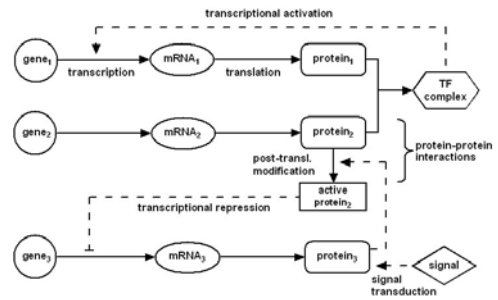


Understanding the dynamics and function of cellular networks

Cells are complex systems

- functionally diverse elements
- diverse interactions that form networks
 - signal transduction-, gene regulatory-, metabolic-
- have a function that needs to be performed
 - sense and respond to the environment
 - maintain homeostasis
 - replicate
- need certain dynamical features
 - sensitive to some changes, insensitive/adaptable to others
 - robust to unwanted perturbations
 - evolvable, shaped by evolution
- What is the relationship between the topological features of intracellular interaction networks and the dynamic behavior of cells?

Signaling, gene regulation and protein interactions are intertwined



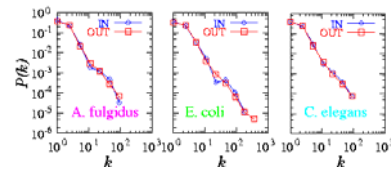
Mapping of cellular interaction networks

Experimental advances allow the construction of genome-wide cellular interaction networks

- Protein networks:**
 - Uetz et al. 2000, Ito et al., 2001 – *S. cerevisiae*,
 - Giot et al. 2003 – *Drosophila melanogaster*, Li et al. 2004 – *C. elegans*
 - Human interactome
- Metabolic networks:**
 - KEGG, WIT, Ecocyc
- Transcriptional regulatory networks**
 - Shen-Orr et al. 2002 – *E. coli*,
 - Guelzim et al 2002, Lee et al. 2002 - *S. cerevisiae*,
 - Davidson et al. 2002 – sea urchin
- Signal transduction networks**
 - Ma'ayan et al. 2005 – mammalian hippocampal neuron

Graph analysis uncovered common architectural features of cellular networks: **Connected, short path length, heterogeneous (scale-free), conserved interaction motifs**

node degree: number of edges (indicating regulation by/of multiple components)
degree distribution: fraction of nodes with a given degree



Metabolites

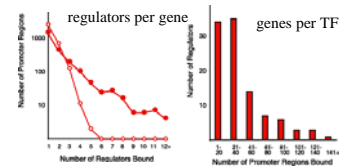
$$P_{in}(k) \approx k^{-2.2}$$

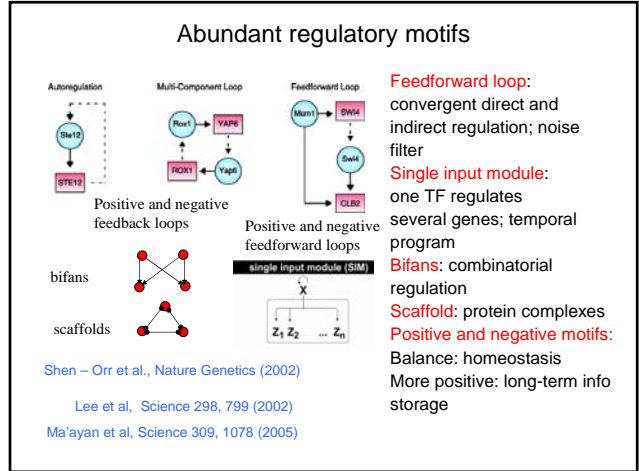
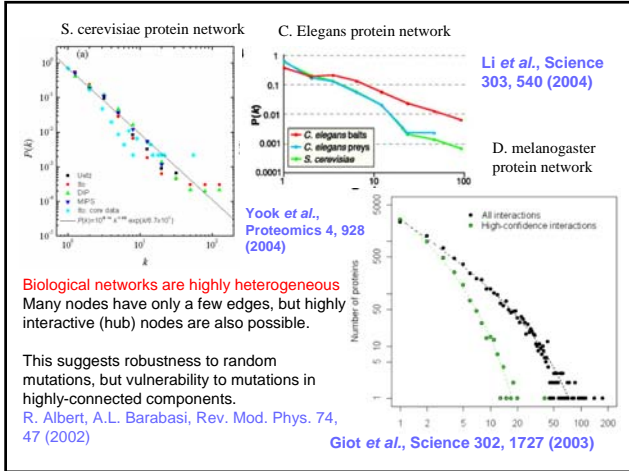
$$P_{out}(k) \approx k^{-2.2}$$

H. Jeong et al., Nature 407, 651 (2000)

S. cerevisiae
transcriptional network

Lee et al., Science 298, 799 (2002)





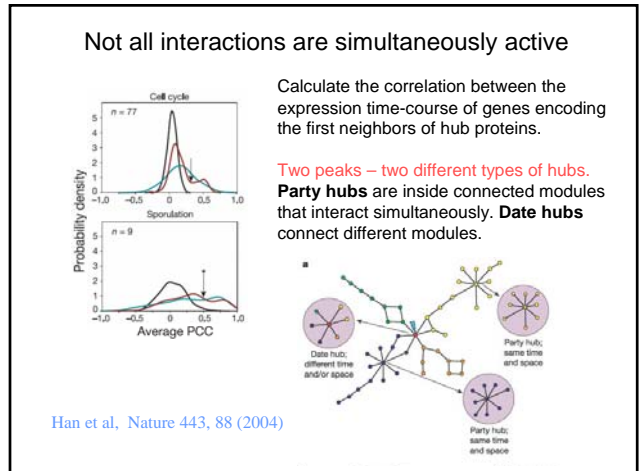
Importance of a dynamical understanding

Only subsets of the genome-wide interaction networks are active in a given external condition

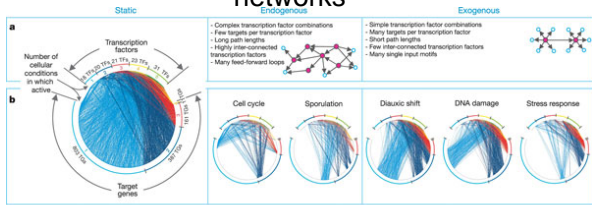
Han et al. 2004 – dynamical modularity of protein interaction networks

Luscombe et al. 2004 – endogenous and exogenous transcriptional subnetworks (see next two slides for a recap)

Q: How can we incorporate the information on the presence/absence or abundance of the molecules represented as nodes?



Condition-dependent transcription sub-networks



| Endogenous | Exogenous | 72 | 63 |
|-------------------------|-------------------------|-------------|------------|
| •Complex TF combination | •Simple TF combination | 676 | 362 |
| •Few targets per TF | •Many targets per TF | 262 | 566 |
| •Long path length | •Short path length | 1.6 | 1.6 |
| •Inter connected TF | •Few Inter connected TF | 2.2 | 2.2 |
| •Many FFL | •Single input motifs | 0.09 | 0.08 |
| | | 65.7% | 66.1% |
| | | 228 (57.3%) | 78 (55.2%) |
| | | 141 (17.0%) | 80 (50.7%) |
| | | 829 | 386 |

Luscombe et al, Nature 431, 308 (2004)

Toward network dynamics

Network topology needs to be complemented by a description of network dynamics – states of the nodes and changes in the state

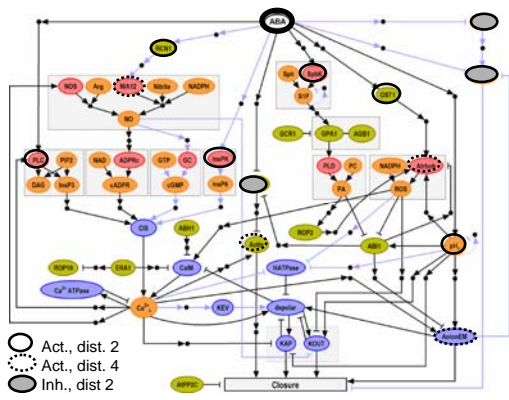
First step - **pseudo-dynamics**: propagation of reactions in chemical (interaction) space, starting from a source (signal)

This can only be done in directed networks. In effect we use topological analysis as a proxy for dynamic information on signal propagation.

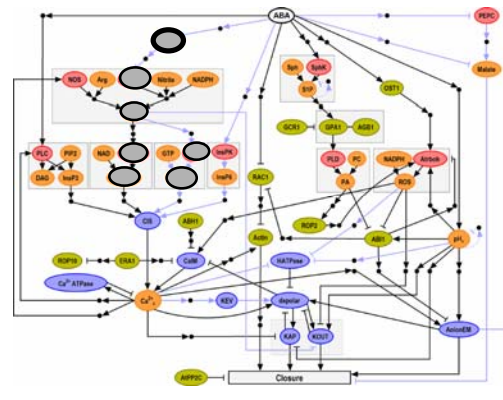
Q: What topological properties should be studied and what dynamic properties do they reflect?

Complete dynamical description is only feasible on smaller networks (modules): Signal transduction in bacterial chemotaxis, NF- κ B signaling module, the yeast cell cycle, Drosophila embryonic segmentation

Pseudodynamic signal propagation



Pseudodynamic effects of knockouts



Forward and reverse dynamic modeling

Dynamic modeling of interaction network:

Input: components; interactions; states of components

Hypotheses: interactions; kinetics (rates, parameters)

Output: behavior of components in time

Validation: capture known behavior

Explore: study cases that are not accessible experimentally
change parameters, change assumptions

Reverse problem: Network inference from dynamic information:

Input: components; states of components (in time)

Hypotheses: regulatory framework

Output: proposed regulatory network

Validation: capture known interactions

We will study network inference later in the course.

Types of dynamic models

1. **Continuous** - similar to chemical kinetics
 - differential equations
 2. **Discrete** - assume a small set of qualitative states
 - e.g. active or inactive; basal, intermediate, high
 - the changes in state are given by discrete (logical) rules
-
1. **Deterministic** - no randomness is involved in the development of future states of the system
 2. **Stochastic** - non-deterministic in that the next state of is not fully determined by the previous state.
 - can take into account the fluctuations in mRNA/protein numbers and external noise