COMPLEX SYSTEMS: ORGANIZATION AND DYNAMICS

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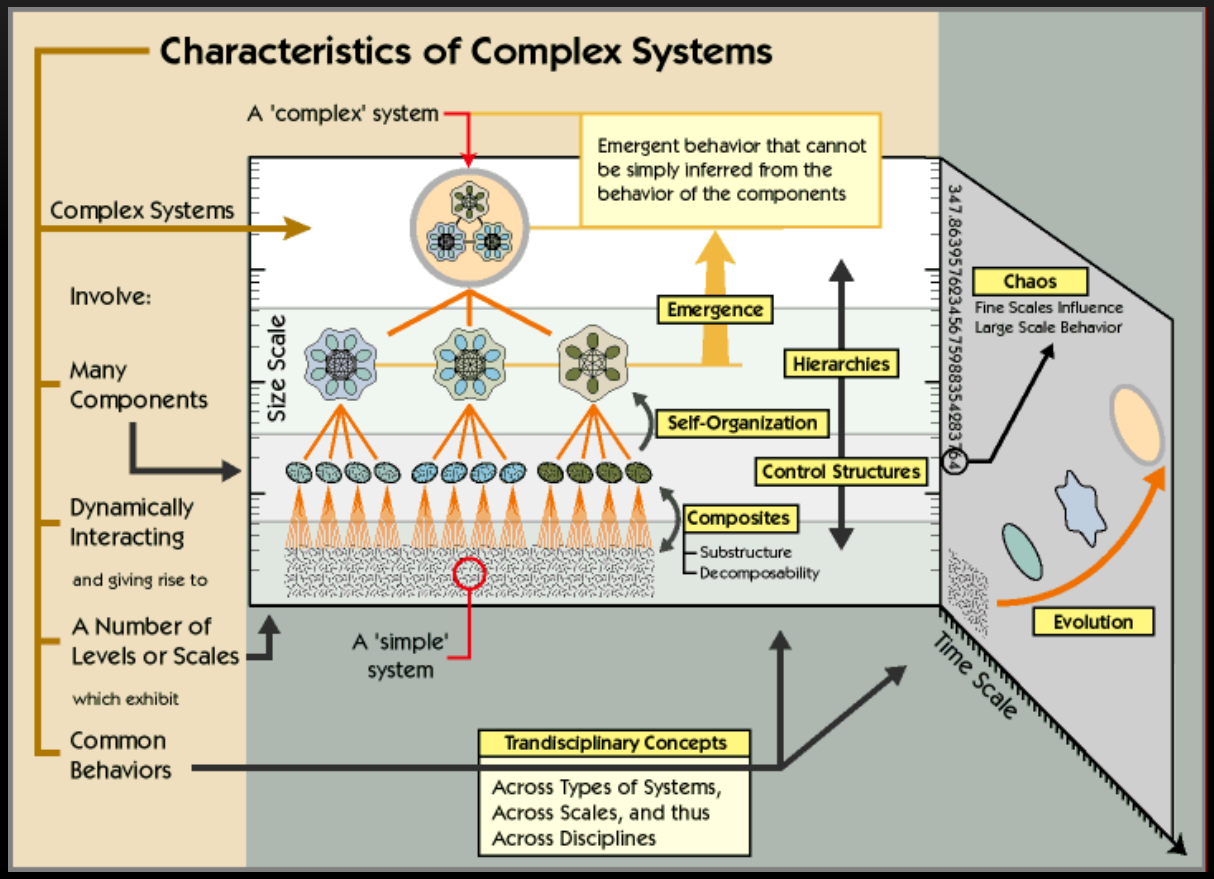
Immunology Group

COMPLEX SYSTEMS



Complex systems are organized as networks, showing hierarchical modularity and scale free structure

TYPES OF BIOLOGICAL NETWORK

- Gene regulatory network
- Metabolic network
- Signal transduction network
- Protein-protein interaction network

At different scale

- Immunological network
- Ecological network
- Intracellular vesicular network

CHALLENGES

- Identifying complex macromolecular interaction between genes, proteins and metabolites

Once identified, Network models can be used to:

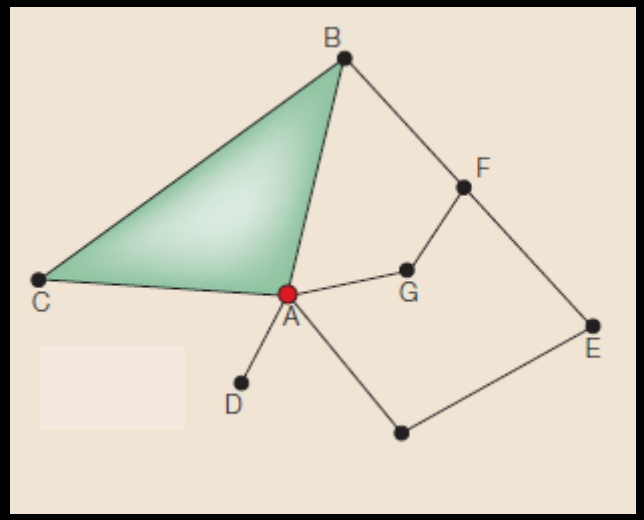
- Simulate the process it represents
- Predict the features of its dynamic behavior
- Extrapolate cellular phenotypes

FEATURES OF GRAPHS

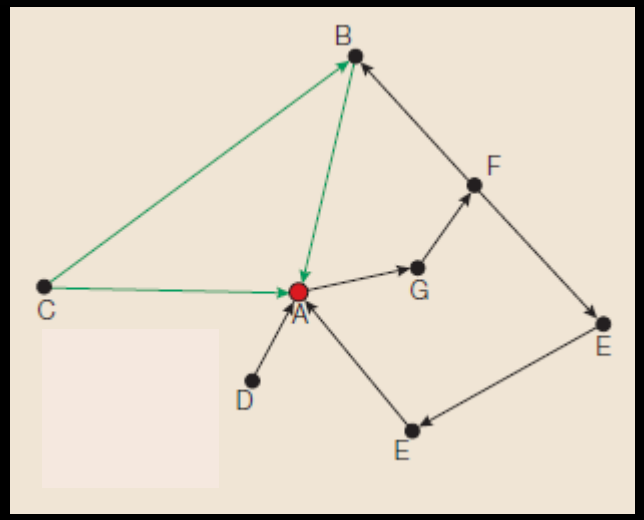
- Biological networks are best described and visualized using graphs
- Node degree (in- and out- degree for directed graphs)
- Average degree distribution (*k*), *k=N/E* (N=total number of nodes in a graph, E=edges)
- Shortest and mean path length
- Clustering coefficient (interactions among the adjacent nodes)
- Betweenness and stress (centrality parameters)

NODE DEGREE

Undirected network



Directed network



G=(*V*, *E*) G=(*8*, *10*)

DEGREE DISTRIBUTION *P(K)*

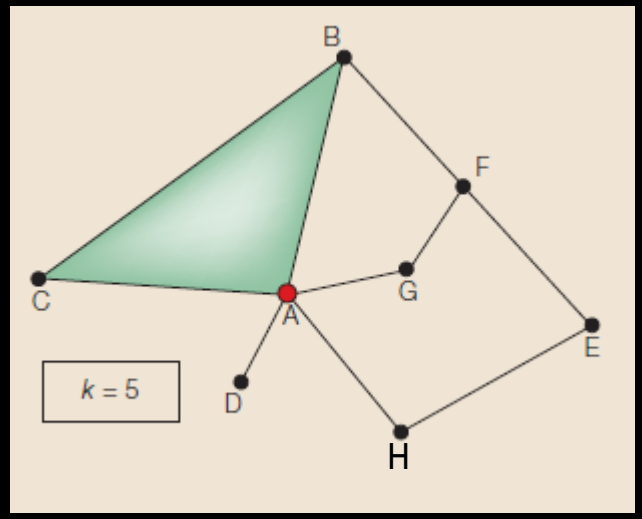
- Degree distribution *P(k):* probability that a given node n has exactly k links in the network

P(k) = N (total no. of Nodes)/K (total no. of links)

Degree distribution: used to classify different kinds of networks

SHORTEST PATH LENGTH AND MEAN PATH LENGTH

- How many links to pass through in order to connect two nodes



Connect node A to E

All possible paths	Steps
A-G, G-F, F-E	3
A-H, H-E	2
A-B, B-F, F-E	3
A-C, C-B, B-F, F-E	4

Shortest path

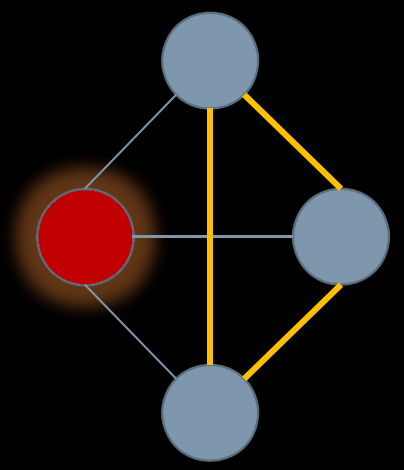
Mean Path Length???

CLUSTERING COEFFICIENT *C(K)*

$C_I = 2n_I / k(k-1)$

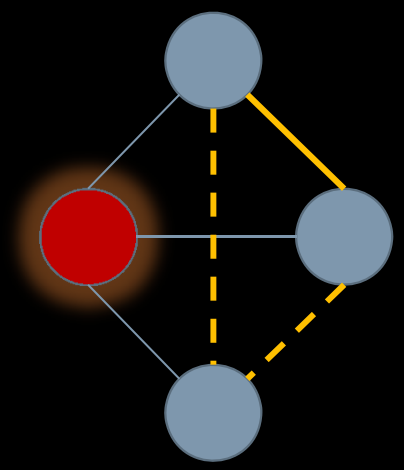
n_I =links between first neighbors

$k(k-1)/2$ = Total possible links between first neighbors



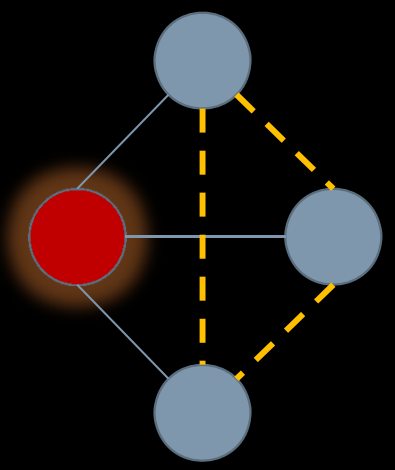
$n_I = 3$, $k(k-1)/2 = 3$

Hence Ci=1



$n_I = 1$, $k(k-1)/2 = 3$

Hence Ci=1/3



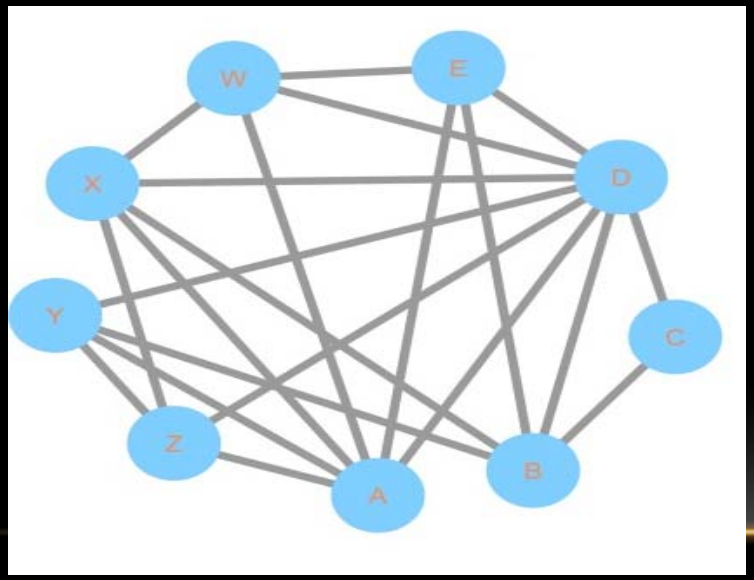
$n_I = 0$, $k(k-1)/2 = 3$

Hence Ci=0/3

CLUSTERING COEFFICIENT OF ENTIRE NETWORK

n_I =links between first neighbors
k(k-1)/2 = Total possible links between first neighbors

$$C_I = 2n_I / k(k-1)$$



21/36 0.583333333

TYPES OF GRAPHS (NETWORKS)

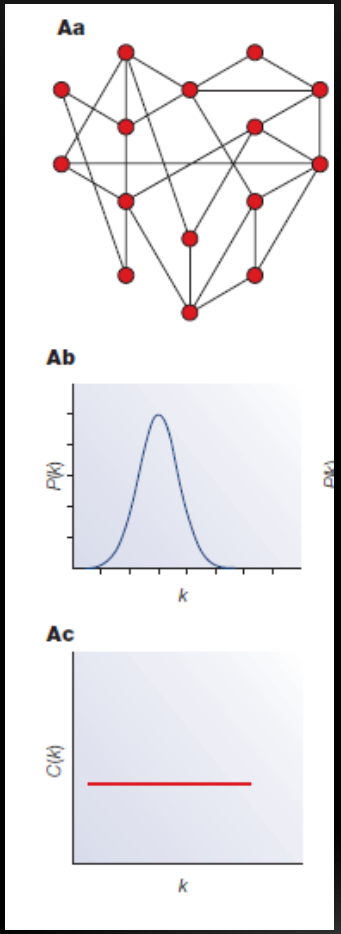
- Random graphs (Erdos-Renyi Network)
- Scale-free Networks
- Hierarchical Networks

Degree distribution and clustering together defines network types

RANDOM NETWORKS

Degree distribution

Clustering coefficient



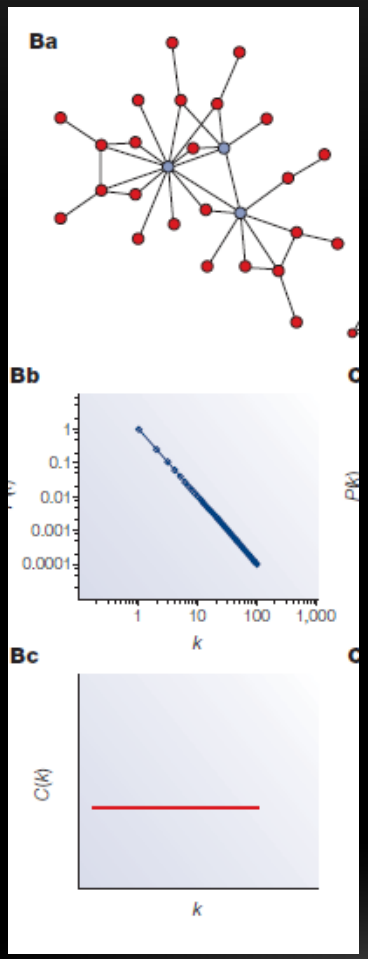
Equal probability for each pair of nodes to be connected

Most of the nodes have degree distribution very similar to the average

Clustering coefficient independent of nodes

Random networks have no preferential interactions
And hence contain hardly any information

SCALE FREE NETWORK



Power-law degree distribution

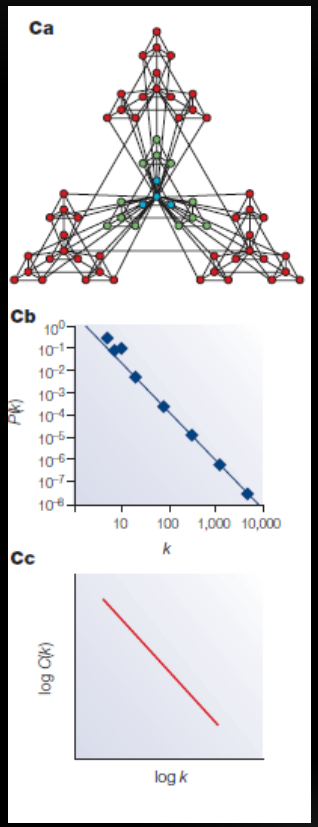
Frequency of event varies with power of some attribute

Degree distribution???

Clustering coefficient is independent of *k*
No modularity

Preferential attachment of new incoming node to
The highly connected node (hub) in the network

HIERARCHICAL NETWORK



Modularity, local clustering and scale free organization!!

Sparsely connected nodes are part of highly clustered areas

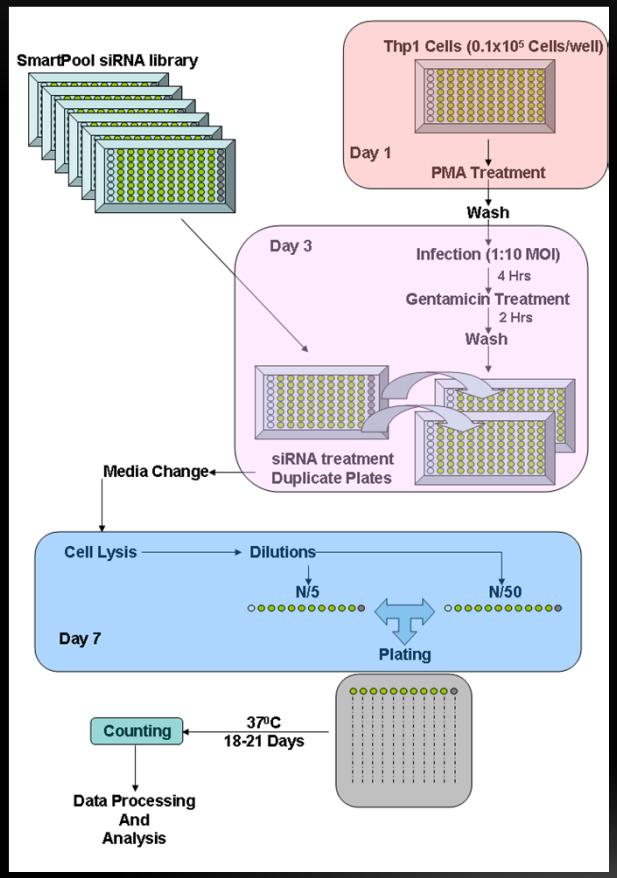
Communication between different clustered area maintained by Interactions between few hubs!!!

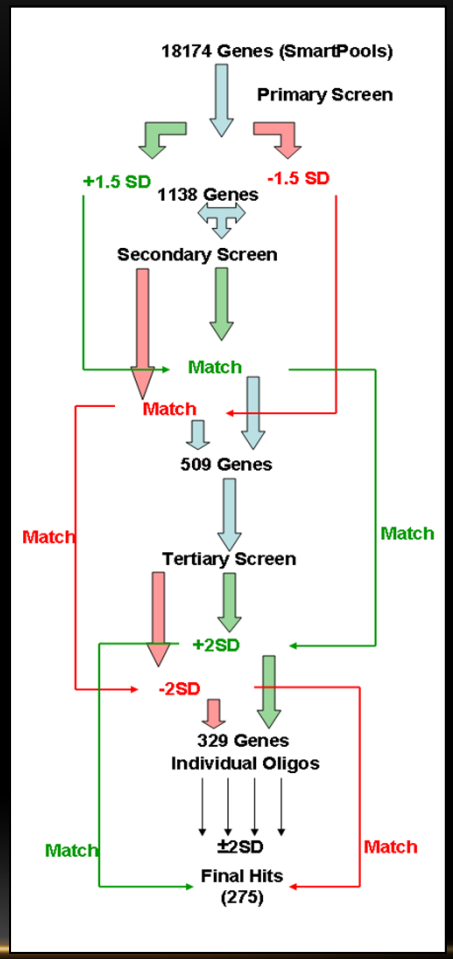
Modular architecture, C(k) dependent on k

MOST REAL-WORLD NETWORKS ARE MODULAR

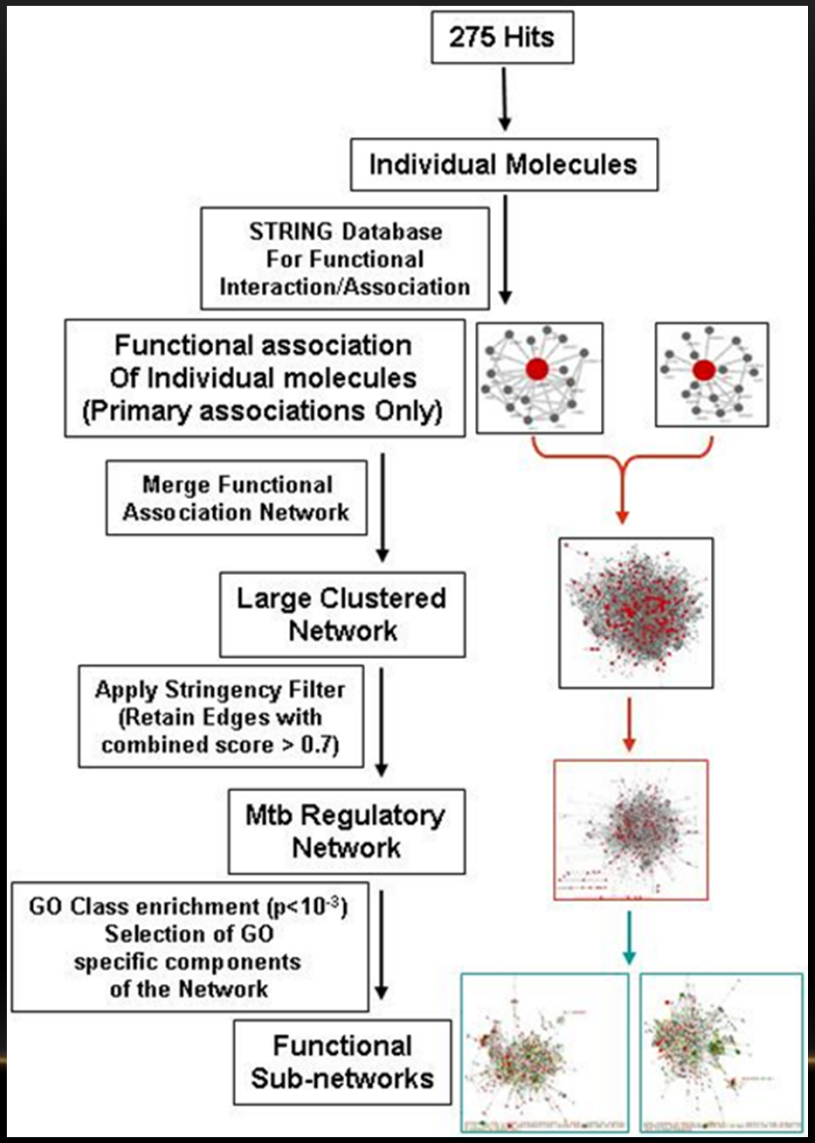
- They exhibit scale-free property
- Sub-modules of the larger network show similar property as the parent network

EXAMPLE: RECONSTRUCTING OF MTB REGULATORY NETWORK FROM HOST FACTORS

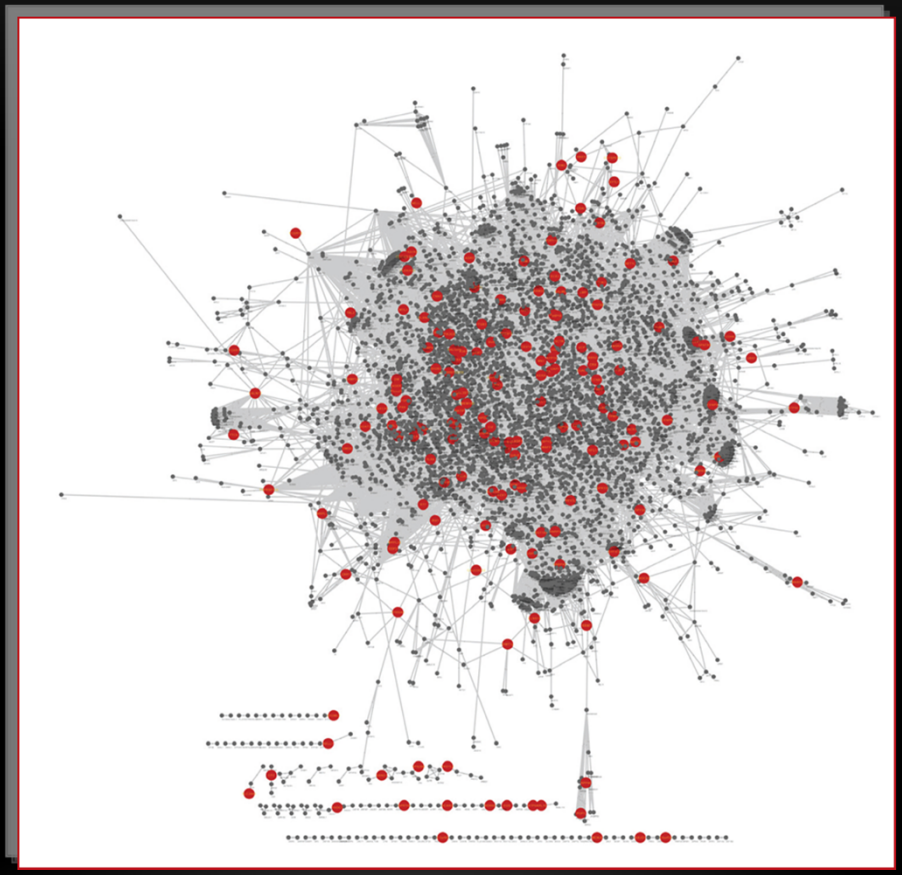




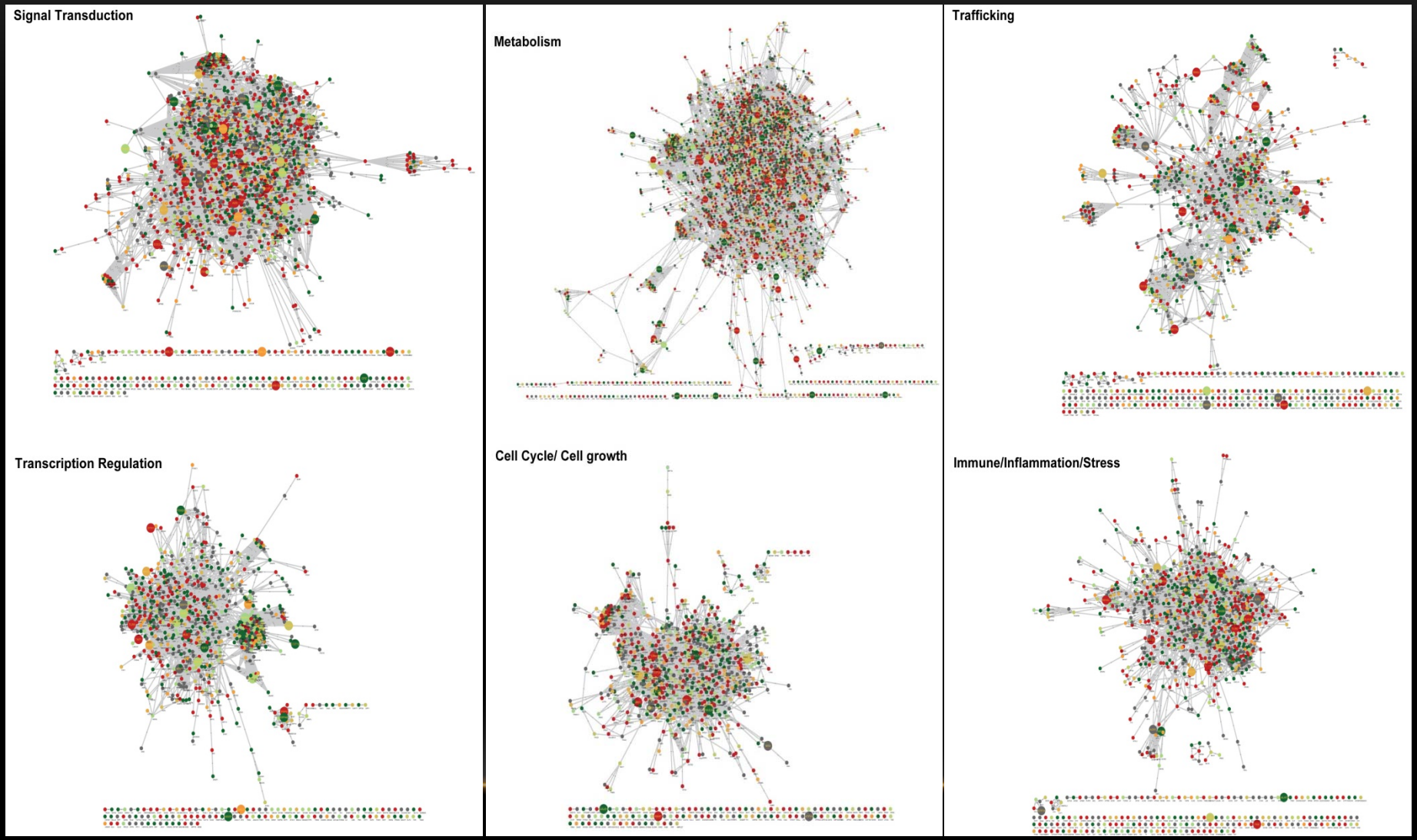
MTB REGULATORY NETWORK RECONSTRUCTION



MTB REGULATORY NETWORK

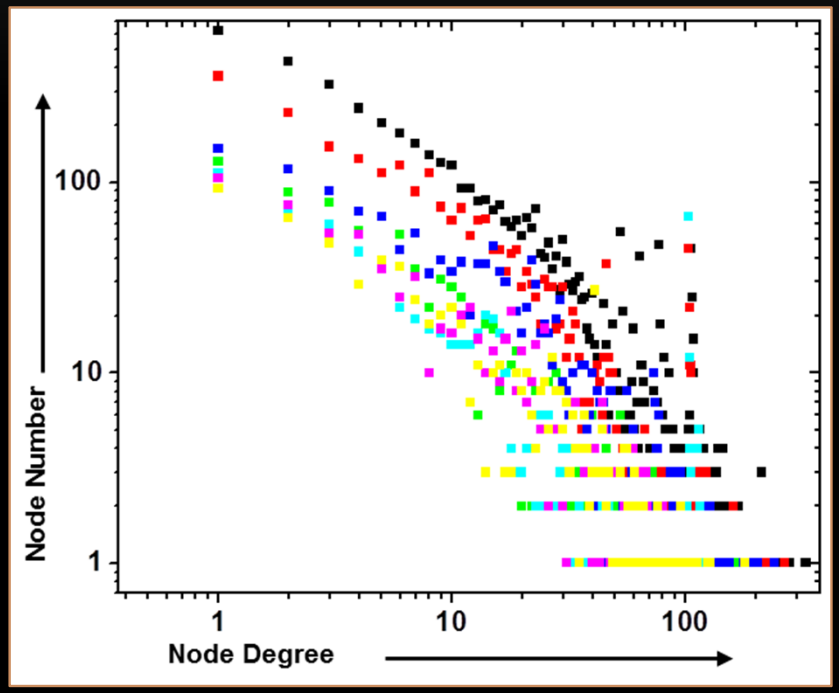


IDENTIFY SUB-NETWORKS INVOLVED WITH SPECIFIC BIOLOGICAL FUNCTION



FEATURES OF THE PARENT AND SUB-NETWORKS

Network	Avg. Clustering Coefficient	Avg. Path Length	Avg. Node Degree
Mtb RN	.526	3.99	21.66
Metabolism	.494	3.9	17.839
ST	.493	3.304	18.81
Im/St	.388	3.358	11.068
Traffic	.449	4.059	10.803
TF	.457	3.346	20.809
CCR	.448	3.145	14.889



Modular and scale-free organization of the Mtb regulatory network

CENTRALITY PARAMETERS OF NETWORKS

- Degree
- Clustering
- Mean path length
- Stress
- Betweenness

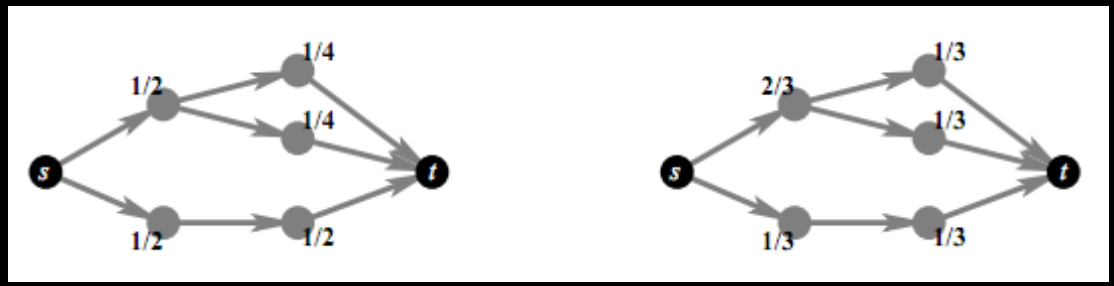
STRESS AND BETWEENNESS

Number of shortest paths passing through a node

- Calculate shortest paths between each pair of nodes in the network
- Nodes present in higher number of shortest path compared to the average are stressed nodes

- Betweenness refers to the no. of shortest path passing through a given node between two different regions in the network.

STRESS AND BETWEENNESS



Stress algorithm

Betweenness algorithm

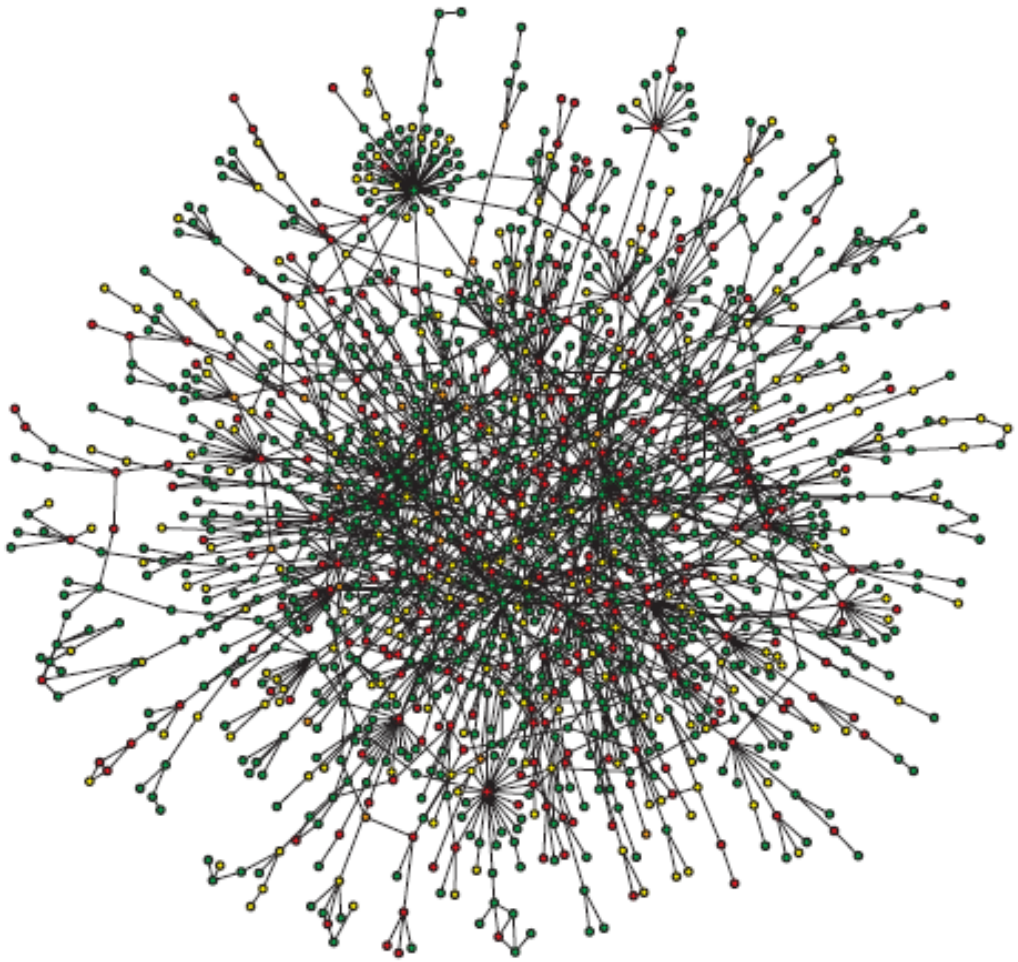


Figure 2 | **Yeast protein interaction network.** A map of protein–protein interactions[18] in *Saccharomyces cerevisiae*, which is based on early yeast two-hybrid measurements[23], illustrates that a few highly connected nodes (which are also known as hubs) hold the network together. The largest cluster, which contains ~78% of all proteins, is shown. The colour of a node indicates the phenotypic effect of removing the corresponding protein (red = lethal, green = non-lethal, orange = slow growth, yellow = unknown). Reproduced with permission from REF. 18 © Macmillan Magazines Ltd.

Nodes with lethal phenotype showed relatively higher betweenness centrality value

DYNAMICS IN BIOLOGICAL NETWORKS

Most of the networks are static in nature, do not incorporate temporal changes in Network topology and parameters related to constituent nodes

How to bring in dynamic features into the network?

What are the advantages of having Dynamic network?

INCORPORATING DYNAMICS IN BIOLOGICAL NETWORK

- Conversion of interaction networks into set of dynamical equations (Boolean or Ordinary Differential Equation based models)

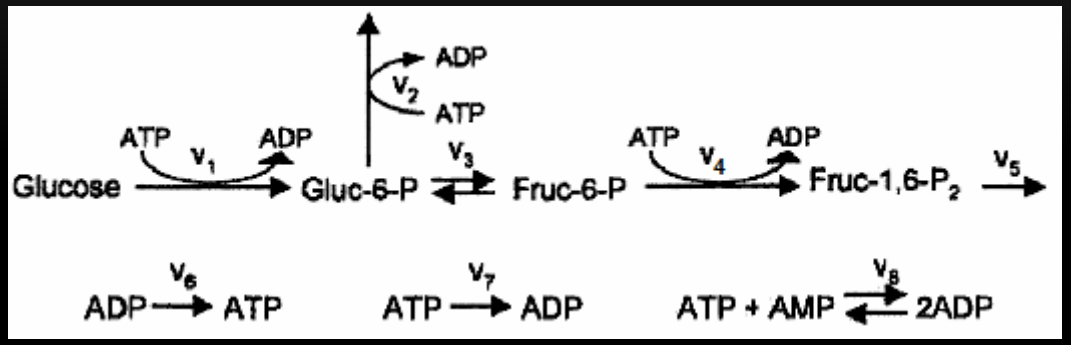
- Breaking down of large biological networks into smaller motifs and study their dynamics

- Most motifs are identified by their unusual frequency of occurrence in the regulatory network

- Incorporation of dynamical experimental data, e.g. Microarrays, protein expression, DNA binding, Protein phosphorylation etc.

Time-resolved protein interaction network!!

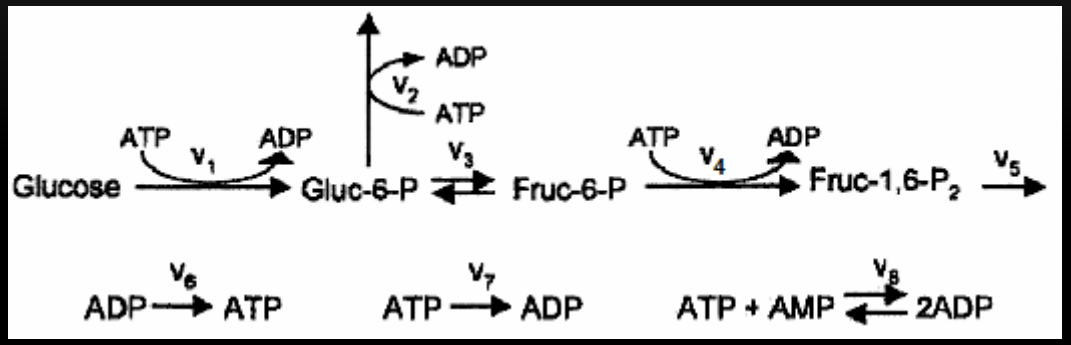
NETWORK DYNAMICS



Reactions

v1: hexokinase
v2: consumption of glucose–6–phosphate in other pathways
v3: phosphoglucoisomerase
v4: phosphofructokinase
v5: aldolase
v6: ATP production in lower glycolysis
v7: ATP consumption in other pathways
v8: adenylate kinase

ODE MODEL OF GLYCOLYSIS



$$\frac{d}{dt} Gluc6P = v_1 - v_2 - v_3$$

$$\frac{d}{dt} Fruc6P = v_3 - v_4$$

$$\frac{d}{dt} Fruc1,6P_2 = v_4 - v_5$$

$$\frac{d}{dt} ATP = -v_1 - v_2 - v_4 + v_6 - v_7 - v_8$$

$$\frac{d}{dt} ADP = v_1 + v_2 + v_4 - v_6 + v_7 + 2\,v_8$$

$$\frac{d}{dt} AMP = -v_8\,.$$

KINETIC RATES FOR THE MODEL

$$v_1 = \frac{V_{max,1}\, ATP(t) \cdot Glucose}{1 + \frac{ATP(t)}{K_{ATP,1}} + \frac{Glucose}{K_{Glucose,1}} + \frac{ATP(t)}{K_{ATP,1}} \cdot \frac{Glucose}{K_{Glucose,1}}}$$

$$v_2 = k_2\, ATP(t) \cdot Gluc6P(t)$$

$$v_3 = \frac{\frac{V^f_{max,3}}{K_{Gluc6P,3}} Gluc6P(t) - \frac{V^r_{max,3}}{K_{Fruc6P,3}} Fruc6P(t)}{1 + \frac{Gluc6P(t)}{K_{Gluc6P,3}} + \frac{Fruc6P(t)}{K_{Fruc6P,3}}}$$

$$v_4 = \frac{V_{max,4}\, (Fruc6P(t))^2}{K_{Fruc6P,4}\left(1 + \kappa\left(\frac{ATP(t)}{AMP(t)}\right)^2\right) + (Fruc6P(t))^2}$$

$$v_5 = k_5\, Fruc1,6P_2(t)$$

$$v_6 = k_6 ADP(t)$$

$$v_7 = k_7 ATP(t)$$

$$v_8 = k_{8f}\, ATP(t) \cdot AMP(t) - k_{8r}\, (ADP(t))^2\,,$$

MODEL PARAMETERS

$Glucose = 12.8174\,\mathrm{mM}$, $V_{\max,1} = 1398.00\,\mathrm{mM} \cdot \mathrm{min}^{-1}$, $K_{ATP,1} = 0.10\,\mathrm{mM}$,
$K_{Glucose,1} = 0.37\,\mathrm{mM}$, $V_{max,1} = 50.2747\,\mathrm{mM} \cdot \mathrm{min}^{-1}$

$k_2 = 2.26\,\mathrm{mM}^{-1} \cdot \mathrm{min}^{-1}$

$V^f_{max,3} = 140.282\,\mathrm{mM} \cdot \mathrm{min}^{-1}$, $V^r_{max,3} = 140.282\,\mathrm{mM} \cdot \mathrm{min}^{-1}$, $K_{Gluc6P,3} = 0.80\,\mathrm{mM}$,
$K_{Fruc6P,3} = 0.15\,\mathrm{mM}$

$V_{max,4} = 44.7287\,\mathrm{mM} \cdot \mathrm{min}^{-1}$, $K_{Fruc6P,4} = 0.021\,\mathrm{mM}^2$, $\kappa = 0.15$

$k_5 = 6.04662\ \mathrm{min}^{-1}$

$k_6 = 68.48\ \mathrm{min}^{-1}$

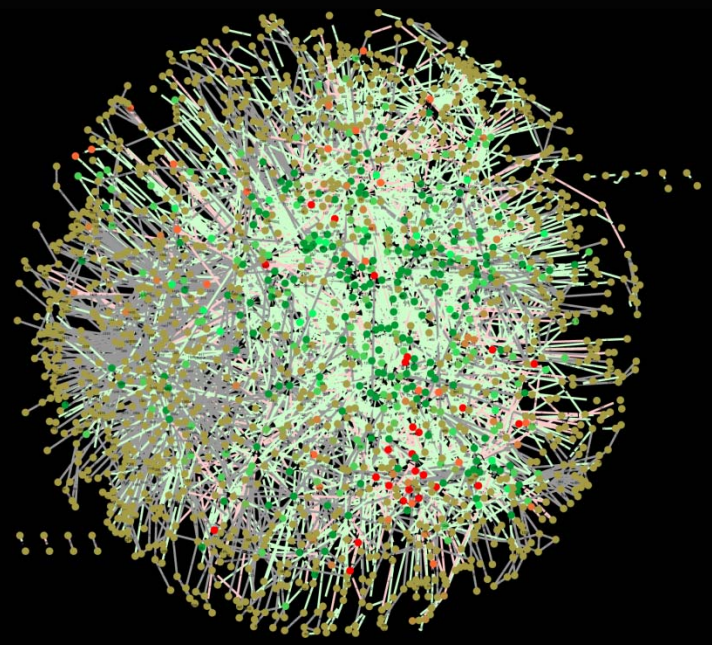
$k_7 = 3.21\ \mathrm{min}^{-1}$

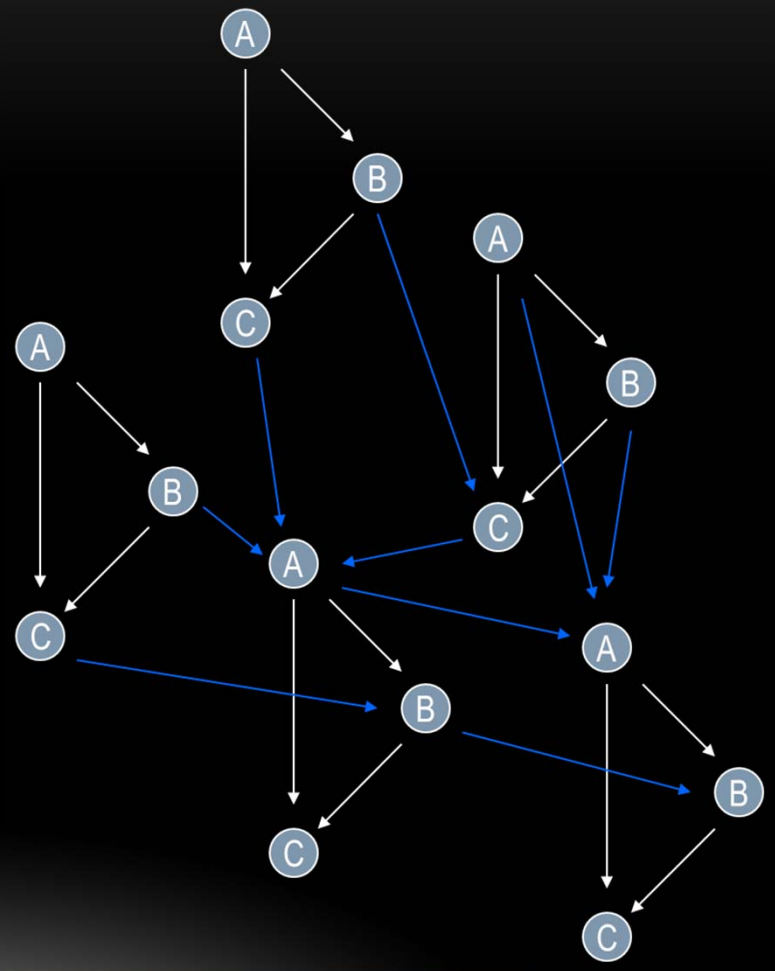
$k_{8f} = 432.9\,\mathrm{mM}^{-1} \cdot \mathrm{min}^{-1}$, $k_{8r} = 133.33\,\mathrm{mM}^{-1} \cdot \mathrm{min}^{-1}$

DYNAMICS IN LARGE BIOLOGICAL NETWORKS

ADVANCE CELL AND MOLECULAR BIOLOGY
(ICG601)

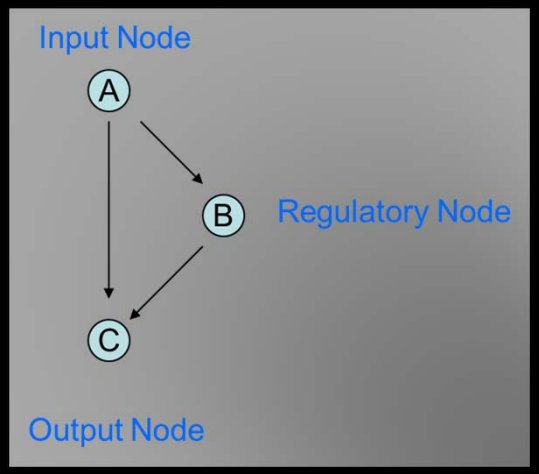
BIOLOGICAL NETWORKS: HIGHER ORDER ORGANIZATION OF SMALLER STRUCTURES





MOTIFS : SIMPLE BUILDING BLOCKS OF NETWORKS

- Large biological networks seems to be made of smaller motifs organized in certain fashion
- Motifs can be of many types, displaying variety of dynamical properties



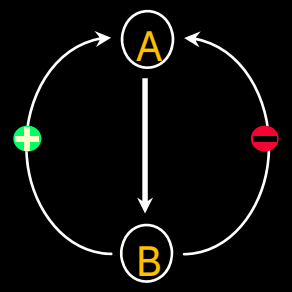
Transcriptional Networks
Signaling Networks
Metabolic Networks

Dynamical properties:

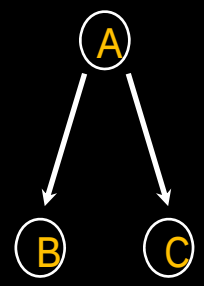
Bi-stable/ultrasensitive/adaptable
Oscillating/delayed response/persistent response

REGULATORY MOTIFS IN SIGNALING

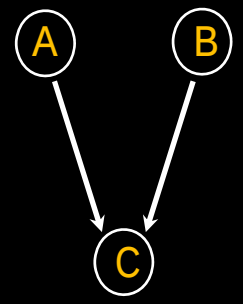
Feedback loops



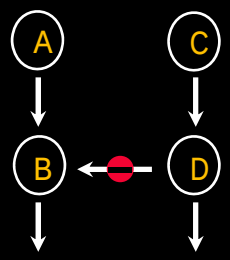
Branching



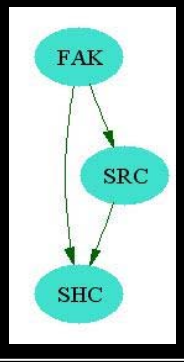
Convergence



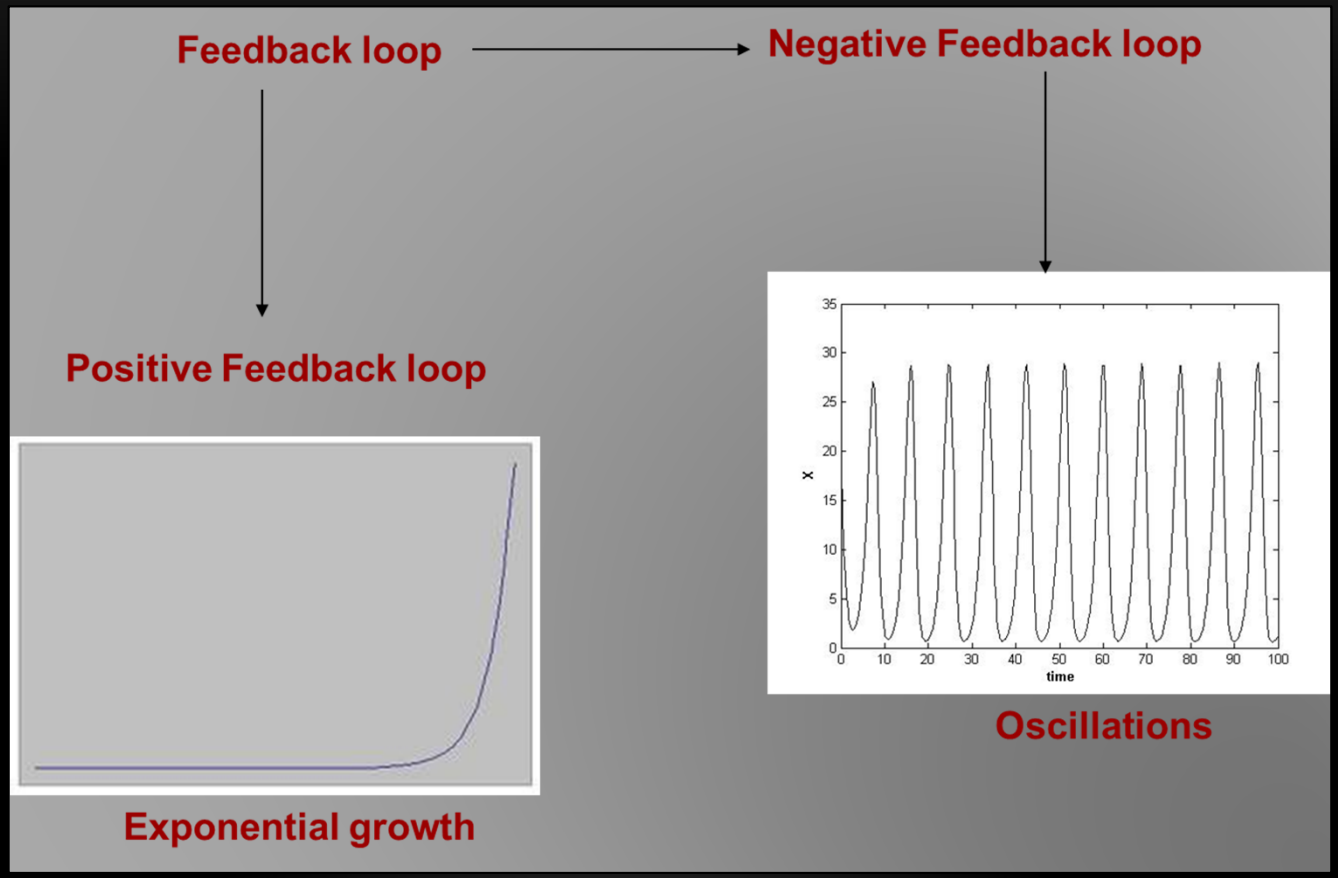
Crosstalk



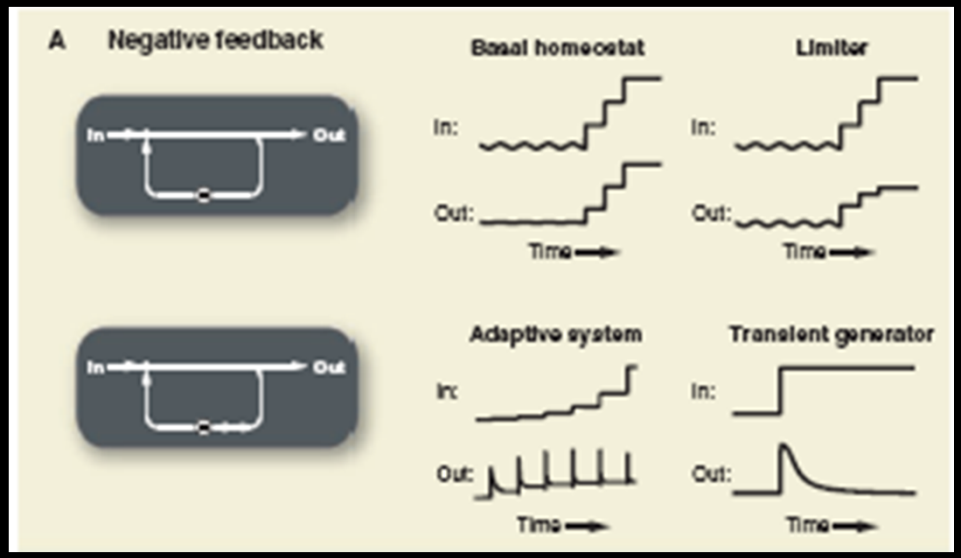
Feed-forward Loops



FEEDBACK DYNAMICS



NEGATIVE FEED-BACK: HOMEOSTAT, LIMITAR, ADAPTABILITY, TRANSIENT RESPONSE



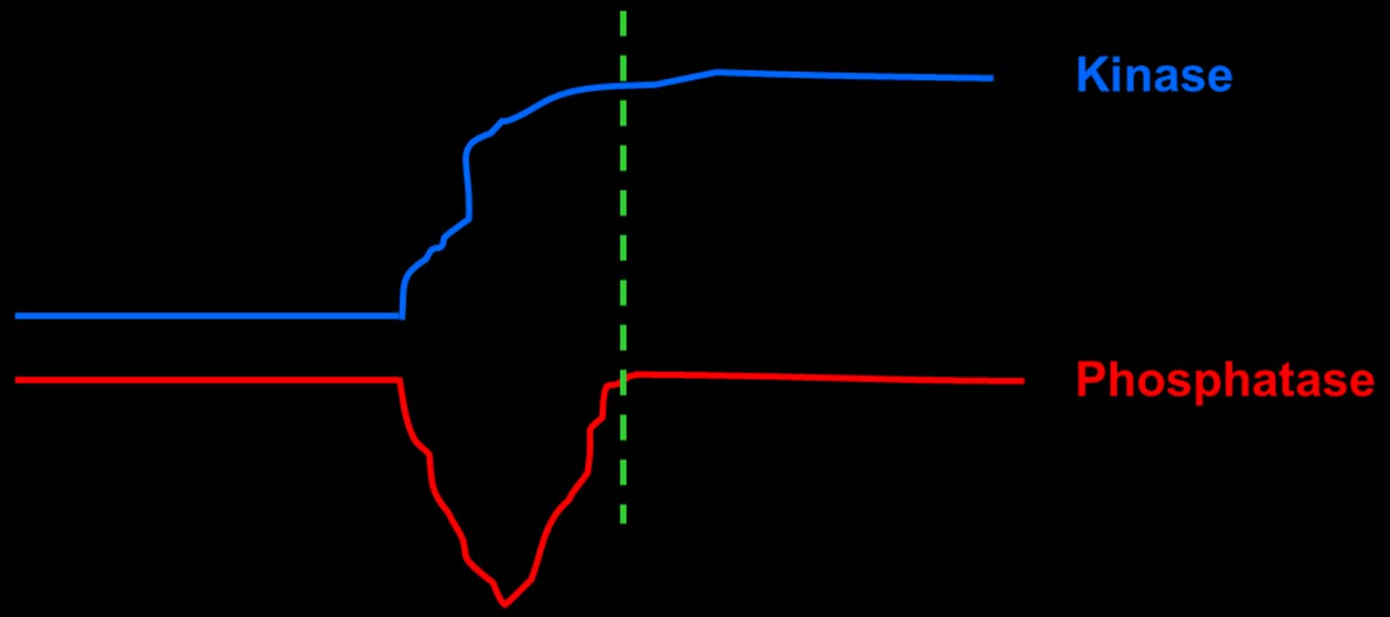
Small Amplitude negative feedback: small deviation→ no effect, needs large deviation in input (eg: STIM2 feed back for calcium regulation in ER)

Limit maximum output, mitochondrial uptake of cytosolic calcium

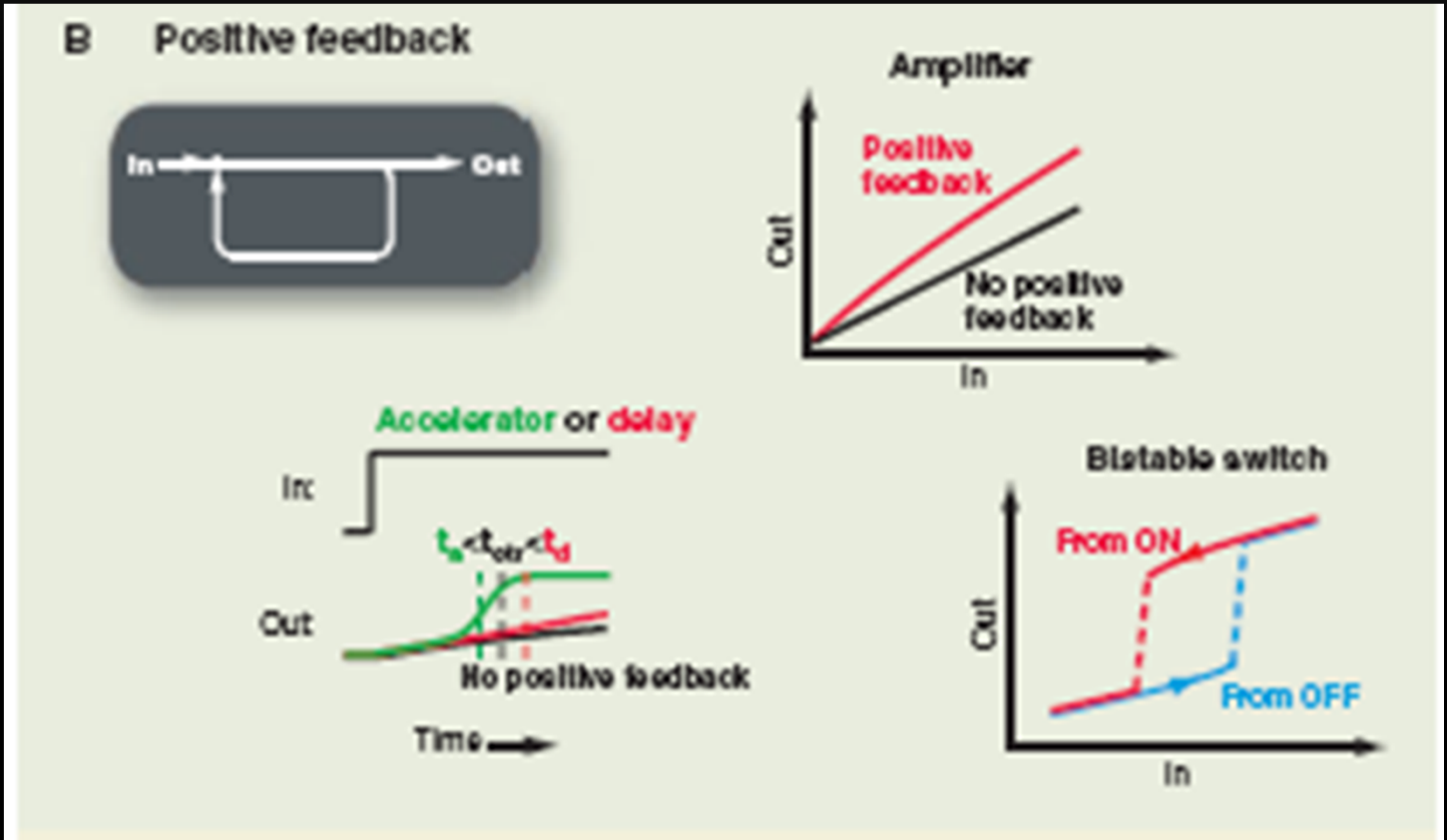
Adaptive system: eg Bacterial chemotaxis, visual perception, chemokine gradient sensing by immune cells Through→ receptor downregulation and reemergence to perceive further signal without getting saturated

A strong negative feedback induced with a delay→ transient response

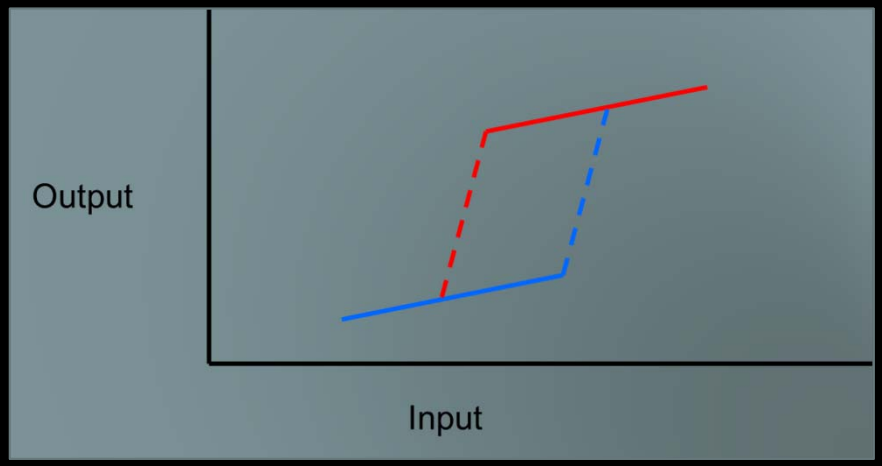
IMPORTANCE OF TRANSIENT RESPONSES IN CELLULAR SIGNALING EVENTS

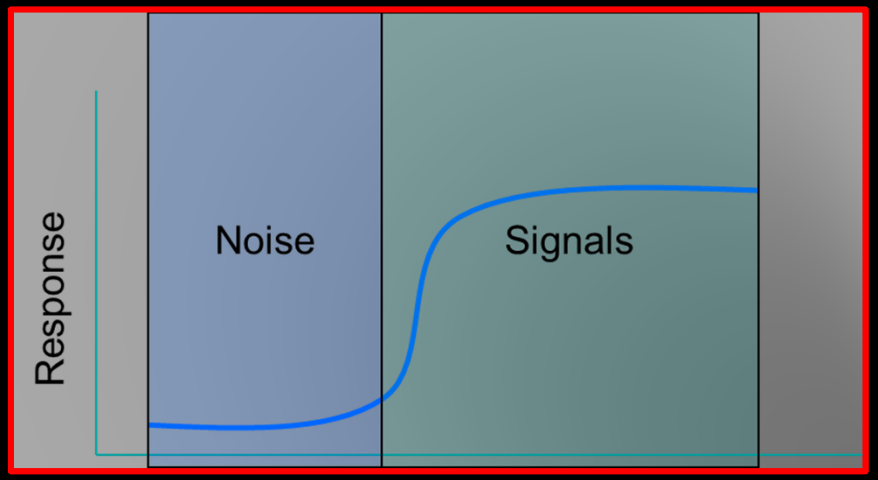


SIGNAL AMPLIFICATION/ACCELERATION/DELAY: POSITIVE FEEDBACK LOOPS



BI-STABLE SWITCHES: ONE OF THE MOST IMPORTANT REGULATORY MOTIFS IN CELL SIGNALING



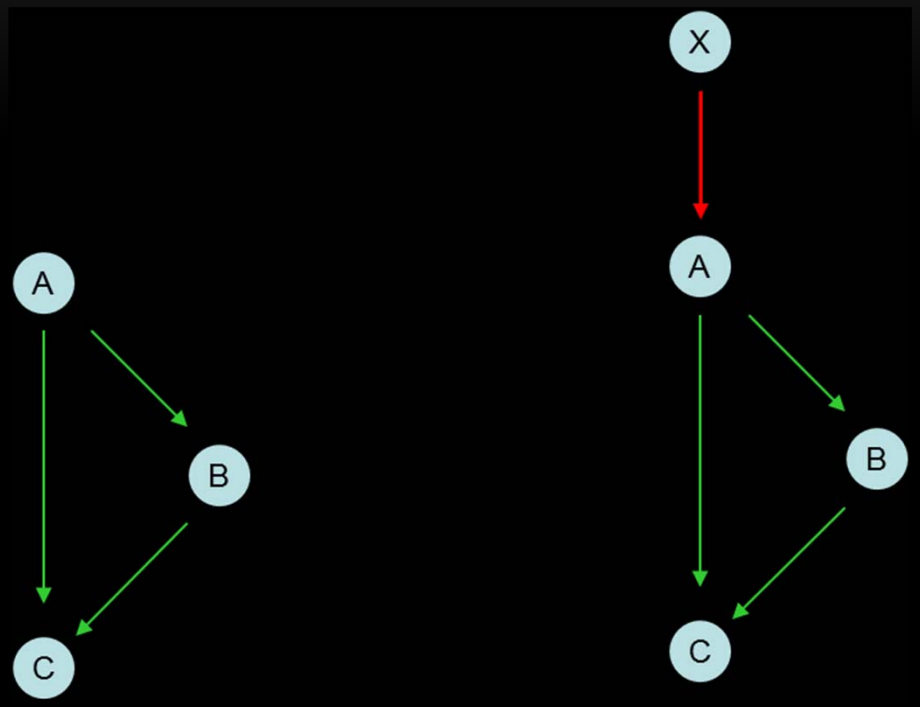


Robust to non-specific perturbations while sensitive to specific signals

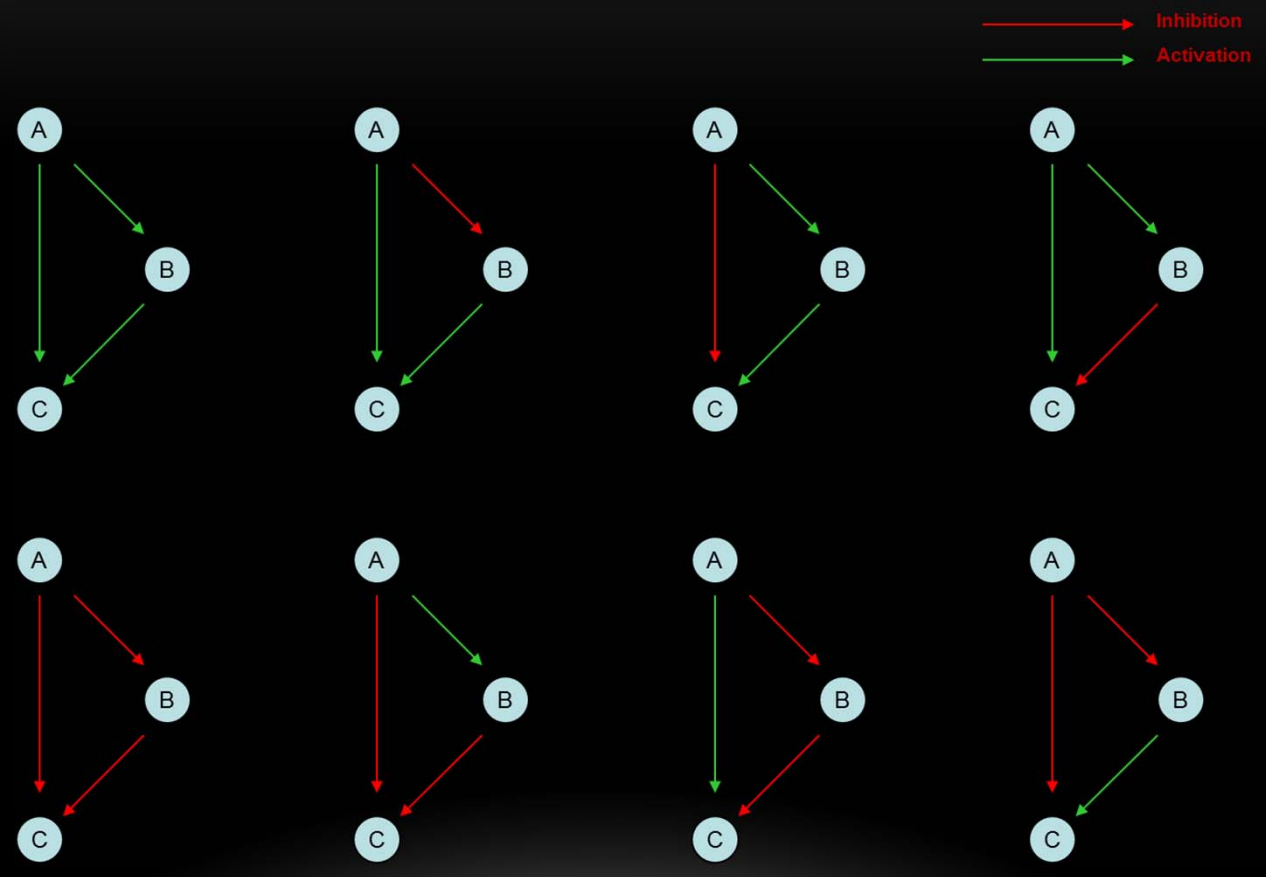
Eg: Signal initiation and downstream processing
During chemotaxis, oocyte maturation etc

Key feature that confers robustness to biological systems

FEED-FORWARD LOOP MOTIFS (FFL)



SIMILAR ARCHITECTURE OF MOTIFS WITH DISTINCT DYNAMICS



PROPERTIES DISPLAYED BY FFL

Accelerator

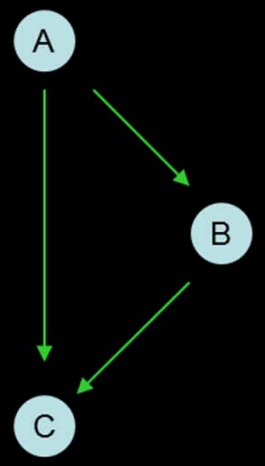
Delay Element

Co-operativity

Pulses

Adaptability

CLASSIFICATION OF FFLS

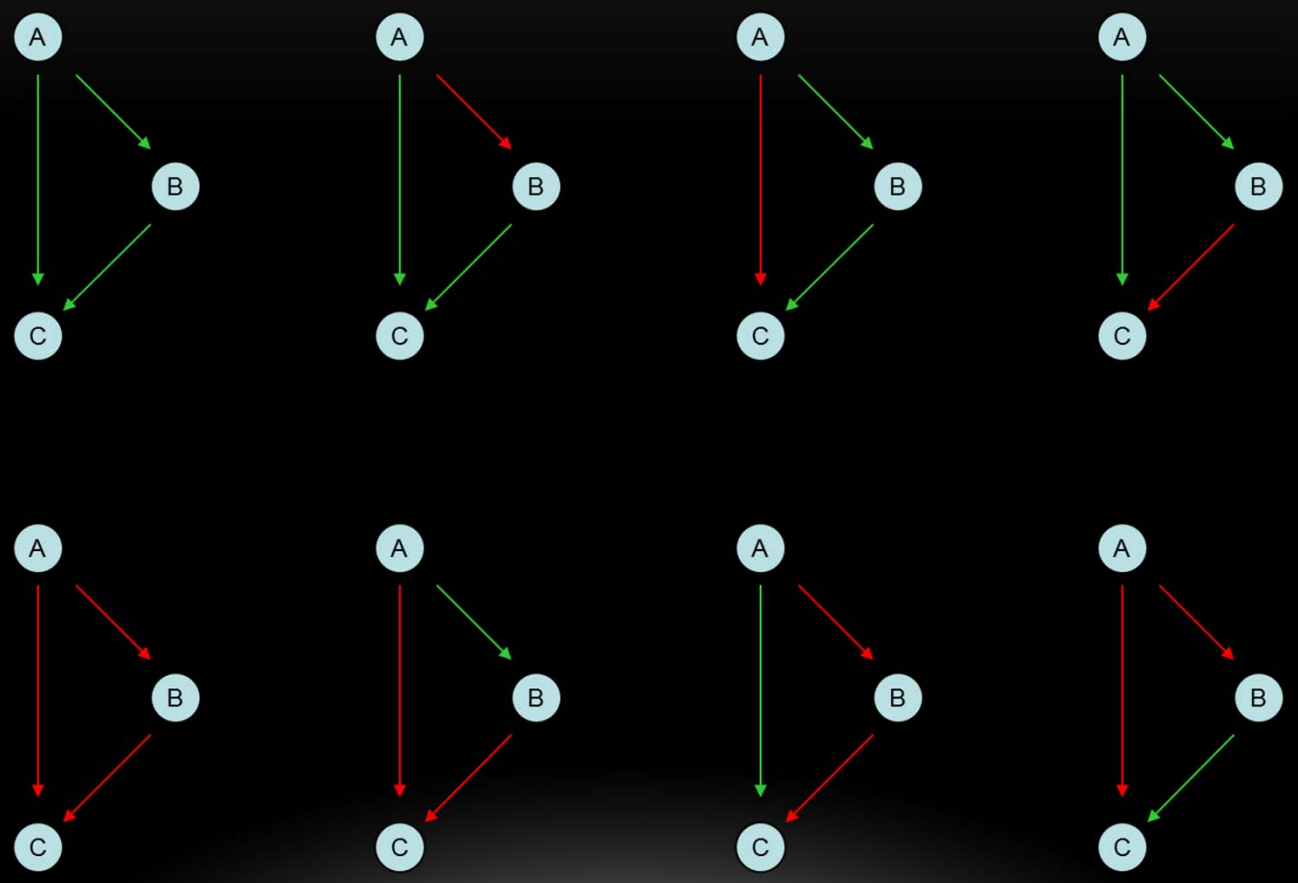


Two Paths of information

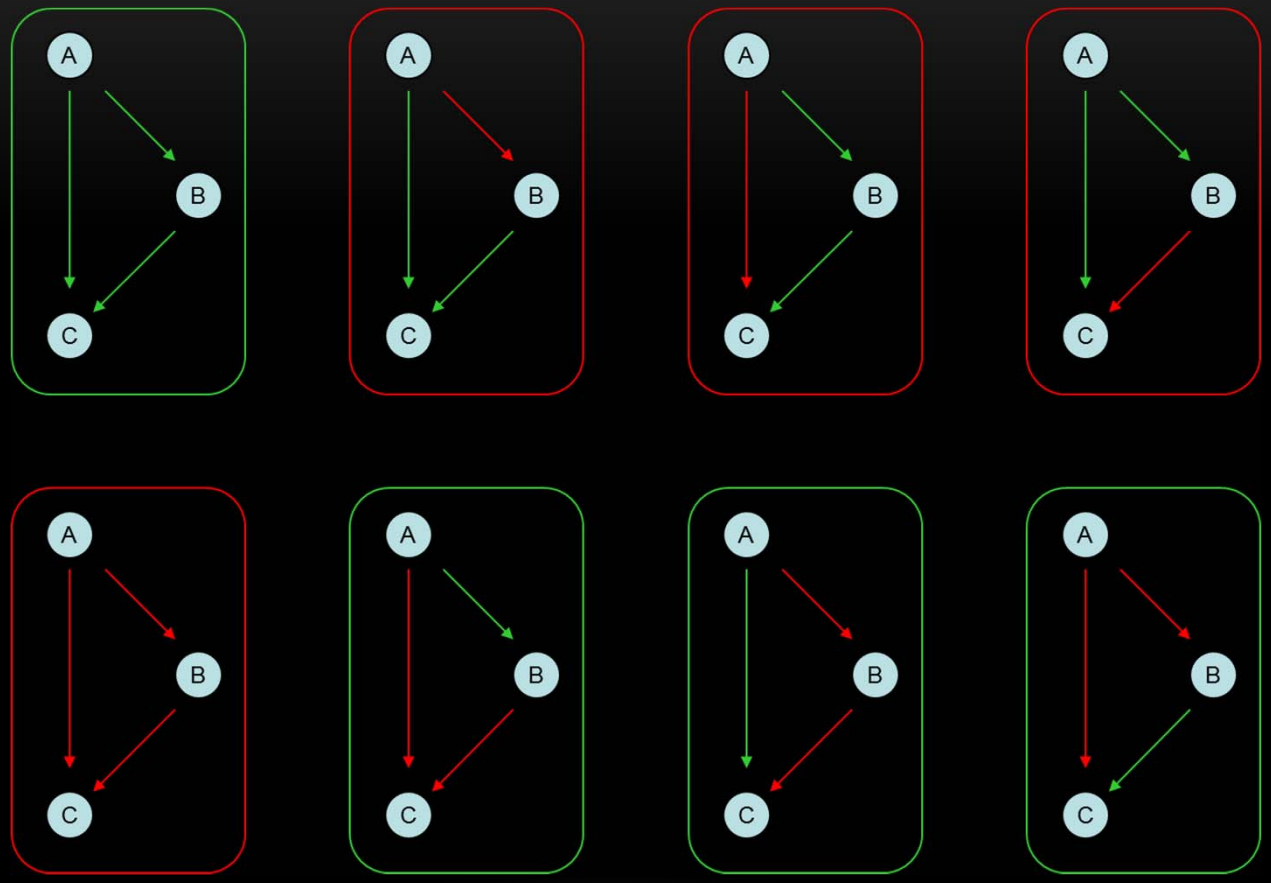
Both of same Sign: Coherent

Opposite Sign: Incoherent

DEFINE THE TYPE OF FFL



COHERENT AND INCOHERENT FFLS



Together (FFLs, Feedbacks etc) constitute building blocks of Biological networks