*Reviews in Computational Biology:*

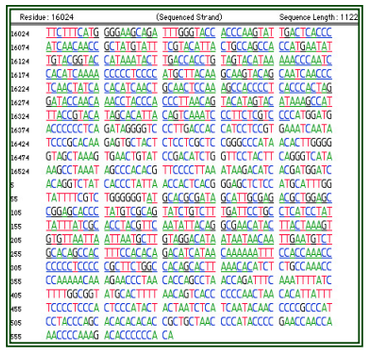
# Can biophysical properties of PPIs improve the network descriptions of metabolism?

**James Smith**

Department of Biochemistry,
University of Cambridge

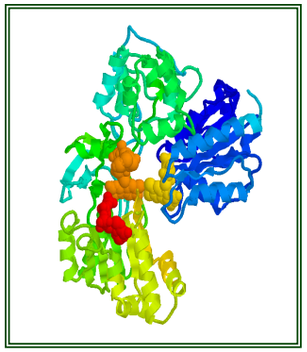
# History of Network Biology

Sequence Analysis



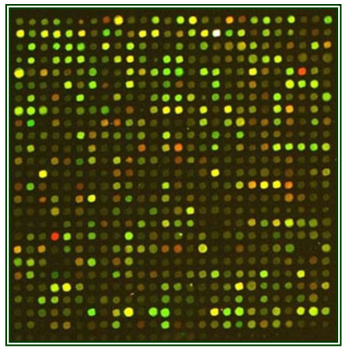

- Gene sequencing
- Sequence alignments
- Homologue searches
- Sequence motif finding

Structure Analysis



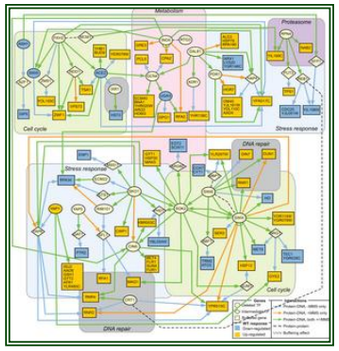
- Homologue searches
- Protein folding
- Binding site prediction
- Functional predictions

Expression Analysis



- Function prediction
- Gene clustering
- Sample classification

Network Analysis

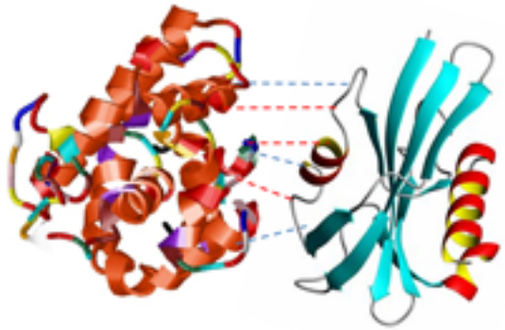


- Function prediction
- Pathway identification
- Module detection
- Network modelling

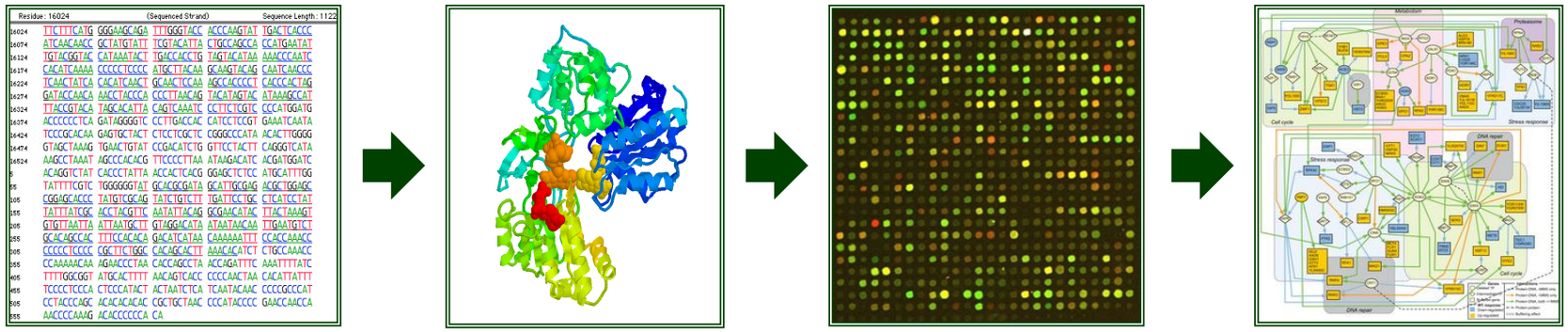
**Bioinformatics** → **Functional Genomics** → **Systems Biology**

# History of Network Biology

Incorporating PPIs



Sequence Analysis | Structure Analysis | Expression Analysis | Network Analysis



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- Protein folding
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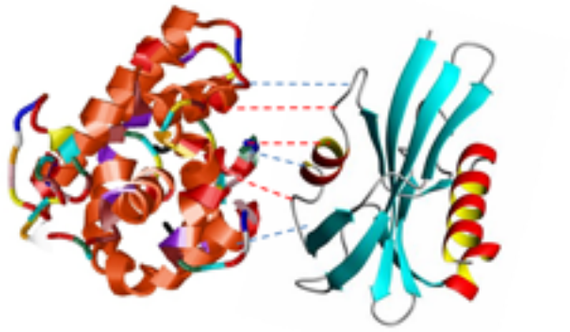
**Bioinformatics** → **Functional Genomics** → **Systems Biology**

# 1. Protein-Protein Interactions



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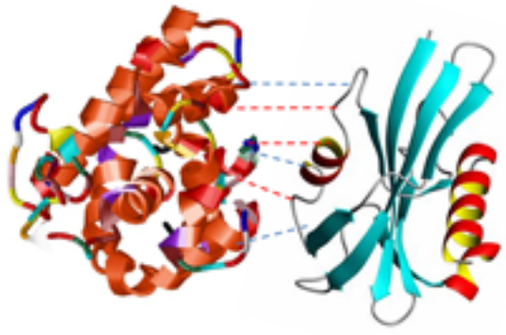
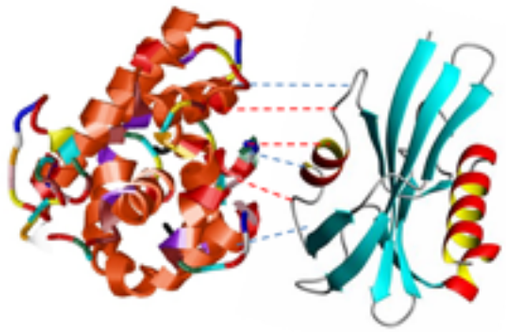
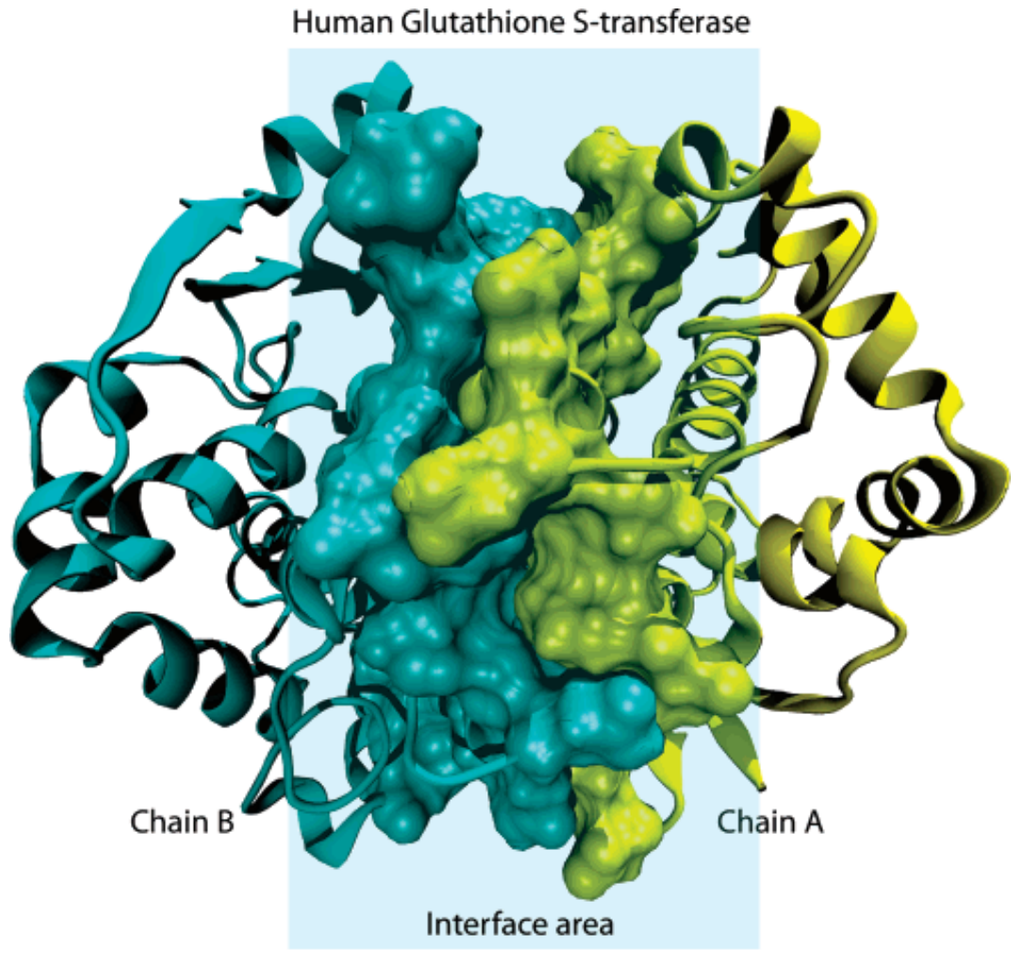


Is there a precise definition within the range of biomolecular interactions?

# 1. Protein-Protein Interactions



- Protein-pairs, direct physical contact, specific-distinct interface, functional role



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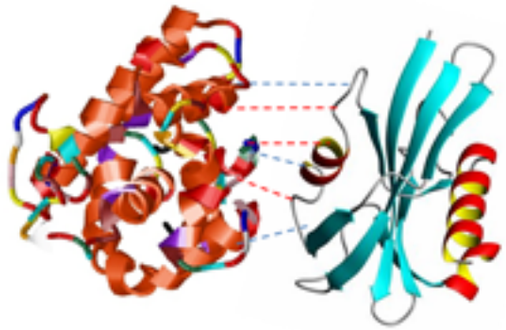
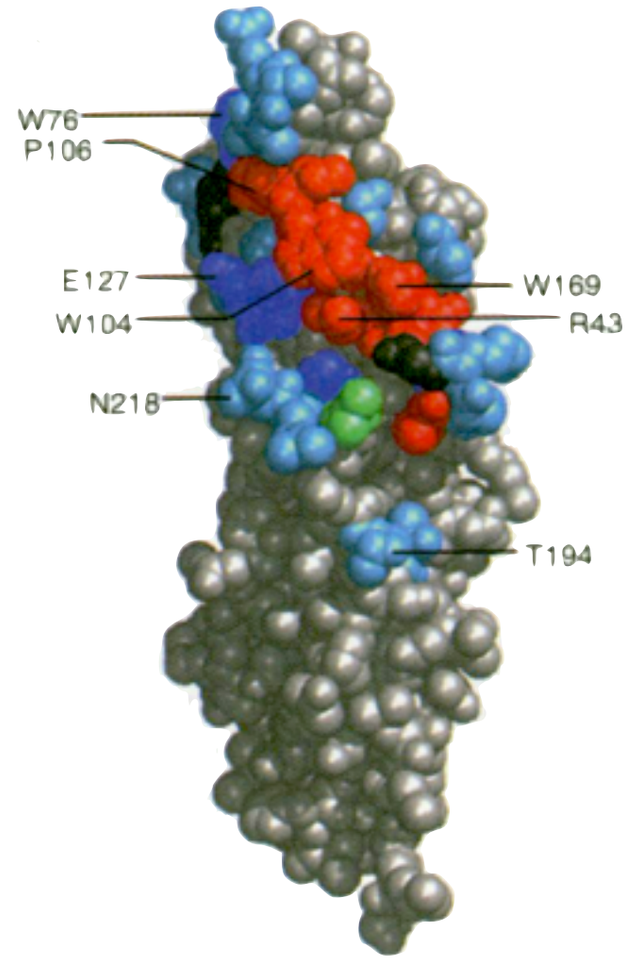


- Protein-pairs, direct physical contact, specific-distinct interface, functional role
- Surface complementarity, well-defined interface, includes clusters of residues



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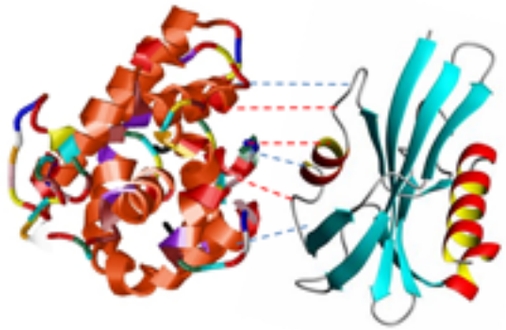
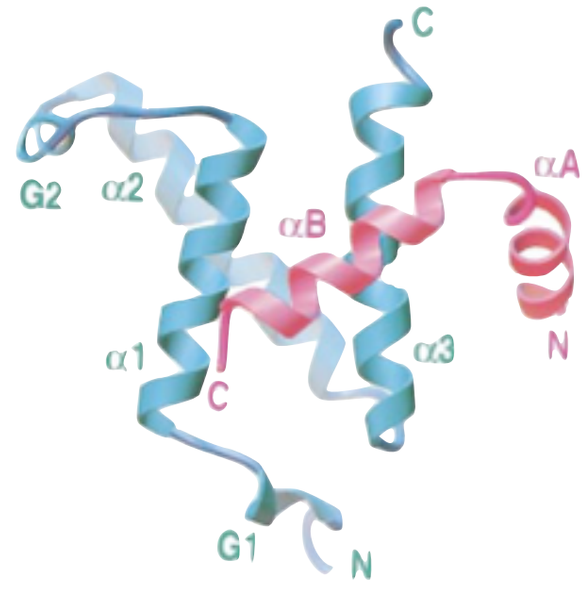
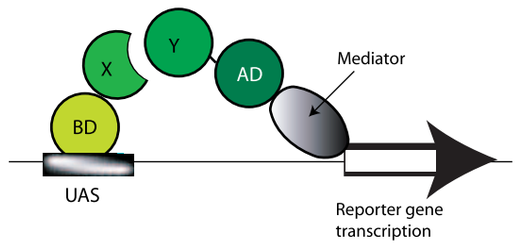


- Protein-pairs, direct physical contact, specific-distinct interface, functional role
- Surface complementarity, well-defined interface, includes clusters of residues
- Concerted binding of SSEs, localised disordered to ordered transitions of SSEs

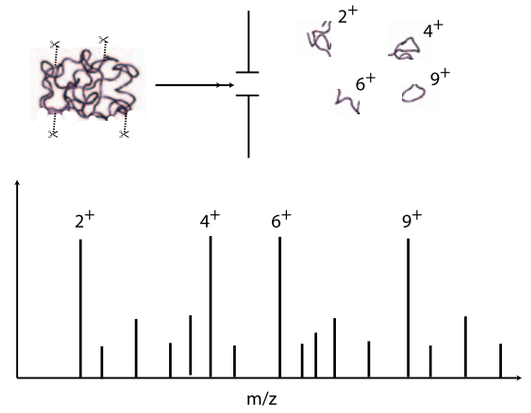


# Methods to identify PPIs

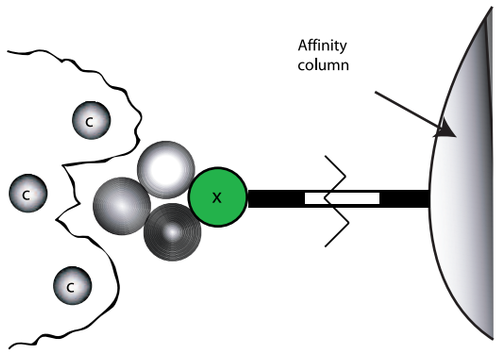
A Y2H



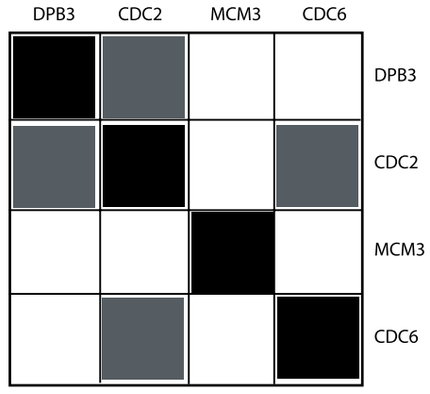

B MS



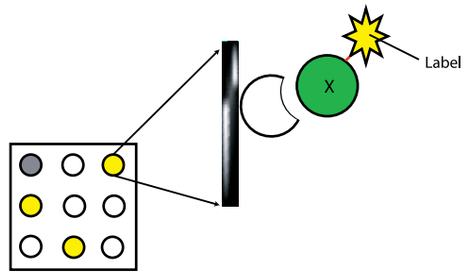

C TAP



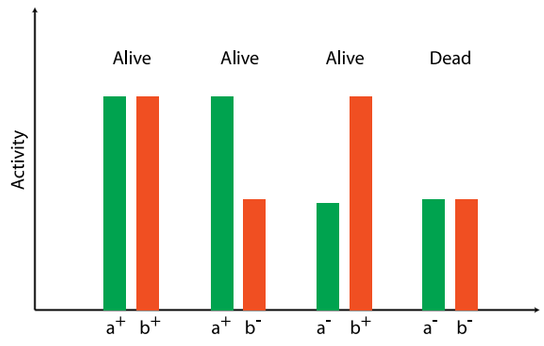

D Gene co-expression




E Protein Microarray



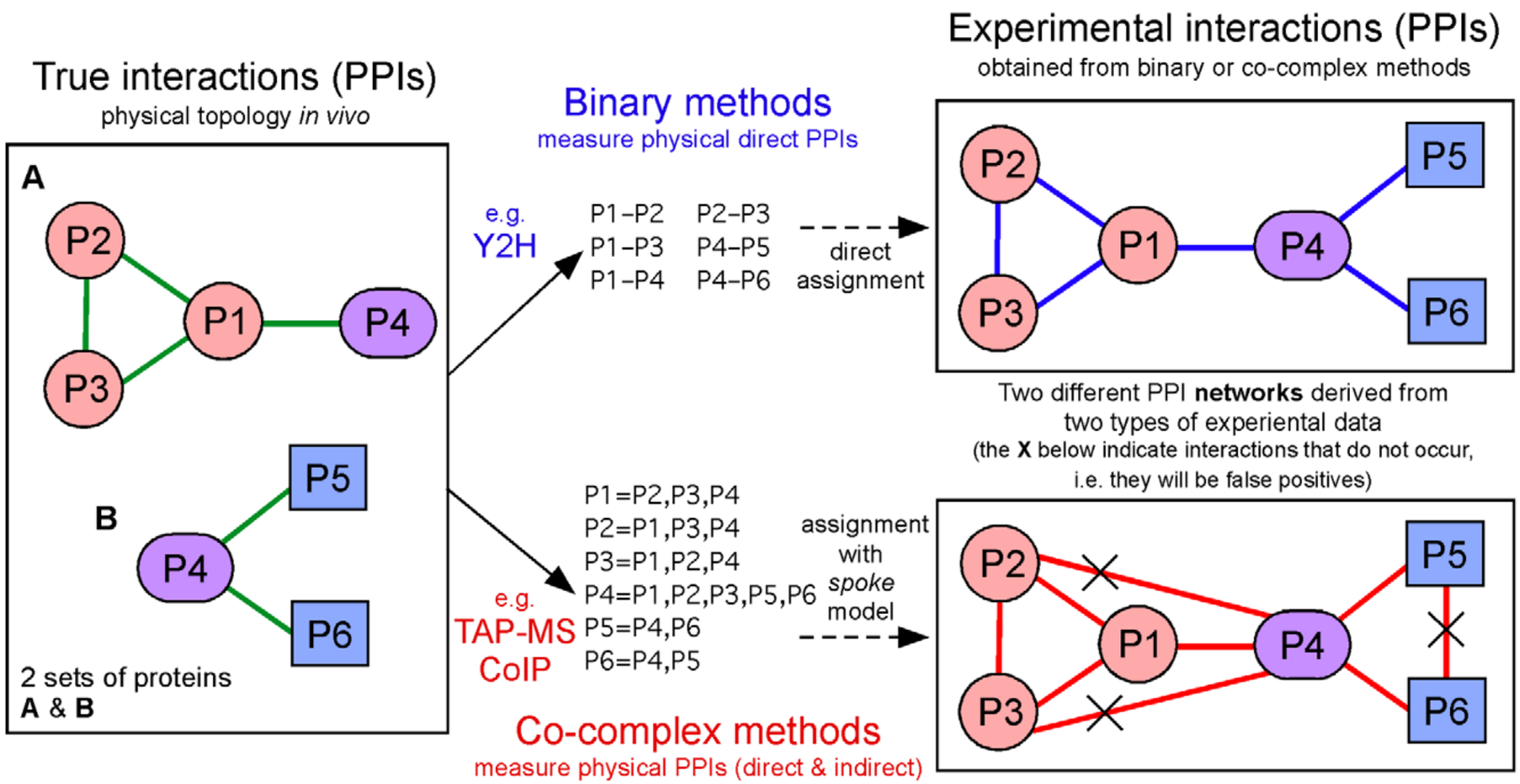

F Synthetic lethality




Taken from doi:10.1371/journal.ppat.0030042.g001

# Methods to identify PPIs

**Most widely used is the combination of**
**Yeast Two-Hybrid with Tandem Affinity**
**Purification coupled with Mass Spectrometry**




Taken from doi:10.1371/journal.pcbi.1000807.g001

# Methods to Predict PPIs

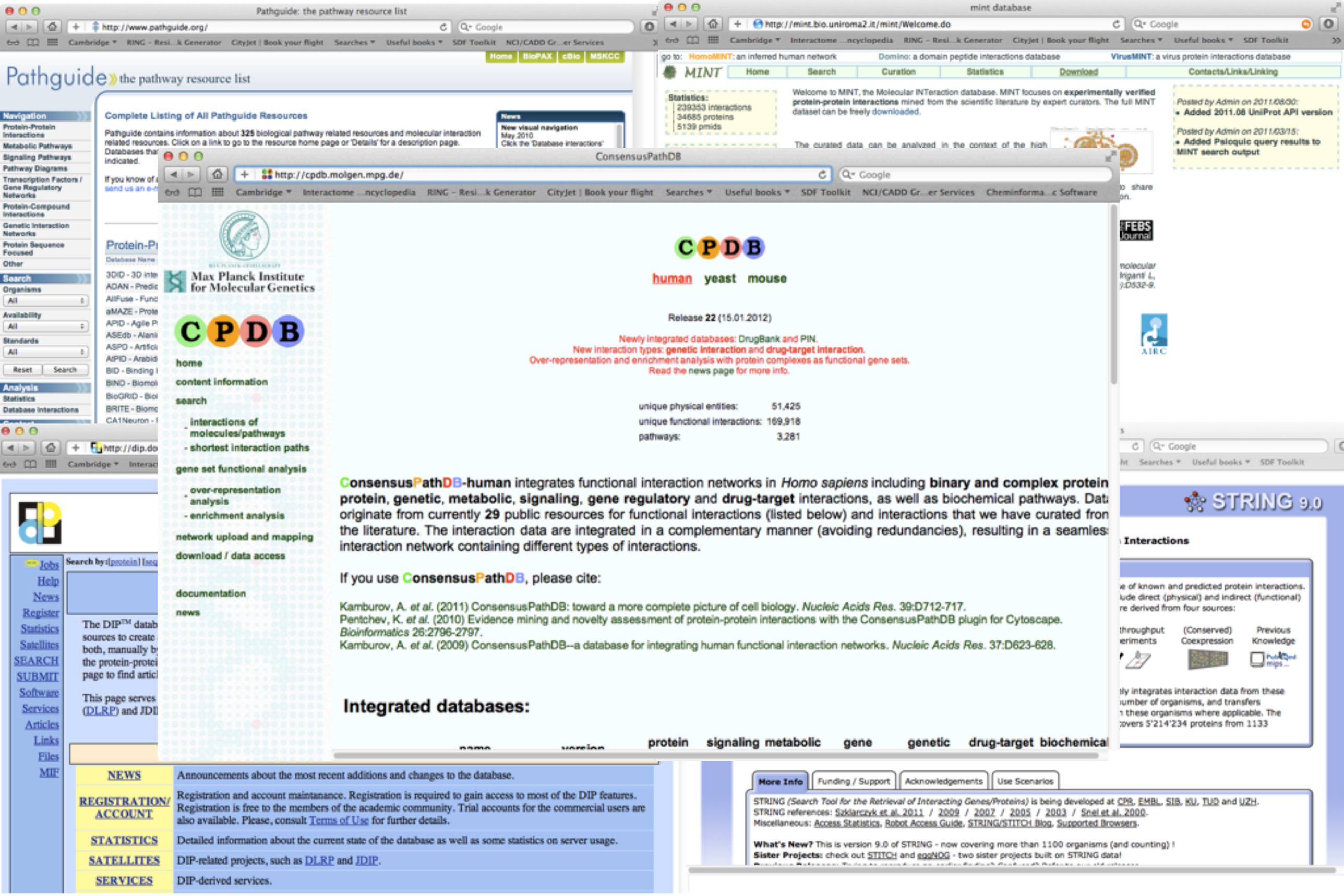
- Rosetta Stone
  infers protein linkage from genomic analyses
- Phylogenetic Profile
  identifies genes that are correlated across genomes
- Conserved Gene Neighbour
  identifies proximal genes across genomes
- Operon/Gene Cluster
  can assign putative function to unknown genes

| Method Name | Protein/Domain Interaction | Physical Interaction/ Functional Association |
|---|---|---|
| Gene co-expression | P | F |
| Synthetic lethality | P | F |
| Gene cluster and gene neighbor | P | F |
| Phylogenetic profile | P, D | F |
| Rosetta Stone | P | F |
| Sequence co-evolution | P, D | F |
| Classification | P, D | P |
| Integrative | P, D | P |
| Domain association | D | P |
| Bayesian networks | P, D | F, P |
| Domain pair exclusion | D | P |
| *p*-Value | D | P |

Second column shows if method is designed to predict protein (P) or domain (D) interactions (note that predicted domains can also be used for verifying protein interactions).
Third column shows if the method can be used to infer direct physical interaction (P) or indirect functional association (F).
doi:10.1371/journal.pcbi.0030043.t001

Only half can infer physical associations

# Example Databases of PPIs



# 2. Biophysics of PPIs

# Biophysics of the PPI complex

- Most detail comes from structural biology

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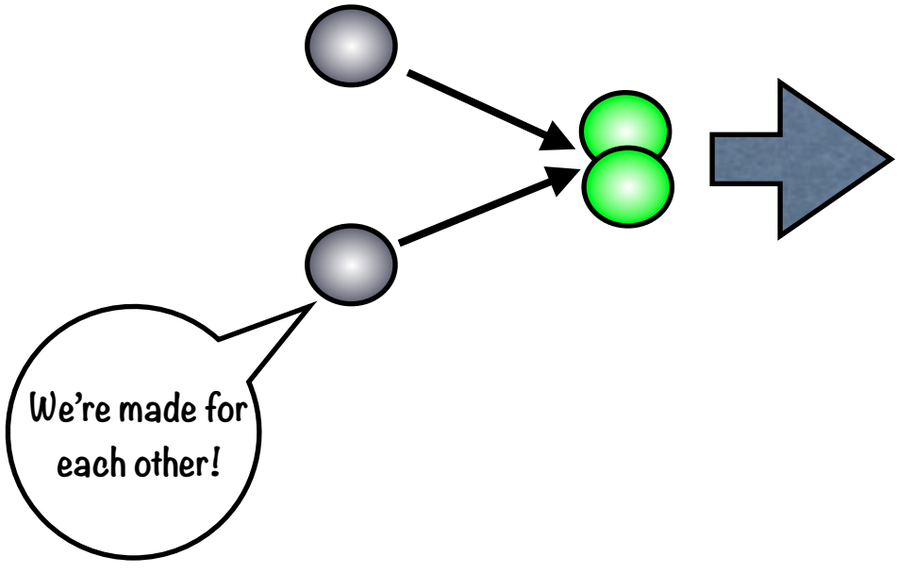
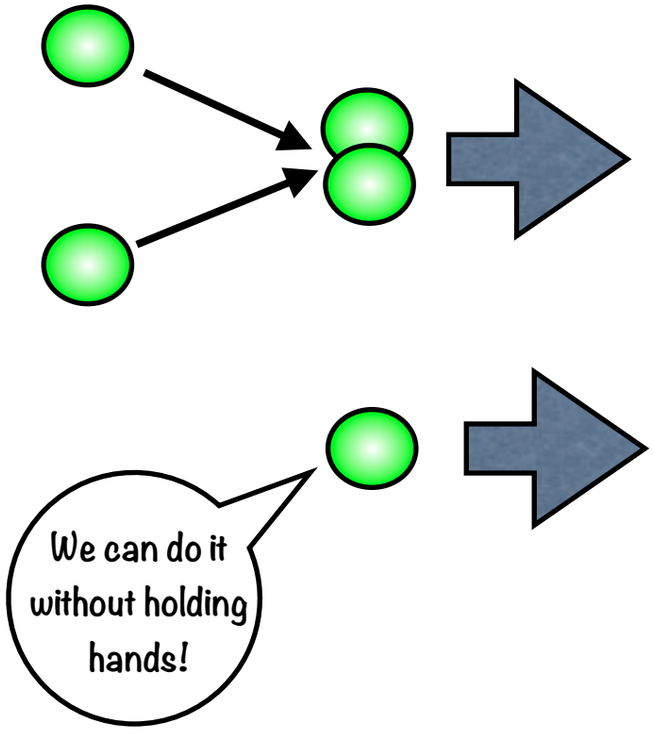
- Most detail comes from structural biology
- Obligatory and Non-obligatory Complexes



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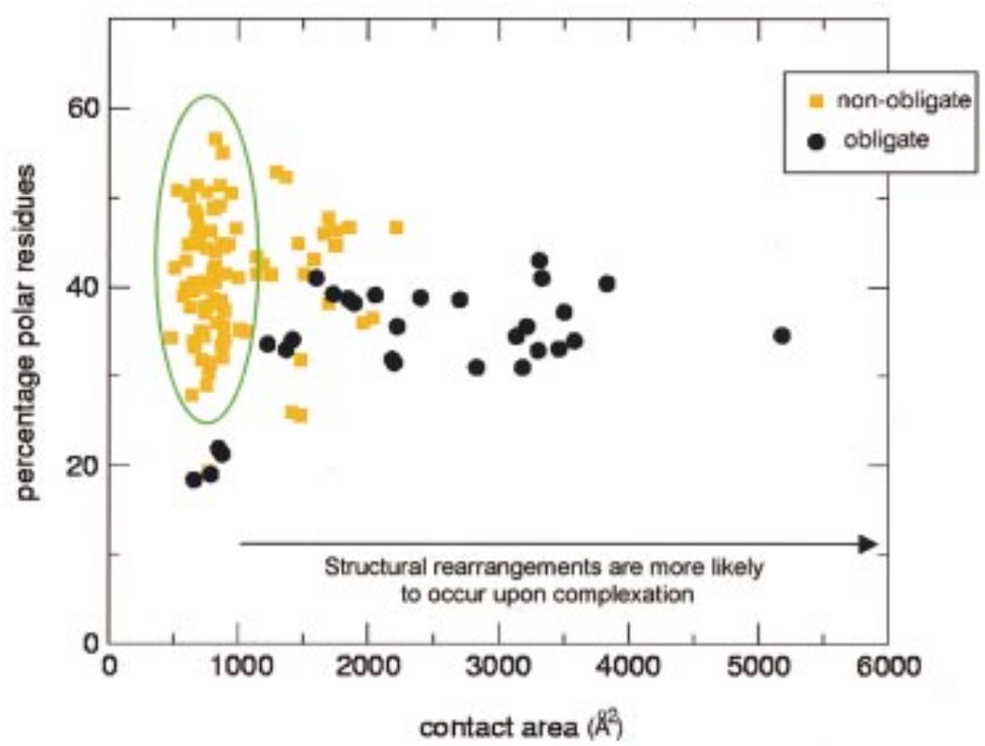


Contact area and polarity of the interfaces of various non-obligate and obligate complexes. Obligate complexes with a small and hydrophobic interface include coiled-coil proteins. The ellipse denotes the contact area–polarity space of weak transient interactions.

**Diversity of protein–protein interactions**

**Irene M.A.Nooren and Janet M.Thornton**

**The EMBO Journal** Vol. 22 No. 14 pp. 3486–3492, 2003

# Biophysics of the PPI complex

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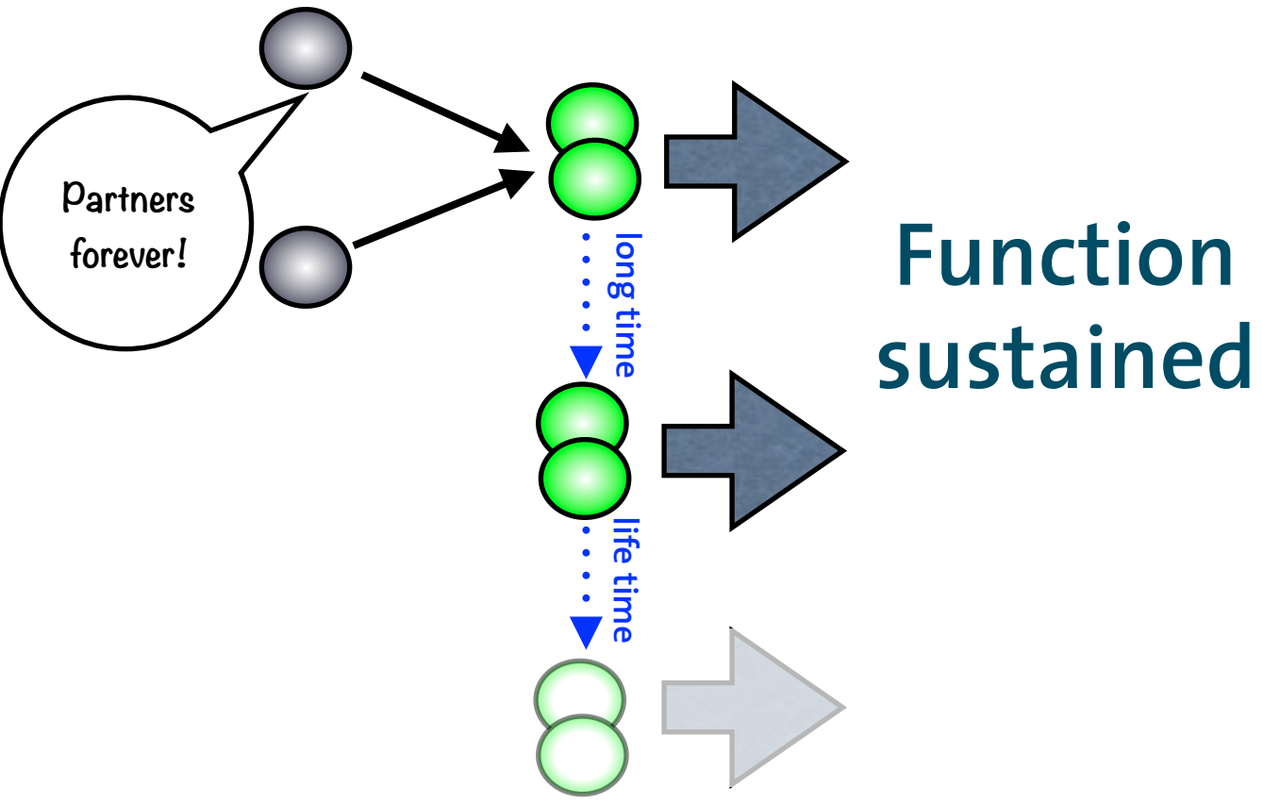


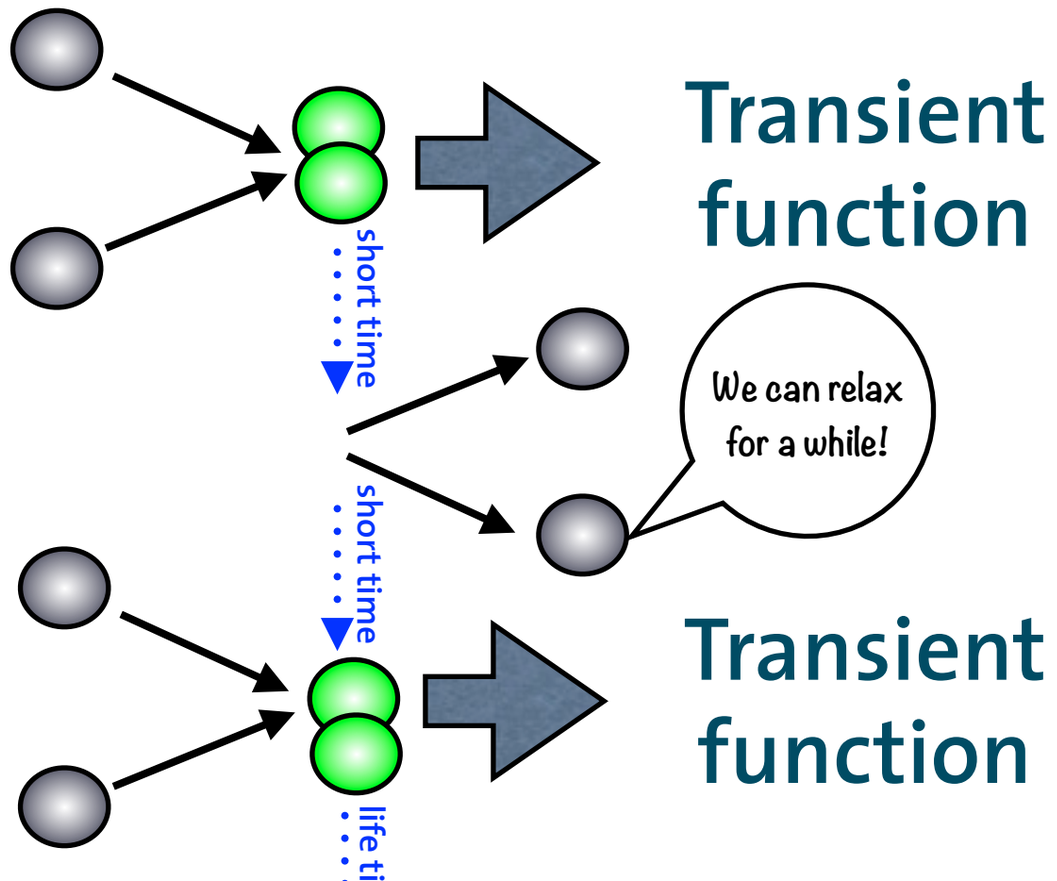

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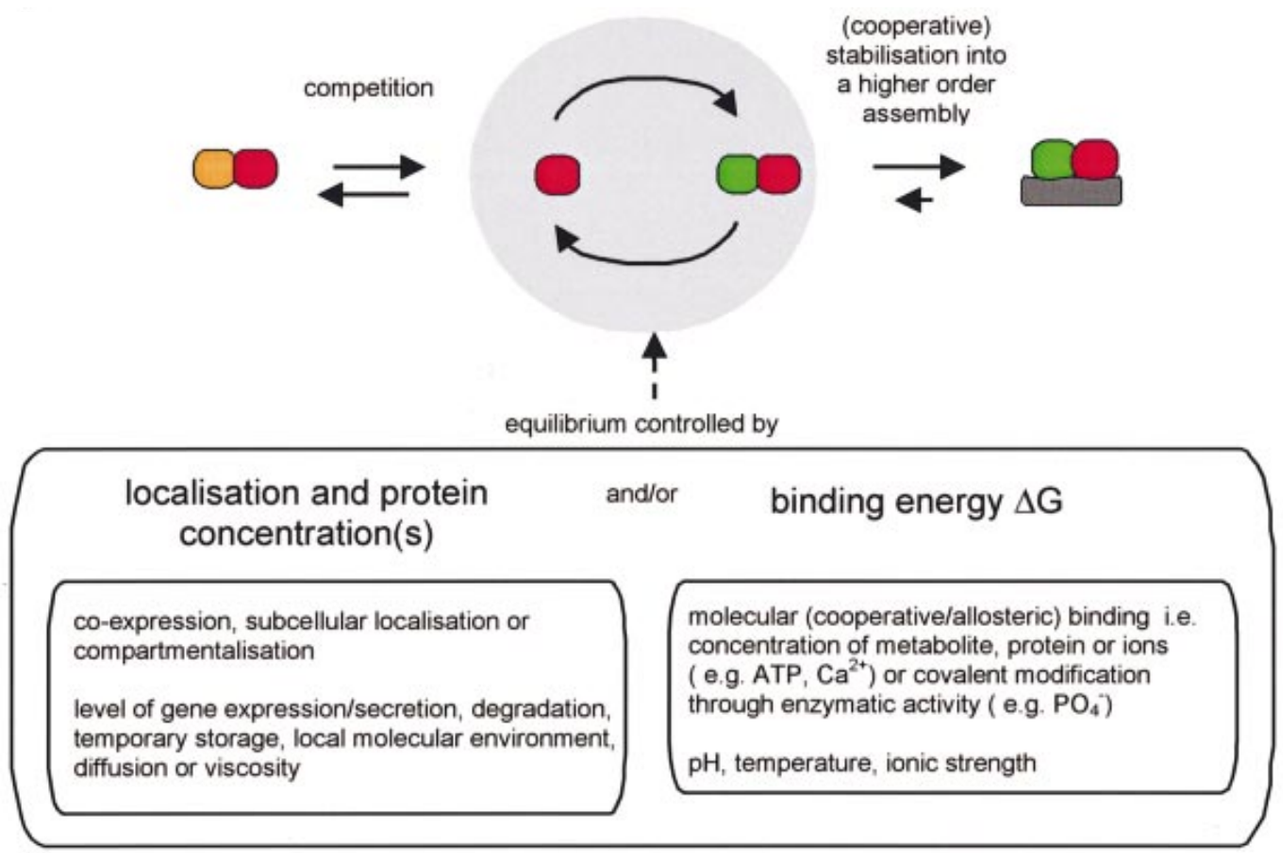

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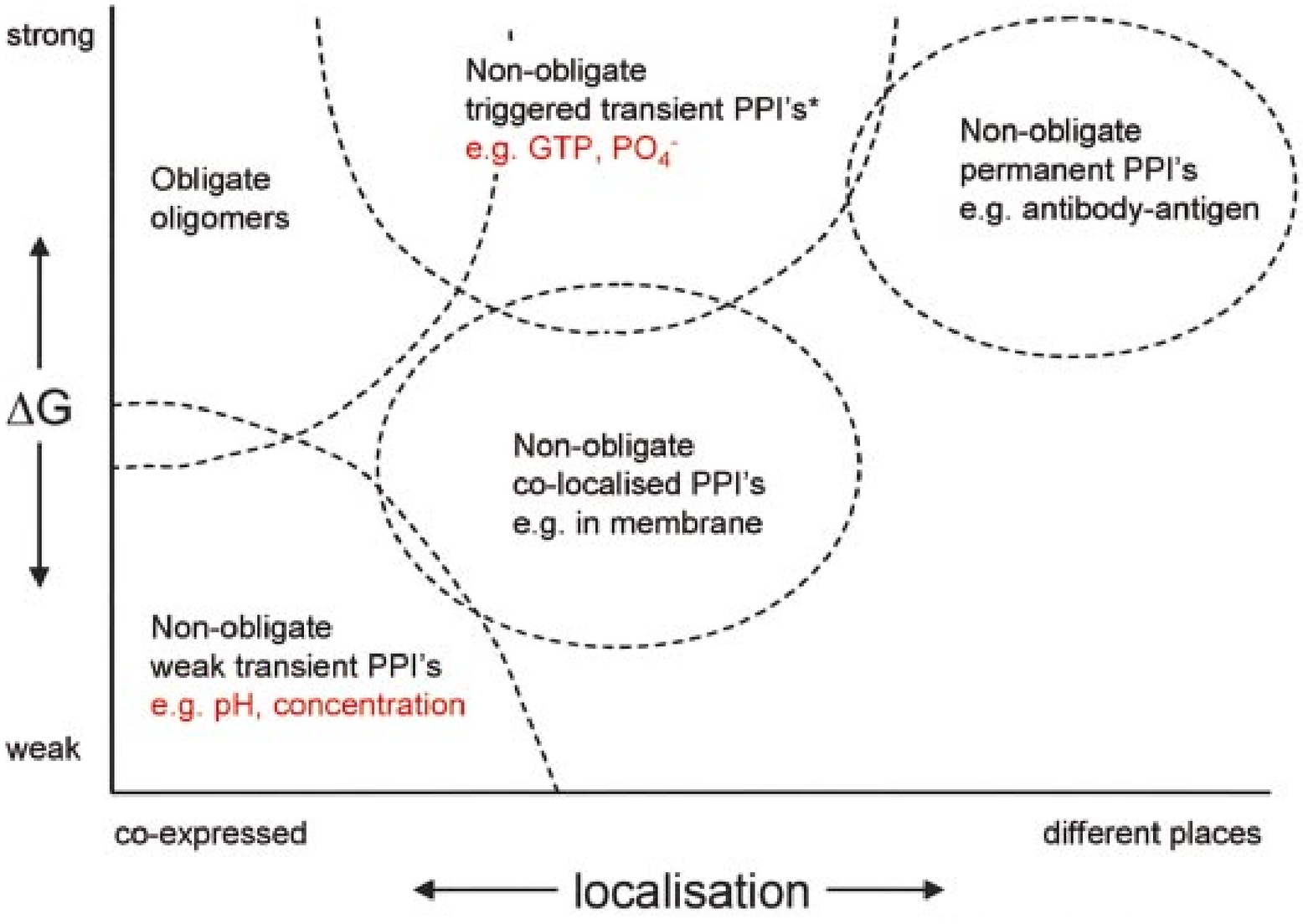



The protein networks found underline the multi-specificity and dynamics of PPIs involving transient interactions, since many proteins were shown to be involved in more than one multiprotein complex or binary interaction. These multicomponent transient complexes have yet to be characterized in terms of their detailed structures or energetics. We can expect the full range of interactions, from rigid to dynamic, weak to strong, obligate and non-obligate. The functional rationale for many of these complexes is not known, and ultimately the optimization of function during evolution will be the key determinant of the observed character of each complex.

**Diversity of protein–protein interactions**

**Irene M.A.Nooren and Janet M.Thornton**

**The EMBO Journal** Vol. 22 No. 14 pp. 3486–3492, 2003

# Thoughts on the Biophysical Properties of Complexation of Transient PPIs?

What's happening at the molecular level (temporally and spatially)?

# Thoughts on the Biophysical Properties of Complexation of Transient PPIs?

- Small scale: on-rates
  affinity driven - long range attractions
  eg electrostatics, solvation and ionic milieu
- Small scale: off-rates
  min destabilising but max stabilising
  intermolecular contact area
- Small scale: reordering and stabilising
  secondary & tertiary structure

# Studies on the Biophysical Properties of Complexation of Transient PPIs?

Current Opinion in Structural Biology

Volume 10, Issue 2, 1 April 2000, Pages 153–159

## Electrostatic aspects of protein–protein interactions

Felix B Sheinerman, Raquel Norel, Barry Honig


**Transient protein–protein interactions**

*Protein Engineering, Design and Selection* (2011) 24(9): 635-648 first published online June 15, 2011

PNAS

## Free-energy distribution of binary protein–protein binding suggests cross-species interactome differences

**Yi Y. Shi*, Gerald A. Miller†, Hong Qian*, and Karol Bomsztyk‡§**

Departments of *Applied Mathematics, †Physics, and ‡Medicine, University of Washington, Seattle, WA 98195

Communicated by Ernest M. Henley, University of Washington, Seattle, WA, May 25, 2006 (received for review April 19, 2006)

*Published online 4 June 2010*

*Nucleic Acids Research, 2010, Vol. 38, Web Server issue* ***W407–W411***
*doi:10.1093/nar/gkq502*

## ANCHOR: a web server and database for analysis of protein–protein interaction binding pockets for drug discovery

**Lidio M. C. Meireles[1], Alexander S. Dömling[2,3,*] and Carlos J. Camacho[1]**

Pattern Recognition in Bioinformatics 5th IAPR International Conference 2010
Conference Proceedings Part IV Protein Protein Interaction and Inference

# Biological Protein-Protein Interaction Prediction Using Binding Free Energies and Linear Dimensionality Reduction

L. Rueda[1], Carolina Garate[2], Sridip Banerjee[1], and Md. Mominul Aziz[1]

[1] School of Computer Science, University of Windsor, 401 Sunset Ave., Windsor, ON, N9B 3P4, Canada
{lrueda,banerje1,azizc}@cs.uwindsor.ca
[2] Department of Computer Science, University of Concepcion, Concepcion, Chile
cgarate@udec.cl

Defined as a continuum not considering localisation

**Abstract.** An important issue in understanding and classifying protein-protein interactions (PPI) is to characterize their interfaces in order to discriminate between transient and obligate complexes. We propose a classification approach to discriminate between these two types of complexes. Our approach uses contact and binding free energies of the residues present in the interaction, which are the input features for the classifiers. A total of 282 features are extracted for each complex, and the classification is performed via recently proposed dimensionality reduction (LDR) methods, including the well-know Fisher's discriminant analysis and two heteroscedastic approaches. The results on a standard benchmark of transient and obligate protein complexes show that LDR approaches achieve a very high classification accuracy (over 78%), outperforming various support vector machines and nearest-neighbor classifiers. An additional insight on the proposed approach and experiments on different subsets of features shows that solvation energies can be used in the classification, leading to a performance comparable to using the full binding free energies of the interaction.

# Thoughts on the Biophysical Properties of Complexation of PPIs?

What's happening at a larger scale of organisation?

# Thoughts on the Biophysical Properties of Complexation of PPIs?

- Large scale: self-organisation around cellular architecture (cytoskeleton, organelles)
- Large scale: transcriptional changes during the cell cycle or under nutrient stress

# Example References

Physical Biology > Volume 2 > Number 2
Ozlem Keskin *et al* 2005 *Phys. Biol.* **2** S24 doi:10.1088/1478-3975/2/2/S03

**Protein–protein interactions: organization, cooperativity and mapping in a bottom-up Systems Biology approach**

Ozlem Keskin[1,2], Buyong Ma[2], Kristina Rogale[3], K Gunasekaran[2] and Ruth Nussinov[2,4]

**The large-scale organization of metabolic networks**

H. Jeong*, B. Tombor†, R. Albert*, Z. N. Oltvai† & A.-L. Barabási*

NATURE | VOL 407 | 5 OCTOBER 2000 | www.nature.com

*Nature* **444**, 383-386 (16 November 2006) | doi:10.1038/nature05201; R
4 September 2006; Published online 15 October 2006

**Protein–protein interaction networks: how can a hub protein bind so many different partners?**
*Trends in Biochemical Sciences, Volume 34, Issue 12, December 2009, Pages 594-600*
Chung-Jung Tsai, Buyong Ma, Ruth Nussinov View Abstract

Visualization of transient encounter complexes in protein–protein association

Chun Tang[1], Junji Iwahara[1] & G. Marius Clore[1]

1. Laboratory of Chemical Physics, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892-0520, USA

Correspondence to: G. Marius Clore[1] Correspondence and requests for materials should be addressed to G.M.C.
(Email: mariusc@intra.niddk.nih.gov).

**BMC Systems Biology**

BioMed Central

Research article

Open Access

**The integrated analysis of metabolic and protein interaction networks reveals novel molecular organizing principles**

Pawel Durek* and Dirk Walther

# 3. Graph and Network representations

# Graph and Network representations

**Algorithms for Molecular Biology** BioMed Central

Research

Open Access

## Decomposition of overlapping protein complexes: A graph theoretical method for analyzing static and dynamic protein associations

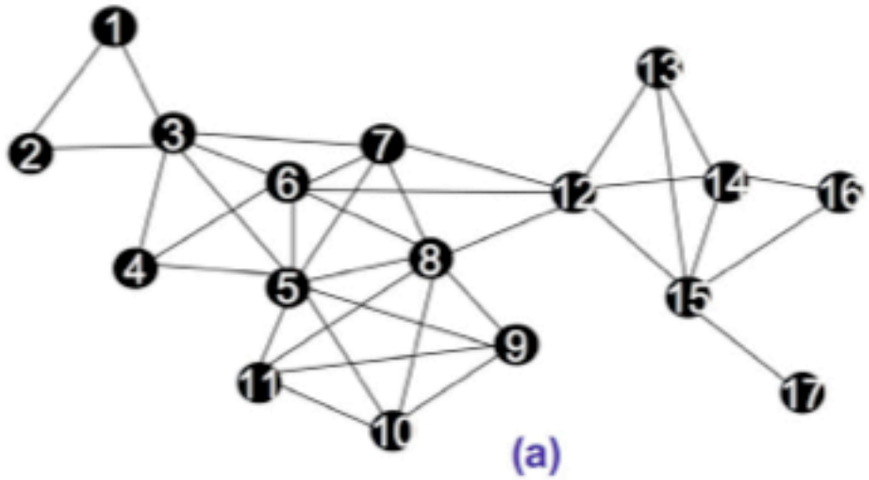
Elena Zotenko[1,2], Katia S Guimarães[1,3], Raja Jothi[1] and Teresa M Przytycka*[1]

**Abstract**

**Background:** Most cellular processes are carried out by multi-protein complexes, groups of proteins that bind together to perform a specific task. Some proteins form stable complexes, while other proteins form transient associations and are part of several complexes at different stages of a cellular process. A better understanding of this higher-order organization of proteins into overlapping complexes is an important step towards unveiling functional and evolutionary mechanisms behind biological networks.

**Results:** We propose a new method for identifying and representing overlapping protein complexes (or larger units called *functional groups*) within a protein interaction network. We develop a graph-theoretical framework that enables automatic construction of such representation. We illustrate the effectiveness of our method by applying it to TNF$\alpha$/NF-$\kappa$B and pheromone signaling pathways.

**Conclusion:** The proposed representation helps in understanding the transitions between functional groups and allows for tracking a protein's path through a cascade of functional groups. Therefore, depending on the nature of the network, our representation is capable of elucidating temporal relations between functional groups. Our results show that the proposed method opens a new avenue for the analysis of protein interaction networks.



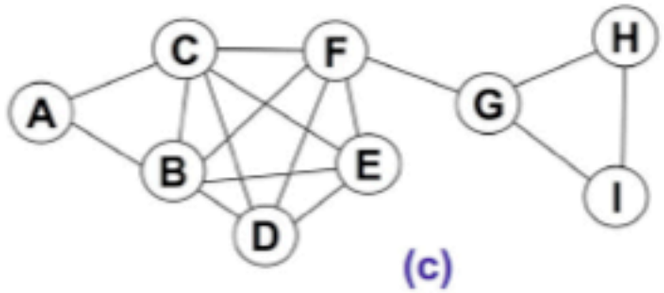

(a)

**Maximal Cliques**

| | |
|---|---|
| A | 1,2,3 |
| B | 3,4,5,6 |
| C | 3,5,6,7 |
| D | 5,6,7,8 |
| E | 5,8,9,10,11 |
| F | 6,7,8,12 |
| G | 12,13,14,15 |
| H | 14,15,16 |
| I | 15,17 |

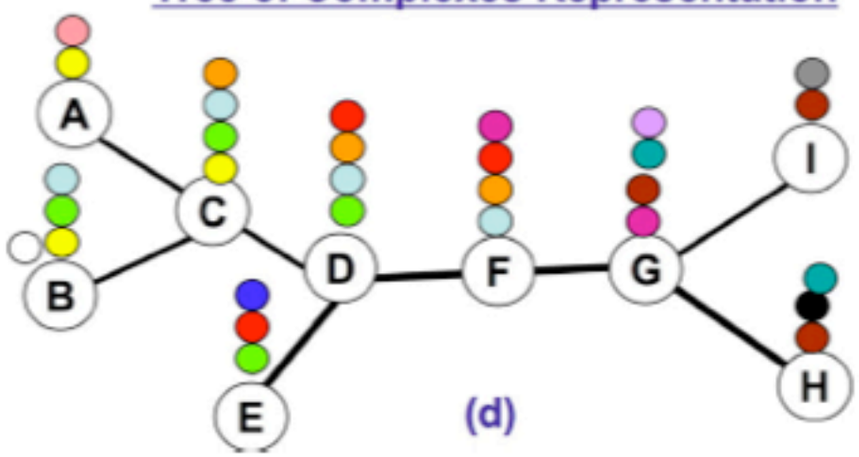
(b)

**Naïve Maximal Clique Overlap Representation**




(c)

**Tree of Complexes Representation**

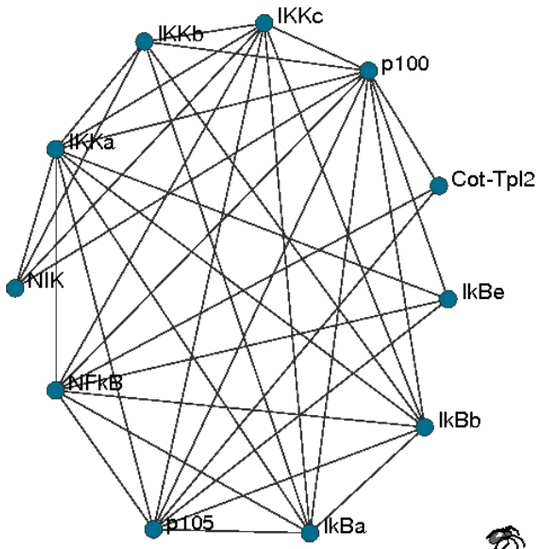



(d)

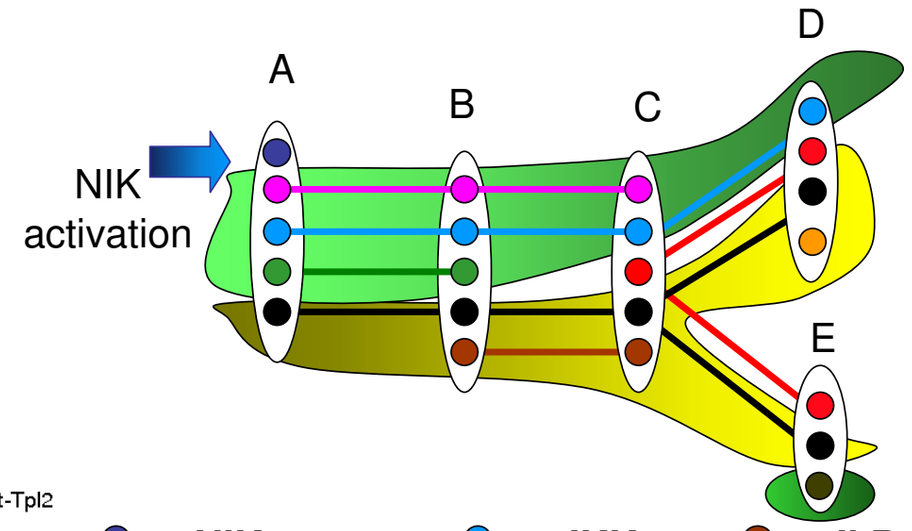

(e)

**Figure 2**

**A Hypothetical Protein Interaction Network**. (a) A hypothetical protein interaction network. (b) A list of all maximal cliques in the network. (c) A naive representation of overlaps between maximal cliques. Each maximal clique is a node and there is an edge between two maximal cliques if and only if they share a protein. (d) The clique tree representation. Once again, every maximal clique is a node, but the cliques are connected in such a way that the resulting graph is a tree. Moreover, cliques that contain a given protein form a connected subgraph. (e) This color scheme is used to show the subtree of every




(a)




= NIK
= p100
= NFkB, p105
= IKKa
= IKKb
= IKKc
= IkBa, IkBb
= IkBe
= Col-Tpl2

*FUNCTIONAL GROUPS*

$$A = NIC \wedge p100 \wedge IKKa \wedge IKKb \wedge IKKc$$

$$B = p100 \wedge IKKa \wedge IKKb \wedge IKKc \wedge IkBa \wedge IkBb$$

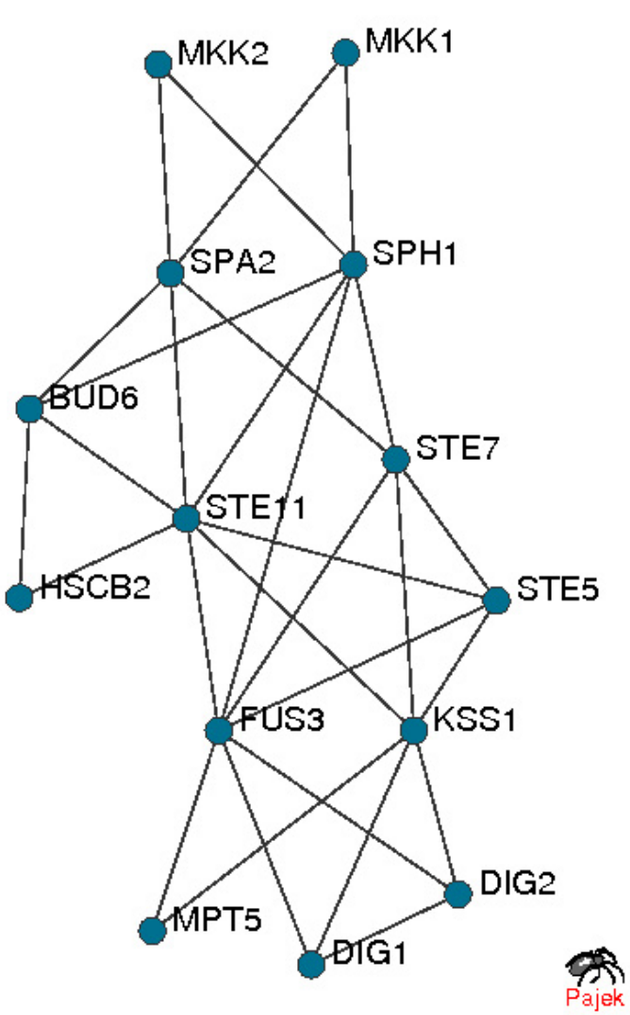
$$C = p100 \wedge IKKa \wedge IKKc \wedge IkBa \wedge IkBb \wedge NFkB \wedge p105$$

$$D = p100 \wedge IKKa \wedge IkBe \wedge NFkB \wedge p105$$

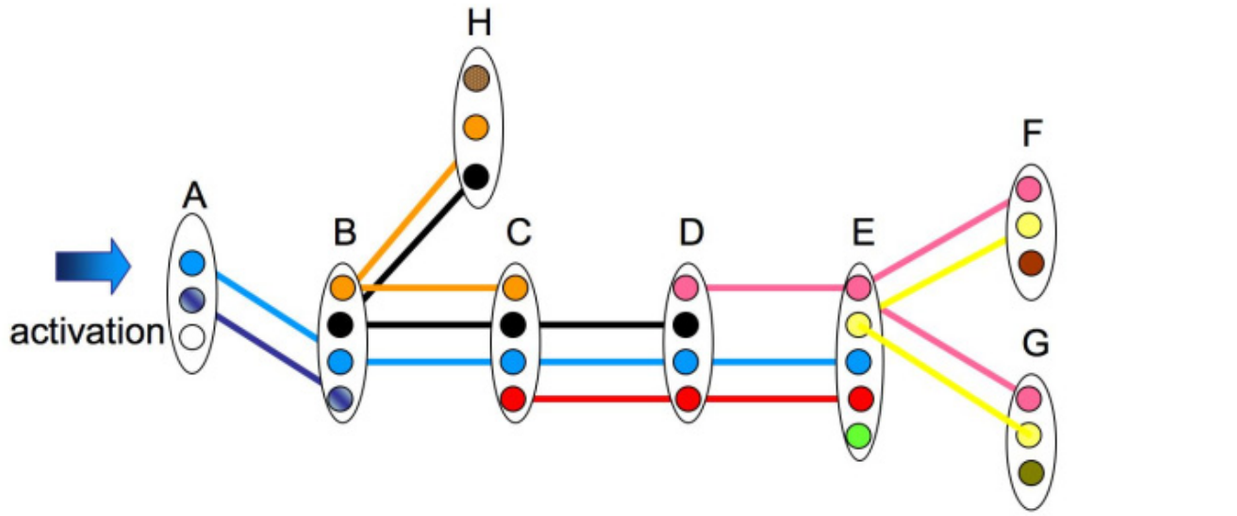
$$E = p100 \wedge NFkB \wedge p105 \wedge Col\text{-}Tpl2$$

(b)

**Figure 3**
**TNF$\alpha$/NF-$\kappa$B Signaling Pathway**. The TNF$\alpha$/NF-$\kappa$B signaling pathway. (a) The network. (b) The Tree of Complexes representation. The flow of action is visually represented by background colors: green for activators (IKKs) and yellow for inhibitors (I$\kappa$Bs, and p100). The NIK kinase is in the first functional group (A), together with all three members of the IKK complex and p100. Functional group B includes, in addition to p100, the IKKs and two inhibitors I$\kappa$B$\alpha$ and I$\kappa$B$\beta$. This group is the beginning of interaction between IKKs and I$\kappa$Bs. Functional group C loses some of the IKKs, continues to show I$\kappa$B and begins to show interaction between I$\kappa$Bs and NF-$\kappa$B factors. Finally, in group E we see the entrance of NIK-independent Col-Tpl2 kinase.




(a)




= MKK1 ∨ MKK2 = STE11 = FUS3 = HSCB2
= SPH1 = STE5 = KSS1 = BUD6
= SPA2 = STE7 = DIG1 ∧ DIG2 = MPT5

*FUNCTIONAL GROUPS*

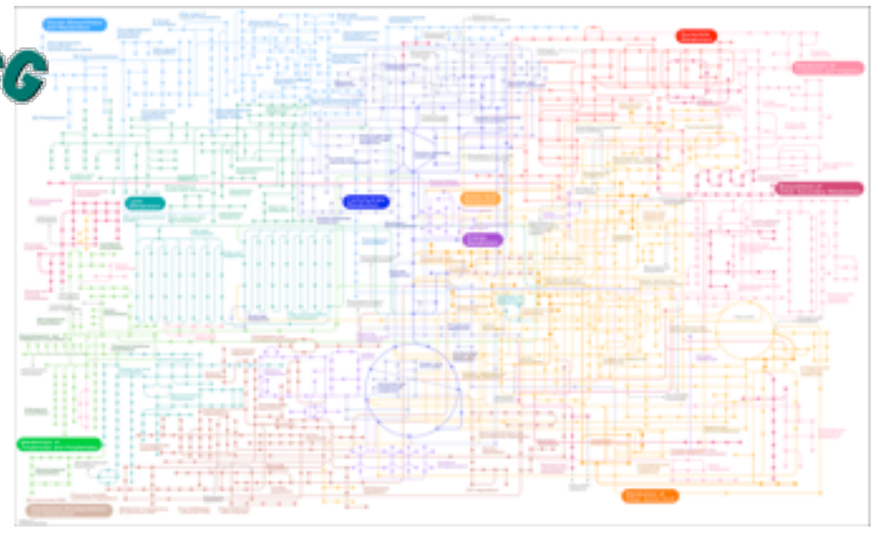
$A = HSCB2 \wedge BUD6 \wedge STE11$
$B = BUD6 \wedge (SPH1 \vee SPA2) \wedge STE11$
$C = (SPH1 \vee SPA2) \wedge (STE11 \vee STE7)$
$D = SPH1 \wedge (STE11 \vee STE7) \wedge FUS3$
$E = STE5 \wedge (STE11 \vee STE7) \wedge (FUS3 \vee KSS1)$
$F = (FUS3 \vee KSS1) \wedge DIG1 \wedge DIG2$
$G = (FUS3 \vee KSS1) \wedge MPT5$
$H = (MKK1 \vee MKK2) \wedge (SPH1 \vee SPA2)$

(b)

**Figure 4**
**Pheromone Signaling Pathway**. The pheromone signaling pathway. (a) The network. (b) The Tree of Complexes representation. For the description of the elements of the tree see the text.

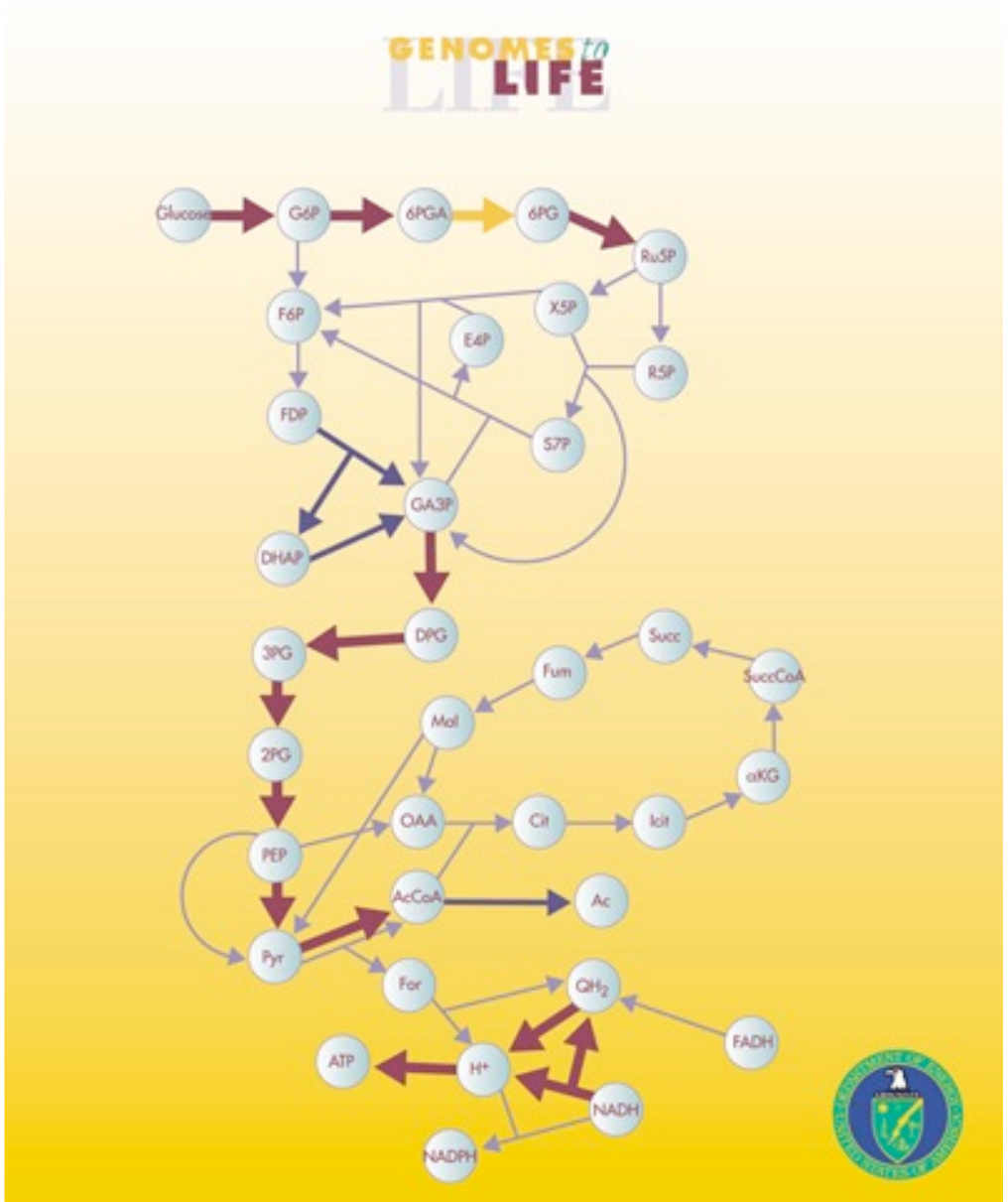
# 4. Descriptions of Metabolic Networks

- Several databases exist for gene/ enzyme/reaction/pathway reconstruction of metabolic pathways
- KEGG, Meta-Cyc, Pathway Tools, ERGO, metaTIGER, ENZYME, Brenda, ModelSEED



# Descriptions of Metabolic Networks

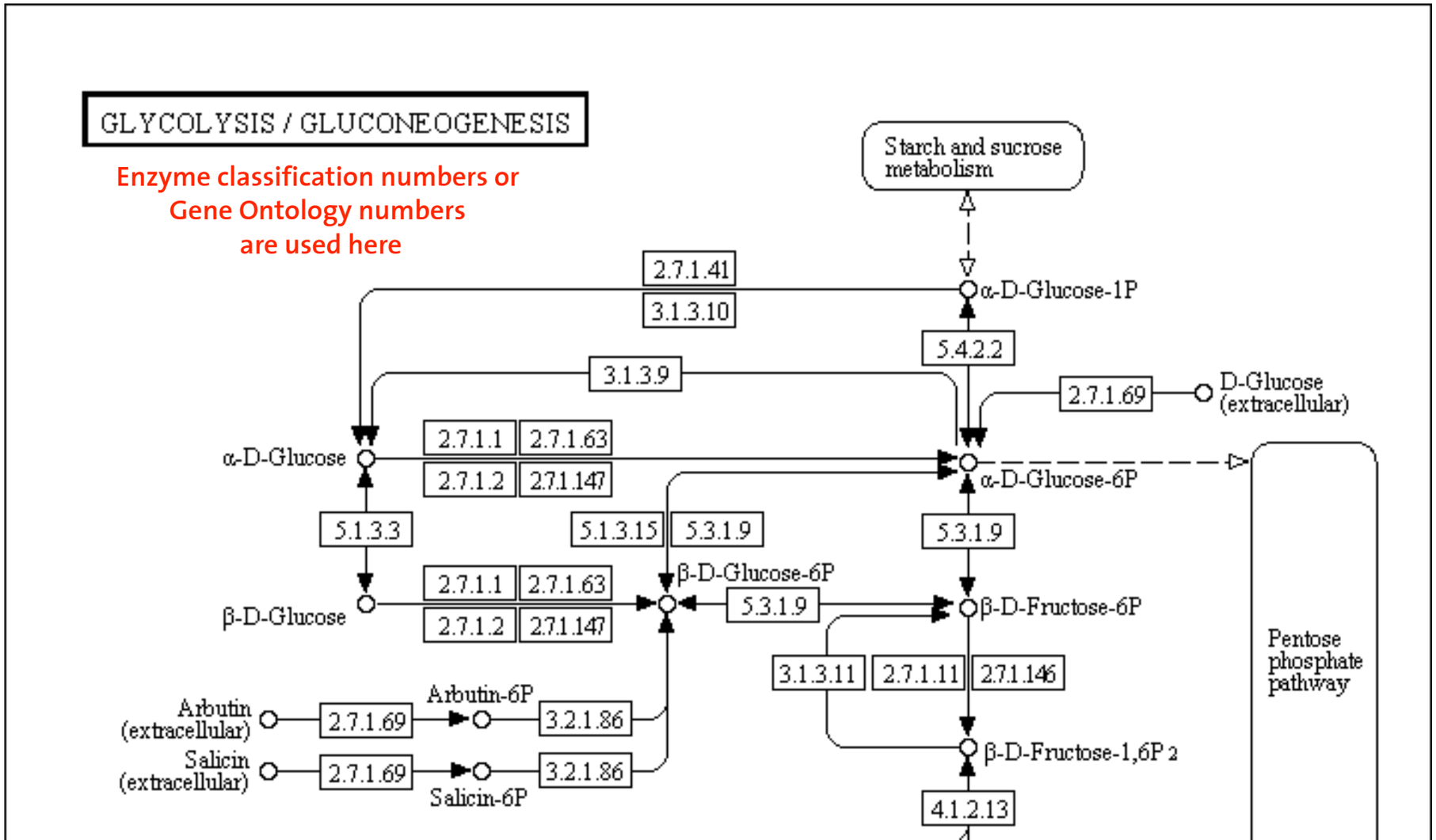
- Metabolite-centric views




**Biotransformations**
**Nodes are metabolites**
**Links are enzymes**

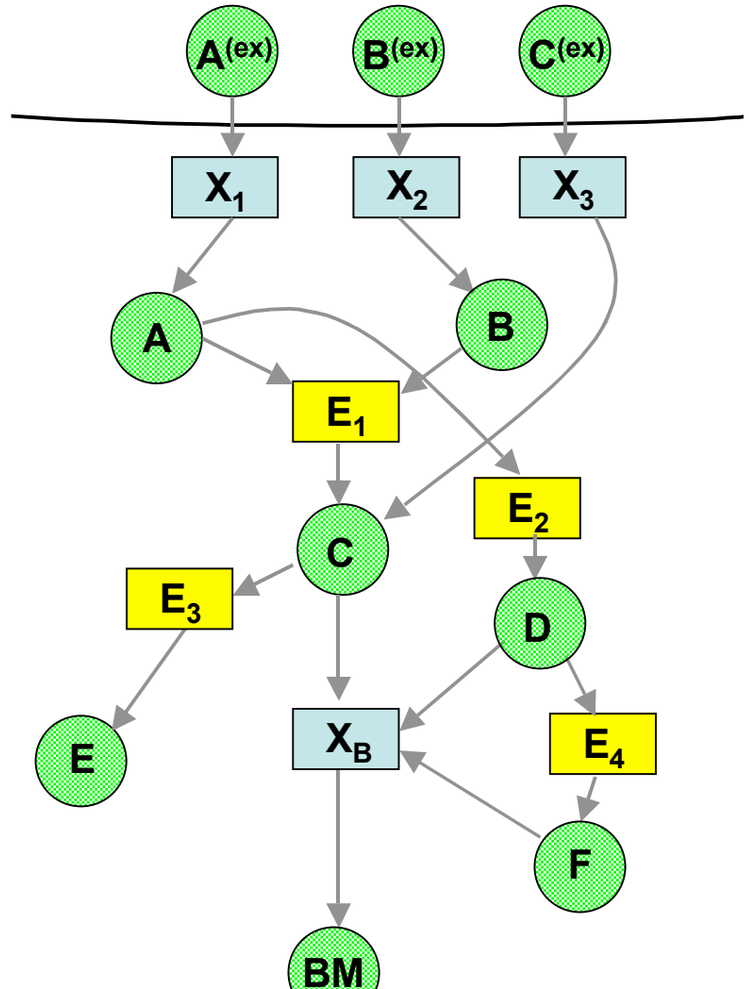
# Descriptions of Metabolic Networks

- Metabolite-centric views
- Gene/Enyzme/Reaction-centric views



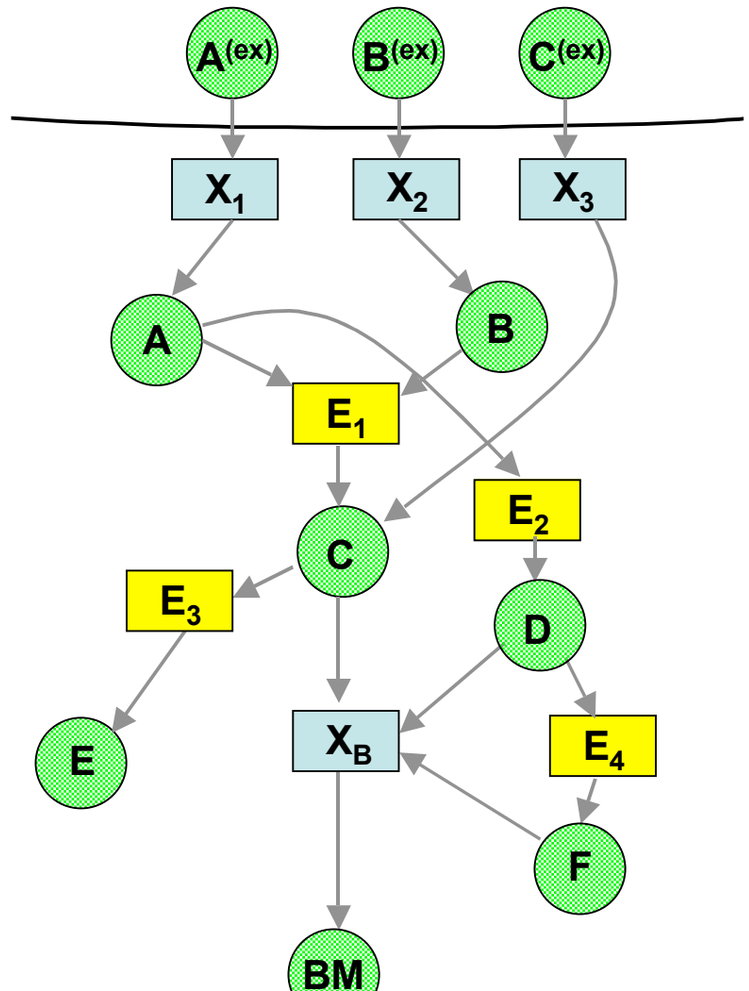
# Descriptions of Metabolic Networks

- Metabolite-centric views
- Gene/Enyzme/Reaction-centric views
- Bipartite representation

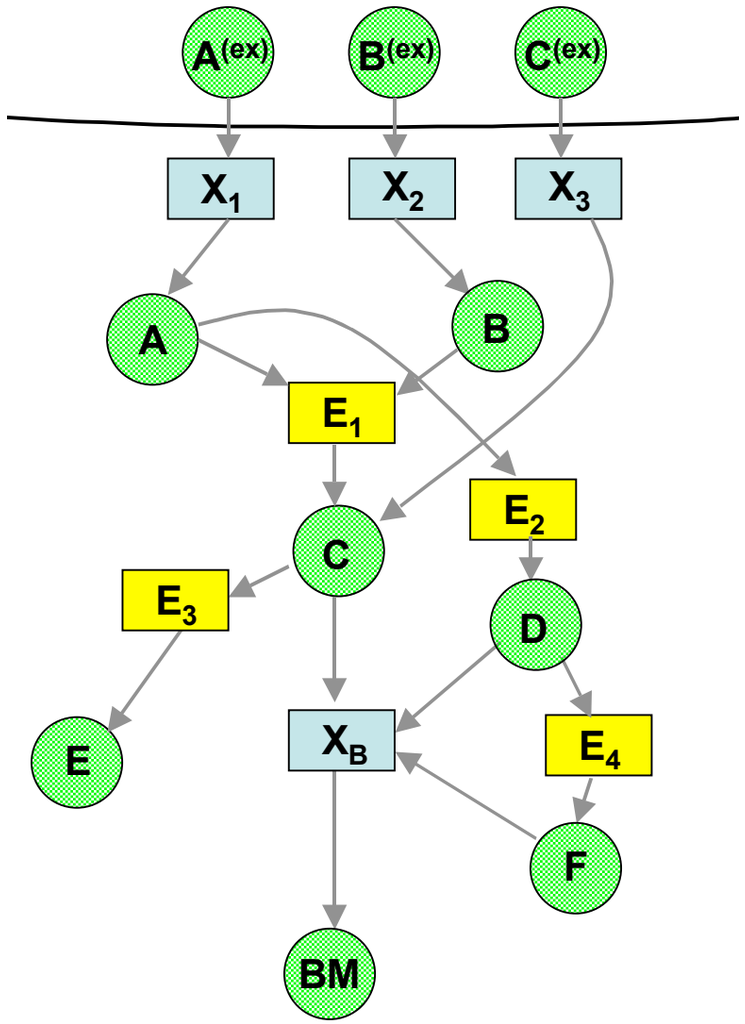


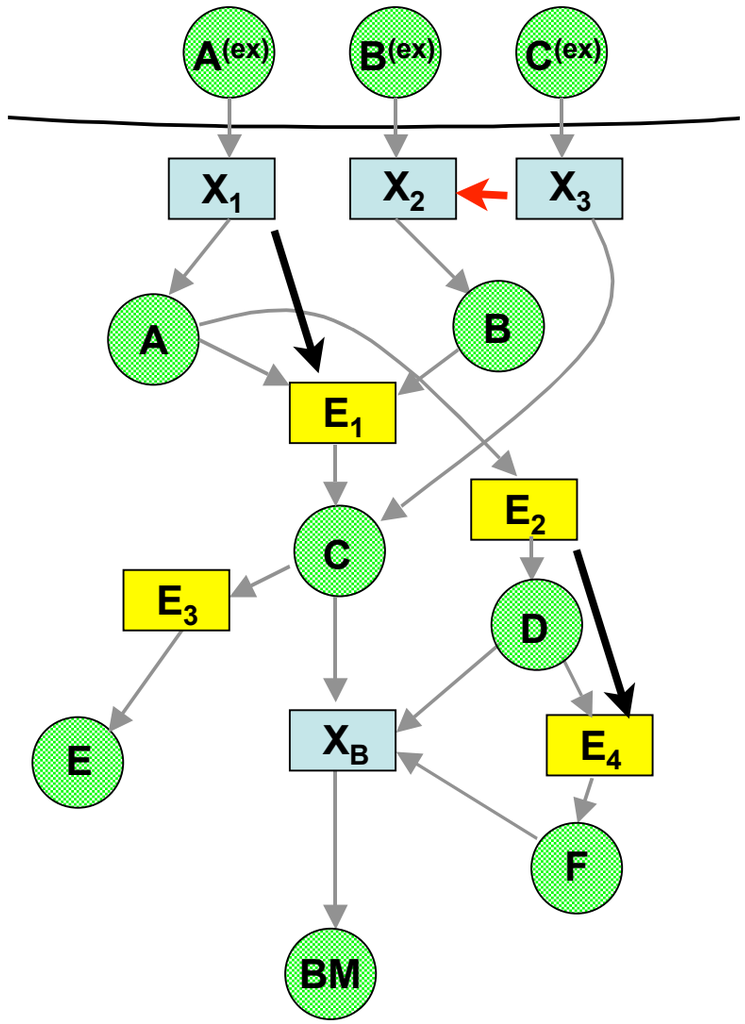
# Descriptions of Metabolic Networks

- Metabolite-centric views
- Gene/Enyzme/Reaction-centric views
- Bipartite representation
- Could we have a multipartite representation for PPIs?



# Example Multipartite Representation



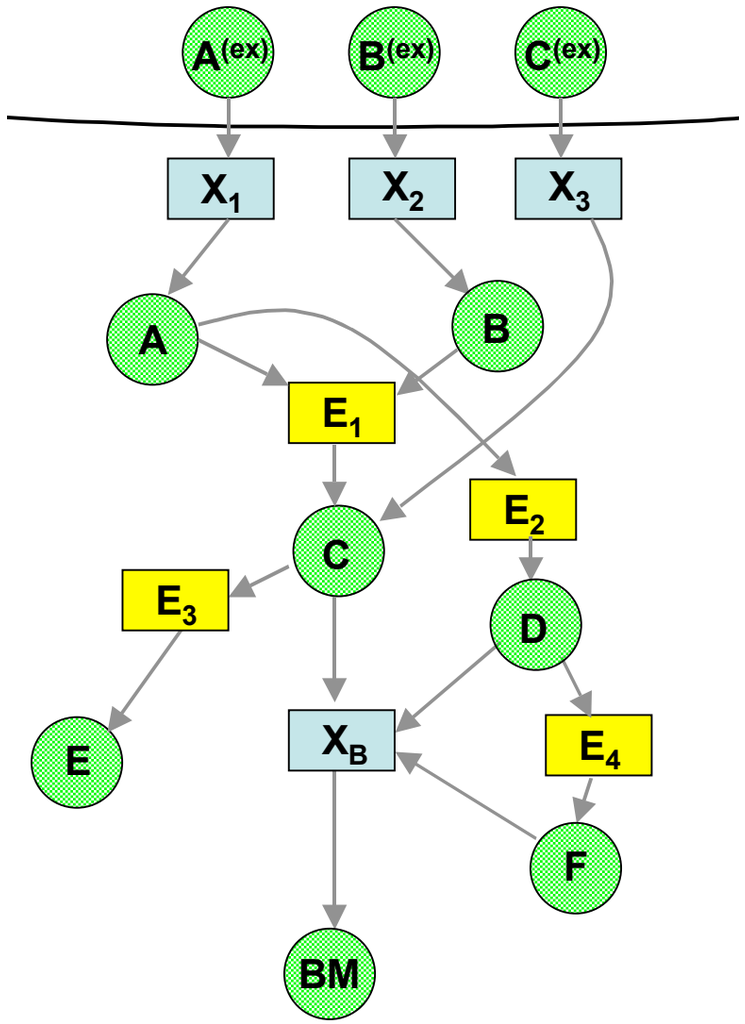



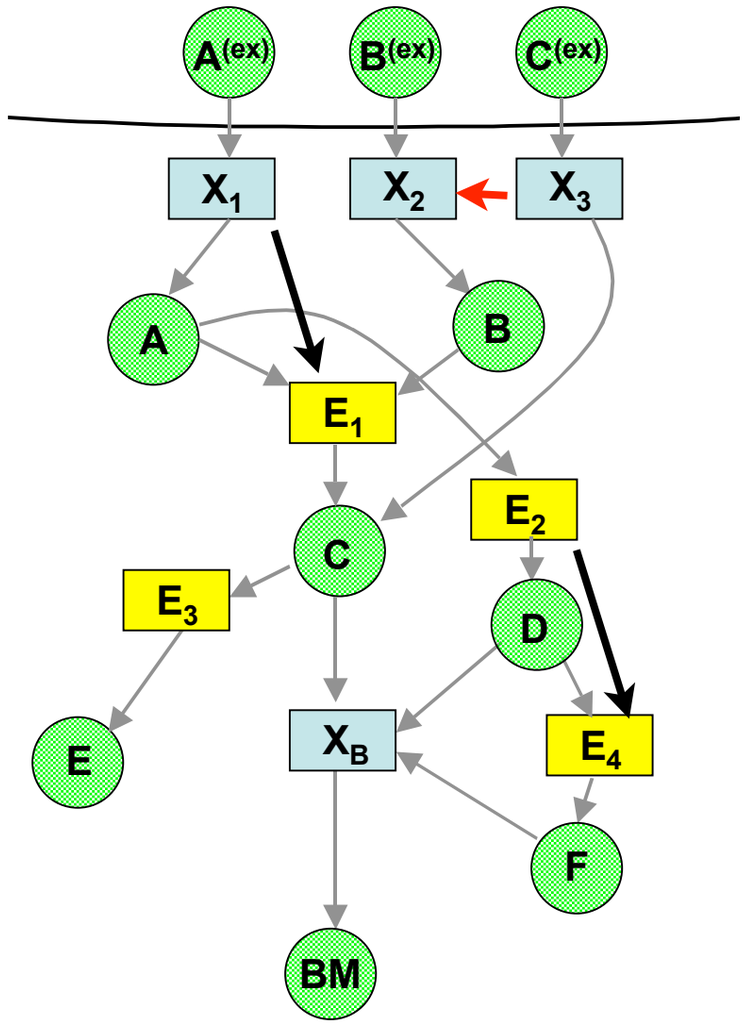

## Addition of PPIs to the network (edges define physical associations)

→ direction of (obligatory) transient PPI on cytoskeleton for catalysis of metabolic intermediate

→ direction of (obligatory) permanent PPI in membrane for transport of metabolites

# Example Multipartite Representation




- Adding PPIs to the network reveals local functionality
- Adding biophysical information describes the nature of the PPIs

## Addition of PPIs to the network (edges define physical associations)

→ direction of (obligatory) transient PPI on cytoskeleton for catalysis of metabolic intermediate

→ direction of (obligatory) permanent PPI in membrane for transport of metabolites

BIOINFORMATICS

Vol. 25 ISMB 2009, pages i247–i252
doi:10.1093/bioinformatics/btp209

# Network-based prediction of metabolic enzymes' subcellular localization

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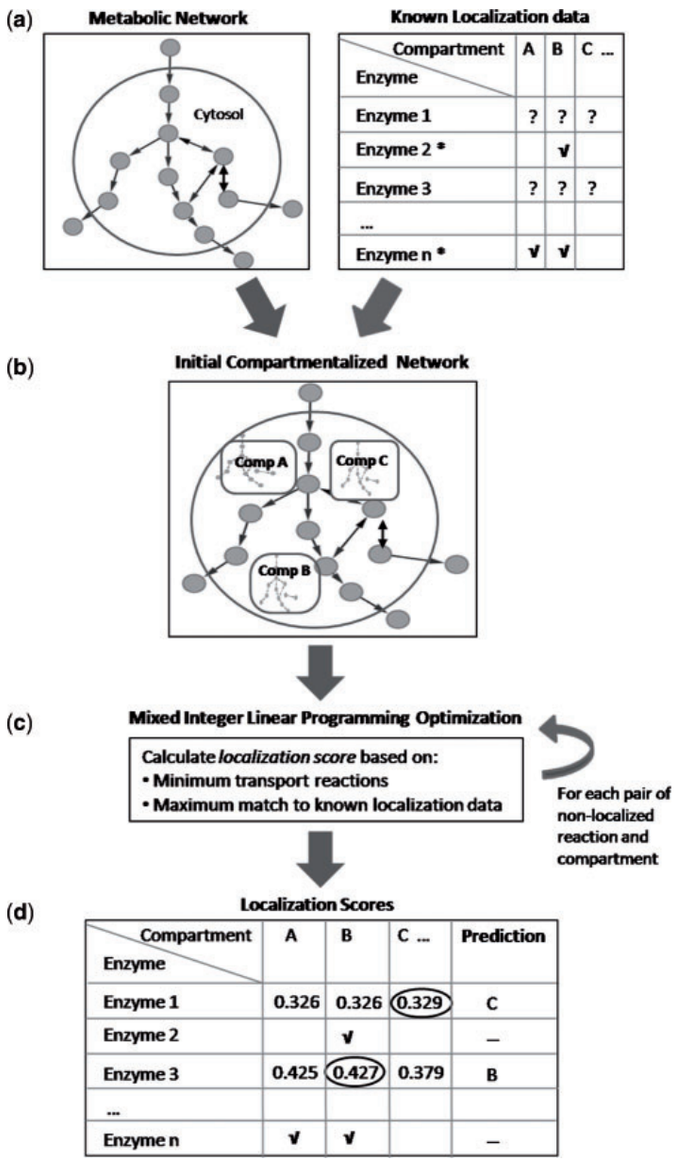



**Fig. 1.** A schematic representation of the enzyme subcellular localization prediction method. (**a**) The input data is a metabolic network, representing a set of enzyme-catalyzed reactions, and the known localization data for a subset of enzymes. (**b**) Integrating the given network and localization data yields an initial compartmentalized network, consisting of several compartments. Localized reactions appear in the corresponding compartments while the non-localized reactions are duplicated to all compartments. (**c**) Mixed Integer Linear Programming (MILP) is applied for each pair of non-localized reaction and compartment to calculate a *localization score*, reflecting the likelihood of this reaction to be present in that compartment. (**d**) Enzymes are predicted to be localized in compartments achieving the highest localization scores.

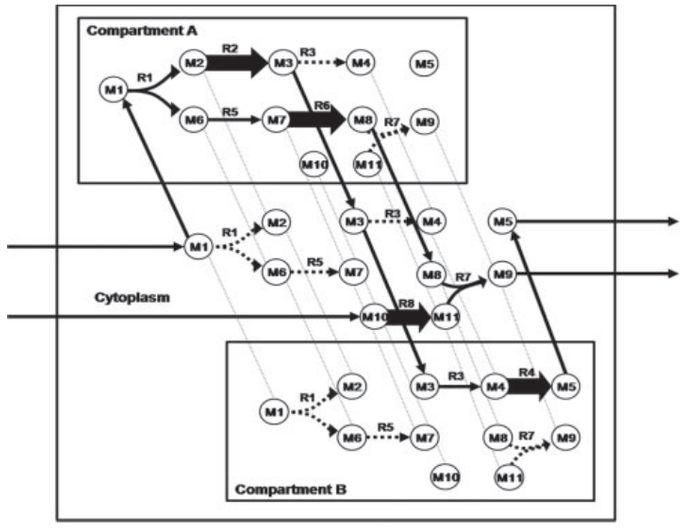



**Fig. 2.** An illustrative example of our method for enzyme subcellular compartment prediction. The initial compartmentalized network consists of three compartments, with instances of 11 metabolites and 8 reactions in each compartment. Thin edges connecting different instances of a metabolite in various compartments represent transport reactions that move metabolites across membrane boundaries. Wide arrows represent localized reactions whose known localization is given as input to the prediction method. Solid arrows represent reactions that are predicted to have non-zero flux by our method reflecting their predicted localization. Dashed arrows represent reactions predicted to have zero flux.

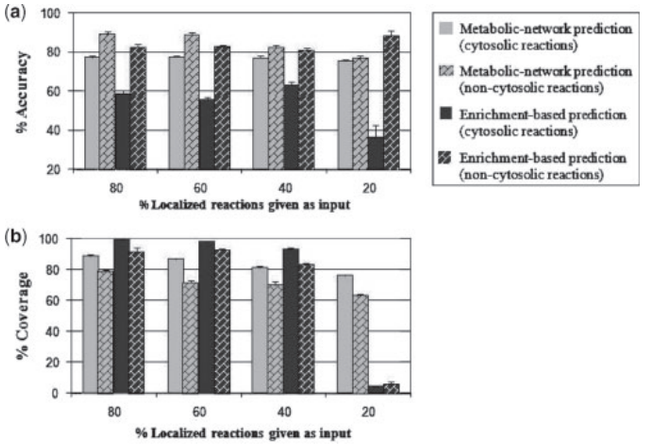



**Fig. 3.** Accuracy (**a**) and coverage (**b**) of enzyme subcellular localization predictions in a cross-validation test in the yeast *S.cerevisiae*. The average and standard error of the accuracy and coverage measures were calculated based on 10 applications of the prediction methods over randomly sampled sets of localized enzymes of similar size that are used as input.

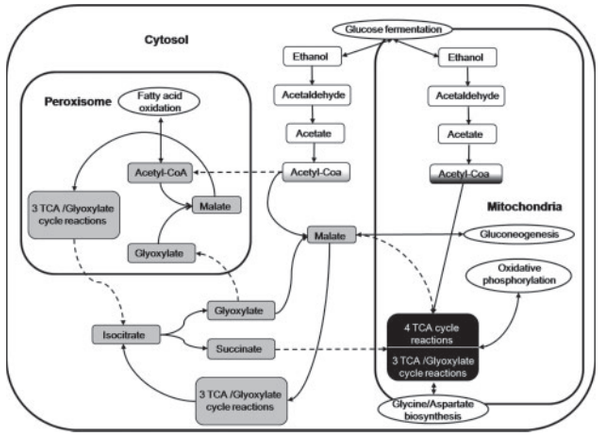



**Fig. 4.** Enzyme subcellular localization prediction of two complete metabolic pathways, including the TCA cycle (black rectangles) and glyoxylate cycle (grey rectangles), and a subset of the ethanol oxidation pathway (white rectangles), given localization data for enzymes in other connected pathways (white ellipses) as input. Transport reactions are marked by dotted arrows.

# 5. Functional units of PPIs

# Descriptions for functional units of PPIs

- Small scale: as network motifs (directed, weighted, associated with $\Delta G$ of binding)

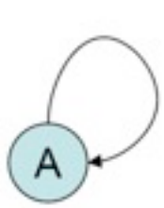
Annu. Rev. Biophys. 2010. 39:43–59

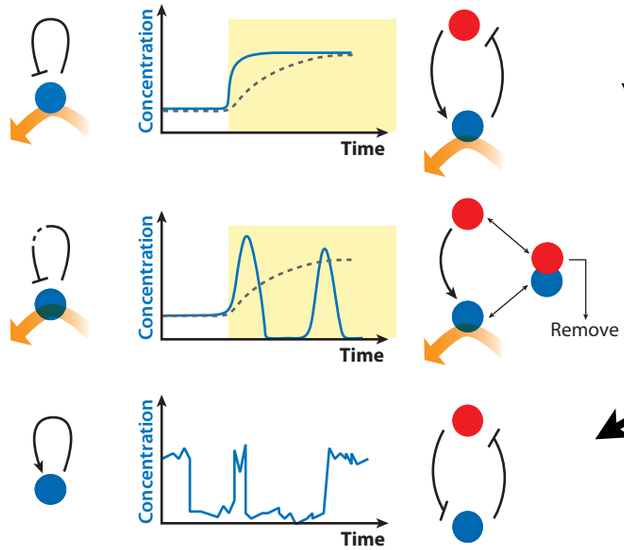
# Simplified Models of Biological Networks

Kim Sneppen, Sandeep Krishna, and Szabolcs Semsey

## DYNAMICS OF SINGLE FEEDBACK LOOPS

Auto regulatory single protein

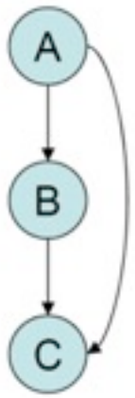



Feedback

Feedforward

Auto regulatory PPIs




Schematic illustration of negative and positive feedback loops along with their respective dynamical behavior. (*a*) Negative feedback stabilizes the output to a near-constant level and allows for fast transient increase in production in response to stress or perturbations. (*b*) If negative feedback is delayed, the protein concentrations may oscillate in time. (*c*) Positive feedback can result in bistability, i.e., the system can exist stably in either of two distinct steady states.

Feedback is an essential part of molecular networks. It allows the cell to adjust the repertoire of functional proteins to current needs.

Combinations of FLs in small-molecule uptake and metabolism can result in new behavioral features that are significantly different from a simple sum of the behaviors of single loops.

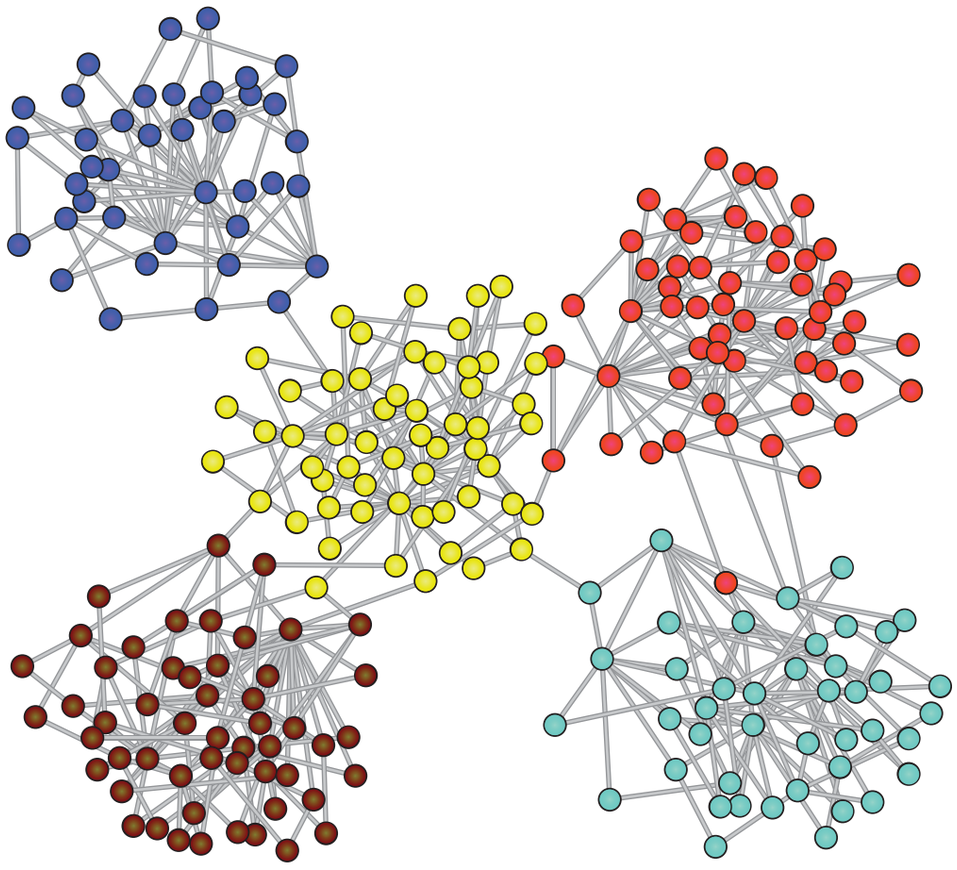
# Descriptions for functional units of PPIs

- Small scale: as network motifs (directed, weighted, associated with $\Delta G$ of binding)
- Larger scale: Location of PPI classes - transient and permanent, obligate & non-obligate
- Larger scale: Classes of PPIs associated with "Hubs" and "Loners" and essentiality.

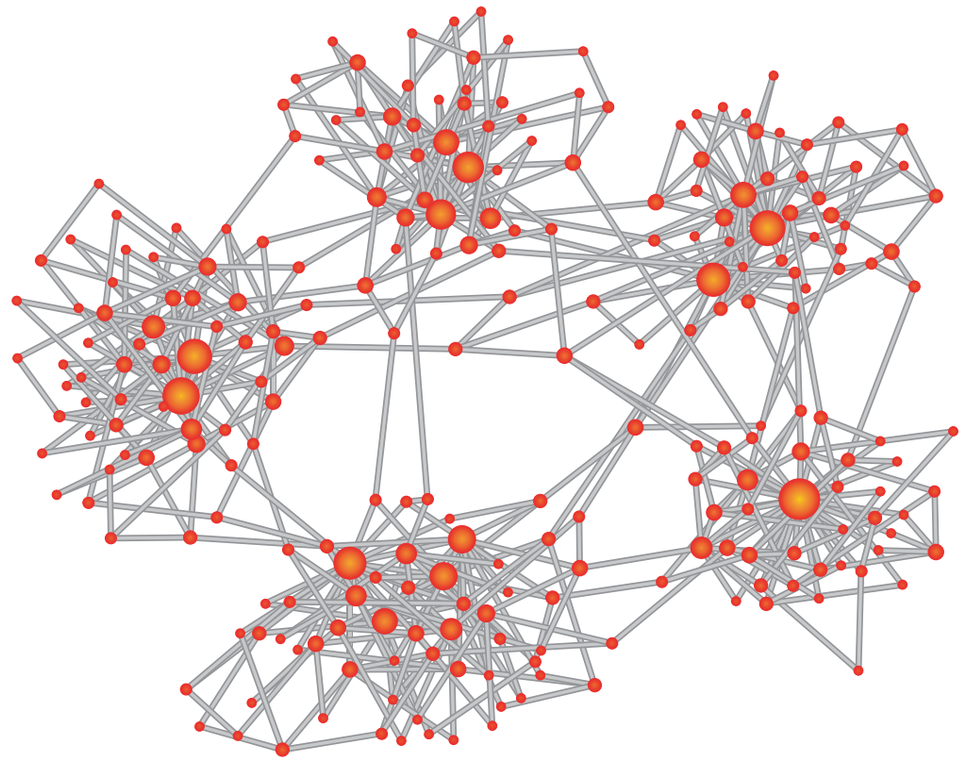
# Defining PPIs essential to metabolism

- PPIs associated network motifs as “hubs” in modules would be critical features in the metabolic network
- PPIs associated network motifs as inter-module links would also be critical to a metabolic network

# Close large scale models of metabolic pathways



Graph of a modular scale-free structure



Graph of distributed “hubs” in modules

Published in final edited form as:
*J Proteomics Bioinform*. 2008 May ; 1(2): 47–60.

# Integrated Bioinformatics for Radiation-Induced Pathway Analysis from Proteomics and Microarray Data

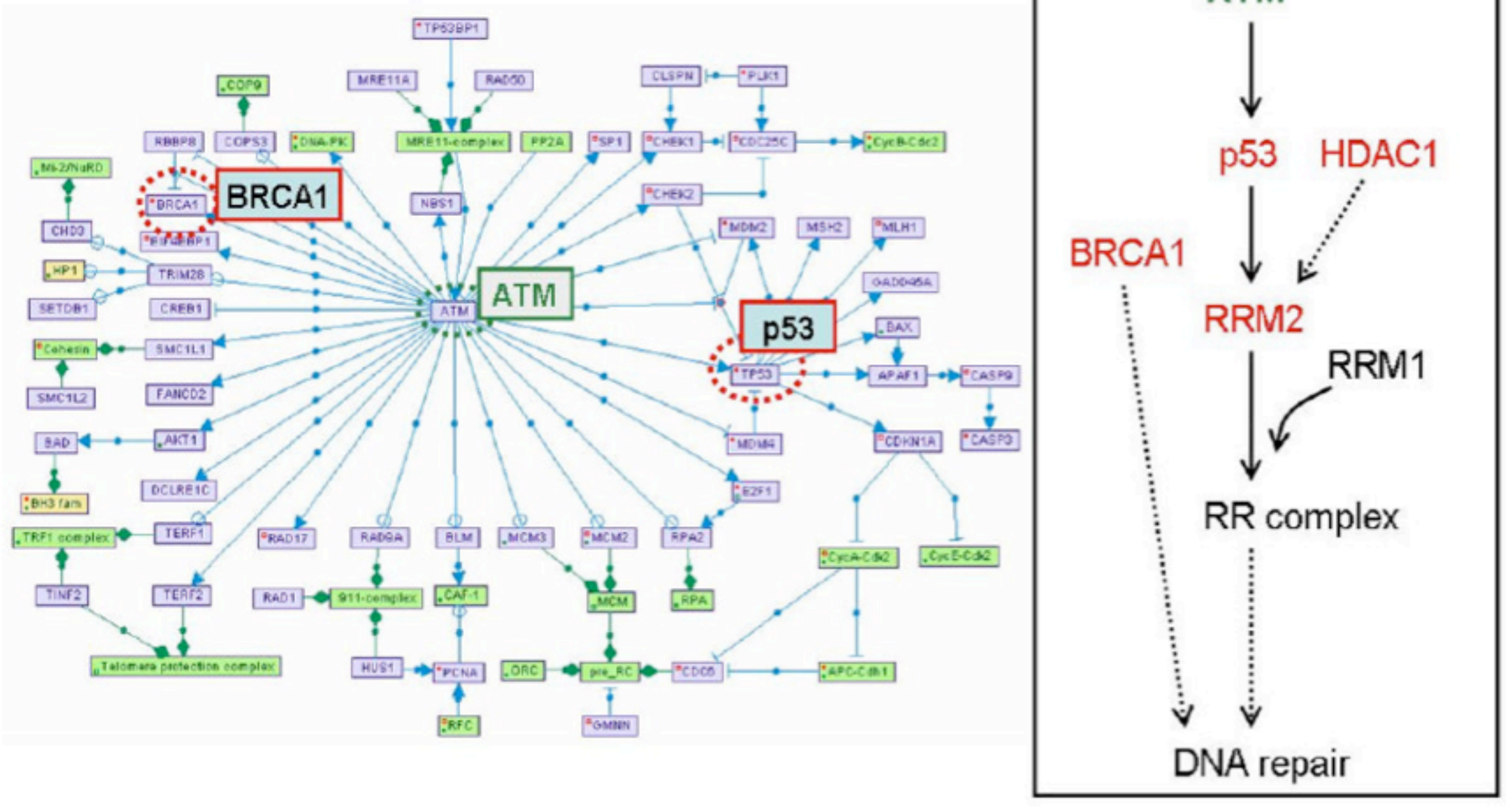



**Figure 6. RRM2 is involved in radiation-induced ATM-p53-mediated DNA repair pathway**

# Example References

Biochemical Society Transactions (2008) Volume 36, part 6

## Topological properties of protein interaction networks from a structural perspective

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*Center for Computational Biology and Bioinformatics and College of Engineering, Koc University, Rumelifeneri Yolu, 34450 Sariyer Istanbul, Turkey, †Basic Research Program, SAIC-Frederick, Inc., Center for Cancer Research Nanobiology Program, NCI-Frederick, Frederick, MD 21702, U.S.A., and ‡Sackler Institute of Molecular Medicine, Department of Human Genetics and Molecular Medicine, Sackler School of Medicine, Tel Aviv University, Tel Aviv 69978, Israel

IEEE/ACM Trans Comput Biol Bioinform. 2011 Nov 10. [Epub ahead of print]

## Identification of Essential Proteins Based on Edge Clustering Coefficient.

Wang J, Li M, Wang H, Pan Y.

Central South University, ChangSha.

## *In silico* network topology-based prediction of gene essentiality

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(Dated: February 2, 2008)

Physica A: Statistical Mechanics and its Applications (2007)

Volume: 387, Issue: 4, Pages: 1049-1055

**arXiv:** 0709.4206

# Summary

- Structural and experimental data reveals a wealth of PPIs
- Biophysical information defines the nature and class of PPIs
- PPIs are poorly represented in network descriptions
- Incorporating PPI biophysics could better describe the distribution of functional units in Metabolic networks.