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Bioinformática y Sistemas Complejos  
en Biología  
Redes Biológicas

Curso de Bioinformática  
Bragança, Abril 2005

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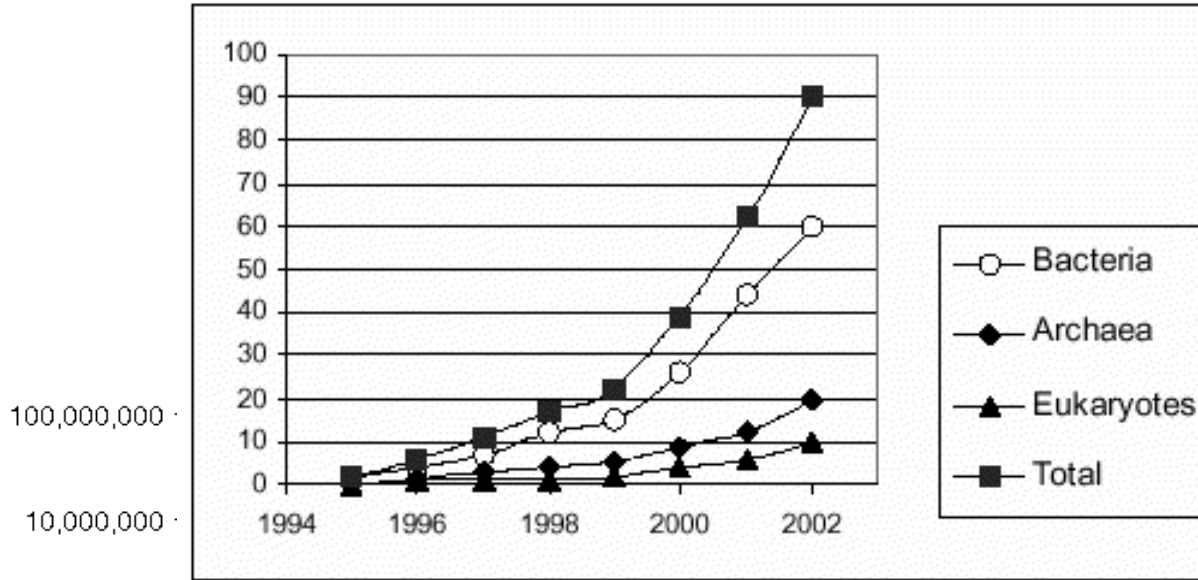
*Dr. Florencio Pazos Cabaleiro*  
*Protein Design Group*  
*Centro Nacional de Biotecnología (CNB-CSIC)*  
*Madrid*  
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*<http://pdg.cnb.uam.es/pazos>*

# Bioinformática y Sistemas Complejos en Biología

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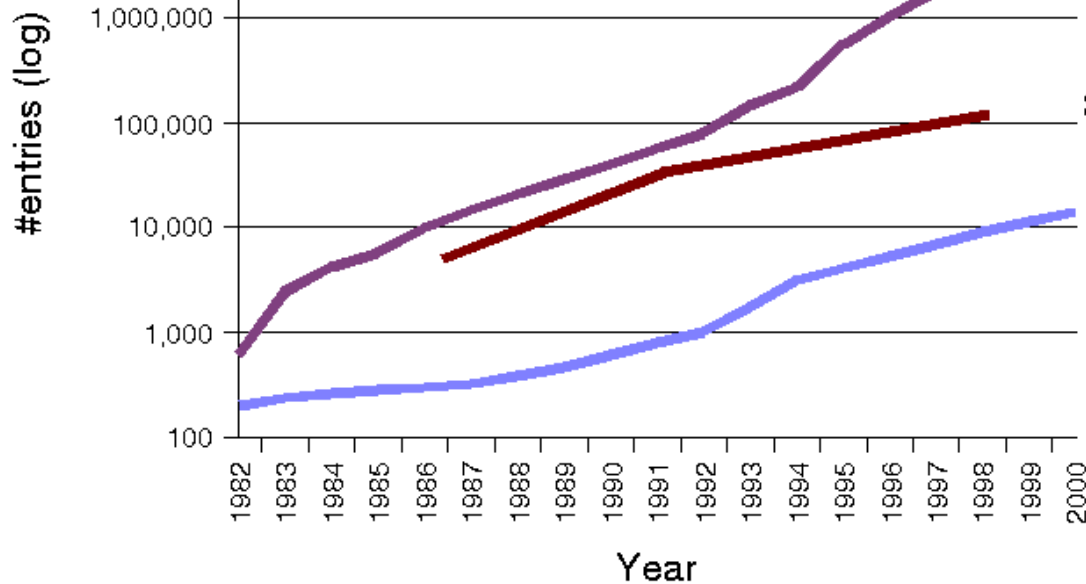
- Biología de Sistemas vs. Biología Molecular
  - Características de sistemas complejos biológicos
  - Nuevas aproximaciones experimentales y computacionales
  - Catalogación de los “componentes” del sistema
  - Estudio de redes biológicas desde el punto de vista de sistemas
  - Aspectos prácticos
  - Conclusiones
-

# Bioinformática y análisis de información biológica



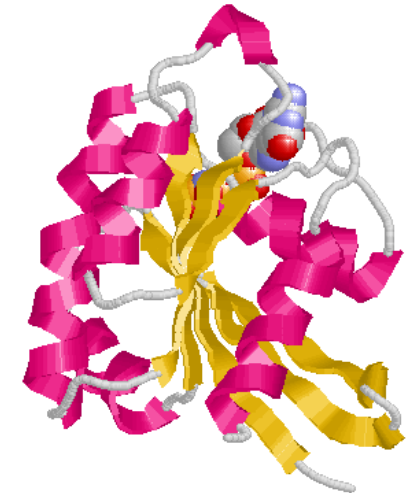
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 EDERVVGKEQQNLARQWCNCAFLESSAKSKINVNEIFYD  
 LVRQINR

MLEILDTA**GTEQFT**AMRDLY**MKNQGQF**AL  
 VYSITAQSTFNDL**QDLREQIL**RVKDTEDVPMIL  
 VGNKCDLEDERV



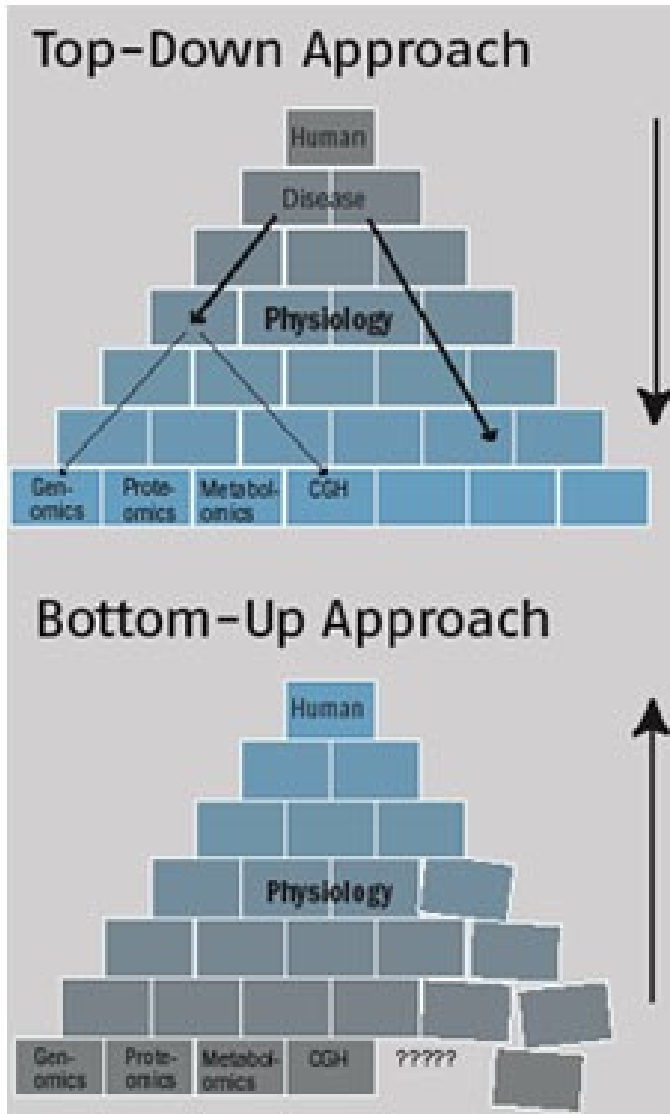
swissprot

PDB



# Bioinformática y Sistemas Complejos en Biología

## Biología de Sistemas vs. Biología Molecular



- Visión desde el punto de vista de sistemas complejos
- Objeto de estudio: **redes, relaciones, propiedades emergentes** (no propiedades de componentes individuales).
- Biología de Sistemas
- **Propiedades “globales” (emergentes, etc.)** -> conocimiento biológico
- Enfermedades (dianas/marcadores = redes, patrones complejos).



- Visión reduccionista
- Objeto de estudio: **componentes (genes proteínas).**
- Biología Molecular
- **Propiedades de los componentes** -> conocimiento biológico
- Enfermedades (dianas/marcadores = proteínas/genes).

# ¿Es suficiente la visión reduccionista?

- Reduccionismo en Biología muy exitoso (Biología Molecular). “*The ultimate aim of the modern movement in biology is to explain all biology in terms of physics and chemistry*”. F. Crick (1966)
- Sistemas biológicos: prototipo de sistemas complejos. => Muchos fenómenos biológicos nunca podrán explicarse a partir de las propiedades de los componentes (“el todo es mas que la suma de las partes”).
- Determinación de “repertorios de componentes” y sus características (secuenciación de genomas, proteómica, genómica estructural ...): Ni el número ni las características de genes y proteínas dan cuenta de muchas características de los organismos:
  - Similar número de genes en *Drosophila* y *C. elegans*.
  - Alta similaridad de secuencia entre humano y ratón.
  - ...

# ¿Es suficiente la visión reduccionista?

- Fallo en tratamiento de cáncer, ... En parte debido al enfoque reduccionista extremo.
- No vacuna HIV, ... “
- Fracaso vacunas de péptidos. “
- Reducción de fármacos en el mercado a pesar de la creciente inversión. (1 fármaco  $\leftrightarrow$  1 diana).
- No resultados esperados para técnicas terapéuticas prometedoras de base reduccionista (terapia génica, RNA antisentido, ...).
- No mejora esperada de estas aproximaciones con secuenciación de genomas, etc.

# ¿Es suficiente la visión reduccionista?

Fallos en aproximaciones *in-vitro* e *in-silico*.

Fallos en técnicas experimentales de base reduccionista (delecciones, *knockout*, ...).

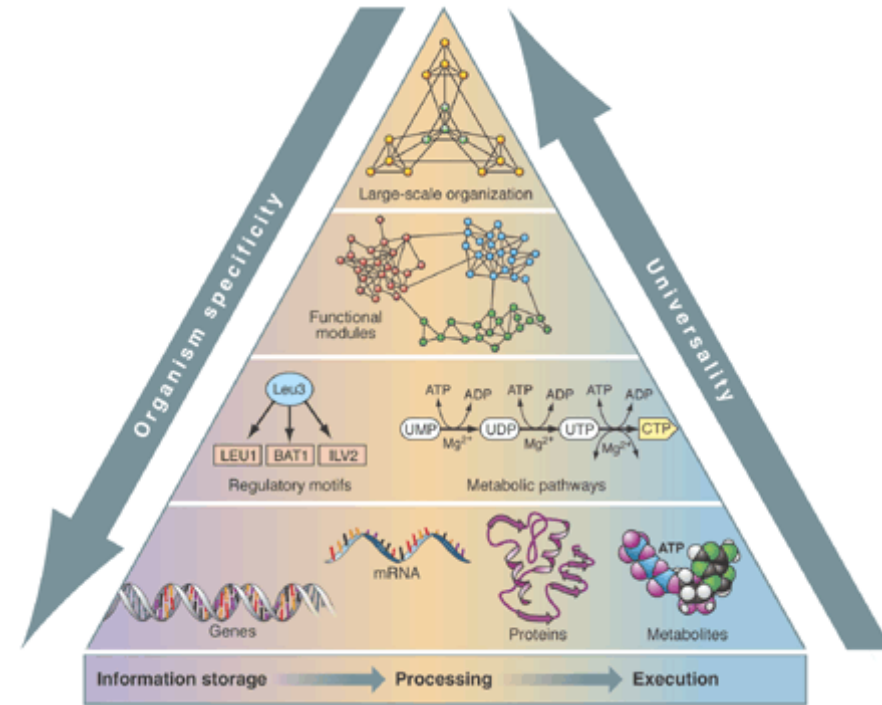
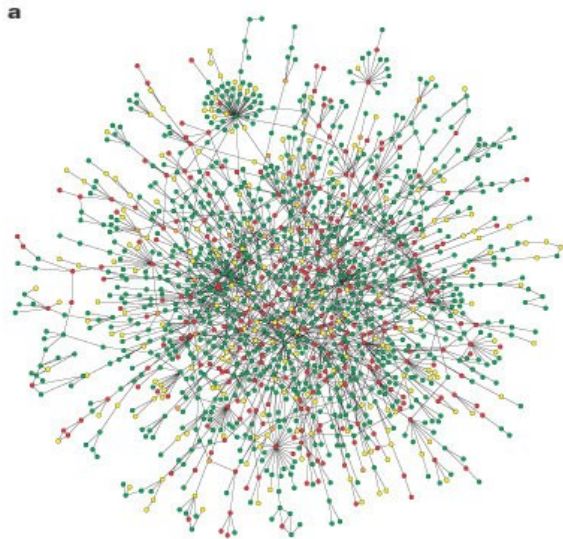
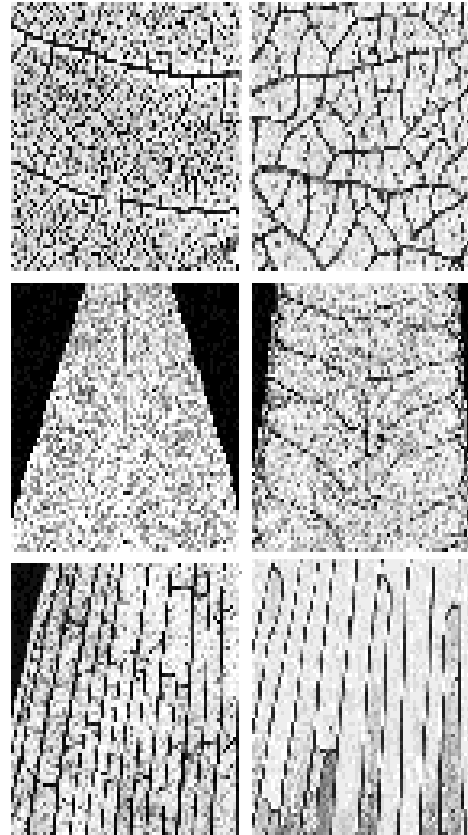
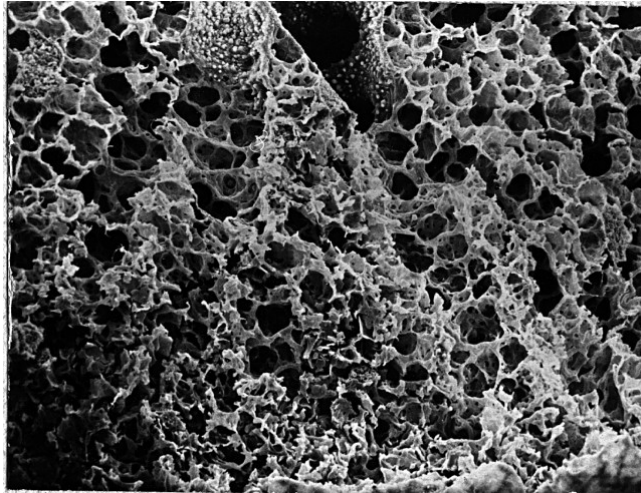
*Knockout*: no efecto, efecto distinto al esperado, o efecto “inespecífico” (cambio expresión 100's genes).

*“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.

# Características de sistemas complejos biológicos que escapan a una explicación reduccionista

## *Emergencia*

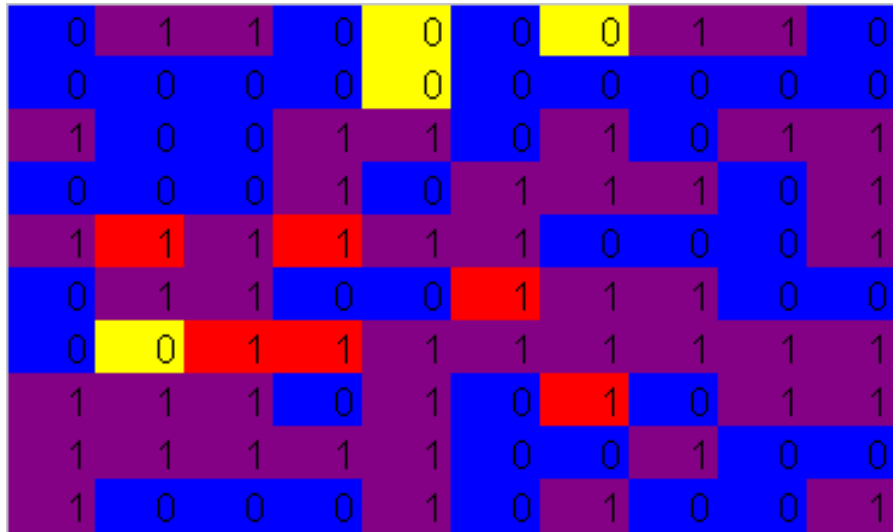


Oltvai, Z.N. and Barabási, A.-L. (2002)  
Life's complexity pyramid. *Science*, **298**, 763–764.

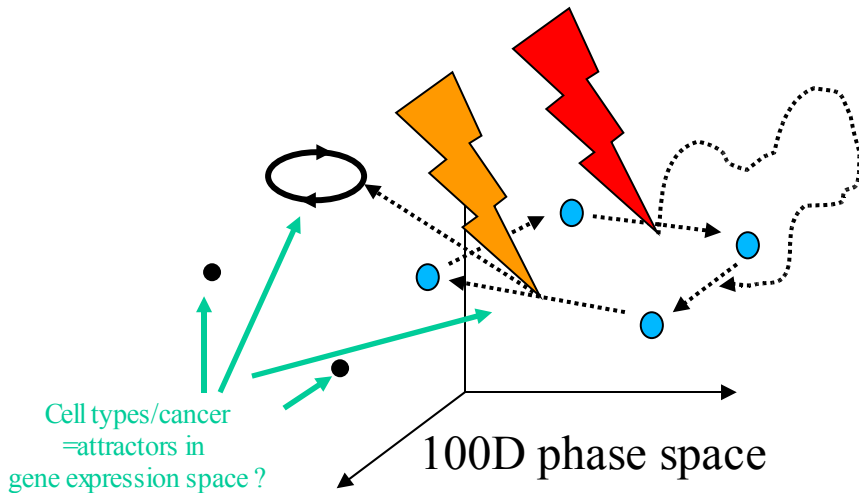


# Características de sistemas complejos biológicos que escapan a una explicación reduccionista

## Robustez

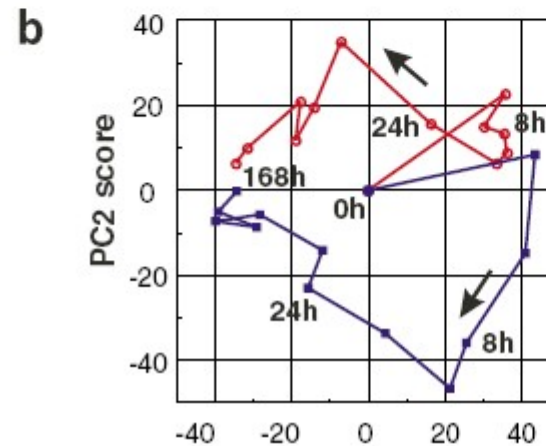
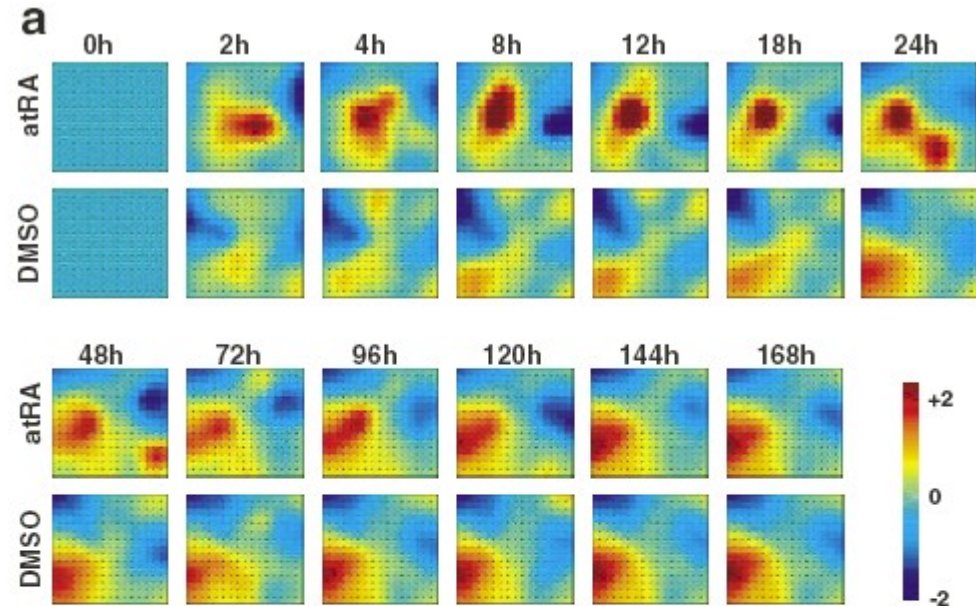


<http://www.bion.si/BoolMrezeE.htm>



Kauffman, S.A. (1993) *The Origins of Order*. Oxford University Press, New York.

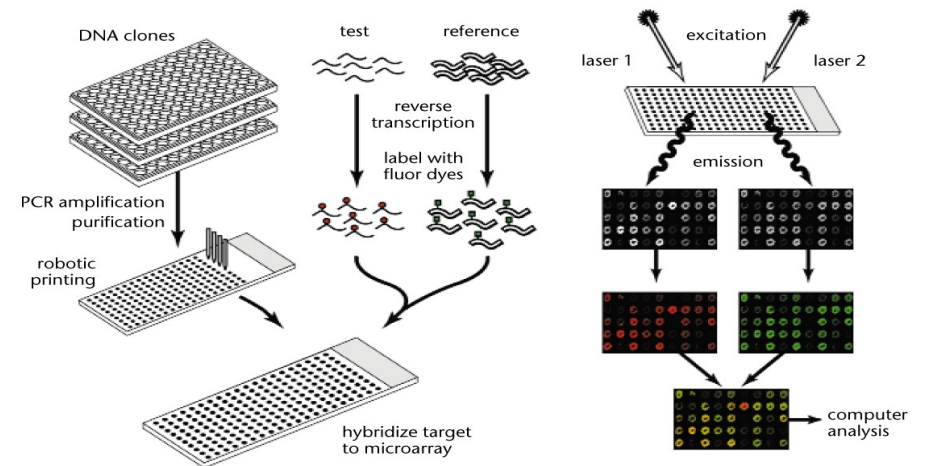
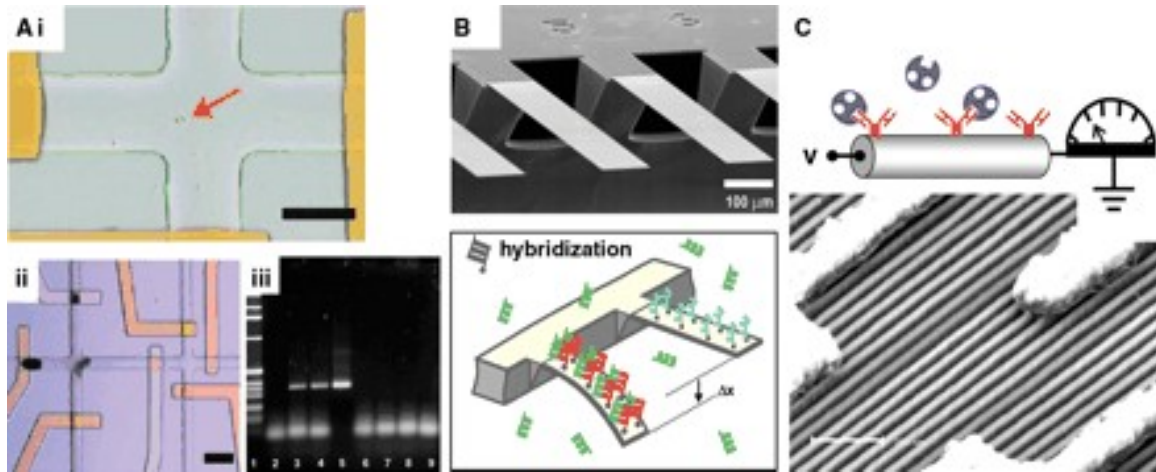
2773D phase space



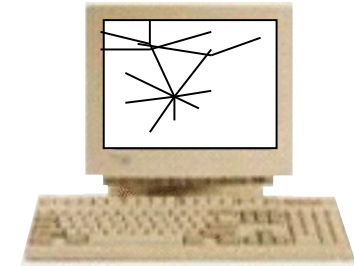
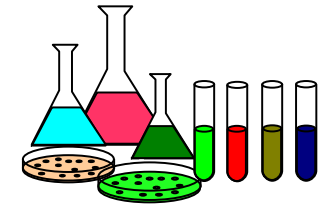
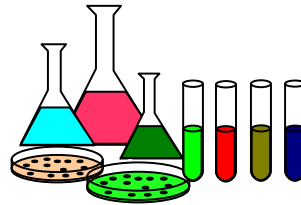
PCA reduction

Huang, S., Eichler, G., Bar-Yam, Y. and Ingber, D.E. (2005) Cell Fates as High-Dimensional Attractor States of a Complex Gene Regulatory Network. *Phys Rev Letters*, **94**, 128701.

# Herramientas Experimentales y Bioinformáticas para la Biología de Sistemas



# Biología de componentes vs. Biología de sistemas



*In vivo*

Características del sistema

*In vivo + in vitro*

Características de los componentes (moléculas)

*In vivo + in vitro + in silico*

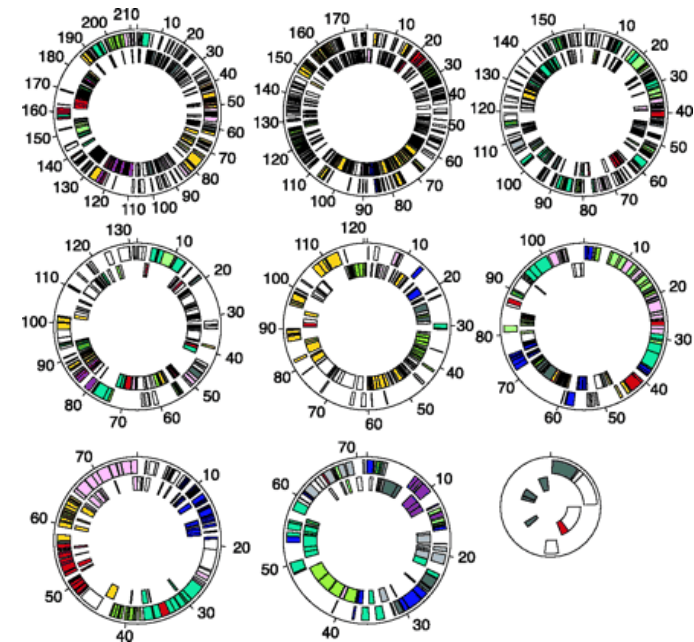
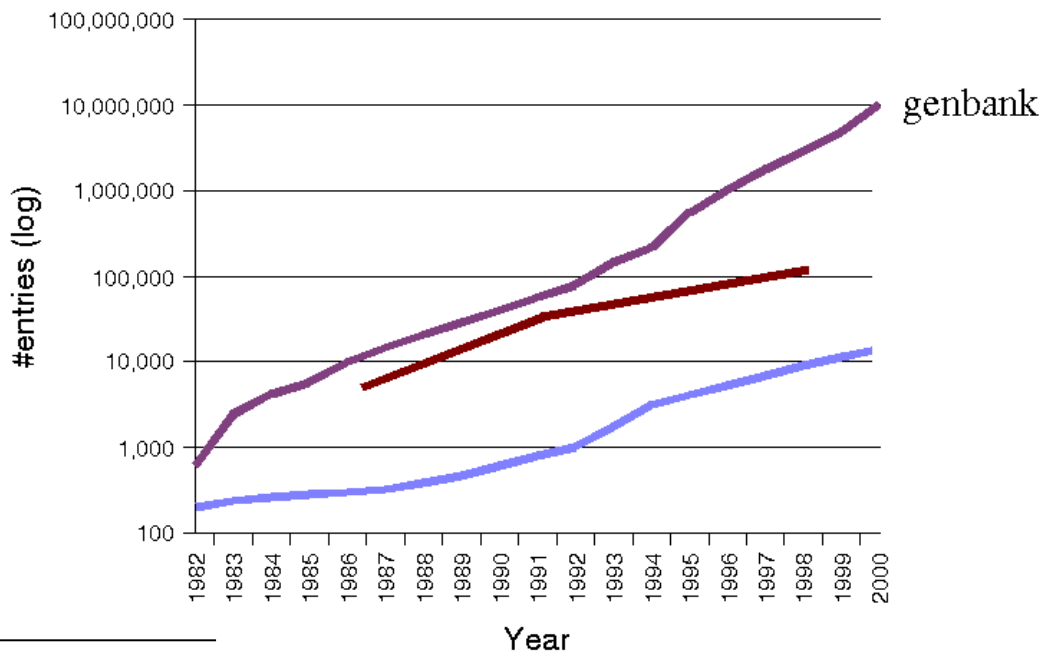
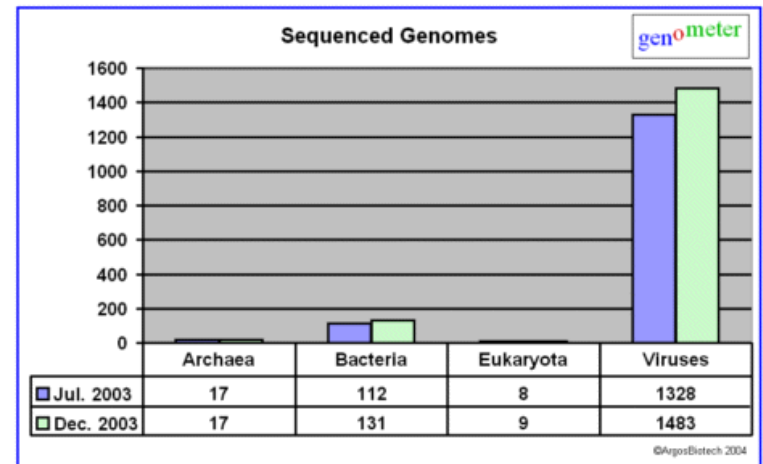
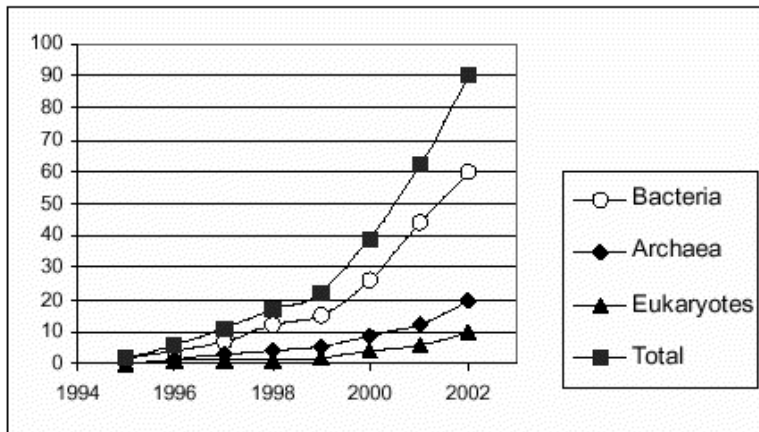
Características del sistema desde el pto. vista de los componentes y sus relaciones  
Propiedades emergentes, ...

# Caracterización masiva de los componentes a varios niveles y sus relaciones

- Secuenciación de genomas completos (“genoma”).
- Caracterización de los transcritos (mRNA) (“transcriptoma”)
- Caracterización del repertorio proteico (“proteoma”)
- Localización celular de los componentes (“localizoma”)
- Redes de regulación génica (“reguloma”)
- Redes de interacciones entre proteínas (“interactoma”)
- Estudios masivos de relaciones gen-fenotipo (“fenoma”)
- Redes metabólicas (“metaboloma”)
- .....

# Caracterización masiva de los componentes a varios niveles y sus relaciones

## Secuenciación de genomas completos (“genoma”)



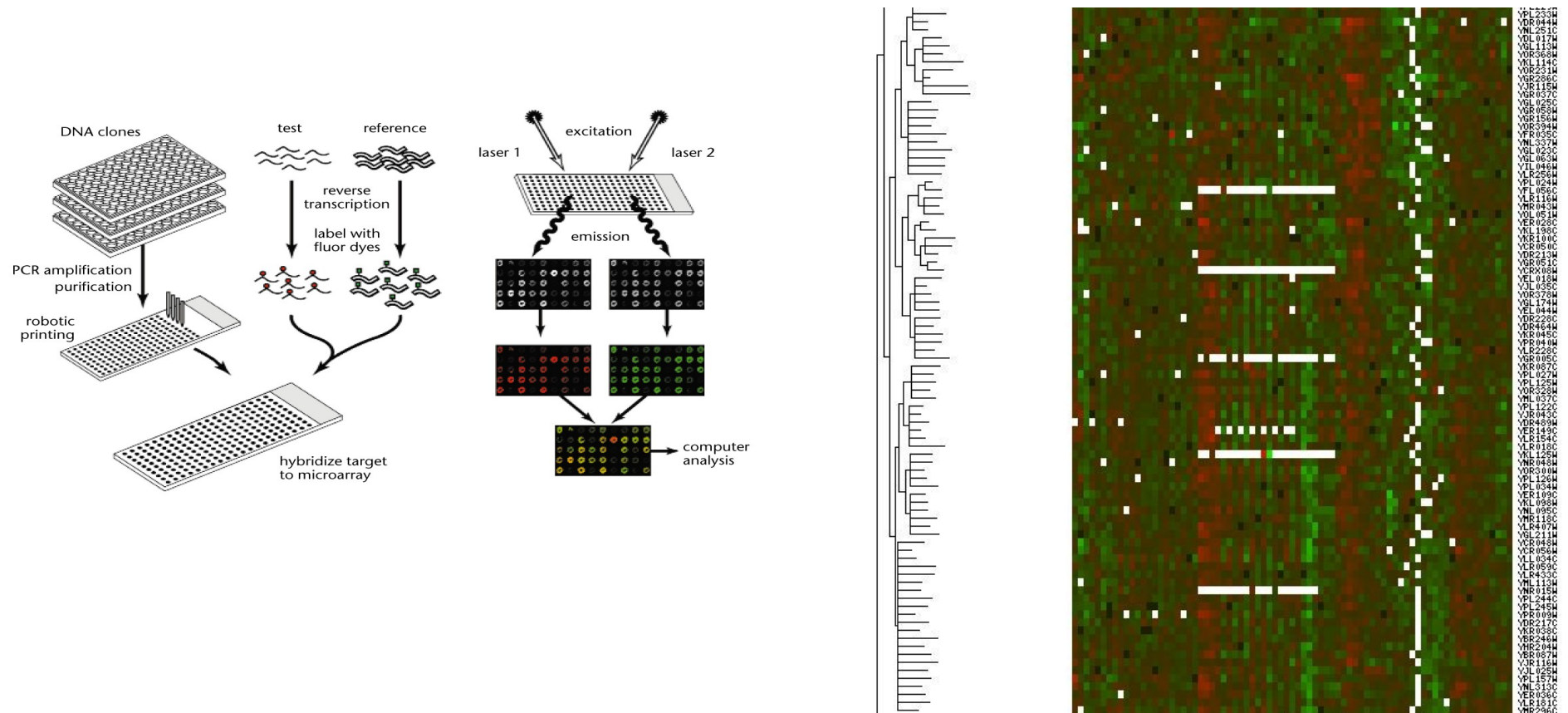
•Collins, F.S., Green, E.D., Guttmacher, A.E. & Guyer, M.S. (2003) A vision for the future of genomic research. *Nature*, **422**, 835-847.

•Venter, J. C. et al. Environmental genome shotgun sequencing of the Sargasso Sea. (2004). *Science* **304**, 66-74.



# Caracterización masiva de los componentes a varios niveles y sus relaciones

## Caracterización de los transcritos (mRNA) (“transcriptoma”)

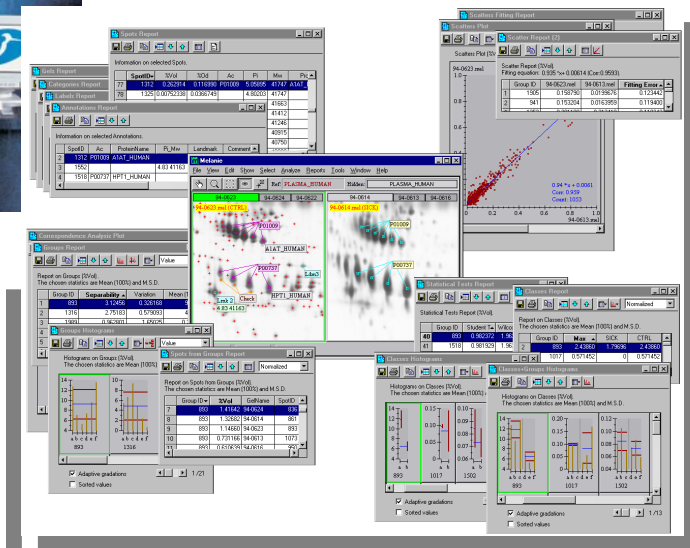
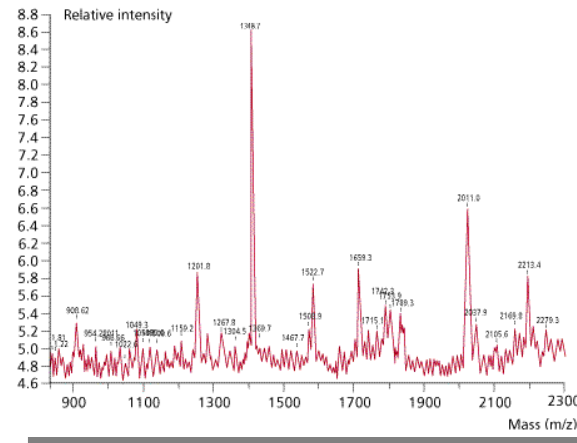
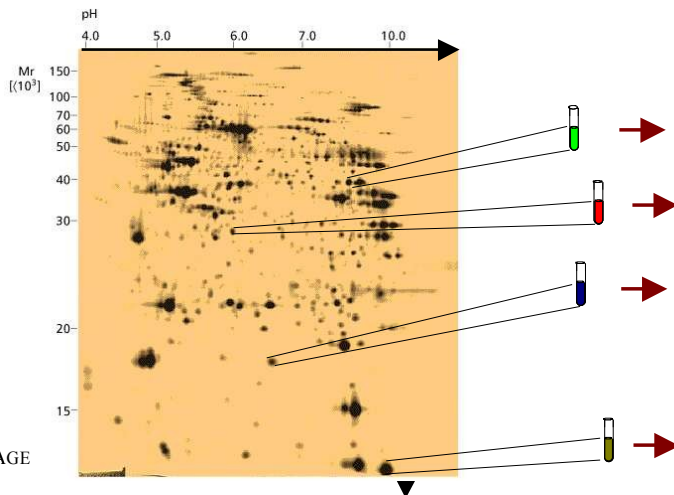


# Caracterización masiva de los componentes a varios niveles y sus relaciones

## Caracterización del repertorio proteico (“proteoma”)

Gel  
2D

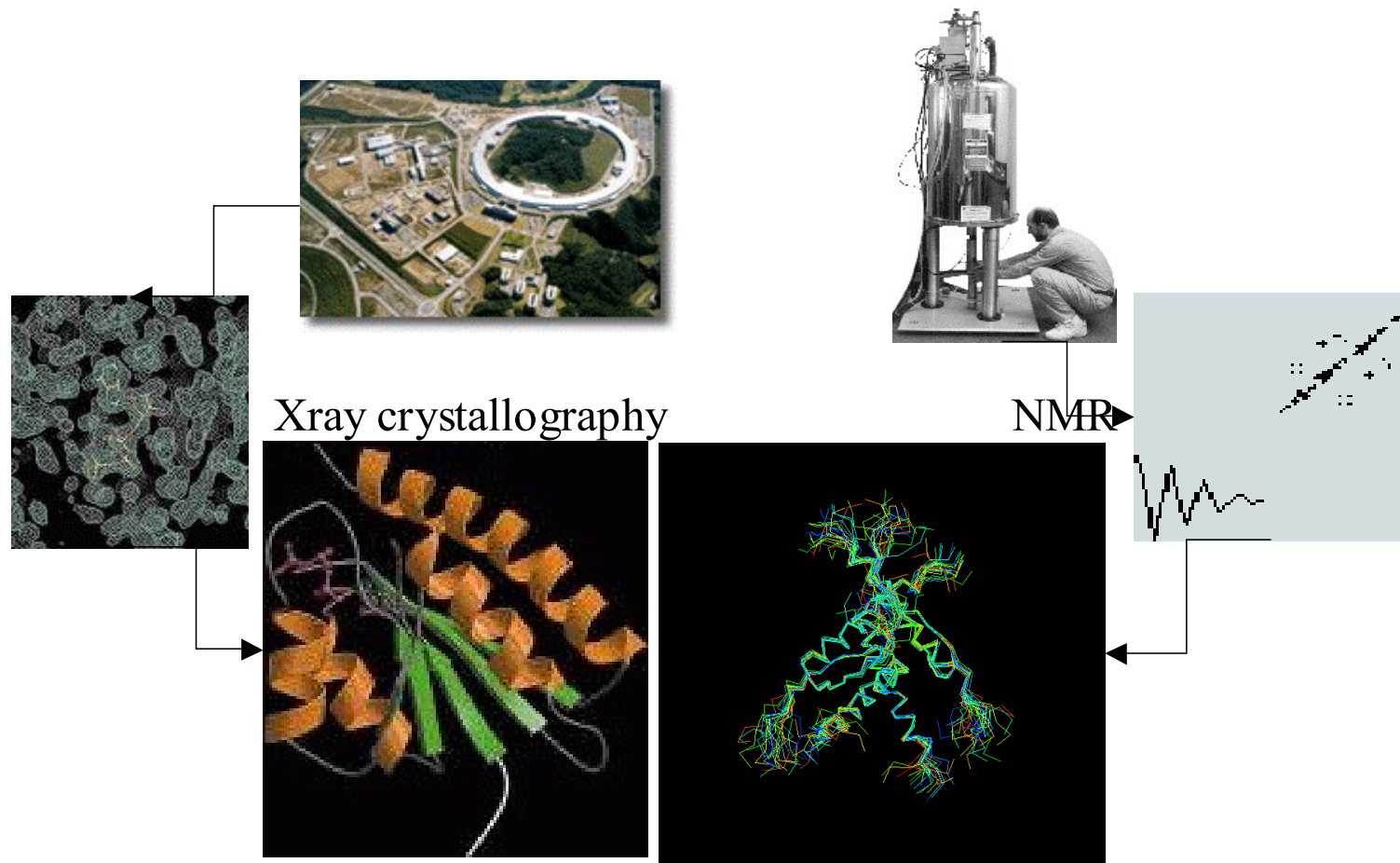
Enfoque isoelectrico



Juan A. G. Ranea

# Caracterización masiva de los componentes a varios niveles y sus relaciones

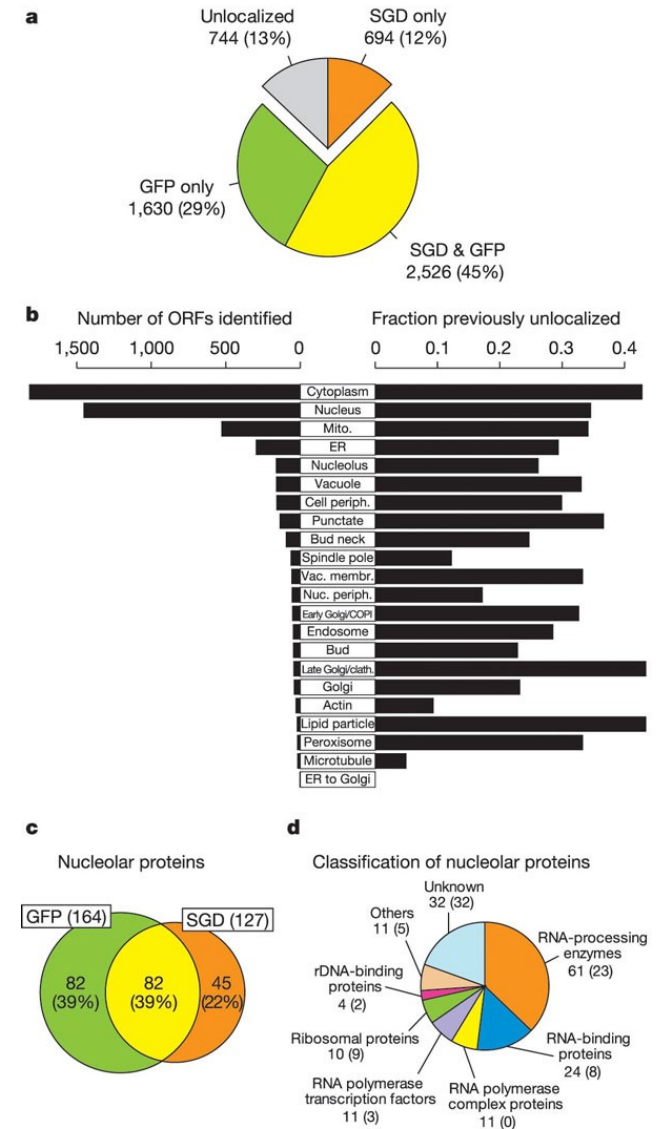
## Caracterización del repertorio proteico (“proteoma”)





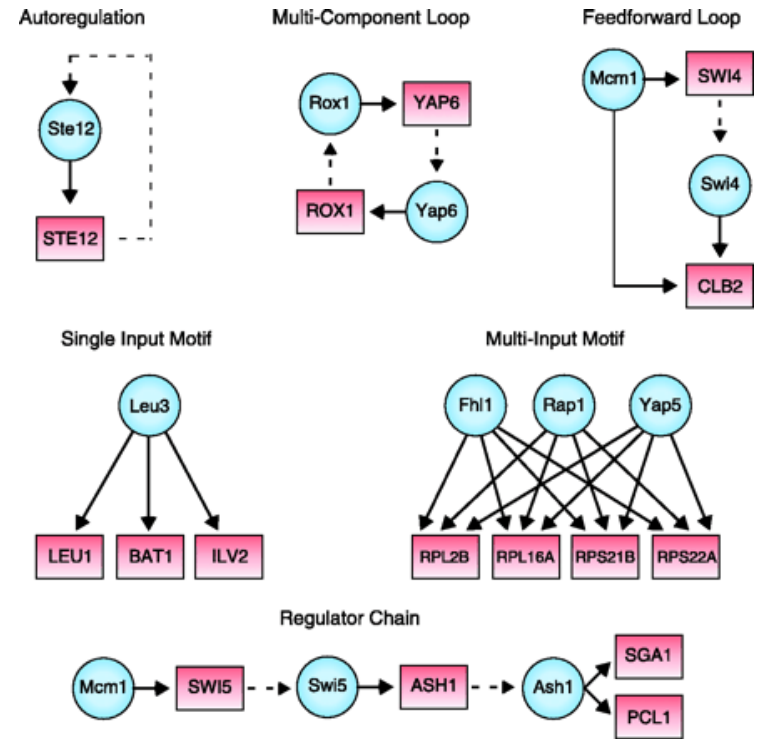
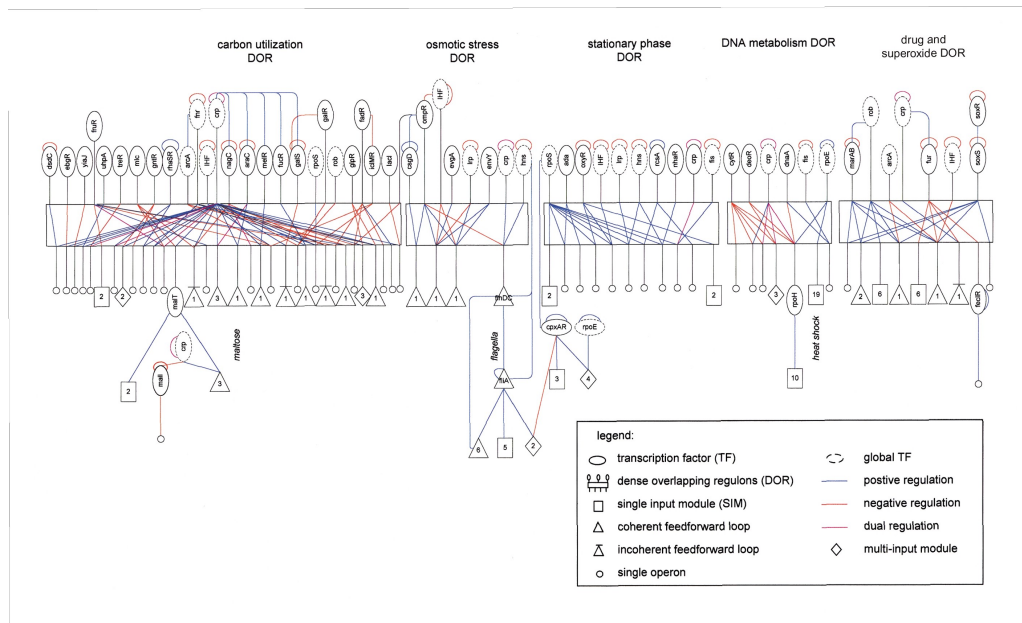
# Caracterización masiva de los componentes a varios niveles y sus relaciones

## Localización celular de los componentes ("localizoma")



# Caracterización masiva de los componentes a varios niveles y sus relaciones

## Redes de regulación génica

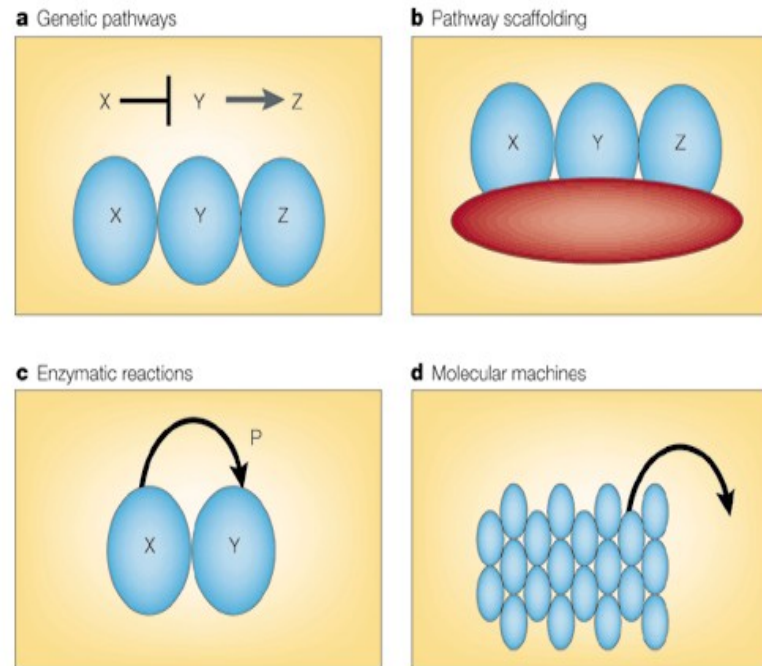


Lee, T.H., *et al.* (2002) Transcriptional regulatory networks in *Saccharomyces cerevisiae*. *Science*, **298**, 799-804.

Shen-Orr, S.S., Milo, R., Mangan, S. & Alon, U. (2002) Network motifs in the transcriptional regulation network of *Escherichia coli*. *Nature Genet*, **31**, 64-68.

# Caracterización masiva de los componentes a varios niveles y sus relaciones

## Redes de interacciones entre proteínas (“interactoma”)



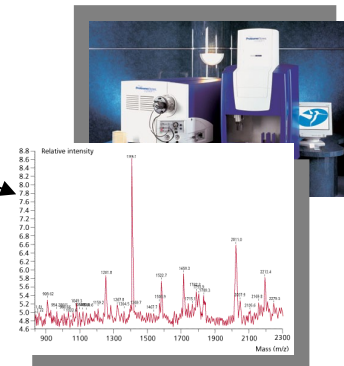
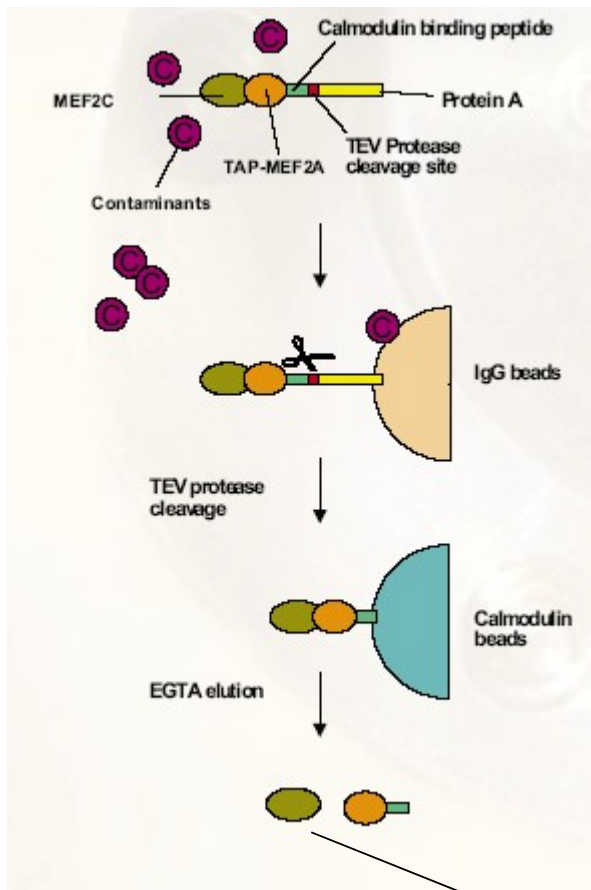
Nature Reviews | Molecular Cell Biology

# Caracterización masiva de los componentes a varios niveles y sus relaciones

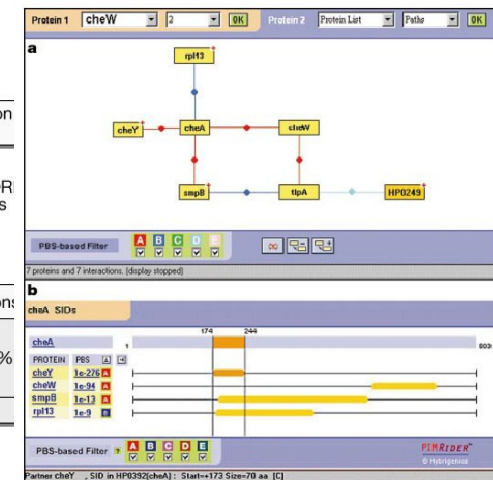
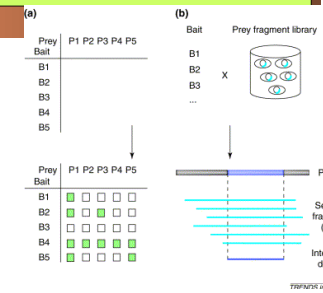
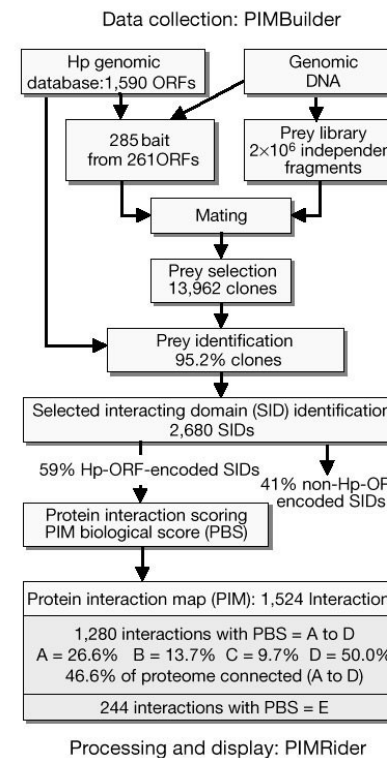
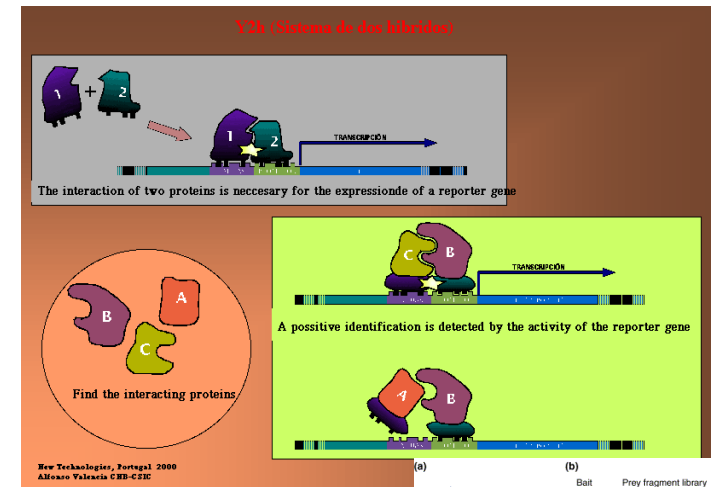
## Redes de interacciones entre proteínas (“interactoma”)

A.Valencia

### TAP/MS

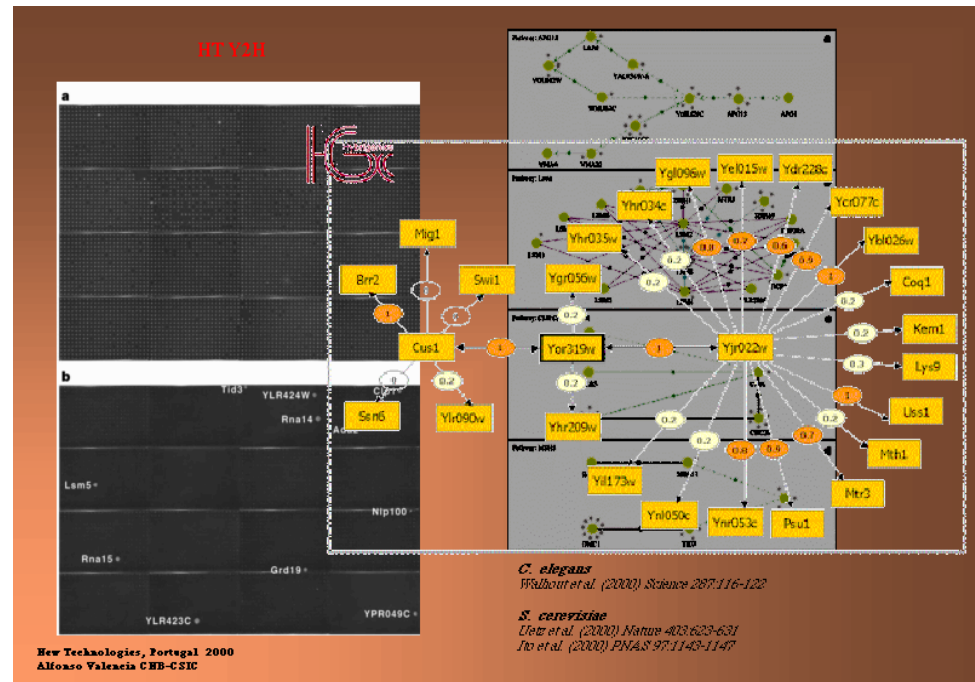


### Y2H



# Caracterización masiva de los componentes a varios niveles y sus relaciones

## Redes de interacciones entre proteínas (“interactoma”)



- Rain, J.C., Selig, L., De Reuse, H., et al. (2001) The protein-protein interaction map of *Helicobacter pylori*. *Nature*, **409**, 211-215.
- Gavin, A.C., et al. (2002) Functional organisation of the yeast proteome by systematic analysis of protein complexes. *Nature*, **415**, 141-147.
- Ho, Y., et al. (2002) Systematic identification of protein complexes in *Saccharomyces cerevisiae* by mass spectrometry. *Nature*, **415**, 180-183.
- Ito, T., et al. (2000) Toward a protein-protein interaction map of the budding yeast: A comprehensive system to examine two-hybrid interactions in all possible combinations between the yeast proteins. *Proc Natl Acad Sci USA*, **97**, 1143-1147.
- Uetz, P., et al. (2000) A comprehensive analysis of protein-protein interactions in *Saccharomyces cerevisiae*. *Nature*, **403**, 623-631.
- Giot, L., Bader, J.S., Brouwer, et al. (2003) A protein interaction map of *Drosophila melanogaster*. *Science*, **302**, 1727-1736.
- Li, S., Armstrong, C.M., Bertin, N., et al. (2004) A map of the interactome network of the metazoan *C. elegans*. *Science*, **303**, 540-543.
- Butland, G., Peregrin-Alvarez, J.M., Li, J., et al. (2005) Interaction network containing conserved and essential protein complexes in *Escherichia coli*. *Nature*, **433**, 531-537.

# Caracterización masiva de los componentes a varios niveles y sus relaciones

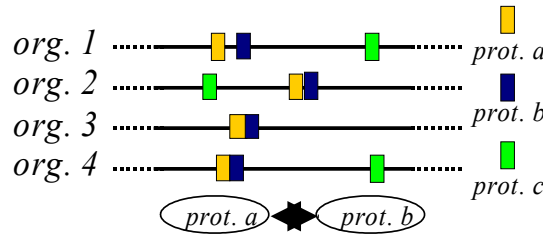
## Redes de interacciones entre proteínas (“interactoma”)

### a) phylogenetic profiles

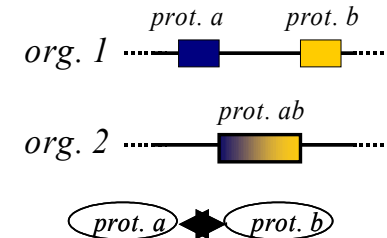
	<i>prot. a</i>	<i>prot. b</i>	<i>prot. c</i>	<i>prot. d</i>
<i>org. 1</i>	1	1	1	1
<i>org. 2</i>	0	1	0	1
<i>org. 3</i>	1	0	1	0
<i>org. 4</i>	1	0	1	1

*prot. a*
↔
*prot. c*

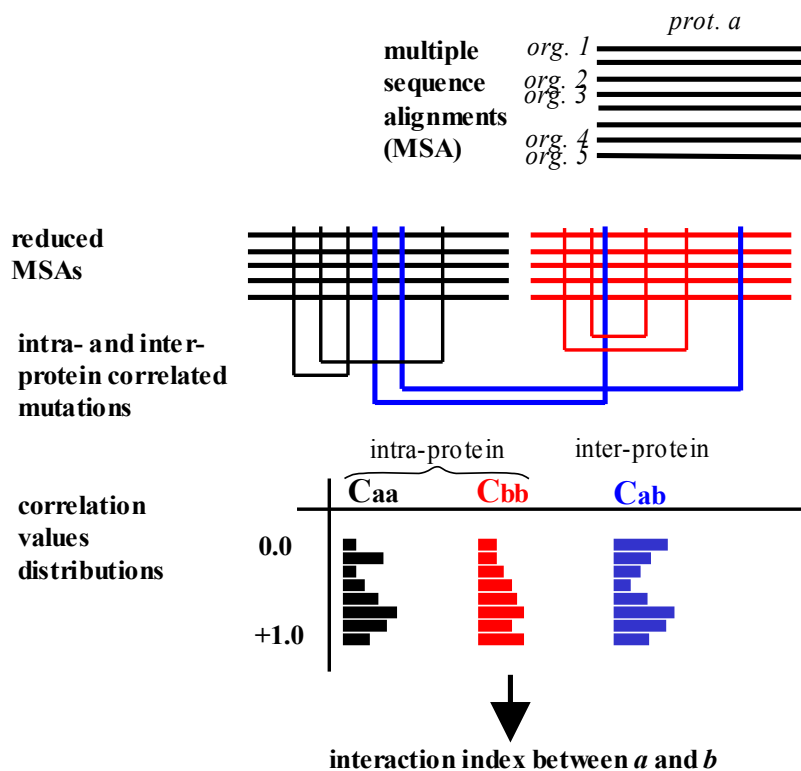
### b) conservation of gene neighbouring



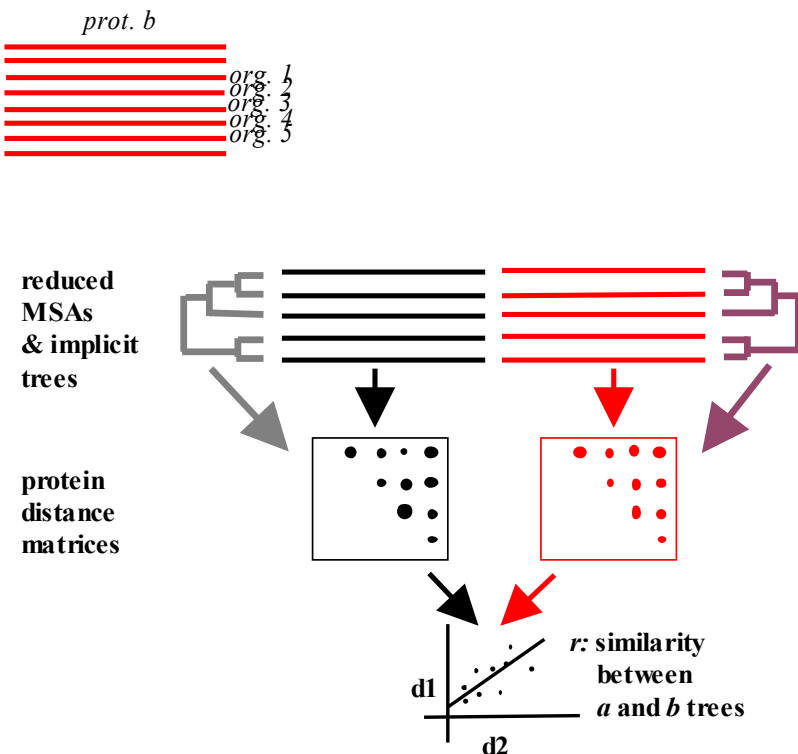
### c) gene fusion



### e) correlated mutations



### d) similarity of phylogenetic trees



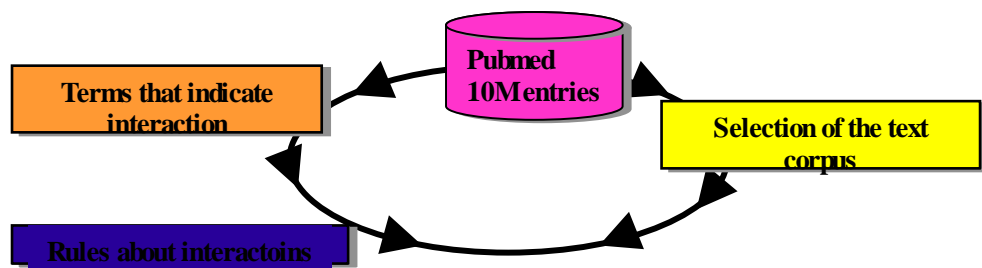
•Huynen, M., Snel, B., Lathe, W. & Bork, P. (2000) Predicting protein function by genomic context: quantitative evaluation and qualitative inferences. *Genome Res*, **10**, 1204-1210.

•Valencia, A. & Pazos, F. (2002) Computational methods for the prediction of protein interactions. *Curr Opin Struct Biol*, **12**, 368-373.



# Caracterización masiva de los componentes a varios niveles y sus relaciones

## Redes de interacciones entre proteínas (“interactoma”)

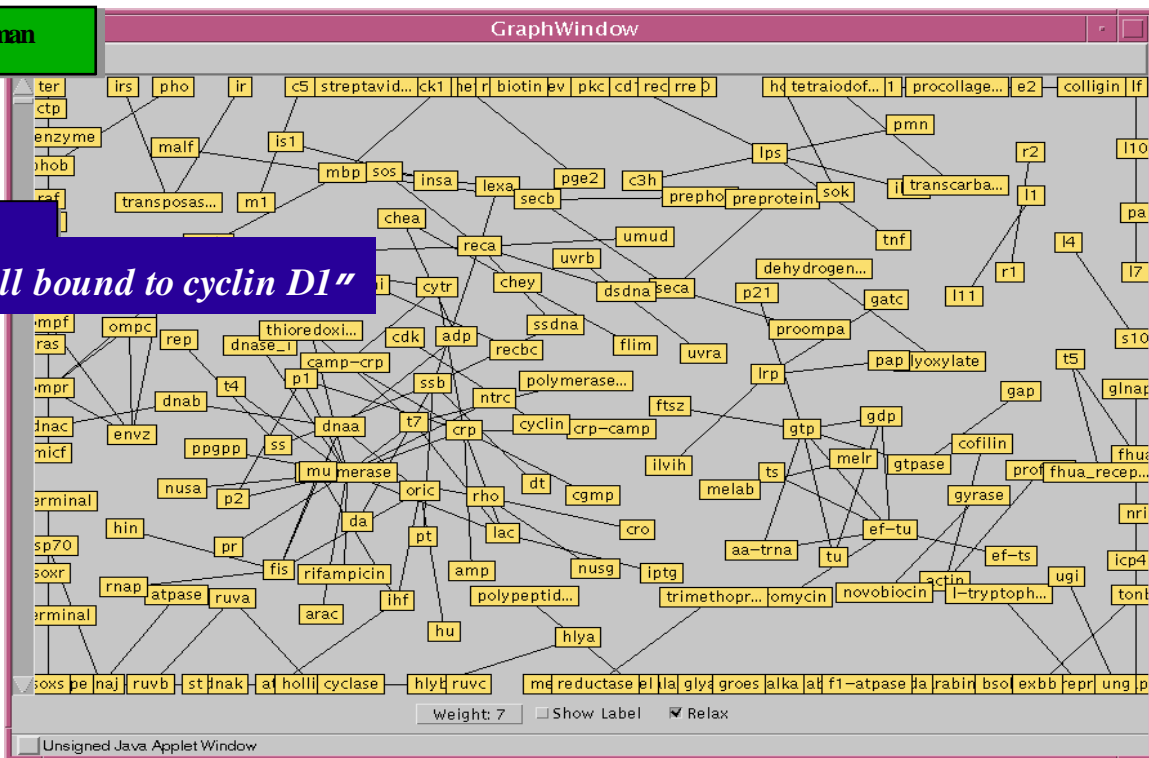


A. Valencia



Action words are for example:  
**afect, asociado with, inhibita, phosphoryte, rgkte**

**“After extensive purification, Cdk2 was still bound to cyclin D1”**



# Caracterización masiva de los componentes a varios niveles y sus relaciones

## Redes de interacciones entre proteínas (“interactoma”)

The screenshot shows the DIP website interface. At the top, there is a navigation bar with links like 'Anterior', 'Siguiente', 'Recargar', 'Inicio', 'Buscar', 'Mozilla', 'Imprimir', 'Seguridad', 'Compras', and 'Parar'. The address bar shows the URL: <http://dip.doe-mbi.ucla.edu/dip/Stat.cgi>. The main content area is titled 'Database of Interacting Proteins' and includes a sidebar with links for 'Help', 'News', 'Register', 'Statistics', 'Satellites', 'Services', 'Articles', 'Search', 'Links', and 'Files'. The main content area displays 'DATABASE STATISTICS' and a table of organism data.

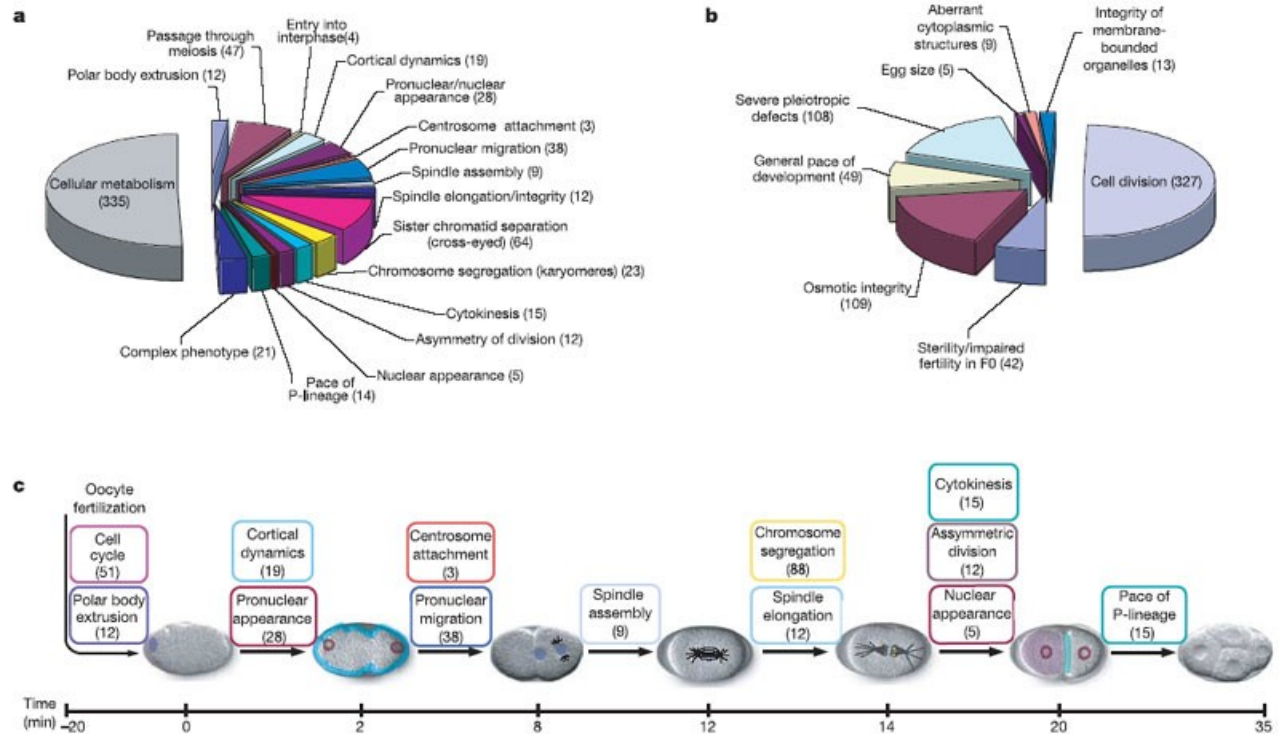
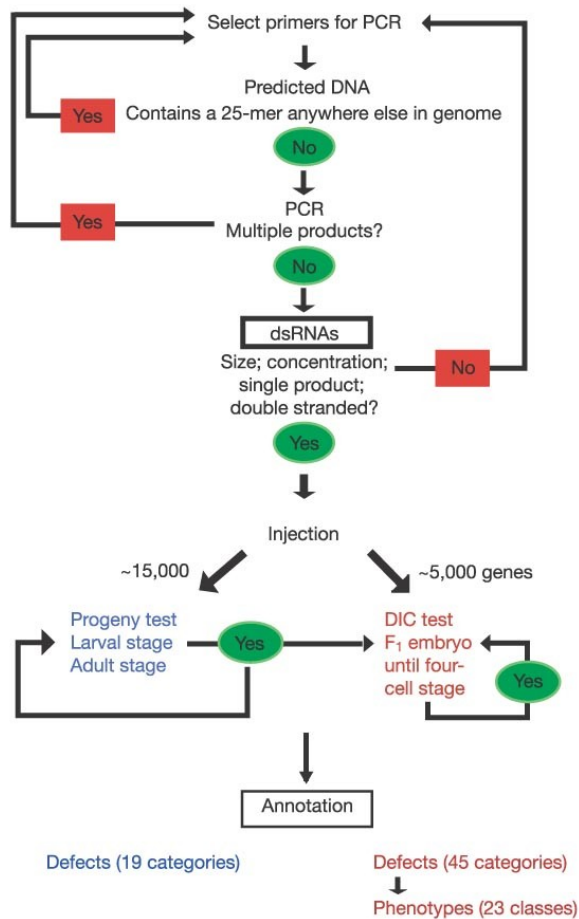
ORGANISM	PROTEINS	INTERACTIONS	#Exp	#Int
			1	13042
			2	1095
<i>Saccharomyces cerevisiae</i> (budding yeast)	4689	14722	3	323
			4	131
			5+	131
<i>Helicobacter pylori</i>	710	1415		
			1	557
			2	100
<i>Homo sapiens</i> (Human)	687	714	3	29
			4	17
			5+	11
			1	81
<i>Mus musculus</i> (house mouse)	177	97	2	13
			3	3
Others	534	714		

Xenarios, I., Salwinski, L., Duan, X.J., Higney, P., Kim, S.M. & Eisenberg, D. (2002) DIP, the Database of Interacting Proteins: a research tool for studying cellular networks of protein interactions. *Nucleic Acids Res*, **30**, 303-305.



# Caracterización masiva de los componentes a varios niveles y sus relaciones

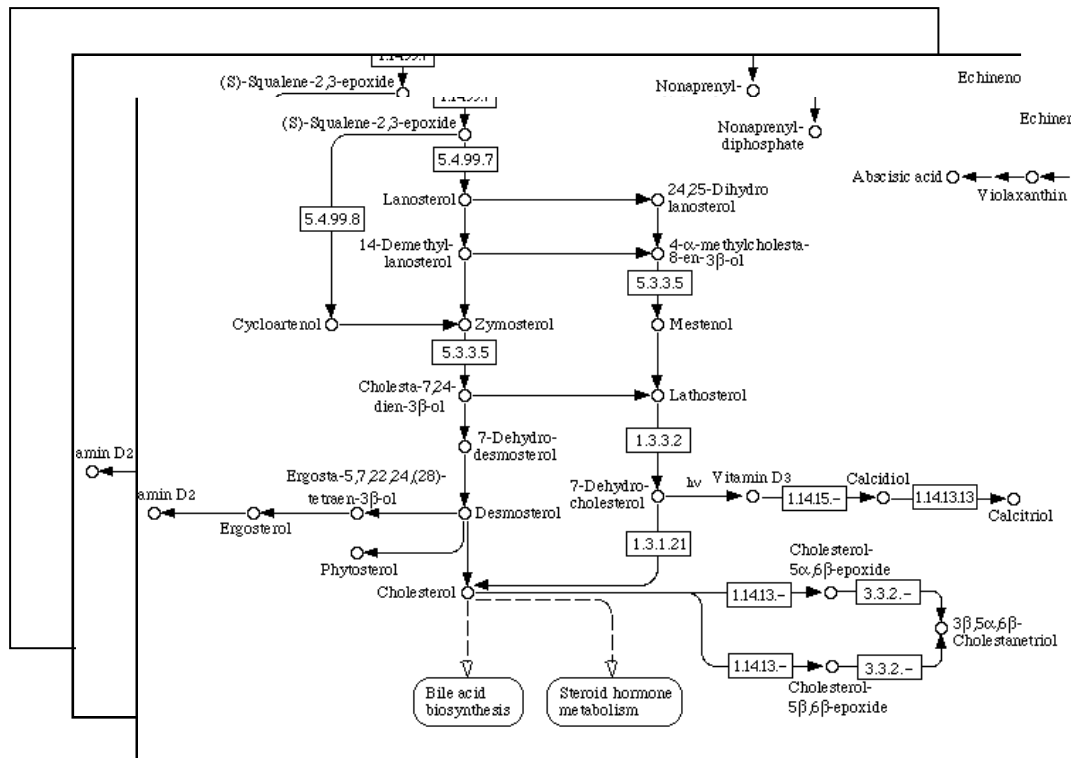
## Estudios masivos de relaciones gen-fenotipo (“fenoma”)



- Winzeler, E.A. & al., e. (1999) Functional characterization of the *S. cerevisiae* genome by deletion and parallel analysis. *Science*, **285**, 901-906
- Kobayashi, K., Ehrlich, S.D., Albertini, A. et al. (2003) Essential bacillus subtilis genes. *Proc Natl Acad Sci U S A*, **100**, 4678-4683.
- Sönnichsen, B., Koski, L.B., Walsh, A., et al. (2005) Full-genome RNAi profiling of early embryogenesis in *Caenorhabditis elegans*. *Nature*, **434**, 462-469.

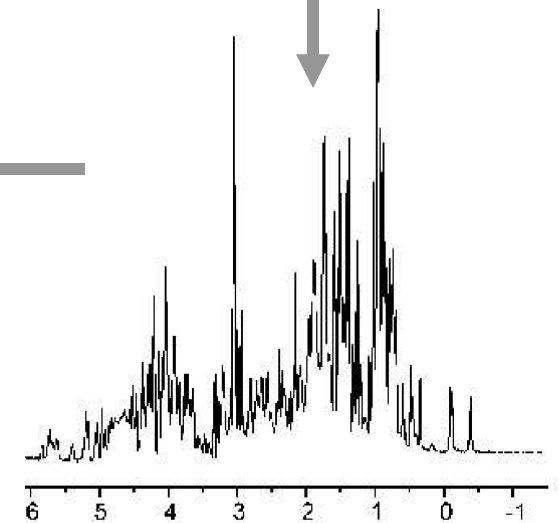
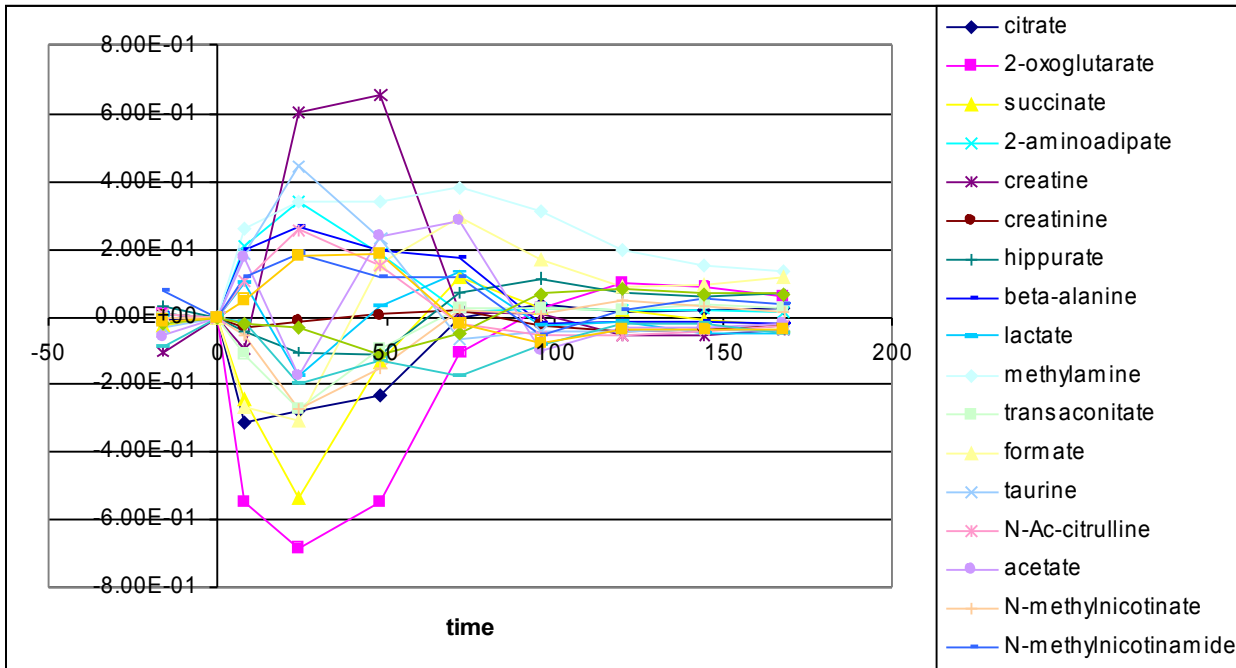
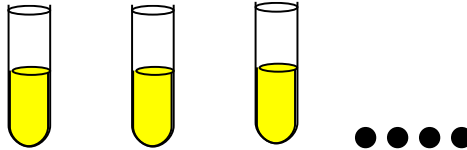
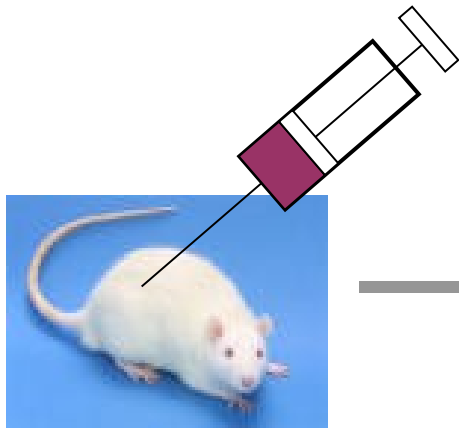
# Caracterización masiva de los componentes a varios niveles y sus relaciones

## Redes metabólicas (“metaboloma”).



# Caracterización masiva de los componentes a varios niveles y sus relaciones

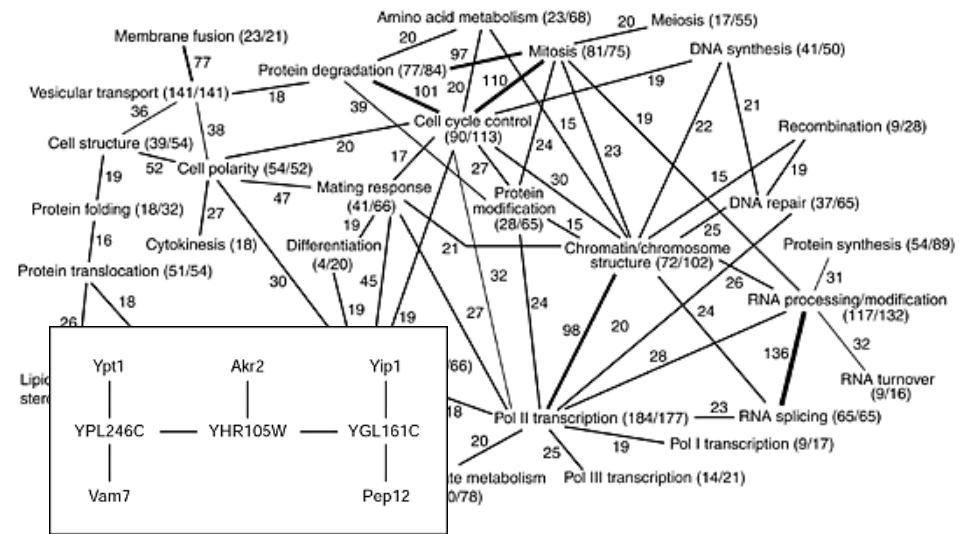
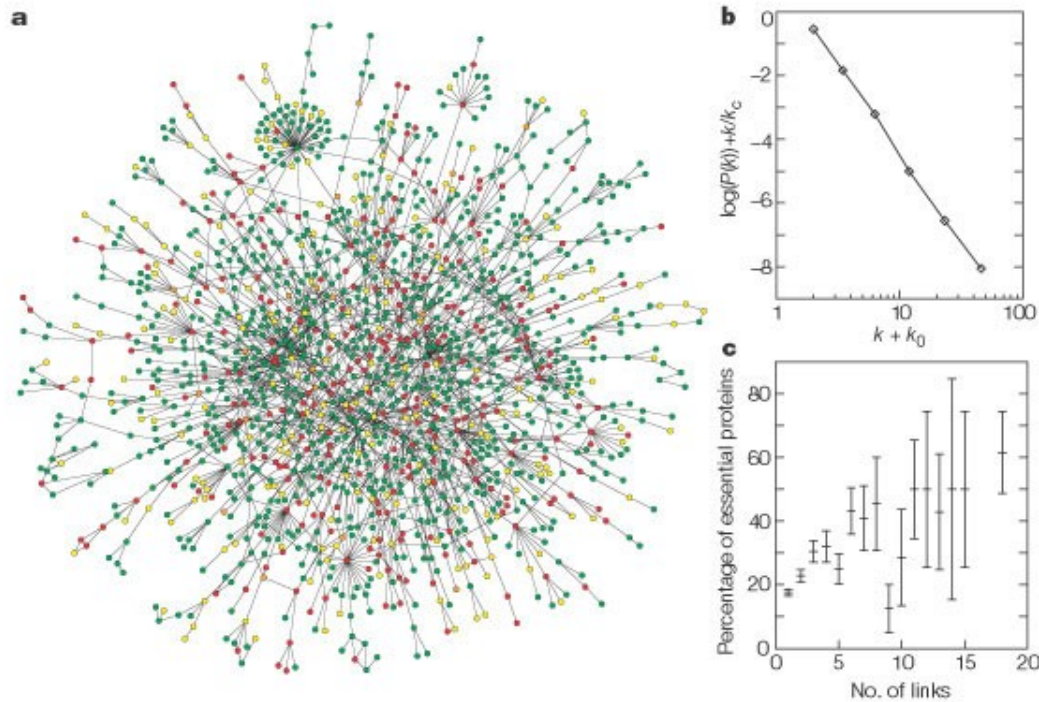
## Redes metabólicas (“metaboloma”)



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.

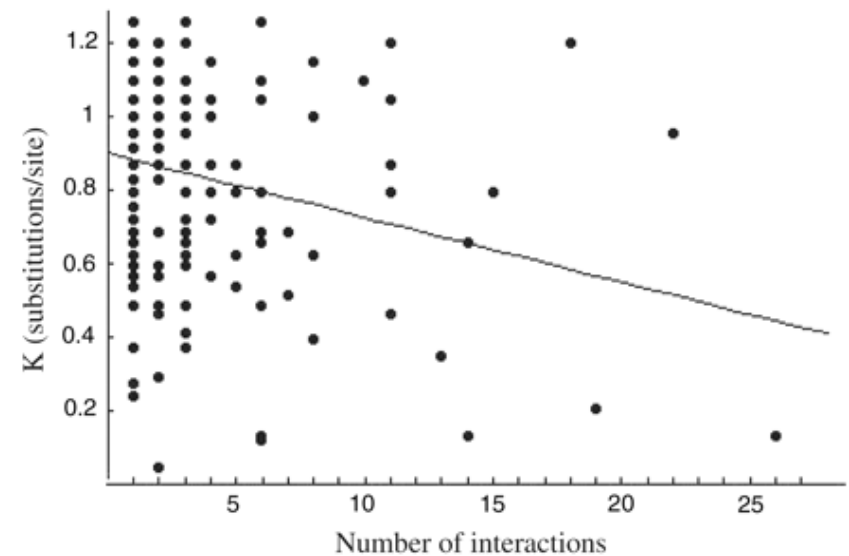
Nicholson J. K., Connelly J., Lindon J. C. & Holmes E. (2002) Metabonomics: a platform for studying drug toxicity and gene function. *Nature Reviews Drug Discovery* **1**, 153 – 161

# Estudio desde un enfoque de “Sistemas” “Interactoma”



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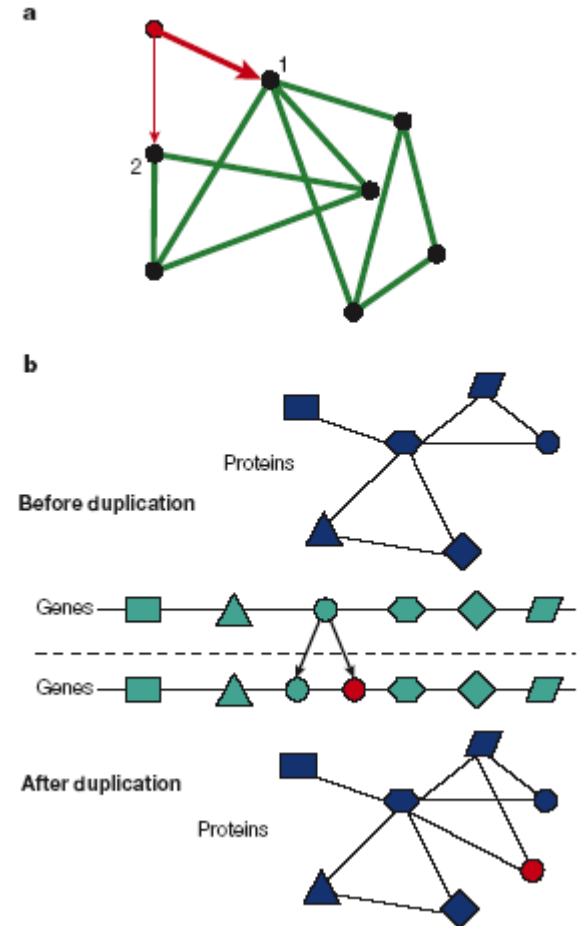
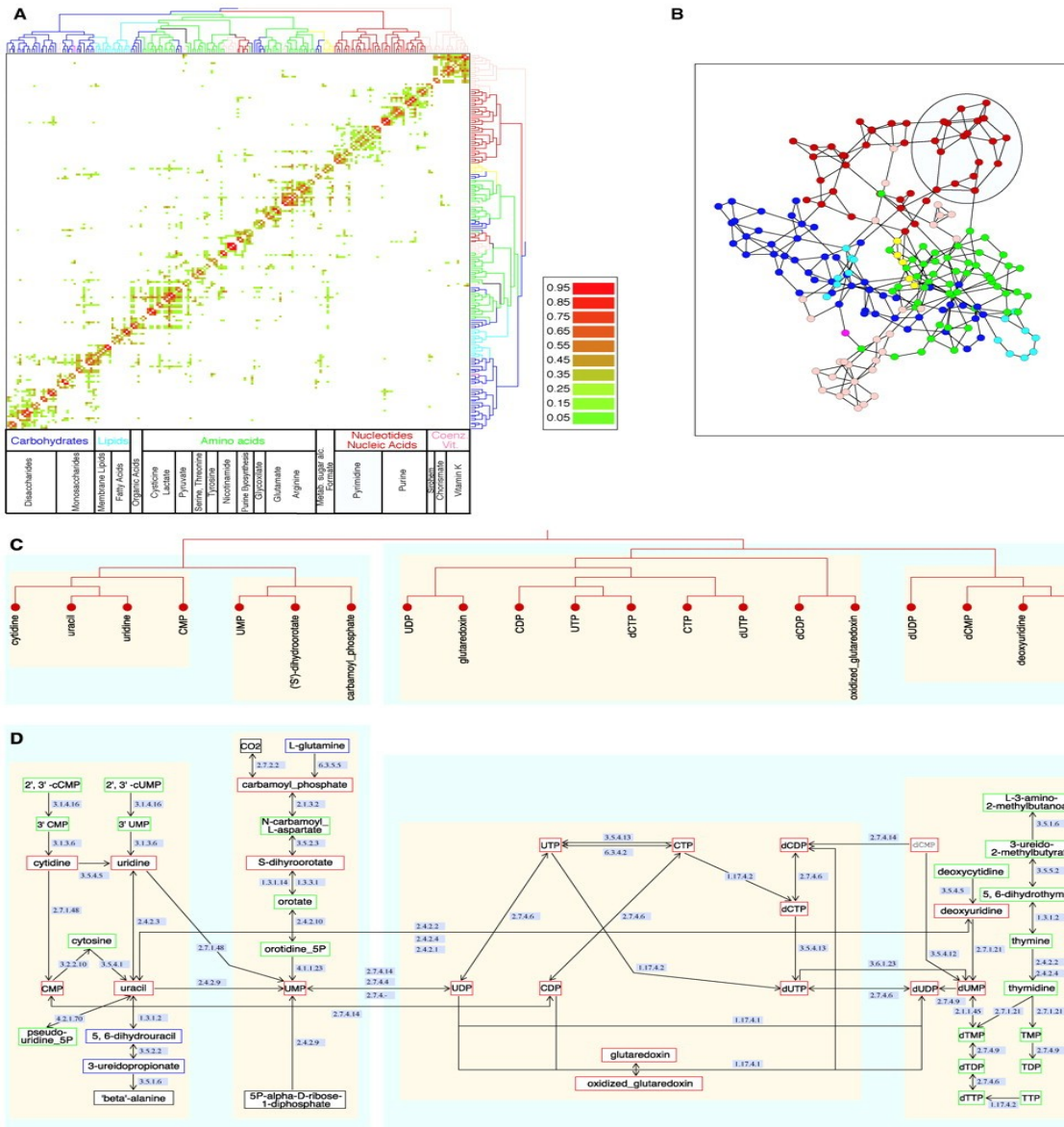
Jeong, H., Mason, S. P., Barabasi, A. L. & Oltvai, Z. N. (2001). Lethality and centrality in protein networks. *Nature* **411**, 41-42.



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# Estudio desde un enfoque de “Sistemas” “Interactoma”

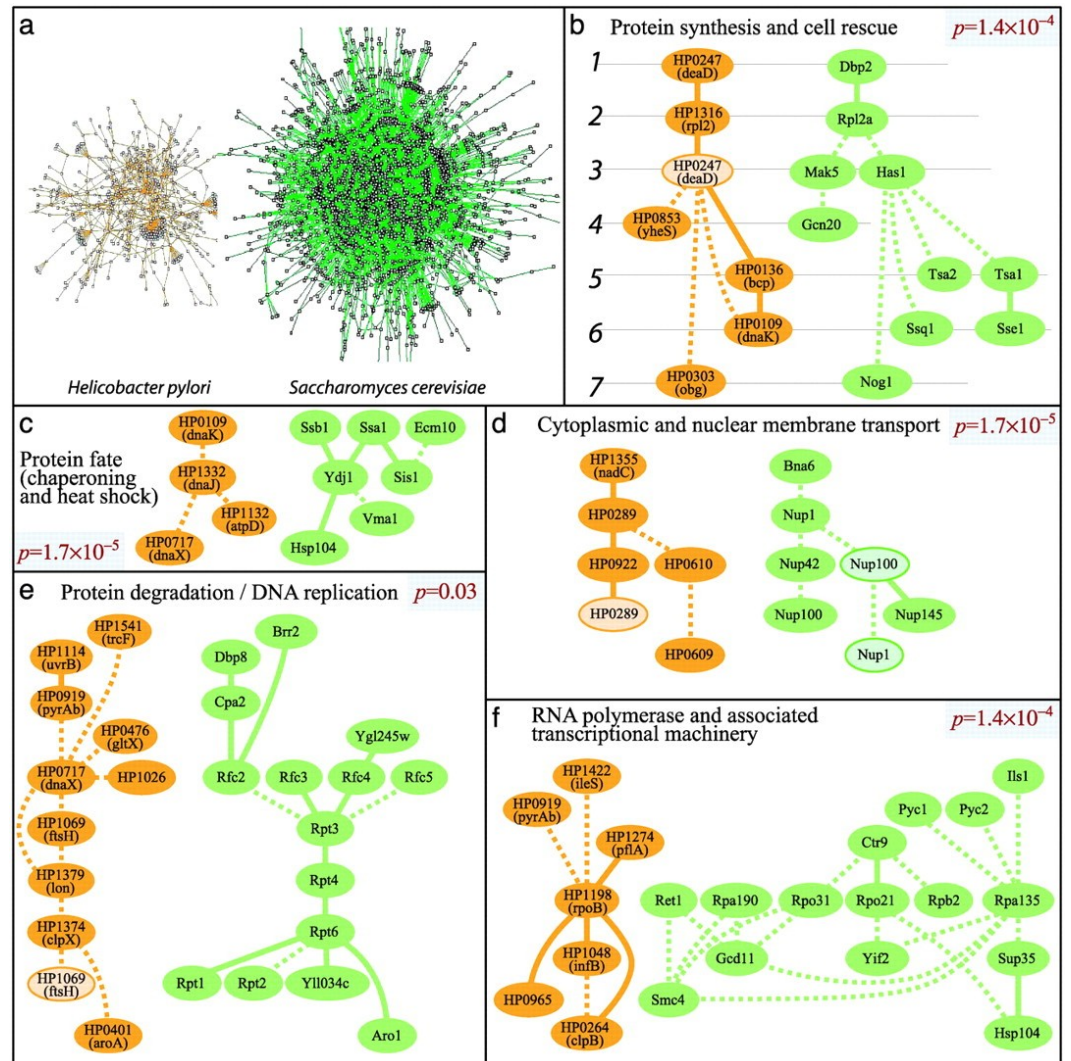


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- Barabasi, A.L. and Oltvai, Z.N. (2004) Network biology: understanding the cell's functional organization. *Nat Rev Genet*, **5**, 101-113.

# Estudio desde un enfoque de “Sistemas” “Interactoma”

**Table 1 Evolutionary conservation of motif constituents**

#	Motifs	Number of yeast motifs	Natural conservation rate	Random conservation rate	Conservation ratio
1		9,266	13.67%	4.63%	2.94
2		167,304	4.99%	0.81%	6.15
3		3,846	20.51%	1.01%	20.28
4		3,649,591	0.73%	0.12%	5.87
5		1,763,891	2.64%	0.18%	14.67
6		9,646	6.71%	0.17%	40.44
7		164,075	7.67%	0.17%	45.56
8		12,423	18.68%	0.12%	157.89
9		2,339	32.53%	0.08%	422.78
10		25,749	14.77%	0.05%	279.71
11		1,433	47.24%	0.02%	2,256.67

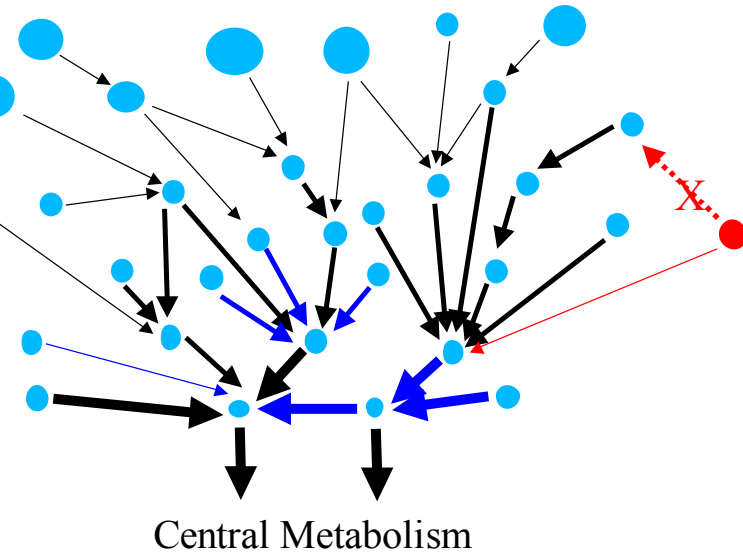
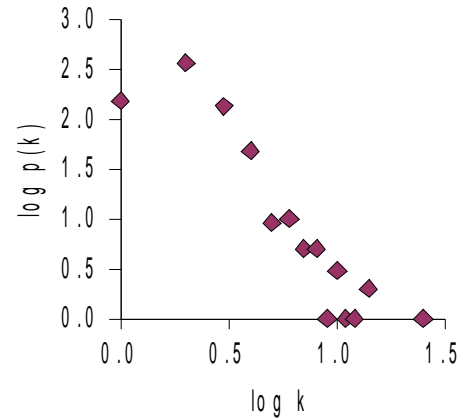
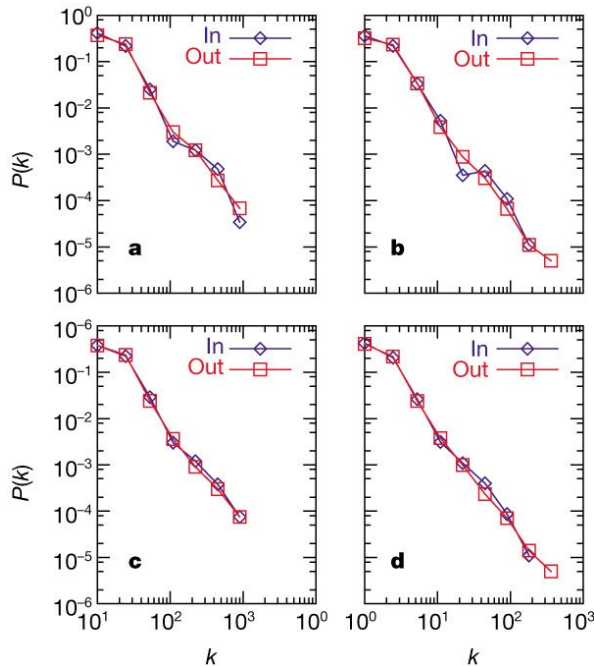


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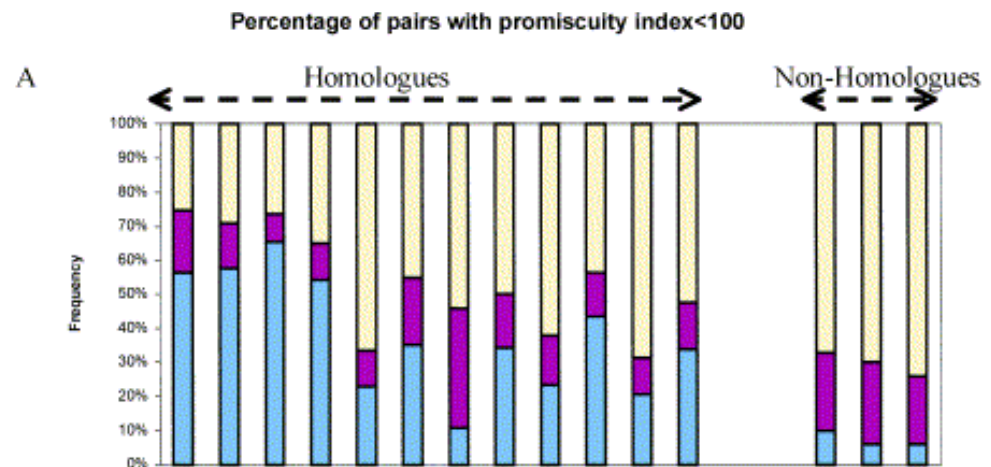
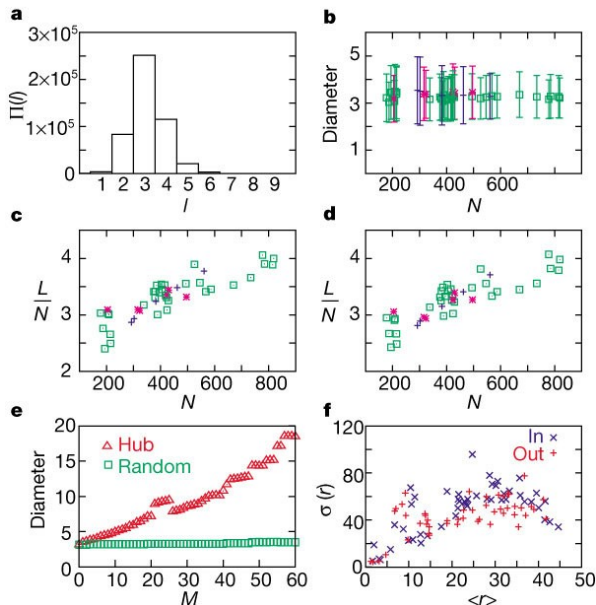
# Estudio desde un enfoque de “Sistemas”

## “Metabonoma”



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[http://pdg.cnb.uam.es/biodeg\\_net](http://pdg.cnb.uam.es/biodeg_net)



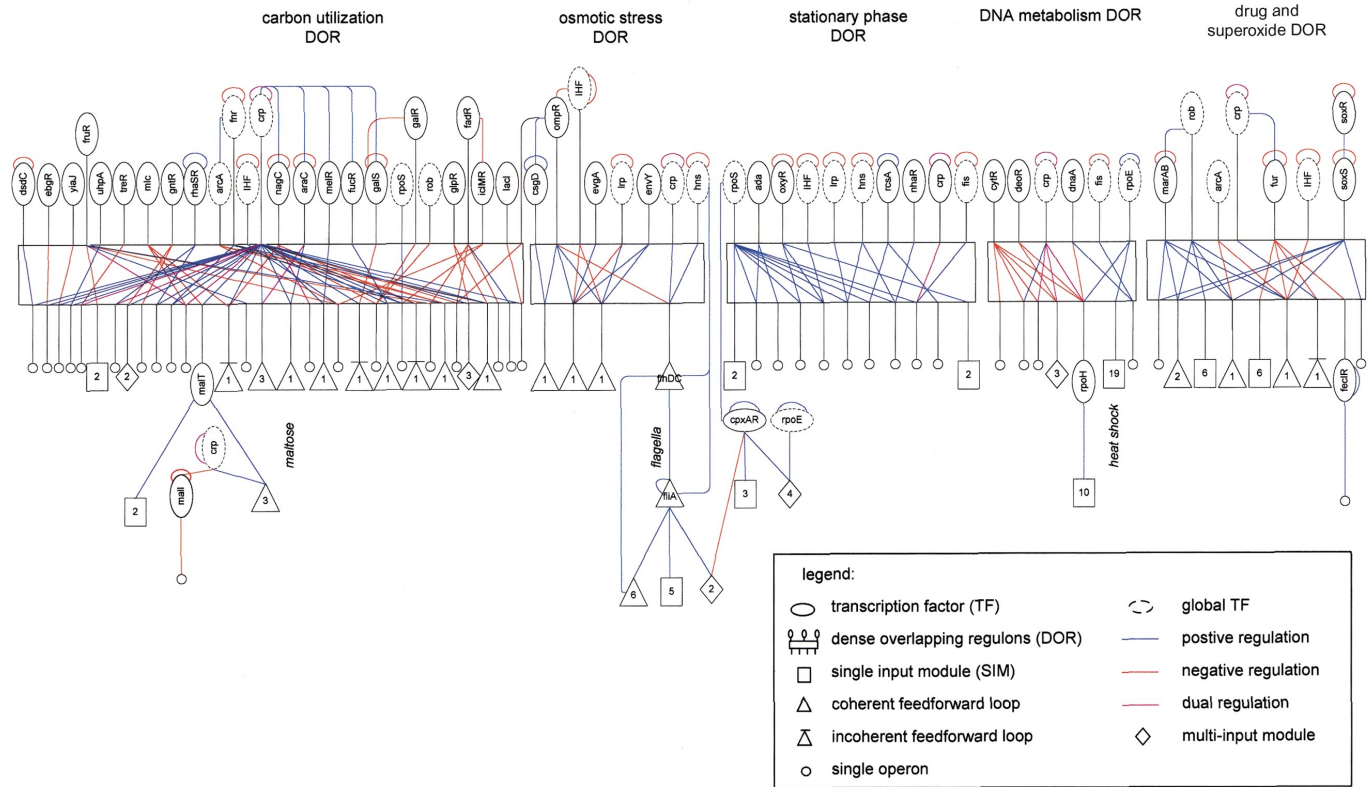
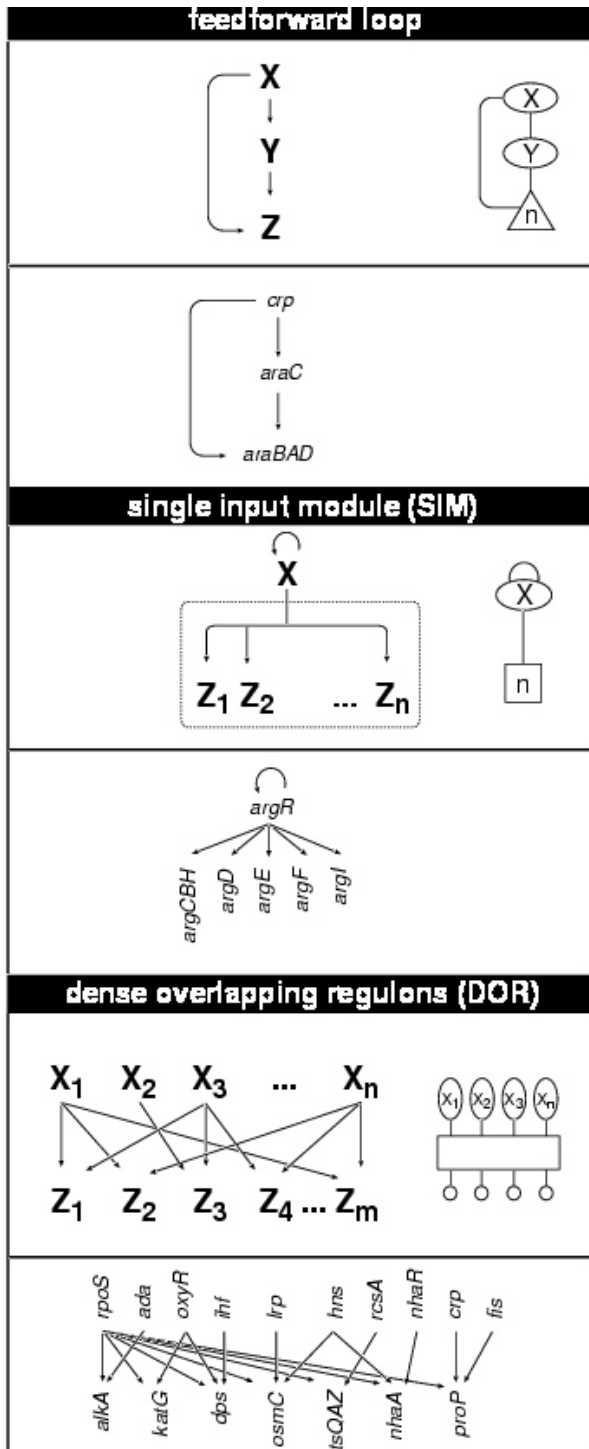
Alves, R., Chaleil, R.A.G. and Sternberg, M.J.E. (2002) Evolution of enzymes in metabolic network perspective. *J Mol Biol*, **320**, 751-770.

Jeong, H., Tombor, B., Albert, R., Oltvai, Z. N. & Barabasi, A. L. (2000). The large scale organisation of metabolic networks. *Nature* **407**, 651-653.



# Estudio desde un enfoque de “Sistemas”

## Red de regulación génica



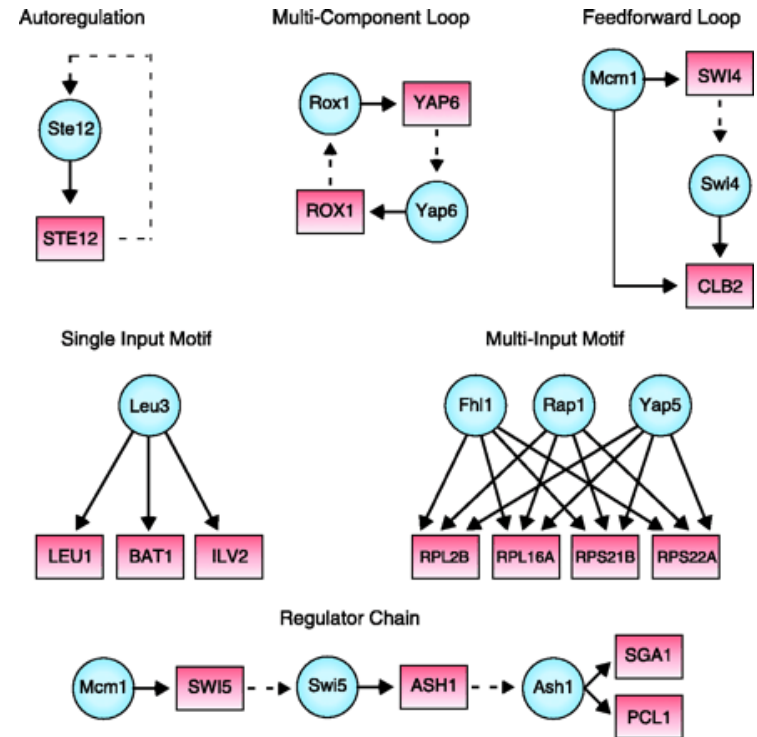
Shen-Orr, S. S., Milo, R., Mangan, S. & Alon, U. (2002). Network motifs in the transcriptional regulation network of Escherichia coli. *Nature Genet* **31**, 64-68.



# Estudio desde un enfoque de “Sistemas”

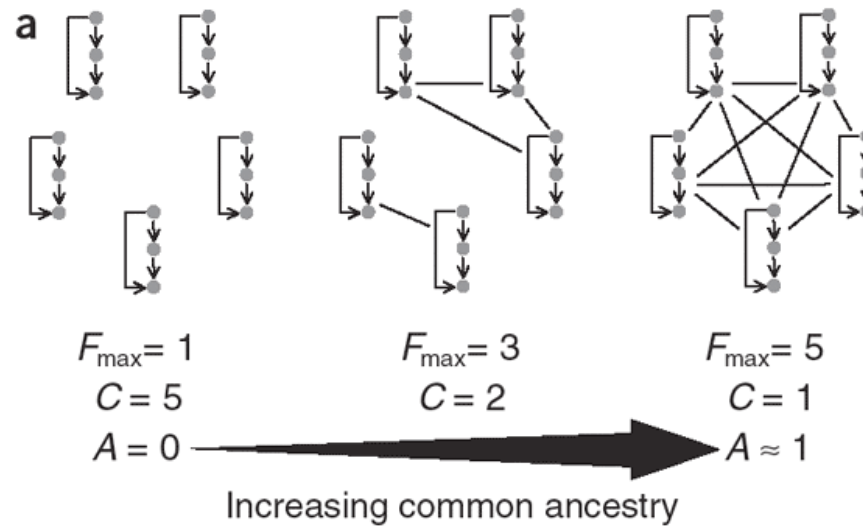
## Red de regulación génica

Network	Nodes	Edges	$N_{real}$	$N_{rand} \pm SD$	Z score	$N_{real}$	$N_{rand} \pm SD$	Z score	$N_{real}$	$N_{rand} \pm SD$	Z score
<b>Gene regulation (transcription)</b>											
					<b>Feed-forward loop</b>			<b>Bi-fan</b>			
<i>E. coli</i>	424	519	40	7 ± 3	10	203	47 ± 12	13			
<i>S. cerevisiae*</i>	685	1,052	70	11 ± 4	14	1812	300 ± 40	41			
<b>Neurons</b>											
					<b>Feed-forward loop</b>			<b>Bi-fan</b>			<b>Bi-parallel</b>
<i>C. elegans†</i>	252	509	125	90 ± 10	3.7	127	55 ± 13	5.3	227	35 ± 10	20
<b>Food webs</b>											
					<b>Three chain</b>			<b>Bi-parallel</b>			
Little Rock	92	984	3219	3120 ± 50	2.1	7295	2220 ± 210	25			
Ythan	83	391	1182	1020 ± 20	7.2	1357	230 ± 50	23			
St. Martin	42	205	469	450 ± 10	NS	382	130 ± 20	12			
Chesapeake	31	67	80	82 ± 4	NS	26	5 ± 2	8			
Coachella	29	243	279	235 ± 12	3.6	181	80 ± 20	5			
Skipwith	25	189	184	150 ± 7	5.5	397	80 ± 25	13			
B. Brook	25	104	181	130 ± 7	7.4	267	30 ± 7	32			
<b>Electronic circuits (forward logic chips)</b>											
					<b>Feed-forward loop</b>			<b>Bi-fan</b>			<b>Bi-parallel</b>
s15850	10,383	14,240	424	2 ± 2	285	1040	1 ± 1	1200	480	2 ± 1	335
s38584	20,717	34,204	413	10 ± 3	120	1739	6 ± 2	800	711	9 ± 2	320
s38417	23,843	33,661	612	3 ± 2	400	2404	1 ± 1	2550	531	2 ± 2	340
s9234	5,844	8,197	211	2 ± 1	140	754	1 ± 1	1050	209	1 ± 1	200
s13207	8,651	11,831	403	2 ± 1	225	4445	1 ± 1	4950	264	2 ± 1	200
<b>Electronic circuits (digital fractional multipliers)</b>											
					<b>Three-node feedback loop</b>			<b>Bi-fan</b>			<b>Four-node feedback loop</b>
s208	122	189	10	1 ± 1	9	4	1 ± 1	3.8	5	1 ± 1	5
s420	252	399	20	1 ± 1	18	10	1 ± 1	10	11	1 ± 1	11
s838‡	512	819	40	1 ± 1	38	22	1 ± 1	20	23	1 ± 1	25
<b>World Wide Web</b>											
					<b>Feedback with two mutual dyads</b>			<b>Fully connected triad</b>			<b>Uplinked mutual dyad</b>
nd.edu§	325,729	1.46e6	1.1e5	2e3 ± 1e2	800	6.8e6	5e4 ± 4e2	15,000	1.2e6	1e4 ± 2e2	5000



Milo, R., Shen-Orr, S.S., Itzkovitz, S., Kashtan, N., Chklovskii, D. and Alon, U. (2002) Network motifs: simple building blocks of complex networks. *Nature*, **298**, 824-827.

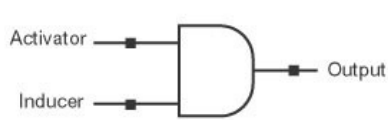
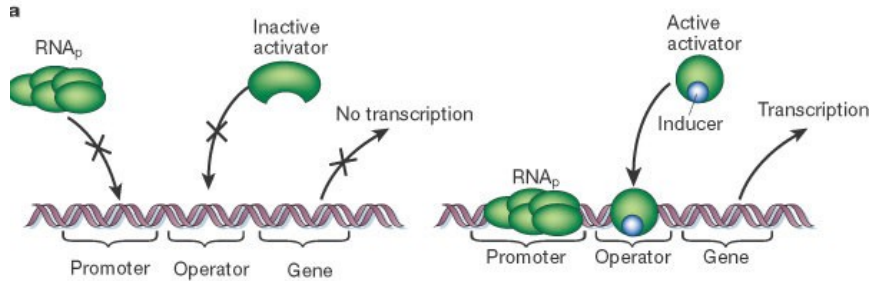
# Estudio desde un enfoque de “Sistemas” Red de regulación génica



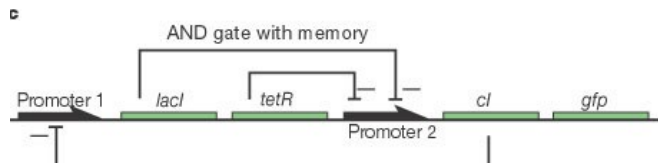
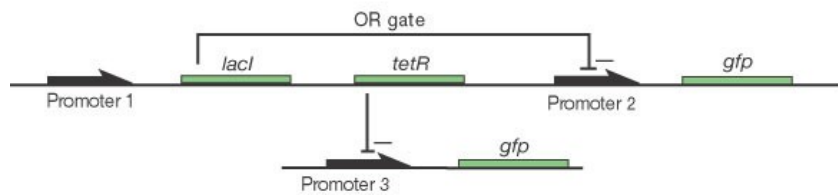
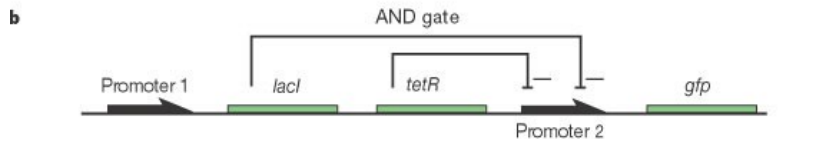
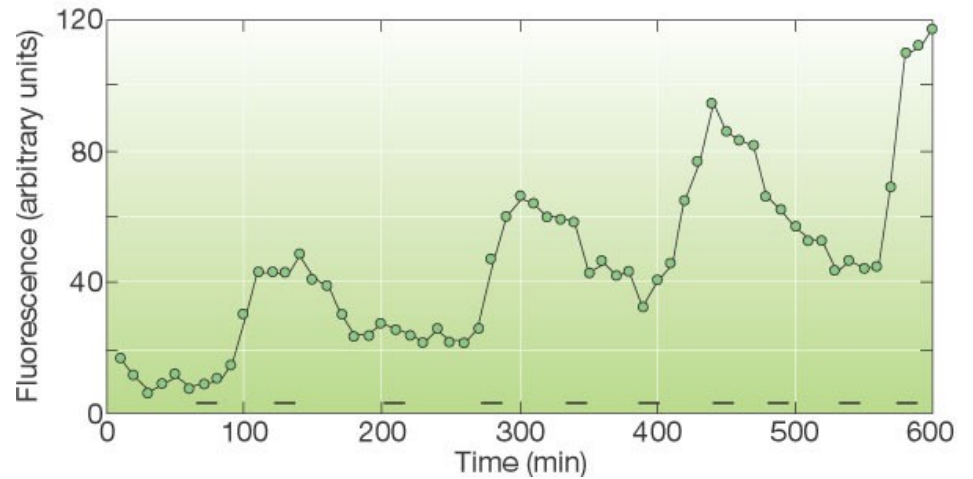
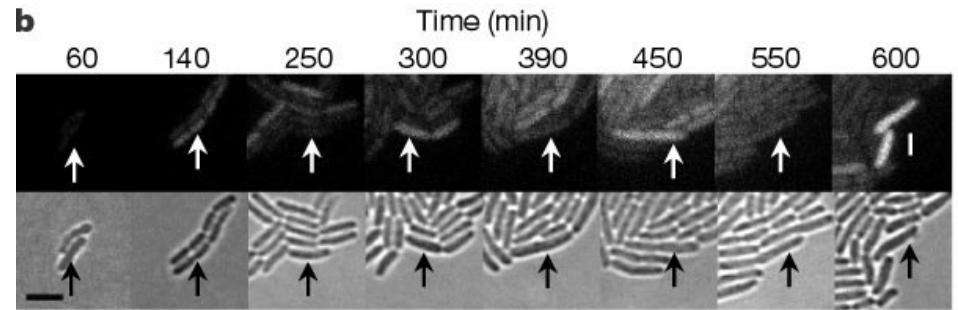
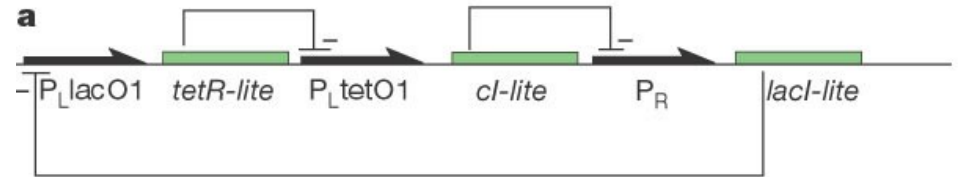
**b**

	Circuit type	Number of circuits	Number of families ( $C$ )	Index of common ancestry ( $A$ )	Largest circuit family ( $F_{\max}$ )
Yeast	Feed-forward	48	44 ( $46.8 \pm 1.9$ ; $P = 0.08$ )	0.082 ( $0.023 \pm 0.035$ ; $P = 0.08$ )	5 ( $1.9 \pm 1.4$ ; $P = 0.05$ )
	Bi-fan	542	435 ( $469.0 \pm 37.7$ ; $P = 0.18$ )	0.197 ( $0.135 \pm 0.070$ ; $P = 0.18$ )	49 ( $41.0 \pm 31.1$ ; $P = 0.33$ )
	MIM-2	176	168 ( $164.5 \pm 8.8$ ; $P = 0.60$ )	0.045 ( $0.065 \pm 0.050$ ; $P = 0.60$ )	5 ( $7.4 \pm 6.2$ ; $P = 0.59$ )
	Reg. chain (3)	33	33	0	1
<i>E. coli</i>	Feed-forward	11	11	0	1
	Bi-fan	27	27	0	1

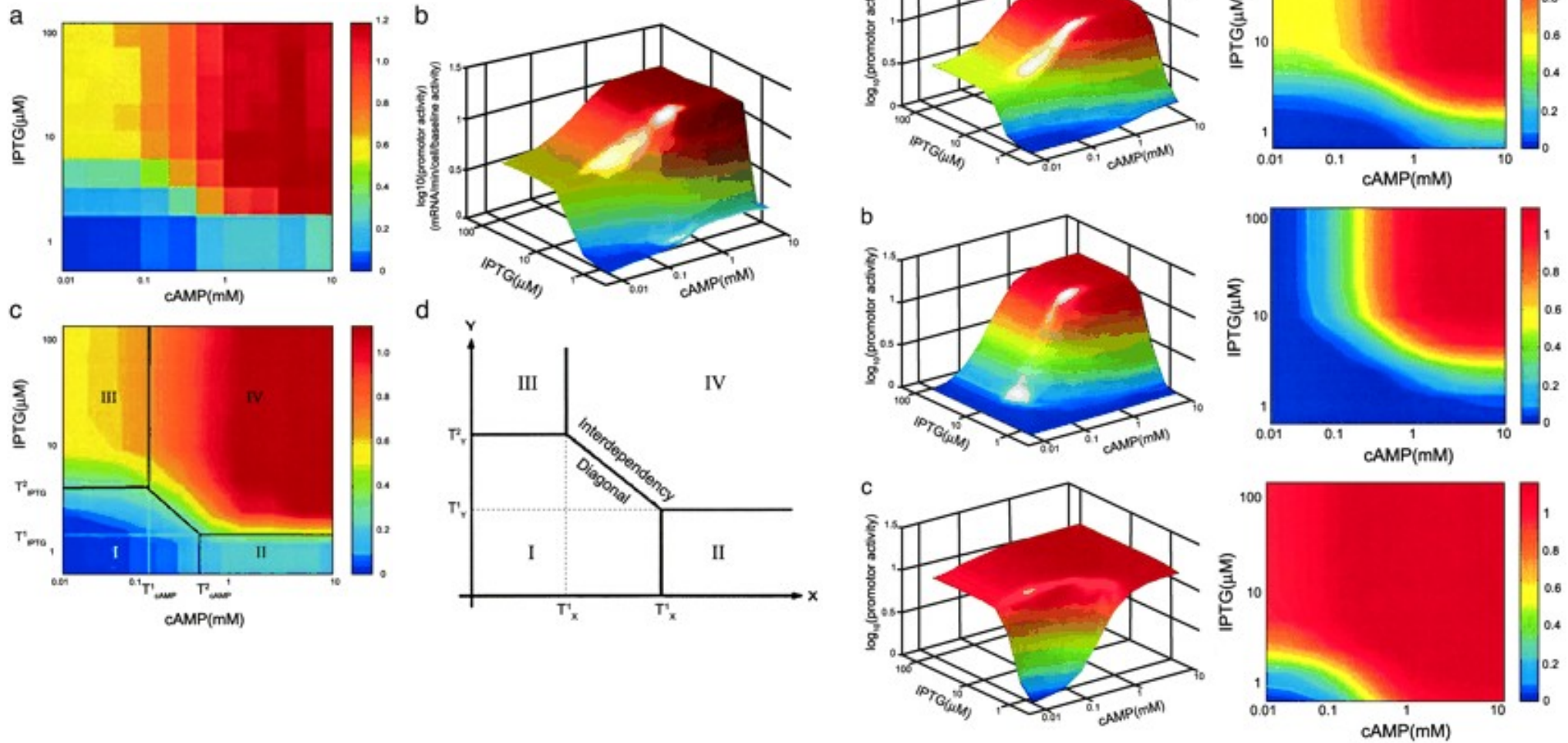
# Ingeniería de circuitos génicos



Activator	Inducer	Output
0	0	0
0	1	0
1	0	0
1	1	1

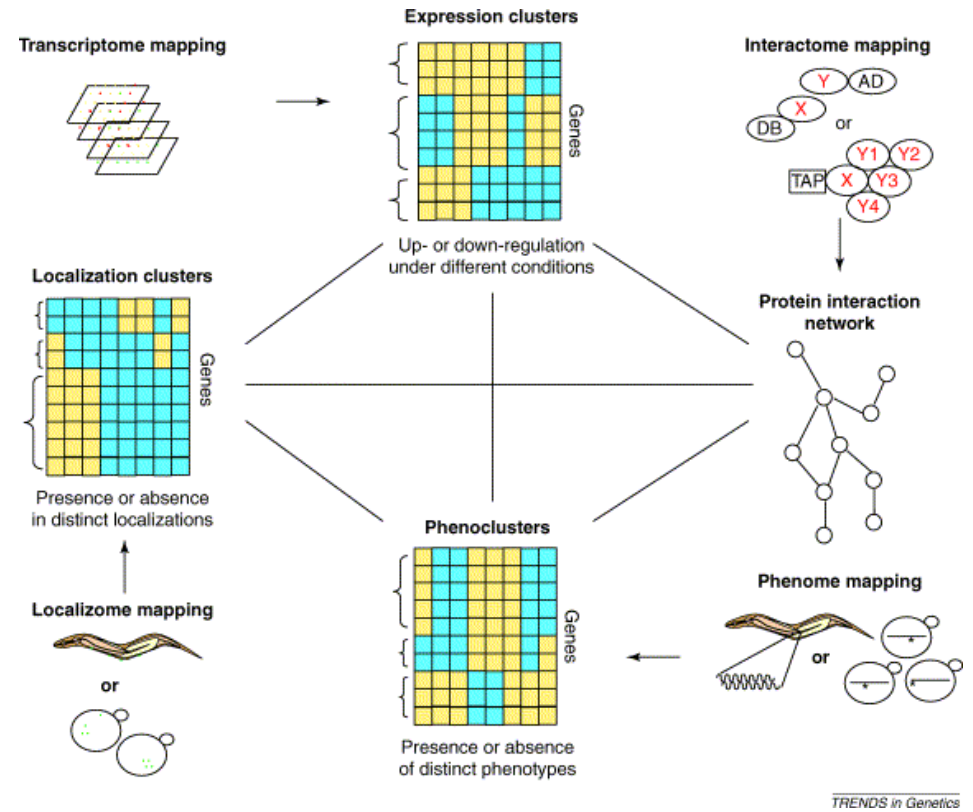
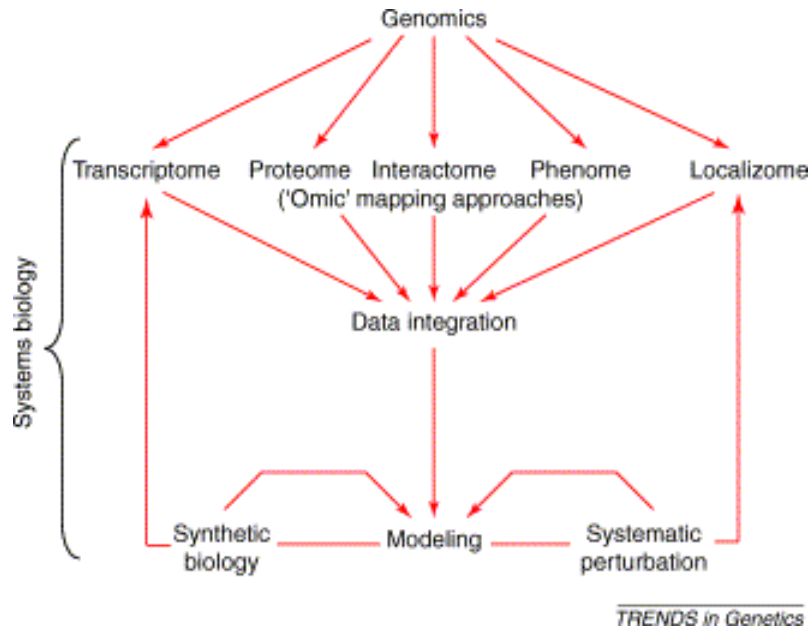


# Ingeniería de circuitos génicos



# Futuro de la Biología de Sistemas

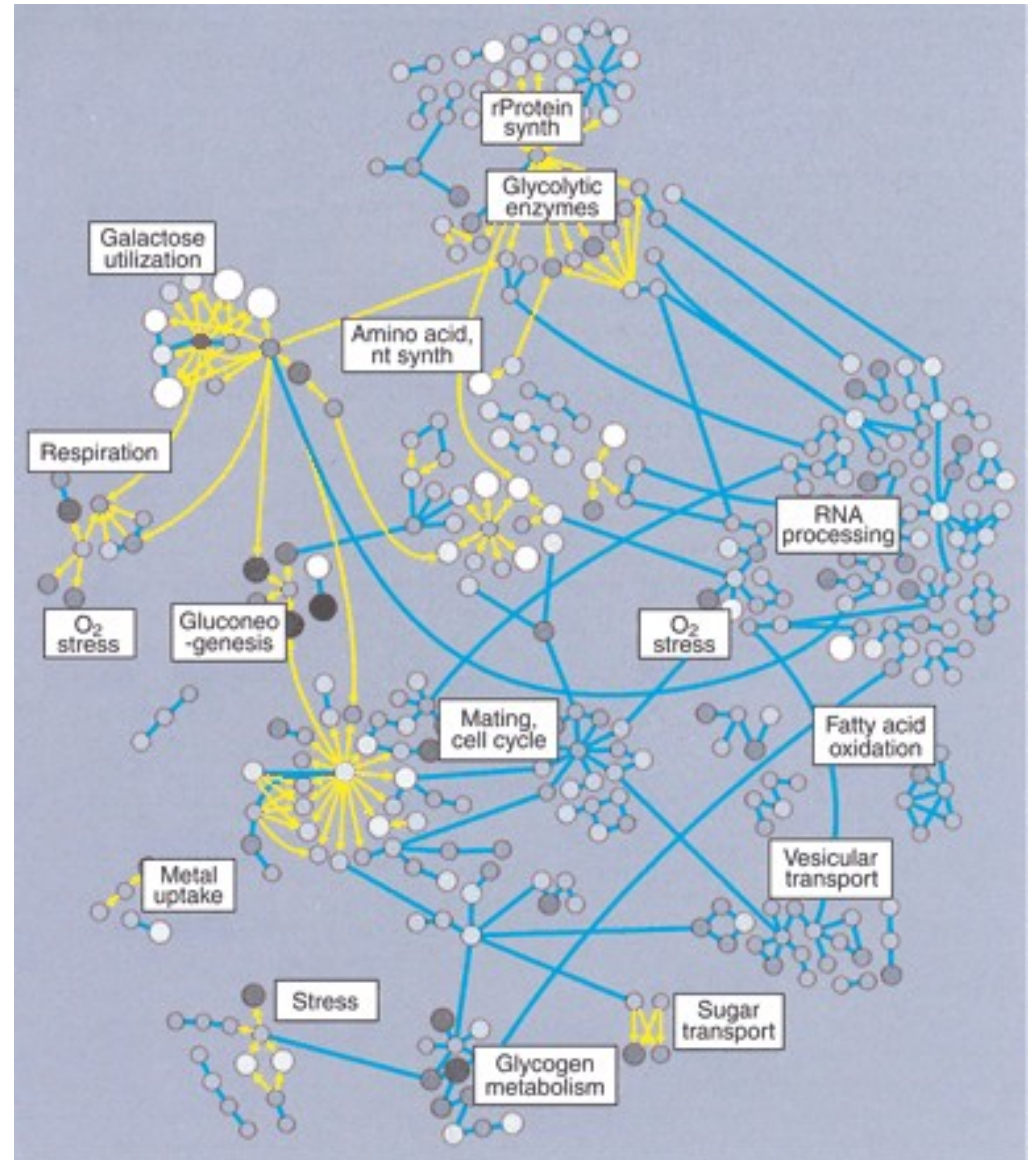
## Combinación de aproximaciones “-omics”





# Aplicaciones “prácticas” de la Biología de Sistemas

- Explicación de enfermedades desde un punto de 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.

# Biología Molecular y Biología de Sistemas

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

## Medicina

reactiva  
generalista



predictiva  
preventiva  
personalizada

*“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*

• Van Regenmortel, MHV. (2001). Pitfalls of reductionism in the design of peptide-based vaccines. *Vaccine*. **19**, 2369-2374

• Hood, L., Heath, J.R., Phelps, M.E. and Lin, B. (2004) Systems biology and new technologies enable predictive and preventative medicine. *Science*, **306**, 640-643.

# Agradecimientos

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