Departamento Biología Molecular
Universidad Autónoma de Madrid

Redes Biológicas y Biología de Sistemas

21-29 Abril 2008

Coordinación: Florencio Pazos (CNB-CSIC)

Otras Redes Biológicas (y otras aplicaciones de conceptos de redes y grafos en Biología Molecular)

Florencio Pazos (CNB-CSIC)

lorencio Pazos Cabaleiro
omputational Systems Biology Group (CNB-CSIC)
azos@cnb.csic.es

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Otras Redes Biológicas y Conceptos de Red en Biología

- **Otros ejemplos de redes biológicas**
- **Redes y datos “-omics”**
- **Conceptos de redes en terapia/diagnóstico**
- **Redes de contactos entre residuos en estructuras 3D**
- **Conclusión**

lorencio Pazos Cabaleiro
omputational Systems Biology Group (CNB-CSIC)
azos@cnb.csic.es

Redes Biológicas

Protein-protein physical interaction networks. Here nodes represent proteins, and links represent direct physical contacts between proteins. In addition to direct interaction, two proteins can interact indirectly through other proteins when they belong to the same complex.

Protein-protein genetic interaction networks. In general, two genes are said to interact genetically if a mutation in one gene either suppresses or enhances the phenotype of a mutation in its partner gene.

Expression networks. Large-scale microarray experiments probing mRNA expression levels yield vast quantities of data useful for constructing expression networks. In an expression network, genes that are coexpressed are considered connected.

Regulatory networks. Protein-DNA interactions are an important and common class of interactions. Most DNA-binding proteins are transcription factors that regulate the expression of target genes. Combinatorial use of transcription factors further complicates simple interactions of target genes for a given transcription factor. A regulatory network consists of transcription factors and their targets with a specific directionality to the connection between a transcription factor and its target.

Metabolic networks. These networks describe the biochemical reactions within different metabolic pathways in the cell. Nodes represent metabolic substrates and products, and links represent metabolic reactions.

Signaling networks. These networks represent signal transduction pathways through protein-protein and protein-small molecule interactions. Nodes represent proteins or small molecules, and links represent signal transduction events.

Other... Phosforilation netowrk, ...

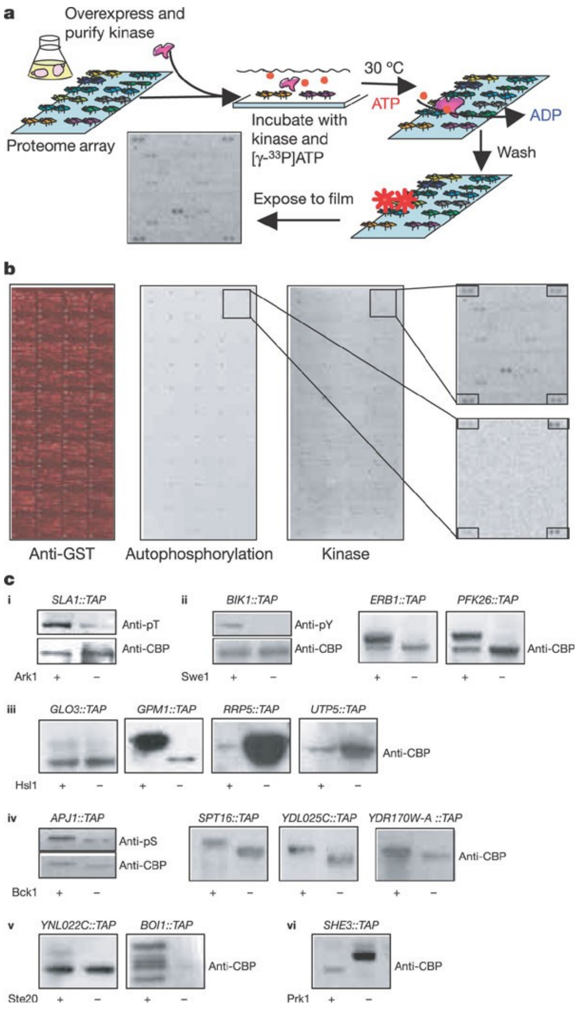
Xia, Y., Yu, H., Jansen, R., Seringhaus, M., Baxter, S., Greenbaum, D., Zhao, H. and Gerstein, M. (2004) Analyzing cellular biochemistry in terms of molecular networks. *Annu Rev Biochem*, **73**, 1051-1087.

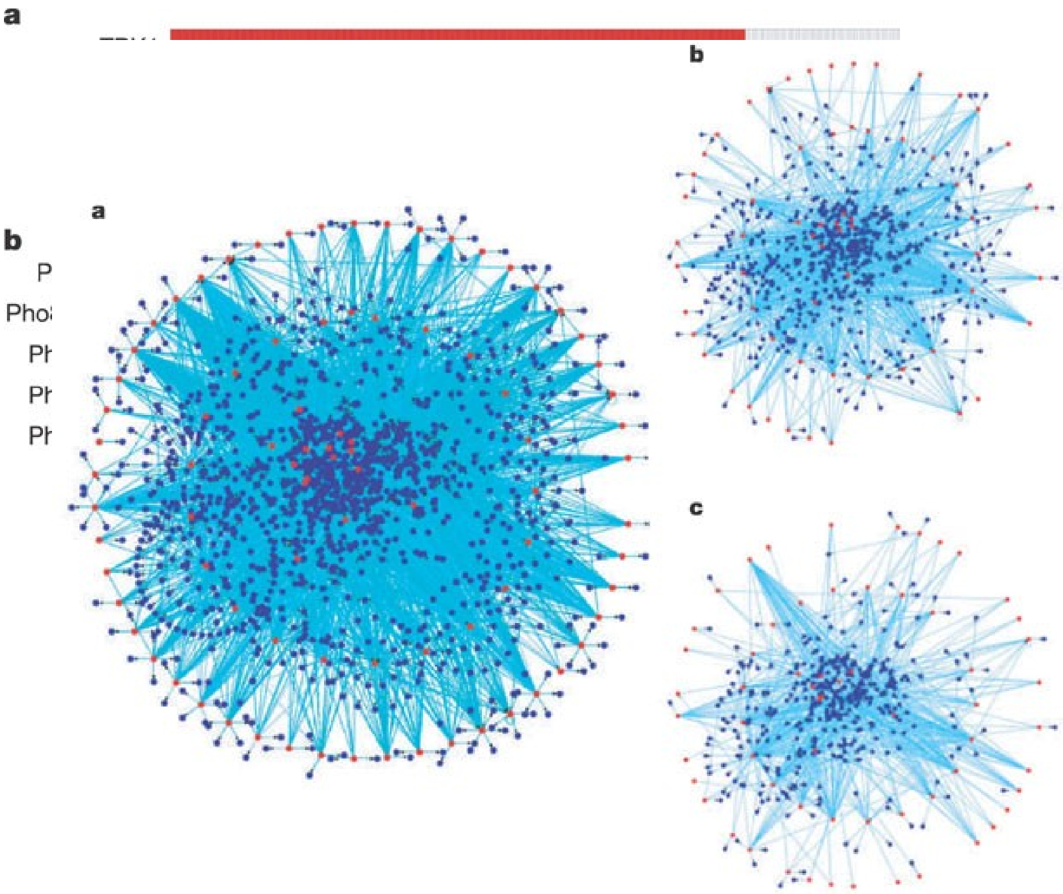
Redes Biológicas y Biología de Sistemas

21-29 Abril 2008

L. 21 **10:00-12:15** Introducción Descripción del curso *F. Pazos (CNB)* **12:30-14:00** Teoría de Grafos (I) *C. Aguirre (UAM)*	**M. 22** **10:00-12:00** Redes de interacciones entre proteínas *D. Juan (CNIO)* **12:00-14:00** Manejo y visualización de redes *D. Juan (CNIO)*	**Mi. 23** **10:00-12:15** Redes de regulación génica *I. Cases (CNIO)* **12:30-14:00** Teoría de Grafos (II) *C. Aguirre (UAM)*	J. 24	**V. 25** **10:00-12:00** Bacterias para el medio ambiente: de la Bioremediación a la Biología Sintética *V. Lorenzo (CNB)* **12:30-14:00** Modelado cuantitativo de circuitos biológicos *S. Moreno (CNB)*	S. 26	D. 27
L. 28 **10:00-12:00** Redes metabólicas *F. Pazos (CNB)* **12:00-14:00** Otras redes en Biología Molecular *F. Pazos (CNB)*	**M. 29** **10:00-14:00** Ejercicios prácticos y trabajos de evaluación *F. Pazos (CNB)*	Las clases serán en el Aula de Informática 0 de la Facultad de Ciencias de la UAM. Excepto el primer dia (L.21) que serán en la sala de seminarios "B" del CNB (Hall). **http://pdg.cnb.csic.es/pazos/cursos/bionet_UAM**				

Otros... “fosforiloma”



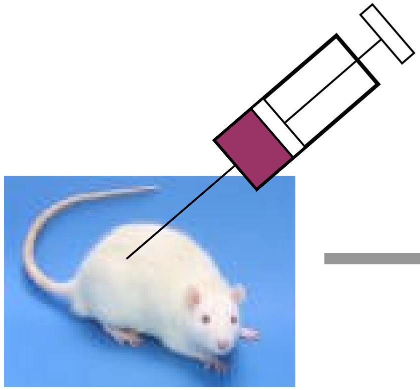


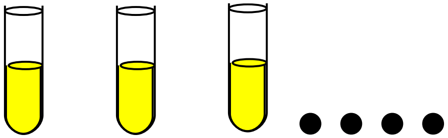
- Ptacek, J., Devgan, G., Michaud, G., Zhu, H., Zhu, X., Fasolo, J., Guo, H., Jona, G., Breitkreutz, A., Sopko, R., *et al.* (2005) Global analysis of protein phosphorylation in yeast. *Nature.*, **438**, 679-684.

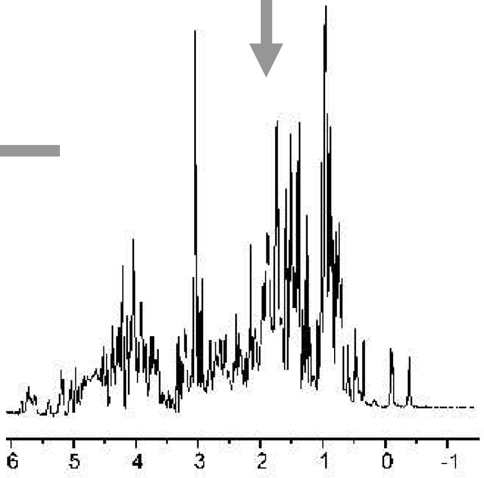
Metabo**n**omic networks

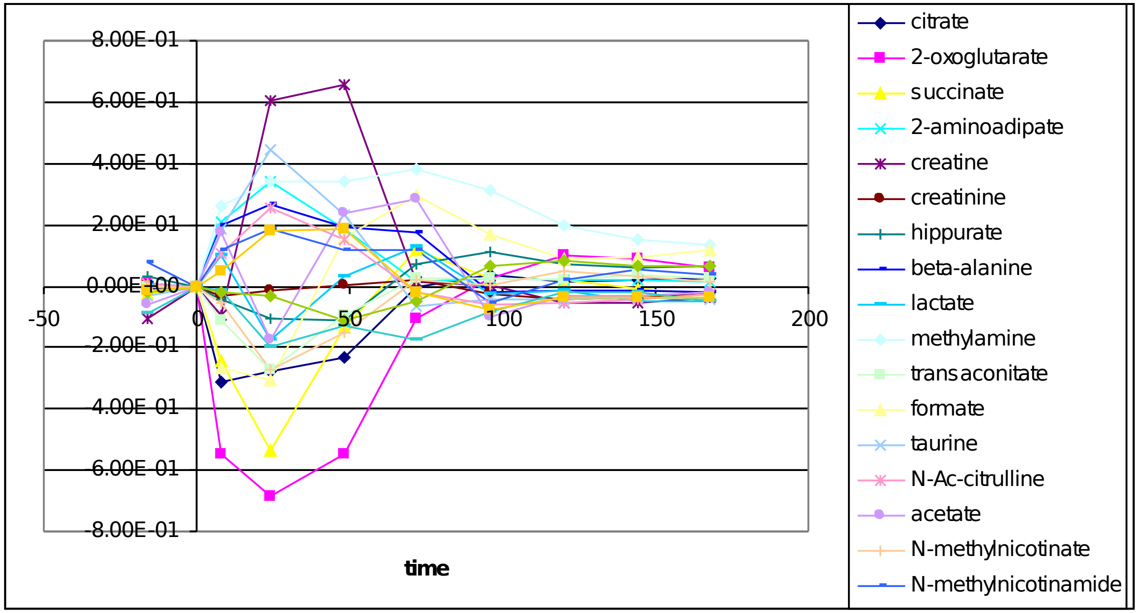
Static -> dynamic

Genome -> DNA arrays
Metabolome -> metabolite profiling





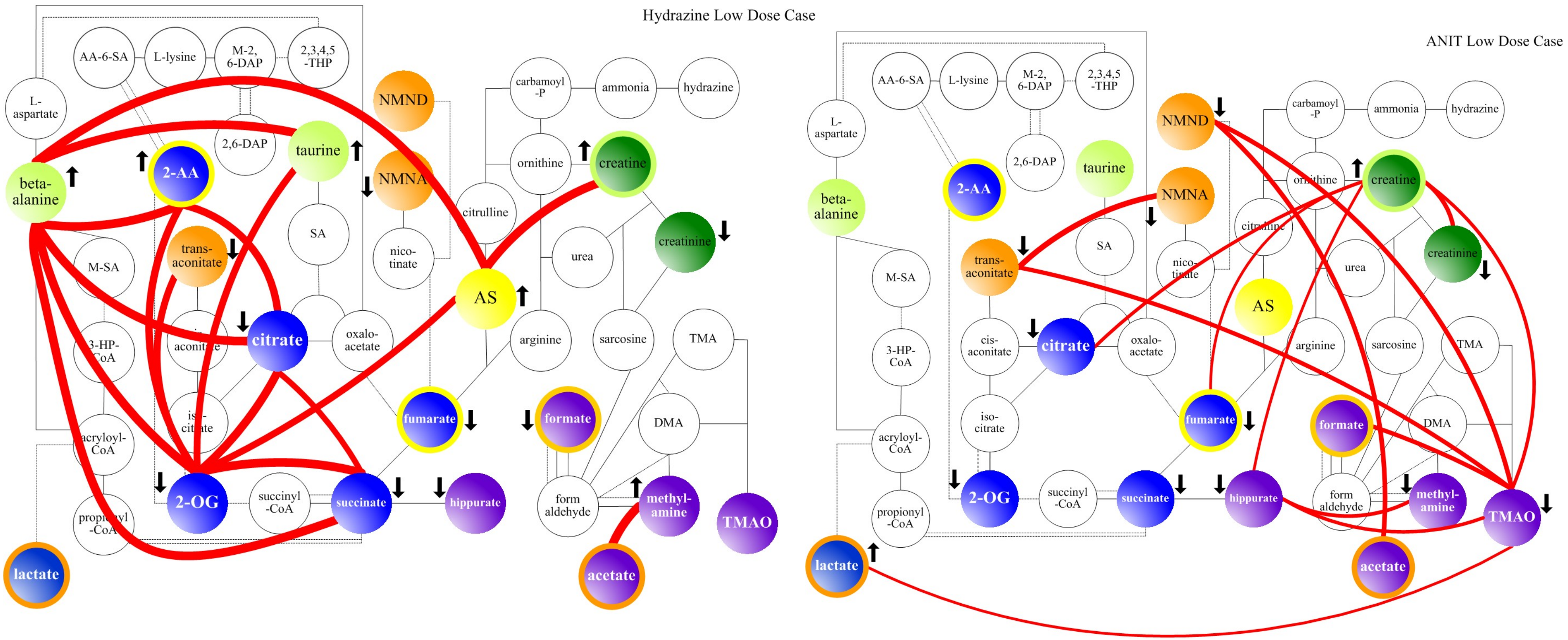




Lindon, J.C., Nicholson, J.K., Holmes, E., et al. (2003) Contemporary issues in toxicology. The role of metabonomics in toxicology and its evaluation by the COMET project. *Tox Appl Pharm*, **187,** 137-146.

Nicholson J. K., Connelly J., Lindon J. C. & Holmes E. (2002) Metabonomics: a platform for studying drug toxicity and gene function. *Nature Reviews Drug Discovery* **1,** 153 – 161

Dependencias entre metabolitos



Hydrazine Low Dose Case

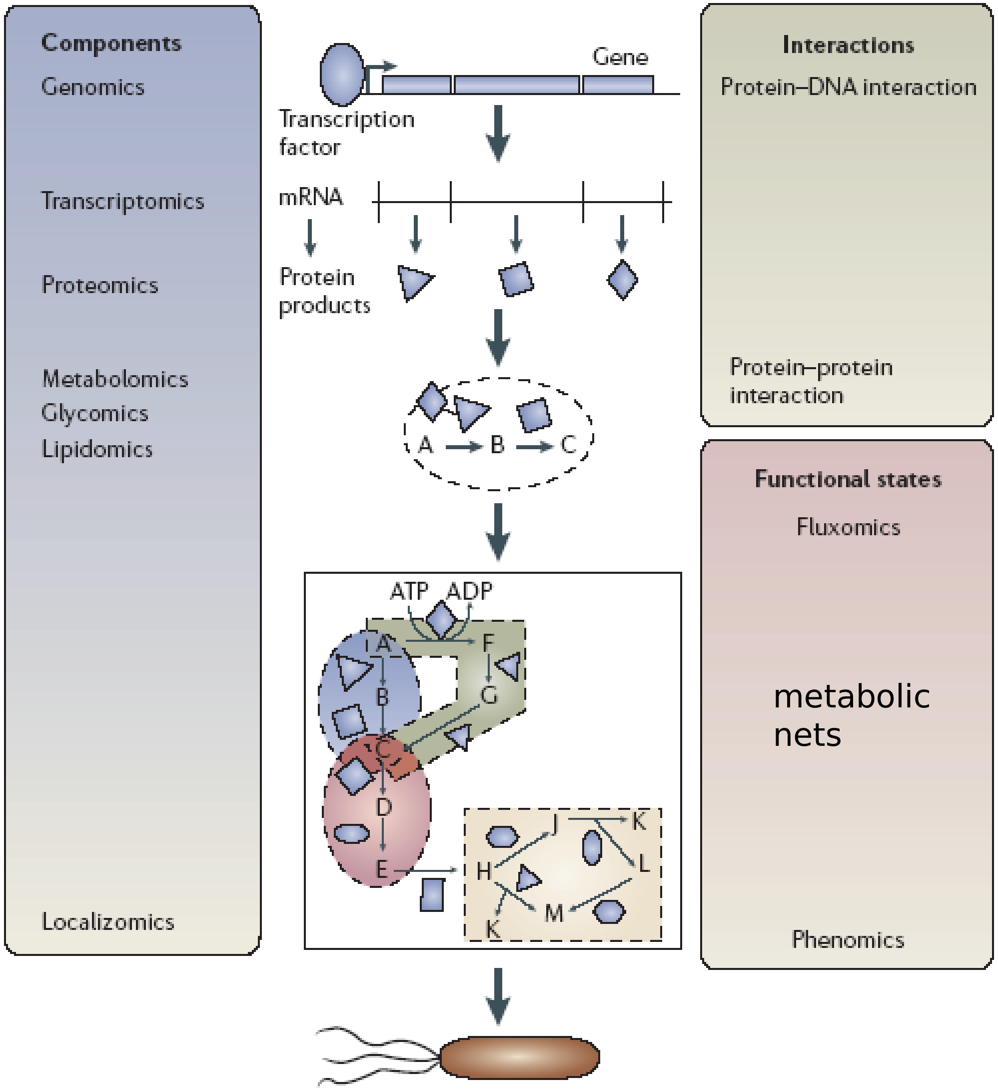
ANIT Low Dose Case

Bang, J.-W., Crockford, D.J., Holmes, E., Pazos, F., Sternberg, M.J., Muggleton, S.H. and Nicholson, J.K. (2006) Integrative Top-Down System Metabolic Modeling in Experimental Disease States via Data-Driven Bayesian Methods. *J Proteome Res*, **7**, 497-503.

“-omics” y redes en el contexto del dogma central

-omics

redes



metabolic nets

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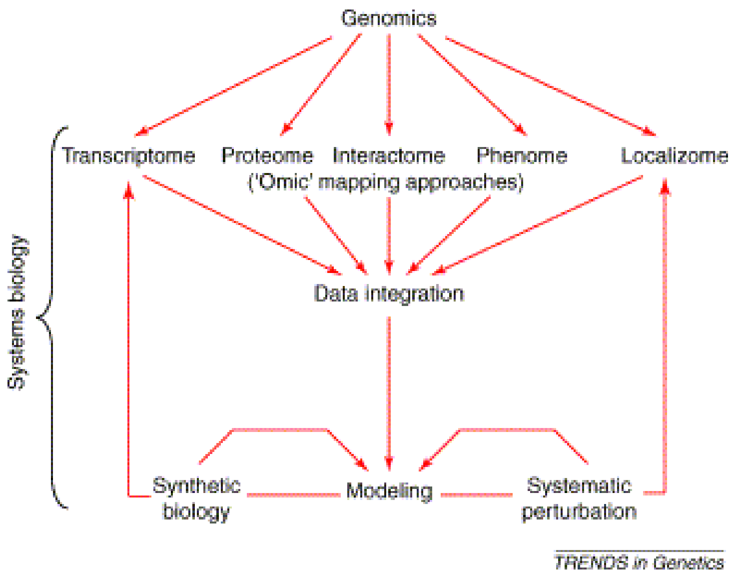
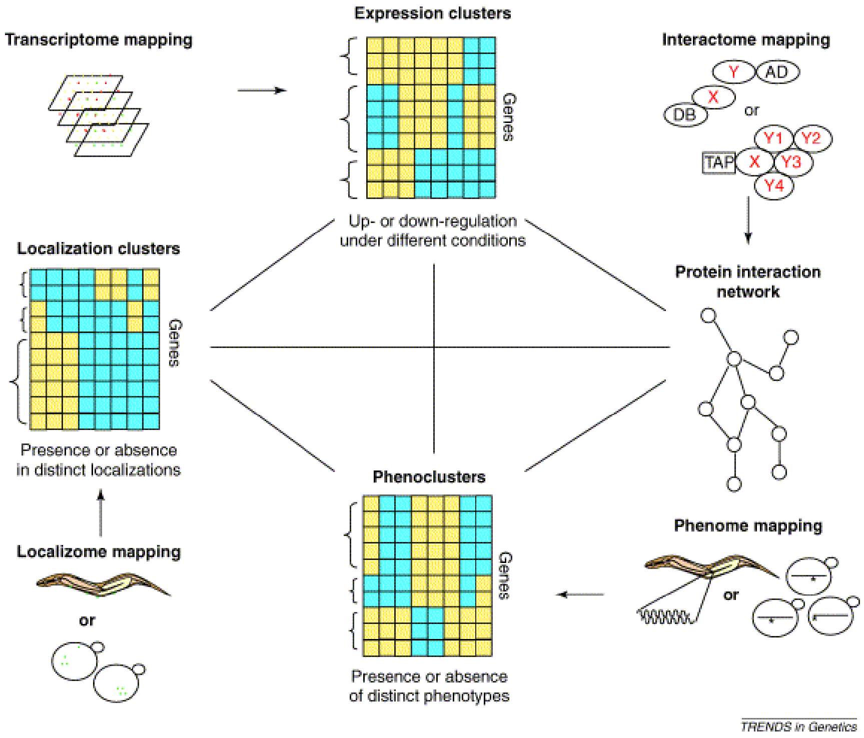
and Palsson, B.O. (2006) The model organism as a system: integrating 'omics' data sets. *Nat Rev Mol Cell Biol.*, **7**, 198

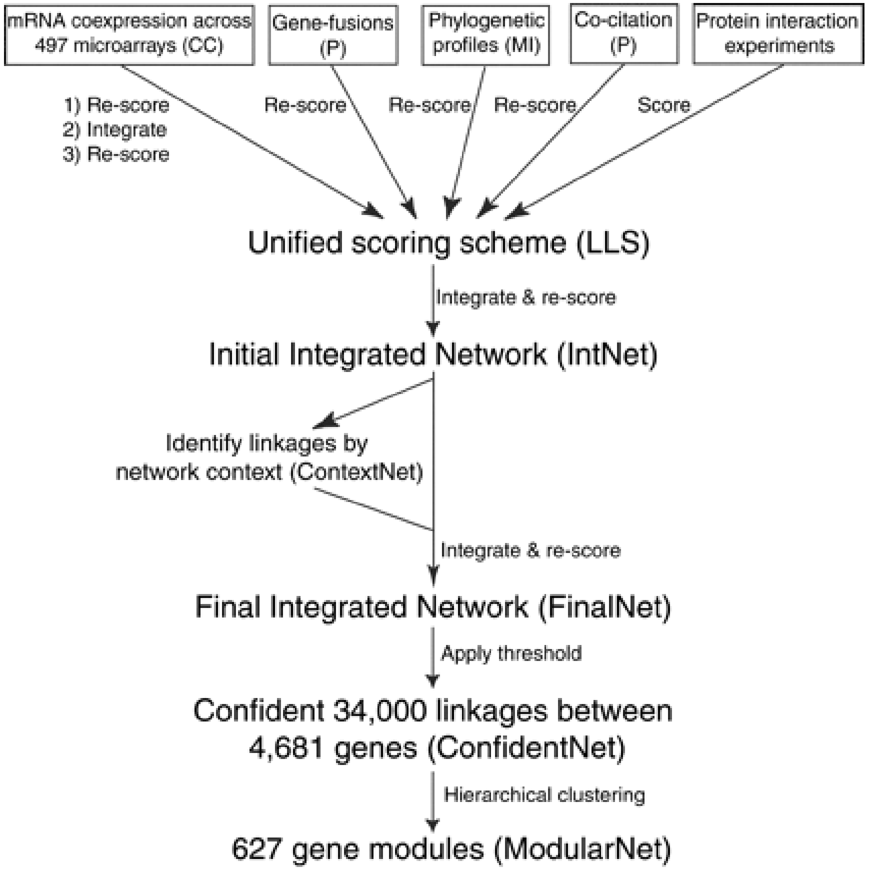
Combinación de datos “-omics”





Ge, H., Walhout, A.J. & Vidal, M. (2003) Integrating 'omic' information: a bridge between genomics and systems biology. *Trends Genet*, **19**, 551-560.

Combinación de datos "-omics"



mRNA coexpression across 497 microarrays (CC)

Gene-fusions (P)

Phylogenetic profiles (MI)

Co-citation (P)

Protein interaction experiments

1) Re-score
2) Integrate
3) Re-score

Re-score

Re-score

Re-score

Score

Unified scoring scheme (LLS)

Integrate & re-score

Initial Integrated Network (IntNet)

Identify linkages by network context (ContextNet)

Integrate & re-score

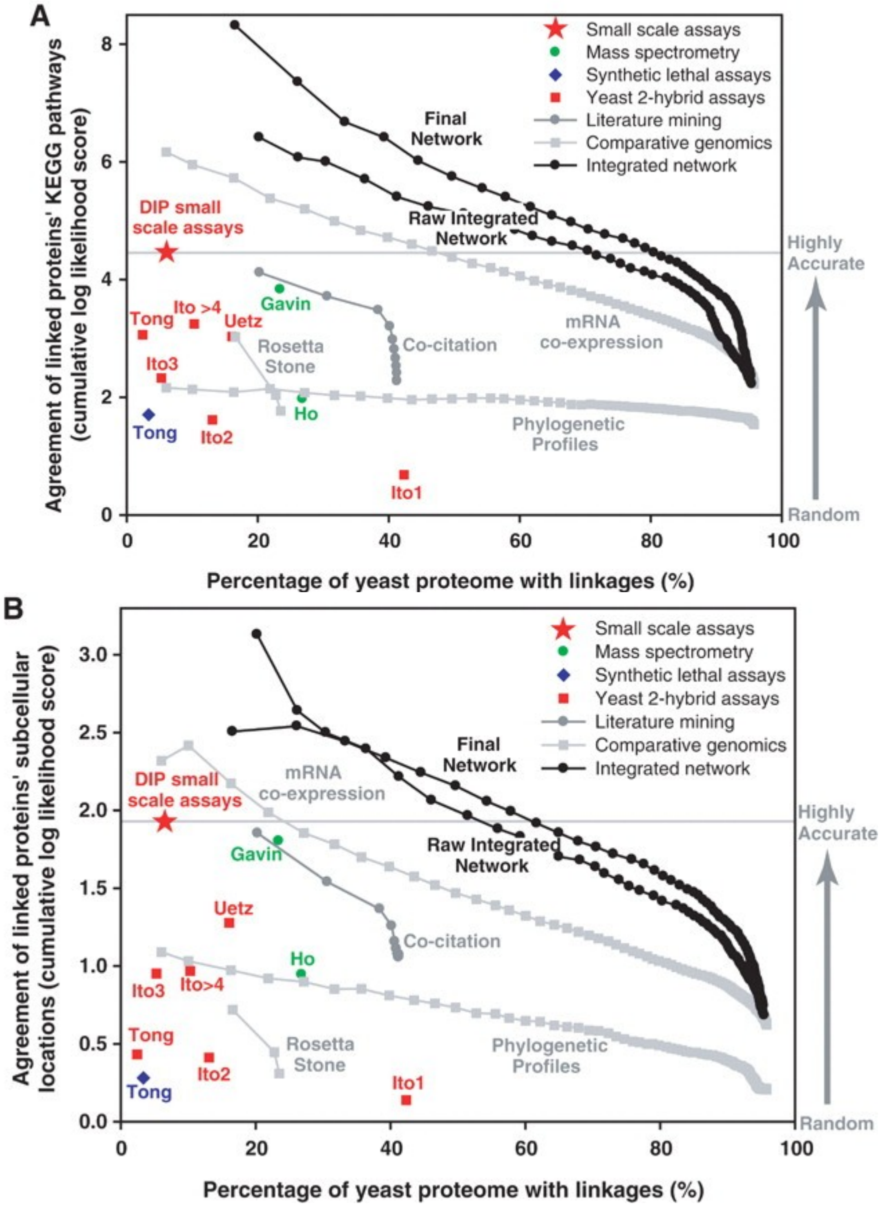
Final Integrated Network (FinalNet)

Apply threshold

Confident 34,000 linkages between 4,681 genes (ConfidentNet)

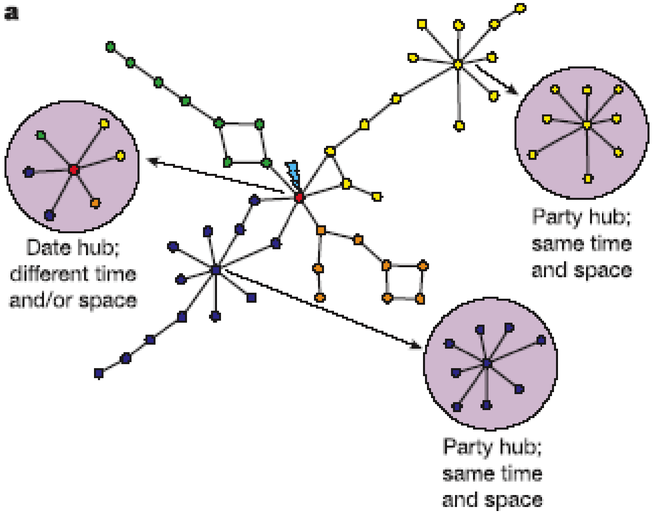
Hierarchical clustering

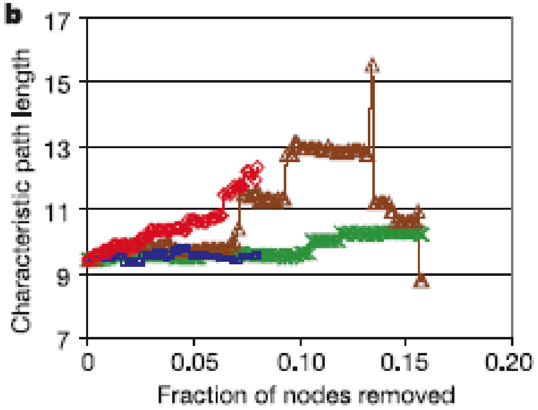
627 gene modules (ModularNet)



Lee, I., Date, S.V., Adai, A.T. and Marcotte, E.M. (2004) A probabilistic functional network of yeast genes. *Science*, **306**, 1555-1558.

Adding ‘dynamic’ information to protein interaction networks
Combination of protein interactions with expression arrays





Random
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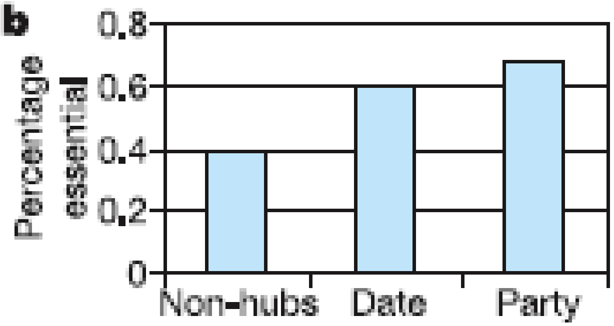
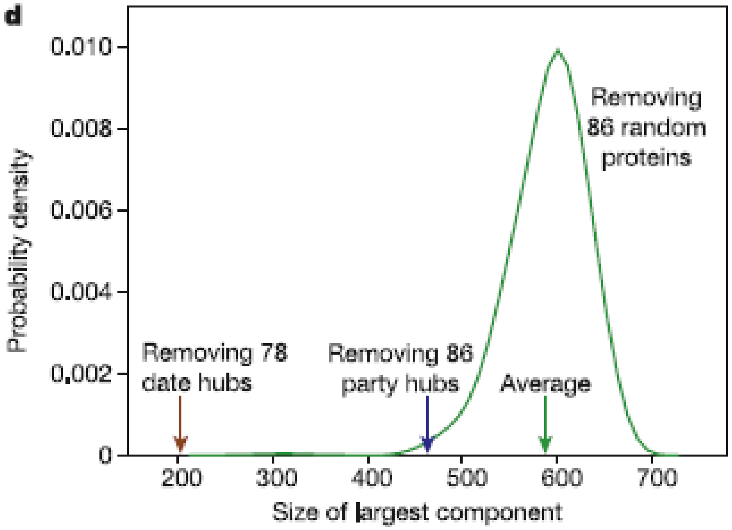
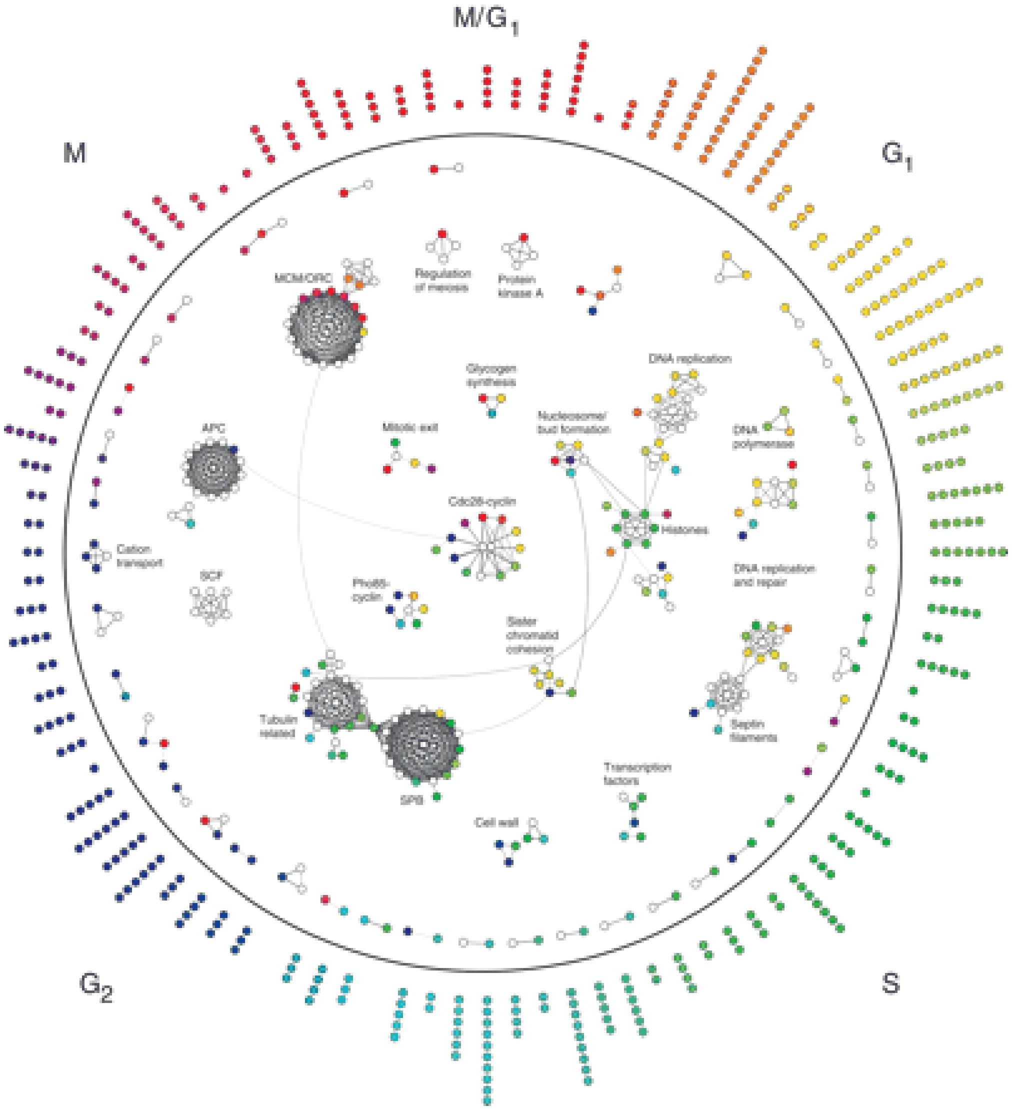




Han, J.D., Bertin, N., Hao, T., Goldberg, D.S., Berriz, G.F., Zhang, L.V., Dupuy, D., Walhout, A.J., Cusick, M.E., Roth, F.P. and Vidal, M. (2004) Evidence for dynamically organized modularity in the yeast protein-protein interaction network. *Nature*, **430**, 88-93. Epub 2004 Jun 2009.

Combination of protein interactions with expression arrays



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rg U, Jensen LJ, Brunak S, Bork P. (2005). Dynamic complex formation during the yeast cell cycle. *Science.* **307(5710**

Repositorios de redes y datos “-omics”

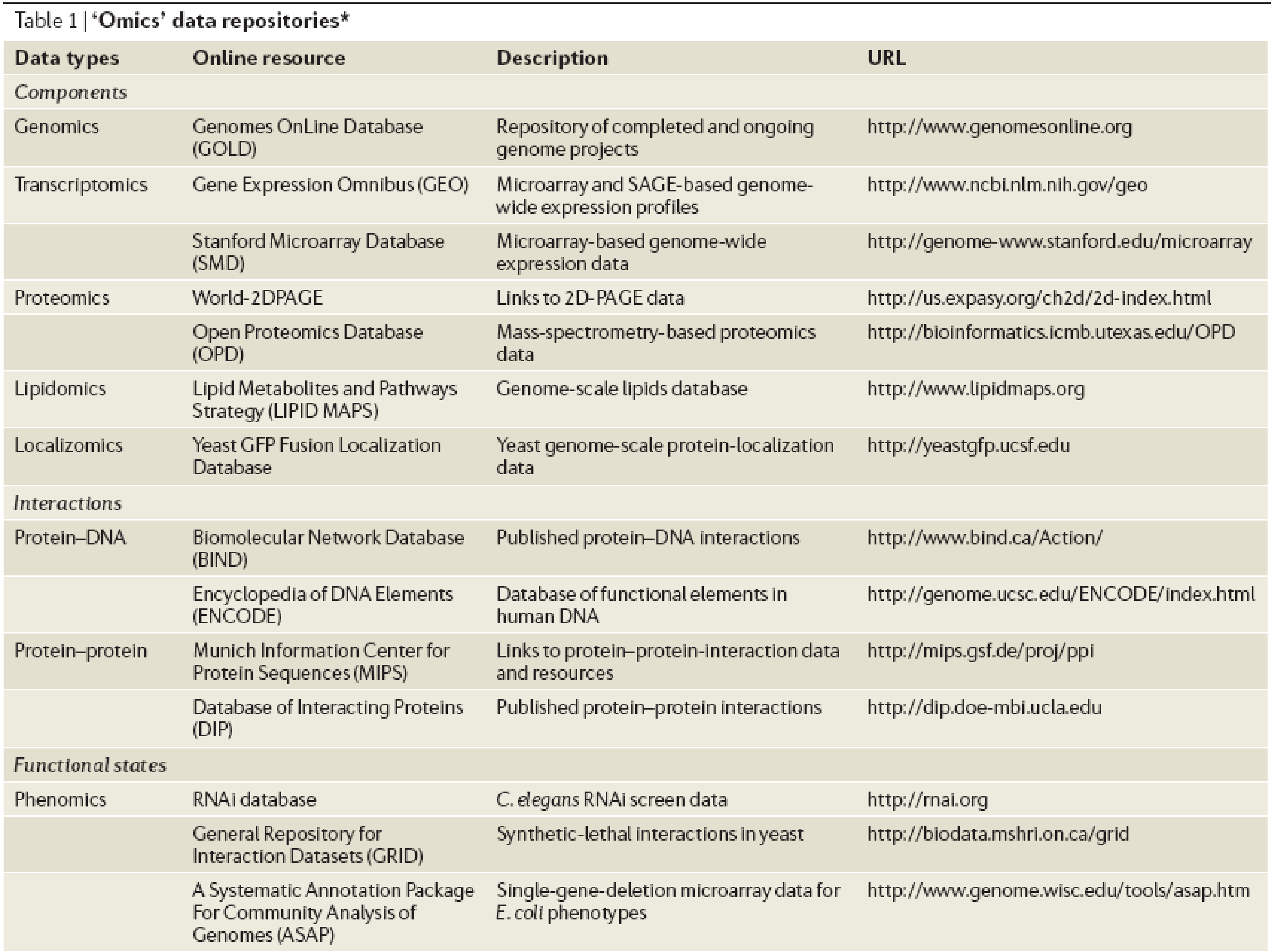

Table 1 | **‘Omics’ data repositories***

Data types	**Online resource**	**Description**	**URL**
Components			
Genomics	Genomes OnLine Database (GOLD)	Repository of completed and ongoing genome projects	http://www.genomesonline.org
Transcriptomics	Gene Expression Omnibus (GEO)	Microarray and SAGE-based genome-wide expression profiles	http://www.ncbi.nlm.nih.gov/geo
	Stanford Microarray Database (SMD)	Microarray-based genome-wide expression data	http://genome-www.stanford.edu/microarray
Proteomics	World-2DPAGE	Links to 2D-PAGE data	http://us.expasy.org/ch2d/2d-index.html
	Open Proteomics Database (OPD)	Mass-spectrometry-based proteomics data	http://bioinformatics.icmb.utexas.edu/OPD
Lipidomics	Lipid Metabolites and Pathways Strategy (LIPID MAPS)	Genome-scale lipids database	http://www.lipidmaps.org
Localizomics	Yeast GFP Fusion Localization Database	Yeast genome-scale protein-localization data	http://yeastgfp.ucsf.edu
Interactions			
Protein–DNA	Biomolecular Network Database (BIND)	Published protein–DNA interactions	http://www.bind.ca/Action/
	Encyclopedia of DNA Elements (ENCODE)	Database of functional elements in human DNA	http://genome.ucsc.edu/ENCODE/index.html
Protein–protein	Munich Information Center for Protein Sequences (MIPS)	Links to protein–protein-interaction data and resources	http://mips.gsf.de/proj/ppi
	Database of Interacting Proteins (DIP)	Published protein–protein interactions	http://dip.doe-mbi.ucla.edu
Functional states			
Phenomics	RNAi database	*C. elegans* RNAi screen data	http://rnai.org
	General Repository for Interaction Datasets (GRID)	Synthetic-lethal interactions in yeast	http://biodata.mshri.on.ca/grid
	A Systematic Annotation Package For Community Analysis of Genomes (ASAP)	Single-gene-deletion microarray data for *E. coli* phenotypes	http://www.genome.wisc.edu/tools/asap.htm

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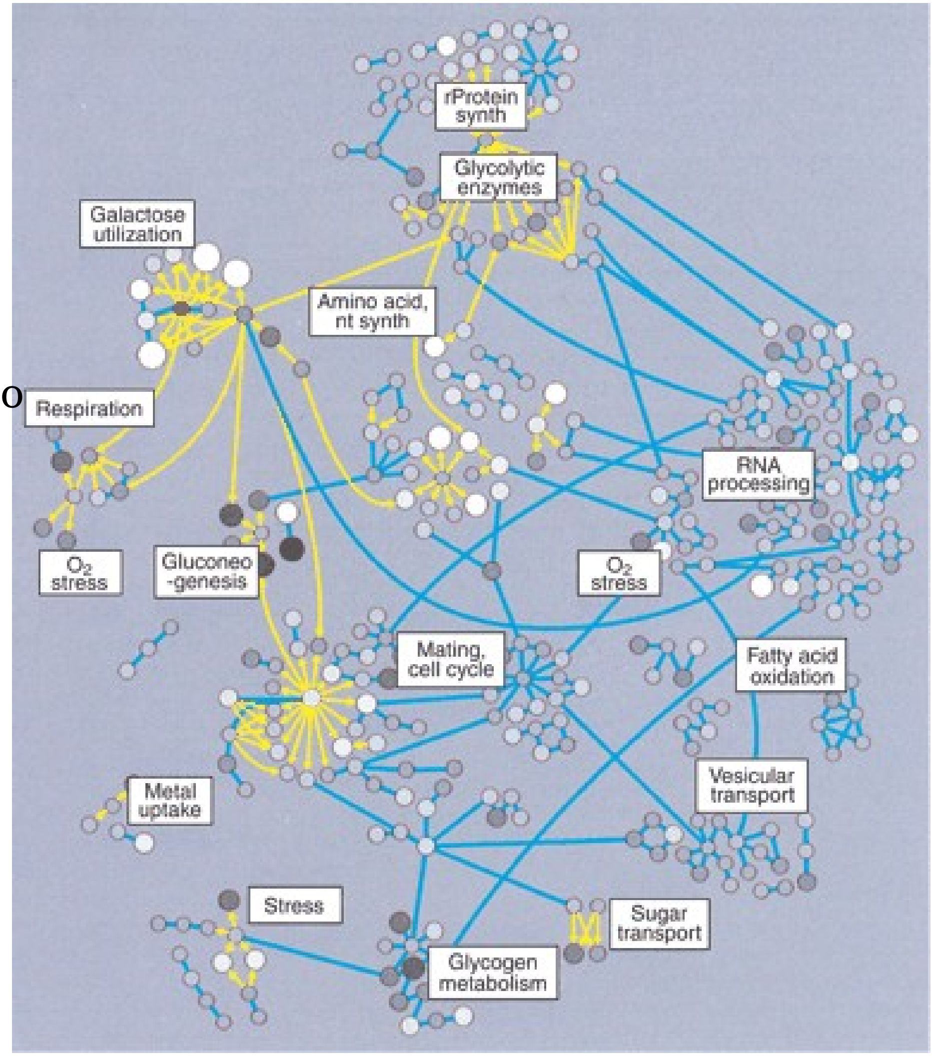
nd Palsson, B.O. (2006) The model organism as a system: integrating 'omics' data sets. *Nat Rev Mol Cell Biol.*, **7**, 198-

Redes Biológicas y Terapia/diagnóstico

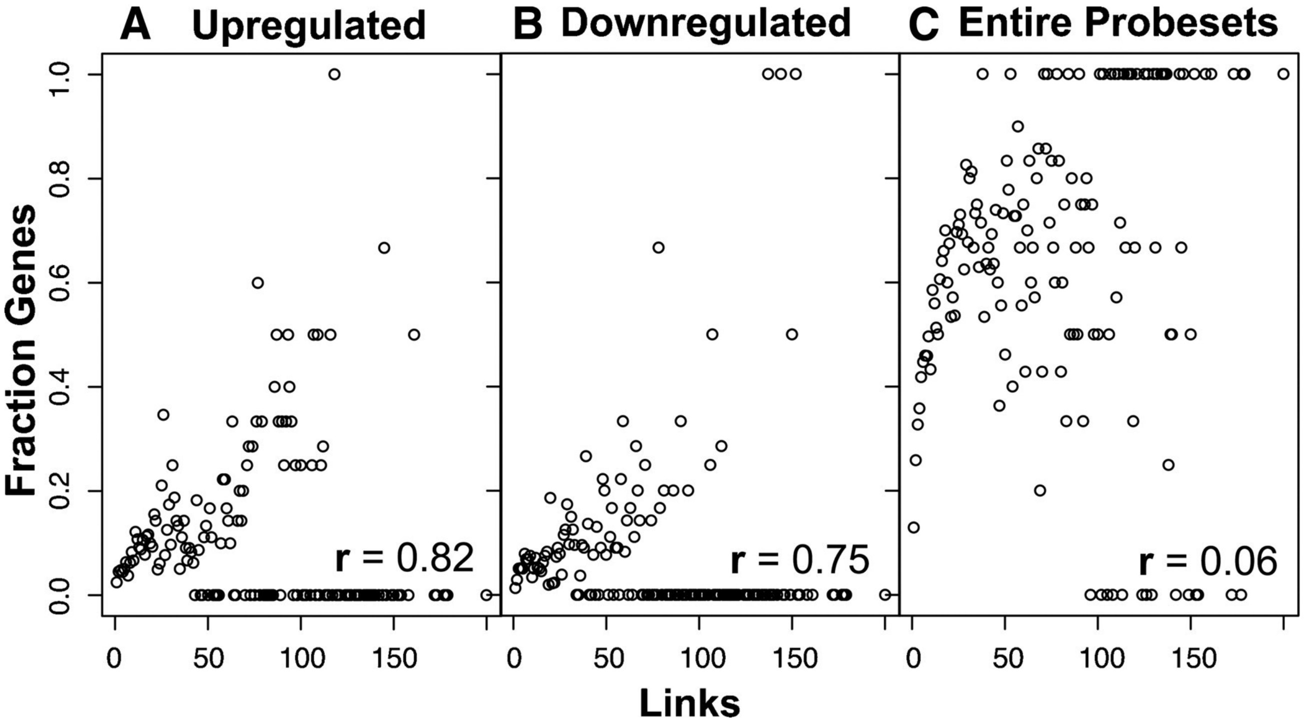
Explicacion de enfermedades desde un punto e vista de redes.

Multimarcadores.



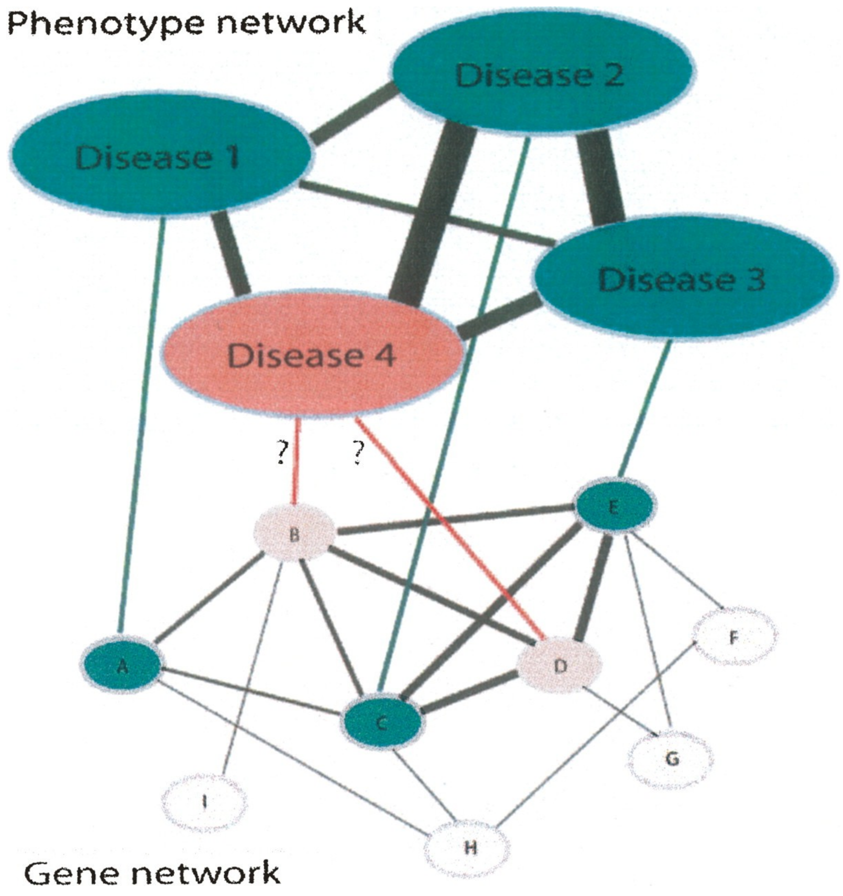
•Ideker, T., Thorsson, V., Ranish, J.A., Christmas, R., Buhler, J., Eng, J.K., Bumgarner, R., Goodlett, D.R., Aebersold, R. and Hood, L. (2001) Integrated genomic and proteomic analyses of a systematically perturbed metabolic network. *Science*, **292**, 929-934.

Características topológicas de genes implicados en cancer



. & Sharan, R. (2008). Protein networks in disease. *Genome Research.* **18(4):**644-652

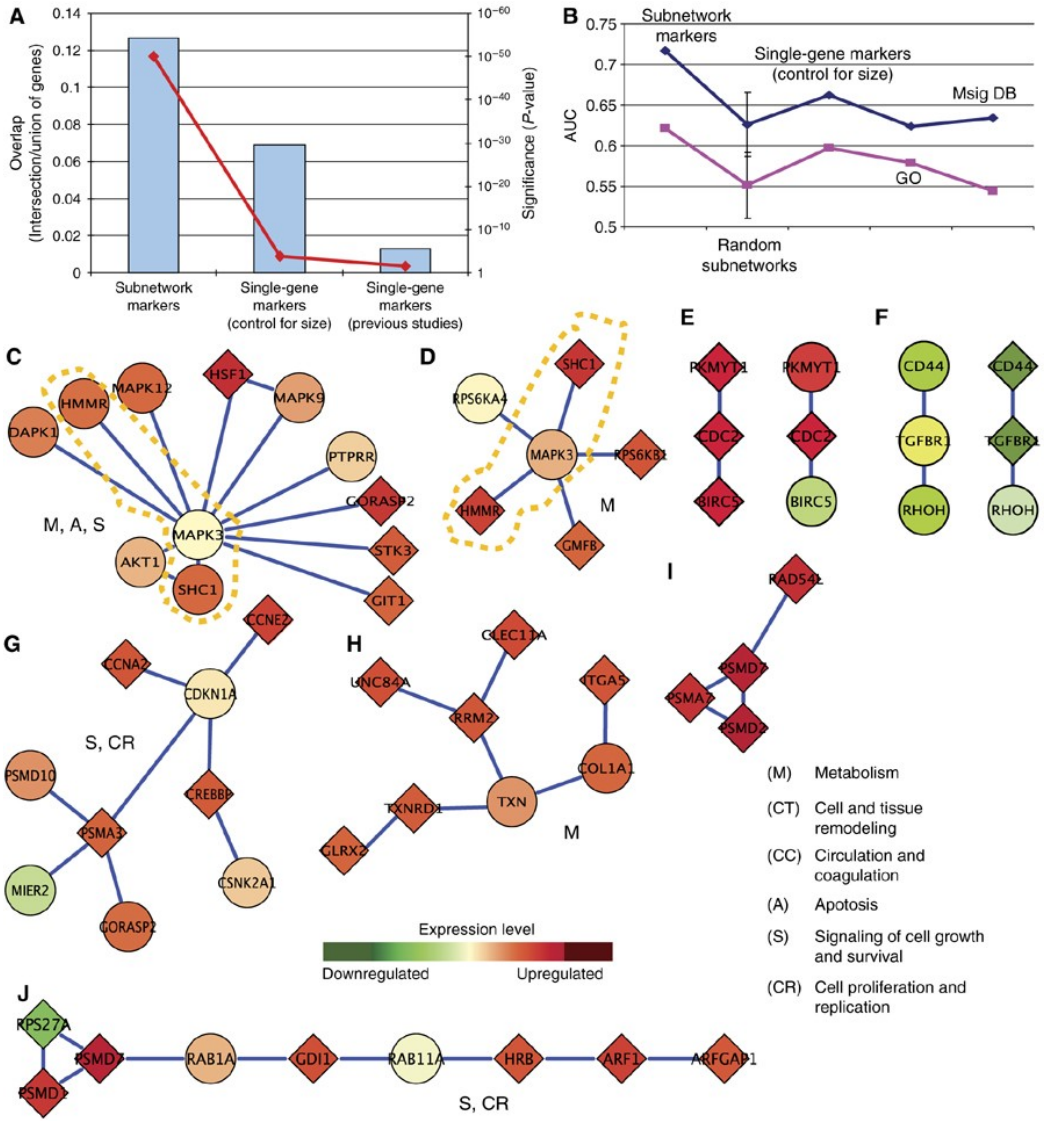
Conceptos de redes en relaciones enfermedad-fenotipo-gen



A gene-phenotype network. Shown is a combined gene–gene, gene–phenotype, and phenotype–phenotype interaction network. In this hypothetical example, diseases 1, 2, and 3 have known causative genes (genes A, C, and E, respectively), and are all phenotypically related to disease 4, which lacks an identified causative gene. If the known causative genes are functionally closely related, as in this case, then candidate genes (genes B and D) can be hypothesized for disease 4 due to their close functional relationships to the known genes of the phenotypically related diseases. Black lines of varying thickness indicate the degree of phenotypic and functional similarity between diseases and genes, respectively. Reproduced from Oti and Brunner (2007) and reprinted with permission from Blackwell Publishing Ltd.

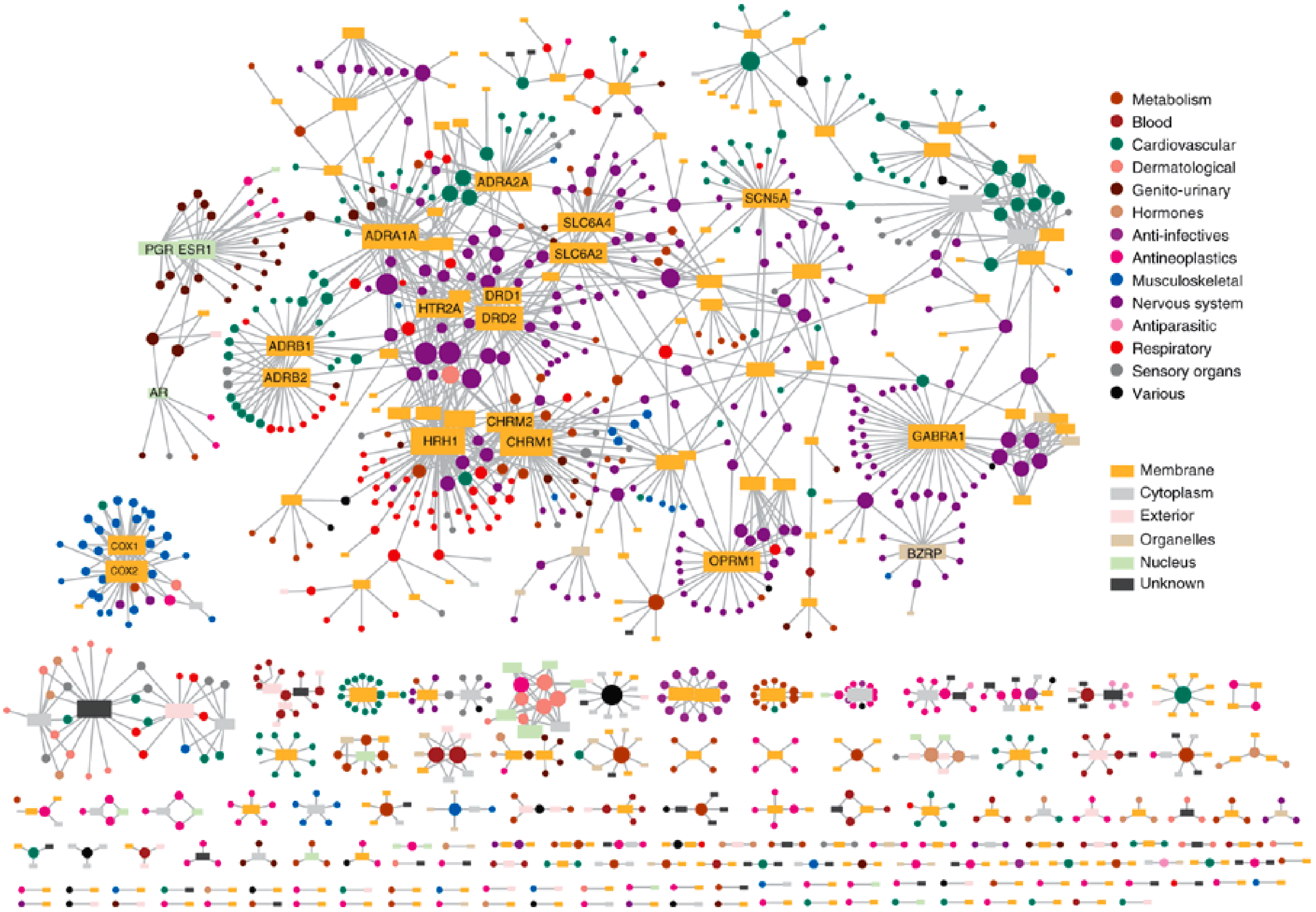
. & Sharan, R. (2008). Protein networks in disease. *Genome Research.* **18(4):**644-652

Redes Biológicas y Terapia/diagnóstico



, Lee, E., Liu, Y.T., Lee, D. and Ideker, T. (2007) Network-based classification of breast cancer metastasis. *Mol Syst Bi*

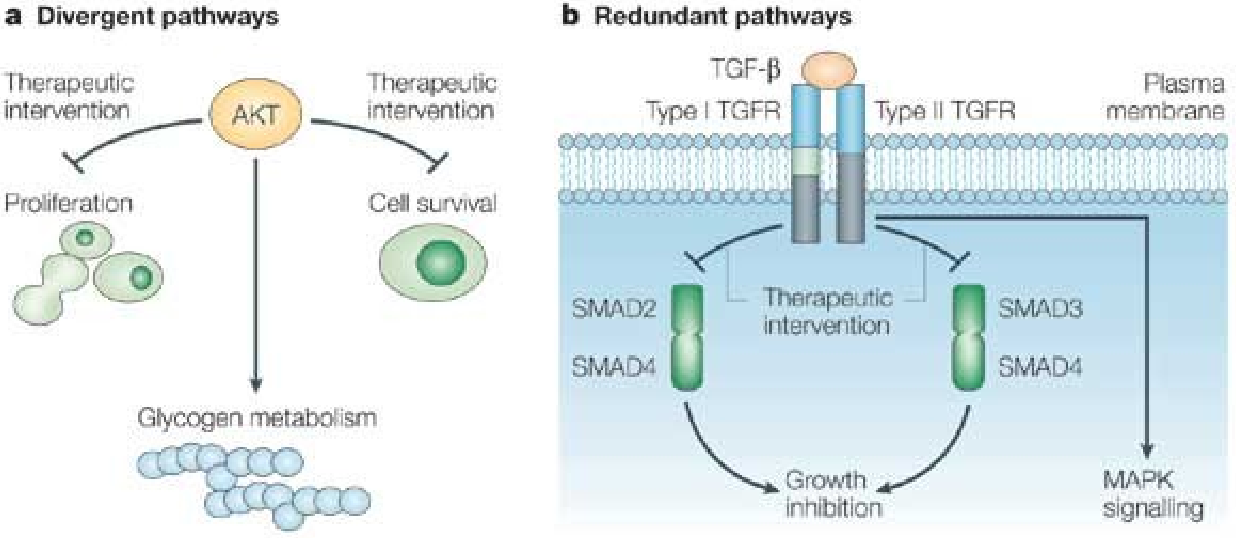
“network pharmacology”
Drug-target network



Yildirim, M.A., Goh, K.I., Cusick, M.E., Barabasi, A.L. and Vidal, M. (2007) Drug-target network. *Nat Biotechnol.*, **25** 1119-1126.

Combinación de Drogas

Networked systems require “networked” drugs

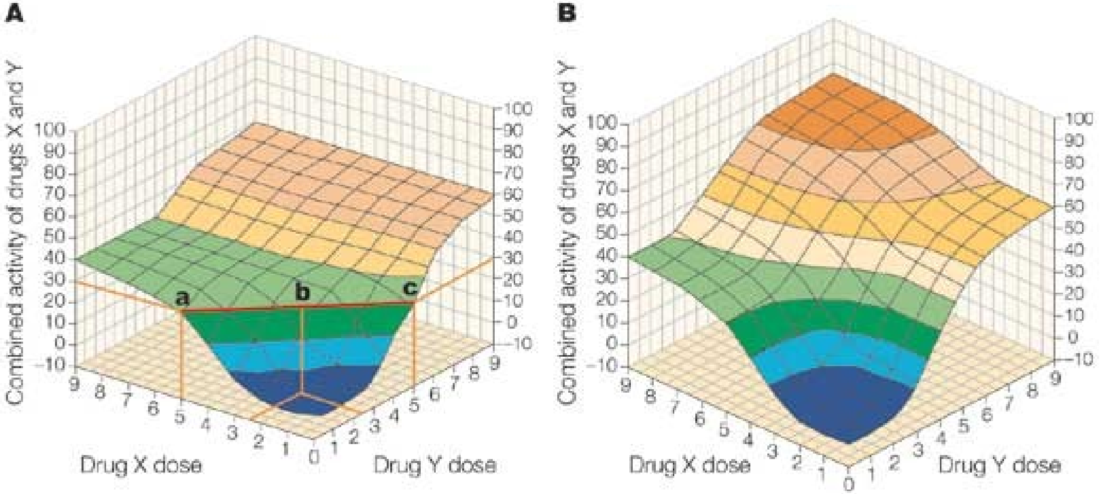


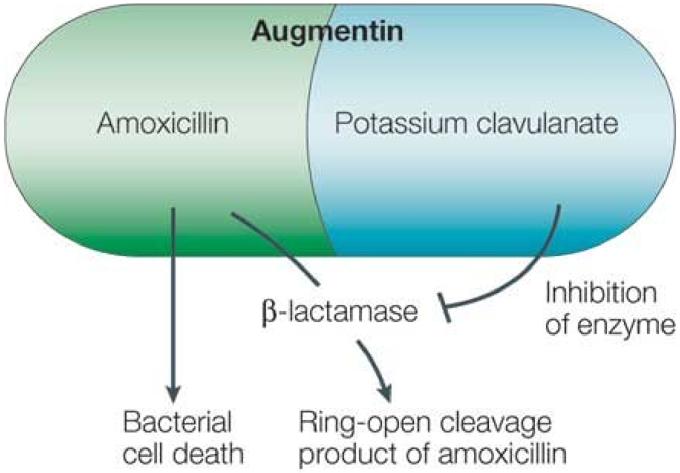
Nature Reviews | Drug Discovery

Networked systems might require multicomponent interventions to modulate signalling outputs. **a** | Targets at divergent pathway nodes might cause undesired side effects when acted on in isolation. For example, AKT regulates several downstream outputs, so inhibiting this protein on its own is not likely to achieve a separation of desired and undesired effects. If we want to inhibit cell-proliferation and cell-survival pathways, for example, without affecting glycogen metabolism, we would need multicomponent drugs to specifically inhibit these two downstream pathways rather than using a single AKT inhibitor. **b** | Redundant pathways can compensate for inhibition of another pathway. For example, SMAD2 and SMAD3 perform largely similar functions in tissue culture experiments. A small-molecule inhibitor of either SMAD2 or SMAD3 alone would therefore not be effective at blocking transforming growth factor- (TGF-) signalling if cells responded by upregulating a redundant SMAD. TGF- regulates several downstream outputs, so inhibiting this protein on its own could cause undesired effects by inhibiting SMAD-independent TGF- effects, such as activation of mitogen-activated protein kinase (MAPK) signalling. Using multicomponent interventions to simultaneously inhibit SMAD2 and SMAD3 would overcome both these problems by blocking SMAD-dependent TGF- effects without inhibiting SMAD-independent TGF- effects. TGFR, TGF- receptor.

Borisy, A.A. and Stockwell, B.R. (2005) Multicomponent therapeutics for networked systems. *Nat Rev Drug Discov.*, **4**,

Combinación de Drogas





Augmentin

Amoxicillin

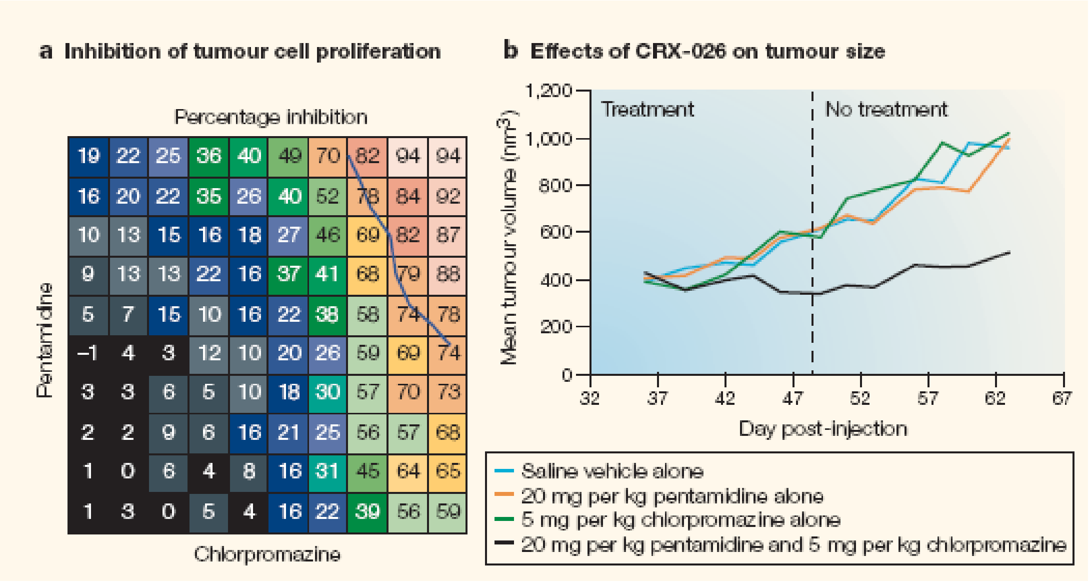
Potassium clavulanate

β-lactamase

Inhibition of enzyme

Bacterial cell death

Ring-open cleavage product of amoxicillin



a **Inhibition of tumour cell proliferation**

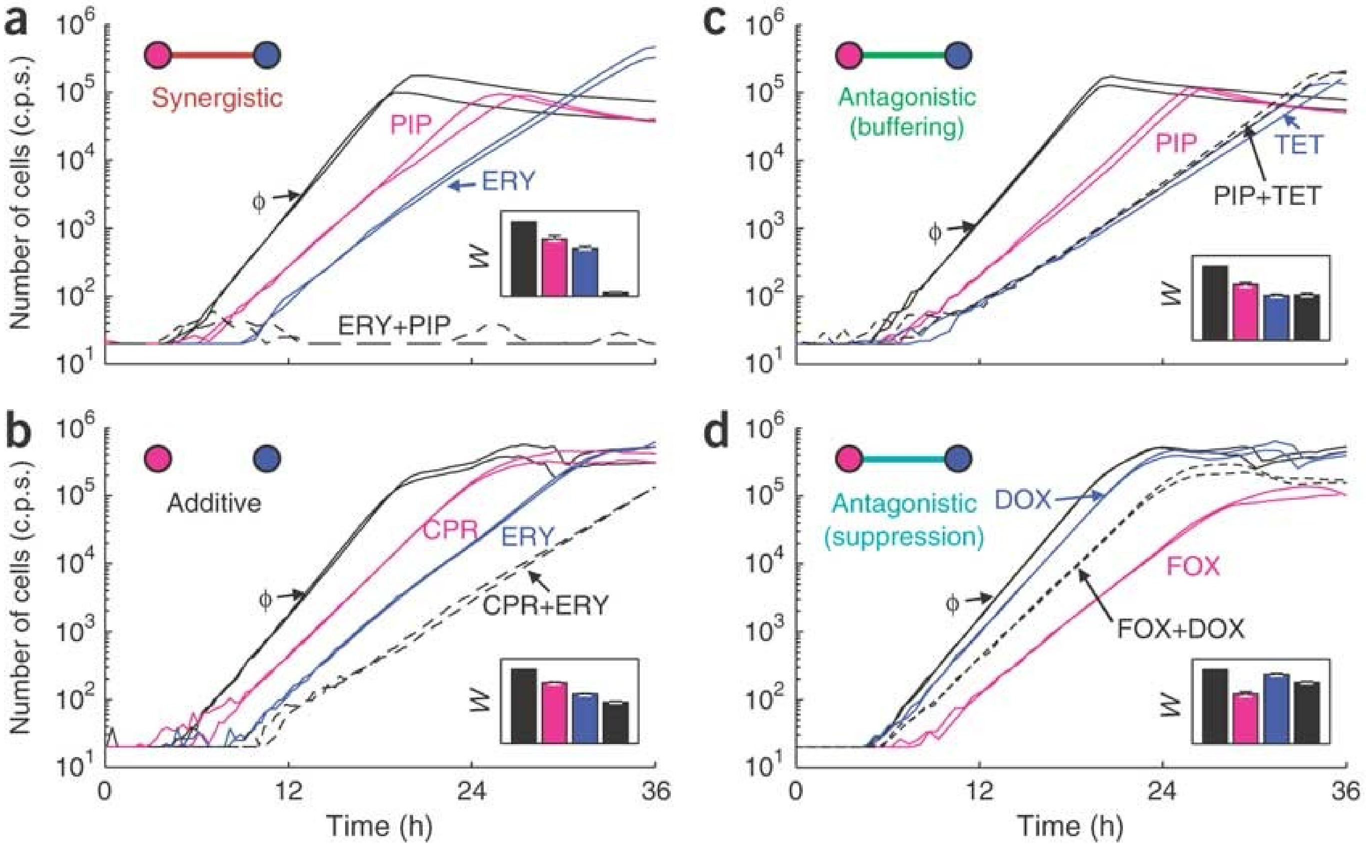
Percentage inhibition

19	22	25	36	40	49	70	82	94	94
16	20	22	35	26	40	52	78	84	92
10	13	15	16	18	27	46	69	82	87
9	13	13	22	16	37	41	68	79	88
5	7	15	10	16	22	38	58	74	78
−1	4	3	12	10	20	26	59	69	74
3	3	6	5	10	18	30	57	70	73
2	2	9	6	16	21	25	56	57	68
1	0	6	4	8	16	31	45	64	65
1	3	0	5	4	16	22	39	56	59

b **Effects of CRX-026 on tumour size**

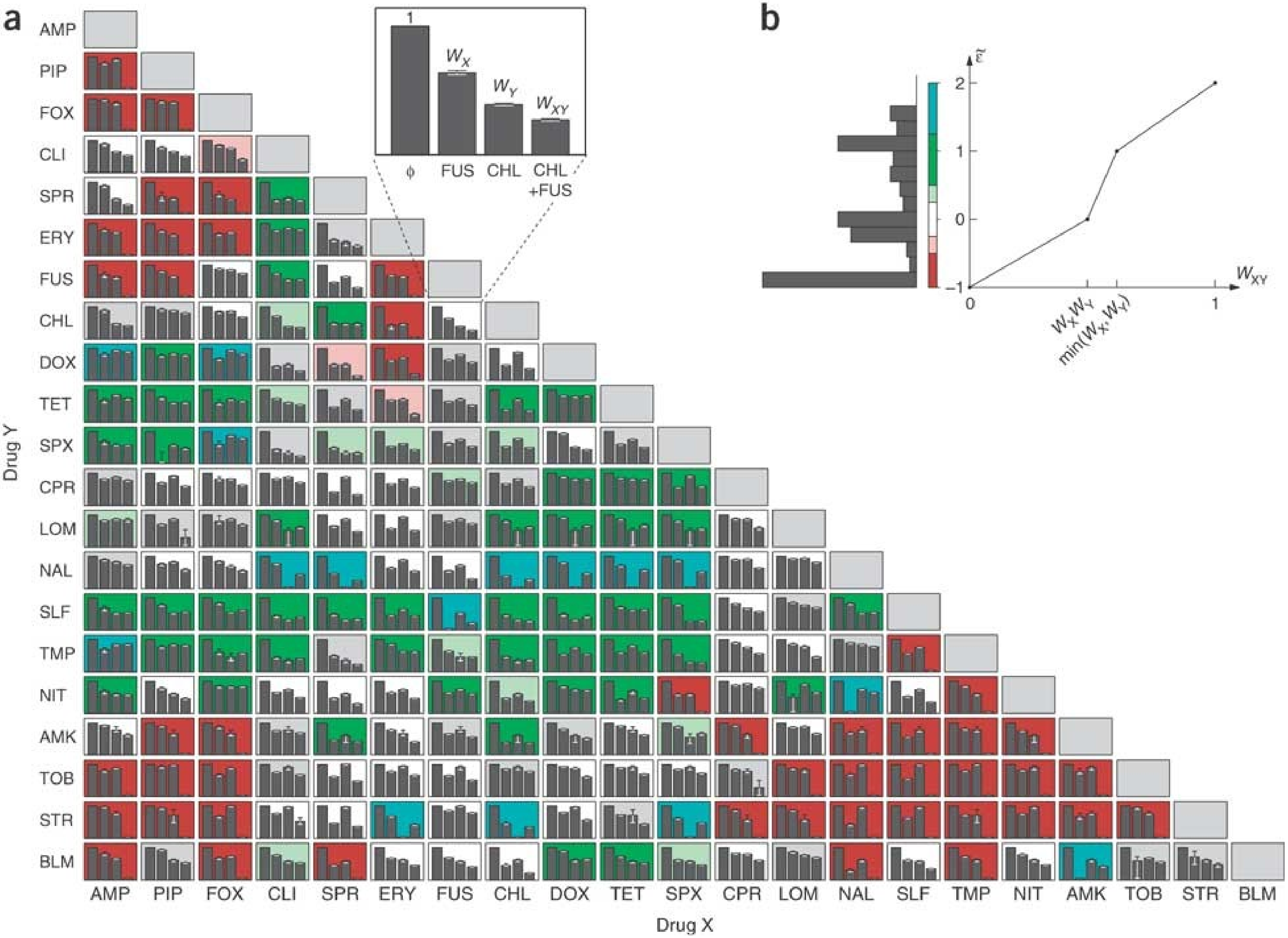
Borisy, A.A. and Stockwell, B.R. (2005) Multicomponent therapeutics for networked systems. *Nat Rev Drug Discov.*, 4

Combinación de Drogas



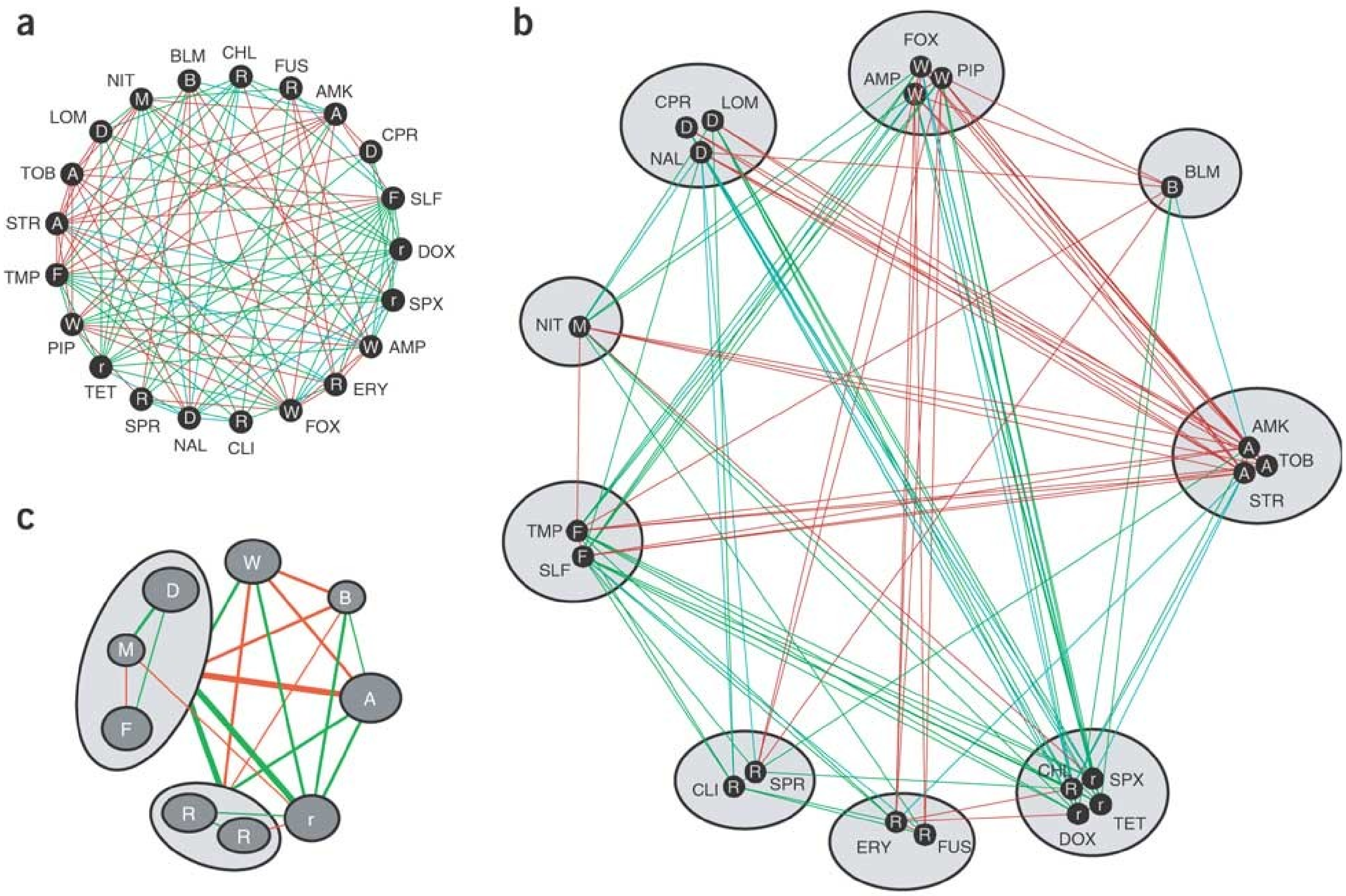
Yeh, P., Tschumi, A.I. and Kishony, R. (2006) Functional classification of drugs by properties of their pairwise interactions. *Nat Genet.*, **38**, 489-494.

Combinación de Drogas



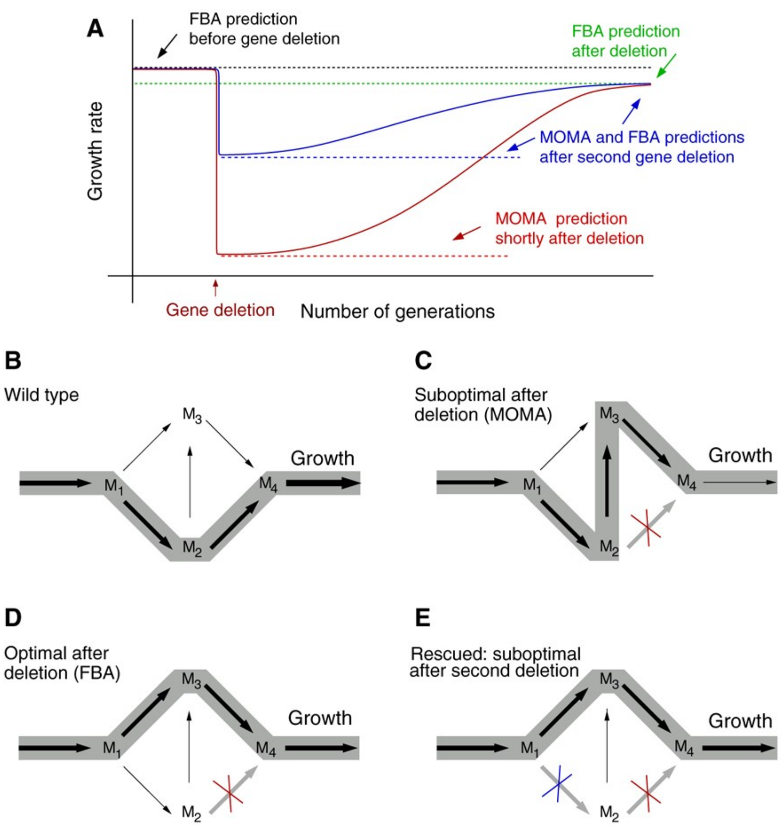
Yeh, P., Tschumi, A.I. and Kishony, R. (2006) Functional classification of drugs by properties of their pairwise interactions. *Nat Genet.*, **38**, 489-494.

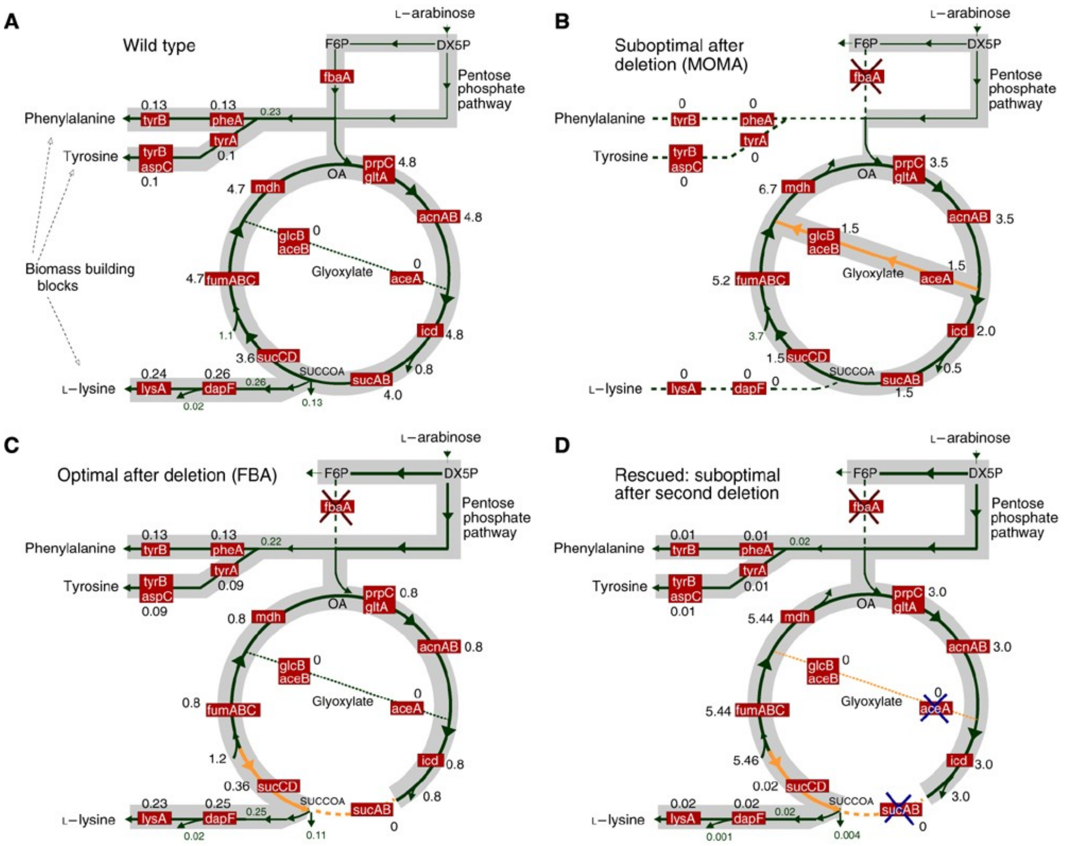
Combinación de Drogas



Yeh, P., Tschumi, A.I. and Kishony, R. (2006) Functional classification of drugs by properties of their pairwise interactions. *Nat Genet.*, **38**, 489-494.

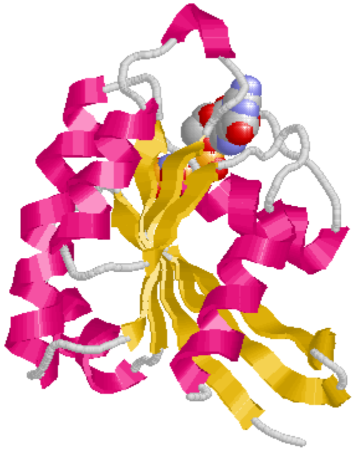
Biología de Sistemas y Terapia

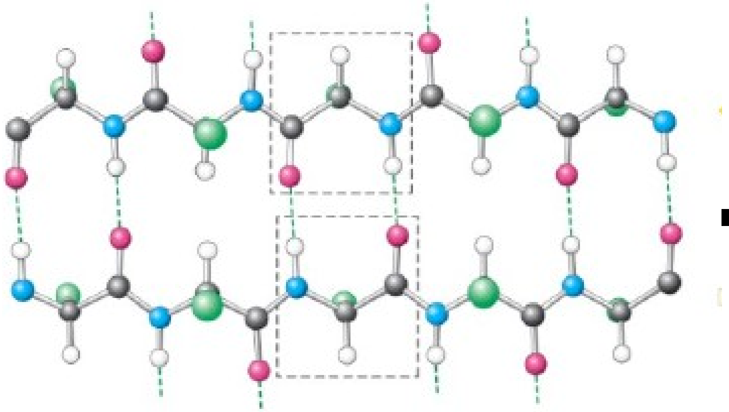


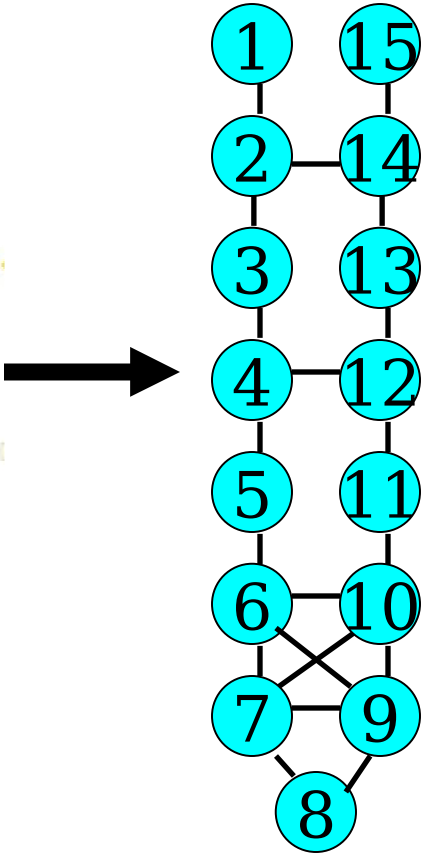


Motter, A.E., Gulbahce, N., Almaas, E. and Barabasi, A.L. (2008) Predicting synthetic rescues in metabolic networks. *Mol Syst Biol.*, **4**, 168.

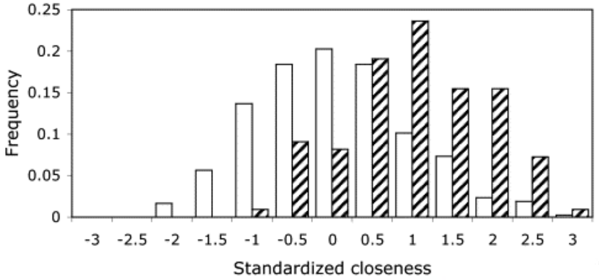
Representación de estructura de proteínas en forma de grafos

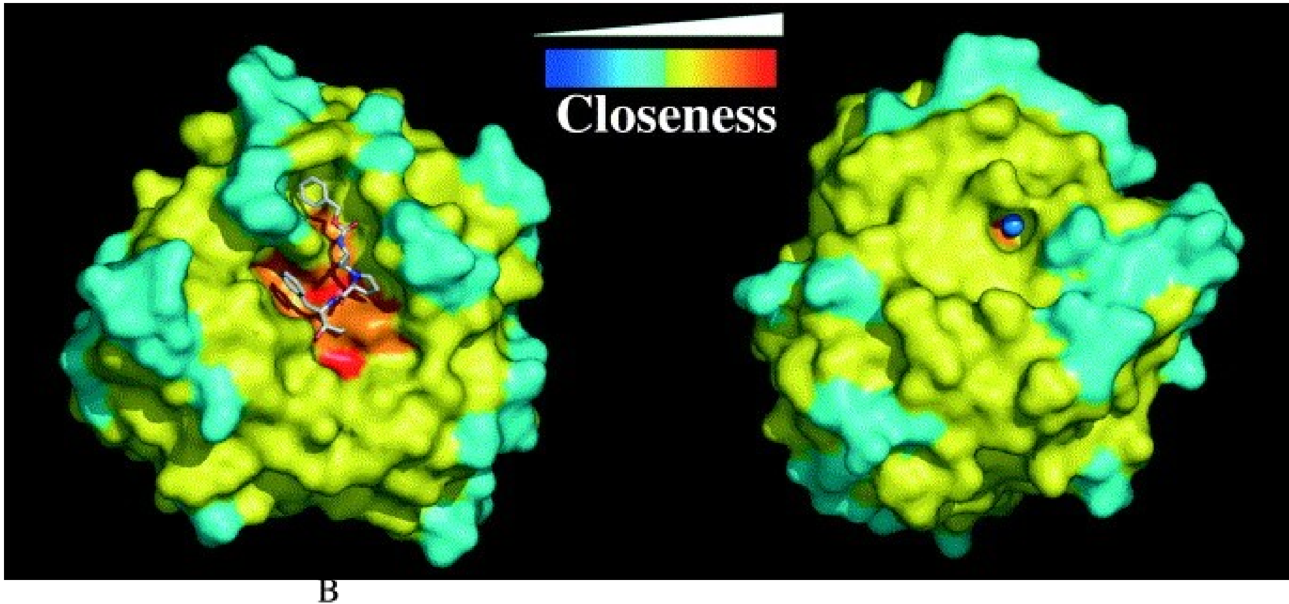


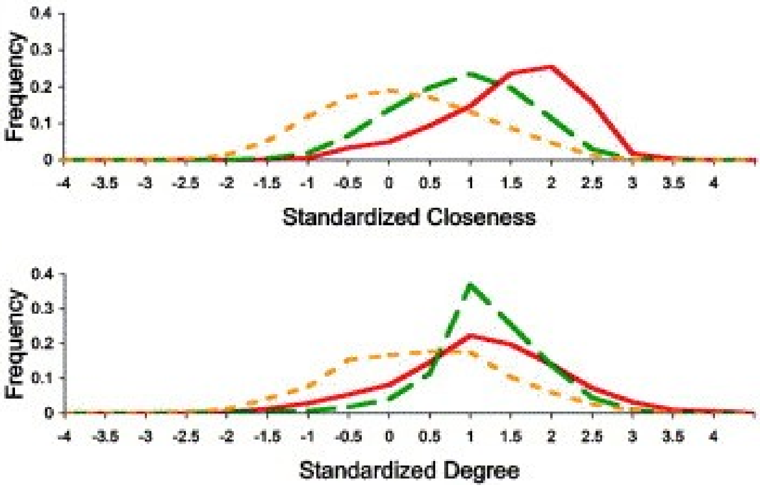


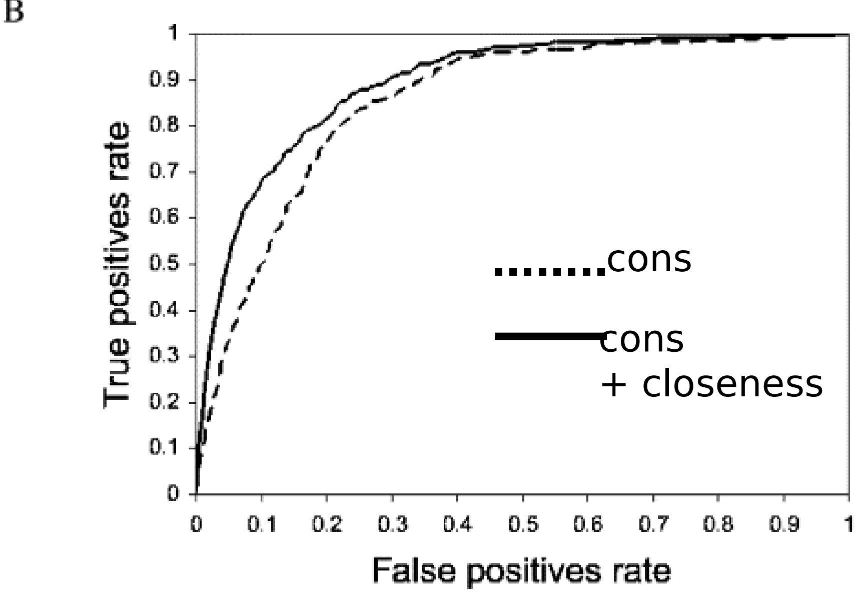


Predicción de sitios funcionales usando representaciones de grafo









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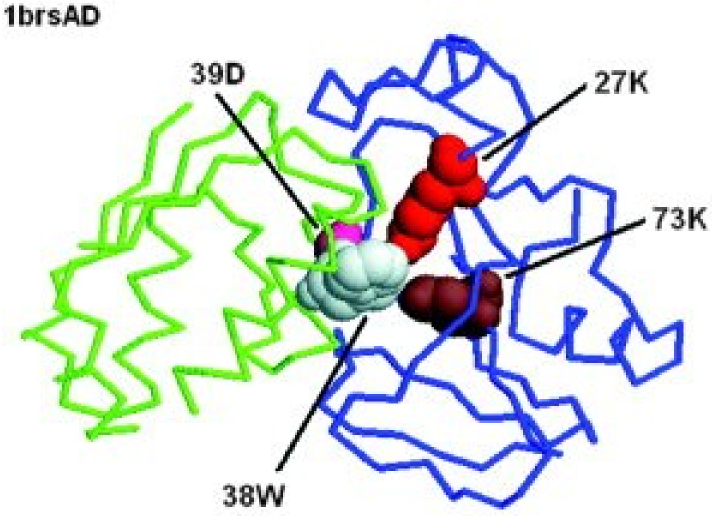

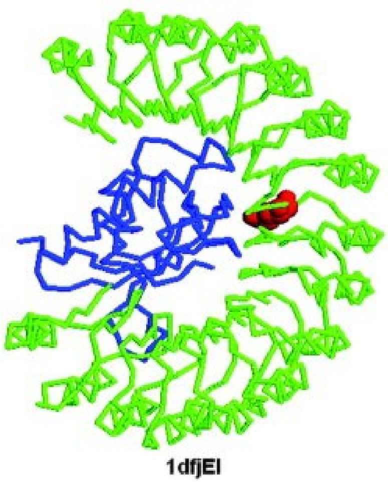

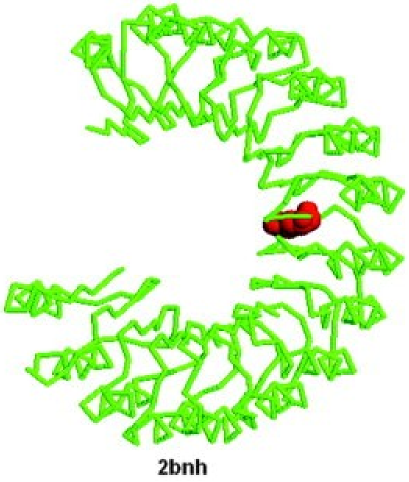

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Repositorios de redes y datos “-omics”

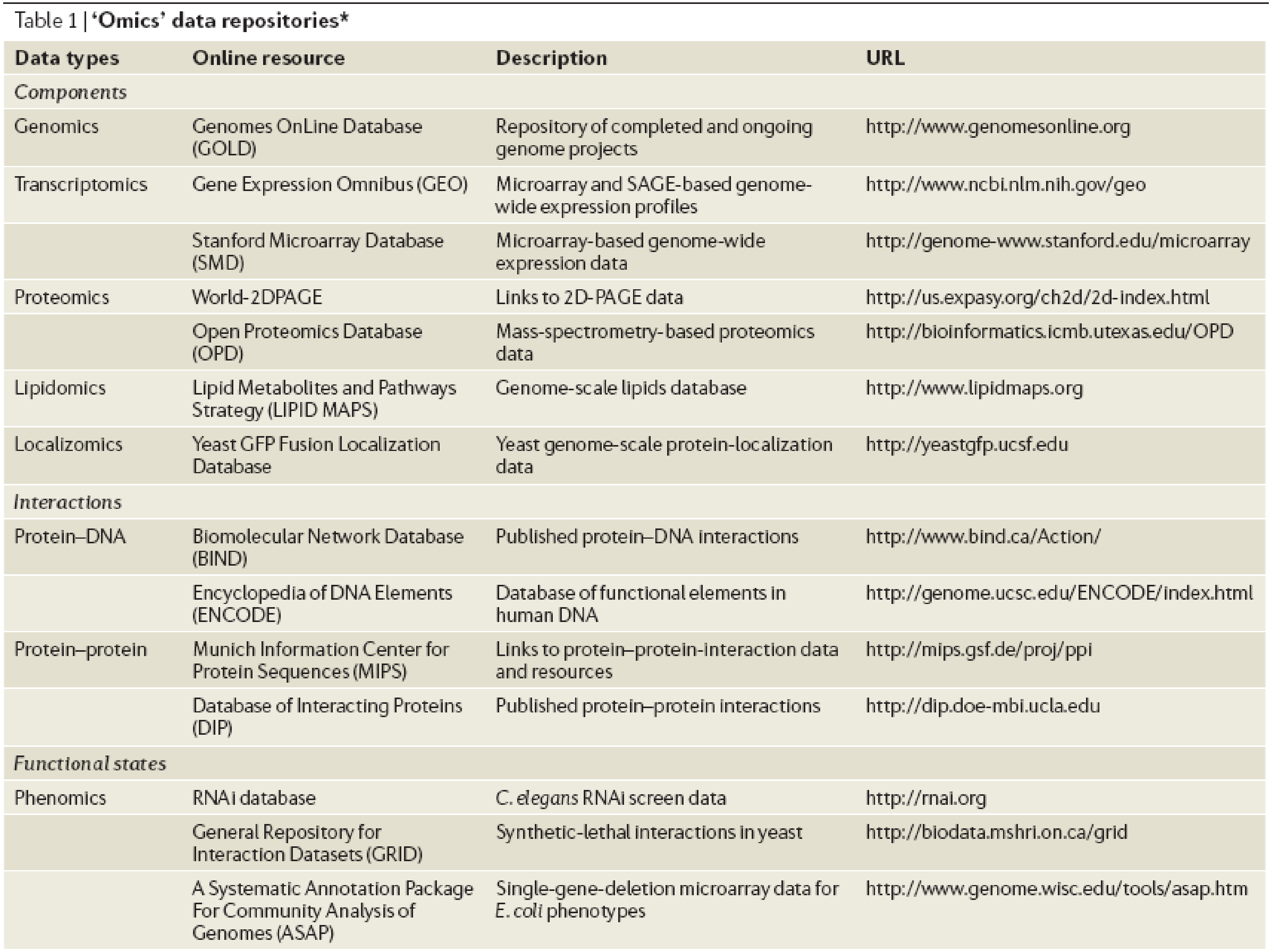

Table 1 | **‘Omics’ data repositories***

Data types	**Online resource**	**Description**	**URL**
Components			
Genomics	Genomes OnLine Database (GOLD)	Repository of completed and ongoing genome projects	http://www.genomesonline.org
Transcriptomics	Gene Expression Omnibus (GEO)	Microarray and SAGE-based genome-wide expression profiles	http://www.ncbi.nlm.nih.gov/geo
	Stanford Microarray Database (SMD)	Microarray-based genome-wide expression data	http://genome-www.stanford.edu/microarray
Proteomics	World-2DPAGE	Links to 2D-PAGE data	http://us.expasy.org/ch2d/2d-index.html
	Open Proteomics Database (OPD)	Mass-spectrometry-based proteomics data	http://bioinformatics.icmb.utexas.edu/OPD
Lipidomics	Lipid Metabolites and Pathways Strategy (LIPID MAPS)	Genome-scale lipids database	http://www.lipidmaps.org
Localizomics	Yeast GFP Fusion Localization Database	Yeast genome-scale protein-localization data	http://yeastgfp.ucsf.edu
Interactions			
Protein–DNA	Biomolecular Network Database (BIND)	Published protein–DNA interactions	http://www.bind.ca/Action/
	Encyclopedia of DNA Elements (ENCODE)	Database of functional elements in human DNA	http://genome.ucsc.edu/ENCODE/index.html
Protein–protein	Munich Information Center for Protein Sequences (MIPS)	Links to protein–protein-interaction data and resources	http://mips.gsf.de/proj/ppi
	Database of Interacting Proteins (DIP)	Published protein–protein interactions	http://dip.doe-mbi.ucla.edu
Functional states			
Phenomics	RNAi database	*C. elegans* RNAi screen data	http://rnai.org
	General Repository for Interaction Datasets (GRID)	Synthetic-lethal interactions in yeast	http://biodata.mshri.on.ca/grid
	A Systematic Annotation Package For Community Analysis of Genomes (ASAP)	Single-gene-deletion microarray data for *E. coli* phenotypes	http://www.genome.wisc.edu/tools/asap.htm

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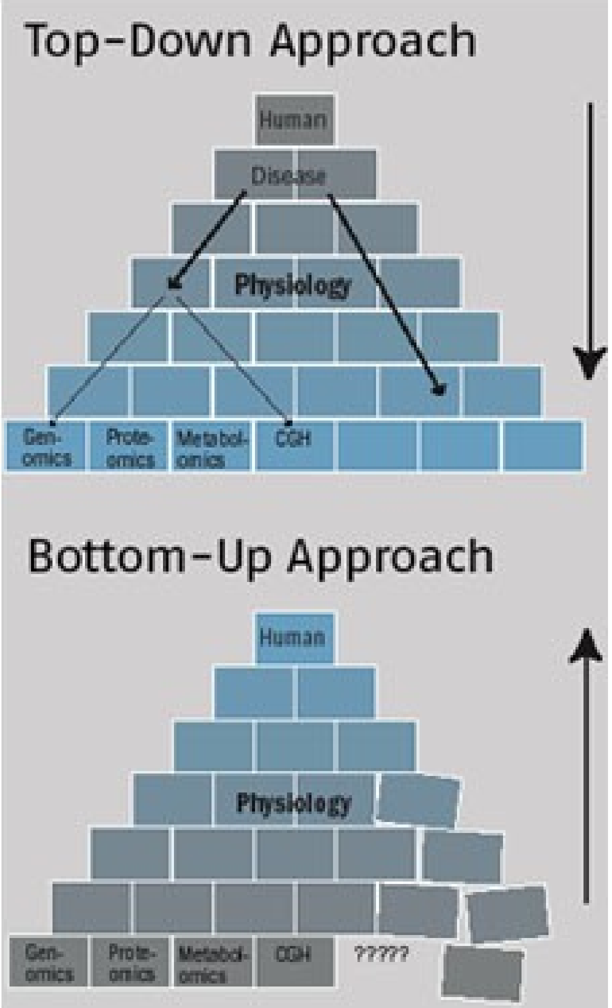

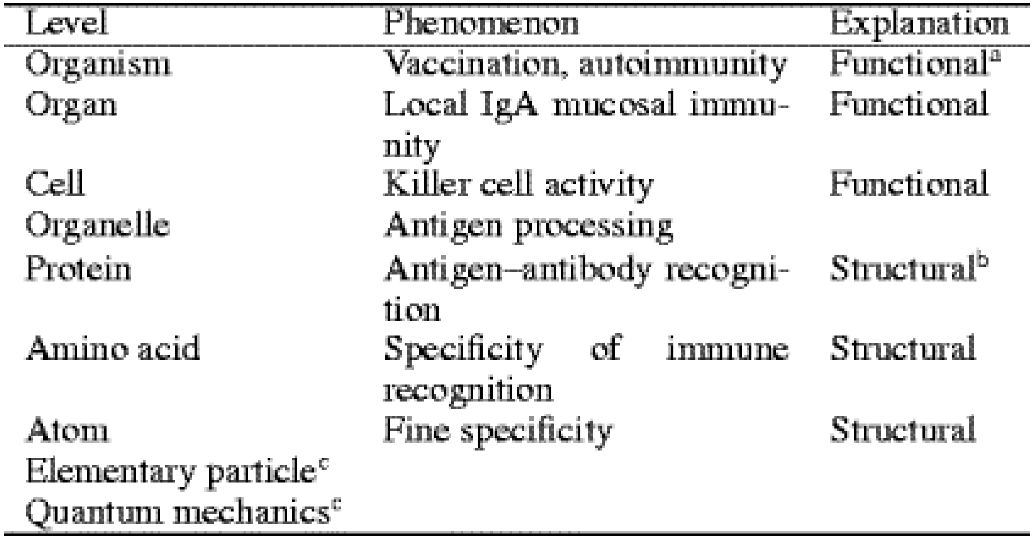

Level	Phenomenon	Explanation
Organism	Vaccination, autoimmunity	Functional[a]
Organ	Local IgA mucosal immunity	Functional
Cell	Killer cell activity	Functional
Organelle	Antigen processing	
Protein	Antigen–antibody recognition	Structural[b]
Amino acid	Specificity of immune recognition	Structural
Atom	Fine specificity	Structural
Elementary particle[c]		
Quantum mechanics[c]		

"Biology is an autonomous discipline that requires its own vocabulary and concepts, that are not found in chemistry and physics".
M.H. V. Van Regenmortel

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Florencio Pazos (CNB-CSIC)
pazos@cnb.csic.es
http://pdg.cnb.uam.es/pazos
Tlf. 91.5854669
Fax. 91.5854506