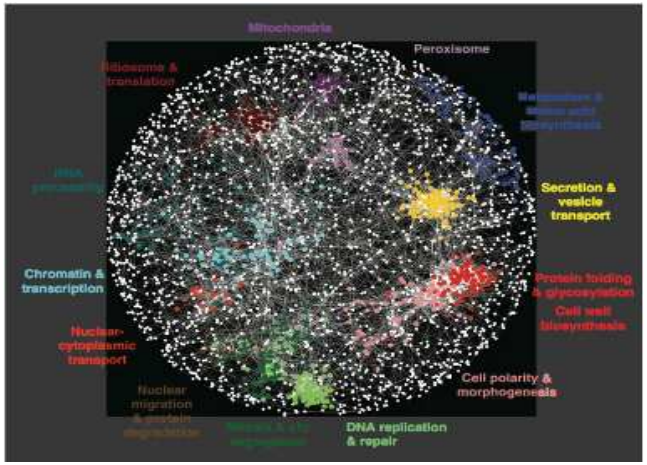
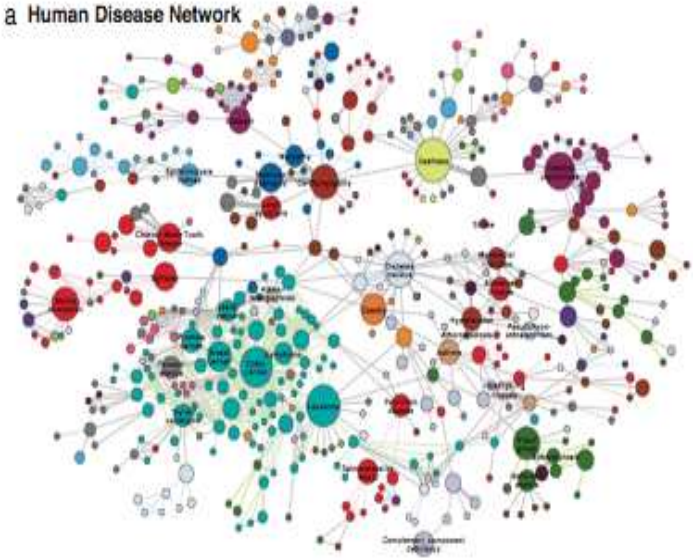




Winter School in Network Theory and Applications

Warwick, Jan 5-9 2011

Evolution of biological networks

Ginestra Bianconi

Physics Department,Northeastern University, Boston,USA

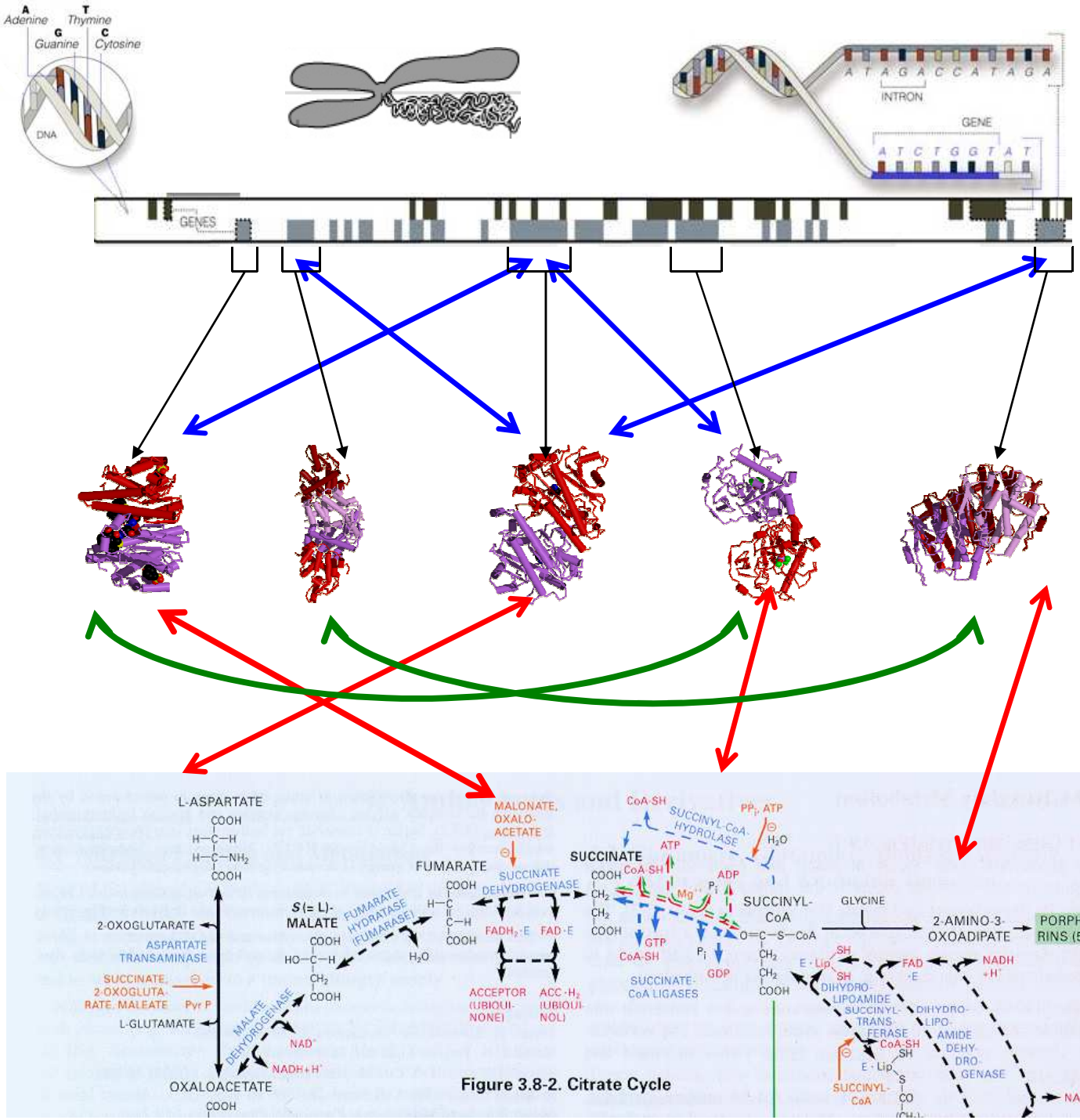


Figure 3.8-2. Citrate Cycle

GENOME

transcription networks

PROTEOME

Protein networks

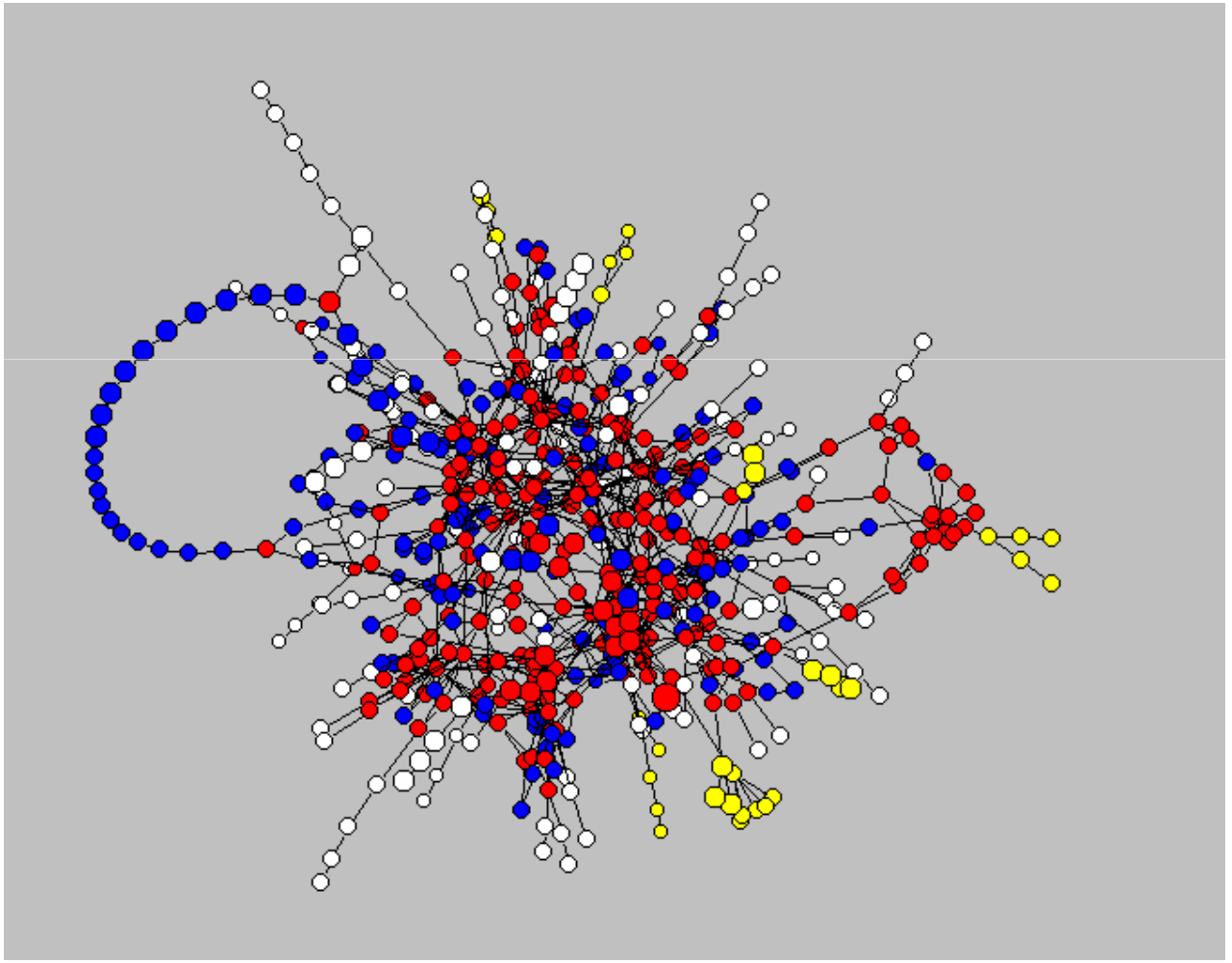
METABOLISM

Bio-chemical reactions

Metabolic Network

Nodes: chemicals (substrates)

Links: bio-chemical reactions



S.cerevisiae

Metabolic network

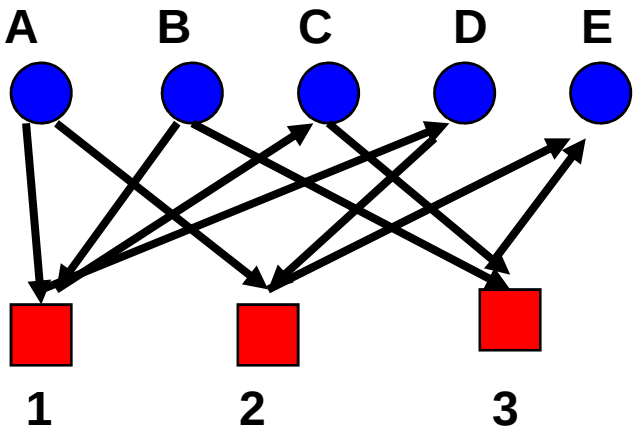
Reaction pathway

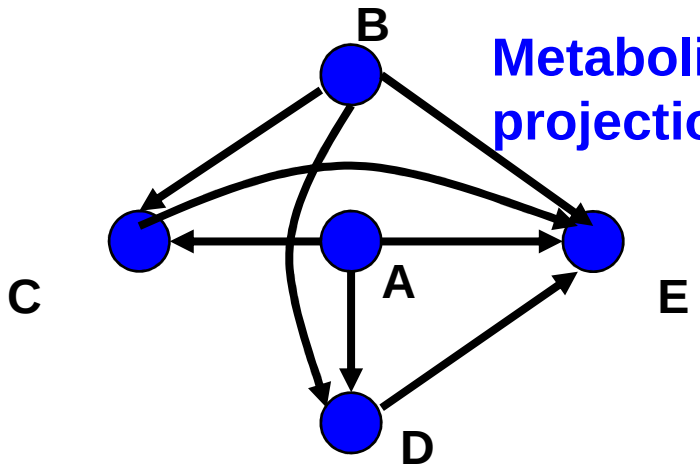
A+B → C+D 1

A+D → E 2

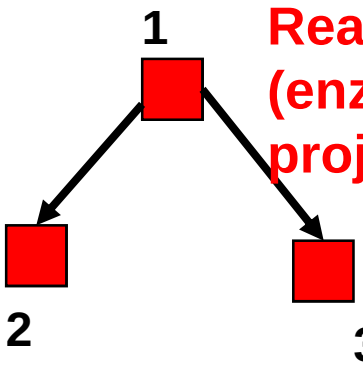
B+C → E 3

Bipartite Graph





Metabolites projection



Reactions (enzymes) projection

Stoichiometric matrix

$$aA + cC \rightarrow dD$$

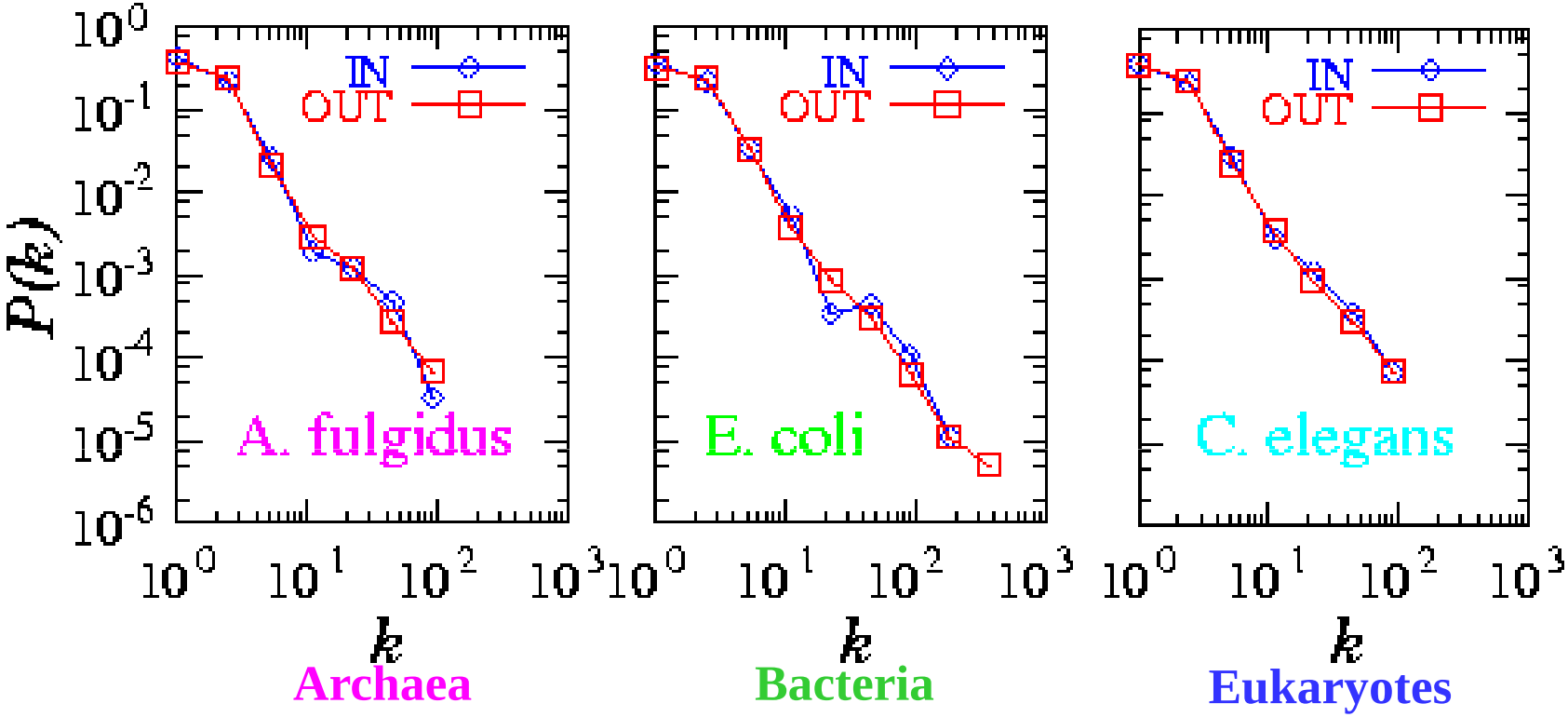
Metabolic Reaction

Reactions

Substrates	ν_1	...	ν_j		...
A	...	...	$-a$	...	...
B	...	...	0	...	...
C	...	...	$-c$	...	...
D	...	...	d	...	...
E	...	...	0	...	...

- Each **gene** can contribute to the flux of multiple reactions.
- **Every reaction** can be catalyzed by the complex of more than one gene product.

Metabolic network



Organisms from all three domains of life are scale-free networks

Some example of hub substrates are ATP, ADP

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

Enzymatic reactions
Michael-Menten model

$$E+S \underset{k_-}{\overset{k_+}{\rightleftharpoons}} ES \xrightarrow{k_{cat}} E+P$$

Enzymes speed up reactions of a factor 10^3-10^{17}

$V=[ES]k_{cat}$

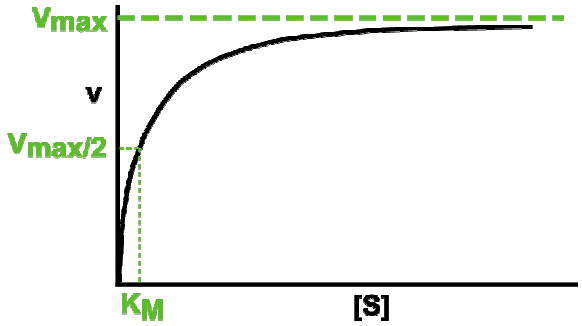
$[ES](k_-+k_{cat})=k_+[E][S]$

$[ES]+[E]=E_0$

$V=V_{max}S/(S+k_M)$

$V_{max}=k_{cat}E_0$

$k_M=(k_{cat}+k_-)/k_+$



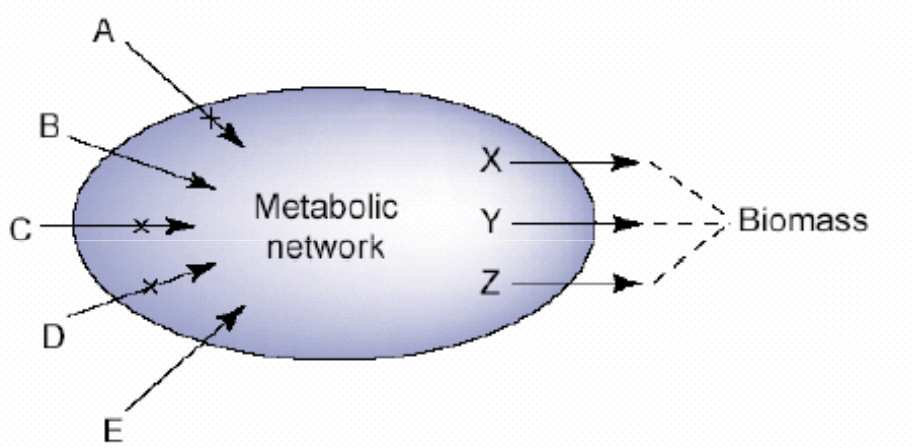
Flux balance analysis

- **Reconstruct the network from genomic and biochemical studies**

  -Transport processes

  -Direction of reactions

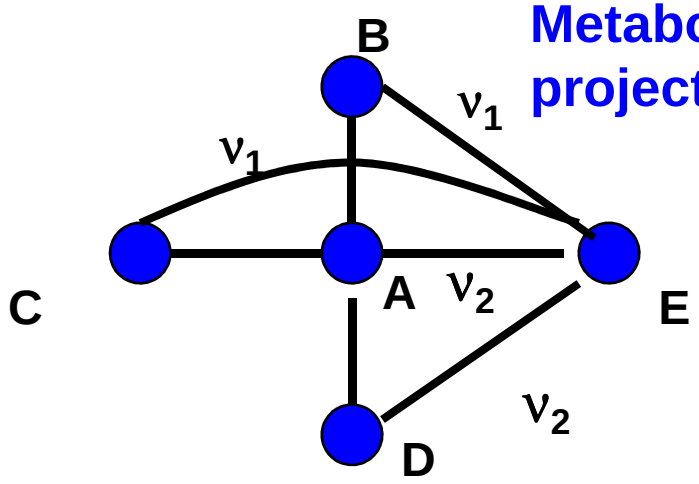
  -Stochiometry of reactions



- **Identify major metabolic components of the cell: biomass (X,Y,Z)**
- **Specify the nutrient present in the environment**

Flux-Balance-Analysis

Flux Balance-Analysis assume that the metabolic network is in the steady state that maximize biomass production and satisfy the physical limitation to the fluxes.



Metabolites projection

$$\frac{d[x_i]}{dt} = \sum_{j=1,N} S_{i,j}\nu_j \quad = 0$$

***i=1,…,M* with typically M<N**
Null space

$$\alpha_j < \nu_j < \beta_j$$

Limitations

$$Z = \sum_{\substack{i \in \text{Biomass} \\ j}} S_{ij}\nu_j$$

Maximize Z i.e. biomass production

What is flux-balance analysis good for?

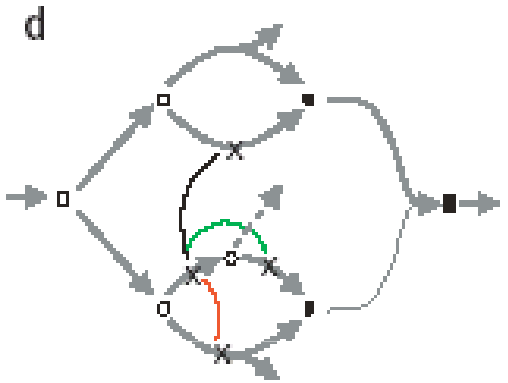
1. It finds flux distribution which maximize biomass production (at steady state for given network and nutrients)

2. Predicts enzymatic flux distribution for wild type and gene knockout experiments

3. Predicts relative growth rate (fitness) estimates for gene knockout strains to the wild type

Epistatic network

Interaction between couple of mutations in the network of 890 metabolic genes in *S. Cervisiae*.



Fitness of mutations:

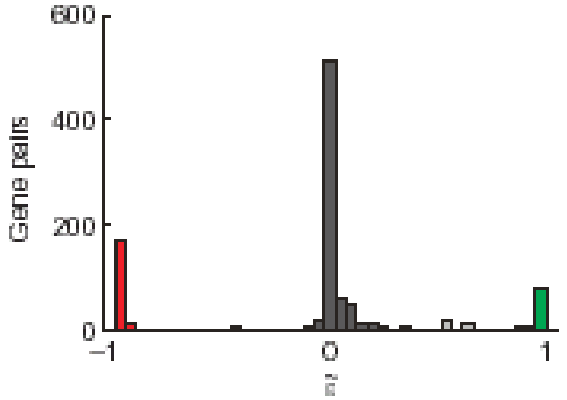
$$W^X = V_{growth}^{\Delta X} / V_{growth}^{WT},$$

V rate of biomass production.

Types of interactions between mutations:

$$\varepsilon = W^{XY} - W^X W^Y$$

No epistasis $\varepsilon = 0$
Aggravating $\varepsilon > 0$
Buffering $\varepsilon < 0$

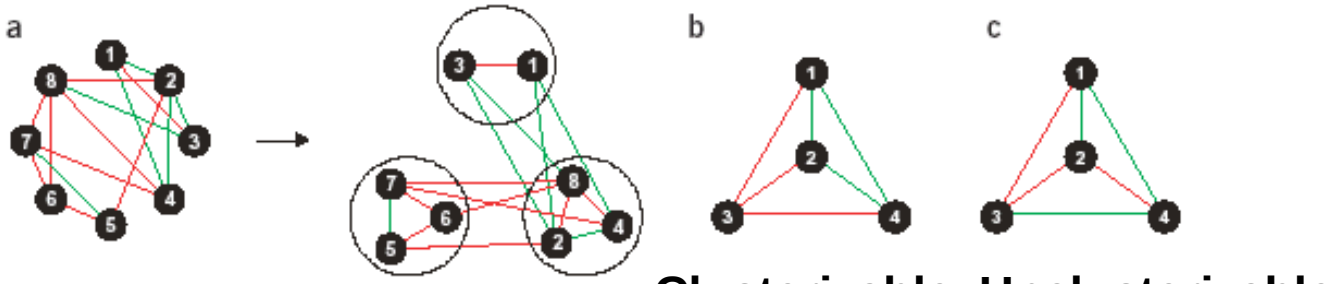


Monochromatic network

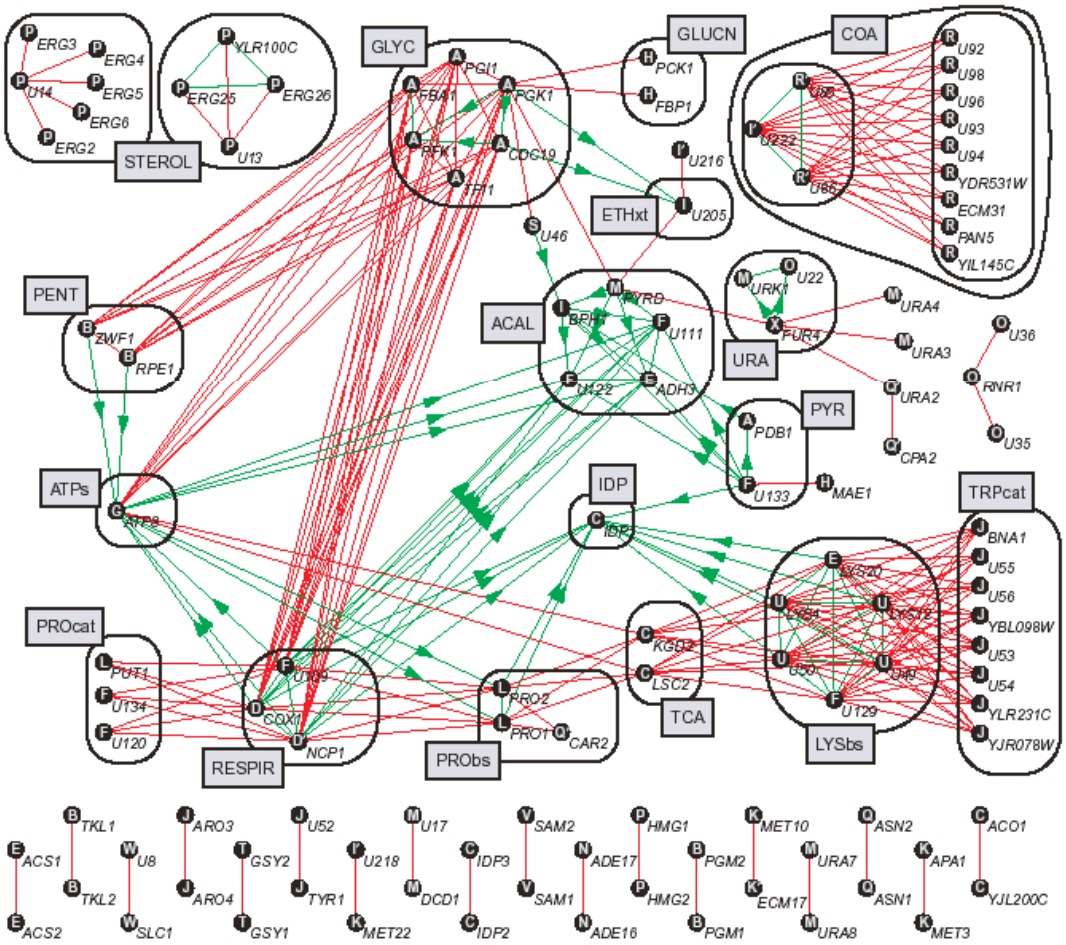
Epistatic interaction between genes assigned to function tend to be monochromatic (of the same sign).

One can then tend to do un unsupervised clustering analysis decomposing the network in monochromatically interacting modules for which the color of intra modules interactions is maximally monochromatic

- **Prism algorithm**

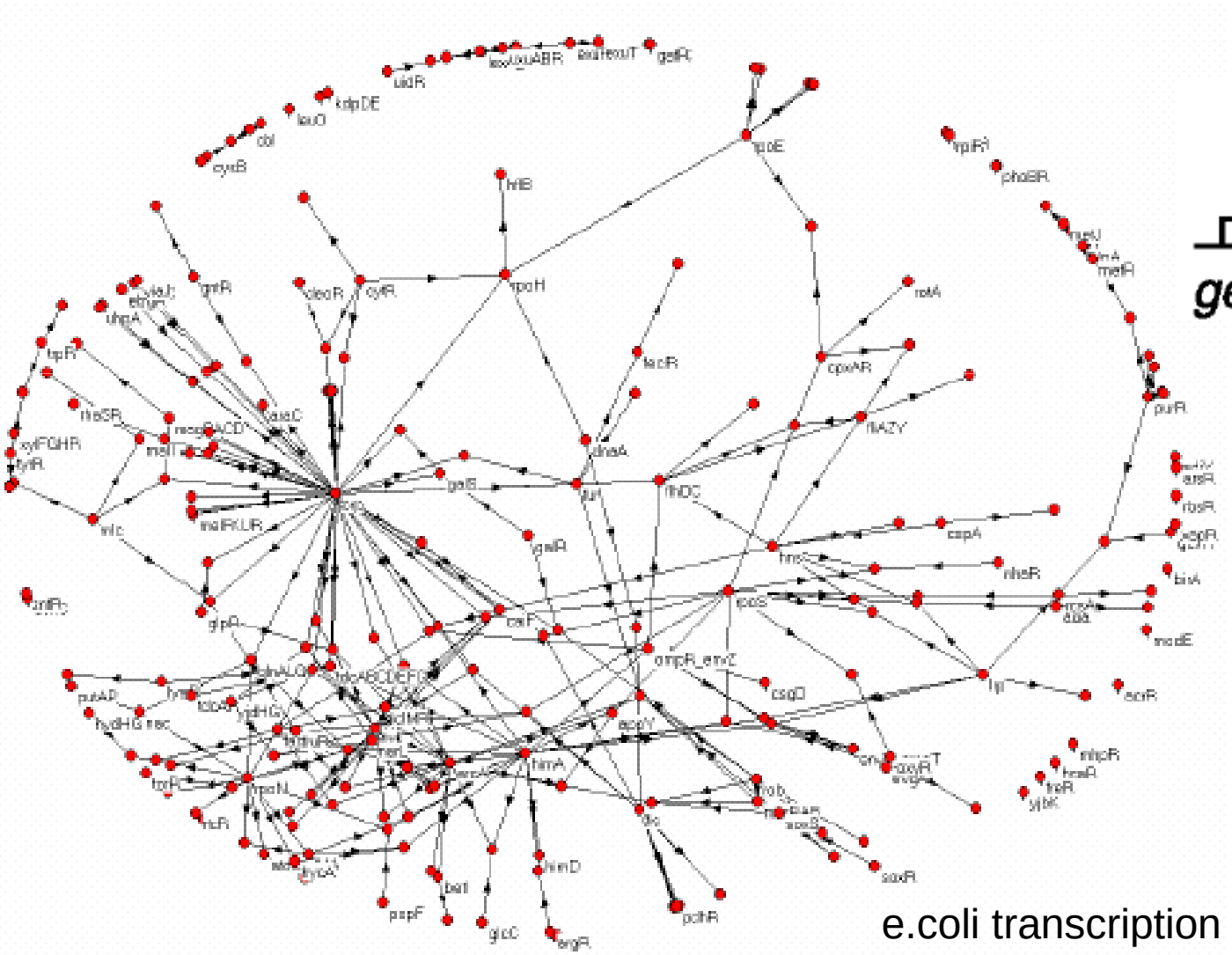


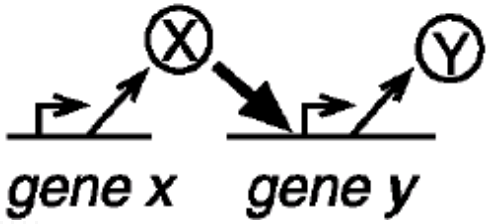
S. Cervisiae epistatic network



Segrè et al. Nature Gen.(2005)

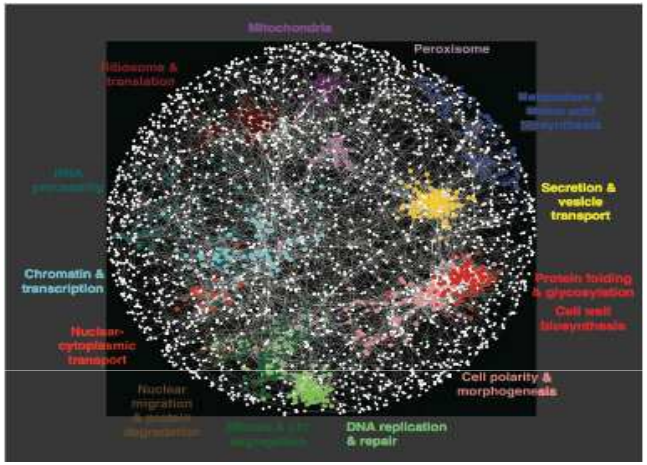
Transcription network





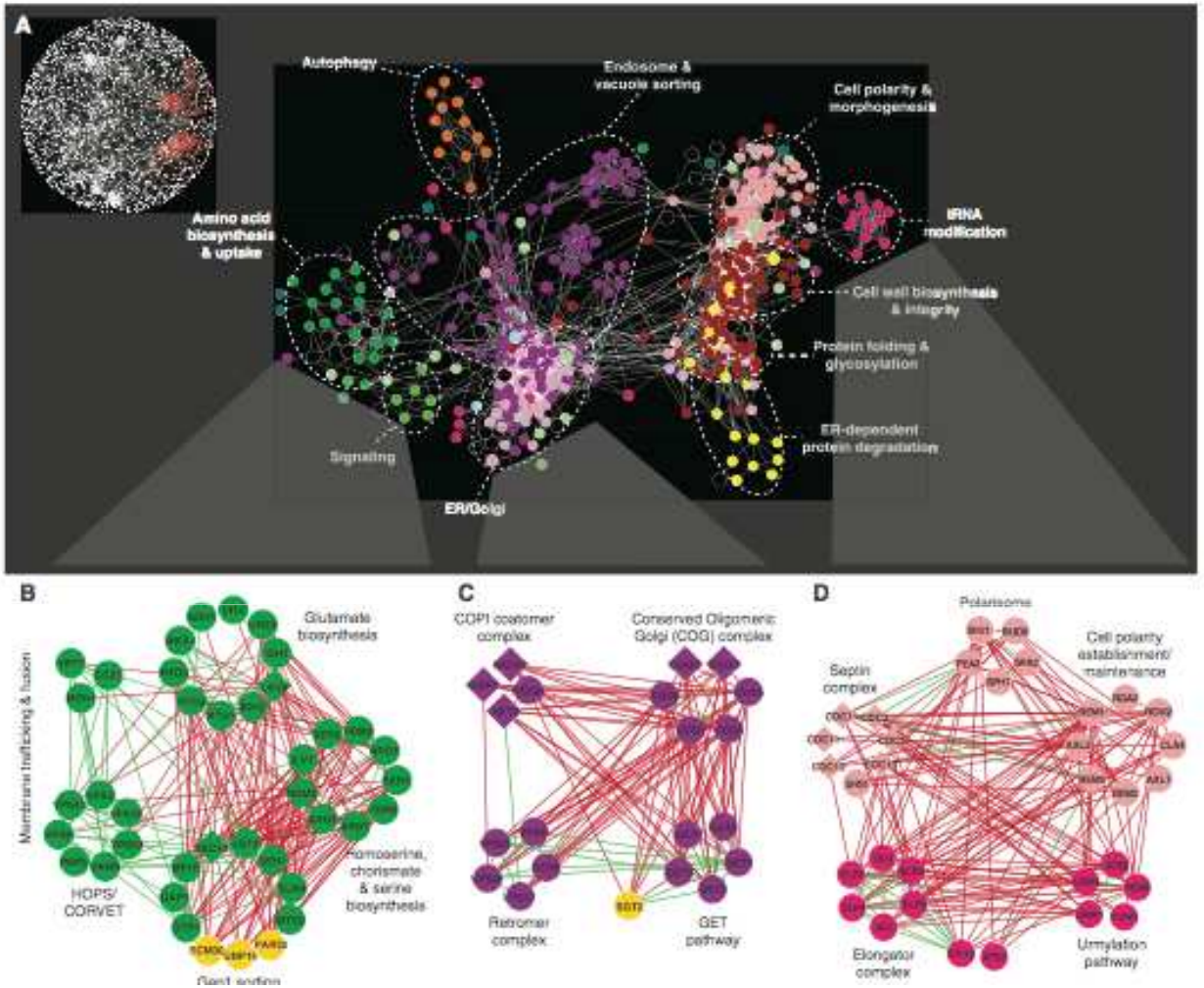
e.coli transcription network
(www.weizmann.ac.il/mcb/UriAlon)

Epistatic network of S. cerevisiae



~5.4 million pairs of double mutations
in 1712 genes out of ~6000 genes
20% genes are essential

More aggravating interactions than buffering interactions
Costanzo et al. Science 2010



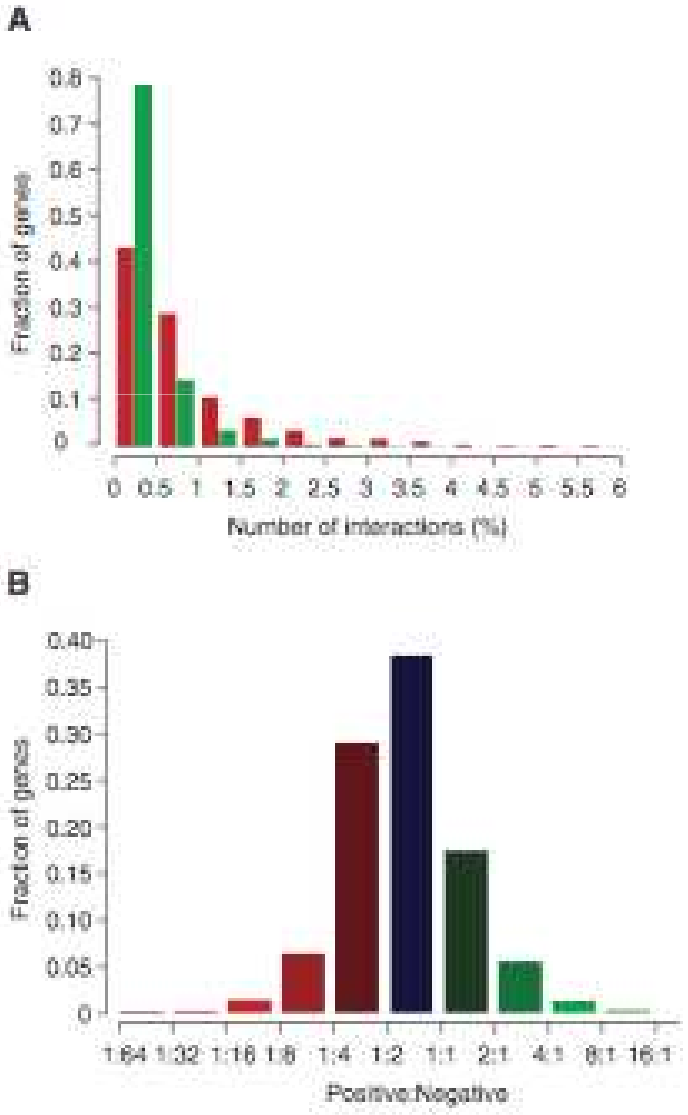
•Genes belonging to the same pathway or biological process tend share similar profile of genetic interactions

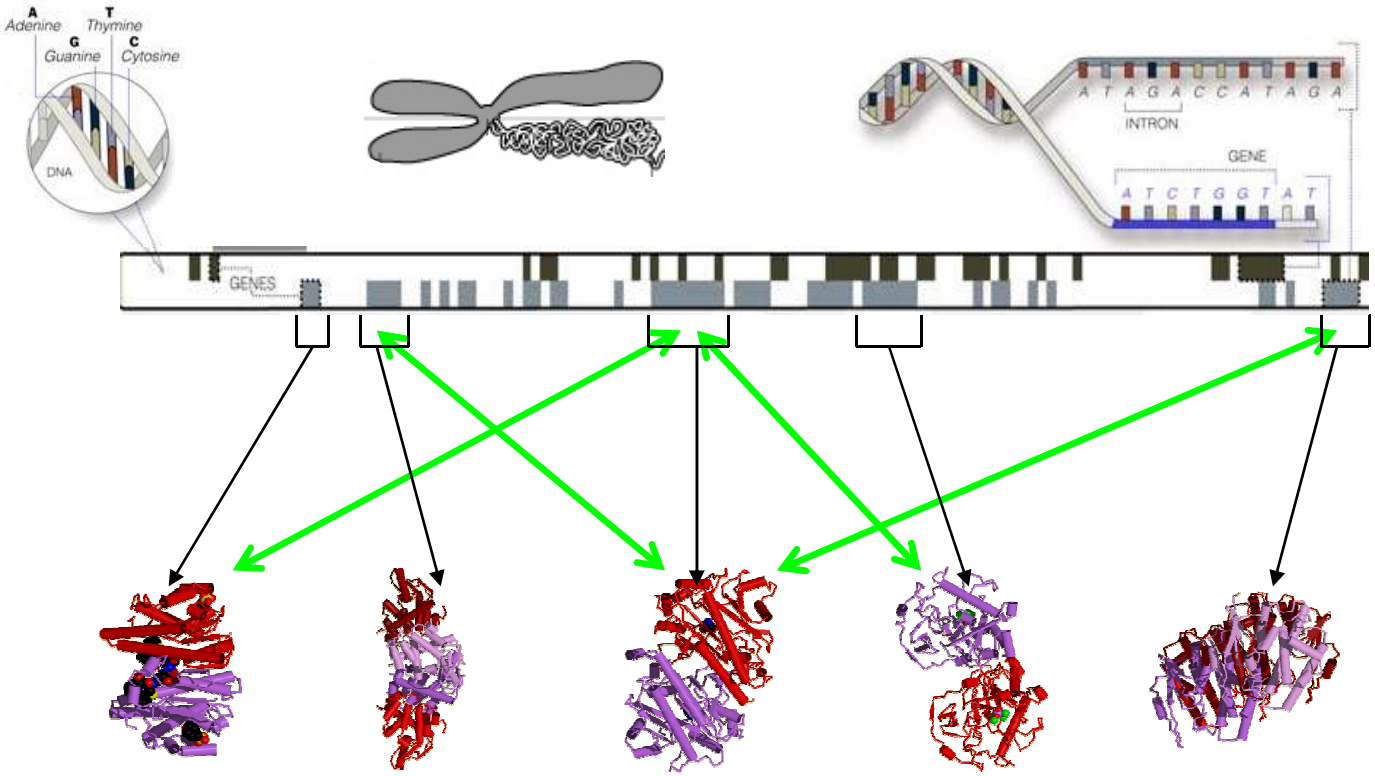
•Functional modules tend to interact monochromatically

Degree distribution of the epistatic network

- Degree distribution of the epistatic network

- The ratio between positive and negative interactions





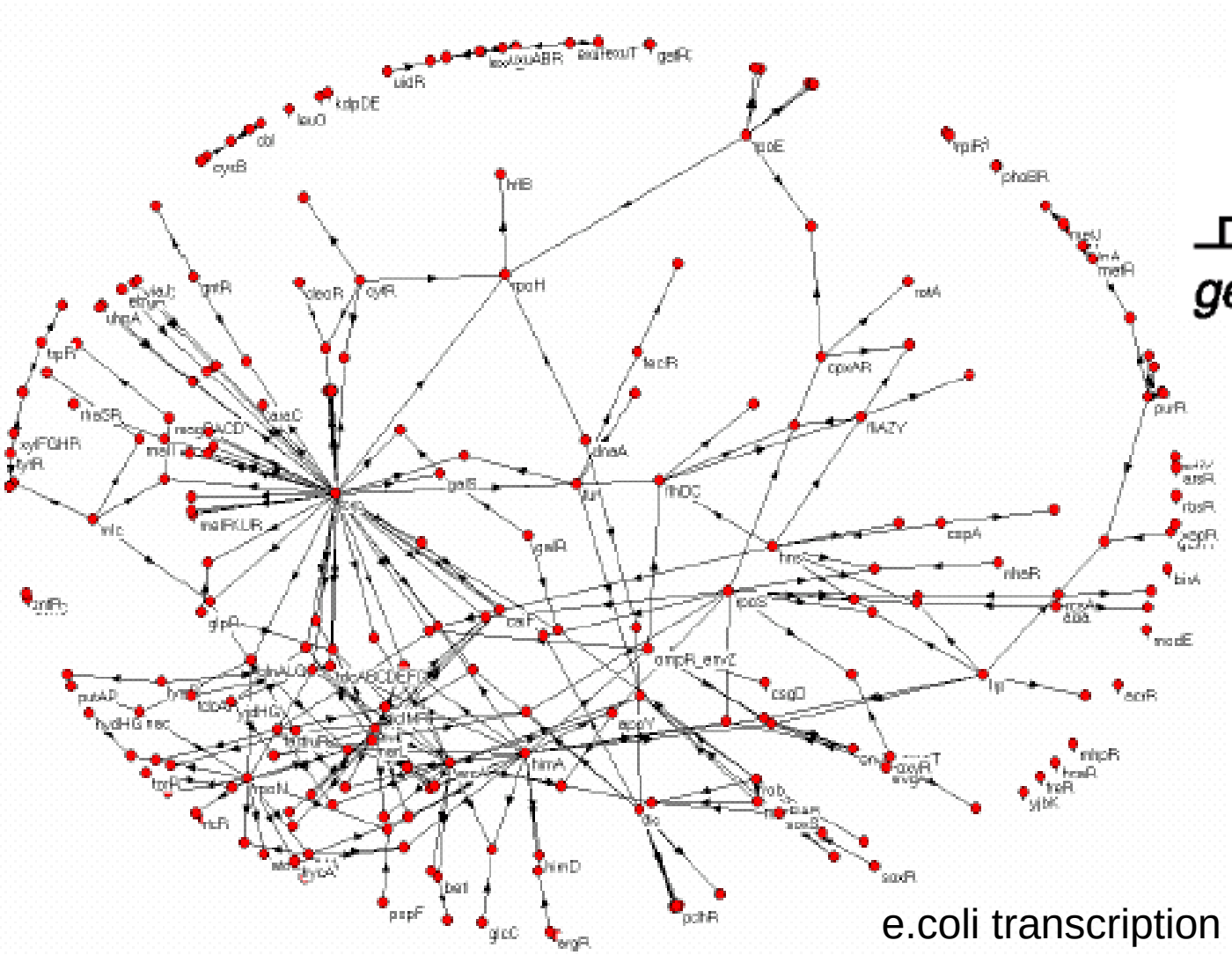
GENOME

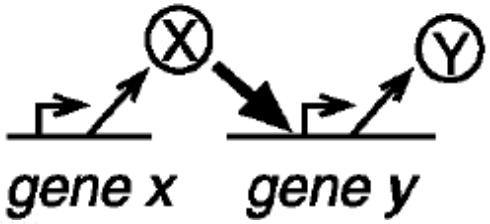
transcription networks

PROTEOME

Transcription networks

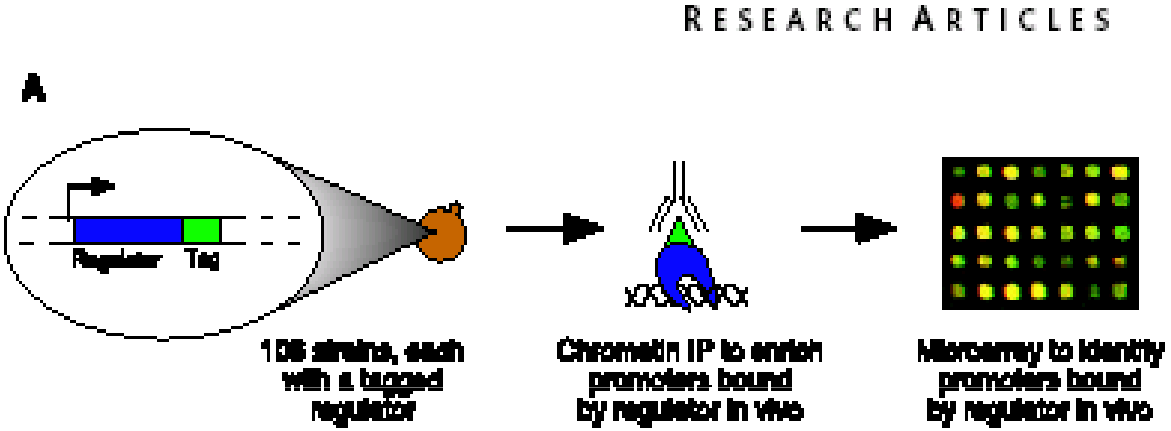
Transcription network





e.coli transcription network
(www.weizmann.ac.il/mcb/UriAlon)

High-throughput experiments



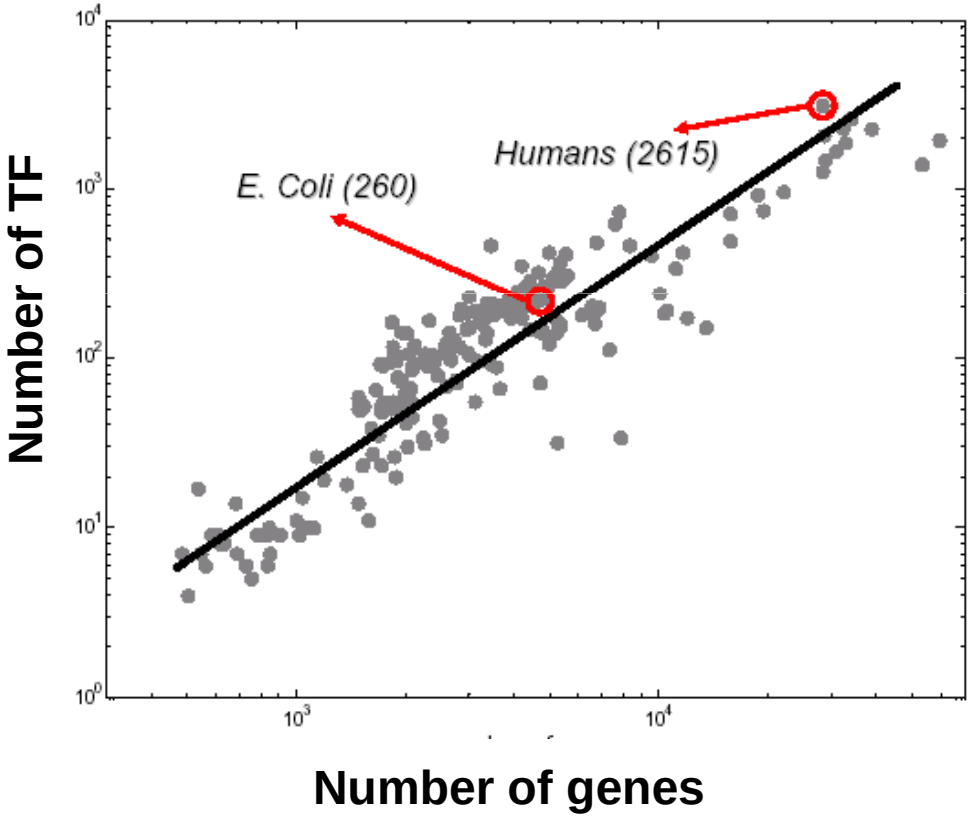
Alternatively or additionally one can consider

Yeast
4000 interactions
2343 regulators and promoter regions
106 transcription factors
Lee et al. Nature 2002

Collection or known regulations from the literature

www.weizmann.ac.it/mcb/UriAlon

Number of Transcription Factors in different organisms



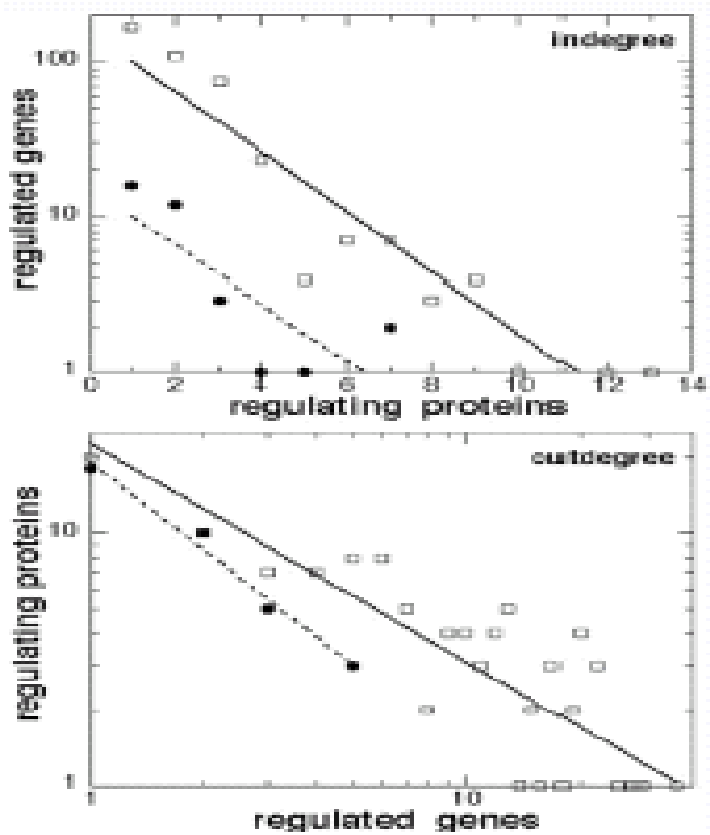
The growth in the picture is faster than linear: organism with larger number of genes have a larger number of transcription factors per gene.

Van-Nimwegen Trends Genet 2003

Degree distribution of transcription network

The in-degree distribution is exponential

the out-degree distribution has fat tails

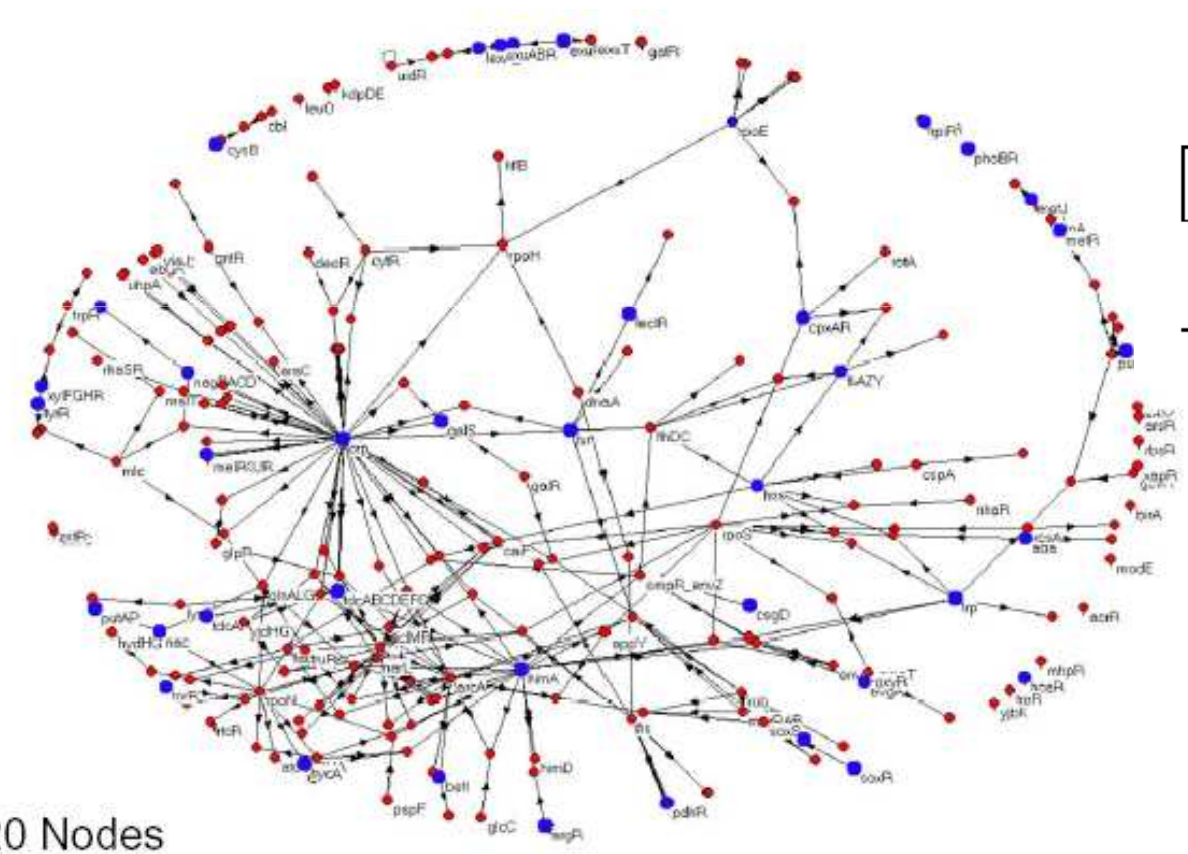


S. cerevisiae

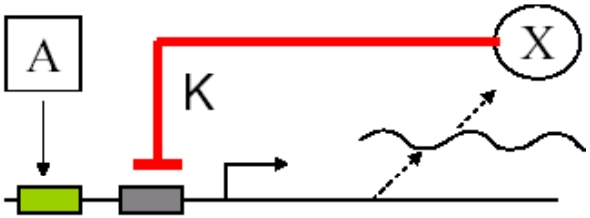
Guelzim et al. Nature Genetics 31,60 (2002)

Lee et al. Science 298 799 (2002)

Negative autoregulation is over-expressed in yeast transcription network



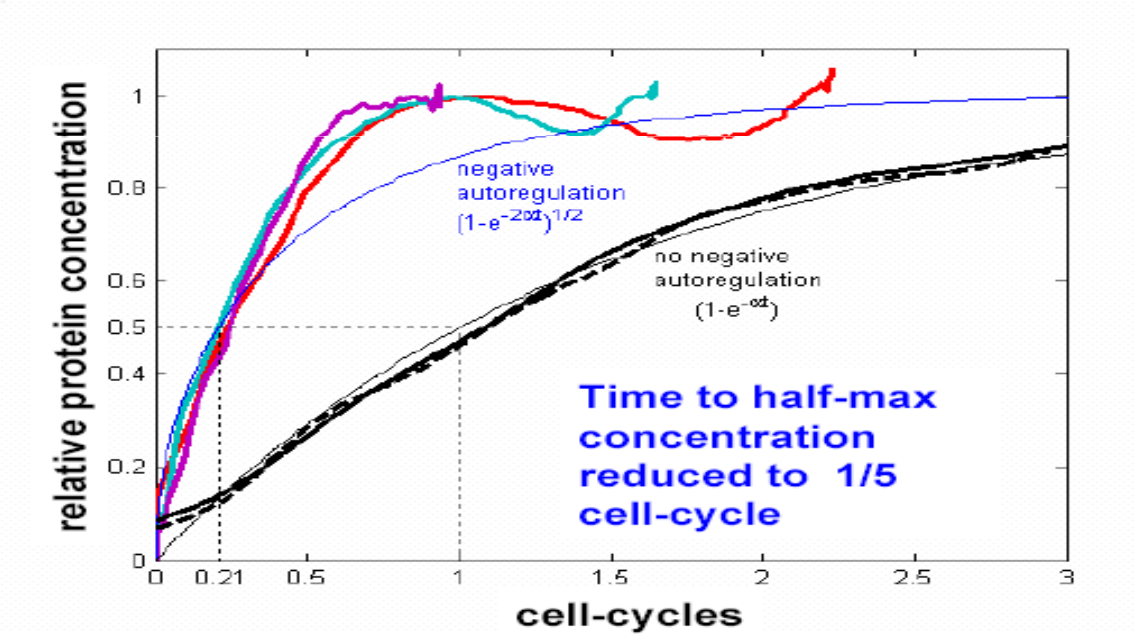
Negative autoregulation



N=420 Nodes
E=520 Edges
Es=40 self-edges

Blue nodes have self-edges

Negative autoregulation speeds up the response time of transcriptional networks



Rosenfeld et al. JMB (2002) 323,785

Motifs in transcription networks (e.coli and s.cervisiae)

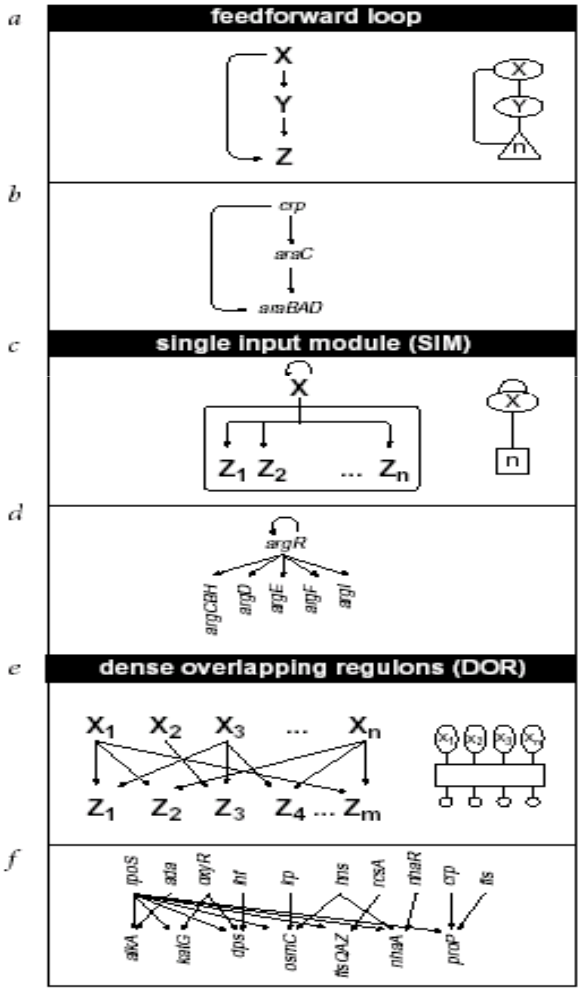
Different networks can be characterized by the frequency of particular subgraphs.

Subgraphs which appear with higher frequency than in random graphs with the same degree distribution are called motifs of the network.

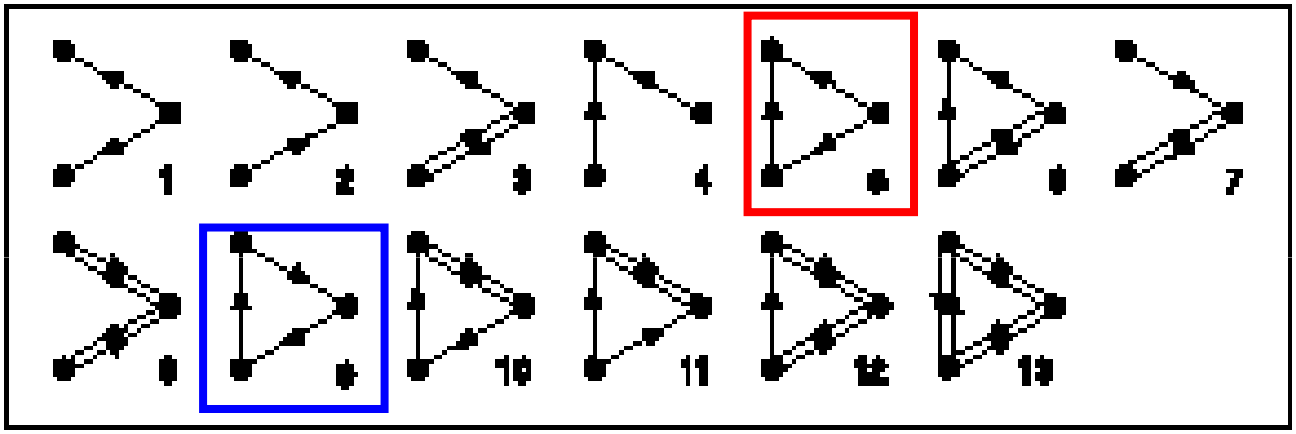
Those motifs usually perform specific functions.

R. Milo et al. Science (2002)

S.S. Shen-Orr,et al, Nature Genetics 31,64 (2002).



3-nodes subgraphs

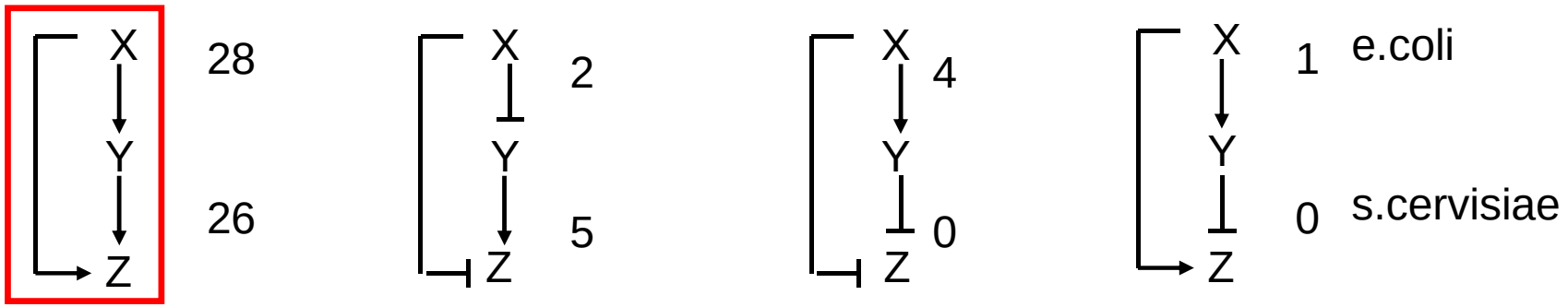


Feed-forward loop MOTIF

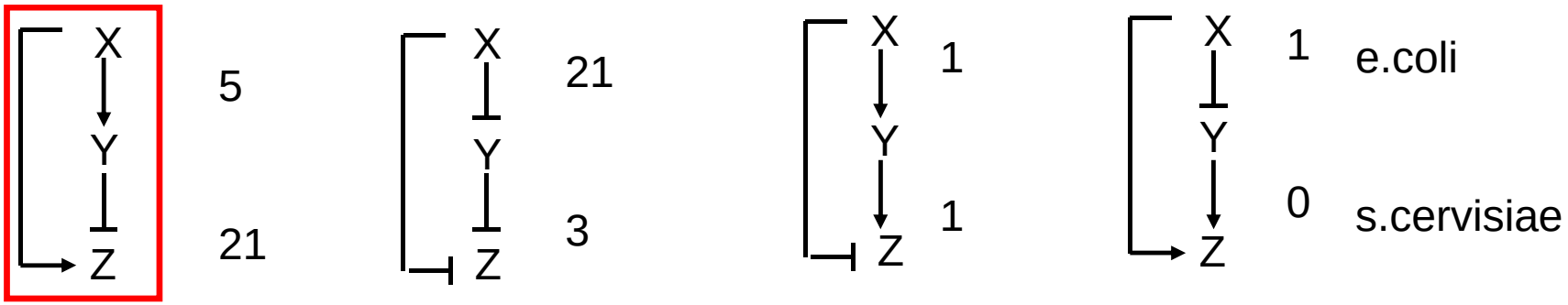
Feedback loop ANTIMOTIF

Abundance of feed-forward loops

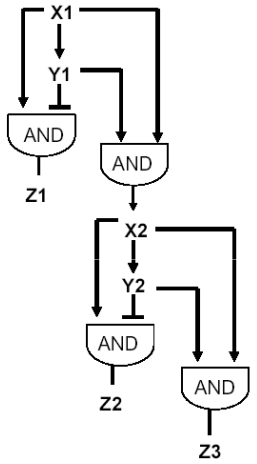
- Coherent FFL

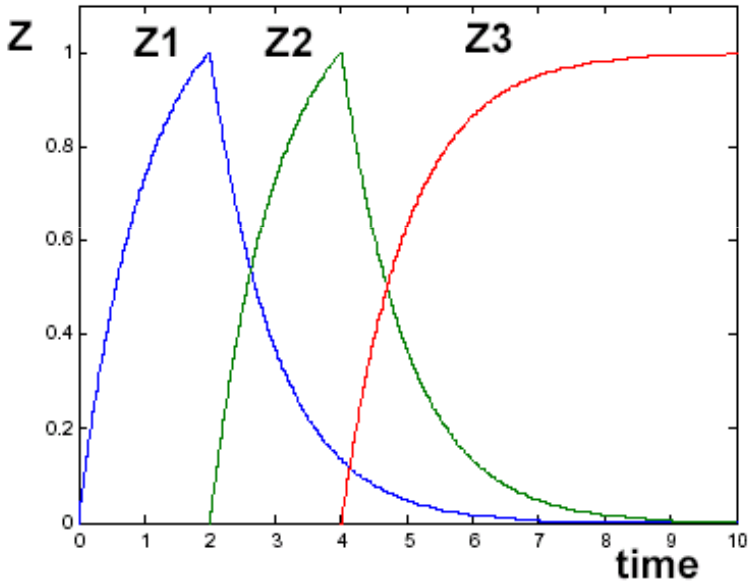


- Incoherent FFL



Feed-forward loops drive temporal pattern of pulses of expression



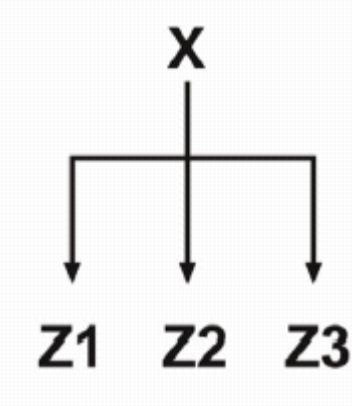


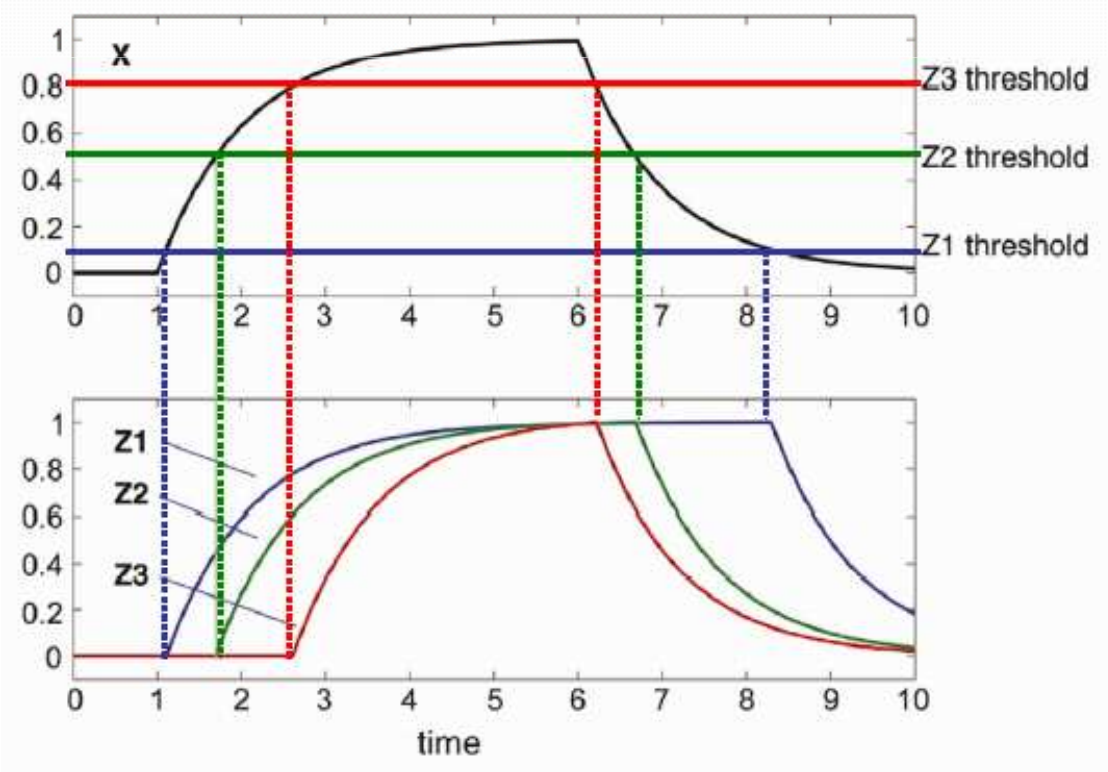
B.subtilis sporulation

R. Losick et al. PLOS 2004

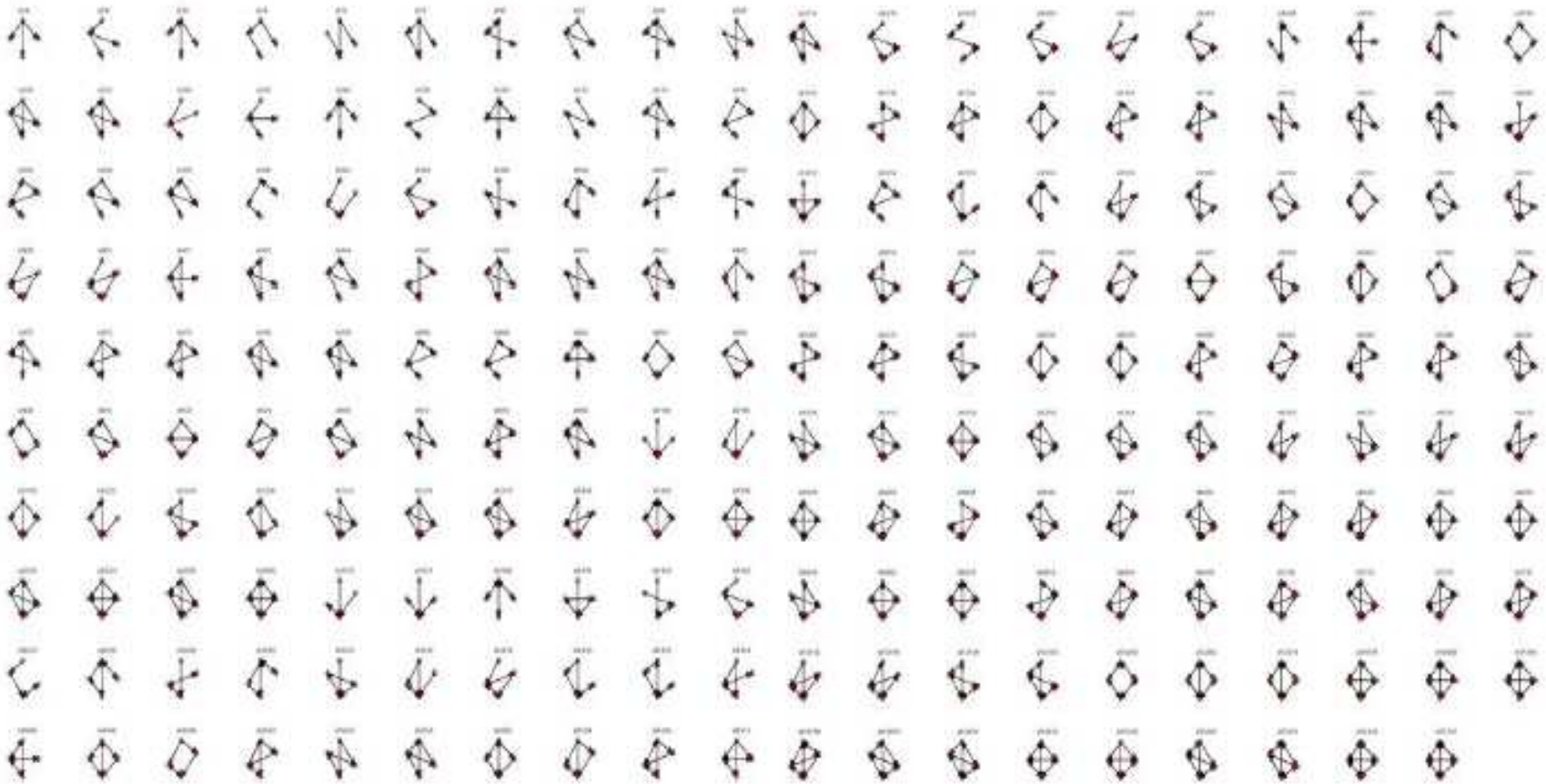
Single Input Module

Single input module can
control timing of gene
expression





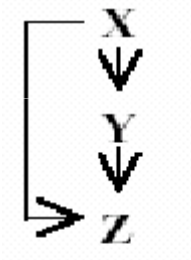
199 4-nodes connected subgraphs



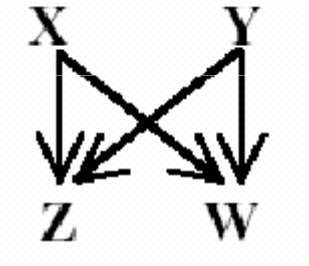
…and one has 9364 5-node subgraphs,
1,530843 6-node subgraphs

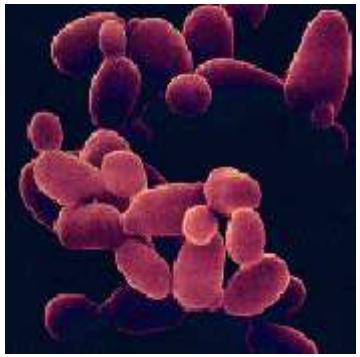
Yeast and e. coli share the same network motifs

Feed-forward loop

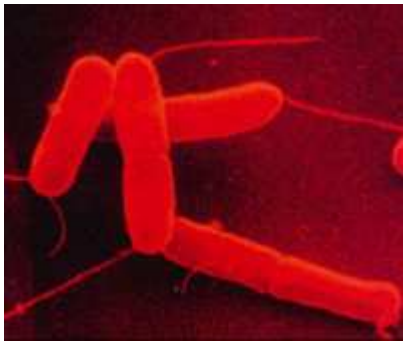


Bi-fan motif

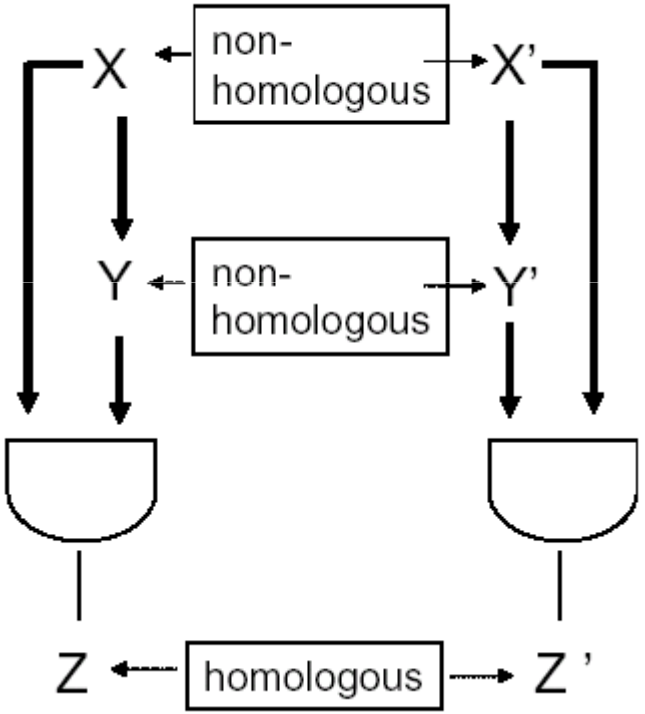




Although they are completely different organism

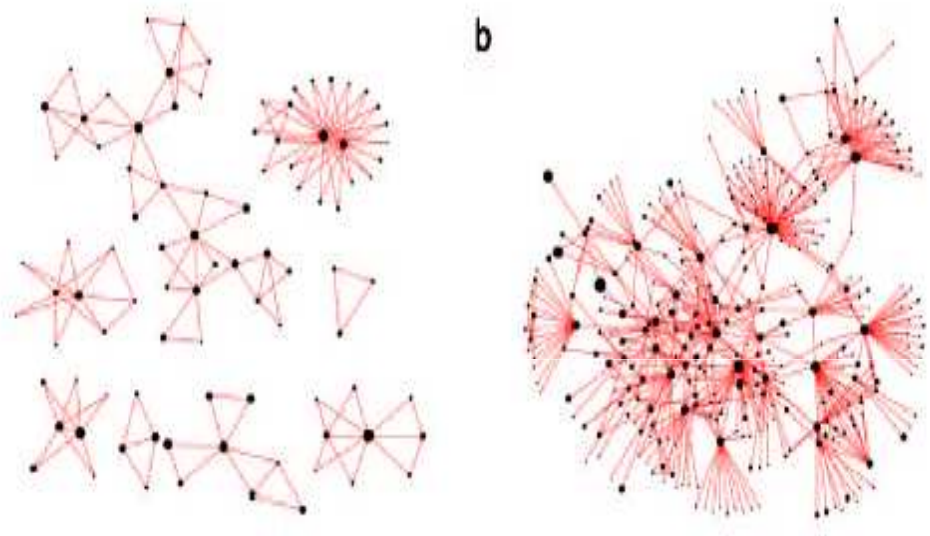


Convergent evolution of transcriptome of yeast and e.coli



G.C Conant , A. Wagner Nature Gen. 34,264 (2003)

Organization (percolation) of motifs



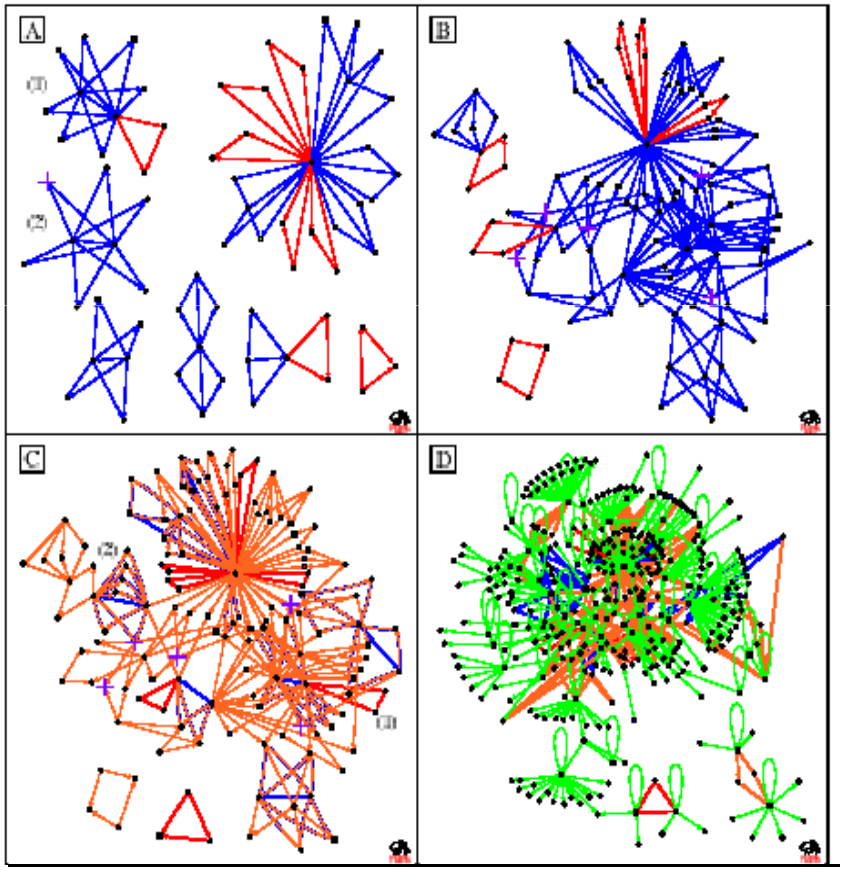
(3,3) subraphs and (5,5) subraphs in s.cervisiae transcription network

Motifs do not work in isolation!

The percolation properties of the subgraph composed by the intersections of the motifs of a given type depend on the value of the power-law exponent γ and the hierarchical exponent α.

Clustering of motifs: the case of e.coli transcription network

Feed-forward loops



Bifan motifs

Feed-forward loops and bifan motifs

Giant component

(1) aerobic-anaerobic switch cluster – (2) flagella cluster

Dobrin et al.BMC bioinformatics 2004

Modeling cell cycle as a boolean network

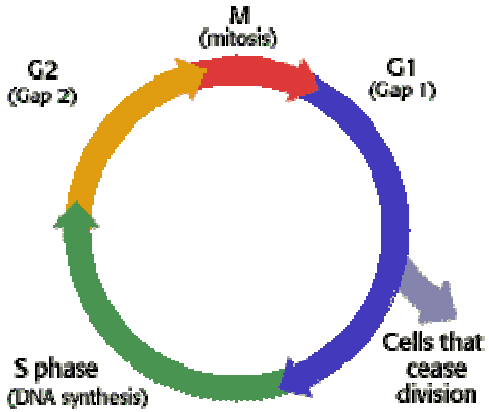
800 genes involved in the cell cycle process in budding yeast

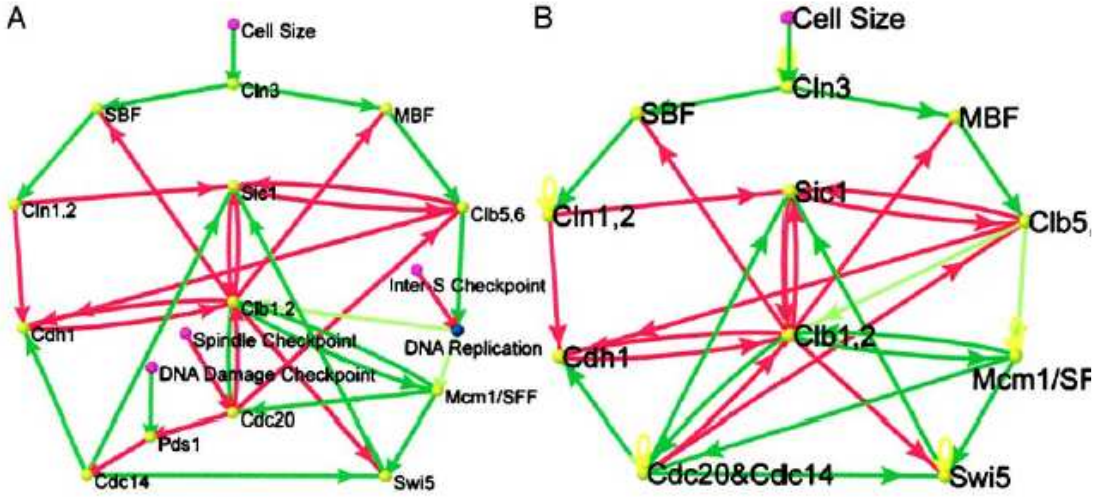
Network constructed form literature analysis

Core of the cell cycle regulatory network:

Cyclins , Inhibitor, degrader and competitors of the cyclin-cdc28 complexes

Checkpoints (cell size, DNA replication and damage spindle assembly)





Li et al. PNAS,101,4781 (2004)

Reconstructed network and its simplification

Boolean model for the cell cycle

The dynamic assumed to hold is the following

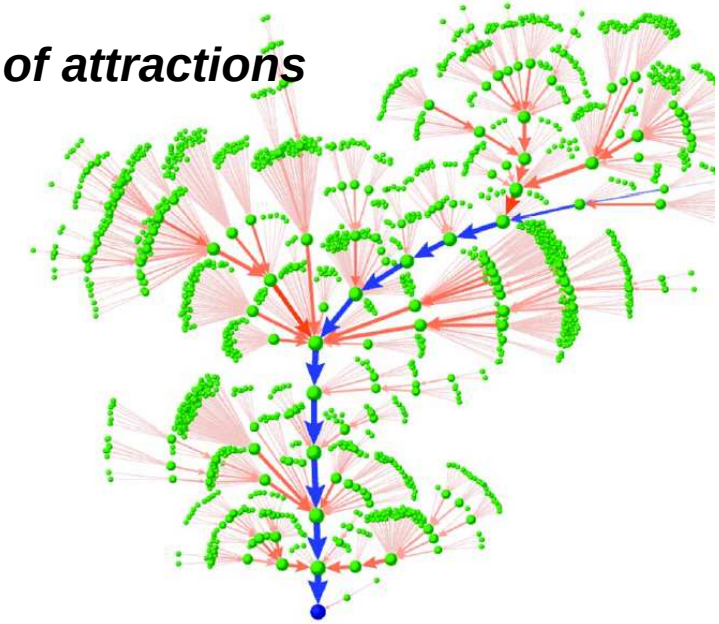
$$S_i(t+1) = \begin{cases} 1 & \sum_j a_{i,j} S_j > 0 \\ 0 & \sum_j a_{i,j} S_j < 0 \\ S_i(t) & \sum_j a_{i,j} S_j = 0 \end{cases}$$

with $a_{ij}=a_g$ for activation
$a_{ij}=-a_r$ for inhibition
but the results do not depend strongly on the values of a_g and a_r

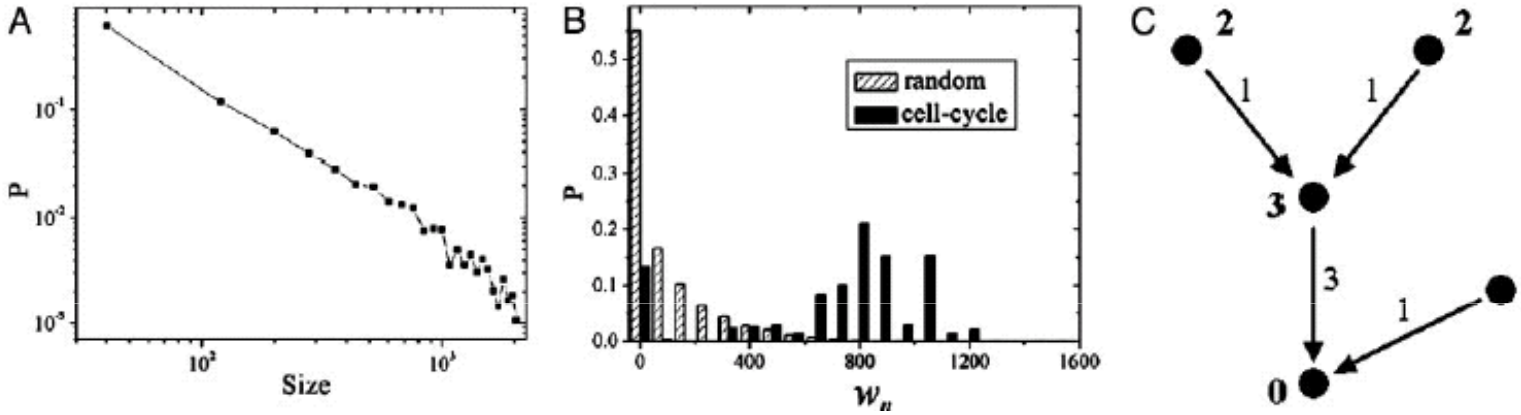
Table 1. The fixed points of the cell-cycle network

Basin size	Cln3	MBF	SBF	Cln1,2	Cdh1	Swi5	Cdc20	Clb5,6	Sic1	Clb1,2	Mcm1
1,764	0	0	0	0	1	0	0	0	1	0	0
151	0	0	1	1	0	0	0	0	0	0	0
109	0	1	0	0	1	0	0	0	1	0	0
9	0	0	0	0	0	0	0	0	1	0	0
7	0	1	0	0	0	0	0	0	1	0	0
7	0	0	0	0	0	0	0	0	0	0	0
1	0	0	0	0	1	0	0	0	0	0	0

Basins of attractions



Comparison with random networks



- The cell cycle is compared with a random network with the same number of links of the same colors as in the cell cycle
- The distribution of basin sizes is scale-free with a probability to have a basin of attraction as large as the one find for the model of 10%
- The total 'traffic' per arrow measured through the quantity w_n is much larger in the cell cycle than in a random network

From small scale to large scale

Topology

Dynamics

Ex. Regulatory network

Metabolic network

Regulatory network

Motifs

Michael-Mentens dynamics

Percolation of motifs and

Modularity

Flux Balance Analysis (continuous variables)

Boolean networks (boolean variables)

Scale-free (fat tail) degree distribution

From random to designed networks

- Fixed connectivity networks
- Poisson (Erdos and Renyi) networks
- Scale-free networks Metabolic, protein interaction networks Transcription networks (fat tails)

- Motifs -characteristic subgraphs in real networks which are related to the function of the network.
- Communities in the networks

The statistical physics and evolutionary dynamics

Raising the challenging question

What is Life?

Erwin Schrödinger,1944

Statistical Mechanics

More is different

P. A. Anderson in Science 1972

Evolutionary Dynamics

Everything in the Universe is the fruit of chance and necessity

(Democritus Cited by Jacques Monod in “Chance and necessity” 1970)

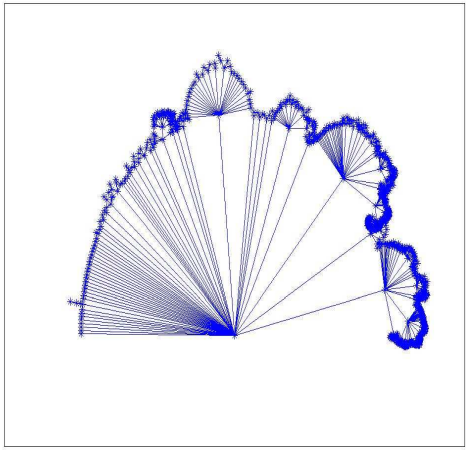
Bose-Einstein condensation in models of evolution

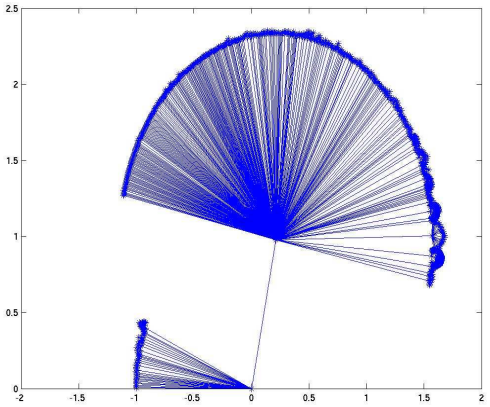
- Bose-Einstein condensation transition in the Kingman model
(J. F. C. Kingman 1978)

- Bose-Einstein condensation in complex evolving complex networks
(G. Bianconi and A.L. Barabasi PRL 2001)

- Bose-Einstein condensation in evolving ecosystems
(G. Bianconi, L. Ferretti, S. Franz EPL 2009)

- Bose-Einstein condensation in model of asexual evolution and pleiotropy
(S. N. Coppersmith, R. D. Blanck and L. P. Kadanoff 2004)





The Kingman model of asexual evolution

Mutations compete with selection in determining the genetic diversity of the population

- Every individual has a reproductive rate $w=e^{-\beta\varepsilon}$

- A mutation occur with probability ν

- When the new mutation occur the new reproductive rate is drawn at random from a distribution $\rho(w)$

The Kingman model

$w = e^{-\beta\varepsilon}$	Average reproductive number of a strain
ε	Fisher fitness of a strain
β	Selection pressure
ν	Rate of mutation

$$p^{t+1}(\varepsilon) = (1-\nu)\frac{1}{\left\langle e^{-\beta\varepsilon}\right\rangle} e^{-\beta\varepsilon}\, p^{t}(\varepsilon) + \nu\rho(\varepsilon)$$

Bose-Einstein distribution in the Kingman model

Stationary distribution

$$p(\varepsilon) = \nu \frac{\rho(\varepsilon)}{1 - e^{-\beta\varepsilon}(1-\nu)\Big/\left\langle e^{-\beta\varepsilon}\right\rangle}$$

Normalization condition

$$1 = \int d\varepsilon\, p(\varepsilon) = \nu\left[1 + \int d\varepsilon \frac{\rho(\varepsilon)}{e^{\beta(\varepsilon-\mu)} - 1}\right]$$

$$e^{-\beta\mu} = \left\langle e^{-\beta\varepsilon}\right\rangle/(1-\nu)$$

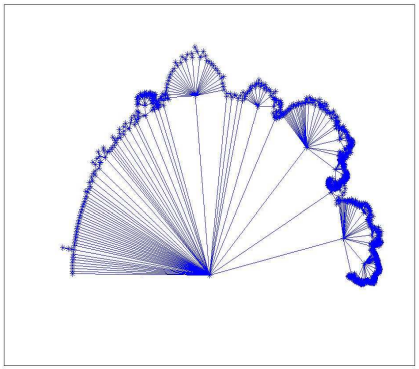
Bose-Einstein condensation in the Kingman model

When the mutation rate is below a critical value and the selection pressure is above a critical value
a finite fraction of individuals in the population have maximal fitness

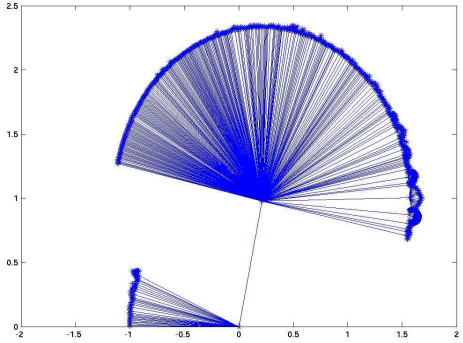
This phase transition it is usually called in the literature quasi-species transition

Bose-Einstein condensation in growing scale-free networks

In evolving network nodes have a fitness indicating their ability to acquire new links



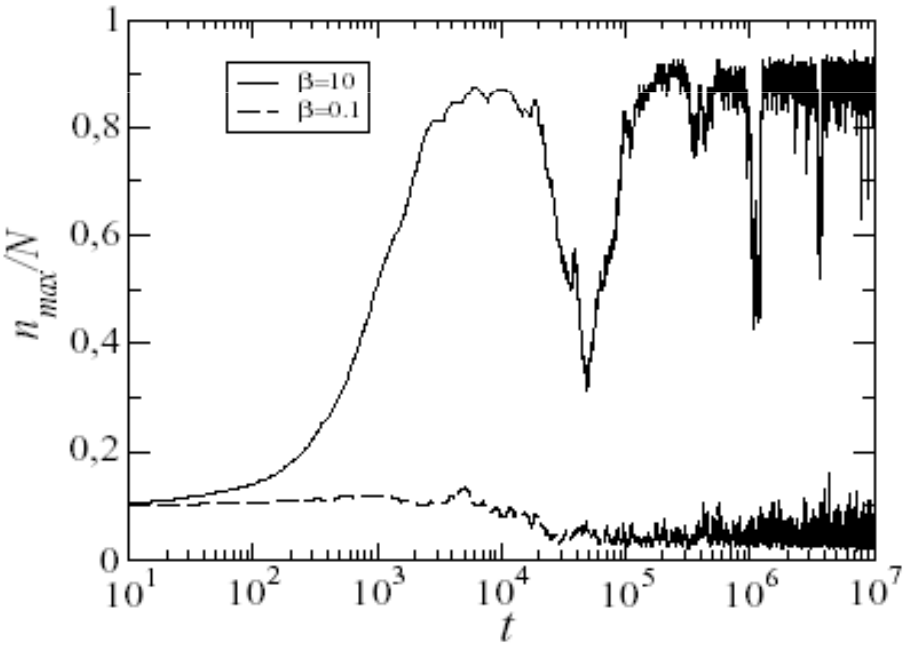
Below the Bose-Einstein condensation transition the most connected node has a finite fraction of all the links



Bose-Einstein condensation in ecology in presence of invasive species

In presence of invasive species there can be a Bose-Einstein condensation in ecological system

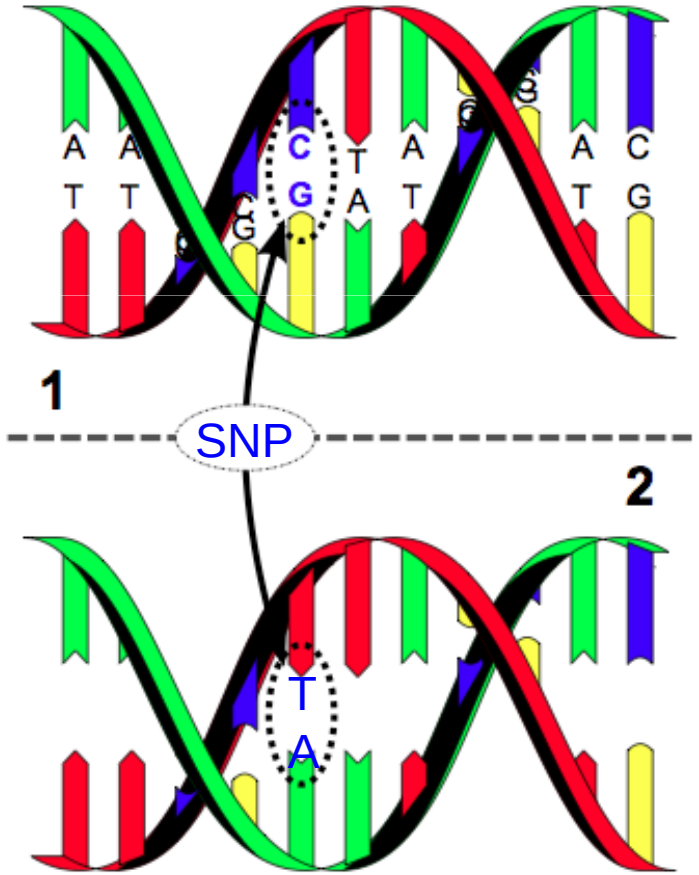
When the condensation occur a finite fraction of individuals of the ecology belongs to the invasive species



Bianconi,Ferretti,Franz EPL 2009

Single nucleotide polymorphisms (SNPs)

SNPs are single nucleotide (CTAG) variations occurring in more than 1% of the population



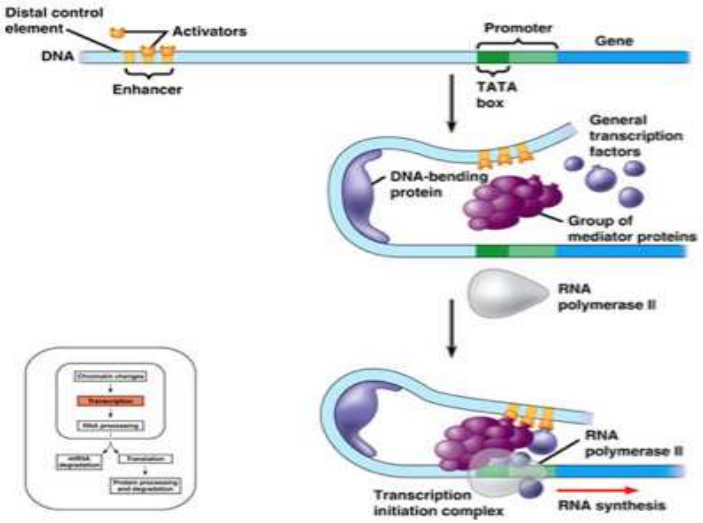
SNPs

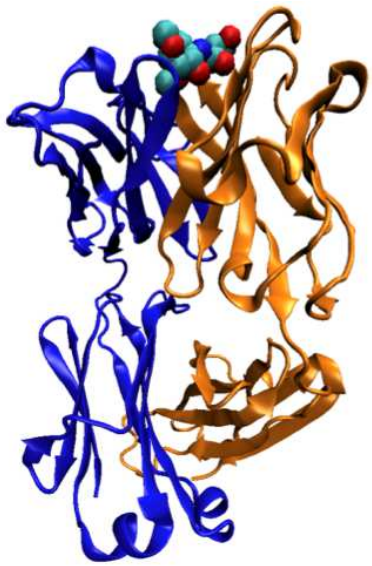
- SNPs might occur
  - ***in the coding region of a gene,***
  - ***in non-coding region of a gene***

- In humans, we have
  - ***5 millions SNPs over a genome of 3 billion base-pairs.***

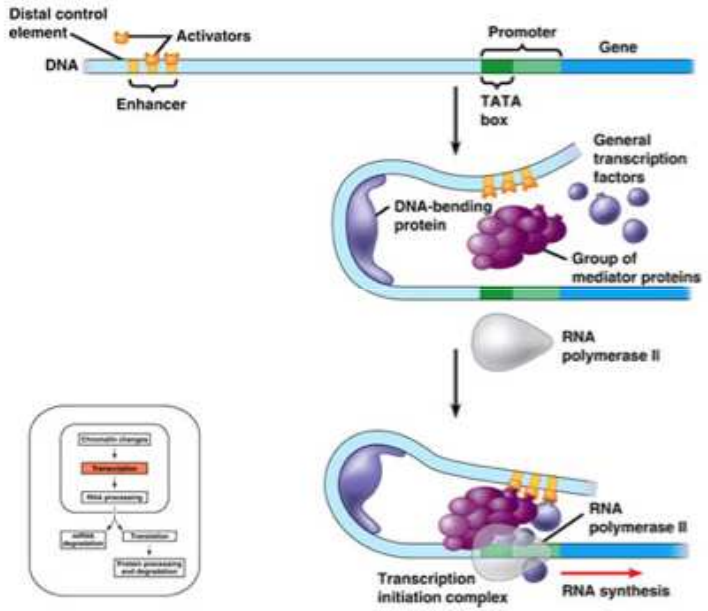
- SNPs
  - ***can affect the the genetic risk for diseases and the response to pathogens and drugs.***

SNPs interact with the complexity of molecular networks encoding for the map between genotype and phenotype.



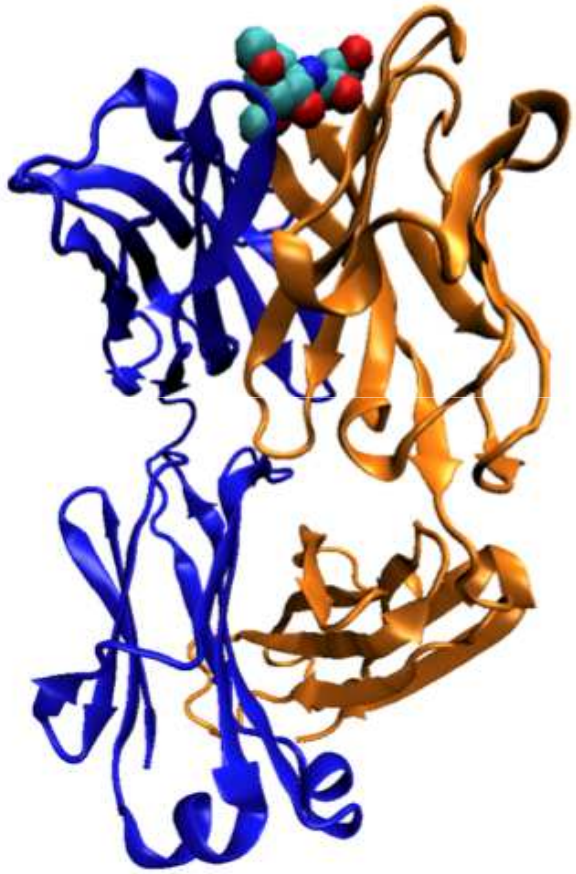


SNPs and transcription networks



A SNP in the promoter region of a gene might change the binding affinity of the transcription factor and introduce a perturbation in the transcription network

SNPs and metabolic networks



SNPs in the coding region
might change
the amino acid composition of
the coded protein
and introduce perturbations in
the katalysis of
chemical reactions or binding of
other proteins

More is different:

The importance of epistatic interactions

Linkage disequilibrium

In a given population,

for each pair of SNPs, (i,j)

with joint allelic frequency $p_{ij}(x_i,x_j)$,

linkage disequilibrium is defined as

$$LD_{ij} = p_{ij}(x_i,x_j) - \sum_{x,x'} p_i(x_i x') p_j(x,x_j)$$

Epistatic interactions

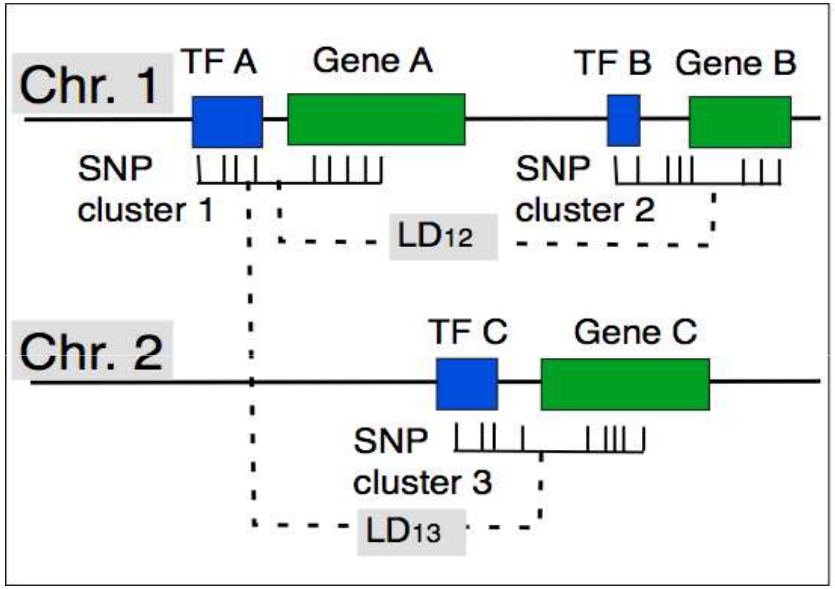
Definition

Epistatic interactions are the non additive contributions that two mutations or genetic variations have on the fitness of one organism

Sign of the epistatic interaction

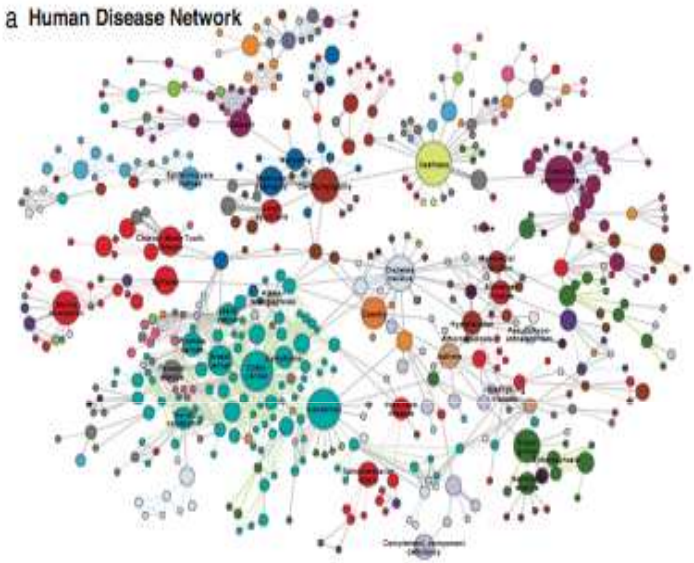
Epistatic interactions can have synergistic, neutral or antagonistic effects.

Epistatic interactions between SNPs



- SNP are organized in cluster in complete linkage equilibrium
- Different cross-over rates cannot explain linkage disequilibrium between very distant SNPs along the same chromosome or in different chromosomes

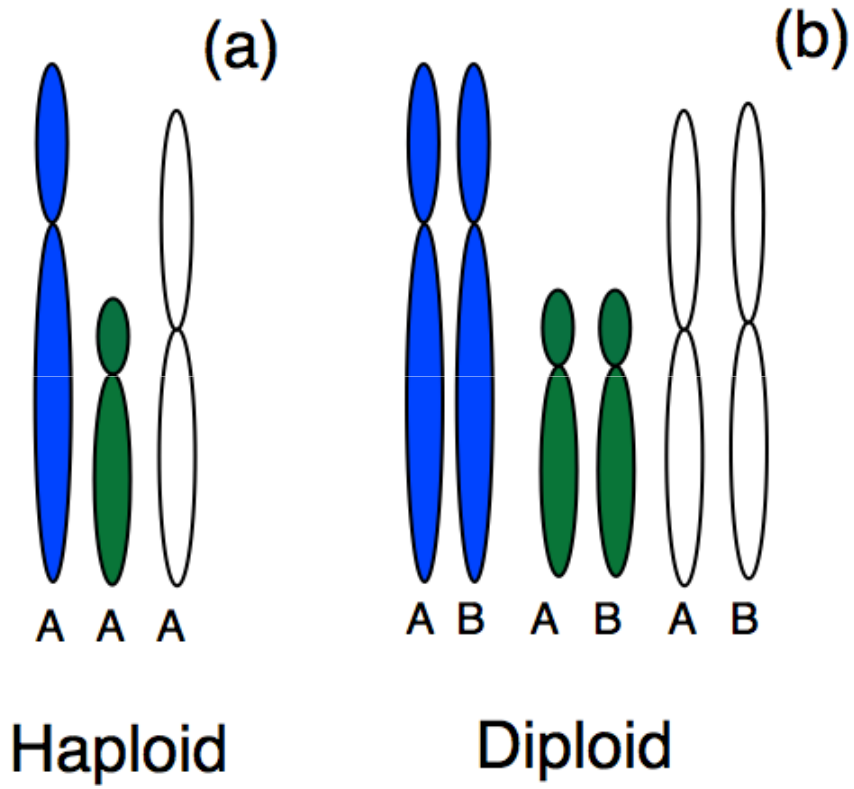
Phenotypes and diseases in Humans



Human Diseasome

- **Most of the disease are complex, i.e. they are due to a large set of genetic loci**
- **Each gene might contribute to the risk of developing different diseases**
- **Uncovering the epistatic network in humans might be essential to prevent diseases and advance in the personalized medicine**

Diploid species



Diploid species have two copies of each chromosome one coming from the father gamete and one coming from the mother gamete

Fitness function without epistasis

$\{x\} = x_1, x_2, \ldots, x_N$

$x_i = 1,2,3,4\ (C,G,T,A)$

Gametes with N genetic loci

$\{x^A\}, \{x^B\}$

Parental gametes

$$W\{x^A, x^B\} = \prod_i \varphi_i(x_i^A, x_i^B)$$

Fitness function with pairwise epistatic interactions

$\langle i, j \rangle$ Pair of genetic loci in epistatic interaction

β Selective pressure

$$W\{x^A, x^B\} = \prod_{\langle i,j \rangle} e^{-\beta U_{ij}(x_i^A, x_j^A, x_i^B, x_j^B)}$$

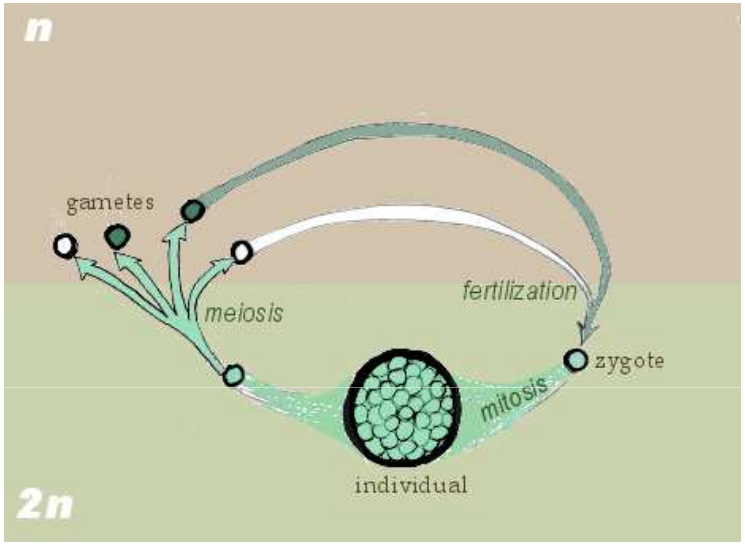
Symmetries also called ‘Robbins proportions’

$$U_{ij}(x, \bar{x}, x', \bar{x}') = U_{ij}(x', \bar{x}', x, \bar{x})$$

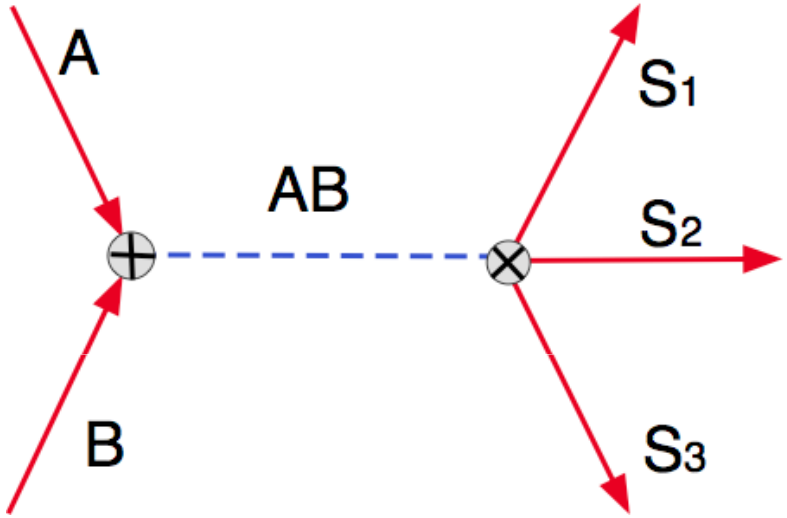
$$U_{ij}(x, \bar{x}, x', \bar{x}') = U_{ij}(x, \bar{x}', x', \bar{x})$$

Gametic cycle

Biological view



Physical view



Gamete

Zygote

Individual

Meiosis

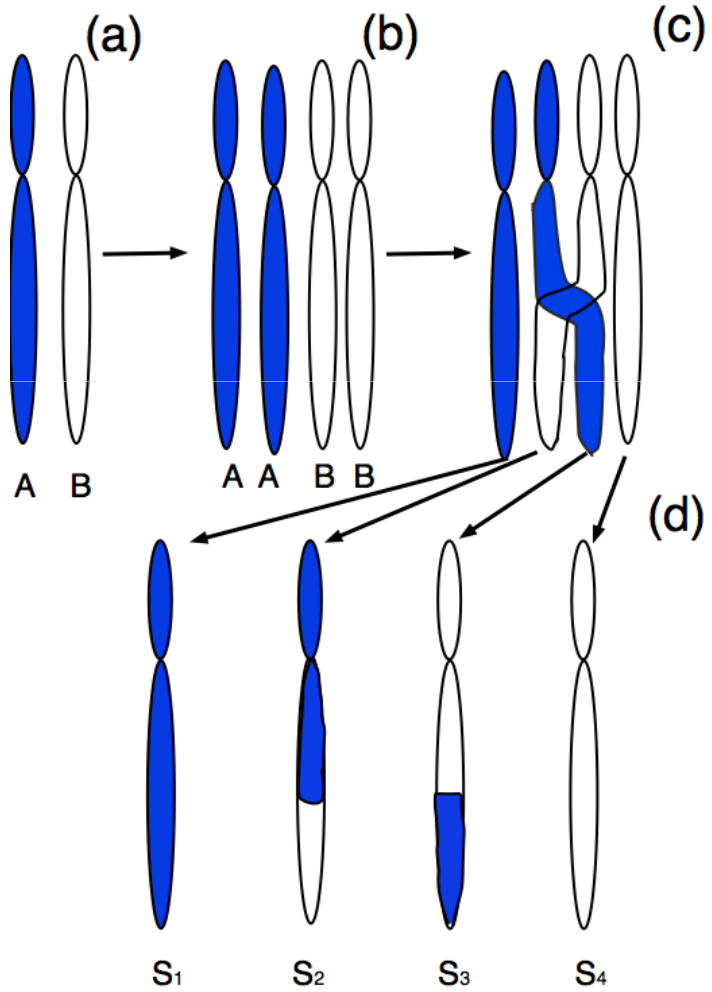
G. Bianconi and O. Rotzschke PRE 2010

Chance and Necessity

Recombination processes
versus selection

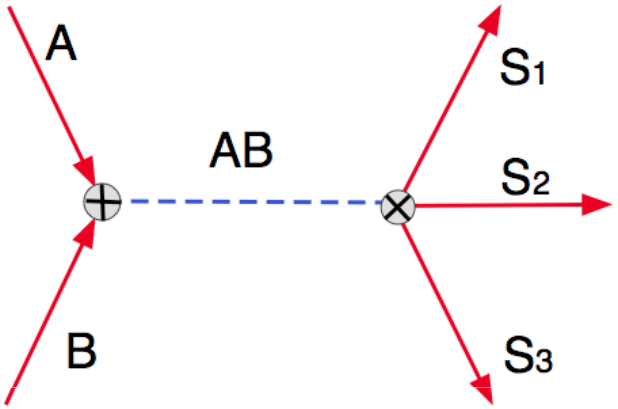
Meiosis

During meiosis
the gametes
of each individual are
formed by a combined
process of
crossing-over and
recombination



Evolution of diploid populations

$P(\{x\})$ Frequency of gametes with allelic configuration {x}



Evolutionary dynamics

$$\frac{dP(\{x\})}{dt} = M_{\{x\}|\{x^A,x^B\}}\left[\frac{W(\{x^A,x^B\})P(\{x^A\})P(\{x^B\})}{\langle W\rangle}\right] - P(\{x\}) \quad \text{with}$$

$$M_{\{x\}|\{x^A,x^B\}}\left[f(\{x^A,x^B\})\right] = \sum_{\{x^A,x^B\}}\prod_i\left(\frac{1}{2}\delta(x_i,x_i^A)+\frac{1}{2}\delta(x_i,x_i^B)\right)f(\{x^A,x^B\})$$

G. Bianconi and O. Rotzschke PRE 2010

Steady state equation

The steady state equation is therefore given by

$$P(\{x\}) = M_{\{x\}|\{x^A,x^B\}}\left[\frac{W(\{x^A,x^B\})P(\{x^A\})P(\{x^B\})}{\langle W\rangle}\right]$$

With the marginals defined as in the following

$$p_{ij}(x,x') = \sum_{\{x\}} P(\{x\})\delta(x_i,x)\delta(x_j,x')$$

Structure of the solution on a locally tree-like epistatic network

On a tree-like network the general solution of the evolutionary dynamics will be of the type

$$P(\{x\}) = \sum_{h} \prod_{\langle i,j \rangle} b_{ij}^{(h)}(x_i, x_j)$$

To solve the problem by analytic methods we look for solution of the stationary distribution of the type

$$P(\{x\}) = \prod_{\langle i,j \rangle} b_{ij}(x_i, x_j)$$

Multiple solutions of the self-consistent equation

The cavity equations and the self consistent equation can be used to find the functions $b_{ij}(x_i,x_j)$

$$b_{ij}(x_i,x_j)=\frac{G_{ij}(x_i,x_j)/F_{ij}(x_i,x_j)}{\langle W\rangle Z_{i|j}(x_i)Z_{j|i}(x_j)/F_{ij}(x_i,x_j)-1}$$

These equations have multiple solutions

Therefore the asymptotic state of the population depends on the initial conditions

Bose-Einstein distribution of the marginal probability of pairs of genetic loci

$$p_{ij}(x_i, x_j) = \frac{1}{\langle W \rangle} G_{ij}(x_i, x_j)\left[1 + n_B(\varepsilon_{ij}(x_i, x_j))\right]$$

$$n_B(\varepsilon) = \frac{1}{e^{\beta[\varepsilon(x_i, x_j) - \mu]} - 1}$$

When $\varepsilon_{ij}(x_i, x_j) = \mu$ the pair of linked loci go to fixation

Condensation as a function of the selective pressure

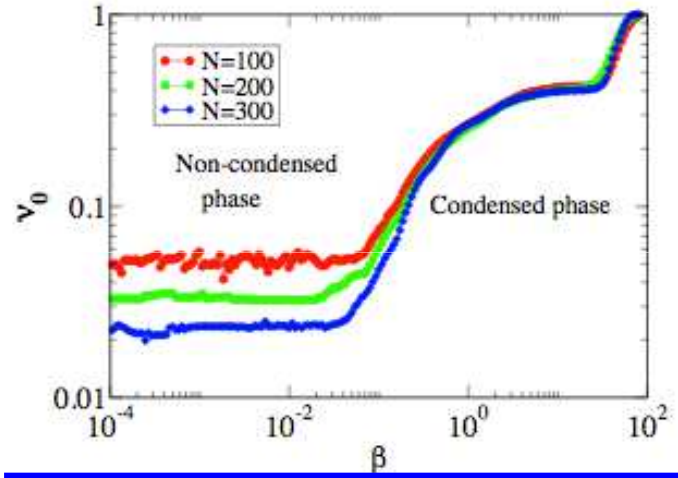
Normalization condition

$$\sum_{x_i, x_j} p_{ij}(x_i, x_j) = 1$$

$$(1-\nu_{ij}) = \frac{1}{\langle W \rangle} \sum_{x_i, x_j} G_{ij}(x_i, x_j)\left[1 + n_B(\varepsilon_{ij}(x_i, x_j))\right]$$

Averaging over all the pairs of SNPs

$$1-\nu_0 = \frac{1}{\langle W \rangle} \int d\varepsilon\, g(\varepsilon)\left[1 + n_B(\varepsilon)\right]$$



A finite fraction ν_0 of linked pairs of SNPs go to fixation for high selection pressure

Conclusions

Biological networks structure and dynamics constitute the richness of living systems.

The complexity of biological networks is reflected at different scales and in their dynamical behavior.

Understanding the interplay between genomic information and biological network can shed light on the genotype-phenotype mapping with relevant future application for devising a personalized medicine.

New developments of the theory of evolution will include the general principles of complex system evolution and the recent new finding about biological and epistatic networks.

Binding of the inducer to the repressor

$$X + Sx \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} [XS_X] \qquad X + [XS_X] = X_T$$

Steady state:

$$X\, S_X\, k_{on} = [XS_X] k_{off}$$

Michaelis-Menten equation

$$[XS_X] = X_T \frac{S_x}{S_X + K_X} \qquad K_X \approx 1{,}000$$

Inducer molecules /cell

$$X^* = X_T \frac{1}{1 + \frac{S_X}{K_X}}$$

Active repressor

Cooperativity of inducer binding
Hill equation

Most transcription factors are composed y several repeated subunits for examples dimers or tetramers. For activating a transcription factor usually all subunits must bound to the inducers.

$$X + nSx \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} [nXS_X]$$

$$[nXS_X] = X_T \frac{S^n{}_x}{S^n{}_X + K^n{}_X}$$

Hill equation

$$X^* = X_T \frac{1}{1 + \left(\frac{S_X}{K_X}\right)^n}$$

Active repressor

Input-function of a gene regulated by a repressor

The input function describes the rate of transcription as a function of the inducer S_X

$$f(S_X) = \beta \frac{K_d}{K_d + X^*} = \beta \frac{K_d}{K_d + X_T \dfrac{1}{1 + (S_X / K_X)^n}}$$

X* -X active- not bound to S_X

The input function reaches half maximal value at

$$S_{1/2} \approx (X_T / K_d)^{1/n} K_X$$

$S_{1/2}$ can be significantly larger than K_X

Input-function of a gene regulated by an activator

The input function describes the rate of transcription as a function of the inducer S_X

$$f(S_X) = \beta \frac{X^*}{K_d + X^*} = \beta \frac{1}{K_d[1 + (K_X / S_X)^n] / X_T + 1}$$

X* -X a active- bound to S_X

The input function reaches half maximal value at

$$S_{1/2} \approx (K_d / X_T)^{1/n} K_X$$

$S_{1/2}$ can be significantly smaller than K_X

Negative auto-regulation

- 34 negative auto-regulations occurrences in e. coli transcription network
- Why is negative auto-regulation a motif?

$$\frac{dX}{dt} = \beta \frac{K_d}{K_d + X} - \alpha X \approx \beta \frac{K_d}{X} \qquad Y >> K_d$$

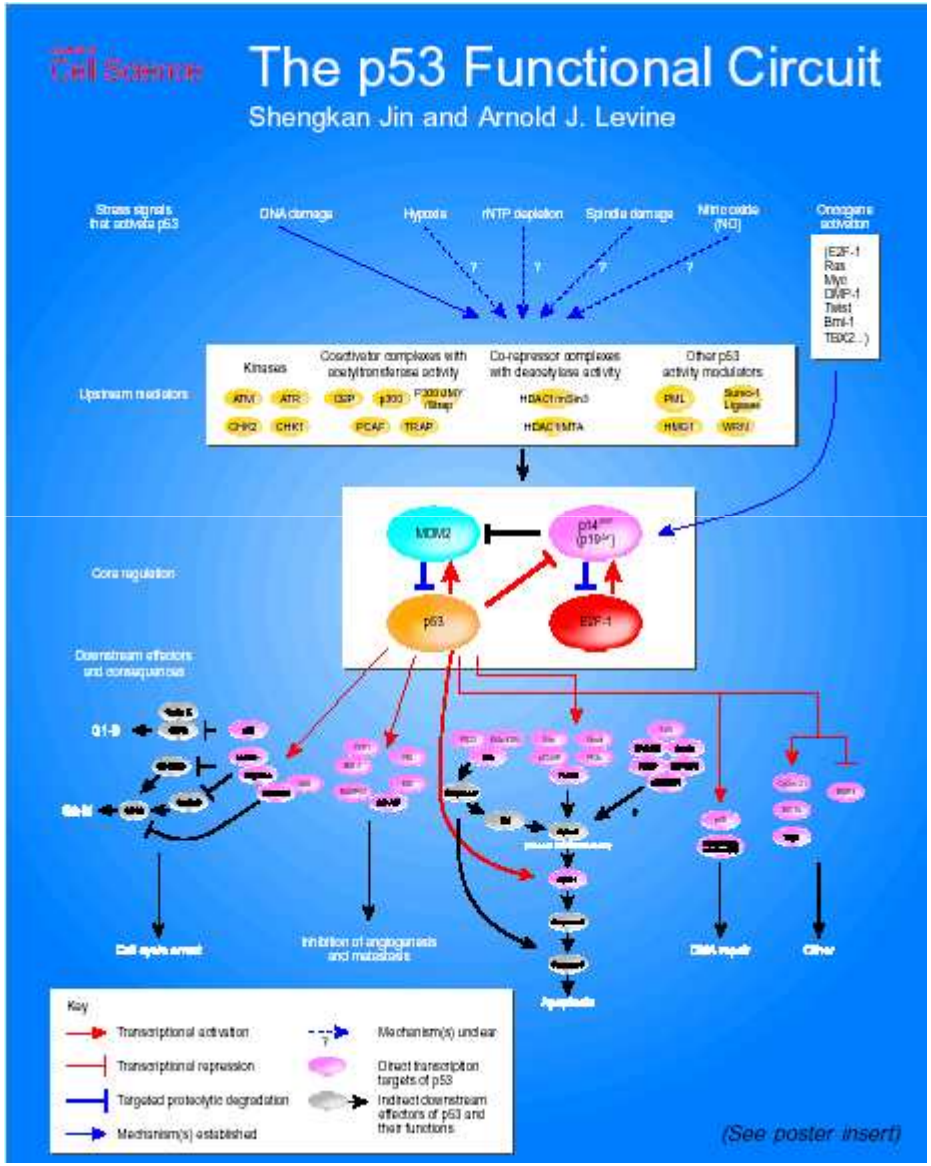
The dynamic of this simplified equation is

$$X(t) = X_{st}\sqrt{1 - e^{-2\alpha t}} \quad X_{st} = \sqrt{\beta \frac{K_d}{\alpha}}$$

The response time is reduced in a relevant way!

$$T_{1/2} = \log(4/3)/2\alpha \approx 0.2 T_{1/2}^{simple}$$

P53 network



p53 is a tumor suppressor gene that plays the role of safeguarding the integrity of the genome.

Is inactivated in almost all cancers

p53 is a binding TF kept at low level in cells under normal conditions

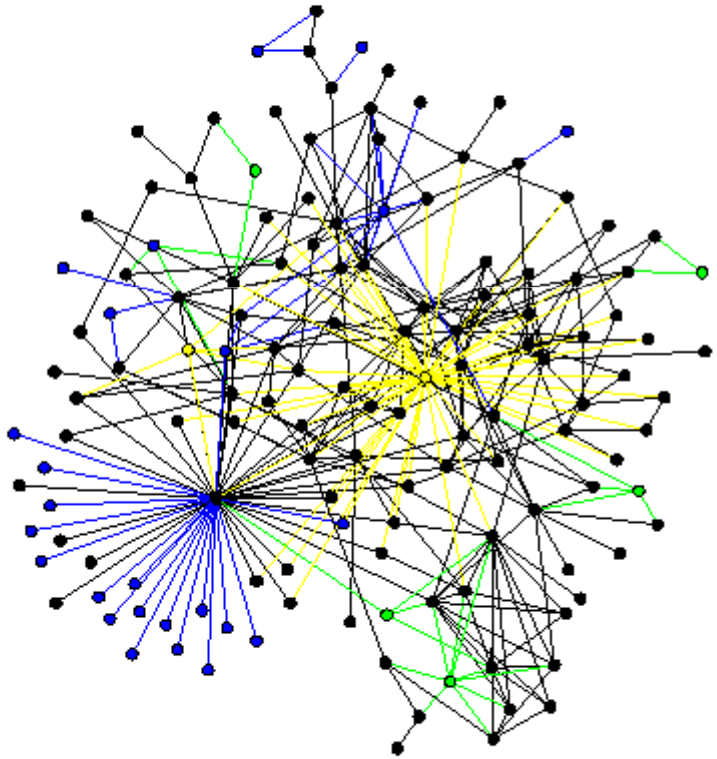
Various stress signals like DNA damage can activate p53

p53 activates tumor suppressing functions as cell cycle arrest, apoptosis, DNA repair ,inhibition of angiogenesis and metastasis

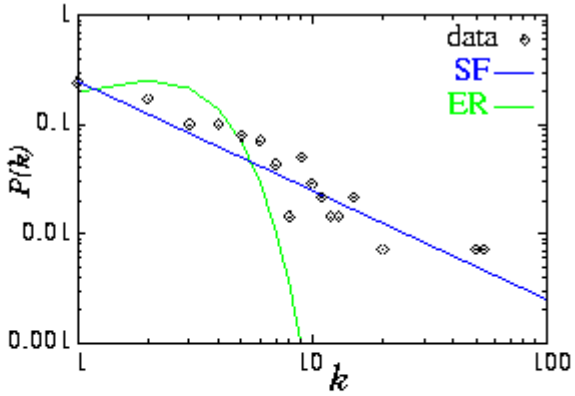
Two feedback loops are the core of the network

p53 network

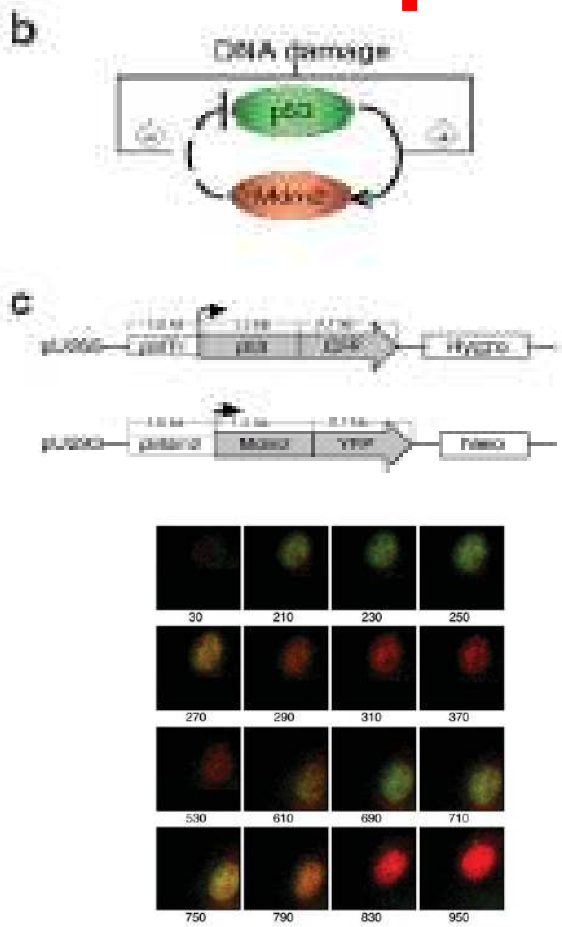
(mammals)



Degree distribution of the p53 network



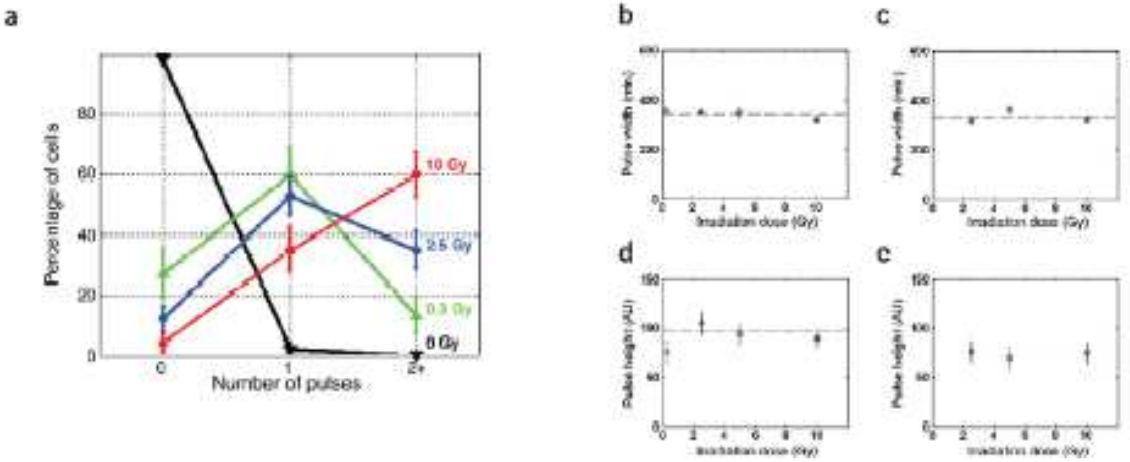
Dynamics of p53-Mdm2 feedback loop in individual cells

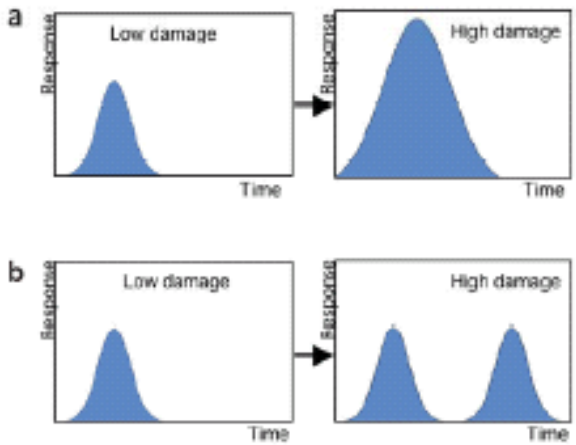


- The authors generated stable cells lines that expressed p53 and Mdm2 fused to fluorescent proteins
- P53 fused with CFP (cyan fluorescent promoter) Mdm2 fused with yellow fluorescent protein (YFP)
- They were able to observe damped oscillations of expression of p53-mdm2.
- There oscillations could be one or more

Lahav et al. Nature Genet. 2004

Non-analogic behavior under stress



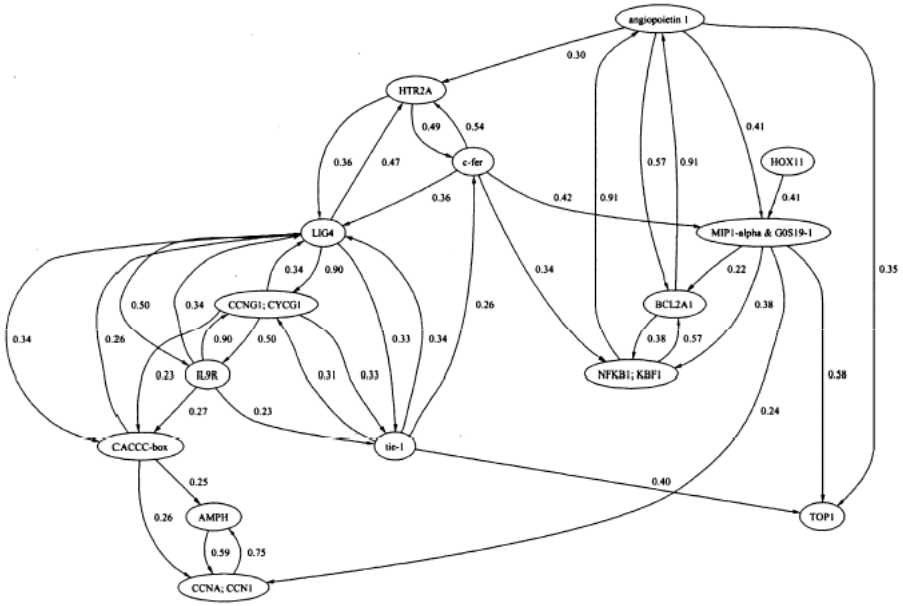


Fraction of cells with zero, one, two or more pulses as a function of g irradiation.

The irradiation dose dependency of the width of first and second pulse and the height of the first and second pulse is compatible with a digital behavior of the p53 oscillations a as response to stress.

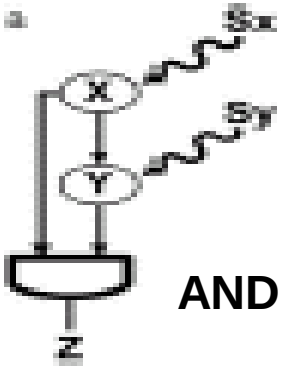
Glioma network

- **This technique would be useful to design target drugs to perturb the state of the cell (for example a tumor cell) in the desired state.**
- **In particular probabilistic boolean networks would provide the information about the timing of the effect of a perturbation on one particular gene which is a crucial problem in many pharmaceutical applications**

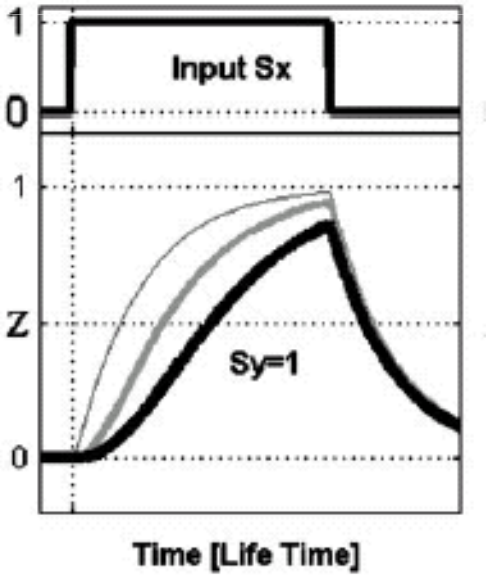


For a review I. Schmulevic et al. Proc. IEEE,90 (2002)

Type 1 FFL-AND



AND



S_X increases ⇒ X* at saturation
Y increases exponentially in time and only when it cross the activation value K_{dzy} it activates Z

⇒ delay in Z production when increasing S_X

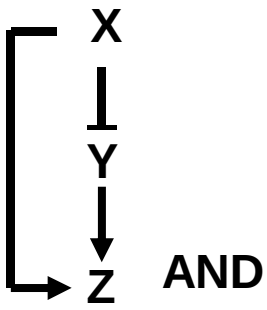
When SX goes to zero X* goes to zero

⇒ immediately Z production goes to zero

The type 1 FFL is a sign-sensitive delay element

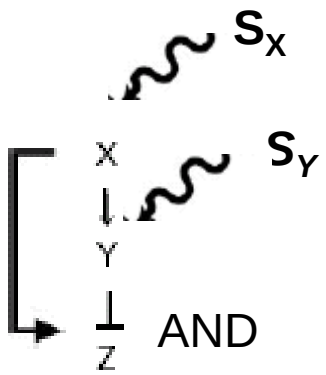
Some FFL are badly malfunctioning

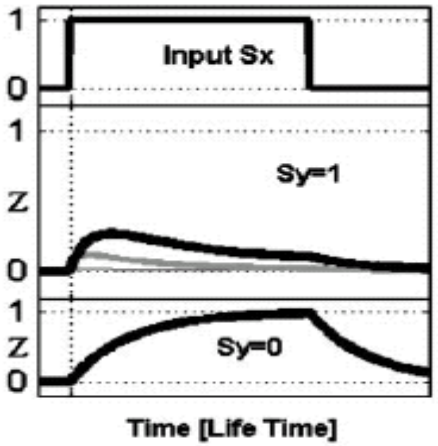
For example the 4-Type IFFL is insensitive to the presence of the inducer S_Y



S_X	S_Y	4IFFL
0	0	0
0	1	0
1	0	0
1	1	0

Type 1 IFFL-AND





Dynamics with S_Y=1

X* is at saturation.

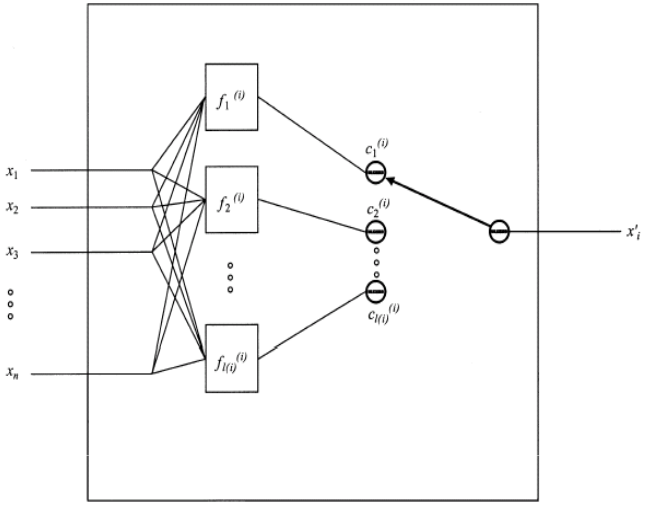
While Y(t) increases Z(t) increases also.

When Y(t)>K_{dzy} Z(t) start to decrease.

The Type1IFFL-AND acts as a weak pulse generator

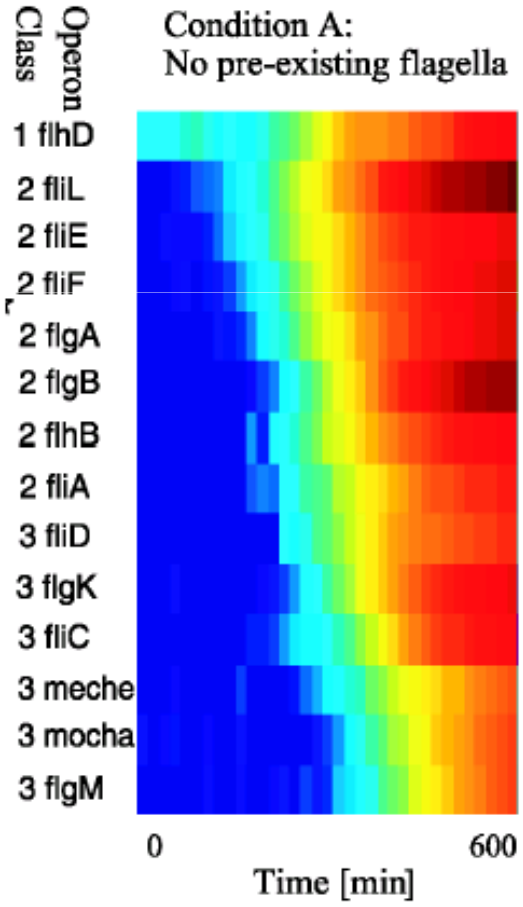
Probabilistic boolean networks

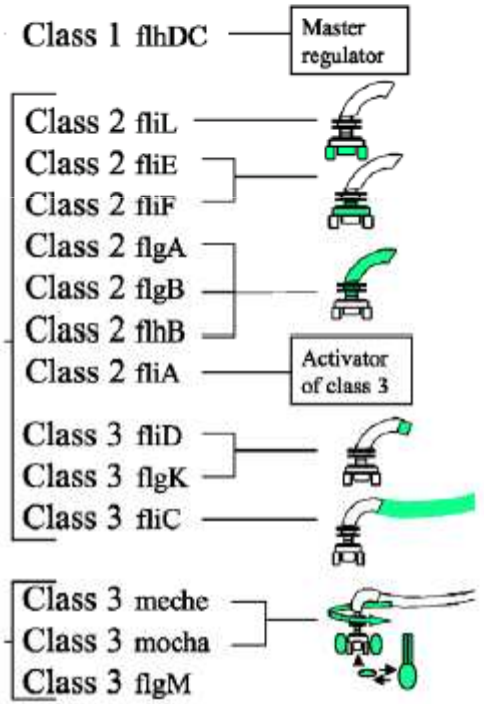
- **Given the data in a probabilistic boolean network one wants to find the nature of the boolean functions and their wiring which gives the results closer to the real data.**
- **The goal of probabilistic boolean network is to infer minimal dependencies between the genes which is still able to describe the data and infer form a bottom-up approach the structure and nature of the regulatory interaction with reasonable error**



To make the convergence of the search faster one doesn't look for the best boolean function for each gene but for a set of plausible boolean functions to use with probability c_i

Single input motif is responsible for the timing of flagella assembly





Kalir et al. Science 2001