Systems Biology: A Personal View
IX. Intra-cellular Systems I: Regulatory Networks and Motifs

Sitabhra Sinha
IMSc Chennai

Intra-cellular biochemical networks

- Metabolic networks
  Nodes: metabolites (substrates & products of metabolism)
  Links: chemical reactions (directed)
- Genetic regulatory networks
  Nodes: Genes & Proteins
  Links: regulatory interactions (directed)
- Protein-Protein interaction network
  Nodes: Proteins
  Links: physical binding and formation of protein complex (undirected)
- Signaling network
  Nodes: Signaling molecules e.g., kinase, cyclicAMP, Ca
  Links: chemical reactions (directed)

Intra-cellular biochemical networks

- ☐ Metabolic networks
  Nodes: metabolites (substrates & products of metabolism)
  Links: chemical reactions (directed)
- ☐ **Genetic regulatory networks**
  Nodes: Genes & Proteins
  Links: regulatory interactions (directed)
- ☐ Protein-Protein interaction network
  Nodes: Proteins
  Links: physical binding and formation of protein complex (undirected)
- ☐ Signaling network
  Nodes: Signaling molecules e.g., kinase, cyclicAMP, Ca
  Links: chemical reactions (directed)

Macroscopic properties such as avg path length and avg clustering tell us only about coarse-grained features of the network… to know how one part of the network behaves in relation to the others we need a more detailed view… We can focus on the properties of interactions between a few nodes of the network at a time

Microscopic properties of networks

Example: Motifs

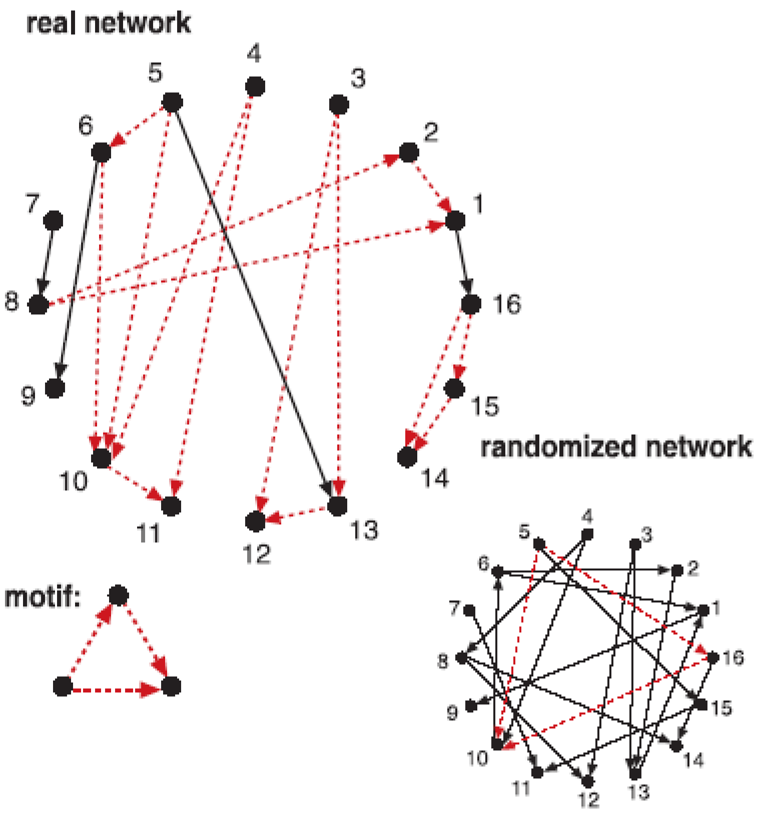
The network may be built out of putting together commonly occurring circuits

What are motifs ?

Subnetwork connection patterns that occur more frequently than expected in an equivalent random network

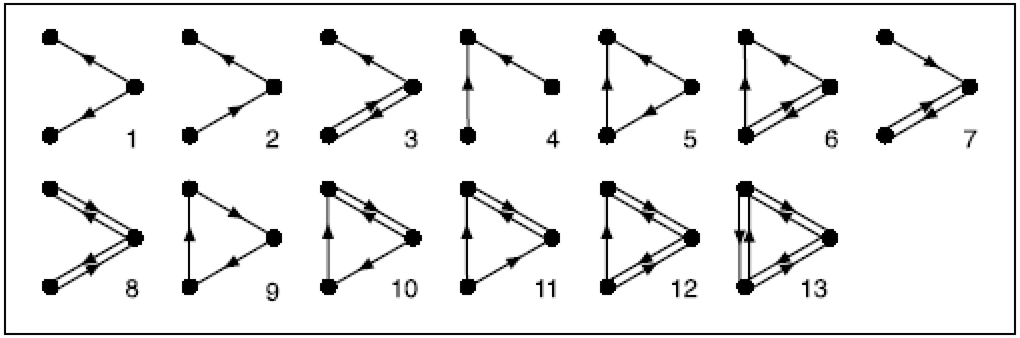
Motifs: recurring subnetworks of interactions

R Milo et al, Science 298 (2002) 824



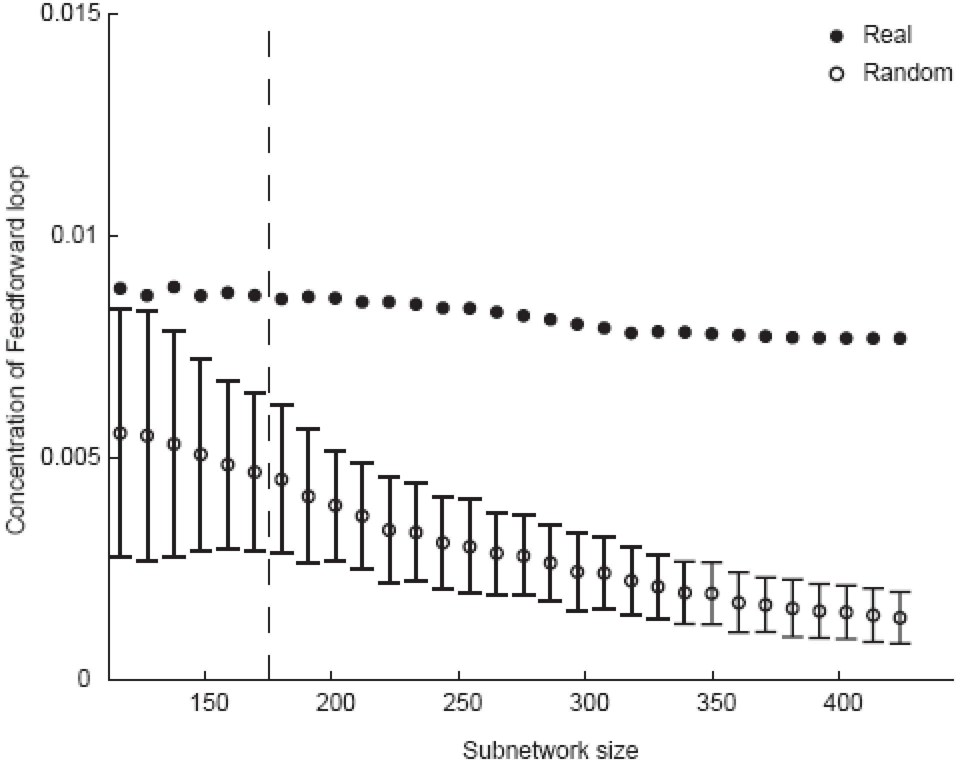
Each network motif may carry out specific functions

- Feed-forward loops
- Single-input modules
- Multi-input motifs



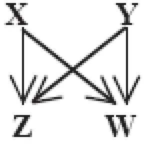
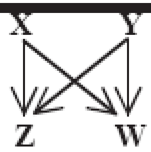
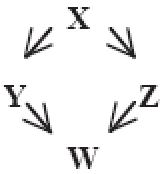
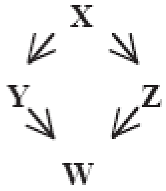
All connected three-node subgraphs

R Milo et al, Science 298 (2002) 824



Network motifs found in Biological Networks

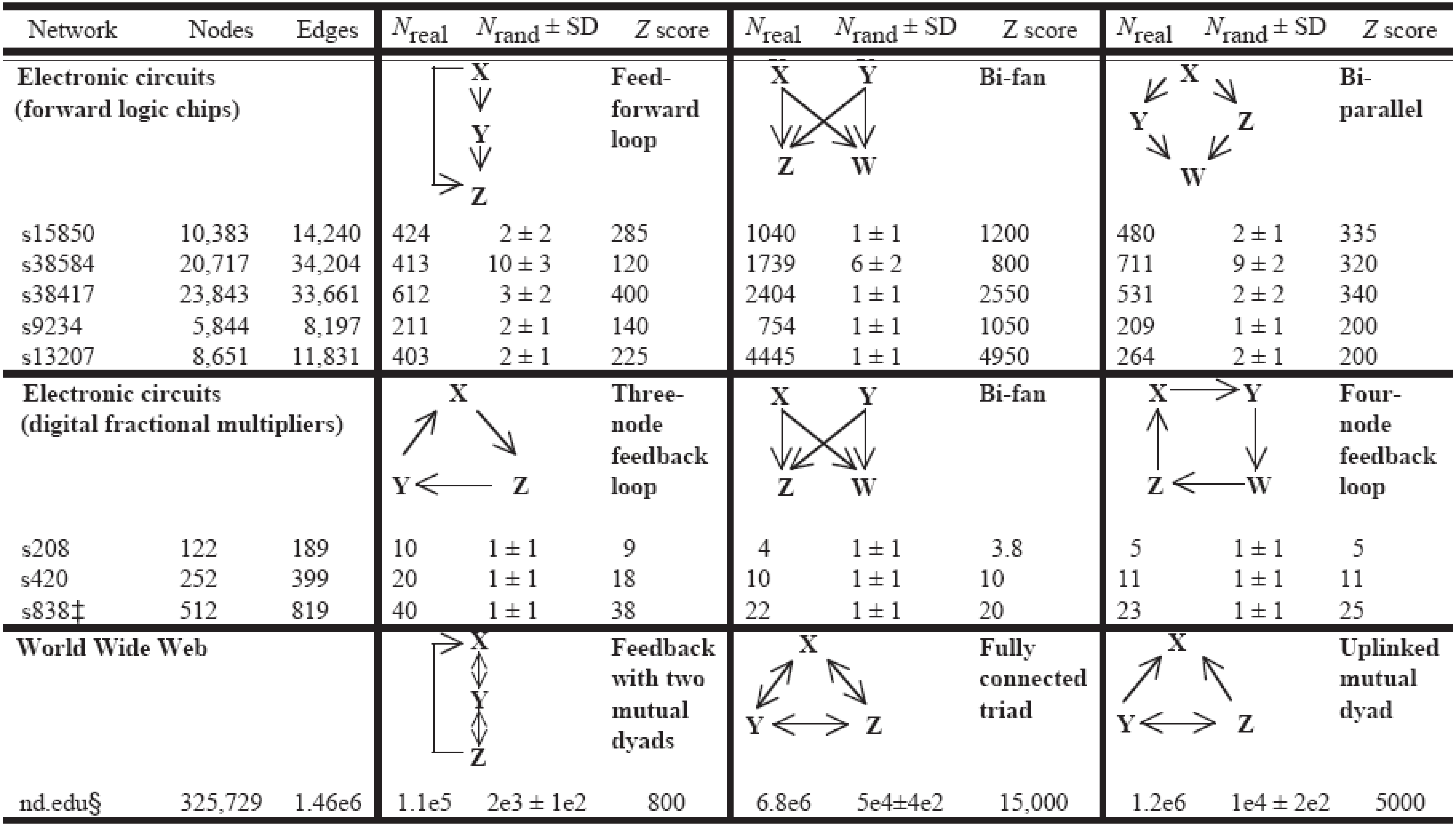
R Milo et al, Science 298 (2002) 824

Network	Nodes	Edges	N_{real}	N_{rand} ± SD	Z score	N_{real}	N_{rand} ± SD	Z score	N_{real}	N_{rand} ± SD	Z score
Gene regulation (transcription)					**Feed-forward loop**			**Bi-fan**			
E. coli	424	519	40	7 ± 3	10	203	47 ± 12	13			
*S. cerevisiae**	685	1,052	70	11 ± 4	14	1812	300 ± 40	41			
Neurons					**Feed-forward loop**			**Bi-fan**			**Bi-parallel**
C. elegans†	252	509	125	90 ± 10	3.7	127	55 ± 13	5.3	227	35 ± 10	20
Food webs					**Three chain**			**Bi-parallel**			
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			

For comparison, let us look at

Network motifs found in Technological Networks

R Milo et al, Science 298 (2002) 824



Network	Nodes	Edges	N_{real}	N_{rand} ± SD	Z score	N_{real}	N_{rand} ± SD	Z score	N_{real}	N_{rand} ± SD	Z score
Electronic circuits (forward logic chips)					**Feed-forward loop**			**Bi-fan**			**Bi-parallel**
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
Electronic circuits (digital fractional multipliers)					**Three-node feedback loop**			**Bi-fan**			**Four-node feedback loop**
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
World Wide Web					**Feedback with two mutual dyads**			**Fully connected triad**			**Uplinked mutual dyad**
nd.edu§	325,729	1.46e6	1.1e5	2e3 ± 1e2	800	6.8e6	5e4±4e2	15,000	1.2e6	1e4 ± 2e2	5000

Example: Transcription Regulation Networks

☐ Each gene expresses a protein
☐ Some genes express proteins which control (promoting or suppressing) the rate at which other genes express proteins
☐ Thus genes can regulate each other (via the proteins they express)

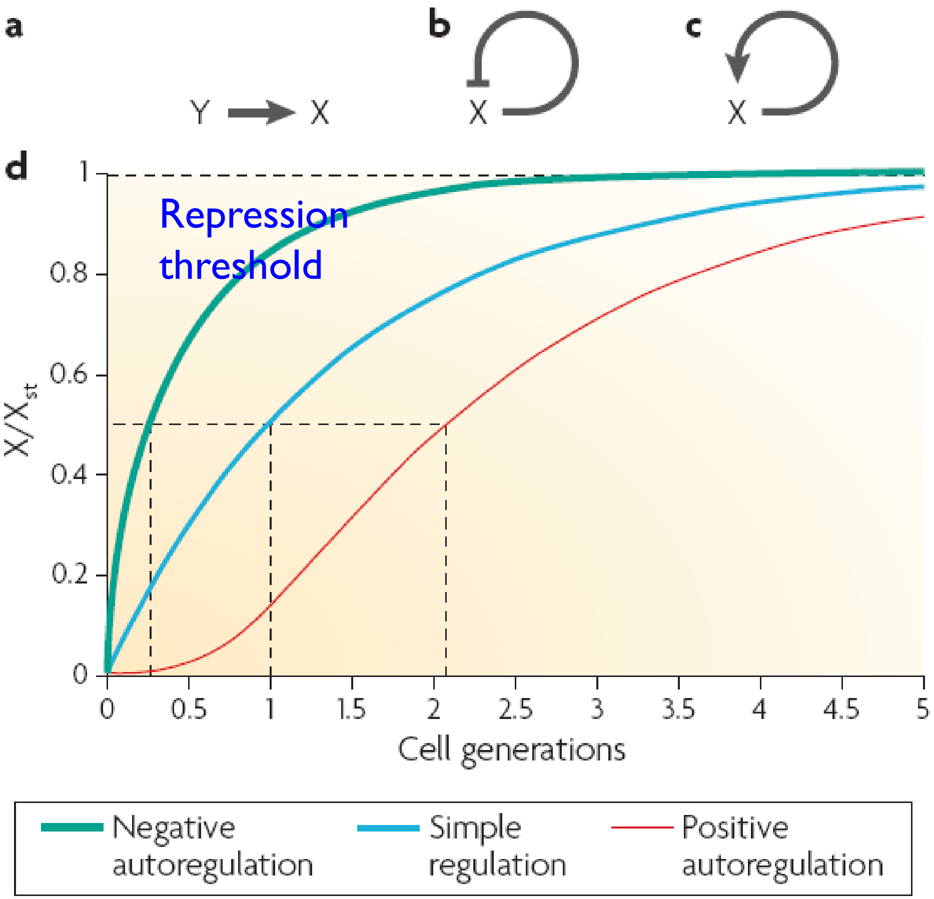
Gene or Transcription Regulation Network: A pair of genes are connected if the expression of one gene modulates expression of another one by either activation or inhibition

- Controls expression of genes
- Interaction between transcription factor proteins and the genes they regulate
- In response to signals, transcription rate of genes varied → allow cells to make proteins at appropriate times and amounts

The network is built out of commonly occurring regulation circuits (motifs)

Simple regulation and Positive & Negative Autoregulation

Alon, Nature Rev Genetics 8 (2007) 450



Repression threshold

Negative autoregulation:

Transcription factor (TF) represses its own promoter

Faster response time relative to simple regulation

Positive autoregulation:

TF activates its own promoter

Slower response time

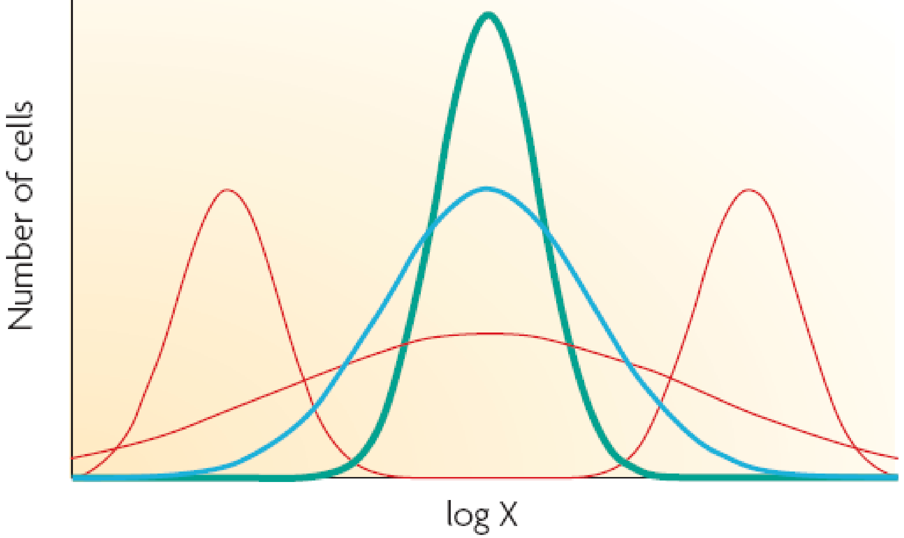
characteristic sigmoid activity profile

Cell-cell distribution of protein levels:

Negative autoregulation ⇒ sharply peaked distribution

Positive autoregulation ⇒ broadly peaked or bimodal distributions

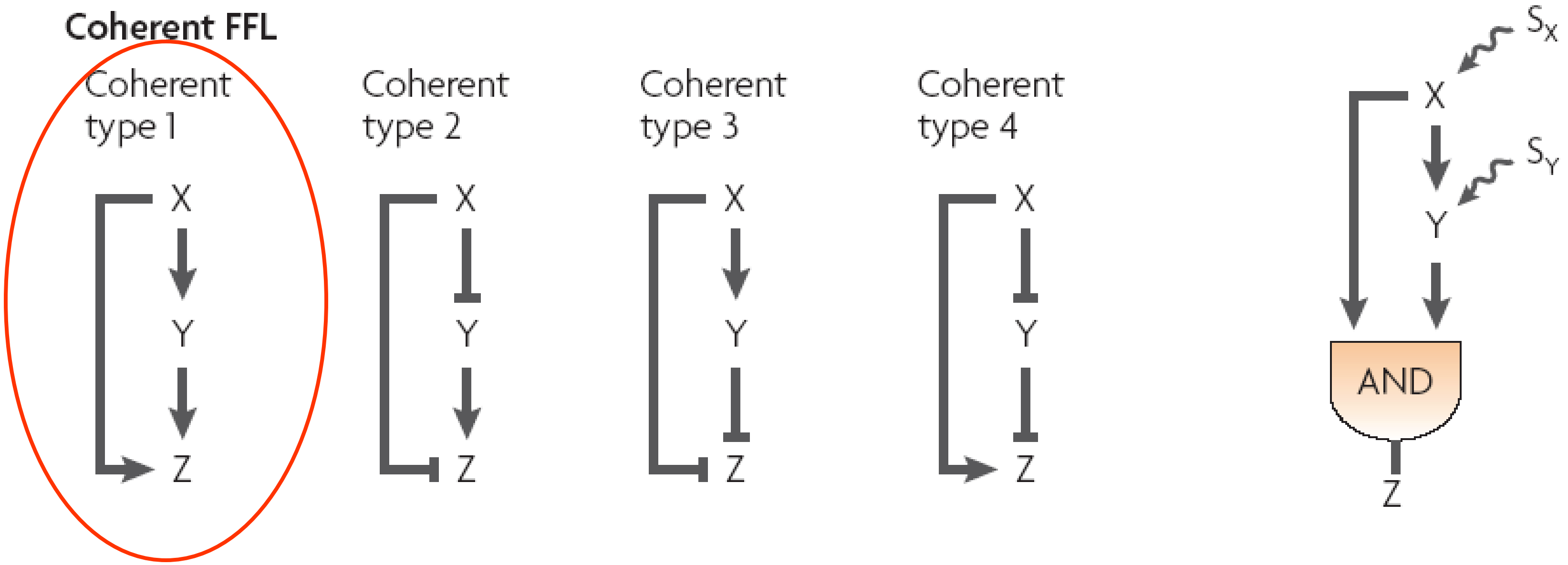
Alon, Nature Rev Genetics 8 (2007) 450



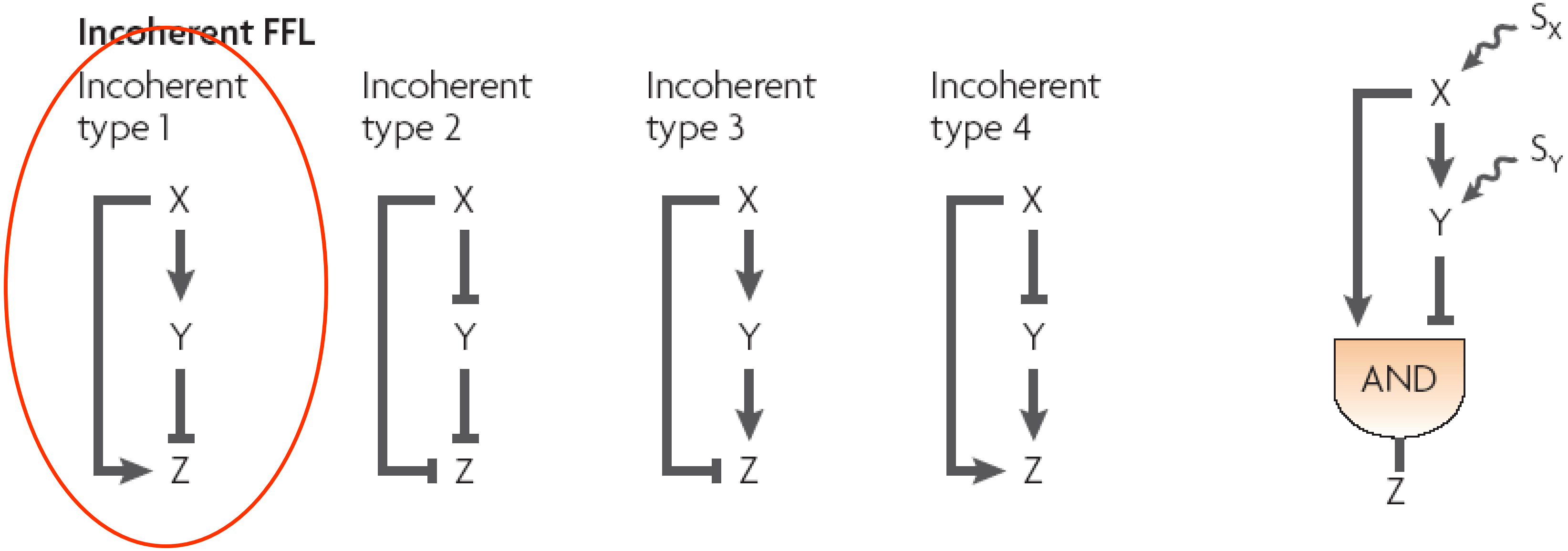
Feedforward loop

Alon, Nature Rev Genetics 8 (2007) 450

Coherent FFL



Incoherent FFL

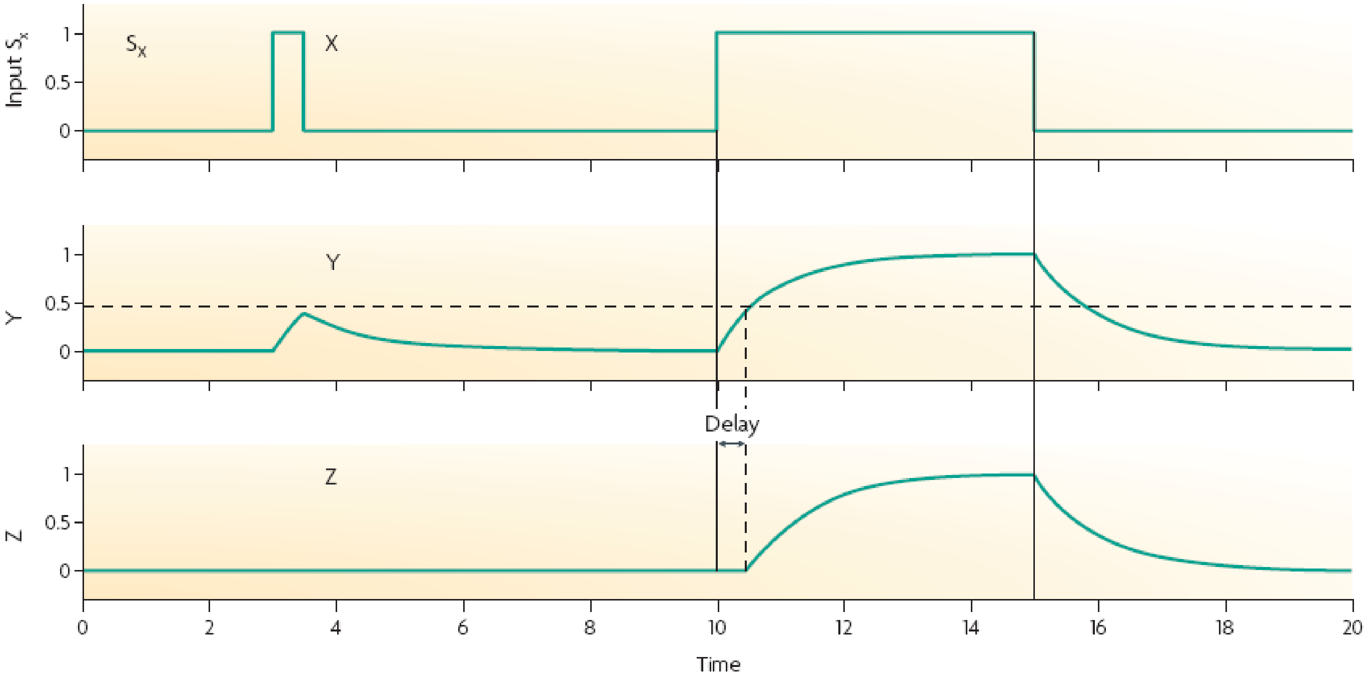


Coherent Feedforward loop: persistence detector

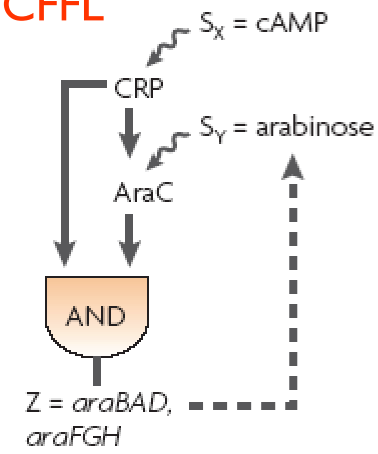
Alon, Nature Rev Genetics 8 (2007) 450

The CFFL shows a delay after stimulation starts but no delay after stimulation stops:

A 'sign-sensitive' delay element for filtering out brief spurious signal pulses



CFFL



S_X = cAMP

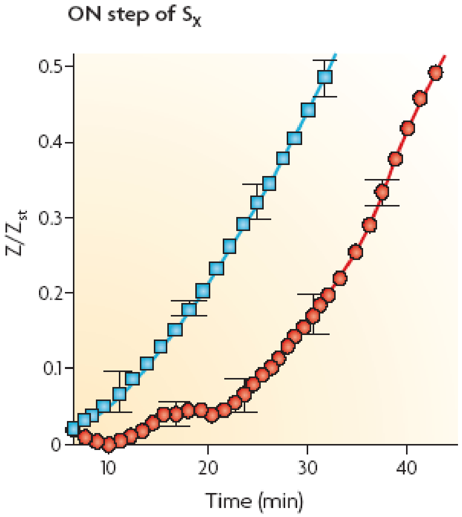
CRP

S_Y = arabinose

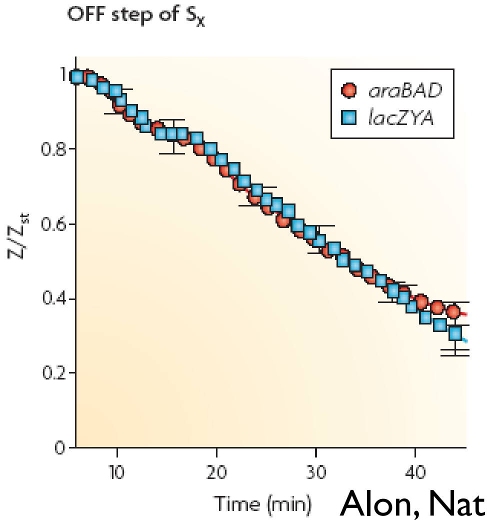
AraC

AND

Z = *araBAD*, *araFGH*

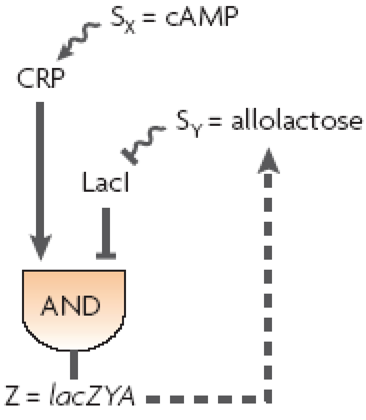


ON step of S_X



OFF step of S_X

Simple regulation



S_X = cAMP

CRP

S_Y = allolactose

LacI

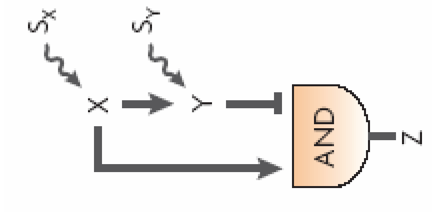
AND

Z = *lacZYA*

Alon, Nature Rev Genetics 8 (2007) 450

Incoherent Feedforward loop: pulse generator

Alon, Nature Rev Genetics 8 (2007) 450

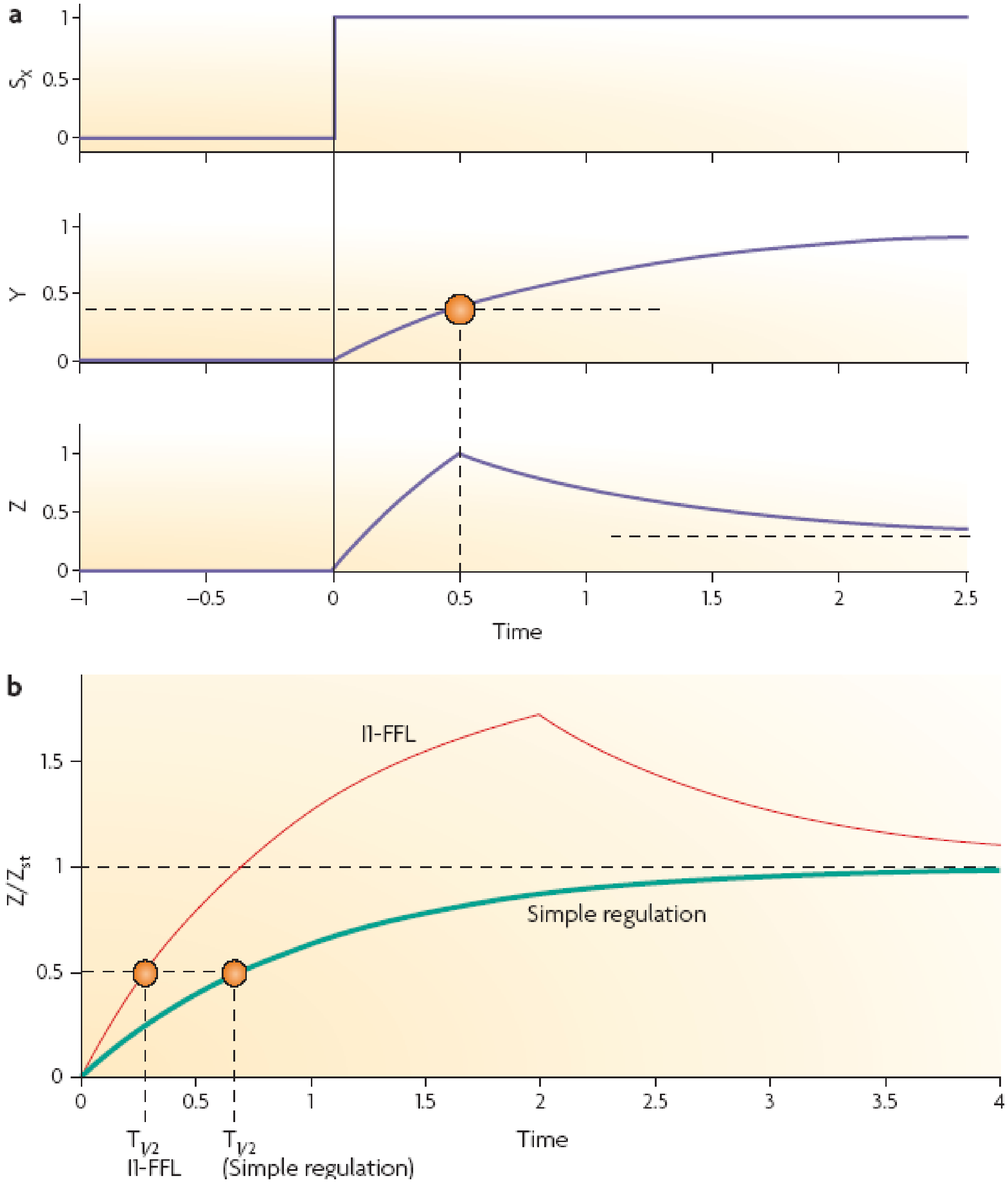


The two branches of IFFL act in opposition

X activates Z, but indirectly represses Z by activating its repressor Y

Initially, signal activating X causes rapid production of Z Later Y levels accumulate to repression threshold for Z, decreasing its production

Pulse-like dynamics and response acceleration relative to simple regulation

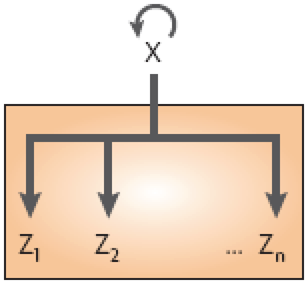


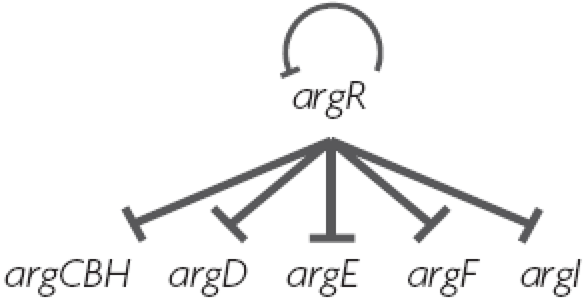
Single-input module

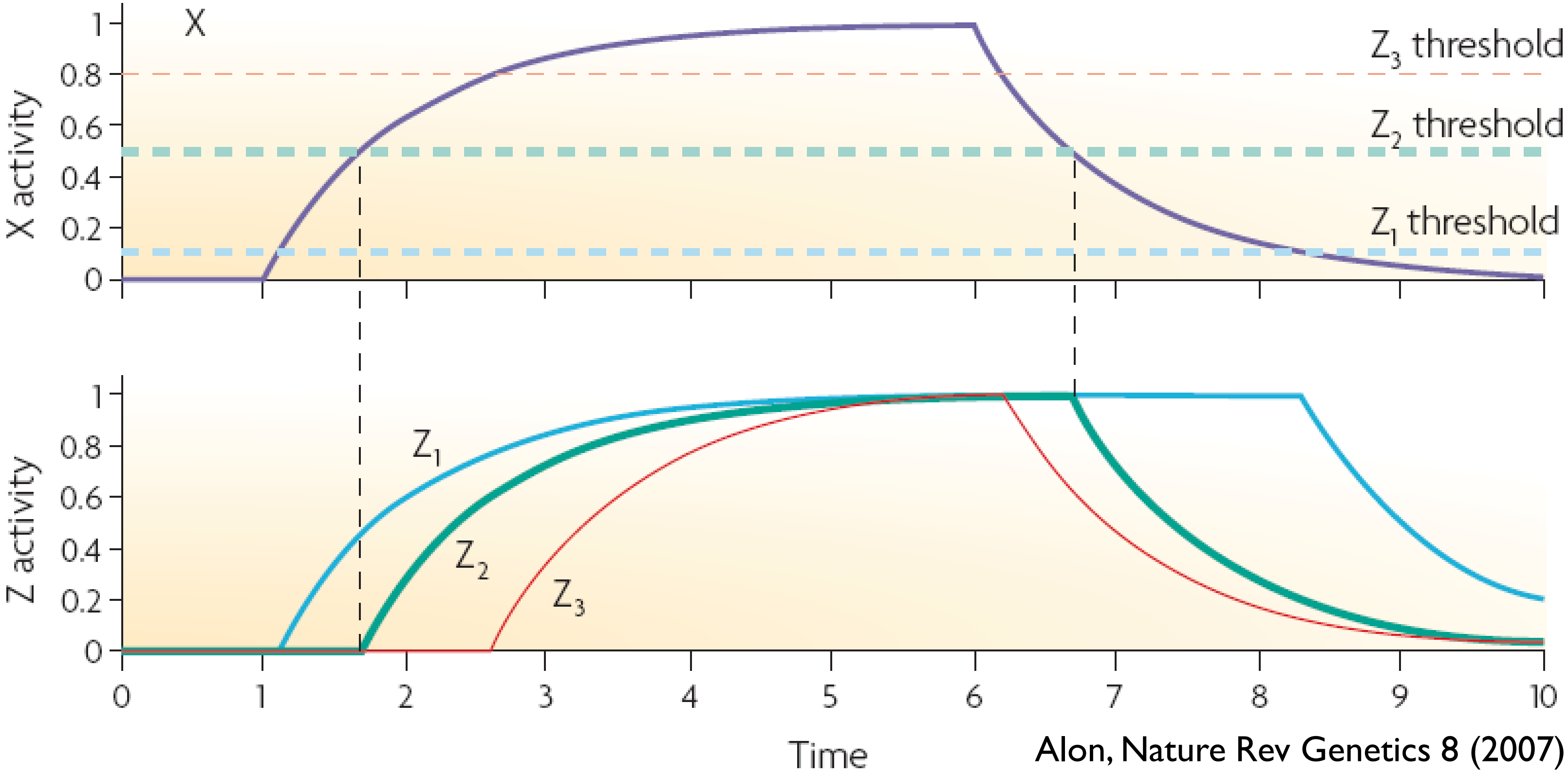
Allows coordinated expression of a group of genes with shared function

Can generate a temporal expression program with a defined sequence of activation of each target by using different thresholds

A single regulator X controls a group of target genes $Z_1, Z_2, \ldots Z_n$







Alon, Nature Rev Genetics 8 (2007) 450

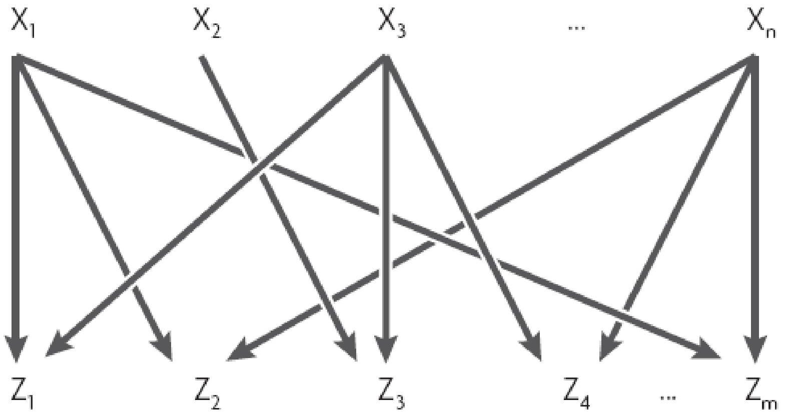
Multi-input motifs

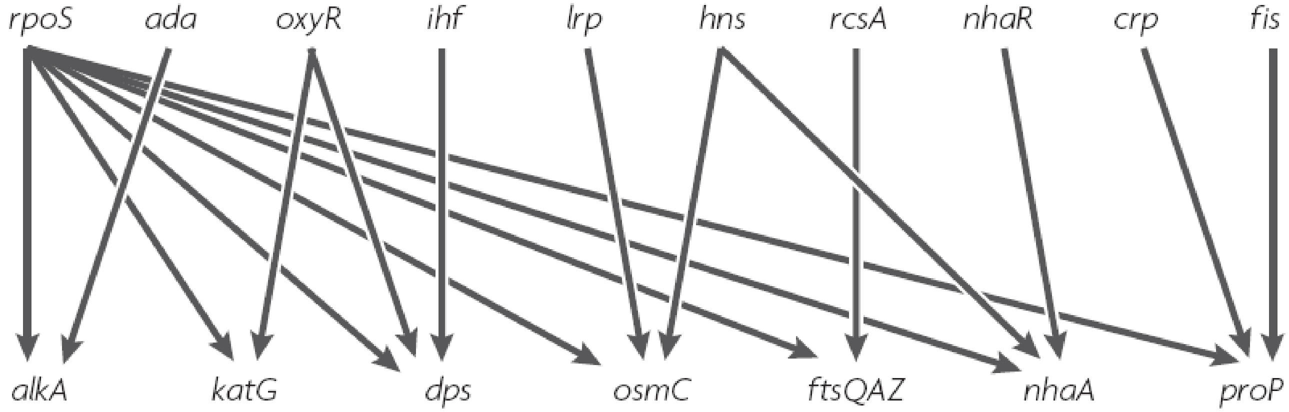
Many inputs regulate many outputs

Alon, Nature Rev Genetics 8 (2007) 450

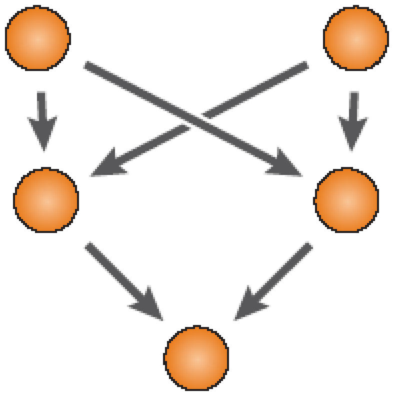
A set of regulators combinatorially control a set of output genes

Can be responsible for a broad function, e.g., carbon utilization, stress response, anaerobic growth (E Coli), etc.





Multi-layer perceptrons



Similar to multi-layer perceptron model of neural networks – but only one layer !