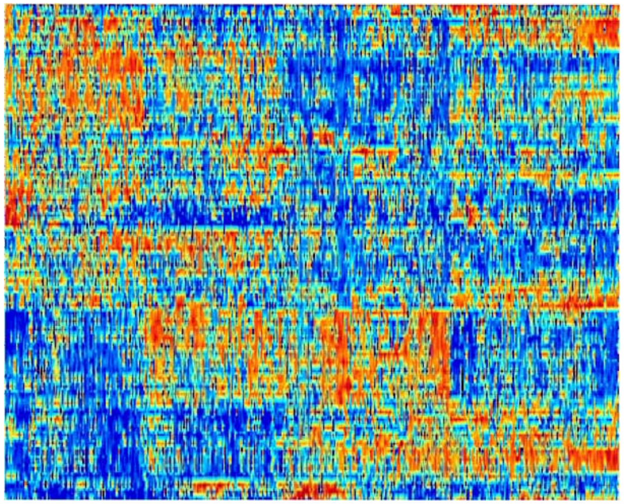
Gene Regulatory Networks

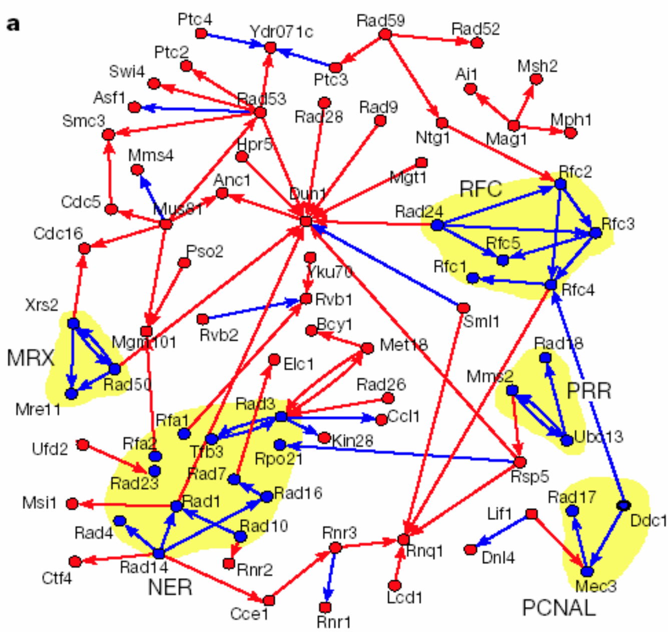
slides adapted from

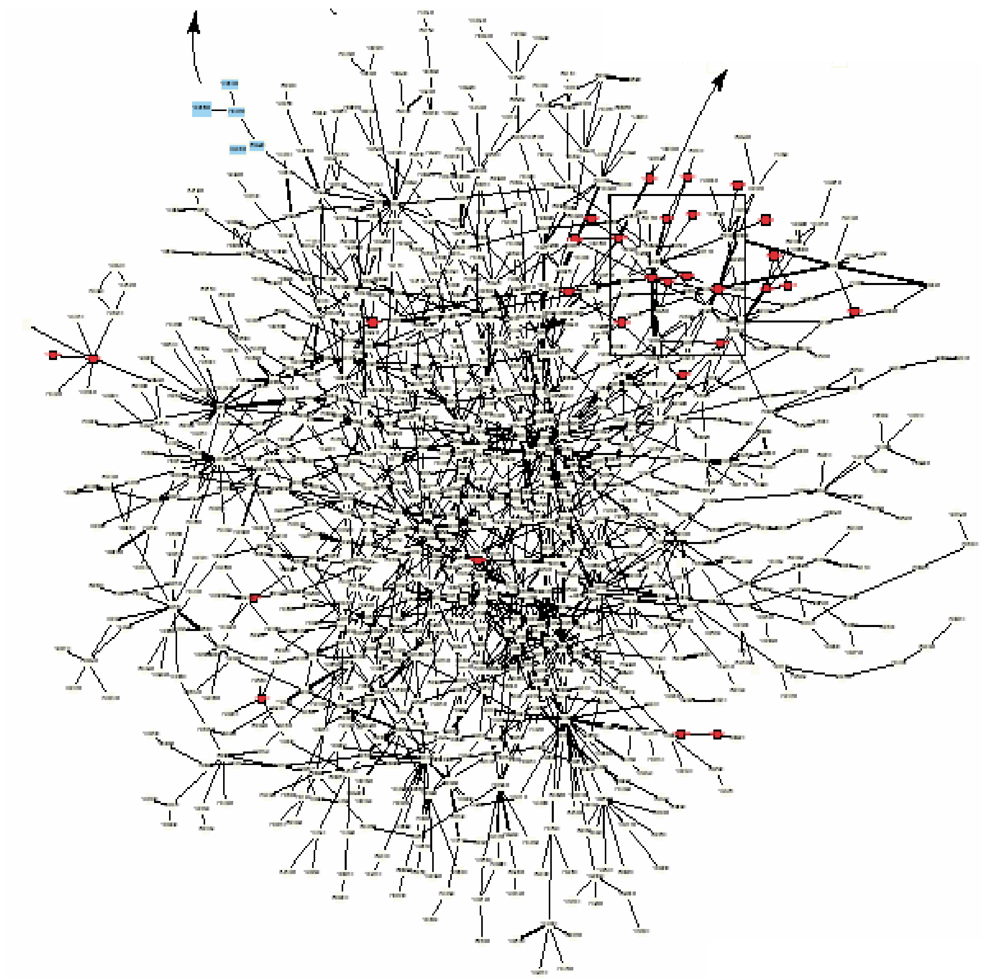
Shalev Itzkovitz's talk

given at IPAM UCLA on July 2005

Protein networks - optimized molecular computers







E. coli – a model organism

Single cell, 1 micron length

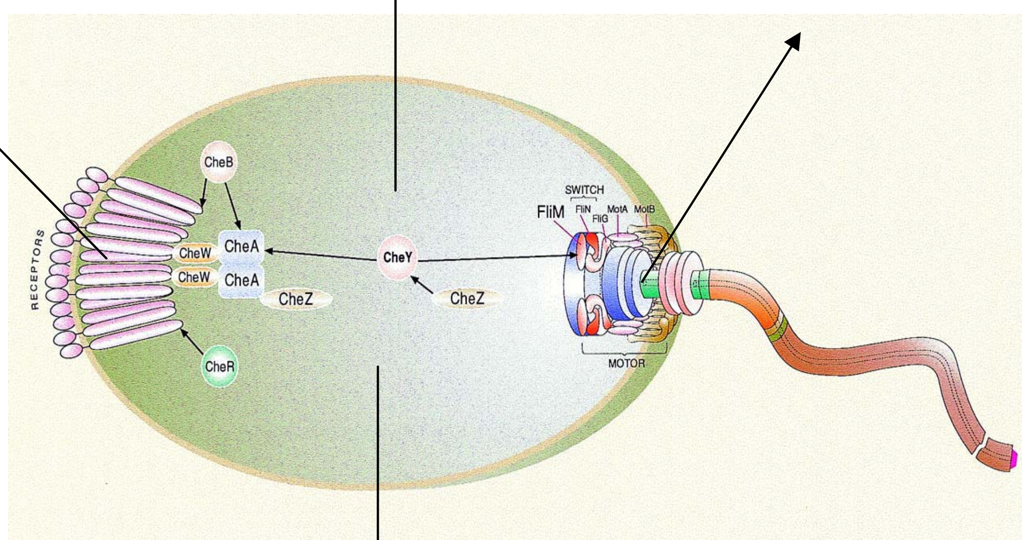
Contains only ~1000 protein types at any given moment

still : **Amazing technology**

computer

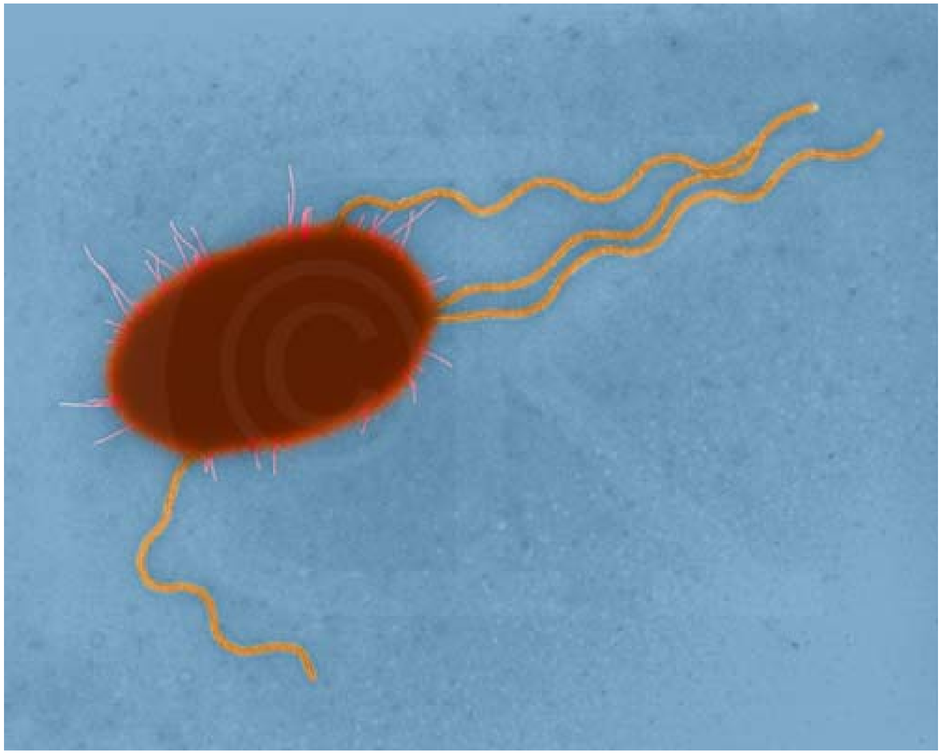
sensors

engine

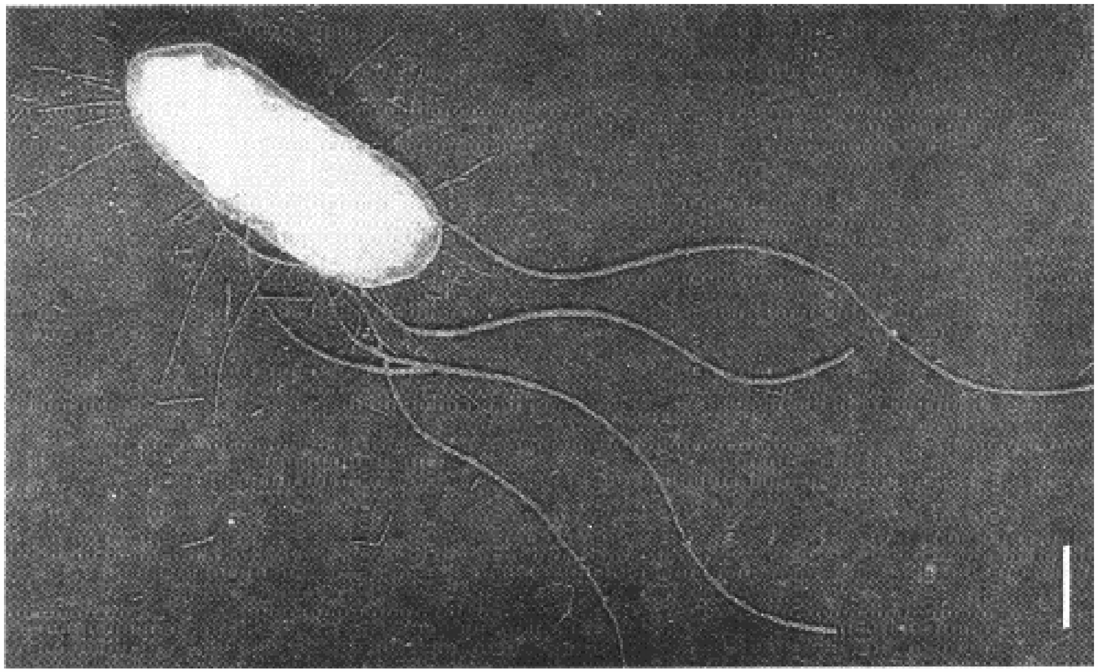


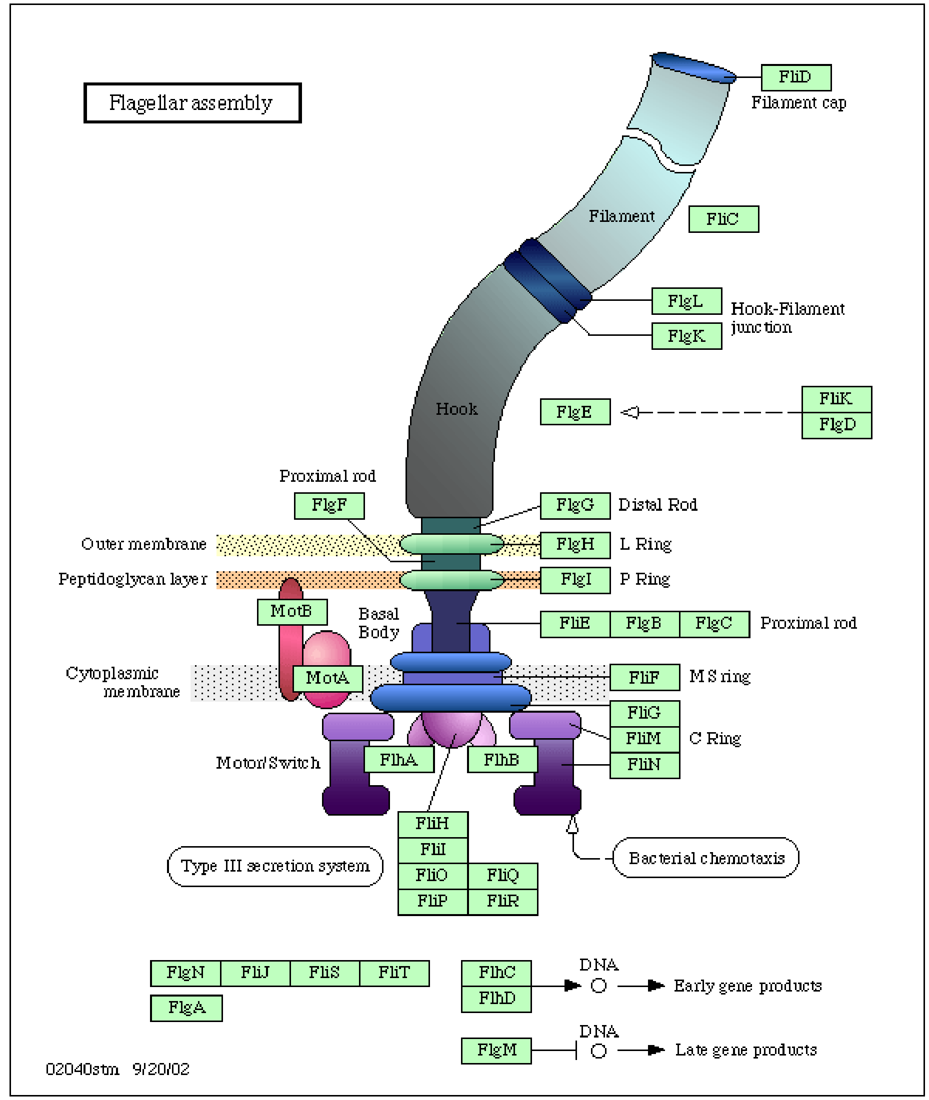
Communication bus

Can move toward food and away from toxins



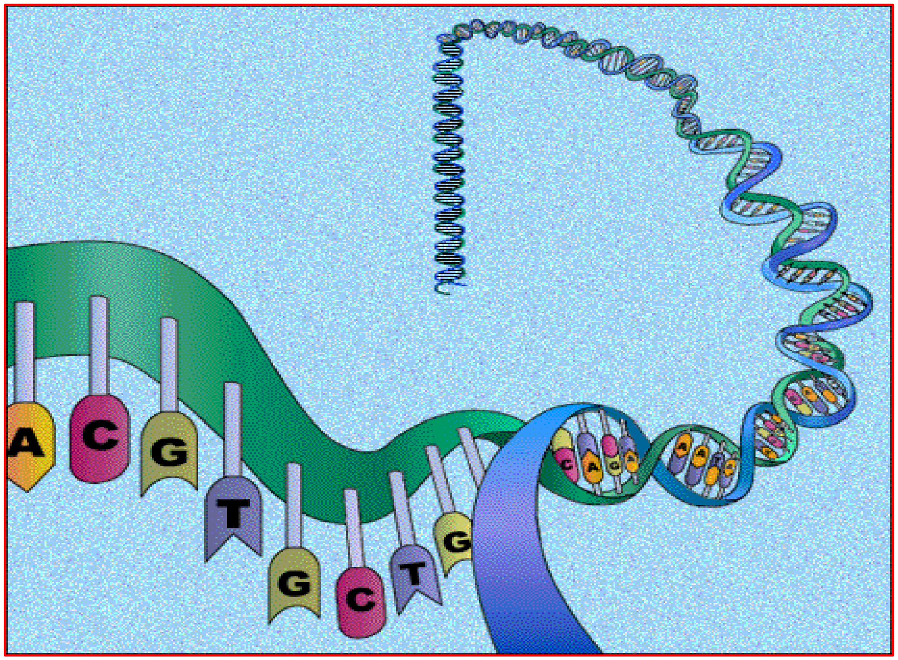
Flagella assembly

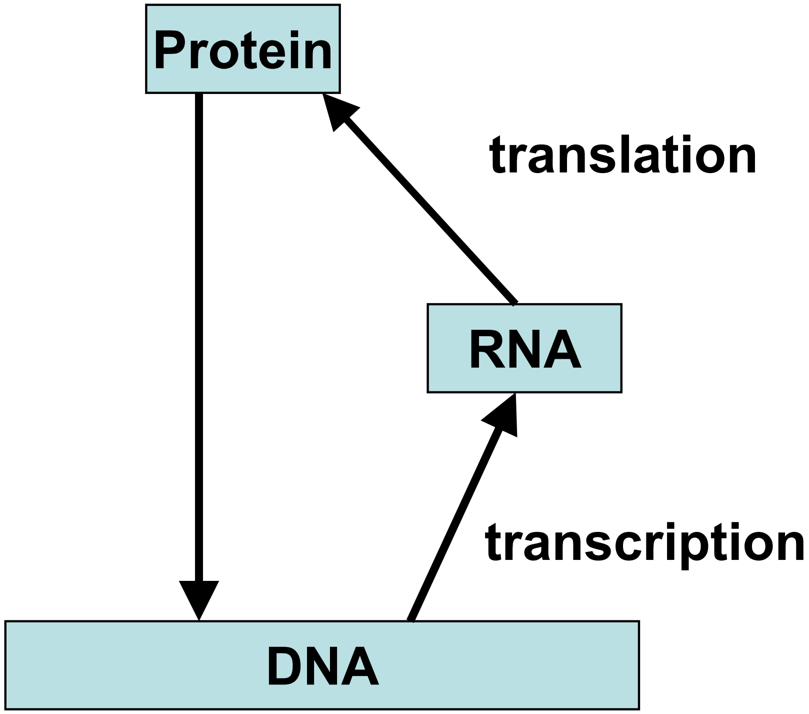




- Composed of 12 types of proteins
- Assembled only when there is an environmental need for motility
- Built in an efficient and precise temporal order

Proteins are encoded by DNA





DNA – same inside every cell, the instruction manual, 4-letter chemical alphabet – A,G,T,C

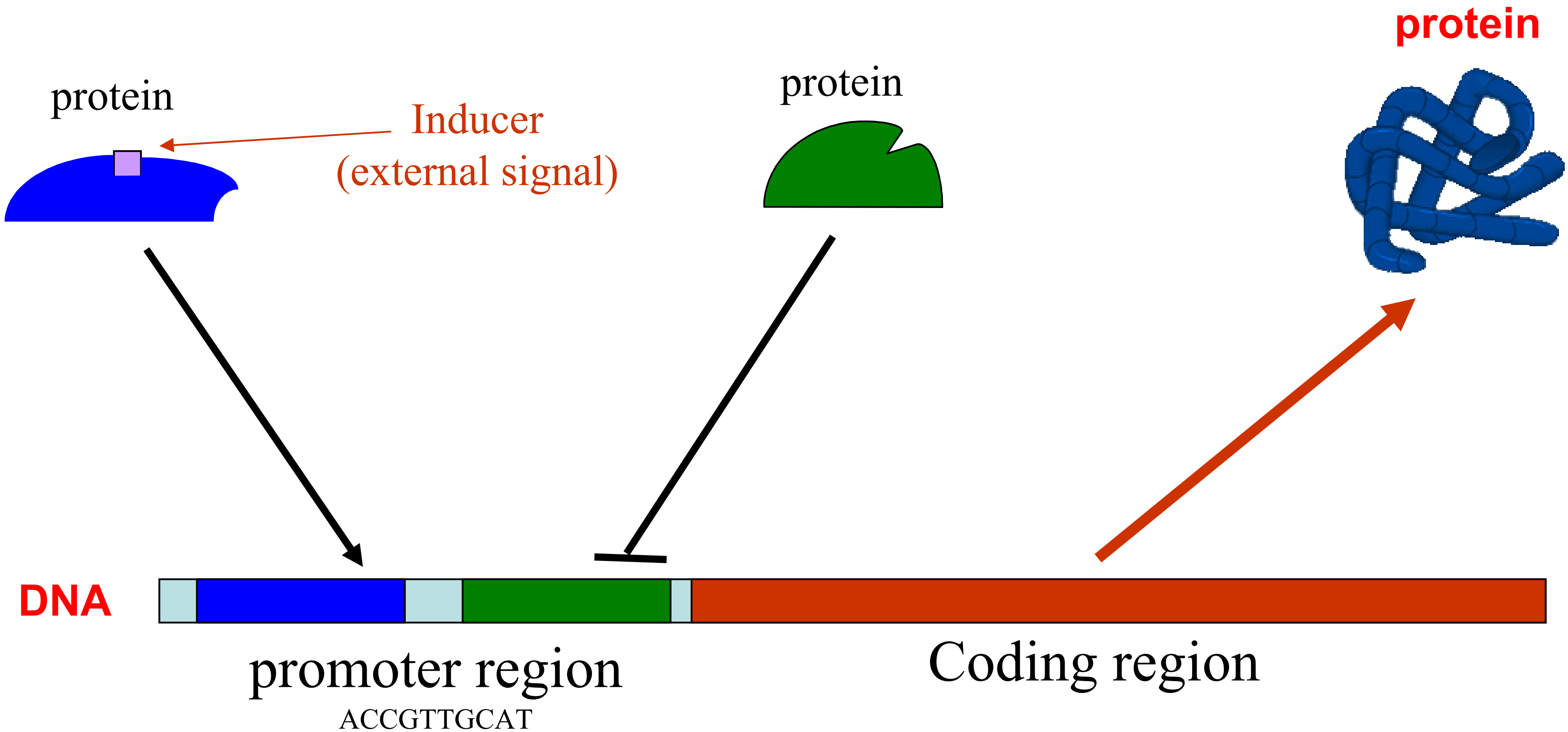
E. Coli – 1000 protein types at any given moment

>4000 genes (or possible protein types) – need regulatory mechanism to select the active set

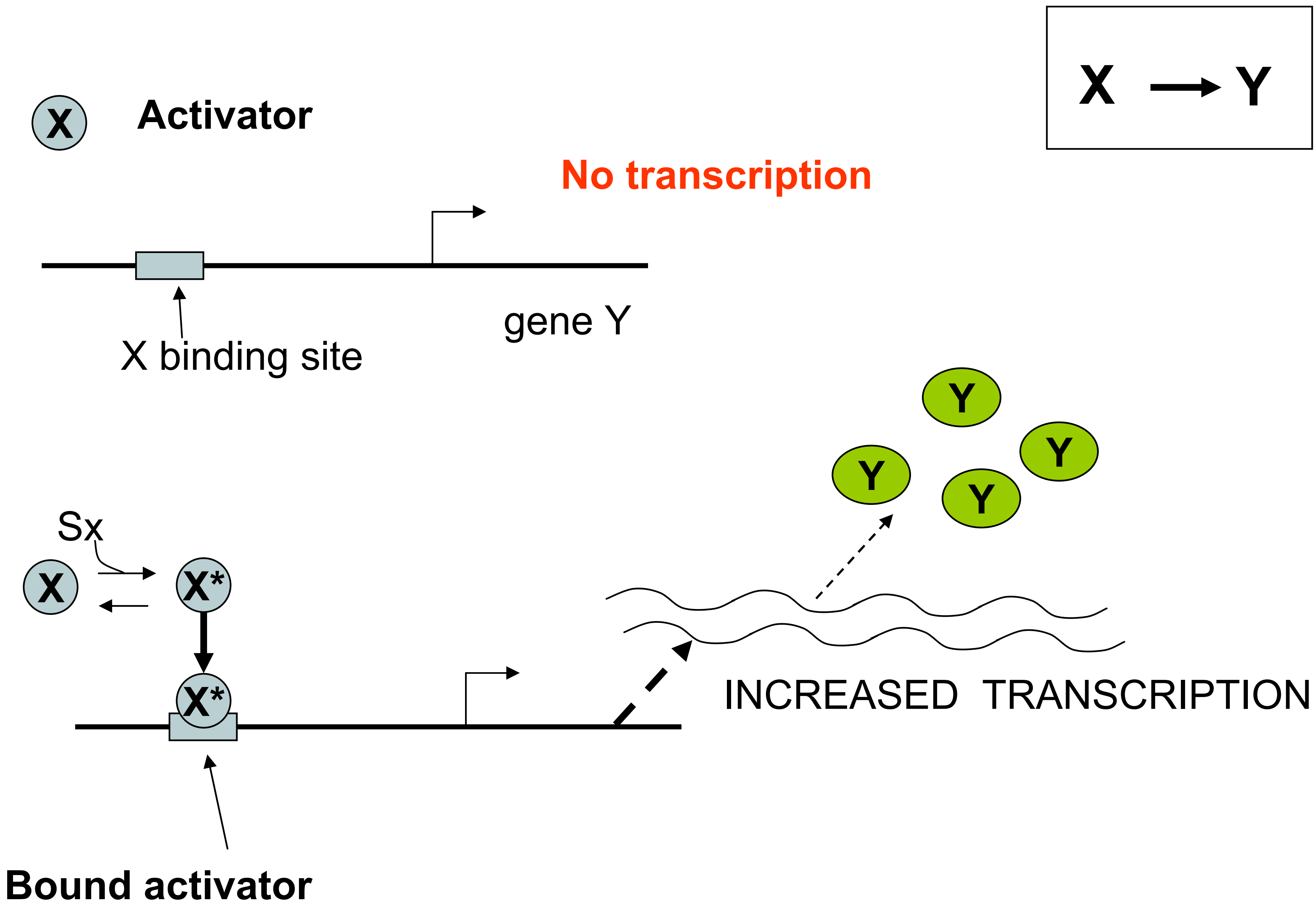
Gene Regulation

•Proteins are encoded by the DNA of the organism.

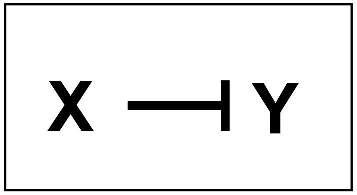
•**Proteins regulate expression of other proteins by interacting with the DNA**

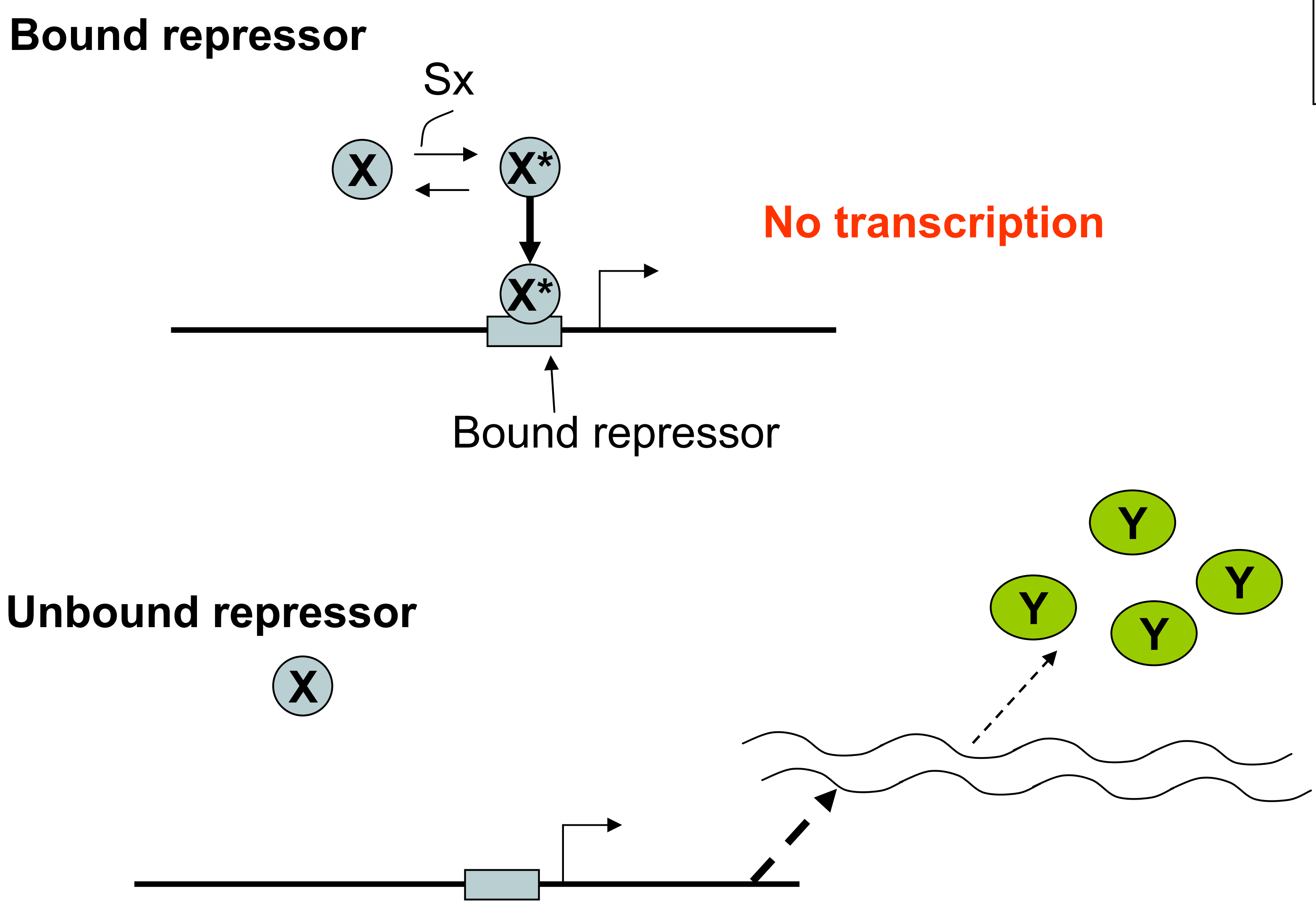


Activators increase gene production

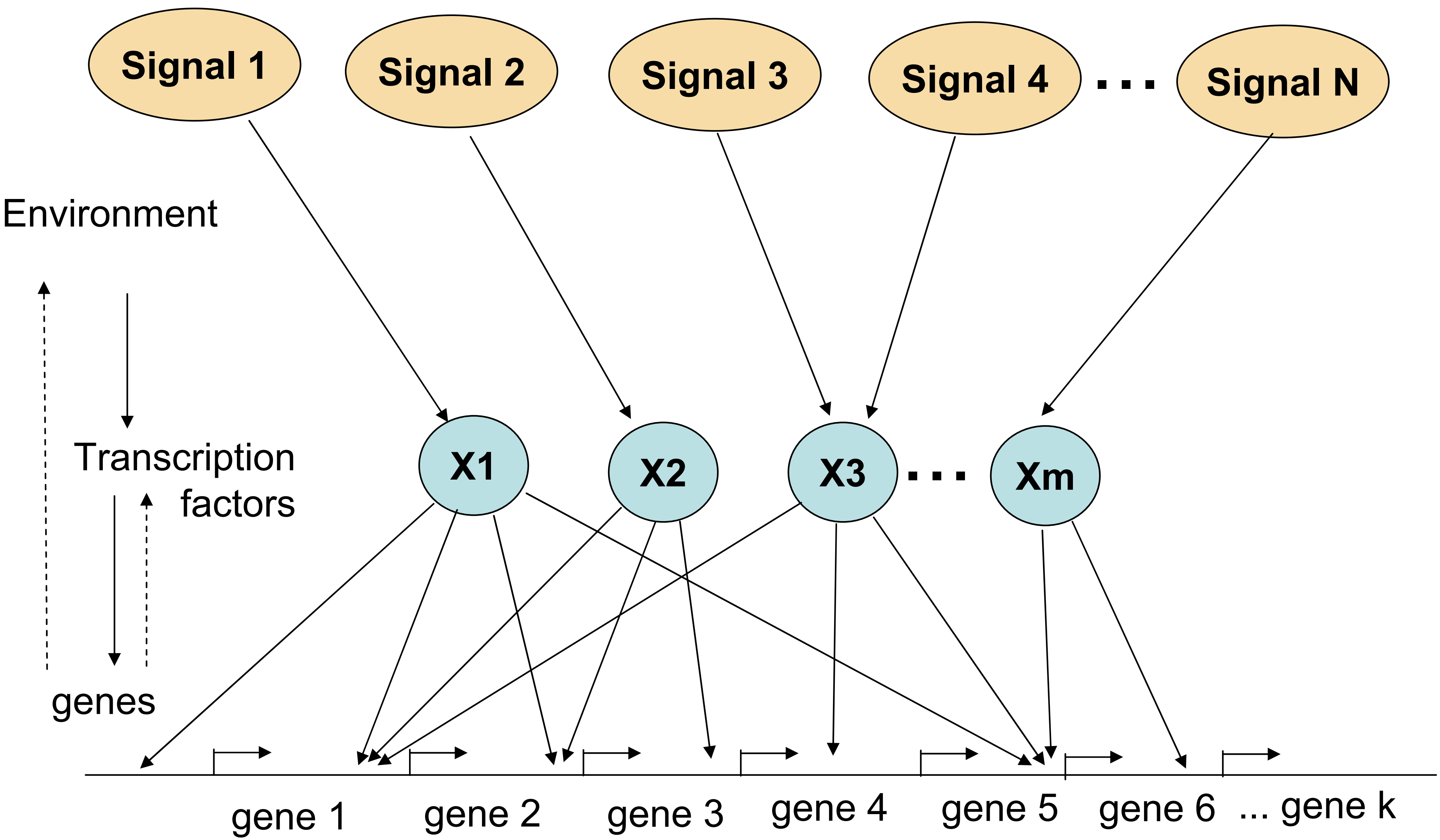


Repressors decrease gene production



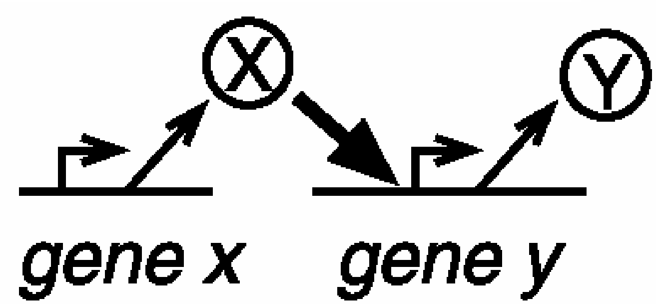


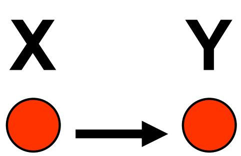
An environmental sensing mechanism

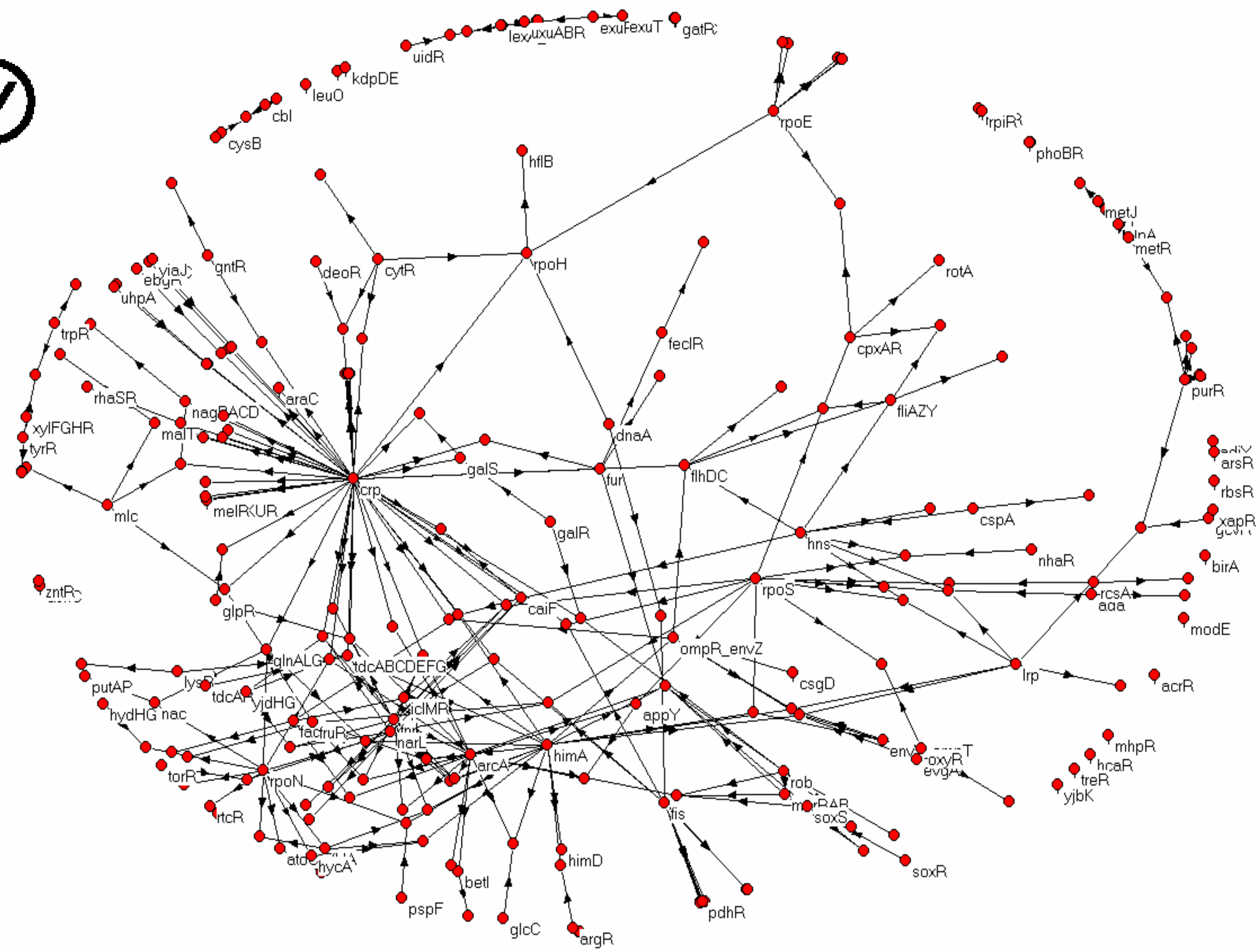


Gene Regulatory Networks

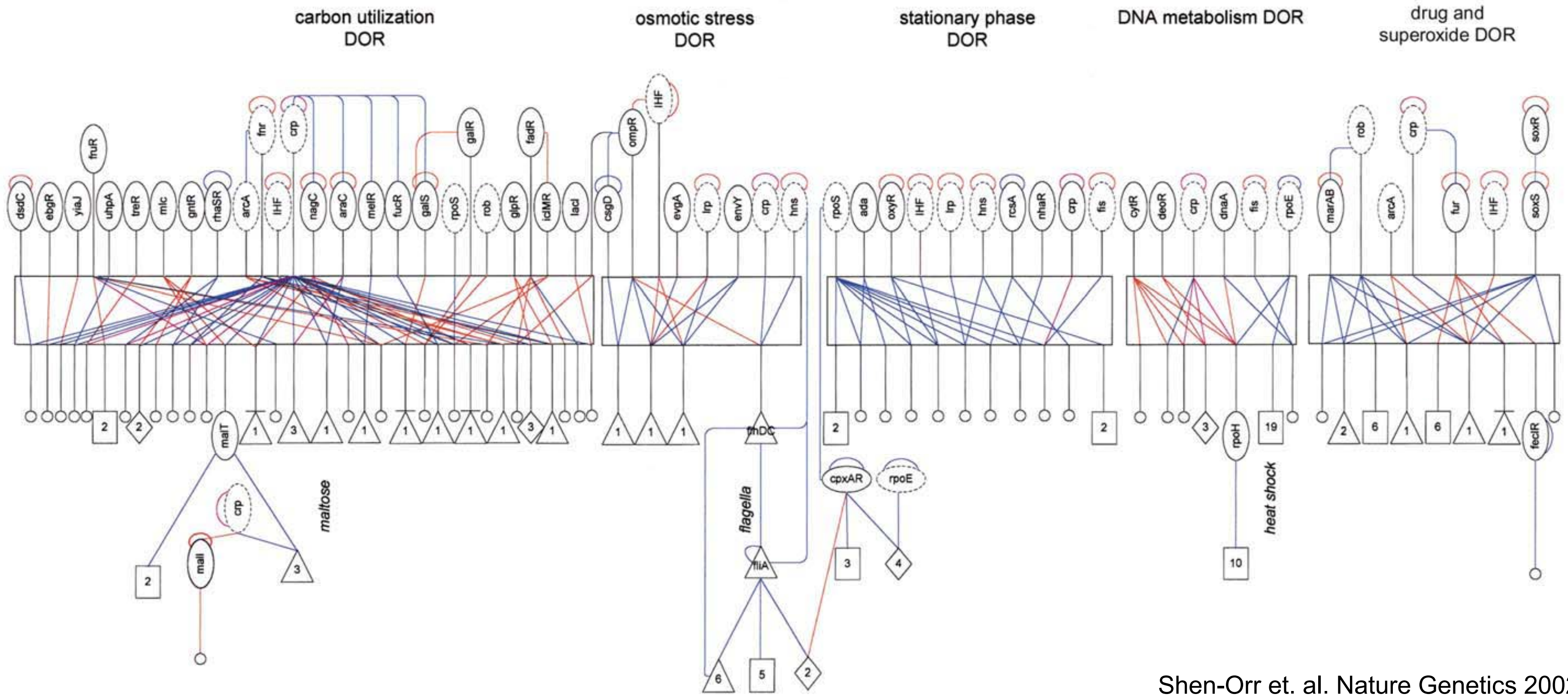
•Nodes are proteins (or the genes that encode them)







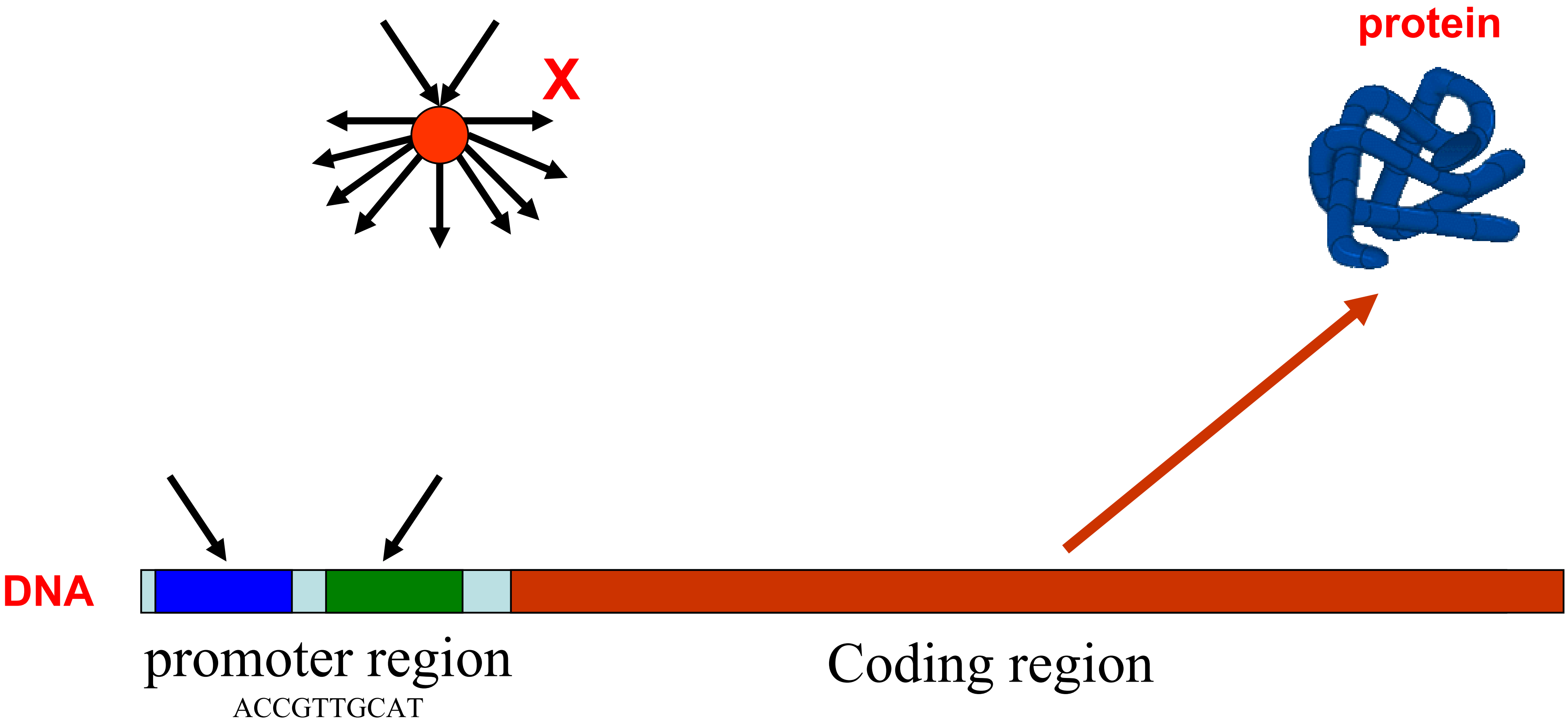
The gene regulatory network of E. coli



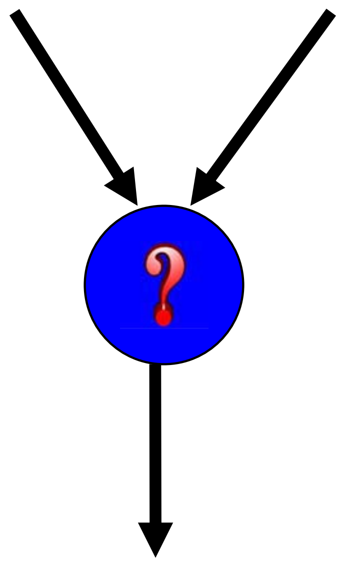
Shen-Orr et. al. Nature Genetics 2002

- **shallow network**, few long cascades.
- modular
- compact in-degree (promoter size limitation)

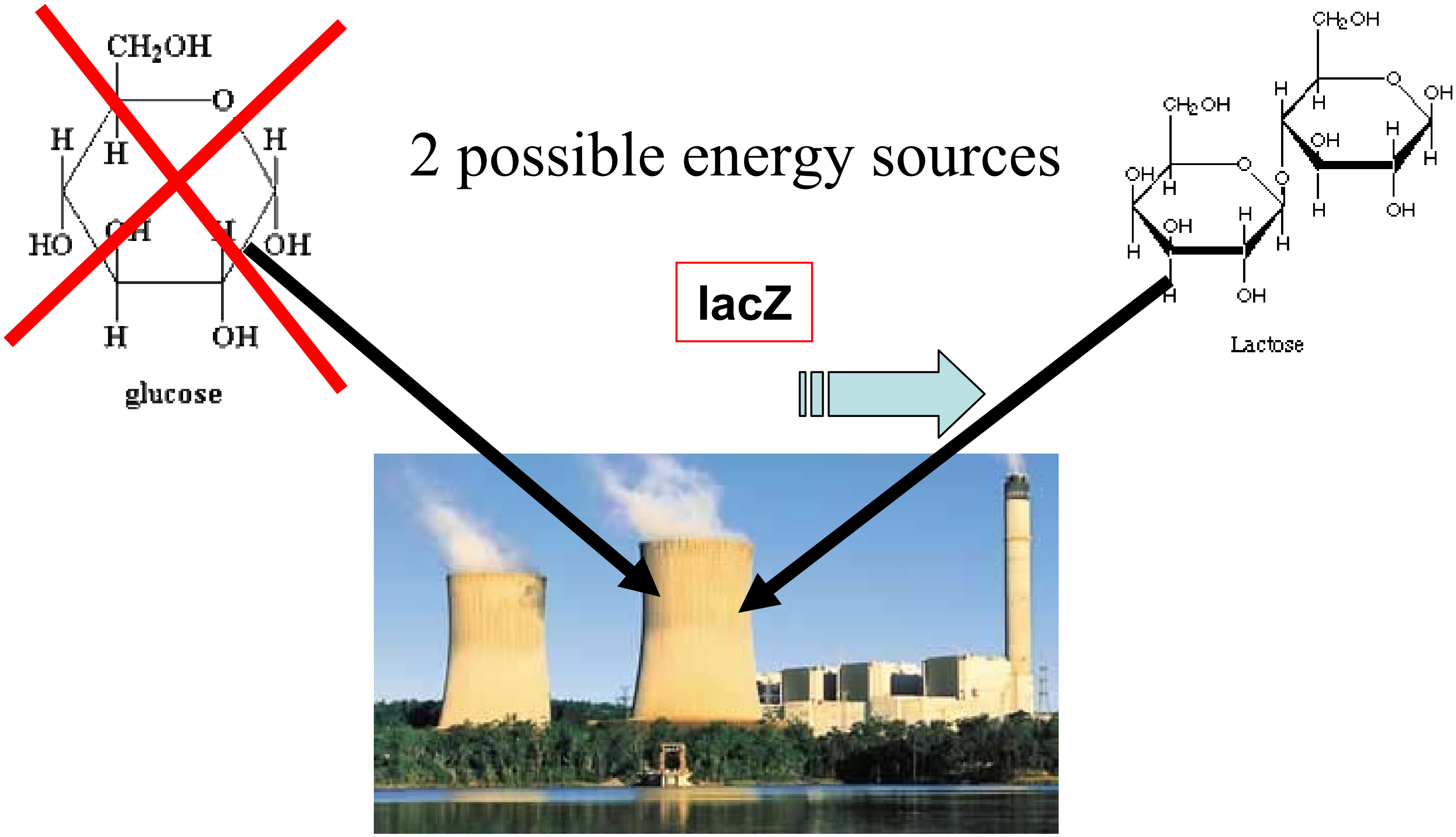
Asymmetric degree distribution due to Promoter size limitation



What logical function do the nodes represent?



Example – Energy source utilization



The E. coli prefers glucose

lacZ is a protein needed to break down lactose into carbon

How will the E. coli decide when to create this protein?

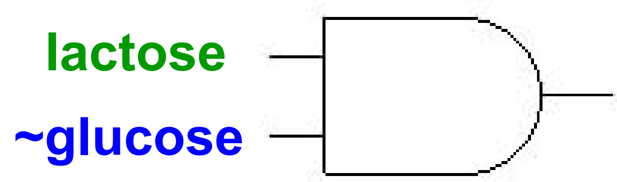
Proteins have a cost

- E. Coli creates ~10^6 proteins during its life time

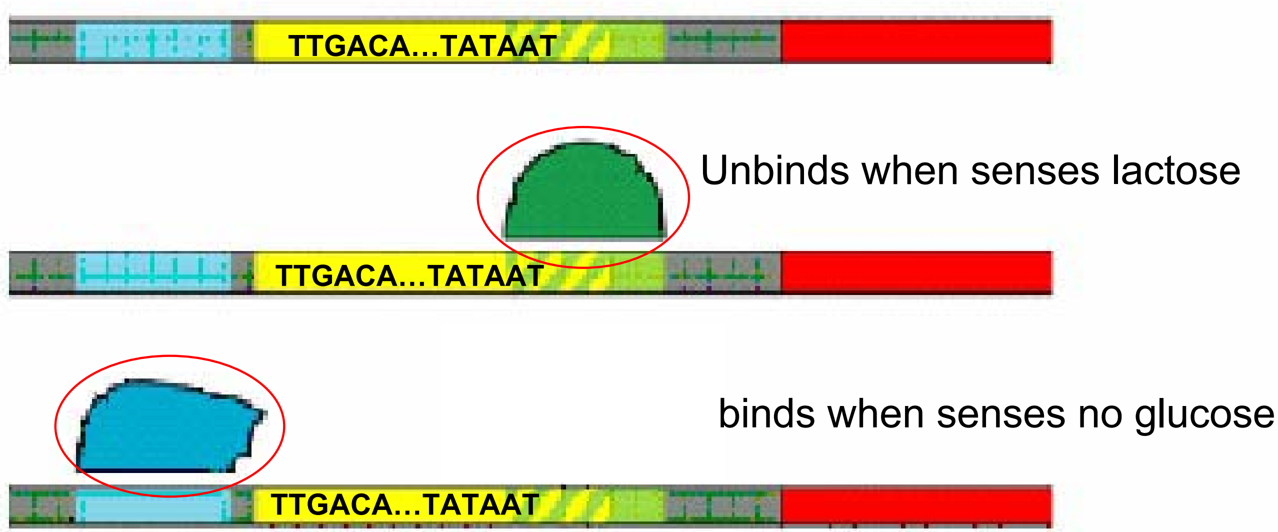
- ~1000 copies on average for each protein type

→ **E. Coli will grow 1/1000 slower,
Enough for evolutionary pressure**

AND gate encoded by proteins and DNA



lacZ gene is controlled by 2 "sensory" proteins :

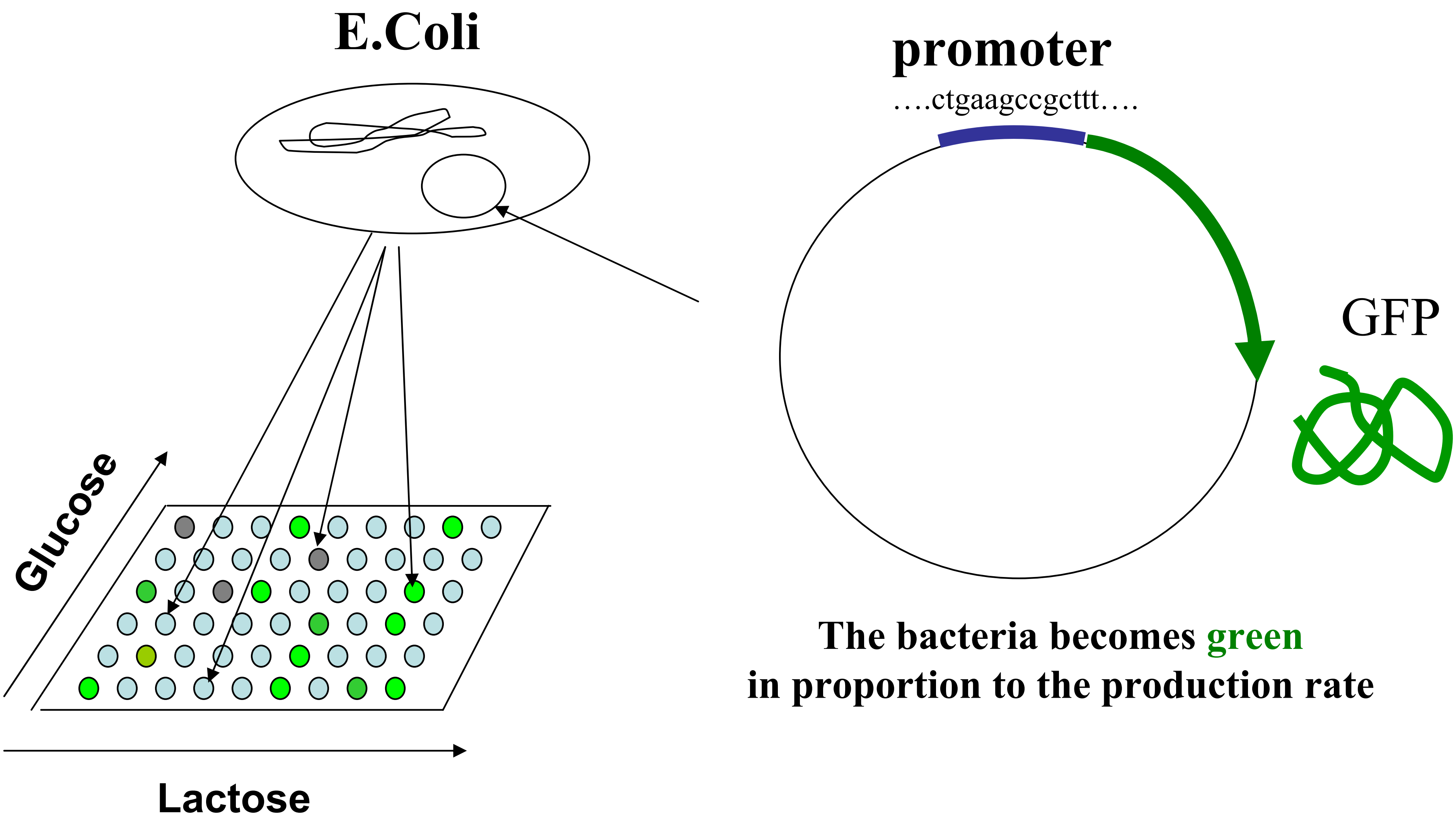


lactose sensor

glucose absence sensor

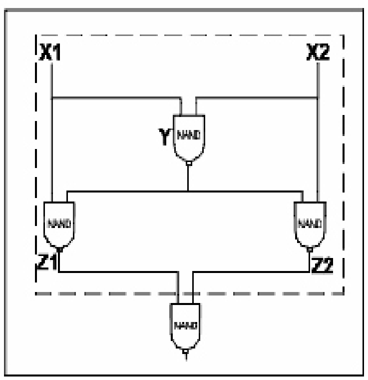
Jacob & Monod, J. Mol. Biol. 1961

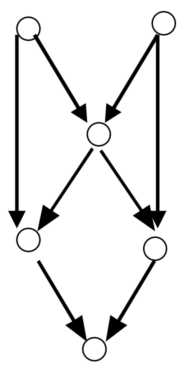
Experimental measurement of input function

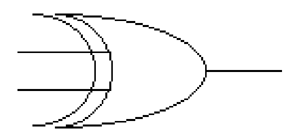


The bacteria becomes green in proportion to the production rate

Are there large recurring patterns which play a defined functional role ?







XOR

logic network

Recurring pattern

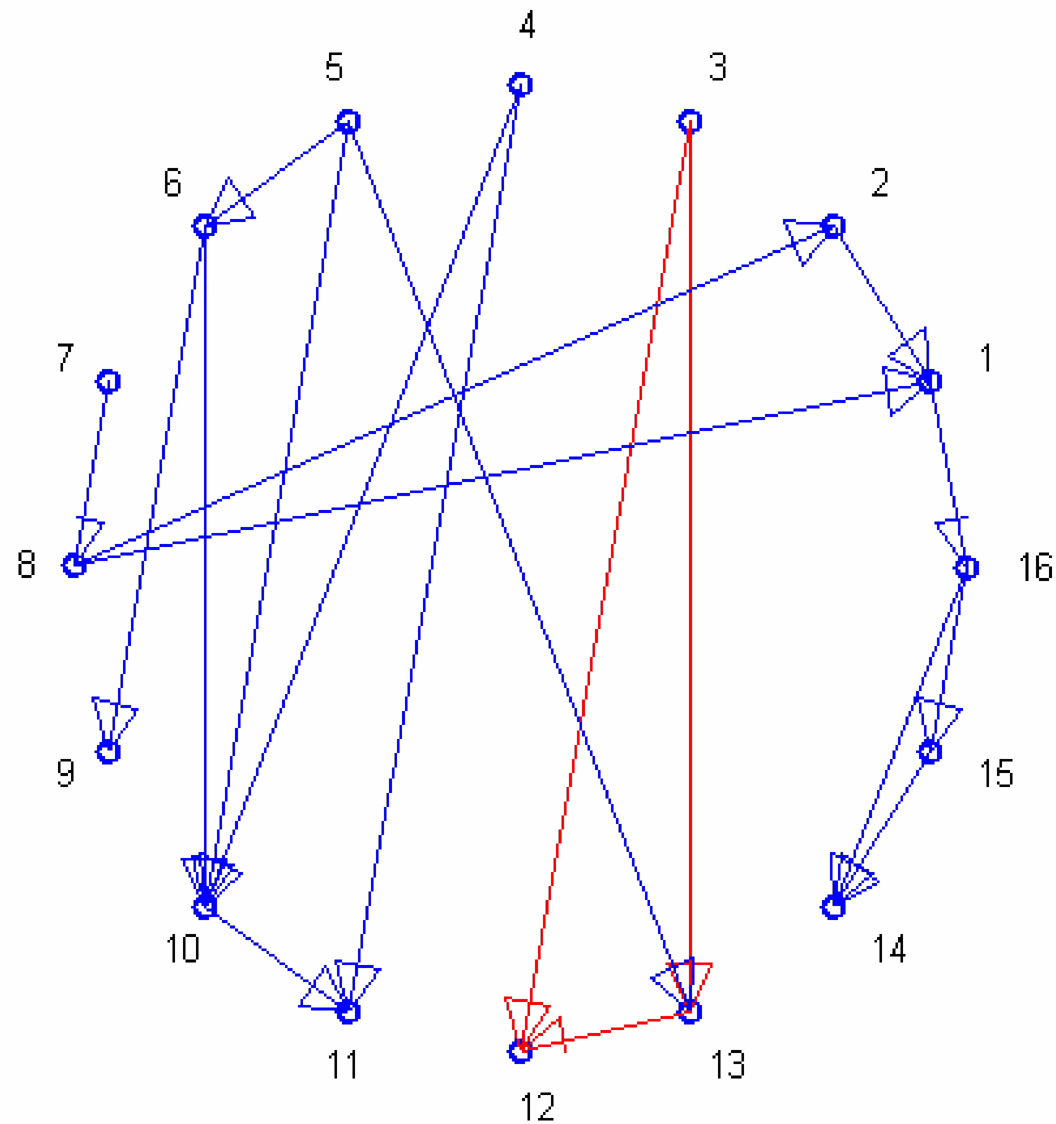
Defined function

Network motifs

Subgraphs which occur in the real network significantly more than in a suitable random ensemble of networks.

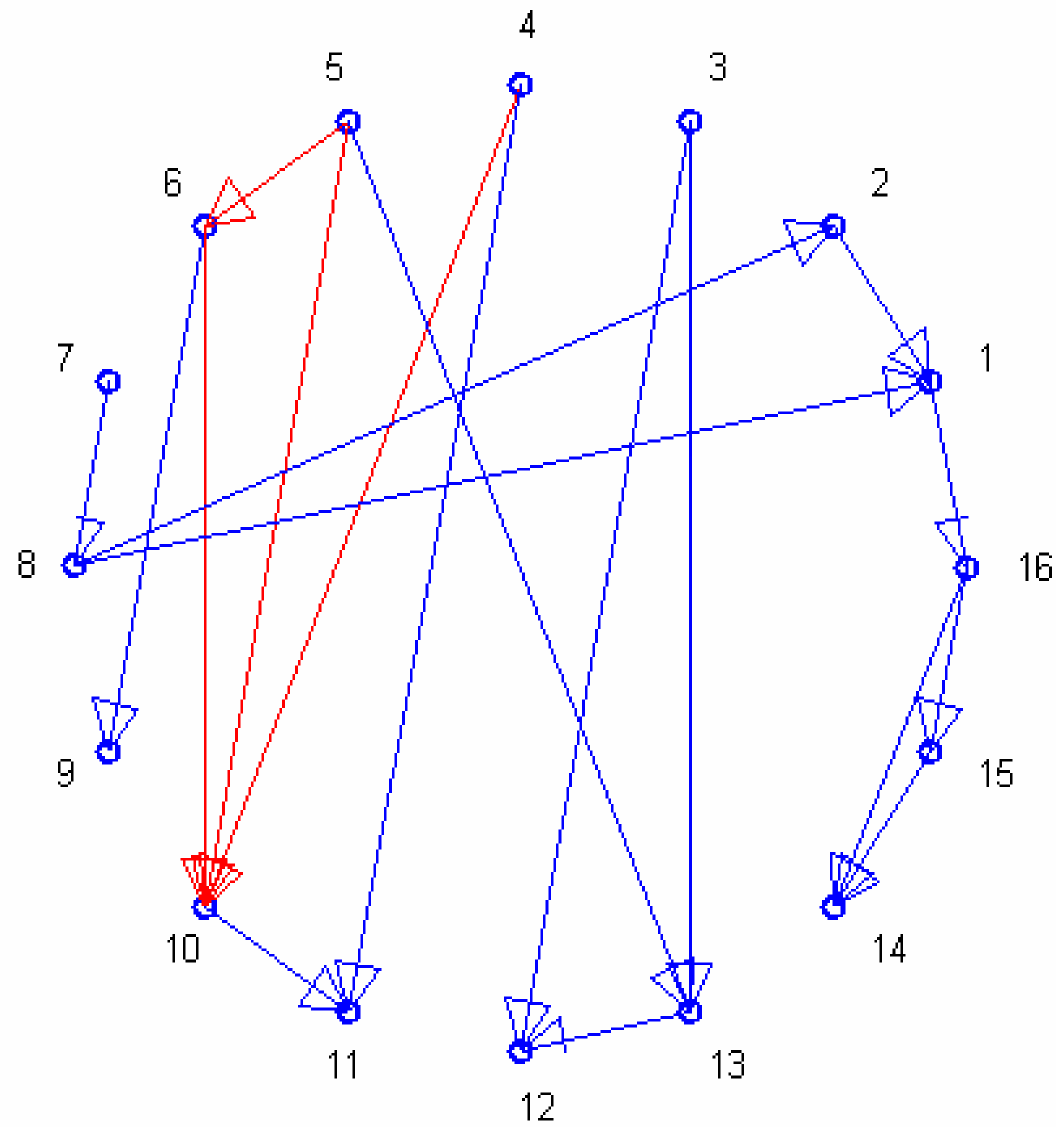
Basic terminology

3-node subgraph

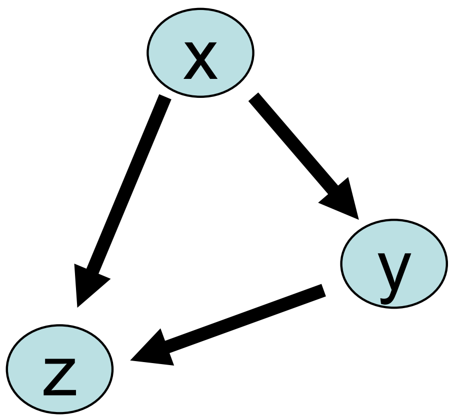


Basic terminology

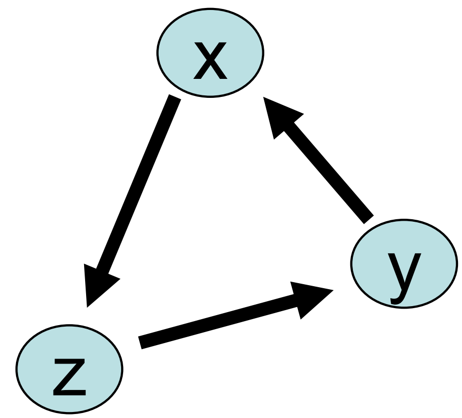
4-node subgraph



Two examples of 3-node subgraphs

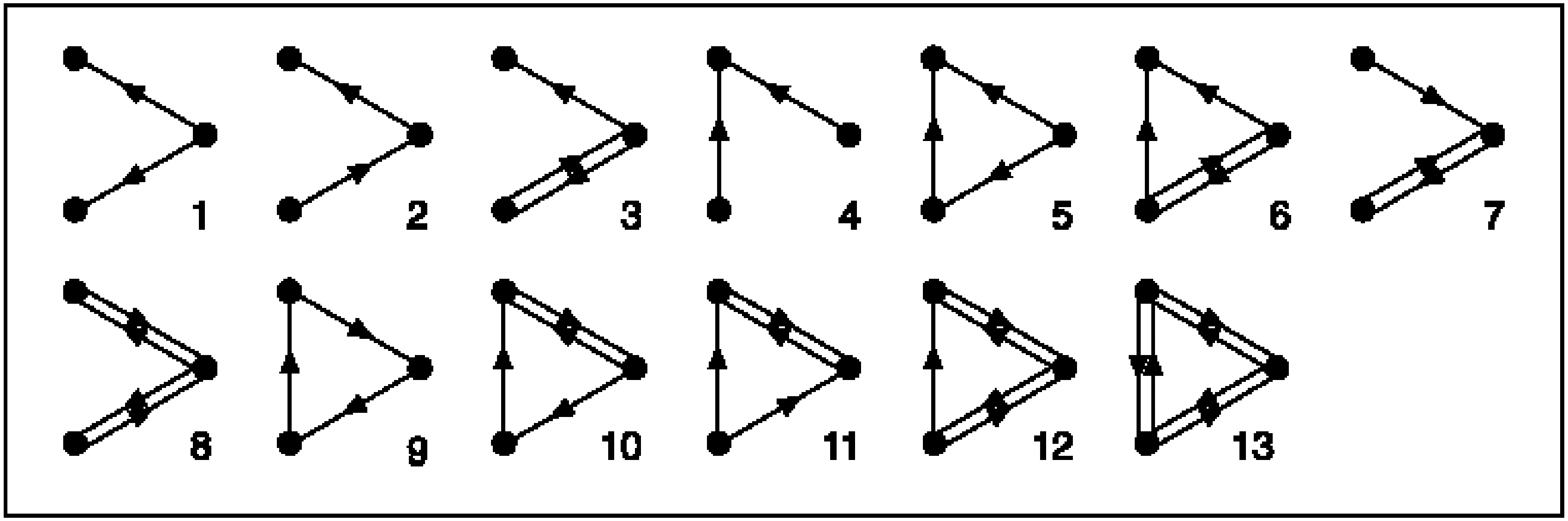


Feed-forward loop

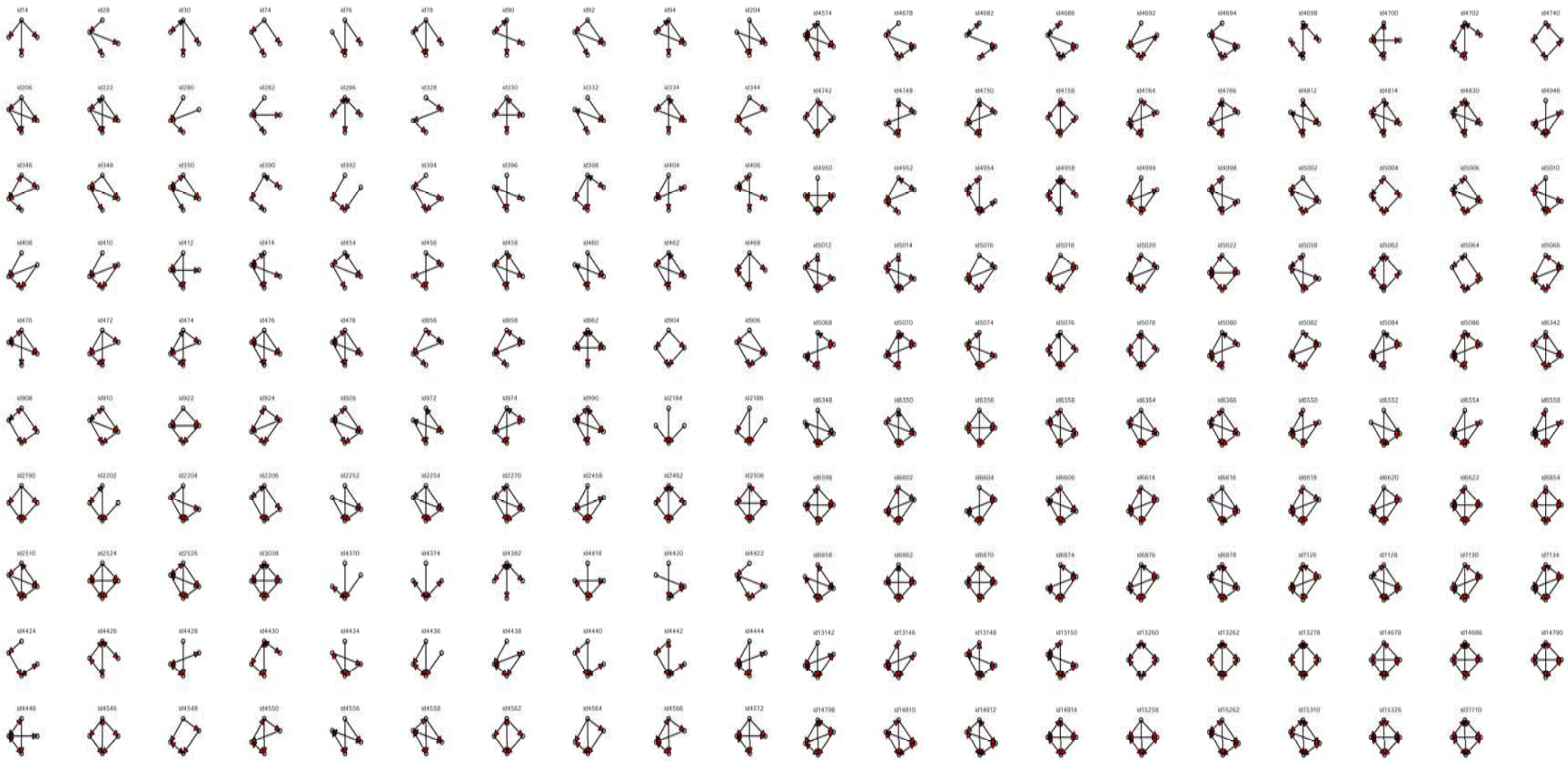


3-node feedback loop
(cycle)

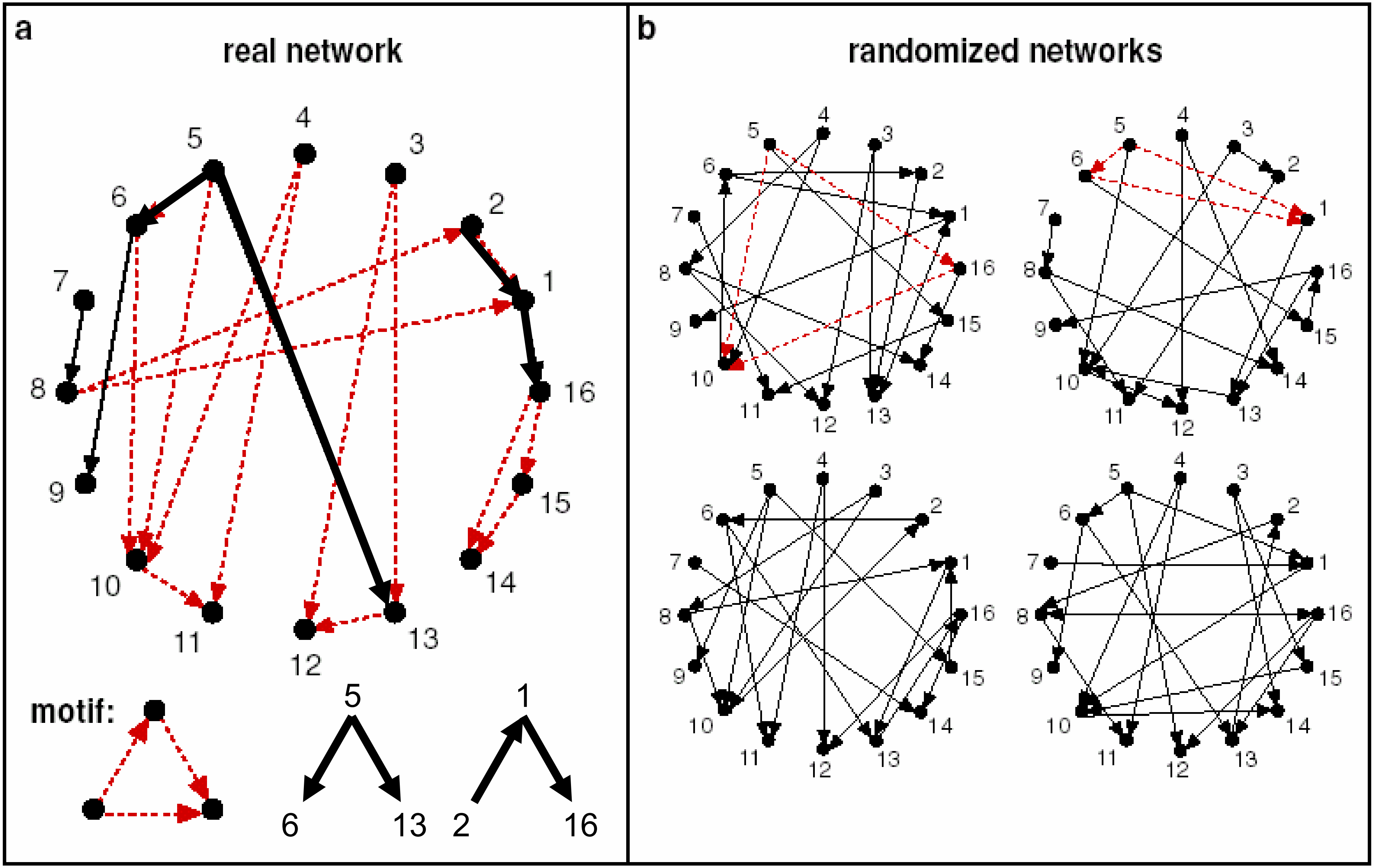
13 directed connected 3-node subgraphs



199 4-node directed connected subgraphs



And it grows pretty fast for larger subgraphs : 9364 5-node subgraphs, 1,530,843 6-node…



Real = 5

Rand=0.5±0.6

Zscore (#Standard Deviations)=7.5

Network motifs

Subgraphs which occur in the real network significantly more than in a suitable random ensemble of networks.

Algorithm :

1) count all n-node connected subgraphs in the real network.

2) Classify them into one of the possible n-node isomorphic subgraphs

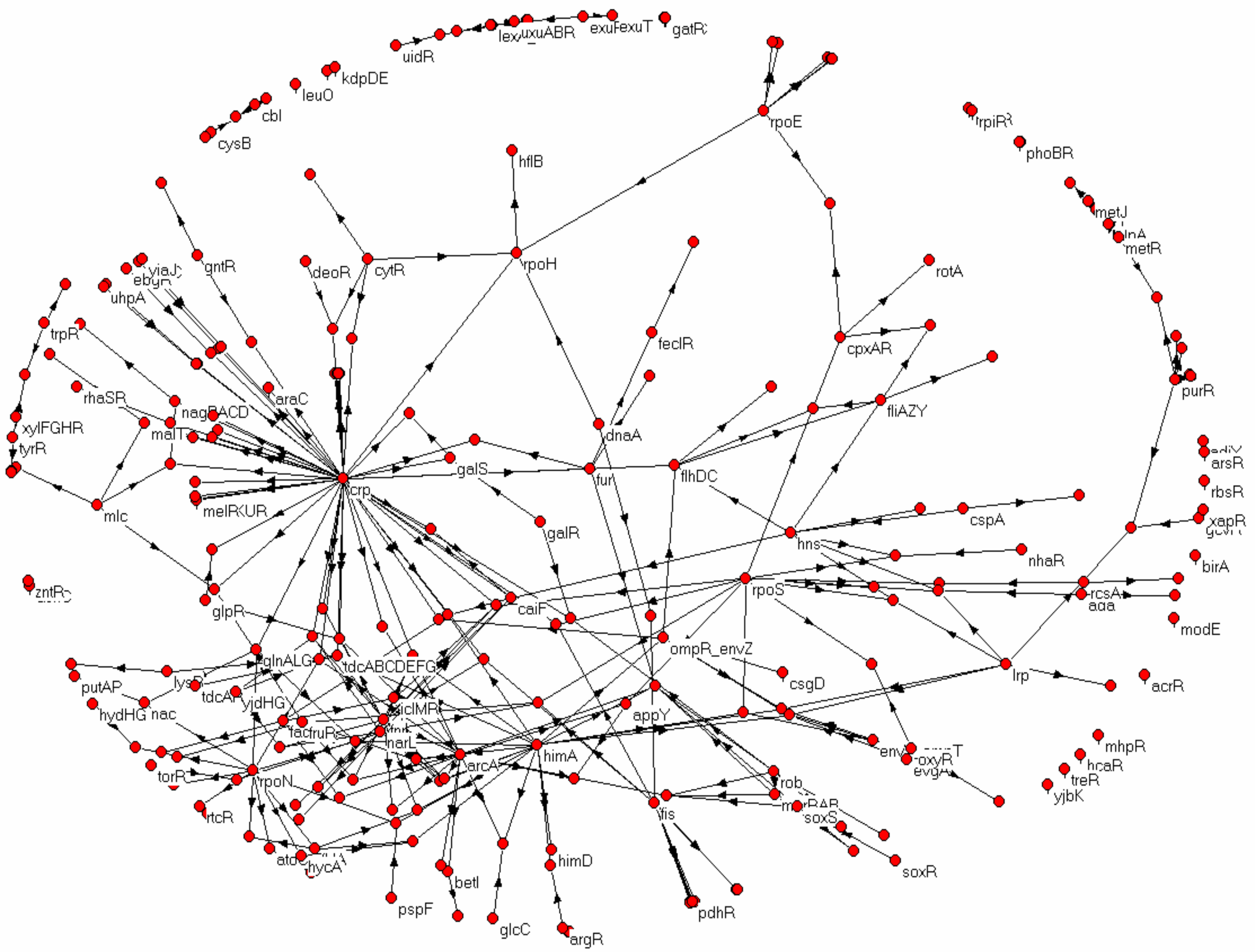
3) generate an ensemble of random networks- networks which preserve the degree sequence of the real network

4) Repeat 1) and 2) on each random network

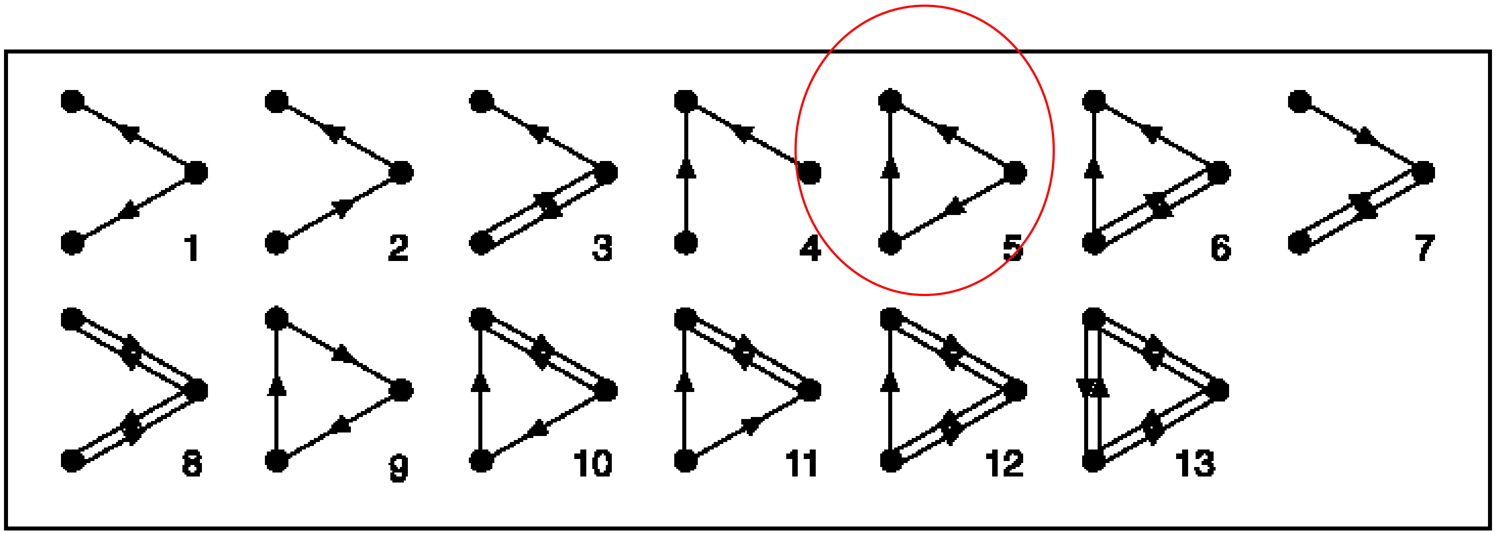
•Subgraphs with a high Z-score are denoted as network motifs.

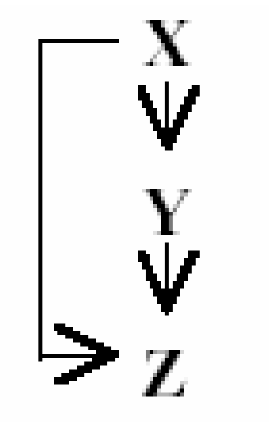
$$Z = \frac{N_{real} - N_{rand}}{\sigma_{rand}}$$

Network motifs in E. coli transcription network



Only one 3-node network motif – the feedforward loop

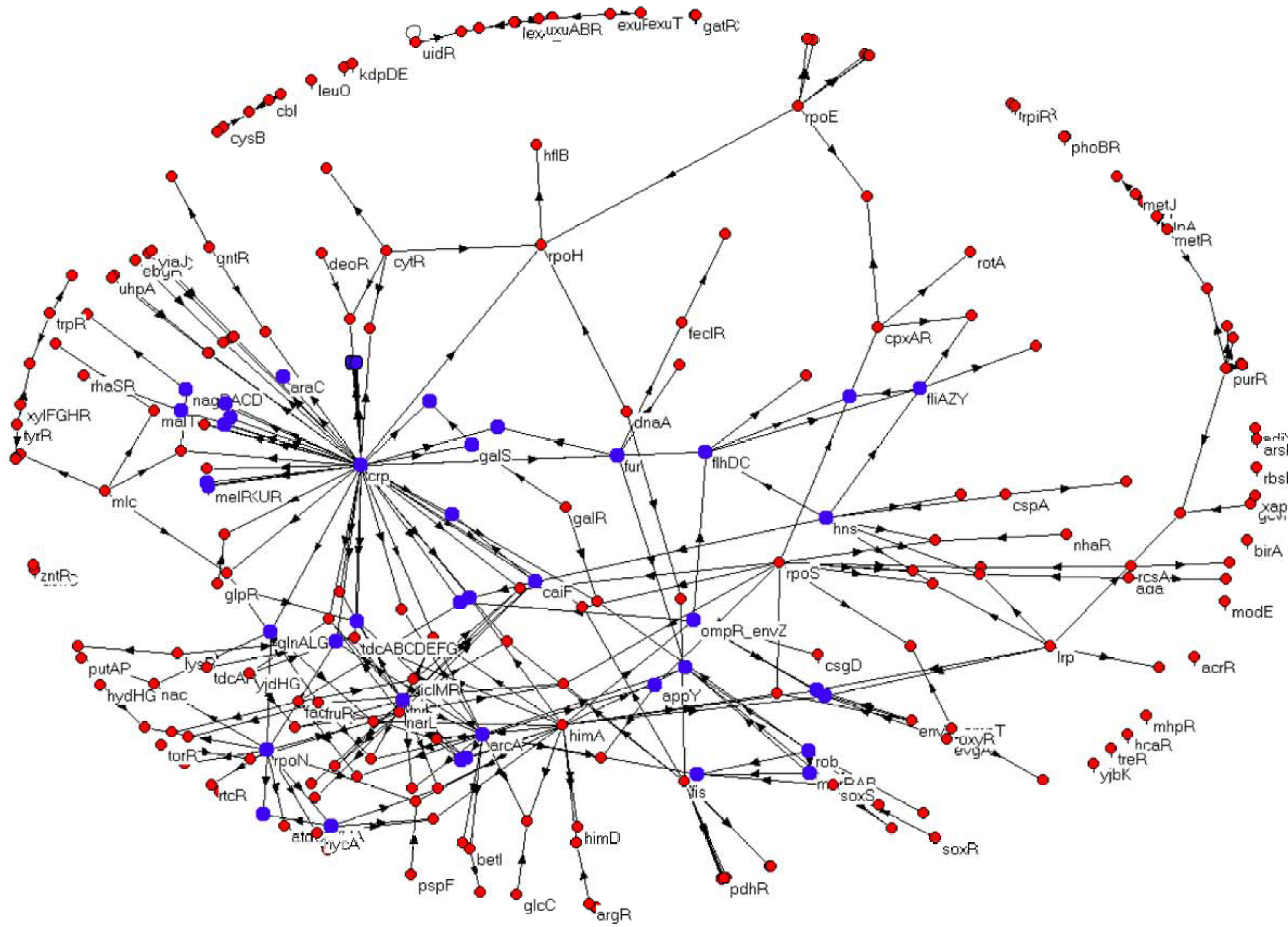




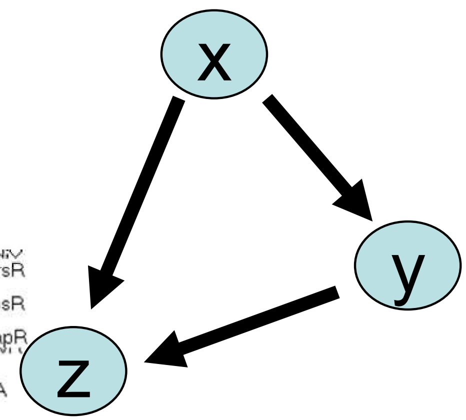
Nreal=40

Nrand=7±3

Z Score (#SD) =10

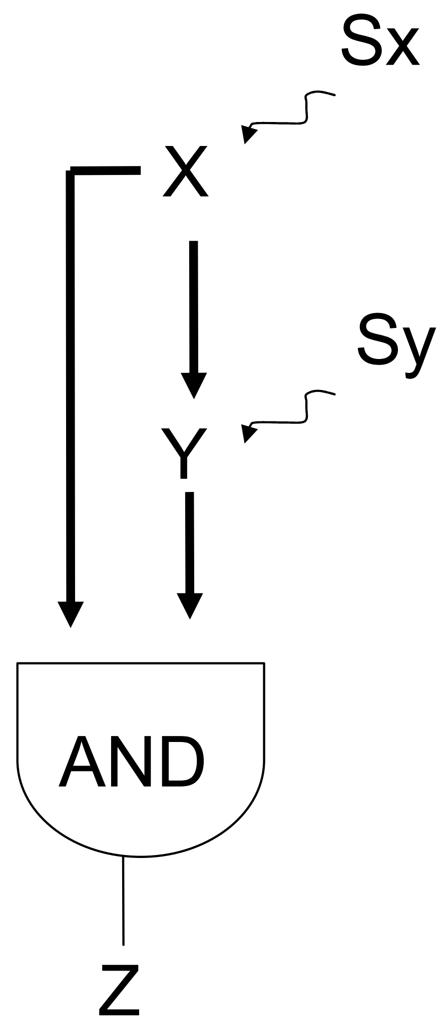


Blue nodes=

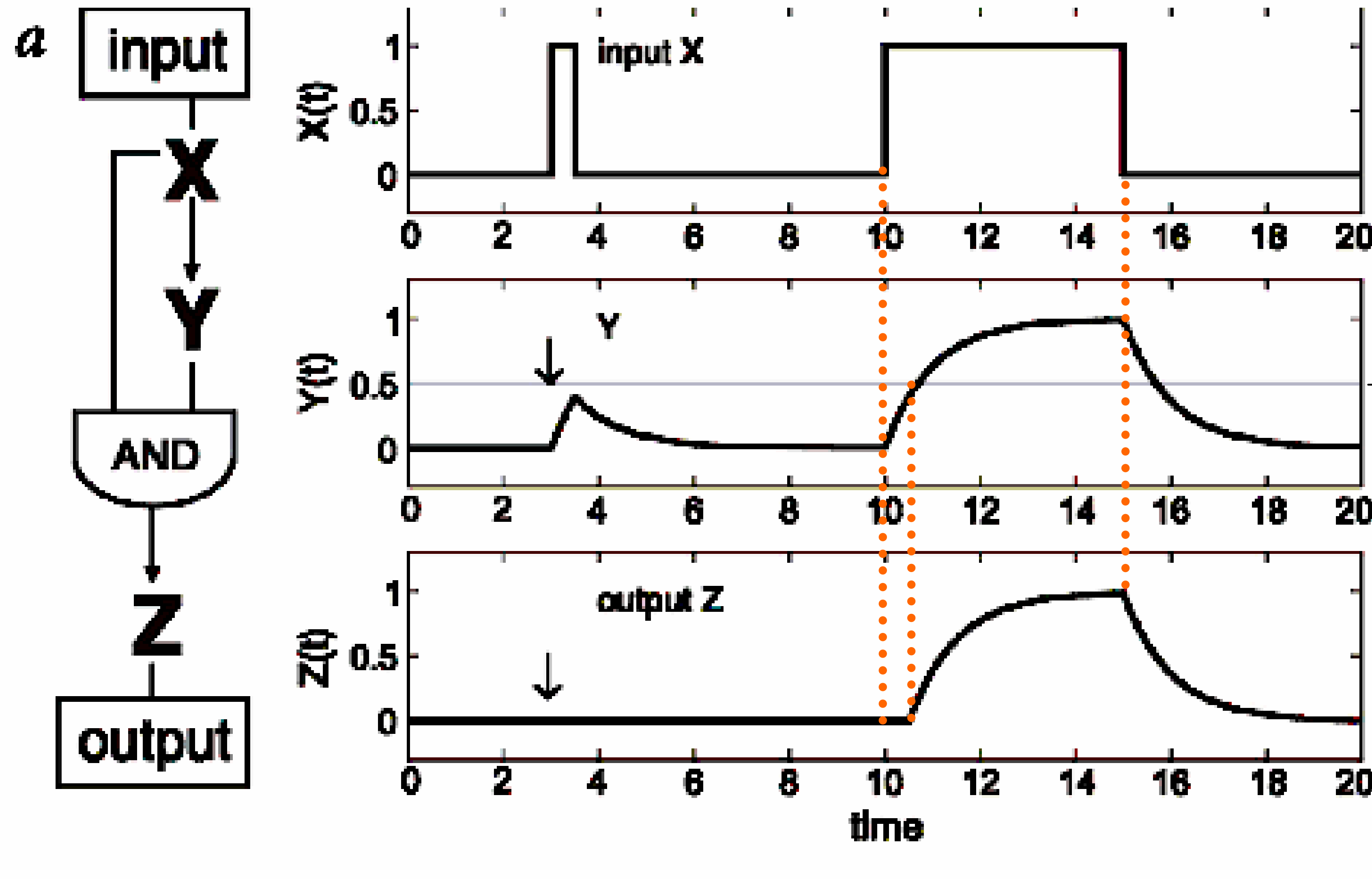


FFL

The coherent FFL circuit

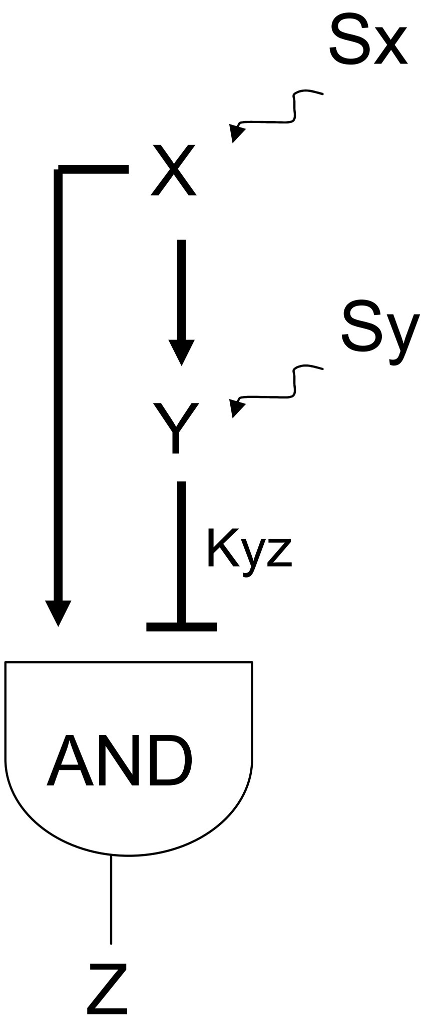


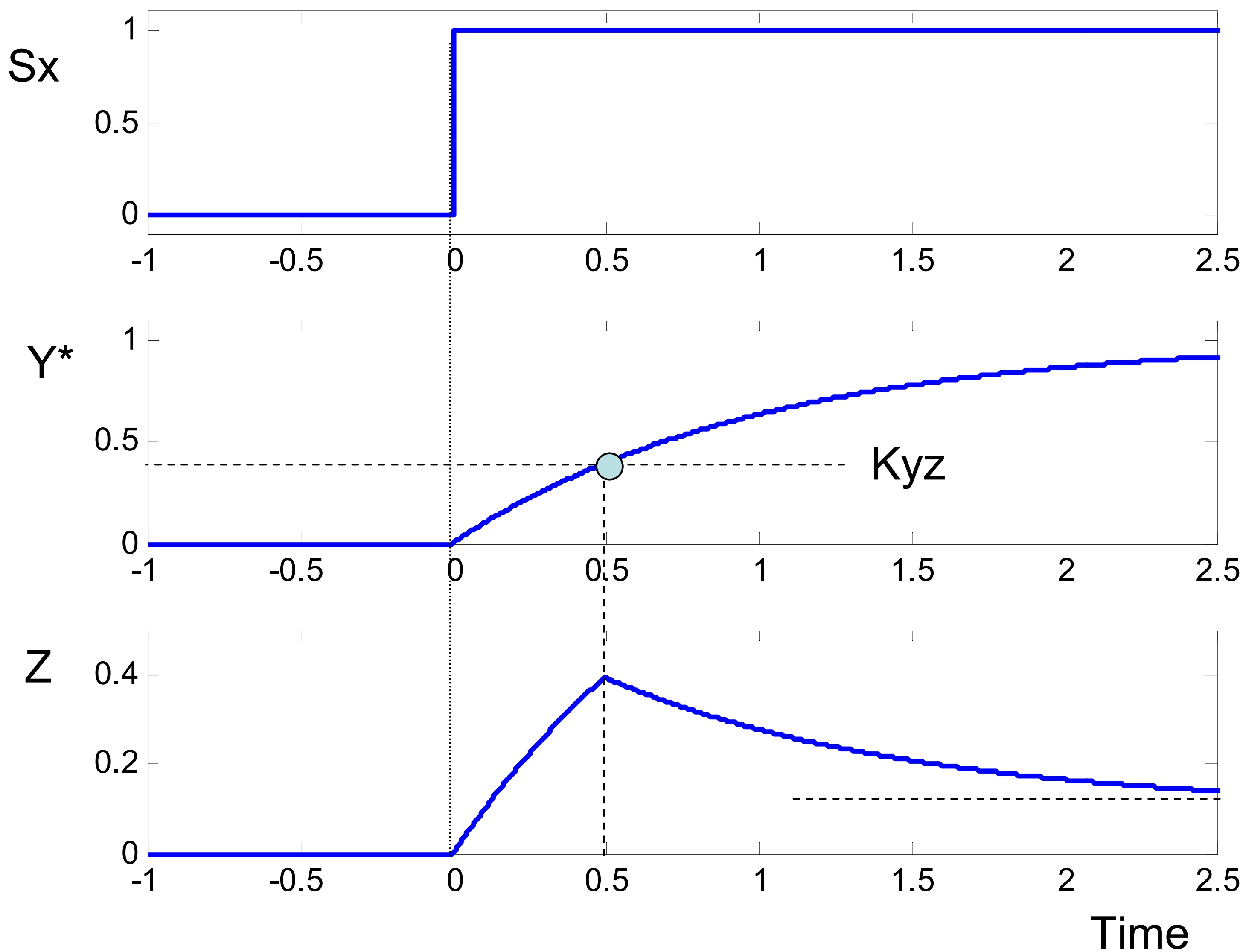
Coherent FFL – a sign sensitive filter



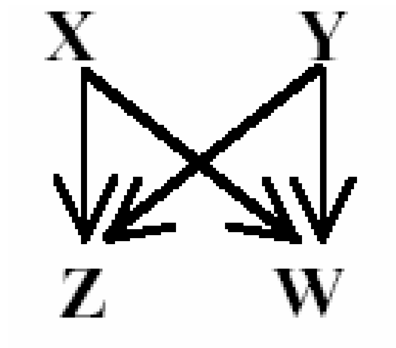
Threshold for activating Y

Incoherent FFL – a pulser circuit





A motif with 4 nodes : bi-fan

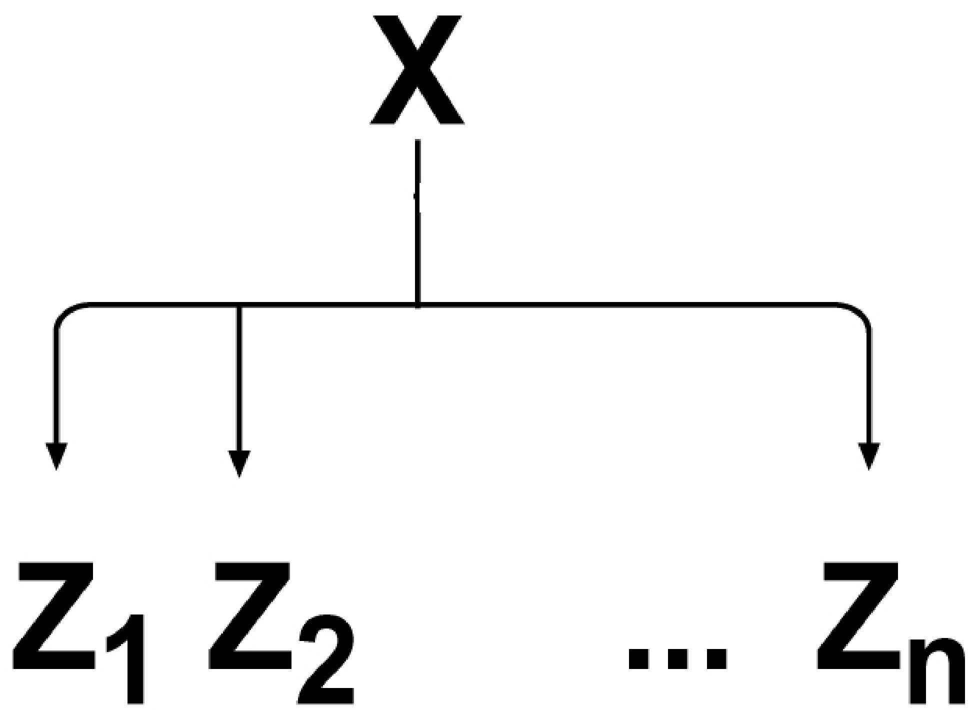


Nreal=203

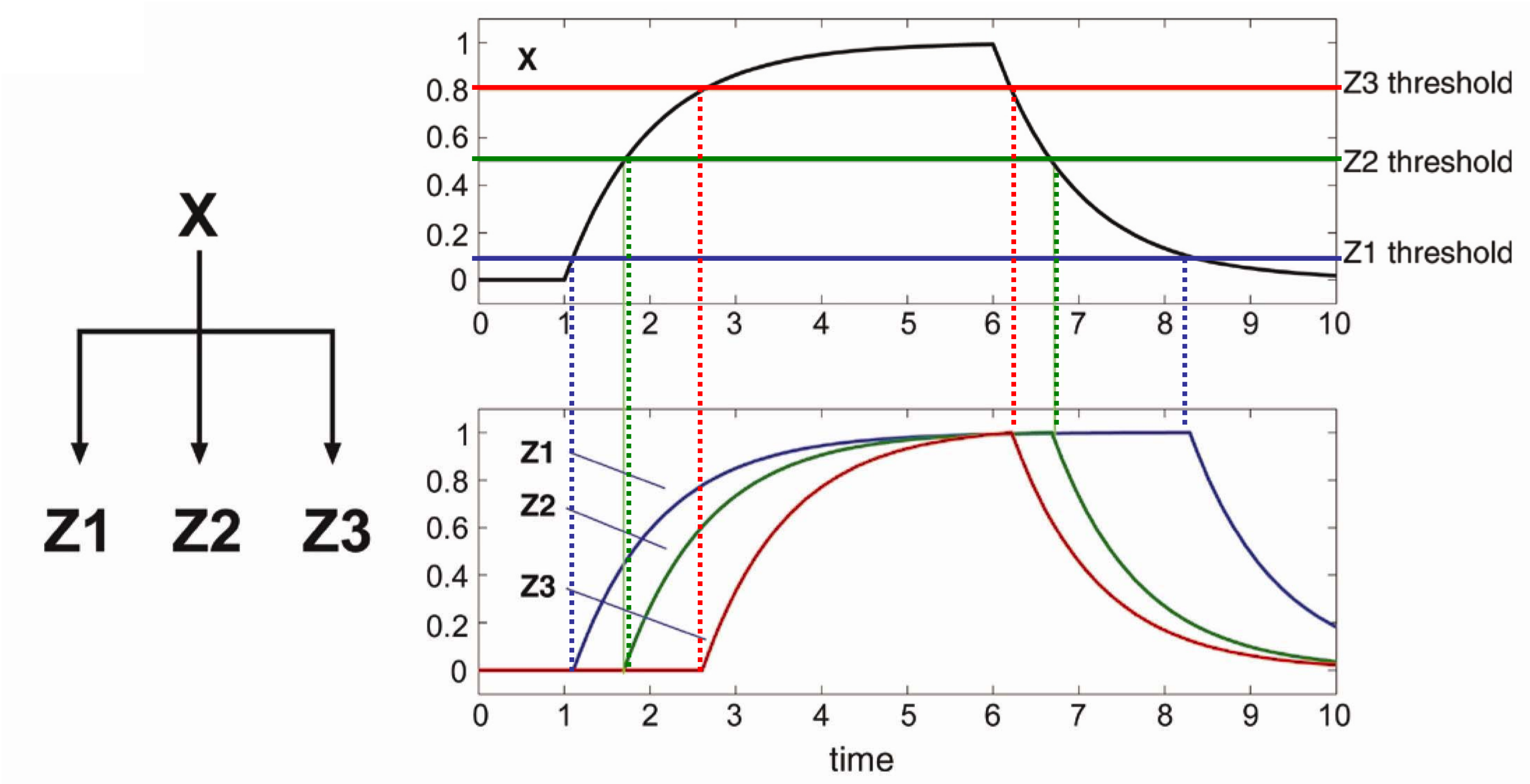
Nrand=47±12

Z Score=13

Another motif : Single Input Module

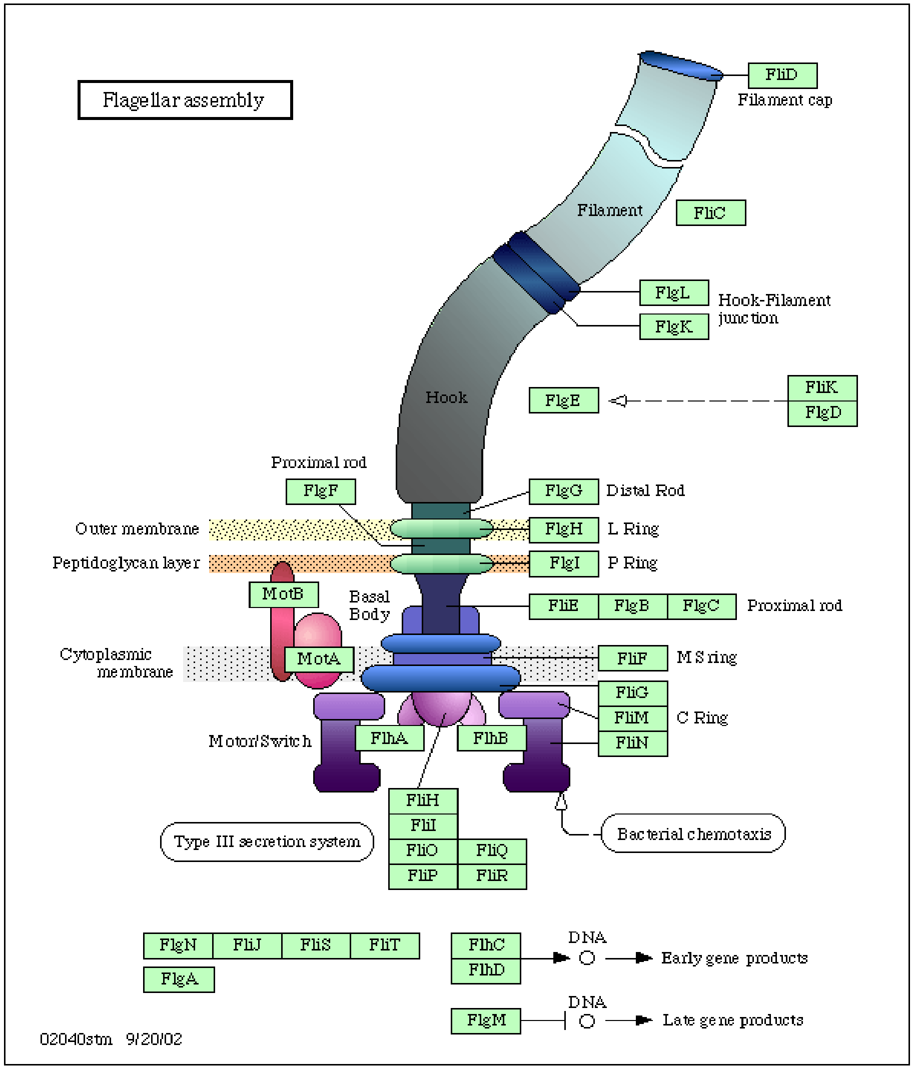


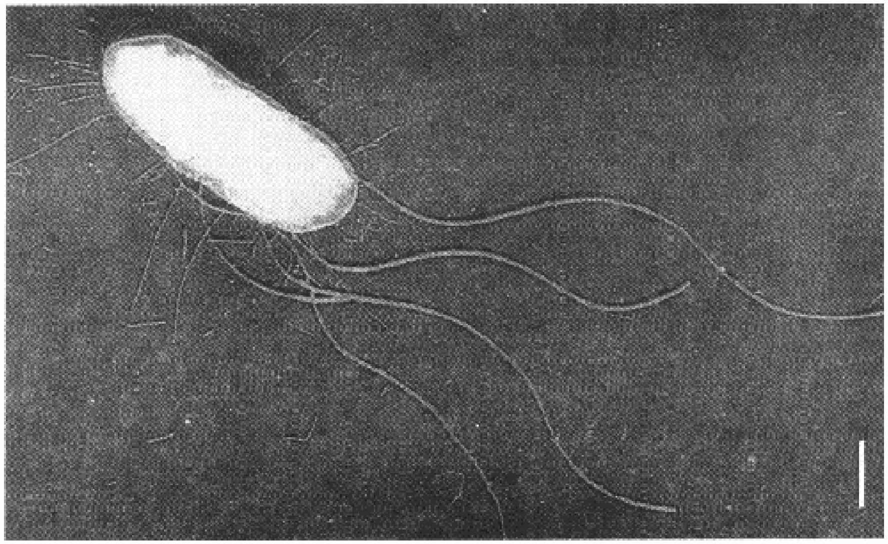
Single Input Module motifs can control timing of gene expression



Shen-Orr et. al. Nature Genetics 2002

Single Input Module motif is responsible for exact timing in the flagella assembly





Gene regulation networks can be simplified in terms of recurring building blocks

Network motifs are functional building blocks of these information processing networks.

Each motif can be studied theoretically and experimentally.

Efficient detection of larger motifs?

- The presented motif detection algorithm is exponential in the number of nodes of the motif.
- More efficient algorithms are needed to look for larger motifs in higher-order organism that have much larger gene-regulatory networks.

More information :

http://www.weizmann.ac.il/mcb/UriAlon/

Papers
mfinder – network motif detection software
Collection of complex networks