



UNIVERSIDAD  
DE MÁLAGA



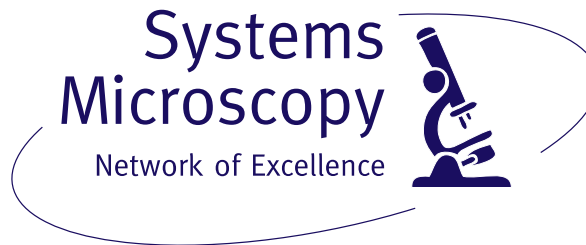
Bases Moleculares de la  
**Proliferación Celular**  
Departamento de Biología Molecular y Bioquímica



# ***Modelado de redes de interacción molecular y su aplicación en la predicción funcional de nuevas dianas.***

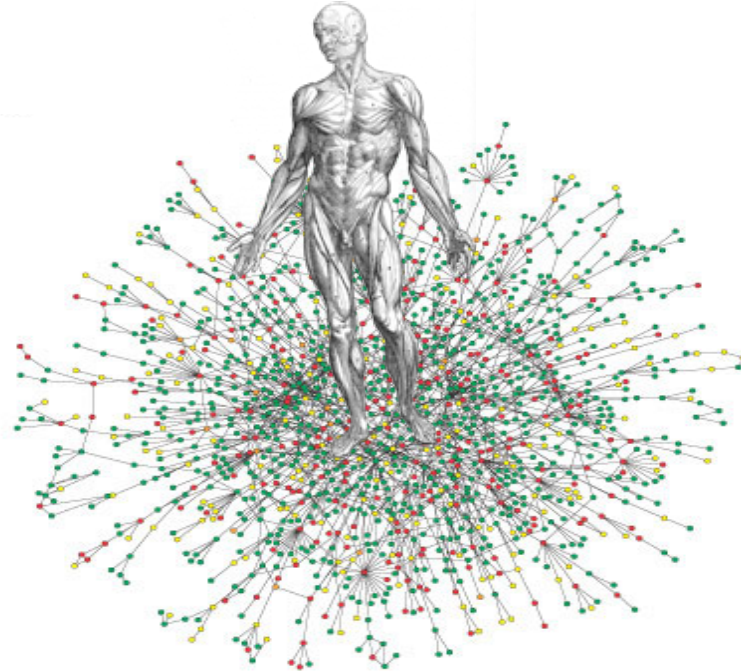
**Juan A. G. Ranea**

**13 Junio 2013, Málaga.**





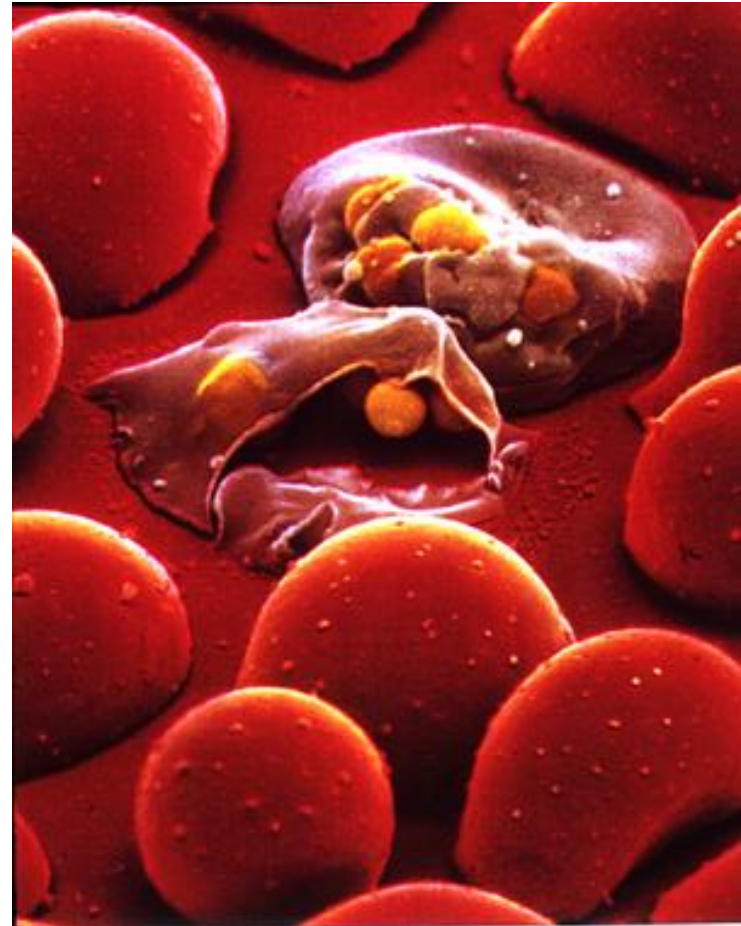
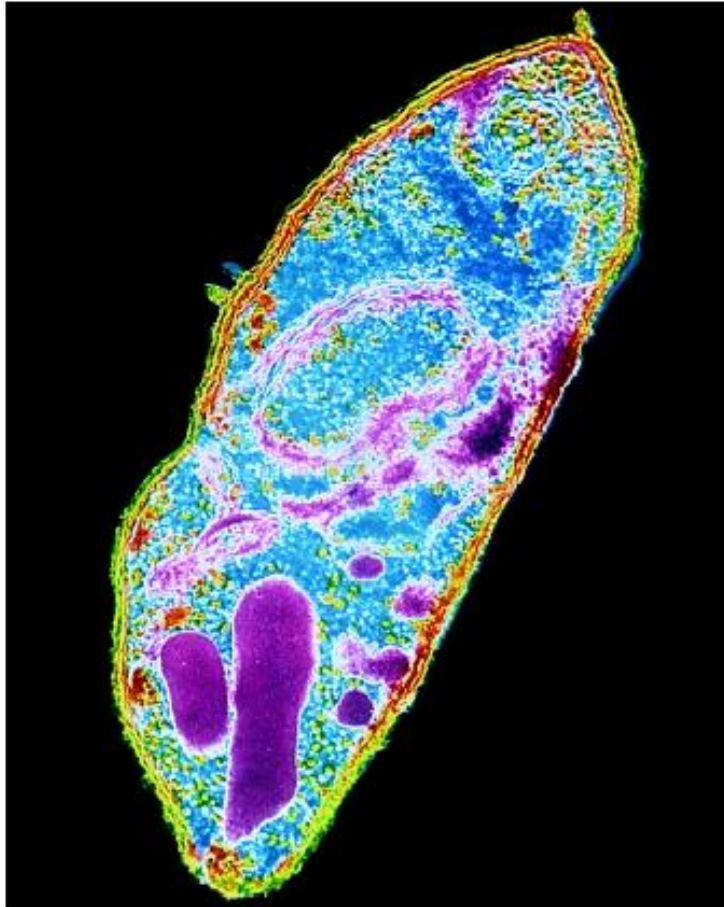
**<10% of PPI interactions in humans have been experimentally characterized.**



**Despite the main resources providing experimental information on protein associations: Intact, MINT, DIP, BIOGRID, HPRD, REACTOME, etc.**

Outside the model organisms the number of known interactions drops rapidly.

For example medically important pathogens have been screened such as malaria, but these isolated data sets are relatively small.



# Emergent property: the black box

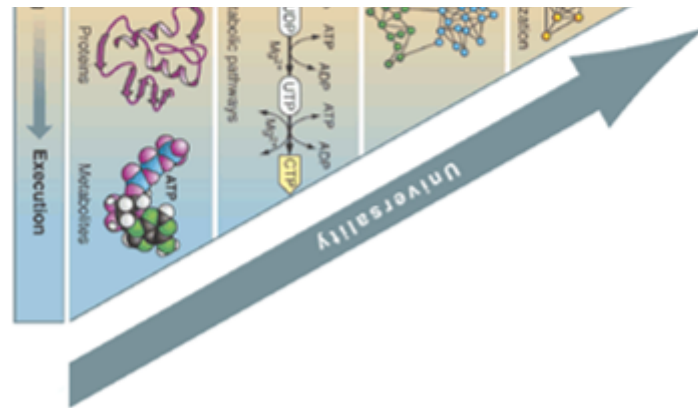
1 gene -> 1 function ?



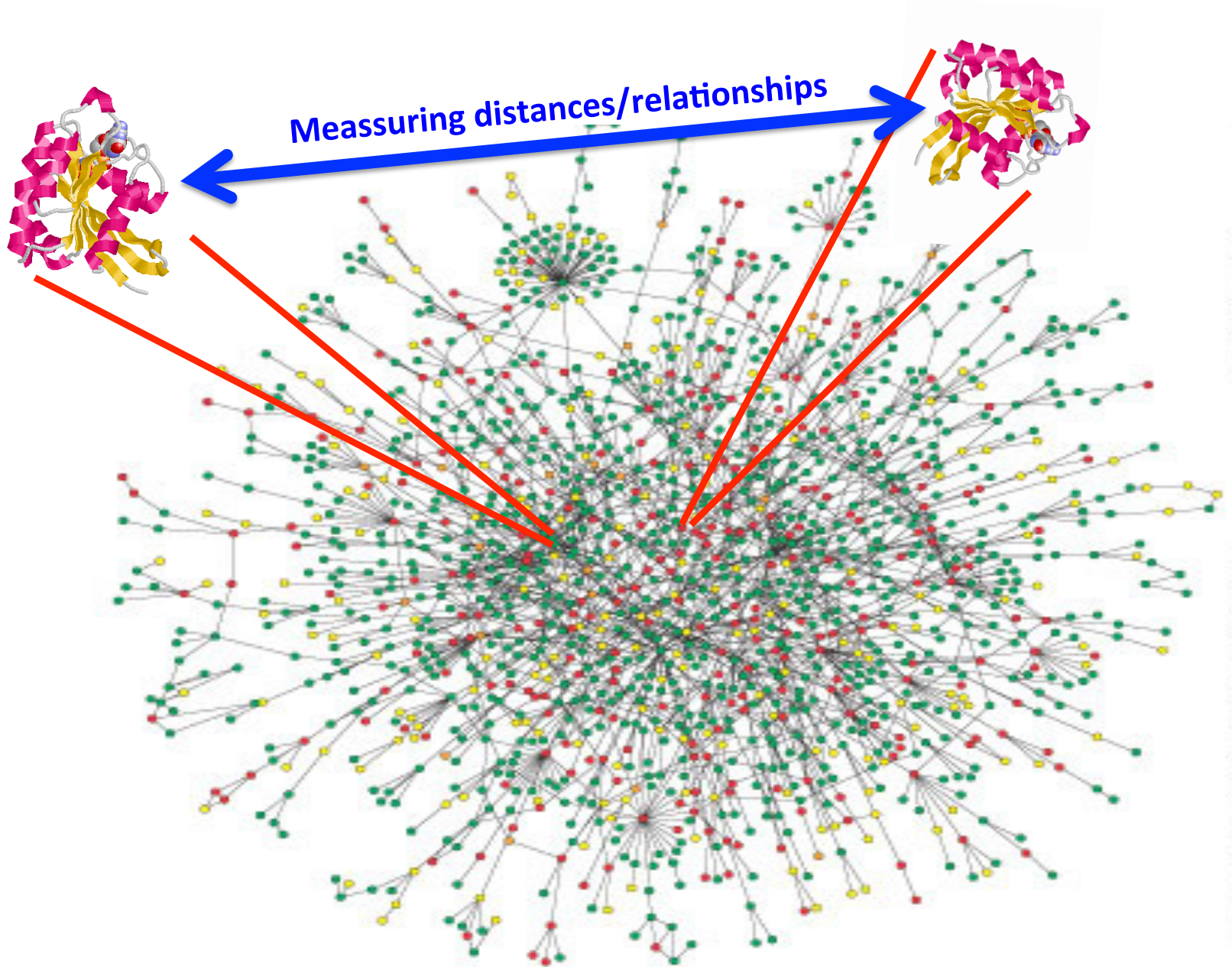
**Mutat**

*“Some mice should, by rights, be dead. At the very least, Teyumuras Kurzchalia expected his to be critically ill. But the most prominent symptom of his genetically engineered mice was a persistent erection”*

Pearson, H. (2002) Surviving a knockout blow. *Nature*, **415**, 8-9.



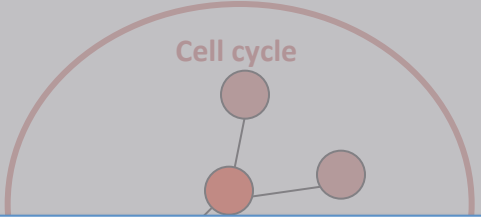
## Exploiting the network structure



## Functional association predictions based on context information

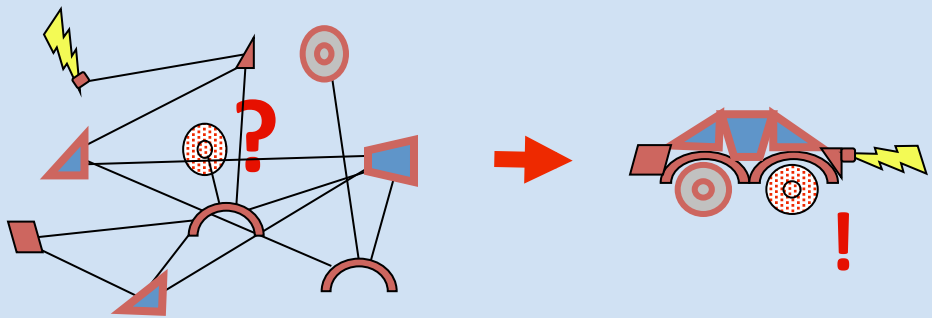
Matriz de la red de interacciones

	1	2	3	4	5	6	7	8	9	...
1						X	X		X	
2						X	X		X	
3	X	X			X					
4	X	X			X					
...										



Functional prediction

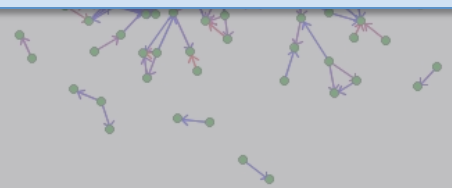
### Searching the function in the network context



Prot. 8 – Prot. 10

- 
- 
- 
- 

Associated pairs

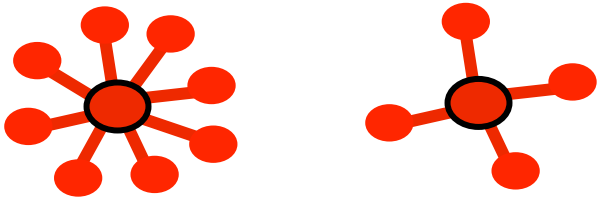




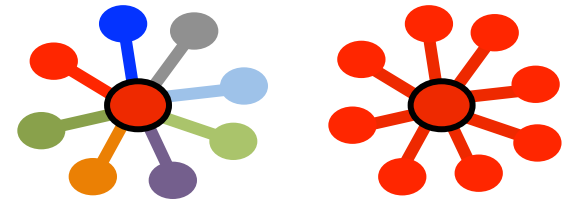
## ¿POR QUÉ UTILIZAR MODELOS DE REDES?

El estudio topológico y modular en la red de los genes puede ayudar a optimizar la generación de hipótesis así como a interpretar su función:

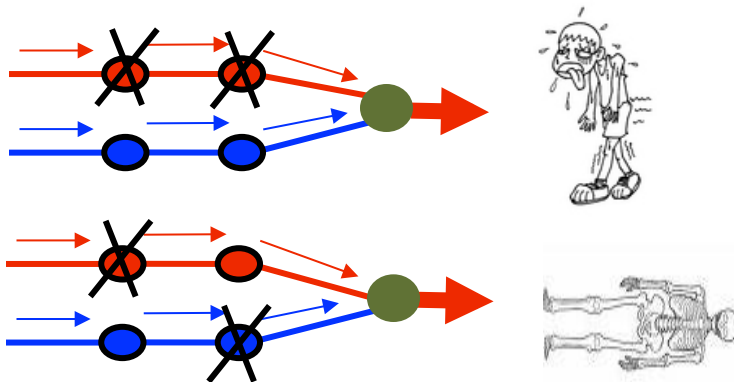
### Esencialidad (hubs) / No esencialidad



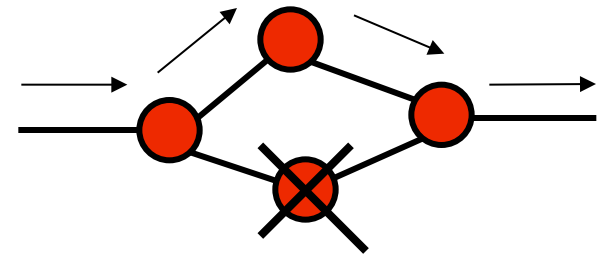
### Pleiotropía / Especificidad fenotípica



### Letalidad sintética/ Sinergia



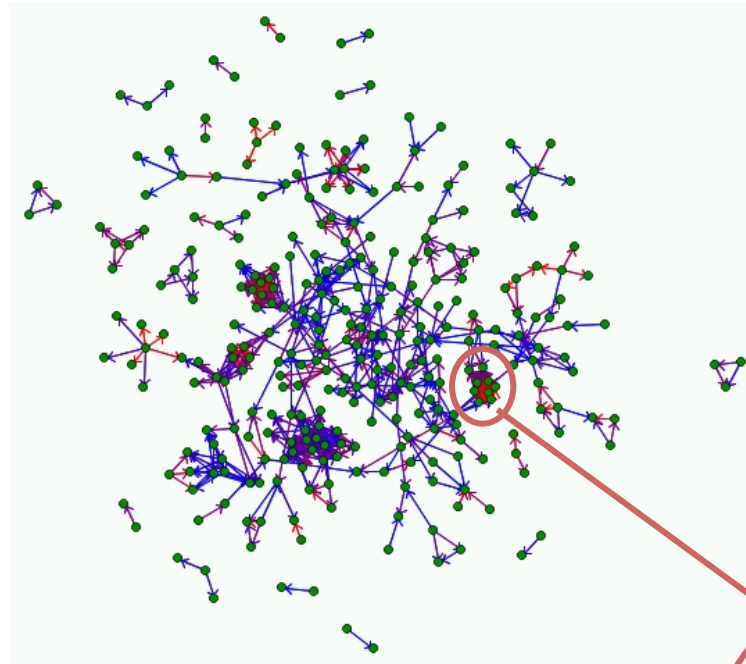
### Mutation Buffering



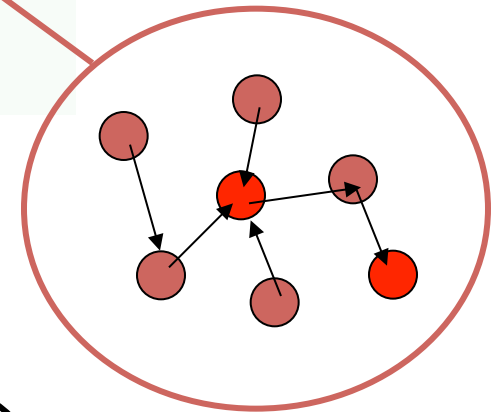
# SYSTEM MODELLING: building up step by step

Prot. 1 – Prot. 2  
Prot. 1 – Prot. 3  
Prot. 1 – Prot. 4  
Prot. 2 – Prot. 3  
Prot. 2 – Prot. 4  
Prot. 3 – Prot. 4  
Prot. 3 – Prot. 6  
Prot. 4 – Prot. 5  
Prot. 5 – Prot. 7  
Prot. 5 – Prot. 8  
Prot. 6 – Prot. 7  
Prot. 6 – Prot. 10  
Prot. 7 – Prot. 8  
Prot. 8 – Prot. 10

**Discrete  
functional  
predictions**



**Network reconstruction**



**Systems modelling**

**1**

**2**

**3**

# Systematic computational prediction of protein interaction networks

**(i) Protein association prediction methods:** the principles behind the different computational methods available to predict pairwise protein–protein interactions (PPIs)

**(ii) Integrating prediction methods:** ways of combining these individual methods in order to increase accuracy and coverage while reducing noise in predicting PPIs.

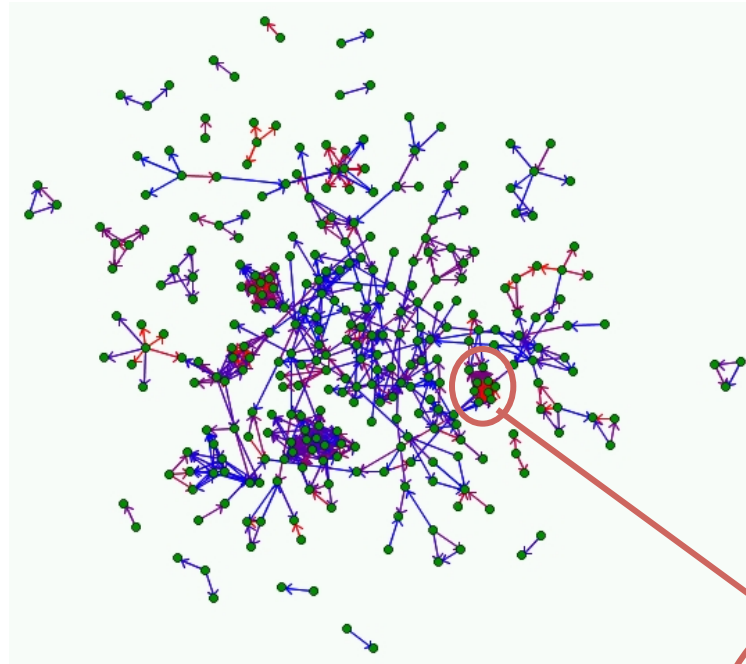
**(iii) Exploiting the network structure:** some successful applications of computational and mathematical methods that exploit network context to predict novel interactions or novel members of different biological processes.

# SYSTEM MODELLING: building up step by step

Prot. 1 – Prot. 2  
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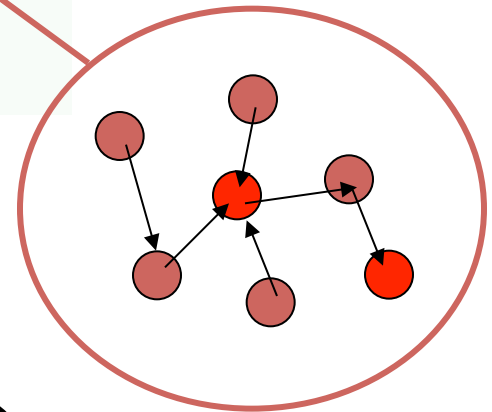
**Discrete  
functional  
predictions**

**1**



**Network reconstruction**

**2**



**3**

**Systems modelling**

# 1. Protein association prediction methods:

## Physical / Functional Association

### 1.1. Genomic context methods

1.1.1 Co-occurrence profiles

1.1.2. Gene/Domain fusion.

1.1.3. Genomic neighborhood.

### 1.2. Sequence-based prediction

1.2.1. Sequence co-evolution: mirror trees.

1.2.2. Sequence co-evolution: Correlated mutations.

1.2.1. Inheriting protein interactions from sequence.

### 1.4. Exploiting experimental data

1.3.1. mRNA expression.

1.3.2. Other experimental screens of PPIs.

1.3.3. Phenotypic vectors comparison

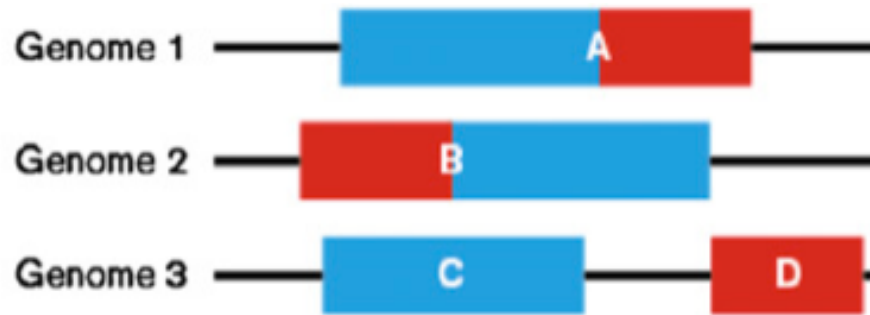
### 1.5. Literature-derived associations

1.4.1. Text mining.

1.4.2. Functional semantic similarity.

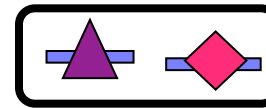
# Gene/domain fusion

## Gene fusion

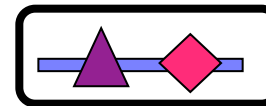


## Protein domain fusion

Proteome 1

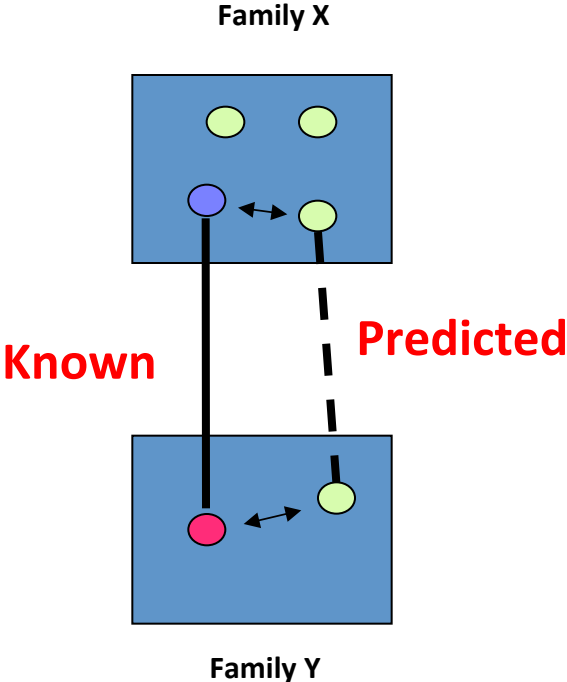
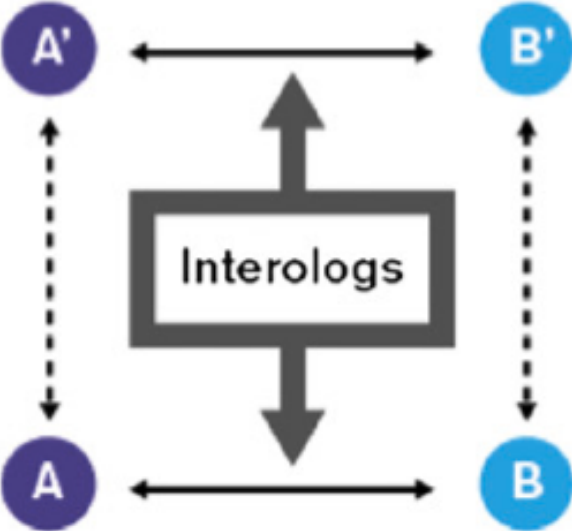


Proteome 2



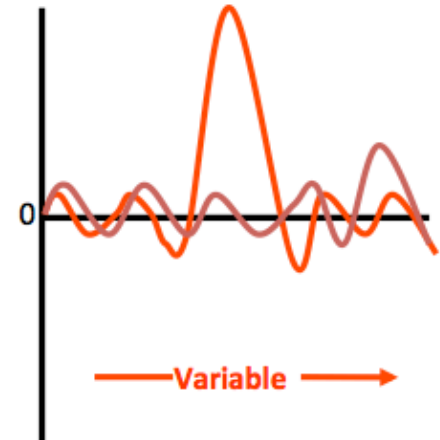
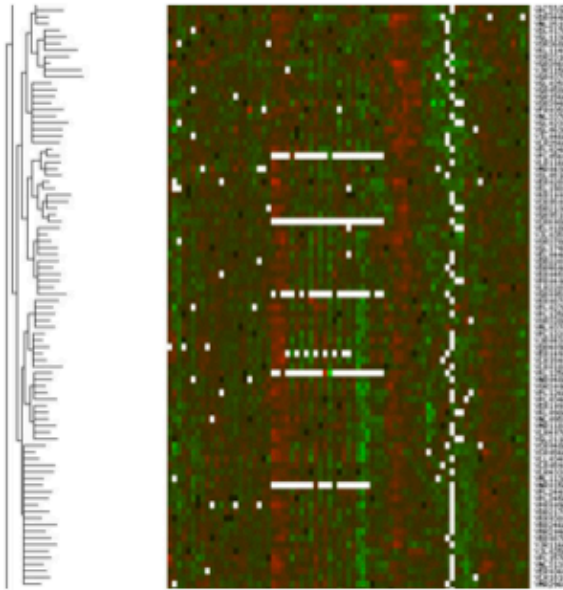


# Inheriting protein interactions from sequence

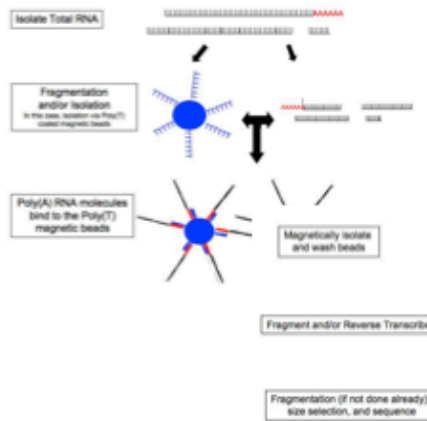
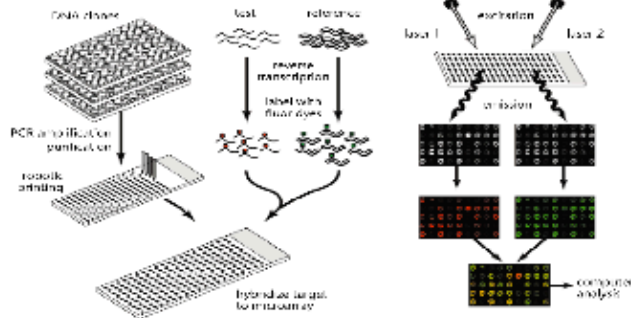




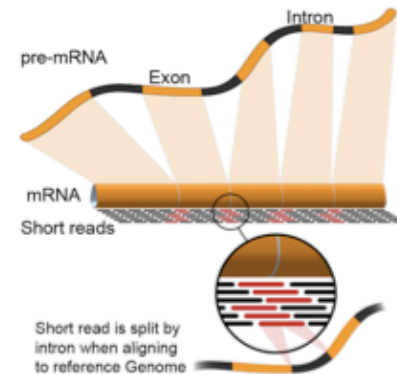
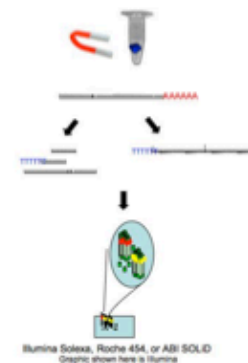
# Exploiting experimental data: RNA-seq / Microarray.



## Microarray



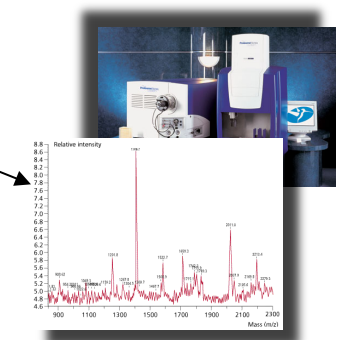
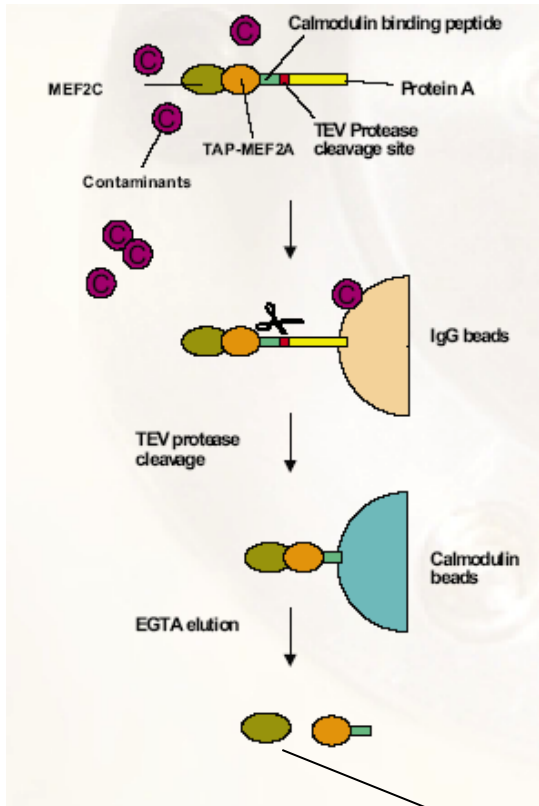
## RNA-seq



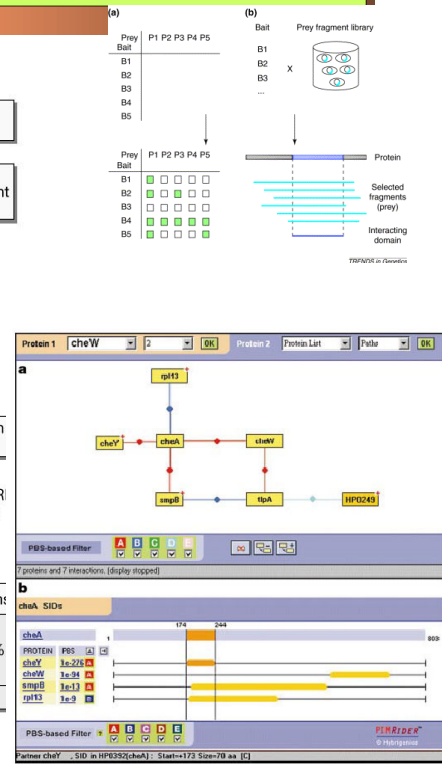
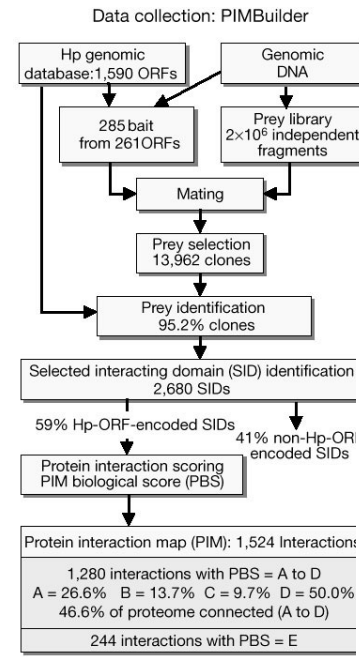
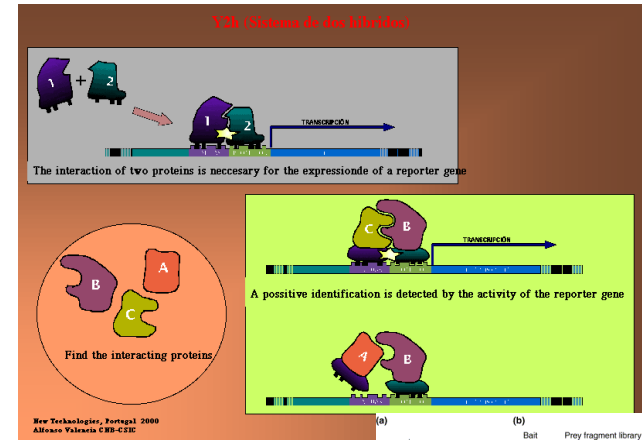
# Exploiting experimental data: Other experimental screens of PPIs

A.Valencia

## Tandem Affinity Purification TAP/MS



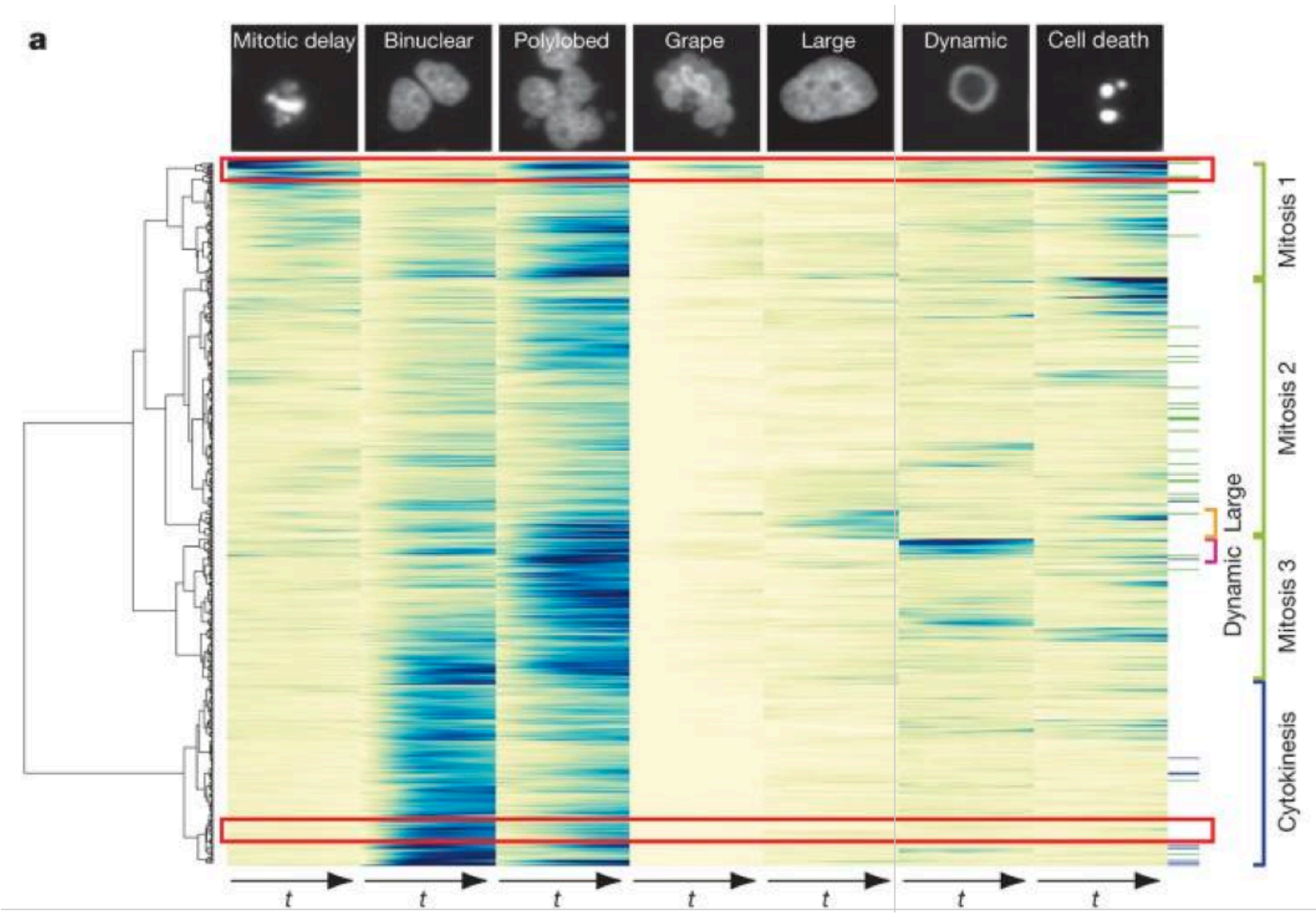
## Y2H



Processing and display: PIMRider



# Exploiting experimental data: Phenotypic vectors comparison



Neumann et al. (2010). Phenotypic profiling of the human genome by time-lapse microscopy reveals cell division genes. Nature. 464(7289): 721-7.

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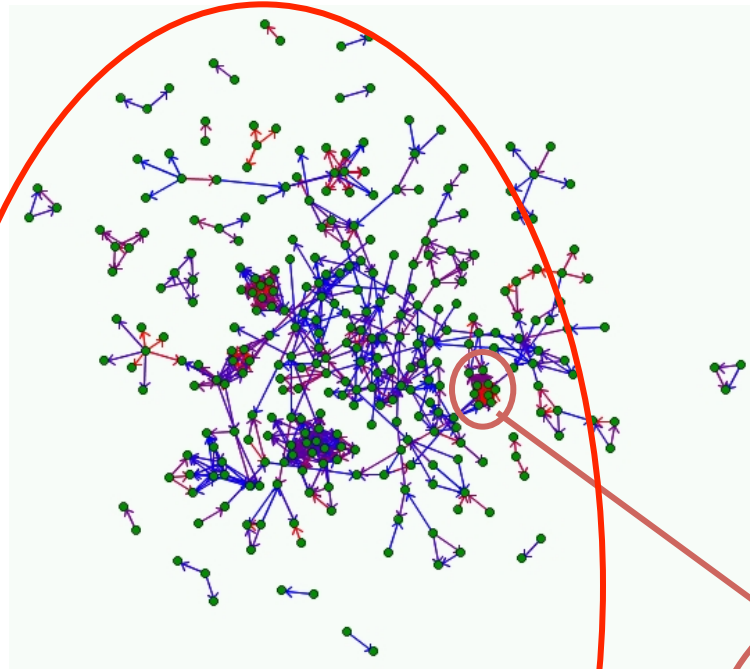
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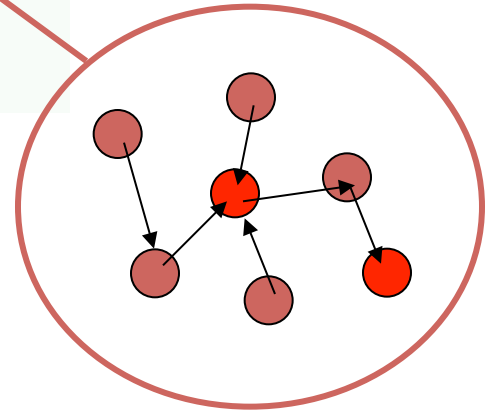
# Modelling networks and exploiting functional context

- Prot. 1 – Prot. 2
- Prot. 1 – Prot. 3
- Prot. 1 – Prot. 4
- Prot. 2 – Prot. 3
- Prot. 2 – Prot. 4
- Prot. 3 – Prot. 4
- Prot. 3 – Prot. 6
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- Prot. 5 – Prot. 7
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**Discrete functional predictions**



**Network reconstruction**



**Systems modelling**

**1**

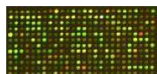
**2**

**3**

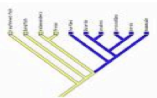
# Predicting PPIs



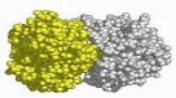
MEM



HIPPO



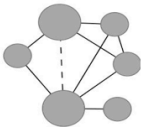
CODA



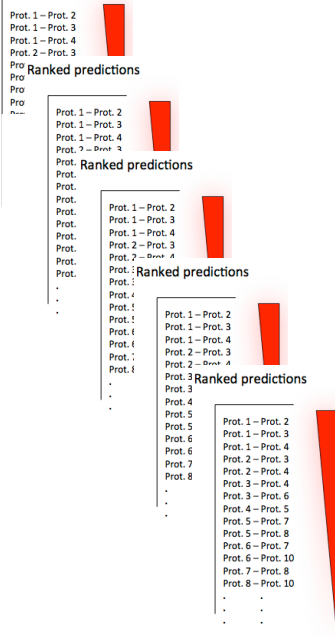
GOSS



Topology

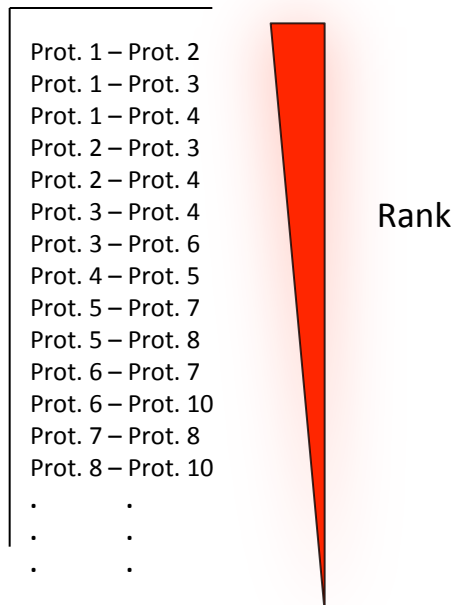


Ranked predictions



Integration

Integrated Ranked predictions



## **2. Integrating prediction methods:**

*2.1. Fisher*

*2.2. Bayes*

*2.3. Kernels*

*2.n Others ..*

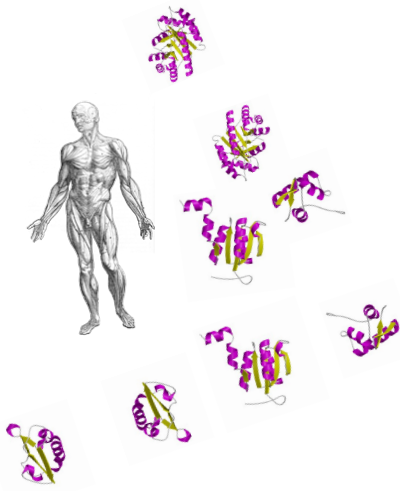


# Integration methods comparison

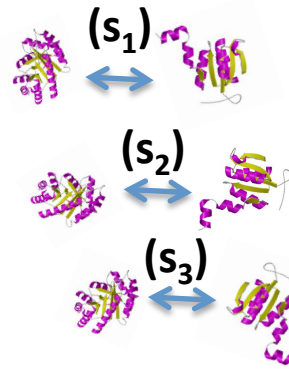
Advantageous property	Integration method/example reference			
	Naïve Bayes [80, 90]	Fisher's [85, 91]	SVM [92, 93]	Graph kernel + SVM [46, 88]
Copes well with missing values	1	1	0	0
Importance of input features can be readily obtained	1	0	0	0
Copes well with high-dimensional data	0	0	1	1
Complex relationships between input variables can be learned	0	0	1	1
Probability estimate readily obtained from output	1	0	0	0
No parameter optimization required	0	1	0	0
No requirement for independence between input data	0	0	1	1
No training data required	0	1	0	0

# Fisher's method application and Scores' p\_value calculation:

Human genome/  
proteome



PPI Prediction  
Methods  
scoring



Ranked predictions

Prot. 1 – Prot. 2
Prot. 1 – Prot. 3
Prot. 1 – Prot. 4
Prot. 2 – Prot. 3
Prot. 2 – Prot. 4
Prot. 3 – Prot. 4
Prot. 3 – Prot. 6
Prot. 4 – Prot. 5
Prot. 5 – Prot. 7
Prot. 5 – Prot. 8
Prot. 6 – Prot. 7
Prot. 6 – Prot. 10
Prot. 7 – Prot. 8
Prot. 8 – Prot. 10
.
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.

Rank



## Fisher Integration Method:

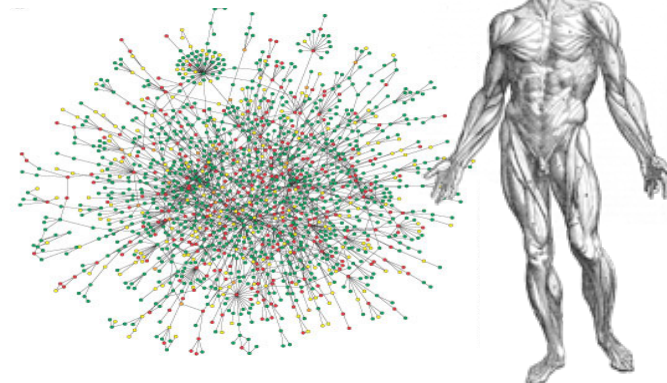
Prot. 1	Prot. 2	Method's predicts. 1	Method's predicts. 2	Method's predicts. 3	Method's predicts. 4
1	2	P_val(1,2)	-	P_val(1,2)	-
1	3	-	P_val(1,3)	P_val(1,3)	-
1	4	-	P_val(1,4)	-	-
2	3	P_val(2,3)	P_val(2,3)	P_val(2,3)	P_val(2,3)
2	4	-	P_val(2,4)	-	P_val(2,4)
3	4	P_val(3,4)	-	-	-
...	...	...	...	...	...

**P-values of the Single Methods Matrix**

For each pair (prot 1 – prot 2):  
 - Fisher (W) =  $-2 \sum_{(1 \rightarrow i)} w_i \log(p_i)$



Integrated Pvalues



Hwang D. et al.(2005) "A data integration methodology for systems biology".  
*PNAS* 102(48), 17296-17301.

Shannon C. (1948) "A Mathematical Theory of Communication". *The Bell System Technical Journal*, Vol. 27, pp. 379-423, 623-656.

# 1. Construcción del modelo: datos experimentales

Bases de datos de pares de proteínas interaccionantes

## HRPD

Prot. 1 – Prot. 2  
 Prot. 1 – Prot. 3  
 Prot. 1 – Prot. 4  
 Prot. 2 – Prot. 3  
 Prot. 2 – Prot. 4  
 Prot. 3 – Prot. 4  
 Prot. 3 – Prot. 6  
 Prot. 4 – Prot. 5  
 Prot. 5 – Prot. 7  
 Prot. 5 – Prot. 8  
 Prot. 6 – Prot. 7  
 Prot. 6 – Prot. 10  
 Prot. 7 – Prot. 8  
 Prot. 8 – Prot. 10  
 . . .  
 . . .  
 . . .

## MINT

Prot. 1 – Prot. 2  
 Prot. 1 – Prot. 3  
 Prot. 1 – Prot. 4  
 Prot. 2 – Prot. 3  
 Prot. 2 – Prot. 4  
 Prot. 3 – Prot. 4  
 Prot. 3 – Prot. 6  
 Prot. 4 – Prot. 5  
 Prot. 5 – Prot. 7  
 Prot. 5 – Prot. 8  
 Prot. 6 – Prot. 7  
 Prot. 6 – Prot. 10  
 Prot. 7 – Prot. 8  
 Prot. 8 – Prot. 10  
 . . .  
 . . .  
 . . .

## Reactome

Prot. 1 – Prot. 2  
 Prot. 1 – Prot. 3  
 Prot. 1 – Prot. 4  
 Prot. 2 – Prot. 3  
 Prot. 2 – Prot. 4  
 Prot. 3 – Prot. 4  
 Prot. 3 – Prot. 6  
 Prot. 4 – Prot. 5  
 Prot. 5 – Prot. 7  
 Prot. 5 – Prot. 8  
 Prot. 6 – Prot. 7  
 Prot. 6 – Prot. 10  
 Prot. 7 – Prot. 8  
 Prot. 8 – Prot. 10  
 . . .  
 . . .  
 . . .

## Kegg

Prot. 1 – Prot. 2  
 Prot. 1 – Prot. 3  
 Prot. 1 – Prot. 4  
 Prot. 2 – Prot. 3  
 Prot. 2 – Prot. 4  
 Prot. 3 – Prot. 4  
 Prot. 3 – Prot. 6  
 Prot. 4 – Prot. 5  
 Prot. 5 – Prot. 7  
 Prot. 5 – Prot. 8  
 Prot. 6 – Prot. 7  
 Prot. 6 – Prot. 10  
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 Prot. 8 – Prot. 10  
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 . . .

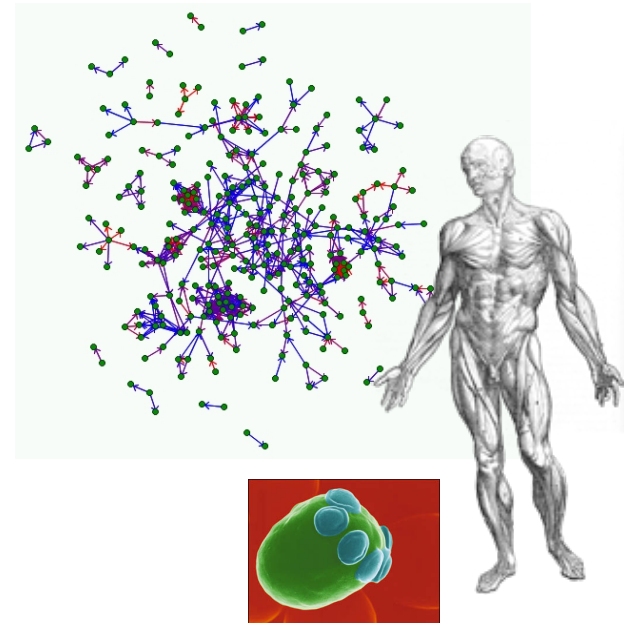
## Intact

Prot. 1 – Prot. 2  
 Prot. 1 – Prot. 3  
 Prot. 1 – Prot. 4  
 Prot. 2 – Prot. 3  
 Prot. 2 – Prot. 4  
 Prot. 3 – Prot. 4  
 Prot. 3 – Prot. 6  
 Prot. 4 – Prot. 5  
 Prot. 5 – Prot. 7  
 Prot. 5 – Prot. 8  
 Prot. 6 – Prot. 7  
 Prot. 6 – Prot. 10  
 Prot. 7 – Prot. 8  
 Prot. 8 – Prot. 10  
 . . .  
 . . .  
 . . .

Combinación de todas las bases de datos

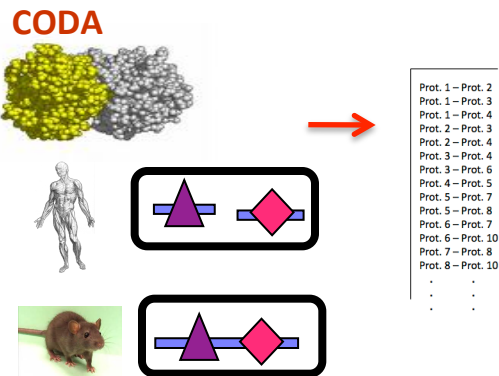
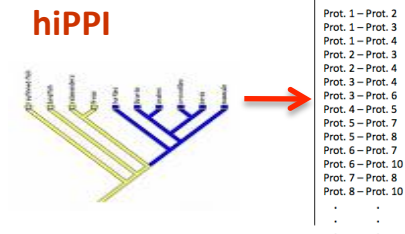
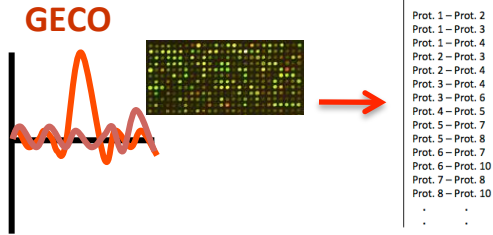
Prot. 1 – Prot. 2  
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 . . . .  
 . . . .

Reconstrucción de la red: KnowledgeGram (KG)



# 1. Construcción del modelo: predicciones

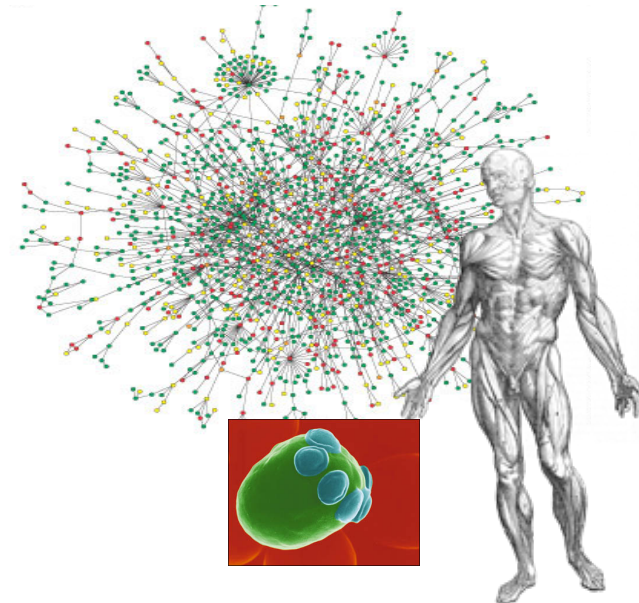
## Predicciones de interactomas completos



## Integración por: Fisher, Bayes, Kernels, etc.

- Prot. 1 – Prot. 2
- Prot. 1 – Prot. 3
- Prot. 1 – Prot. 4
- Prot. 2 – Prot. 3
- Prot. 2 – Prot. 4
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- Prot. 8 – Prot. 10
- . . .
- . . .

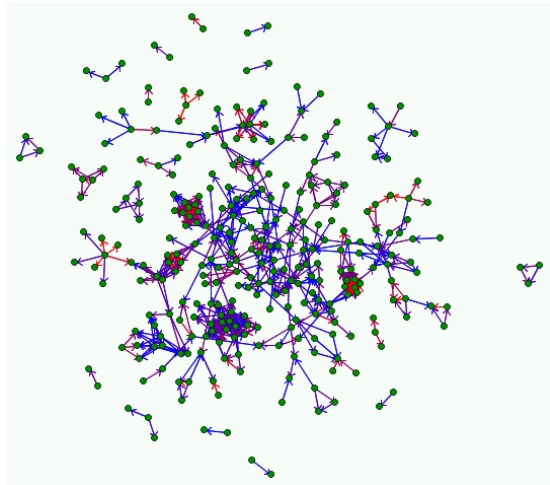
## Reconstrucción de la red: PredictioGram (PG)



# Predictogram (PG) / Knowledgegram (KG)

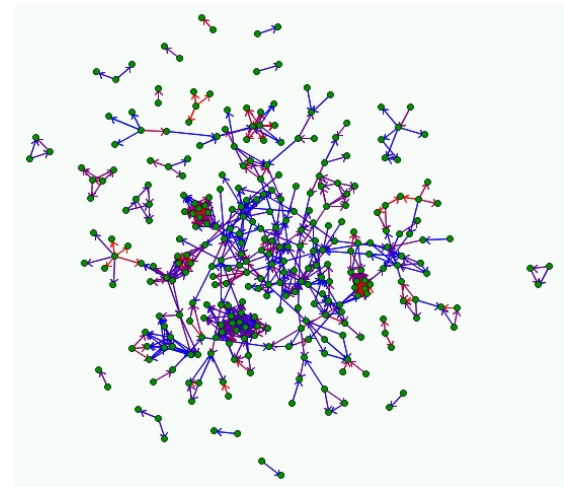
## Predictogram:

Integrated PPIs datasets from CODA, GECO  
and hiPPI predictions



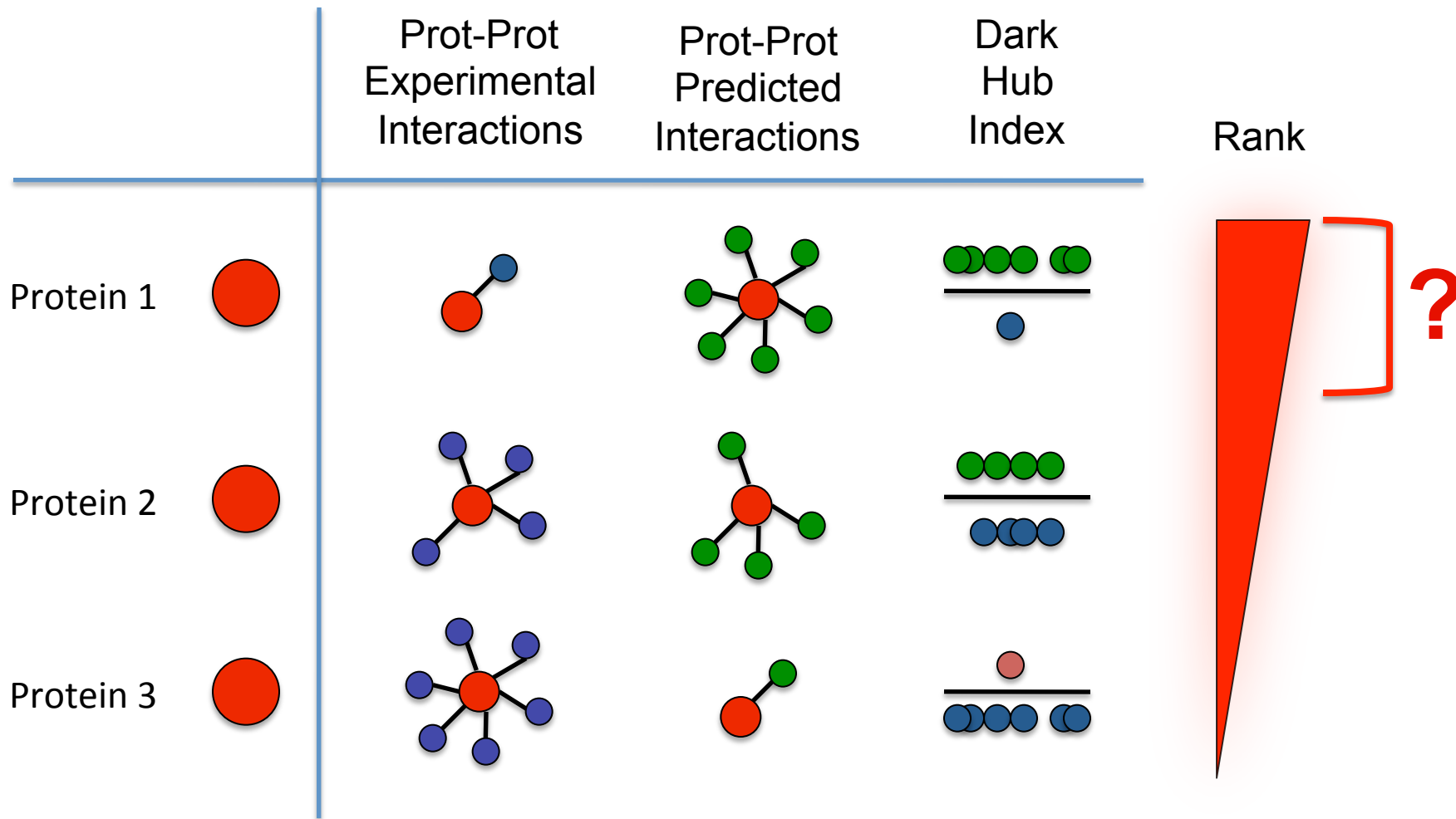
## Knowledgegram:

Combination of all PPIs in HRPD, MINT, Intact,  
Reactome, Kegg, FunCat and GO databases



PG/KG network models comparison at  
different reliability levels

# Analysing the 'dark matter' in the Predicted PPI network models



## Analysing the ‘dark matter’ in the Predicted PPI models: Membrane proteins / Extracellular proteins

	GO term	GO cat.	Top 10 %	Bot. 10 %	Tot. %	P-val	GO: number Ids	GO definition
<b>Yeast</b>	Intrinsic to membrane	cc	111		23	9,10 E-06	0031224	Located in a membrane such that some covalently attached portion of the gene product, for example part of a peptide sequence or some other covalently attached moiety such as a GPI anchor, spans or is embedded in one or both leaflets of the membrane.
	Integral to membrane	cc	106		22	1,80 E-05	0016021	Penetrating at least one phospholipid bilayer of a membrane. May also refer to the state of being buried in the bilayer with no exposure outside the bilayer. When used to describe a protein, indicates that all or part of the peptide sequence is embedded in the membrane.
	Regulation of transcription	bp		110	21	1,20 E-08	0045449	Any process that modulates the frequency, rate or extent of the synthesis of either RNA on a template of DNA or DNA on a template of RNA.
	Non-membrane-bounded organelle	cc		132	25	2,60 E-03	0043228	Organized structure of distinctive morphology and function, not bounded by a lipid bilayer membrane. Includes ribosomes, the cytoskeleton and chromosomes.
	Intracellular non-membrane-bounded organelle	cc		132	25	2,60 E-03	0043232	Organized structure of distinctive morphology and function, not bounded by a lipid bilayer membrane and occurring within the cell. Includes ribosomes, the cytoskeleton and chromosomes.
<b>human</b>	Extracellular region	cc		423	21	2,00 E-24	0005576	The space external to the outermost structure of a cell. For cells without external protective or external encapsulating structures this refers to space outside of the plasma membrane. This term covers the host cell environment outside an intracellular parasite



**Analyzing the ‘dark matter’ in the Predicted PPI models:  
Transient interactions**

	<b>GO term name</b>	<b>GO code</b>	<b>P-value</b>	<b>N</b>	<b>B</b>	<b>n</b>	<b>b</b>	<b>E.</b>
<b>Biol. proc.</b>	Protein amino acid phosphorylation	GO:0006468	7.63E-22	12769	508	991	111	3
	Regulation of small GTPase mediated signal transduction	GO:0051056	1.64E-13	12769	124	982	39	4
	└ Regulation of Ras protein signal transduction	GO:0046578	2.27E-10	12769	85	982	28	4
<b>Molecular function</b>	Protein kinase activity	GO:0004672	3.62E-21	12769	480	991	106	3
	└ Protein serine/threonine kinase activity	GO:0004674	4.83E-14	12769	349	984	75	3
	└ Protein tyrosine kinase activity	GO:0004713	2.73E-10	12769	146	972	37	3
	GTPase regulator activity	GO:0030695	7.06E-13	12769	319	908	63	3
	└ Guanyl-nucleotide exchange factor activity	GO:0005085	1.92E-11	12769	123	982	36	4
	└ Small GTPase regulator activity	GO:0005083	1.59E-10	12769	211	982	47	3
	ATP binding	GO:0005524	4.61E-25	12769	1097	991	190	2

## Systematic computational prediction of protein interaction networks

**(i) Protein association prediction methods:** the principles behind the different computational methods available to predict pairwise protein–protein interactions (PPIs)

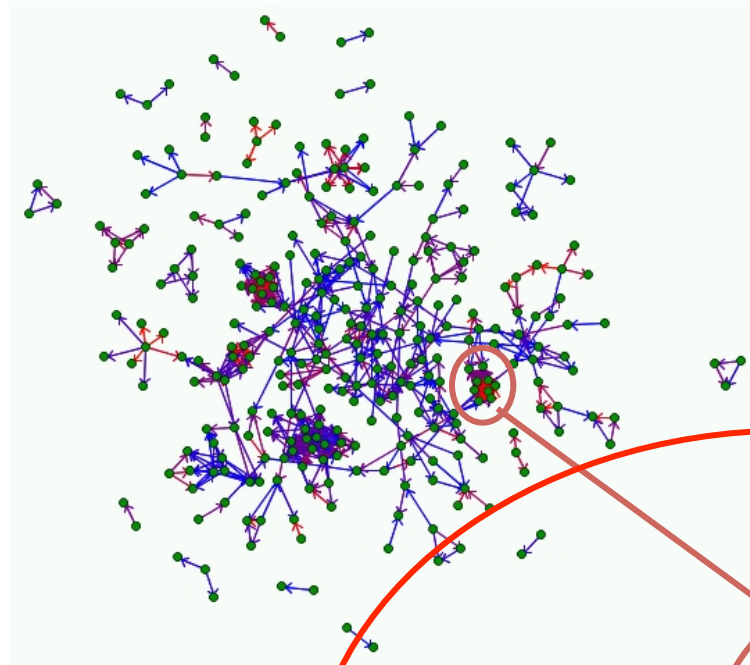
**(ii) Integrating prediction methods:** ways of combining these individual methods in order to increase accuracy and coverage while reducing noise in predicting PPIs.

**(iii) Exploiting the network structure:** some successful applications of computational and mathematical methods that exploit network context to predict novel interactions or novel members of different biological processes.

# Modelling networks and exploiting functional context

Prot. 1 – Prot. 2  
Prot. 1 – Prot. 3  
Prot. 1 – Prot. 4  
Prot. 2 – Prot. 3  
Prot. 2 – Prot. 4  
Prot. 3 – Prot. 4  
Prot. 3 – Prot. 6  
Prot. 4 – Prot. 5  
Prot. 5 – Prot. 7  
Prot. 5 – Prot. 8  
Prot. 6 – Prot. 7  
Prot. 6 – Prot. 10  
Prot. 7 – Prot. 8  
Prot. 8 – Prot. 10

**Discrete  
functional  
predictions**



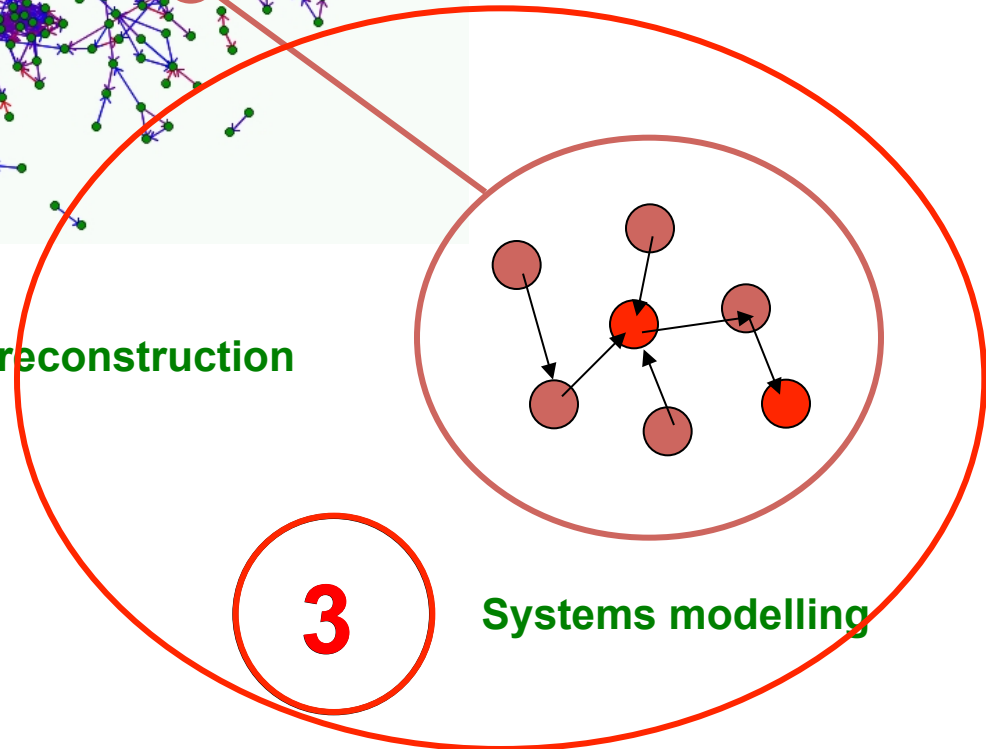
**Network reconstruction**

**1**

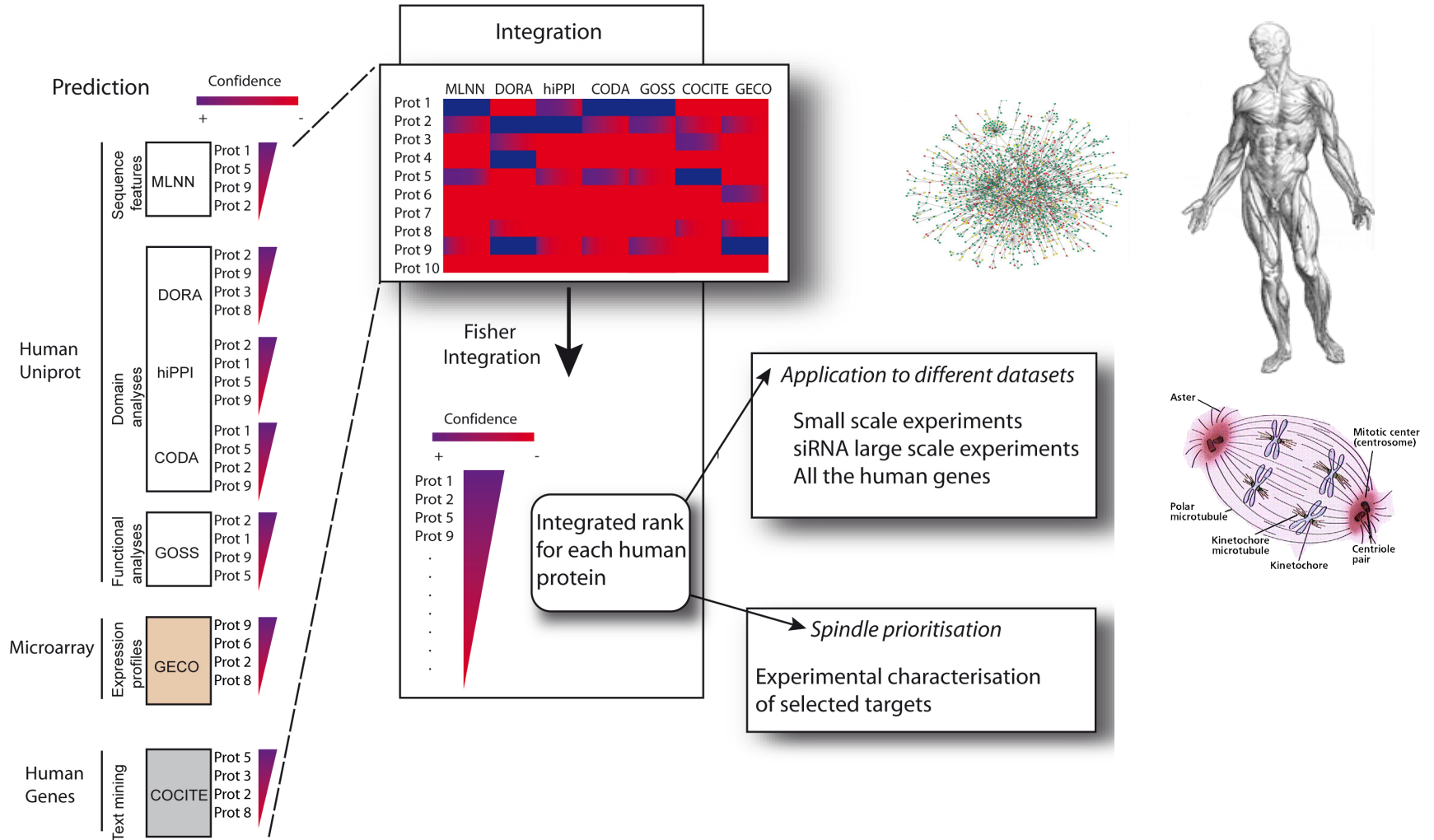
**2**

**3**

**Systems modelling**



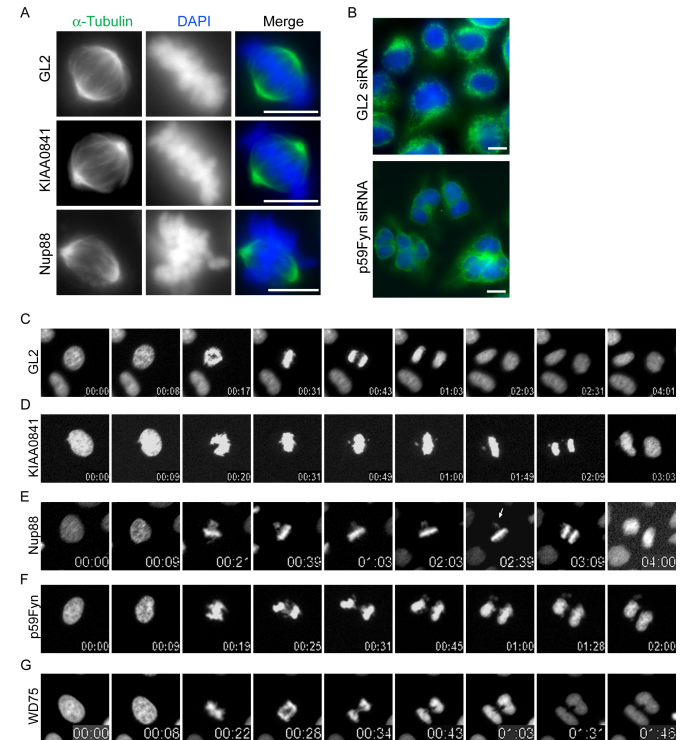
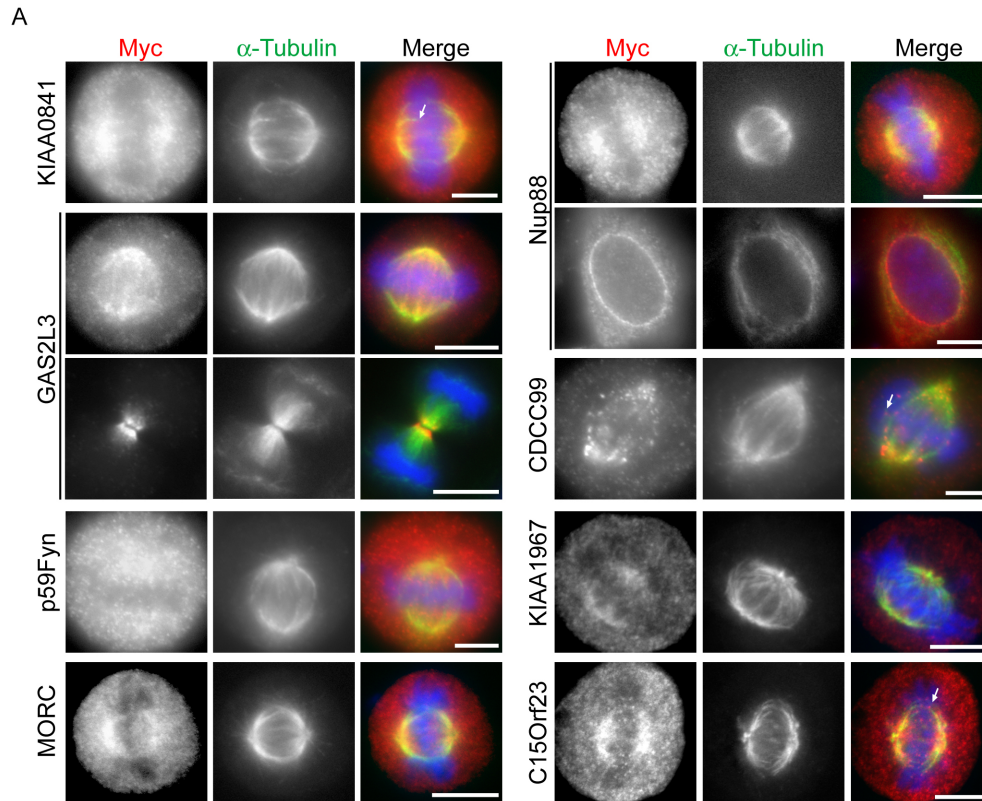
# Spindle Prediction Integrated Platform (SPIP)



**Uncovering the molecular machinery of the human spindle: an integration of wet and dry systems biology.** Ana M. Rojas, Thomas Skøt Jensen, Anna Santamaria and Rainer Malik, Roman Körner, David de Juan, Martin Krallinger, Daniel Aaen Hansen, Robert Hoffmann, Jonathan Lees, Adam Reid, Corin Yeats, Anja Wehner, Sabine Elowe, Ian Morilla, Søren Brunak, Erich Nigg, Christine Orengo, Alfonso Valencia, **Juan A. G. Ranea.** PLoS ONE 2012.

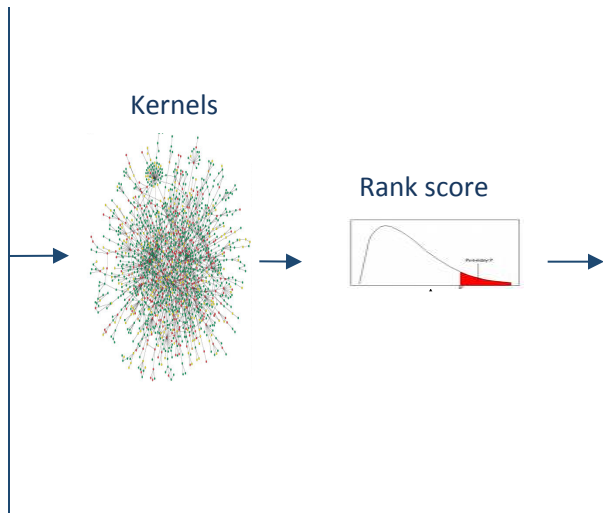
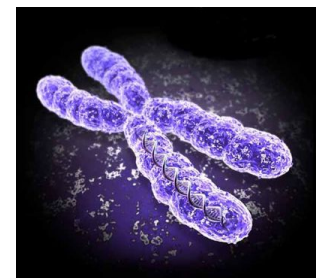
# Validación experimental de la plataforma SPIP :

Más de un 70% de éxito encontrando nuevas proteínas del huso mitótico



**Uncovering the molecular machinery of the human spindle: an integration of wet and dry systems biology.** Ana M. Rojas, Thomas Skøt Jensen, Anna Santamaria and Rainer Malik, Roman Körner, David de Juan, Martin Krallinger, Daniel Aaen Hansen, Robert Hoffmann, Jonathan Lees, Adam Reid, Corin Yeats, Anja Wehner, Sabine Elowe, Ian Morilla, Søren Brunak, Erich Nigg, Christine Orengo, Alfonso Valencia, **Juan A. G. Ranea.** PLoS ONE 2012.

# Prediction of novel mitotic chromosome condensation proteins

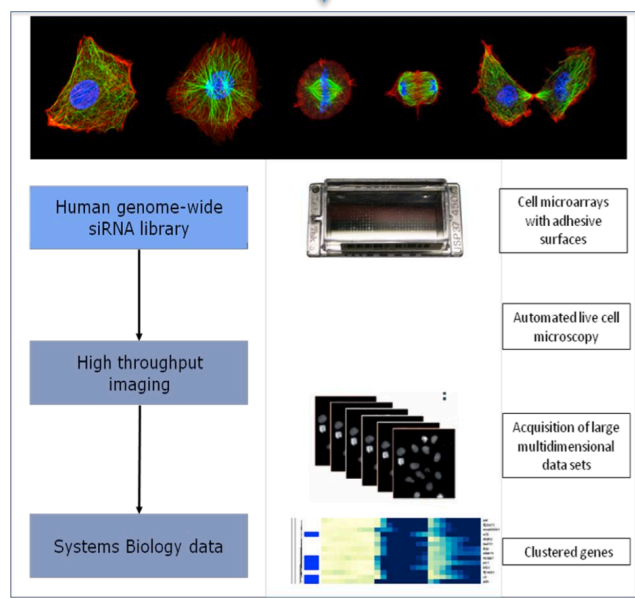


### Predictions

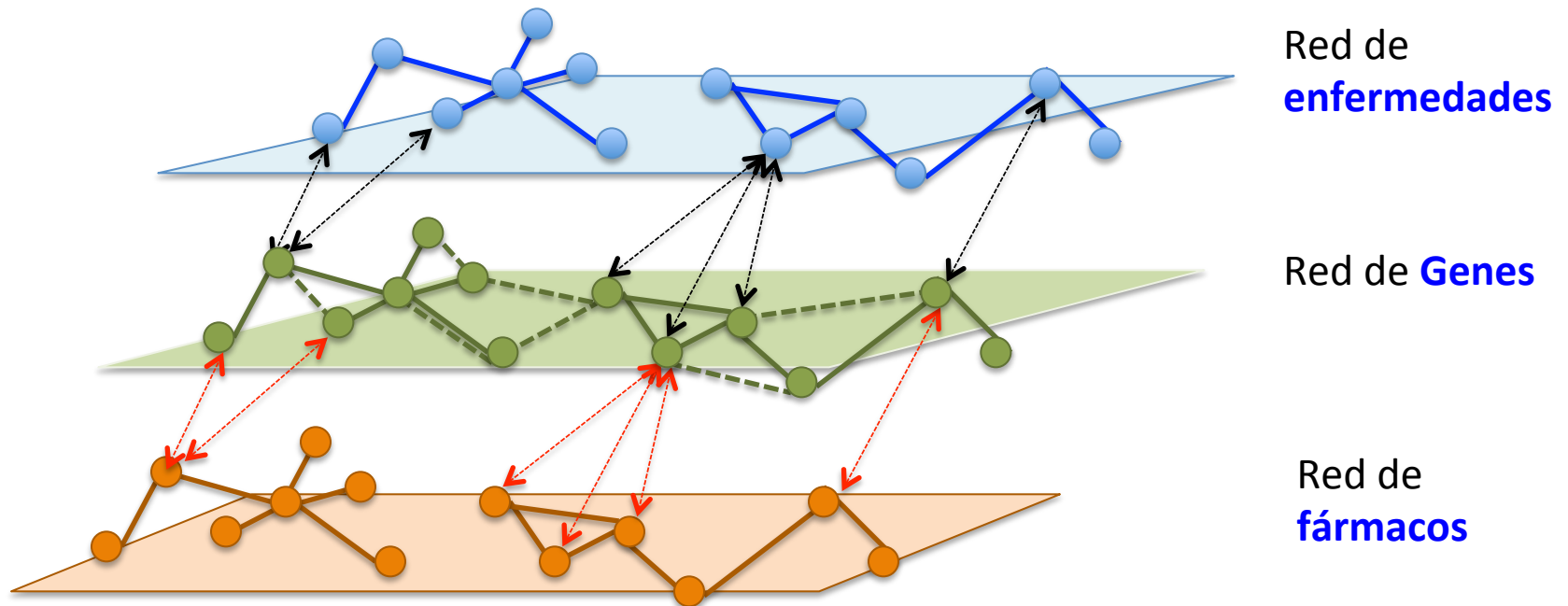
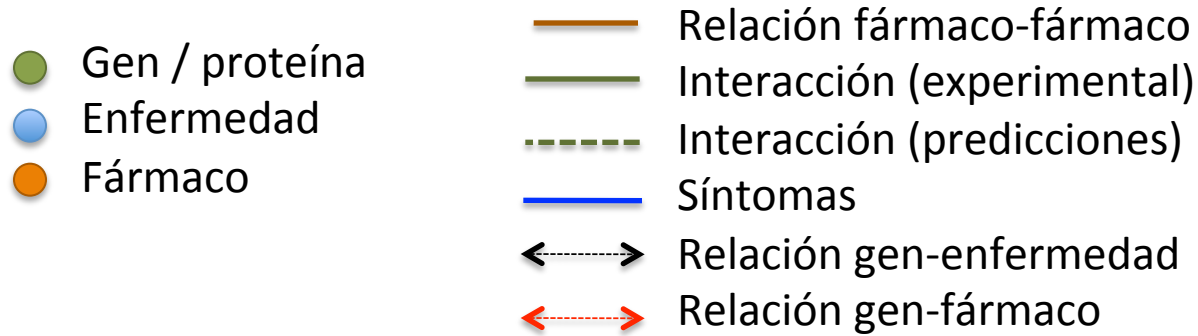
Filter score	Target IDs	ENVIADO	DTU	UCI	Ref ID	Size	AA	Uniprot_Accession
2	3972	ENVIADO_HUMAN	0.00	2.22	AAP2C	272	272	E-ADP-activated protein kinase subunit beta-2
3	11211	ENVIADO_HUMAN	0.00	1.00	AAP2C	609	609	E-ADP-activated protein kinase subunit gamma-2; PRKSD3
4	2474	PRKSD1_HUMAN	0.00	0.00	AAP2C	136	136	Protein 136
5	2463	PRKSD1_HUMAN	0.00	0.00	AAP2C	231	231	E-ADP-activated protein kinase subunit gamma-1
6	2466	ENVIADO_HUMAN	0.00	0.00	ENVIADO	279	279	Protein kinase subunit beta-1; ENVIADO
7	2149	PRKSD1_HUMAN	0.00	0.00	AAP2C	431	431	E-ADP-activated protein kinase subunit gamma-1
8	2148	ENVIADO_HUMAN	0.00	0.00	AAP2C	381	381	Protein kinase subunit beta-1; ENVIADO
9	2147	ENVIADO_HUMAN	0.00	0.00	AAP2C	270	270	E-ADP-activated protein kinase subunit beta-1
10	2146	ENVIADO_HUMAN	0.00	0.00	AAP2C	270	270	E-ADP-activated protein kinase subunit beta-1
11	2121	ENVIADO_HUMAN	0.00	0.00	ENVIADO	1647	1647	Protein kinase subunit beta-1; ENVIADO
12	2145	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
13	2144	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
14	2143	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
15	2142	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
16	2141	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
17	2140	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
18	2139	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
19	2138	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
20	2137	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
21	2136	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
22	2135	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
23	2134	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
24	2133	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
25	2132	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
26	2131	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
27	2130	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
28	2129	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
29	2128	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
30	2127	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
31	2126	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
32	2125	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
33	2124	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
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37	2120	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
38	2119	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
39	2118	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
40	2117	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
41	2116	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
42	2115	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
43	2114	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
44	2113	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
45	2112	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
46	2111	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
47	2110	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
48	2109	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
49	2108	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
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53	2104	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
54	2103	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
55	2102	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
56	2101	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
57	2100	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
58	2099	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
59	2098	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
60	2097	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
61	2096	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
62	2095	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
63	2094	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
64	2093	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
65	2092	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
66	2091	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
67	2090	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
68	2089	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
69	2088	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
70	2087	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
71	2086	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
72	2085	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
73	2084	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
74	2083	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
75	2082	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
76	2081	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
77	2080	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
78	2079	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
79	2078	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
80	2077	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1
81	2076	ENVIADO_HUMAN	0.00	0.00	ENVIADO	270	270	E-ADP-activated protein kinase subunit beta-1

## RNAi cell screening system

Integration of biological data by kernels on graph nodes allows prediction of genes involved in mitotic chromosome condensation  
 Jean-Karim Hériché, Jon G. Lees, Ian Morilla, Thomas Walter, Boryana Petrova, Priit Adler, José M. Fernández, Christian Haering, Jaak Vilo, Alfonso Valencia, Juan A. Ranea, Christine Orengo and Jan Ellenberg. (ENVIADO)



# Construcción de redes heterogéneas de genes, enfermedades raras y fármacos



- Moya-García AA, Ranea JA. Insights into Polypharmacology from Drug-Domain Associations. *Bioinformatics*. 2013 Jun 5. [Epub ahead of print]

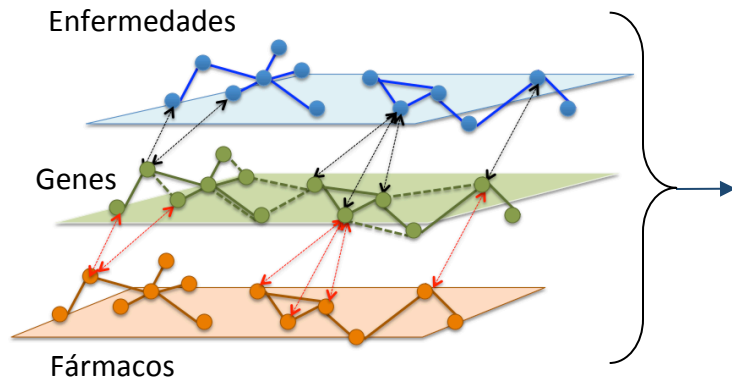
- Reyes-Palomares A, Rodríguez-López R, Ranea JA, Sánchez Jiménez F, Medina MA. Global analysis of the human pathophenotypic similarity gene network merges disease module components. *PLoS One*. 2013;8(2):e56653.

- Moya-García AA, Rodríguez CE, Morilla I, Sanchez-Jimenez F, Ranea JA.. The function of histamine receptor H4R in the brain revealed by interaction partners. *Front Biosci (Schol Ed)*. 2011 Jun 1;3:1058-66.

- Lees JG, Heriche JK, Morilla I, Ranea JA, Orengo CA. . Systematic computational prediction of protein interaction networks. *Phys Biol*. 2011 Jun;8(3):035008.

# Explotación de redes heterogéneas de genes, enfermedades raras y fármacos Para predecir nuevos genes y fármacos

## Redes heterogéneas



## Kernels



## Predicciones priorizadas

1	Filter_score	Target_Db	UMCQIN	DTU	UCL	Emb_ID	UCL	Size_AA	Uniprot_description
2	36.72	Q8PFLA:AAE2_HUMAN:OSV	22.99	1.00	2.22	AAPV2	272	51	5-AMP-activated protein kinase subunit beta-2
3	33.01	Q8PFLA:AAE2_HUMAN:OSV	28.05	1.00	0.00	AAPV2	695	51	5-AMP-activated protein kinase subunit gamma-2; HSKD59
4	24.74	P84433:H3_HUMAN:PEB3L.F	40.44	0.28	0.00	AAPV2	136	116	Histone H3
5	24.43	P84433:H3_HUMAN:PEB3L.F	54.79	0.32	0.47	AAPV2	331	116	5-AMP-activated protein kinase subunit gamma-1
6	24.05	Q8B890:Y5C2_HUMAN:GEAL	0.00	0.00	9.02	Snk1	279	116	116C domain-containing protein, mitochondrial, lichenamycin/perfusion-inducible protein homolog
7	23.94	P84433:H3_HUMAN:PEB3L.F	1.420	0.00	1.11	Snk1	453	116	Cytosolic-specific cyclophilin
8	22.84	Q8VAC3:GVAC3_HUMAN	0.00	0.00	9.02	AAPV1	354	116	5-AMP-activated protein kinase subunit beta-1
9	22.07	Q8VAC3:GVAC3_HUMAN:OSV	96.39	0.00	0.00	AAPV2	270	116	5-AMP-activated protein kinase subunit beta-1
10	22.53	Q13885:ACACA_HUMAN:OSV	0.02	1.00	1.85	AAPV1	2345	116	Acetyl-CoA carboxylase 1, AC10-alpha
11	22.21	Q8VAC3:GVAC3_HUMAN:OSV	10.04	0.00	0.07	Snk1	1447	116	Probable post-transcription activator ZNF234, ATP-dependent helicase, DNAREC4L, SNF2b
12	21.96	Q8VAC3:GVAC3_HUMAN	0.00	0.00	9.02	BRSK1	354	116	5-AMP-activated protein kinase subunit beta-1
13	21.45	Q8VAC3:GVAC3_HUMAN	0.00	0.00	9.02	MAK2	354	116	5-AMP-activated protein kinase subunit beta-1
14	21.33	Q8P794:Q8P794_HUMAN	3.87	0.00	2.43	MAK2	6998	116	5-AMP-activated protein kinase subunit beta-1
15	21.19	P80264:MPH1_HUMAN:OSV	3.98	0.00	2.34	MAK2	624	116	5-AMP-activated protein kinase subunit beta-1
16	20.37	Q8VAC3:GVAC3_HUMAN	0.00	0.00	8.99	MAK9A	354	116	5-AMP-activated protein kinase subunit beta-1
17	20.07	P84788:NRX1_HUMAN:OSV	17.91	0.00	1.54	Snk1	1037	116	Mitogen-activated protein kinase 1, Dual specificity phosphatase Cdk25K
18	20.06	P84823:NCK1_HUMAN	34.89	0.00	0.69	AAPV1	377	116	Protein NRX1, TUP1-like enhancer of split protein 1, Cysteine-rich protein NCK1, NCK adaptor protein 1, SH2/SH3 adaptor protein NCK1-alpha
19	20.06	Q8VAC3:GVAC3_HUMAN	0.00	0.00	8.99	MAK2	354	116	5-AMP-activated protein kinase subunit beta-1
20	20.43	Q8M611:WASL_HUMAN:Q72A	17.12	0.00	1.15	AAPV1	606	116	Neural Wiskott-Aldrich syndrome protein
21	20.32	Q8B890:Y5C2_HUMAN:GEAL	0.01	0.00	7.90	MAK2	270	116	116C domain-containing protein, mitochondrial, lichenamycin/perfusion-inducible protein homolog
22	20.30	Q8VAC3:GVAC3_HUMAN	0.00	0.00	8.99	MAK2	354	116	116C domain-containing protein, mitochondrial, lichenamycin/perfusion-inducible protein homolog
23	20.06	Q8B890:Y5C2_HUMAN:GEAL	0.01	0.00	7.90	Snk1	270	116	116C domain-containing protein, mitochondrial, lichenamycin/perfusion-inducible protein homolog
24	20.04	Q15919:FLJ428_HUMAN:Q148	7.93	0.00	1.61	MAK2	400	116	CASP8 and FADD-like apoptosis regulator, Cellular FLICE-like inhibitory protein, Caspase-8
25	20.02	Q8VAC3:GVAC3_HUMAN	0.00	0.00	8.99	Snk1	354	116	5-AMP-activated protein kinase subunit beta-1
26	20.00	P42267:GRIK1_HUMAN:Q2K93	4.86	0.00	1.87	AAPV1	906	116	Glutamate receptor 1, GRIK1, GRIK1c, Glutamate receptor ionotropic, AMPA 1, AMPA1a
27	19.97	Q8VAC3:GVAC3_HUMAN:OSV	0.59	0.35	6.24	BRSK1	417	116	5-AMP-activated protein kinase subunit beta-1
28	19.91	Q8VAC3:GVAC3_HUMAN	0.00	0.00	8.99	Snk1	354	116	5-AMP-activated protein kinase subunit beta-1
29	19.88	Q8VAC3:GVAC3_HUMAN	0.00	0.00	8.99	Snk1	354	116	5-AMP-activated protein kinase subunit beta-1
30	19.82	P11142:HSPTC_HUMAN:OSV	2.26	0.00	2.00	MAK2	646	116	Heat shock cognate 71 kDa protein, Heat shock 70 kDa protein beta
31	19.49	P84809:ORA_HUMAN	3.07	0.00	0.96	AAPV2	354	116	Cdk-like protein
32	19.41	Q8VAC3:GVAC3_HUMAN	0.00	0.00	8.99	Snk1	354	116	5-AMP-activated protein kinase subunit beta-1
33	19.41	Q8B890:Y5C2_HUMAN:GEAL	0.75	0.14	0.96	AAPV2	665	116	ZNF34, WDR57, Helix-helix-interacting protein 1
34	19.22	Q8B890:Y5C2_HUMAN:GEAL	0.00	0.00	6.35	Snk1	270	116	116C domain-containing protein, mitochondrial, lichenamycin/perfusion-inducible protein homolog
35	19.20	Q8B890:Y5C2_HUMAN:GEAL	0.00	0.00	7.90	MAK2	270	116	116C domain-containing protein, mitochondrial, lichenamycin/perfusion-inducible protein homolog
36	19.19	P84803:CYR1_HUMAN:OSV	1.25	0.32	0.36	AAPV2	263	116	Cyflin C
37	19.18	Q8VAC3:GVAC3_HUMAN:OSV	0.00	0.00	7.99	MAK2	622	116	116C domain-containing protein
38	19.04	Q8VLE:CELC_HUMAN:OSV	0.00	0.00	4.06	MAK2	474	116	Signal transduction protein, CELC, CELC2, RING finger protein 59
39	18.92	Q8B890:Y5C2_HUMAN:GEAL	0.00	0.00	7.90	MAK2	270	116	116C domain-containing protein, mitochondrial, lichenamycin/perfusion-inducible protein homolog
40	18.79	Q8V794:CCOL1_HUMAN:AF22	1.78	0.34	0.16	AAPV2	1480	116	Cell division cycle 2-related protein kinase 7, Cdc2-related kinase, arginine/leucine-rich
41	18.78	Q8VLE:CELC_HUMAN:OSV	0.00	0.00	7.90	AAPV1	270	116	116C domain-containing protein, mitochondrial, lichenamycin/perfusion-inducible protein homolog
42	18.78	Q8VLE:CELC_HUMAN:OSV	0.00	0.00	5.53	MAK2	426	116	ADP-5 complex subunit beta-1, Adaptin5, ADP-5 beta chain, Plasma membrane adaptor ADP

**Inmenso Espacio de exploración**

**Pequeño Espacio a explorar  
Enriquecido en Verdaderos Positivos**

- Predecir nuevos genes implicados en enfermedad
- Predecir nuevas relaciones/aplicaciones entre fármacos-proteínas-ERs
- Estudiar los contextos funcionales y moleculares donde antúan los fármacos y las proteínas, o donde se originan las enfermedades



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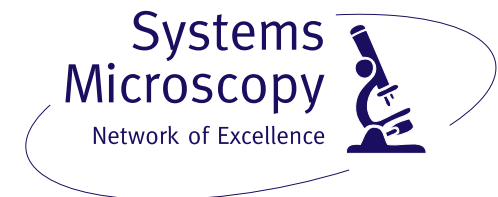
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# La tripulación...



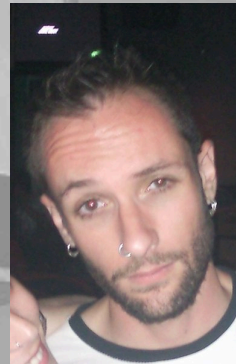
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