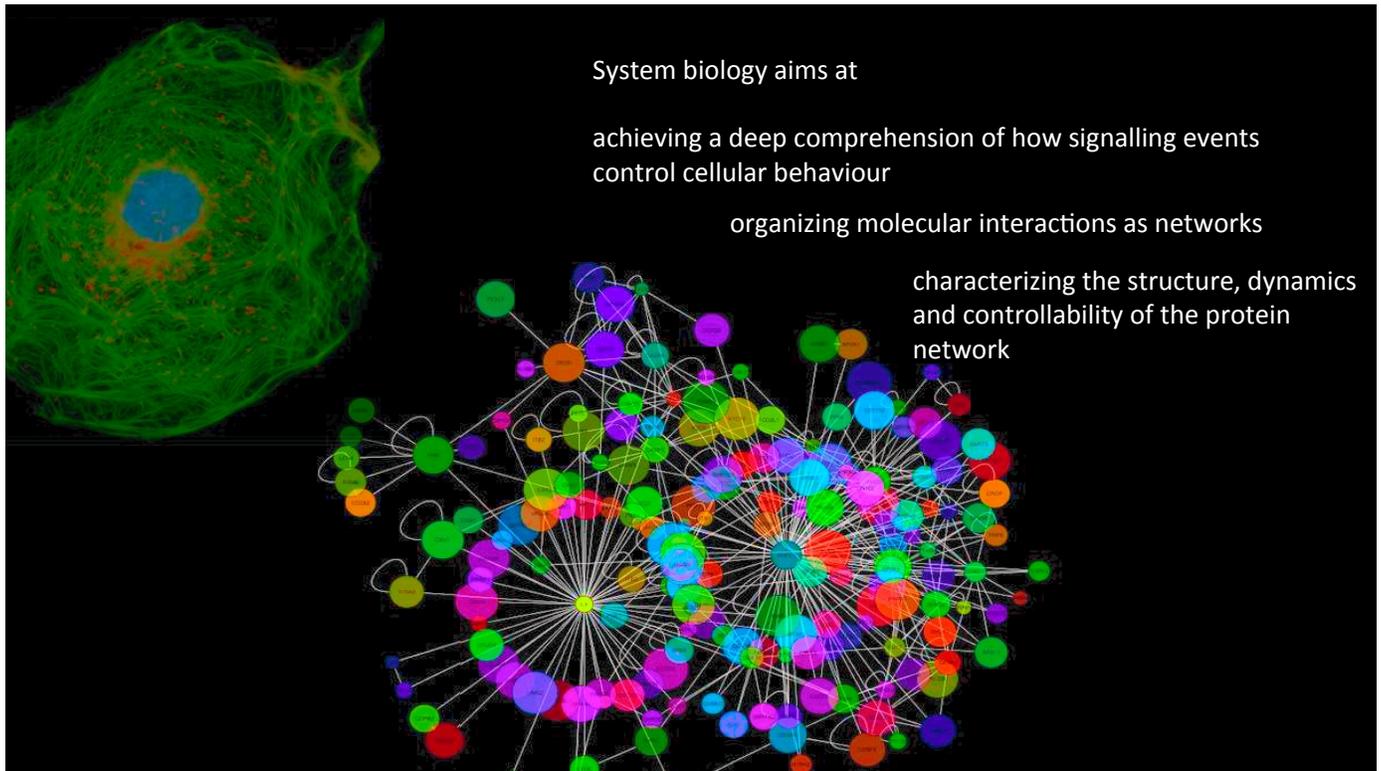




## SIGNOR: a new signaling resource

Developed by **Livia Perfetto, Leonardo Briganti and Alberto Calderone**

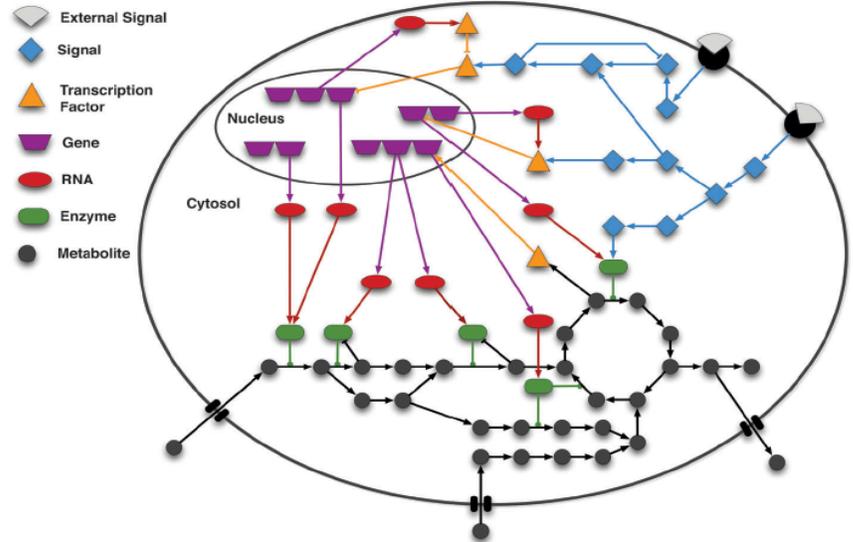
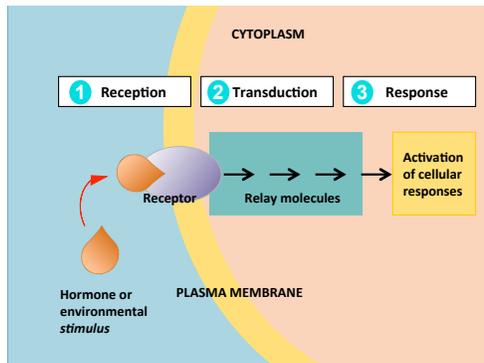
Group Leader: **Gianni Cesareni and Luisa Castagnoli**



System biology aims at

- achieving a deep comprehension of how signalling events control cellular behaviour
- organizing molecular interactions as networks
- characterizing the structure, dynamics and controllability of the protein network

## Signal Transduction



Conçalves et al., 2012 Mol. BioSyst.

## The cell logic model

*“a cellular phenotype results from interactions between various gene products, signalling molecules, metabolites, etc...”*

integrate data from different sources (pathways, PPI, metabolism, transcriptional regulation, miRNA)

the prior Knowledge model is trained and tailored to any specific cell context by confronting with experimental data

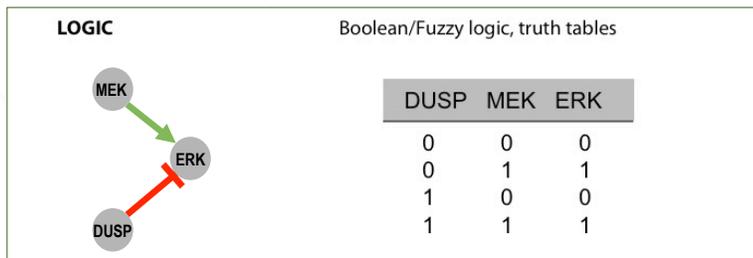
model or predict the cellular response to a stimulus

## SIGNOR a new of causal relationships between biological entities available at <http://signor.uniroma2.it>



(SIGNaling Network Open Resource)

## Signor adopts a boolean representation of signaling interactions

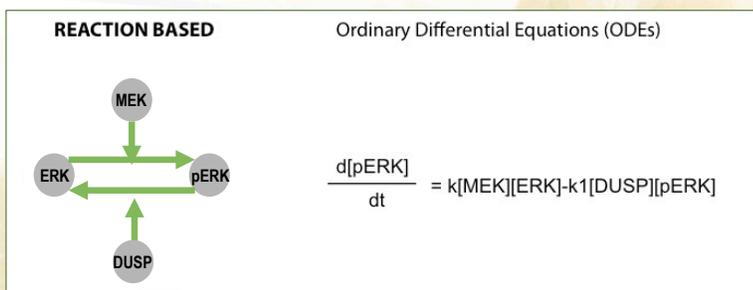


PRO ✓

- Easy to be computed;
- doesn't require a detailed mechanistic understanding of interactions;

CONS ✗

- requires normalization of experimental data;
- extreme simplification of biological complexity.



PRO ✓

- represent biochemical processes in time and space dimension;
- more realistic representations of biological mechanisms.

Cons ✗

- require knowledge of many parameters;
- impractical for large networks.

## Signor is a manually-curated database



NEWLY CURATED  
ARTICLES



Double-checked



5,237 publications  
12,547 interactions

Double-checked

Completed

Re-checked



### ENTITIES

- Molecule Type (e.g. Chemical, Proteins)
- Molecule identifiers (e.g. UniprotKB id)

### RELATIONSHIPS

- Effect (up/down- regulates);
- Mechanism (e.g. phosphorylation);
- Modified residue (i.e. Ser36)
- Cell lines/tissues

### REFERENCE

- PubMedID;
- Short sentence.

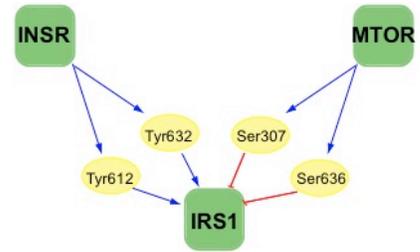
## SIGNOR Controlled Vocabulary



Entity Types	Mechanisms	Effects	Direct
PROTEIN	phosphorylation	UP-REGULATES QUANTITY	YES
COMPLEX	dephosphorylation	UP-REGULATES QUANTITY BY EXPRESSION	NO
SMALL MOLECULES	ubiquitination	UP-REGULATES QUANTITY BY STABILIZATION	UNKNOWN
CHEMICAL	deubiquitination	DOWN-REGULATES	
PHENOTYPE	acetylation	DOWN-REGULATES ACTIVITY	
STIMULUS	deacetylation	DOWN-REGULATES QUANTITY	
PROTEIN FAMILY	binding	DOWN-REGULATES QUANTITY BY REPRESSION	
	transcriptional activation	DOWN-REGULATES QUANTITY BY DESTABILIZATION	
	transcriptional repression	FORM COMPLEX	
	relocalization	UNKNOWN	
	cleavage		
	sumoylation		
	methylation		
	glycosilation		
	Chemical activation		



Gene A	GeneB	effect	effect_mechanism	modified_residue
INSR1	IRS1	activates	phosphorylation	Tyr612
INSR1	IRS1	activates	phosphorylation	Tyr632
PDPK1	AKT1	activates	phosphorylation	Thr308
AKT1	TSC1	inactivates	phosphorylation	Ser939
AKT1	MTOR	activates	phosphorylation	Thr450
MTOR	IRS1	inactivates	phosphorylation	Ser307



Gene A	GeneB	effect	effect_mechanism
INSR1	IRS1_Tyr612	activates	phosphorylation
IRS1_Tyr612	IRS1	activates	-
INSR1	IRS1_Tyr632	activates	phosphorylation
IRS1_Tyr632	IRS1	activates	-
PDPK1	AKT1_Thr308	activates	phosphorylation
AKT1_Thr308	AKT1	activates	-
AKT1	TSC1_Ser939	activates	phosphorylation
TSC1_Ser939	TSC1	inactivates	-
AKT1	MTOR_Thr450	activates	phosphorylation
MTOR_Thr450	MTOR	activates	-
MTOR	IRS1_Ser307	activates	phosphorylation
IRS1_Ser307	IRS1	inactivates	-

- Approx. 4900 phosphorylation reactions;
- Approx. 250 dephosphorylation reactions



SIGNOR, the **S**IGNALING **N**ETWORK **O**PEN **R**ESOURCE, organizes and stores in a structured format signaling information published in the scientific literature. The captured information is stored as binary causative relationships between biological entities and can be represented graphically as activity flow. The entire network can be freely downloaded and used to support logic modeling or to interpret high content datasets. The core of this project is a collection of more than 11000 manually-annotated causal relationships between proteins that participate in signal transduction. Each relationship is linked to the literature reporting the experimental evidence. In addition each node is annotated with the chemical inhibitors that modulate its activity. The signaling information is mapped to the human proteome even if the experimental evidence is based on experiments on mammalian model organisms.

Find out more: **SIGNOR: a database of causal relationships between biological entities:** [Abstract](#) | [Article](#)

Search	Links	Updates
Entity Search: <input type="text" value="dusp1"/> <input type="button" value="Search"/>		14-02-2015 change in the representation of complexes
Pathway Search: <input type="text" value="....."/> <input type="button" value="Search"/>		20-04-2015 10000 entries annotated
Multi-protein Search: <input type="text"/> <input type="radio"/> All <input type="radio"/> Connect <input type="button" value="Clear"/> <input type="button" value="Search"/>		30-06-2015 recuration of most of the entries to annotate the organism used to provide experimental evidence

Paste here your UniProt identifiers (limit 15).

# "entity" search

Feed

phosphorylation	Ser323	HCSAEAGsPAMAVLD	MAPK1	inhibition	↓
phosphorylation	Ser323	HCSAEAGsPAMAVLD	MAPK3	inhibition	↓
phosphorylation	Ser359	SALSYLQsPITTSPTS	MAPK1	activation	↓
phosphorylation	Ser359	SALSYLQsPITTSPTS	MAPK3	activation	↓
phosphorylation	Ser364	LQSPITTsPSC__	MAPK1	activation	↓
phosphorylation	Ser364	LQSPITTsPSC__	MAPK3	activation	↓

**Logic Relationships**

PROTEIN 
  PROTEINFAMILY 
  COMPLEX 
  ANTIBODY 
  SMALL MOLECULE 
  CHEMICAL 
  STIMULUS 
  PHENOTYPE

→ DIRECT ACTIVATION  
 •••→ INDIRECT ACTIVATION  
 ⊖ DIRECT INHIBITION  
 •••⊖ INDIRECT INHIBITION  
 ⊕ FORM COMPLEX  
 ••••• UNKNOWN RELATION

Filter:  Target  Regulator  All

EP300 → acetylation → DUSP1 (0.14)

A recent report shows that mkp1 may also be regulated by acetylation. When raw macrophages are stimulated with lps, mkp1 becomes acetylated on lys57 by p300

Identifier	Tissue	Cell-line	ModificationReg	ModificationTrg	HostOrganism	ModulatorComplex	TargetComplex	Pmid
SIGNOR-166581	-	macrophage	-	✓	Homo sapiens	-	-	20626350

DUSP1 → dephosphorylation → MAPK3 (0.4)

Type Residue: post Lys57  
Sequence: TIVRRRAKGAMGLEH

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Graphical visualizer By Alberto Calderone

# pathways in SIGNOR

SIGNOR, the **S**IGNALING **N**ETWORK **O**PEN **R**ESOURCE, organizes and stores in a structured format signaling information published in the scientific literature. The captured information is stored as binary causative relationships between biological entities and can be represented graphically as activity flow. The entire network was freely downloaded and used to support logic modeling or to interpret high content datasets. The core of this project is a collection of more than 11000 manually-annotated causal relationships between proteins that participate in signal transduction. Each relationship is linked to the literature reporting the experimental evidence. In addition each node is annotated with the chemical inhibitors that modulate its activity. The signaling information is mapped to the human proteome even if the experimental evidence is based on experiments on mammalian model organisms.

- Hippo Signaling
- IL1 Receptor
- IL6
- Inhibition of Apoptosis
- Insulin Receptor
- Mitochondrial Control of Apoptosis
- MTOR Signaling
- Myogenesis
- NF-KB Canonical
- NF-KB Non Canonical
- NOTCH Signaling
- NOTCH Signaling and Myogenesis
- Osteogenesis
- P38 Signaling
- P38 Signaling and Myogenesis
- SAPK/JNK Signaling
- TGFbeta Signaling
- Toll-like Receptor Signaling
- WNT Signaling
- WNT Signaling and Myogenesis

Database of causal relationships between biological entities: [Abstract](#) | [Article](#)

Links	Updates
	14-02-2015 change in the representation of complexes
	20-04-2015 10000 entries annotated
	30-06-2015 recuration of most of the entries to annotate the organism used to provide experimental evidence

Paste here your UniProt identifiers (limit 15).

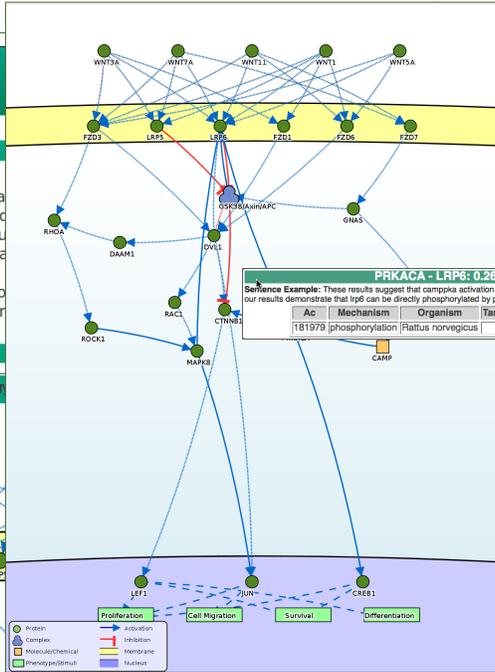
# SIGNOR: Pathway Search



CONTACT CURATION

Feedback

**Name:** WNT Signaling  
**Description:** The Wnt signal and cell fate determination stimulates several intra-cellular pathways that can be divided into the canonical or Wnt/Beta-catenin pathway, the non-canonical pathway, the planar cell polarity pathway, and the Wnt/PCP pathway. Wnt signaling is involved in cell proliferation, cell polarity, and cell fate determination. Wnt pathways are shown: canonical pathway, non-canonical pathway, and Wnt/PCP pathway.



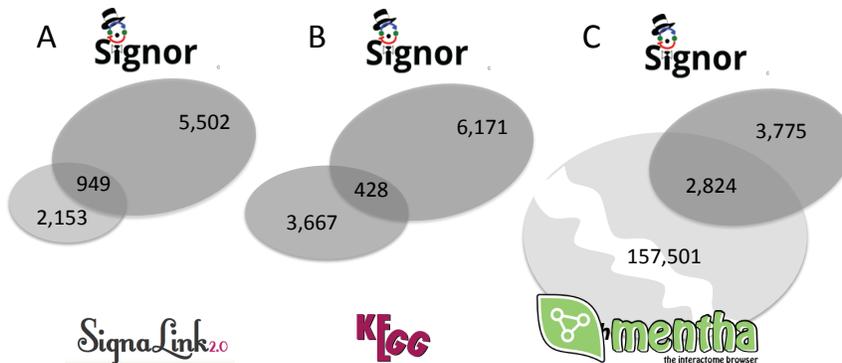
**PRKACA - LRP6: 0.26**  
**Serience Example:** These results suggest that campka activation is involved in activation of lrp6... our results demonstrate that lrp6 can be directly phosphorylated by pka catalytic subunit.

Ac	Mechanism	Organism	TargetMod	Pmid
181979	phosphorylation	Rattus norvegicus	-	18981475

**Pathway seed entities:**

TP	CID:6076
WNT3A	O00755
LRP6	O14640
FZD3	O60353
FZD1	O75084
FZD6	O75197
FZD7	O75581
FZD5	O96014
FZD11	P04628
FZD1	P05412
LRP5	P16220
LRP6	P17612

## SIGNOR vs Signalink2.0, KEGG and mentha a quantitative analysis



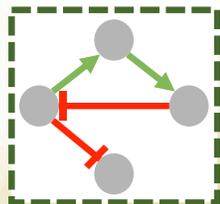
Nucleic Acids Research Advance Access published October 13, 2015

*Nucleic Acids Research*, 2015, 1  
doi: 10.1093/nar/gkv1048

### SIGNOR: a database of causal relationships between biological entities

Livia Perfetto<sup>1</sup>, Leonardo Briganti<sup>1</sup>, Alberto Calderone<sup>1</sup>, Andrea Cerquone Perpetuini, Marta Iannuccelli, Francesca Langone, Luana Licata, Milica Marinkovic, Anna Mattioni, Theodora Pavlidou, Daniele Peluso, Lucia Lisa Petrilli, Stefano Pirrò, Daniela Posca, Elena Santonico, Alessandra Silvestri, Filomena Spada, Luisa Castagnoli and Gianni Cesareni<sup>1</sup>

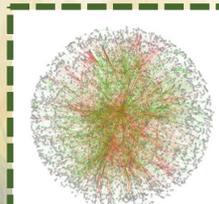
<http://signor.uniroma2.it>



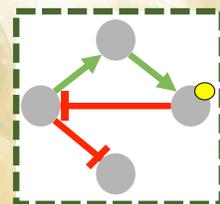
LOGIC  
RELATIONSHIPS



MANUALLY  
CURATED



VALUABLE COVERAGE  
(12,547 INTERACTIONS  
5,237 PUBLICATIONS)



PHOSPHO-MAPPING  
approx. 6,000  
MODIFIED RESIDUES



TOOL FOR  
EXPERIMENTAL  
SETUP

## Aknowledgments

Gianni Cesareni  
Luisa Castagnoli  
**Leonardo Briganti**  
**Alberto Calderone**  
Daniele Peluso  
**The SIGNOR curation team**  
The MINT curation team

THANK YOU!

