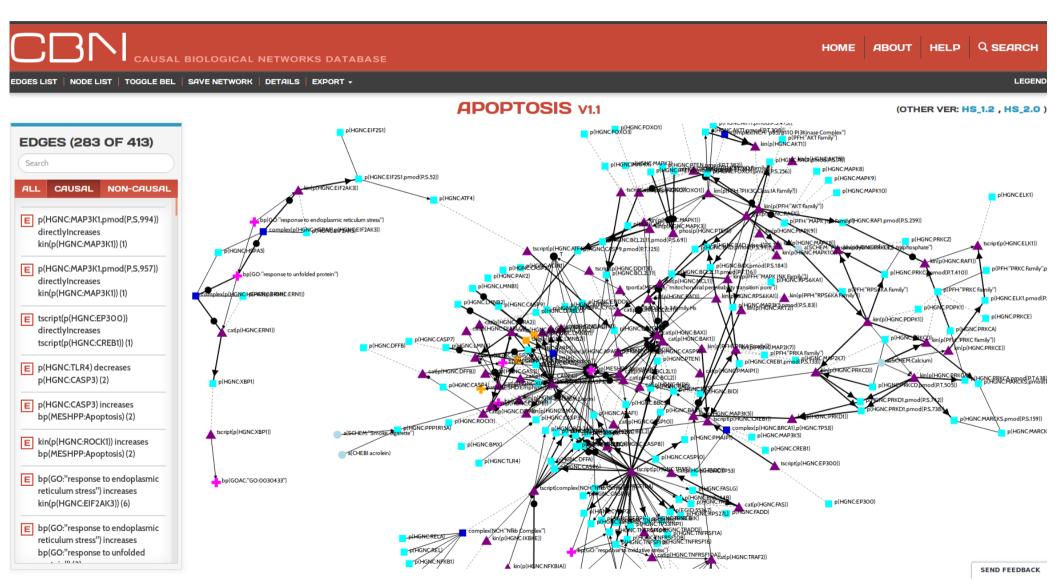
BEL terms contains BEL functions

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



Example of BEL support: CBN database



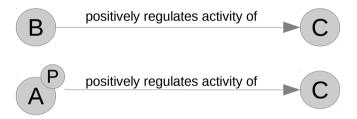
Website: http://causalbionet.com/

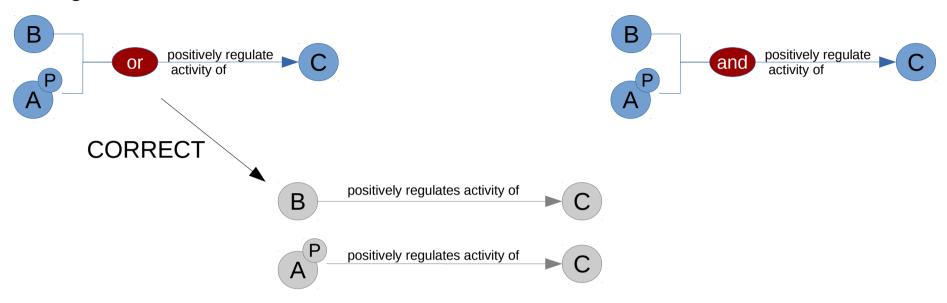
Summary: current state of causality

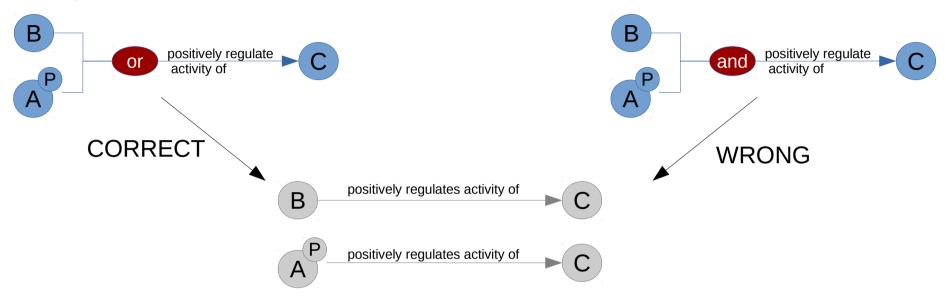
	Entities Identifiers	Directed	Causality annotation	Evidence	Format
MITAB2.7	Entrez gene/Ensembl embl/ddbj/genbank UniProtKB/RefSeq ChEBI	no	Free text: "causality statement:"	PUBMED	tabular
Causaltab	Embl/ddbj/genbank UniprotKB/RefSeq ChEBI/PubChem ComplexPortal Signor_ID	yes	MI – causal interaction	PUBMED	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

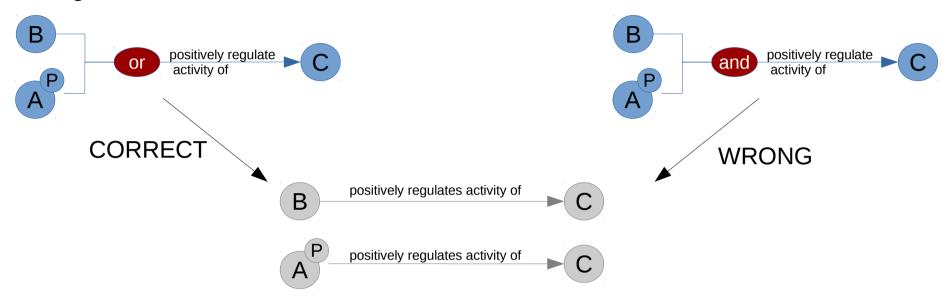




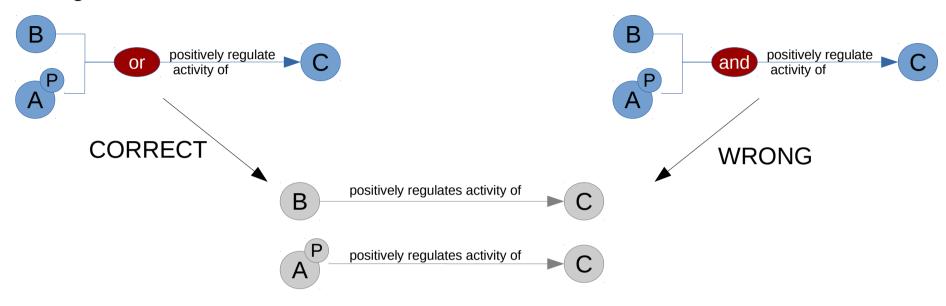




1) Multi-regulated causal interaction

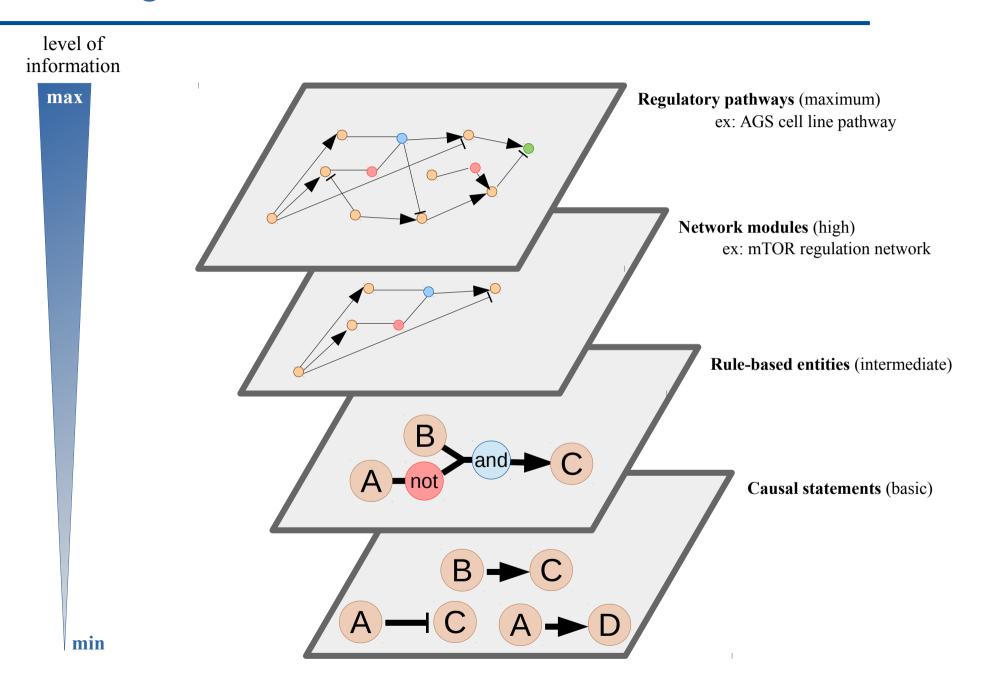


→ introduce logics in formats

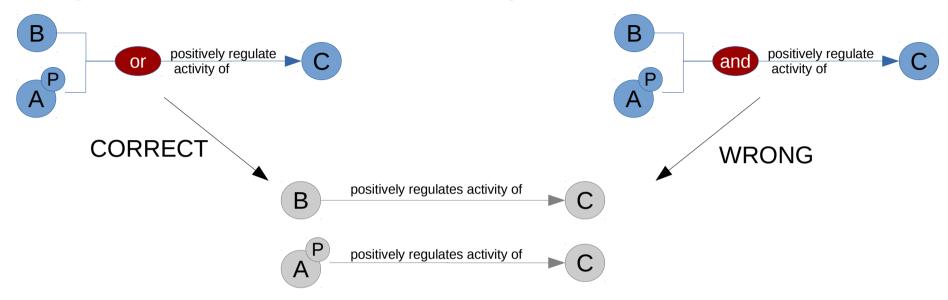


- → introduce logics in formats
- → define levels of abstraction

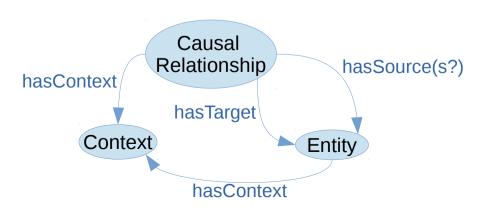
Defining levels of abstraction



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



Mandatory

Example

Minimum Information for Causality Statements

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/in			

fo.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



Mandatory

Minimum Information for Causality Statements

SKT4 has_activity GO:0004672 up-regulates FOXO3 has_activity GO:0003700

Example

Causal Relationship				
Regulation	RO? MI? BEL?	up-regulation		
Mechanism	PSI-MOD	Phosphorylation, binding		
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Type	SBO	0000245	0000245
Activity (MF involved)	GO:MF	0004672	0003700
Name	HGNC	STK4	FOXO3

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

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		
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Text	Scicura			

fo.html

Minimum Information for Causality Statements

SKT4 has_activity GO:0004672 up-regulates FOXO3 has_activity GO:0003700

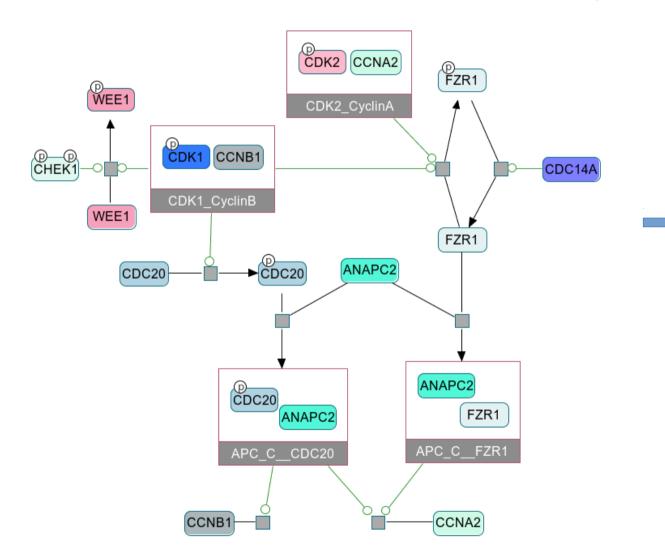
Entity		source	target
Identifiers	Follow MIMIx requests	Q13043	O43524
Type	SBO	0000245	0000245
Activity (MF involved)	GO:MF	0004672	0003700
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observation	Tissue type	BTO, Uberon	-	
	Cell type	BTO, CLO	BTO_0000782	
State	Tissue state	?	-	
	Cell state	?	Apoptotic, s-phase	
Experiment- al condition	?	?	?	

Context 1	source	
Concentration/Level	High, low	
State	?	Active, phosphorylated
Compartment	GO	0005829

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

Causal statement of CDC14A up-regulating the activity of FZR1

Q9UNH5 up-regulates activity of

Q9UM11

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.

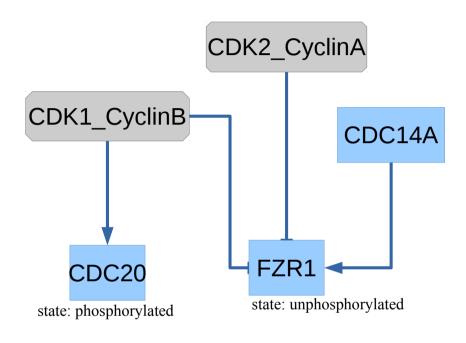
PMID:11598127 Confidence: -Species: 9606 Type: SBO:0000245

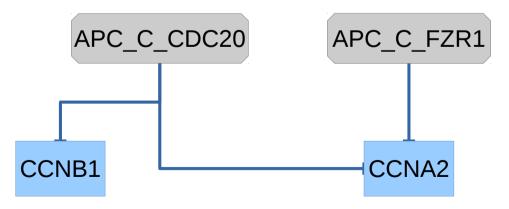
Name: FZR1

Activity: GO:0010997 Concentration: N/A State: unphosphorylated Compartment: Nucleus

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

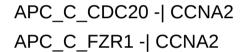






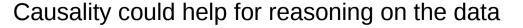
List of causal interactions:

CDK2_CyclinA - FZR1
CDK1_CyclinB - FZR1
CDC14A -> FZR1



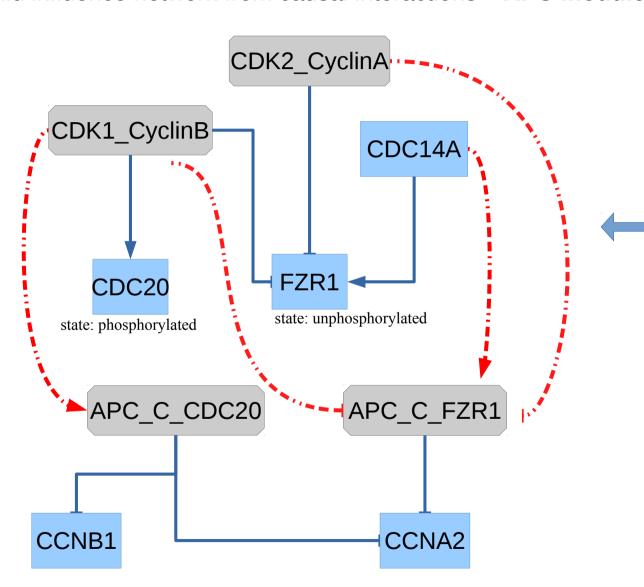
APC_C_CDC20 - | CCNB1

CDK1_CyclinB -> CDC20



Build influence network from causal interactions – 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

Inferred indirect regulations

Causality could help for reasoning on the data

Thank you for your attention!

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