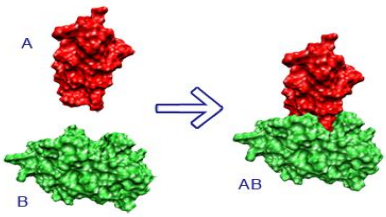
Lecture 9: Network motifs in developmental, signal transduction and neuronal networks

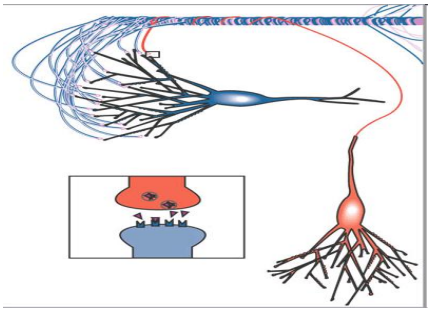
Chap 6 of Alon

6.1 Introduction

- **Developmental transcription network**
  - Main difference between sensory and developmental networks: *timescale and reversibility*
    - Sensory networks: rapid and reversible decisions
    - Developmental networks: irreversible decisions on the slow timescale of one or more cell generations
- **Signal transduction networks**
  - Use interactions between signaling proteins
  - Function on the timescale of seconds to minutes
  - We will describe some network motifs, such as multilayer perceptrons
  - Such toy-models will be used, as many biochemical details are still unknown
- **Neuronal networks**
  - Network of synaptic connections between neurons
  - Example: the worm C. elegans

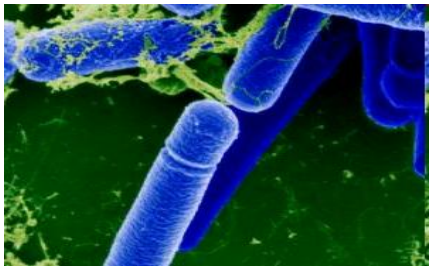


Protein–protein interaction



Synaptic connection

C. elegans



B. subtilis

6.2 Network motifs in developmental transcription networks

- Development of multicellular organisms:
  - Begin life as single celled egg, which divides to form the diverse cell types of the body.
  - As the cells divide, they differentiate into different tissues.
  - To become part of a tissue, the cell needs to express a specific set of proteins which determines whether it will become, say, nerve or muscle
- Developmental transcription networks are known (at least partly) for e.g. fruit flies, worms, sea urchins, humans

6.2.1 Two-node positive feedback loops for decision making

- Fig 6.1: two types of positive feedback loops
- Bi-stable switch – a lock-on mechanism
- **Double-positive** feedback loop
  - Most useful when the genes regulated by X and the genes regulated by Y encode proteins that belong to the *same* tissue
- **Double-negative** feedback loop
  - Most useful when the genes regulated by X belong to *different* cell fates than the genes regulated by Y
  - Example: phage lambda; see footnote 1, page 100/Alon
- Often also positive auto-regulation is present (Fig 6.2 a)

- The bi-stable nature of these motifs allows cells to make irreversible decisions and assume different fates in which specific sets of genes are expressed and others are silent

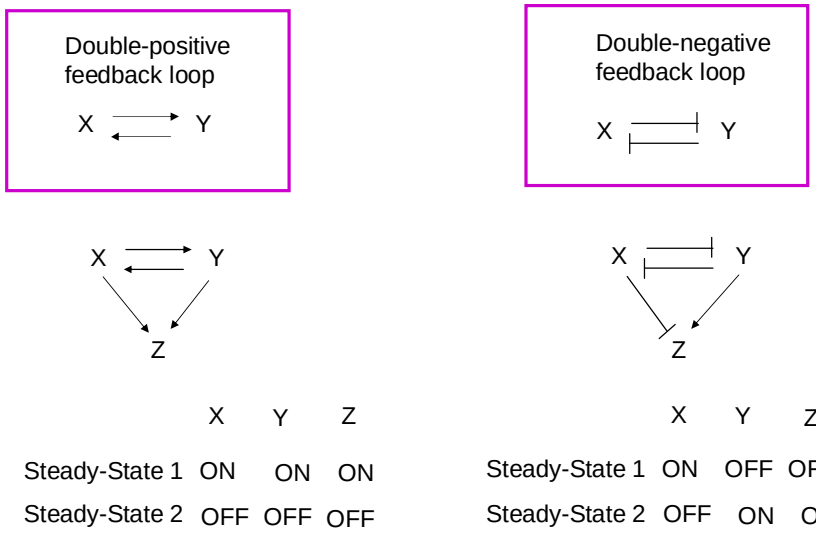


Fig 6.1 Positive transcriptional feedback loops with two nodes. The double positive loop has two activation interactions, and the double negative is made of two repression interactions. An output gene Z is regulated as shown. Each of the feedback loops has two steady states: both X and Y genes ON or OFF in the double-positive loop, and either ON in the double-negative loop.

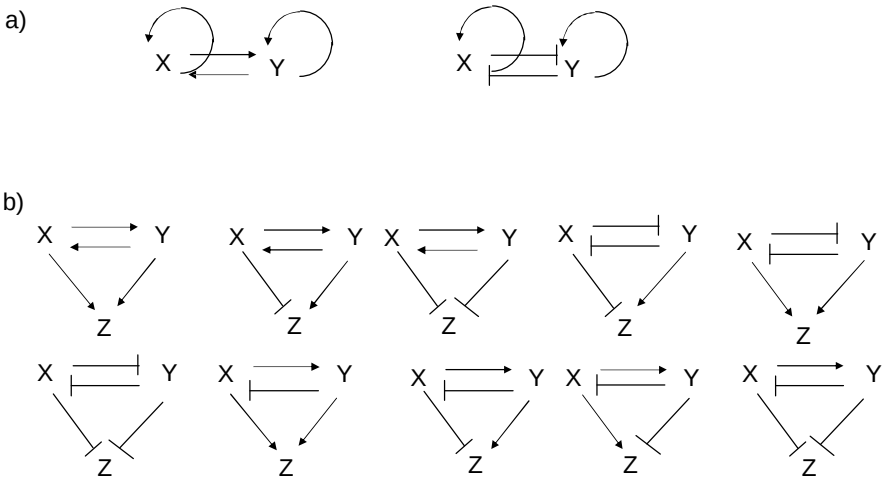
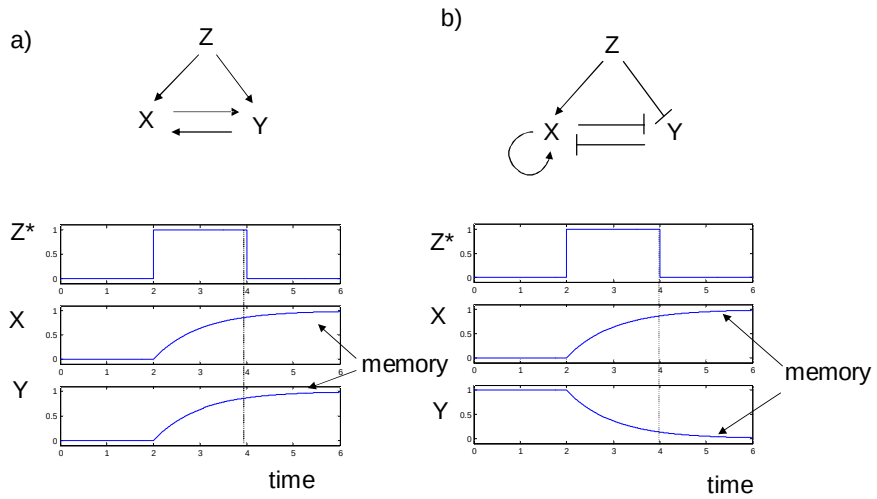


Fig 6.2: a) Two-node feedback loops with auto-regulation are a common network motif in developmental transcription networks. b) The ten distinct types of regulating feedback motifs, each corresponding to a different combination of regulation signs.

6.2.2 Regulating feedback and regulated feedbck

- **Regulating feedback network motif**: a 2-node feedback loop of X and Y regulates a gene Z
  - 10 possible sign combinations: Fig 6.2 b
- **Regulated feedback network motif**: a 2-node feedback loop is regulated by an upstream transcription factor (Fig 6.3)
  - A **memory element**: regulator Z can switch the feedback loop from one state to another such that the state persists even after Z has been deactivated. Hence, the circuit can remember whether Z was active in the past.



6.3 The regulated-feedback network motif in developmental transcription networks.
(a) Double positive feedback loop. When Z is activated, X and Y begin to be produced They can remain locked ON even when Z is deactivated (at times after the dashed line).
(b) Double negative feedback loop. Here Z acts to switch the steady states. Initially Y is high and represses X. After Z is activated, X is produced and Y is repressed. This state can persist even after Z is deactivated. Thus, in both a and b, the feedback implements a memory.

6.2.3 Long transcription cascades and developmental timing

- Fig 6.4
- Response time of each stage of the cascade is

  $T_{1/2} = \ln 2 / \alpha$
- For stable proteins this response time is ≈ cell generation time
- Developmental processes work precisely on this timescale

  => the timescale of transcription cascades is well suited to guide developmental processes
- Development often employs cascades of repressors (Fig 6.4 b) whose timing properties are more robust

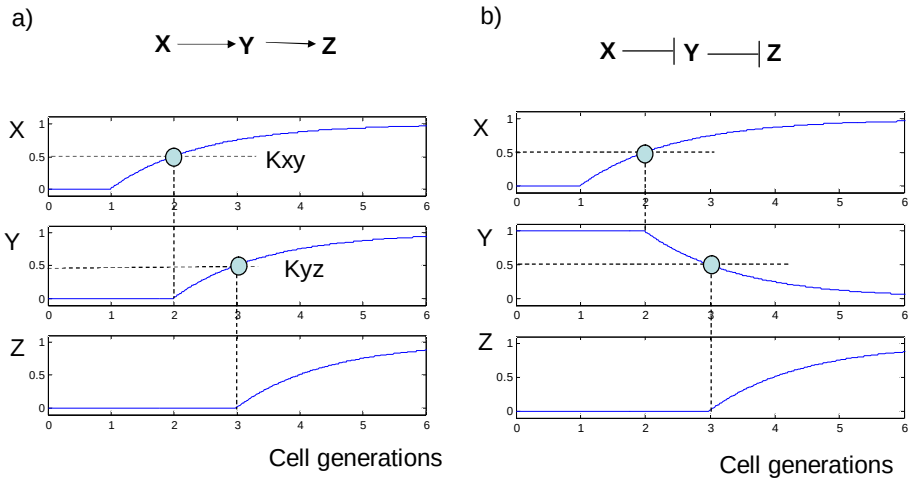
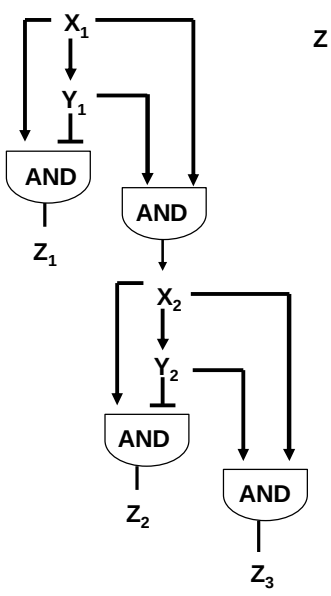


Fig 6.4 Transcription cascades can generate delays on the order of the cell-generation time (in the case of stable proteins). Each step in the cascade activates or represses the next step when it crosses its threshold (dashed lines). Shown are a cascade of activators and a cascade of repressors.

6.2.4 Interlocked feedforward loops in the *B. subtilis* sporulation network

- Developmental network composed of interlocking FFLs govern the differentiation of B. subtilis (a single-celled bacterium)
- When starved, B. subtilis cells stop dividing and differentiate into durable spores
  - **Spore = resting cell, almost completely dehydrated**
  - Placed in the right conditions, the spore converts itself again into normal bacterium
- **Sporulation process**: switch from making one subset of proteins to making another subset; involves hundreds of genes
- Network that regulates sporulation: Fig 6.5 (see the text pp 103-104/Alon)



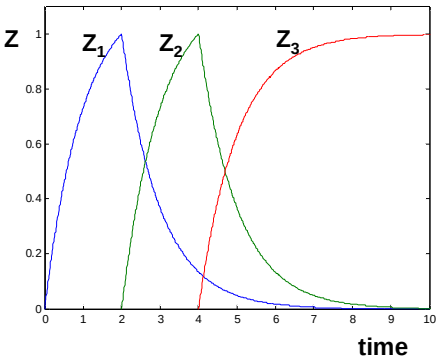


Fig 6.5: The transcription network guiding development of the B. subtilis spore. Z_1, Z_2 and Z_3 represent groups of tens to hundreds of genes.
This network is made of two I1-FFLs, that generate pulses of Z_1 and Z_2, and two C1-FFLs, one of which generates a delayed step of Z_3. Based on R. Losick, PLOS 2004

6.3 Network motifs in signal transduction networks

- **Signal transduction networks** are composed of interactions between signalling proteins
- **Receptor** protein
  - One end of the protein is outside the cell membrane and the other end is inside the membrane
  - The outside end can detect specific molecules called **ligands**
  - Binding the ligand causes a conformational change in the receptor, making the intracellular side to become active and catalyze a specific chemical modification to a messenger protein, that is, **the modification passes one bit of information from the receptor to the messenger**
- Fig 6.6

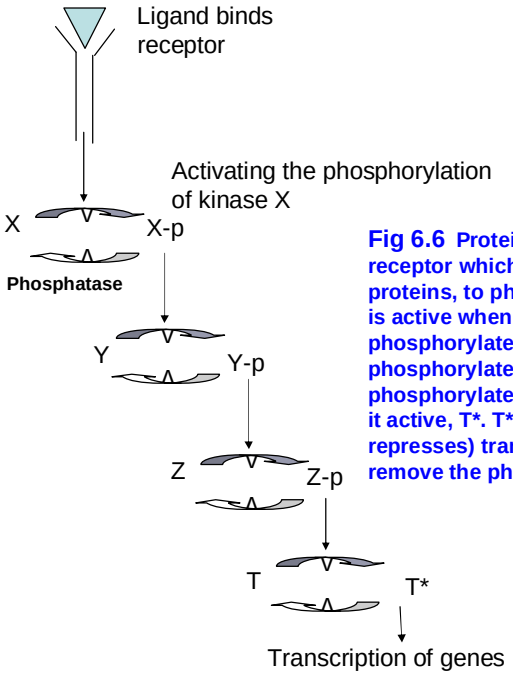


Fig 6.6 **Protein kinase cascade: Ligand binds the receptor which leads, usually through adaptor proteins, to phosphorylation of kinase X. Kinase X is active when phosphorylated, X-p. X-p phosphorylates kinase Y. Y-p, in turn, phosphorylates Z. The last kinase, Z-p, phosphorylates transcription factor T, making it active, T*. T* enters the nucleus and activates (or represses) transcription of genes. Phosphatases remove the phosphoryl groups (light arrows).**

6.4 Information processing using multi-layer perceptrons

- **Signal transduction network**:
  nodes ~ signaling proteins
  edges ~ directed interactions (such as covalent modification of one protein by another)
- Two strong 4-node motifs occur in signal transduction networks: **bi-fan** and **diamond** (Fig 6.7)
- The diamond motif generalizes to **multi-layer patterns**
  - These resemble DOR structures (of Chap 5) arranged in cascades
- ~ *multi-layer perceptrons* of artificial intelligence

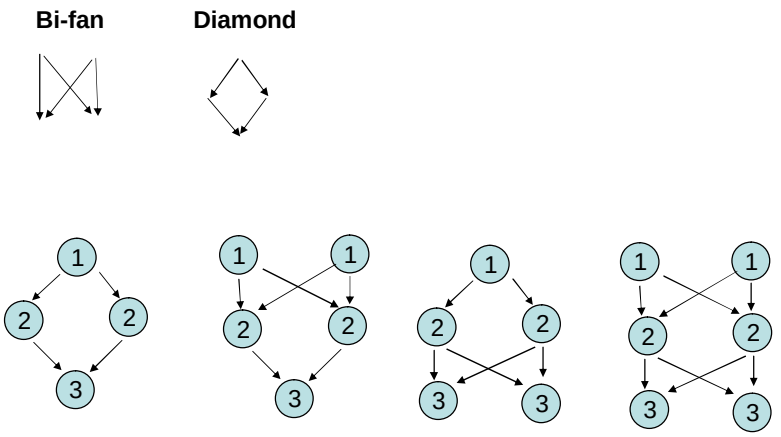


Fig 6.7 **Network motifs in signal transduction networks. The main four-node motifs are the diamond and the bi-fan. The diamond has four nodes, and three different roles, labeled 1,2 and 3. Each generalization is obtained by duplicating one of the nodes and all of its edges. These generalizations are all also network motifs in signal transduction networks.**

6.4.1 Toy-model for protein kinase perceptrons

- Protein kinase cascades (Fig 6.6)
  - Found in most eukaryotic organisms
  - Double phosphorylation (Fig 6.8)
  - Cycles of phosphorylation and dephosphorylation
- Kinase cascades often made of (three) layers (Fig 6.9):
  $X_1, X_2, \ldots$; $Y_1, Y_2, \ldots$; $Z_1, Z_2, \ldots$
- Develop a toy-model for the dynamics: understanding essential dynamics, not a detailed model of the system
- Use the so-called **first-order kinetics** (see Appendix A.7)

Rate of phosphorylation of Y by X = vXY_0

where

X = concentration of active X

Y_0 = concentration of unphosphorylated Y

v = phosphorylation rate of kinase X = the number of phosphorylations per unit time per unit of kinase

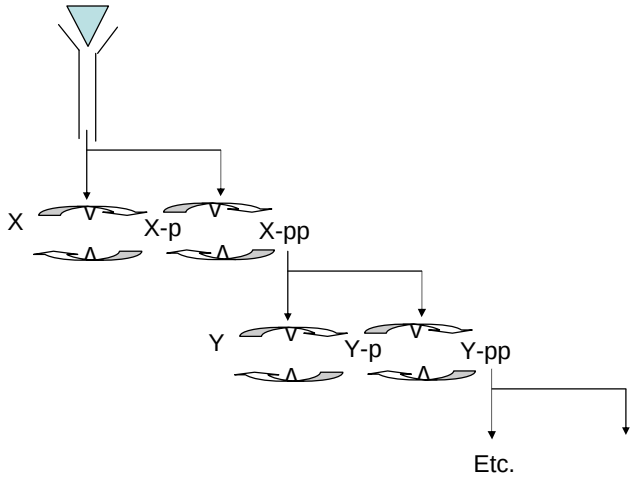
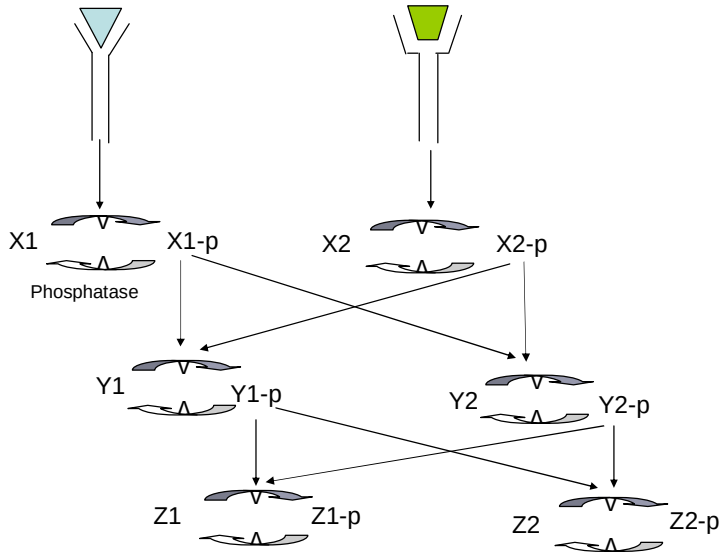


Fig 6.8 Double phosphorylation in protein kinase cascades: Protein kinases X,Y and Z are usually phosphorylated on two sites, and often require both phosphorylations for full activity.



6.9 Multi-layer perceptrons in protein kinase cascades. Several different receptors in the same cell can activate specific top-layer kinases in response to their ligands. Each layer in the cascade often has multiple kinases, each of which can phosphorylate many of the kinases in the next layer.

Toy-model (cont.)

- Assume: kinase Y is phosphorylated by two kinases X_1 and X_2 (Fig 6.10)
  - Let Y_p = phosphorylated form of Y
- The total number of the two forms of Y is conserved:

$$Y_0 + Y_p = Y$$

(transcription of the Y gene produces more Y's but this is slow as compared to phosphorylations)

- The rate of the change of Y_p:

$$dY/dt = v_1X_1Y_0 + v_2X_2Y_0 - \alpha Y_p$$

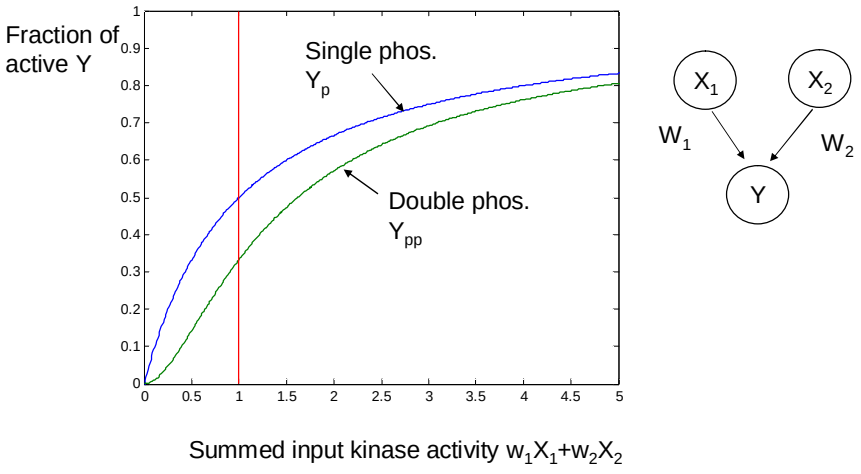
where $-\alpha Y_p$ is the dephosphorylation of Y_p by phosphatase at rate α

- Assume steady state: $dY/dt = 0$
  $\Rightarrow Y_p/Y_0 = w_1X_1 + w_2X_2$ where $w_1 = v_1/\alpha$ and $w_2 = v_2/\alpha$

  $\Rightarrow$ $\boxed{Y_p/Y = f(w_1X_1 + w_2X_2)}$

  where $f(u) = u/(1+u)$; if phosphorylation on two sites is needed, then f is steeper: $f(u) = u^2/(1+u+u^2)$

Fig 6.10: Fraction of active Y as a function of the weighted sum of the input kinase activities, $w_1X_1 + w_2X_2$, in the model with first order kinetics. Shown Is the activation curve for single and double phosphorylation of Y. The weights W1 and w2 are the ratio of the input kinase velocity and the phosphatase rate.



Toy-model (cont.)

- these s-shaped input functions lead to a significant activation of Y only when the total sum of the two inputs is greater than a threshold which is approximately 1:

$$w_1X_1 + w_2X_2 > 1$$

=> threshold of activation: $w_1X_1 + w_2X_2 = 1$

- Graphically (Fig 6.11): the (X_1,X_2)-plane is divided by a straight line into low and high Y_p regions

  Small w_1 and w_2 => AND gate

  Large w_1 and w_2 => OR gate

- More generally: consider kinase layers $X_1,X_2, ..., X_m$ and $Y_1,Y_2, ..., Y_n$
- Activity of Y_i ~ threshold-like function $f(w_{j1}X_1 + w_{j2}X_2 + ... + w_{jm}X_m)$
  - Hyperplane in the m-dimensional space of $X_1, ..., X_m$

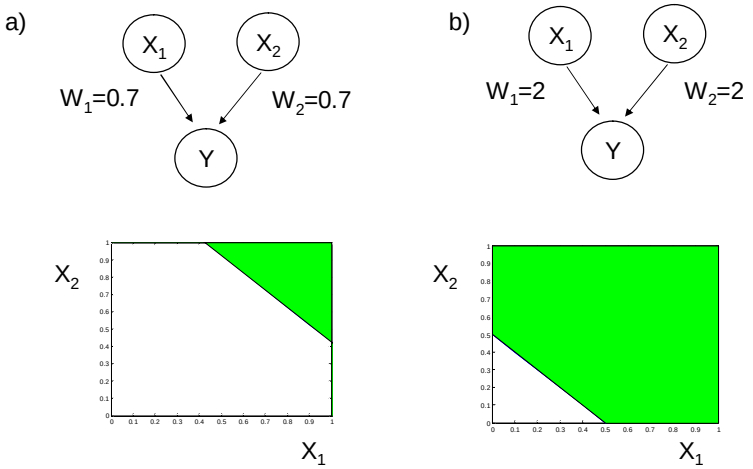


Fig 6. 11 Single-layer perceptrons and their input functions. Node Y sums the two inputs X_1 and X_2 according to the weights w1 and w2. Y is activated in the colored region of the X_1-X_2 plane. In this region $w_1X_1+w_2X_2>1$. In protein kinase cascades, Y is phosphorylated and hence active in the shaded region. In this figure, as well as Fig 6.12-6.13, the range of activities of X_1 and X_2 is assumed to be between zero and one. Activity of one means that all input kinase molecules is active. This defines the square region in X_1-X_2 plane portrayed in the figures.

6.4.2 Multi-layer perceptrons can perform detailed computations

- Adding more perceptron layers allows more complicated decisions than just AND/OR by one straight line
- **Two-layered perceptron** (Fig 6.12):
  $Z_p/Z = f(w_{Z1}Y_1 + w_{Z2}Y_2)$ & Y_p/Y is as before
- Additional possibility: middle layer contains a specific phosphatase instead of a kinase => phosphatase removes the phosphoryl modification and therefore it effectively has a negative weight (see: footnote 1 on page 113)
  - Fig 6.13 examples: (a) wedge-like region (b) exclusive-OR or XOR gate
- In general: more levels => more details in the out functions
- Summary: **Multi-layer perceptrons** can show
  - Discrimination: accurate recognition of differences between vry similar stimuli patterns
  - Generalization: ability to fill in the gaps in partial stimuli patterns
  - Graceful degradation: a (local) damage to the elements of a perceptron does not bring the network to a crashing halt

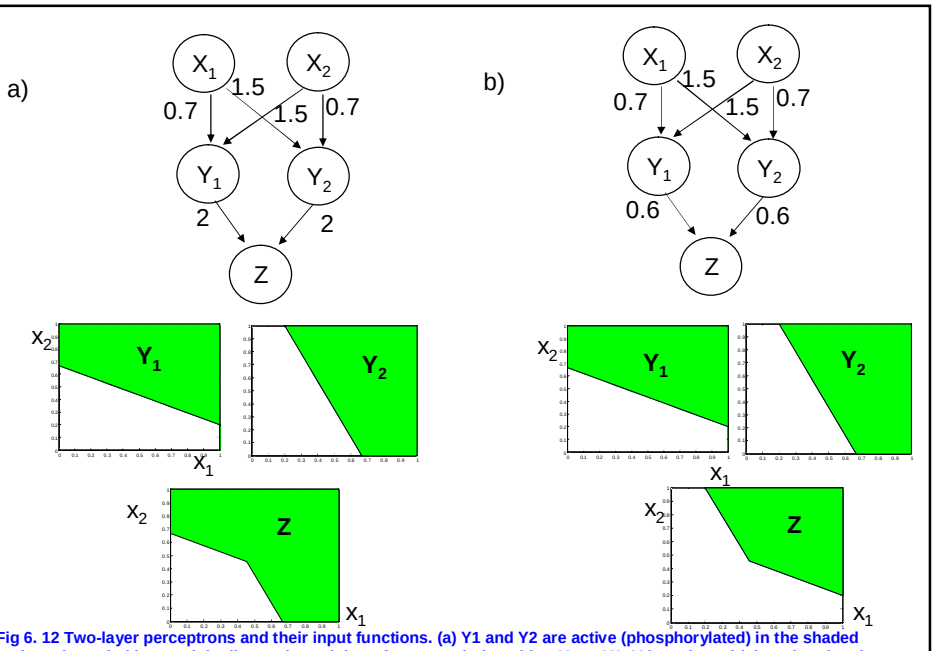


Fig 6. 12 Two-layer perceptrons and their input functions. (a) Y1 and Y2 are active (phosphorylated) in the shaded regions, bounded by straight lines. The weights of Z are such that either Y1 or Y2 Y is activated (phosphorylated above threshold) in the colored regions of the X1-X2 plane. In this region w1X1+w2X2 > 1. (b) Here the weights for Z activation by Y1 and Y2 are such that both Y1 and Y2 need to be active. Hence the activation region of Z is the intersection of the activation regions of Y1 and Y2.

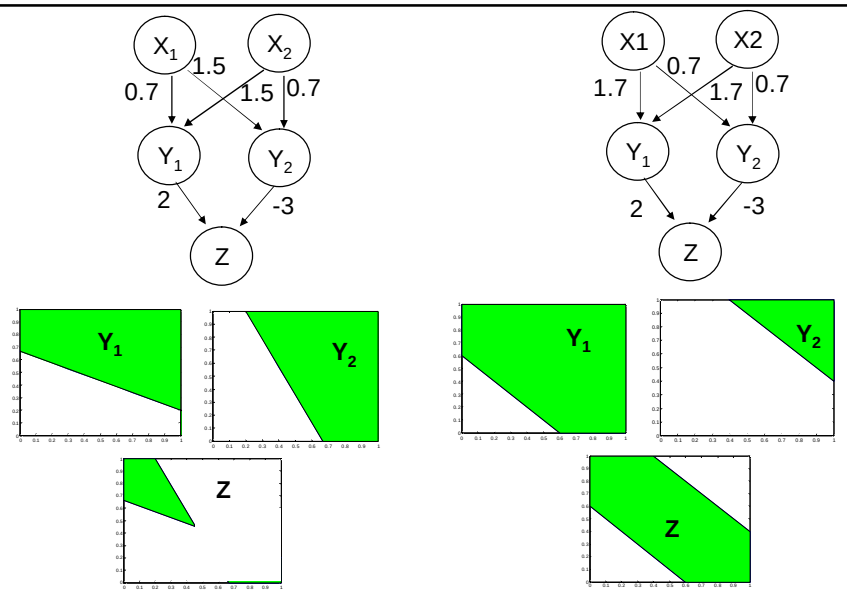


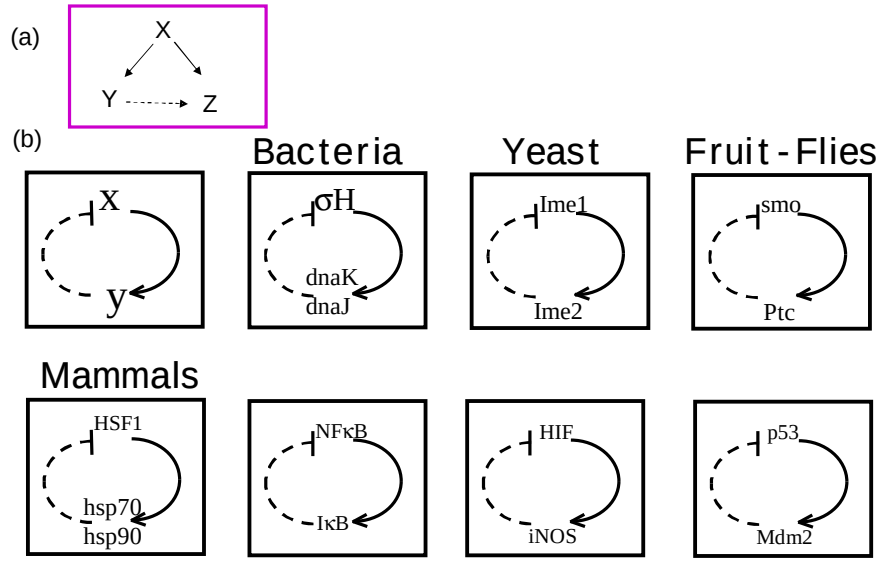
Fig 6. 13 Two-layer perceptrons and their input functions. Y_1 and Y_2 are active in the shaded regions, bounded by straight lines. (a) Y_1 activates Z whereas Y_2 inhibits it (eg a phosphatase). Thus, Z is activated in a wedge-like region in which Y_1 is active but Y_2 is not. (b) An additional example that yields an output Z that is activated when both inputs are intermediate, when either X_1 or X_2 are highly active, but not both (similar to an exclusive-OR gate).

6.5 Composite network motifs: negative feedback and oscillator motifs

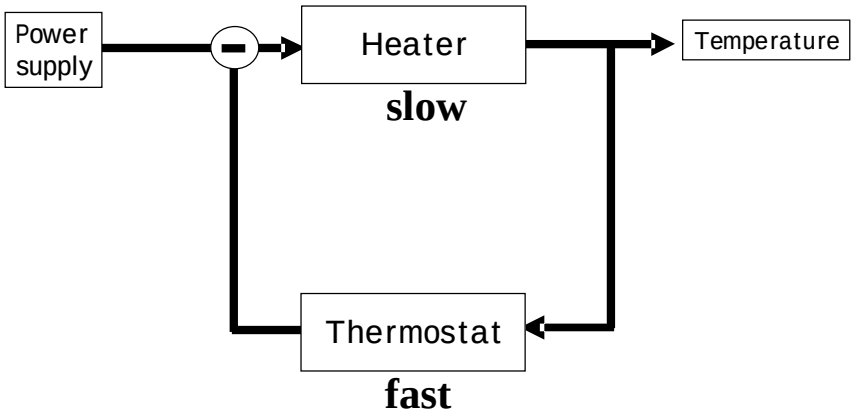
- Different types of networks can be composed to model more compex phenomena
- Example: joining protein signaling network and transcription network
- Fig 6.14

- A very common composite motif: **composite feedback loop** of Fig 6.14 b
  - One interaction is transcriptional (**slow**)
  - Other occurs on the protein level (**fast**)

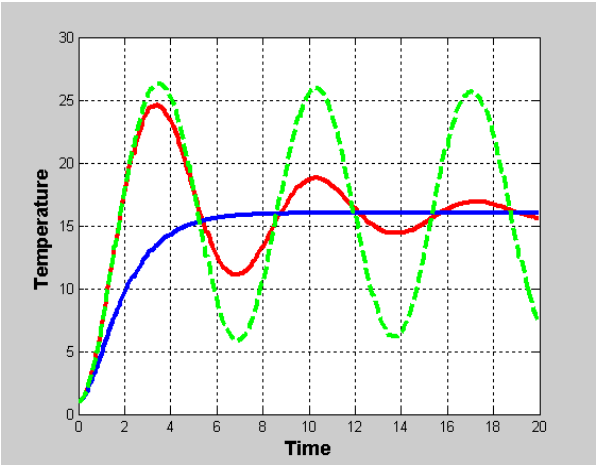
- What is the reason that composite feedback loops (that often are negative) are much more common that the purely transcriptional ones?
  - **Difference in timescales**: a slow component regulated by a fast one is commonly used in engineering, to stabilize the system: Figs 6.15 & 6.16



6.14 Composite network motifs made of transcription interactions (full arrows) and protein-protein interactions. (dashed arrows). (a) Transcription factor X regulates two genes Y and Z, whose protein products interact. (b) A negative feedback loop with one transcription arm and one protein arm is a common network motif across organisms



6.15 Negative feedback in engineering uses fast control on slow devices. A heater, which can heat a room in 15 minutes, is controlled by a thermostat that compares the desired temperature to the actual temperature. If the temperature is too high, the power to the heater is reduced, and power is increased if temperature is too low. The thermostat works on a much faster timescale than the heater. Engineers tune the feedback parameters to obtain rapid and stable temperature control (and avoid oscillations).



6.16 Negative feedback can show over-damped, monotonic dynamics (blue), damped oscillations with peaks of decreasing amplitude (red) or undamped oscillations (green dashed line). Generally, the stronger the interactions between the two nodes in relation to the damping forces on each node (such as degradation rates), the higher the tendency for oscillations.

Negative feedback and oscillator motifs (cont.)

- Stability is desirable sometimes, and sometimes oscillatory behaviour is needed
- Examples of oscillatory dynamics
  - Cell cycle
  - Circadian clock
  - Beating heart cells
  - Spiking neurons
  - Developmental processes that generate repeating modular tissues
- Typical characteristics of biological oscillations: timing is usually more precise that amplitude
  - Reason: internal noise in the protein production rates that is inherent in biochemical circuitry; see Appendix D
- Examples in Fig 6.17: **Oscillator** and **repressilator**

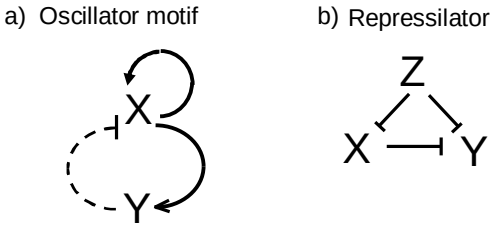


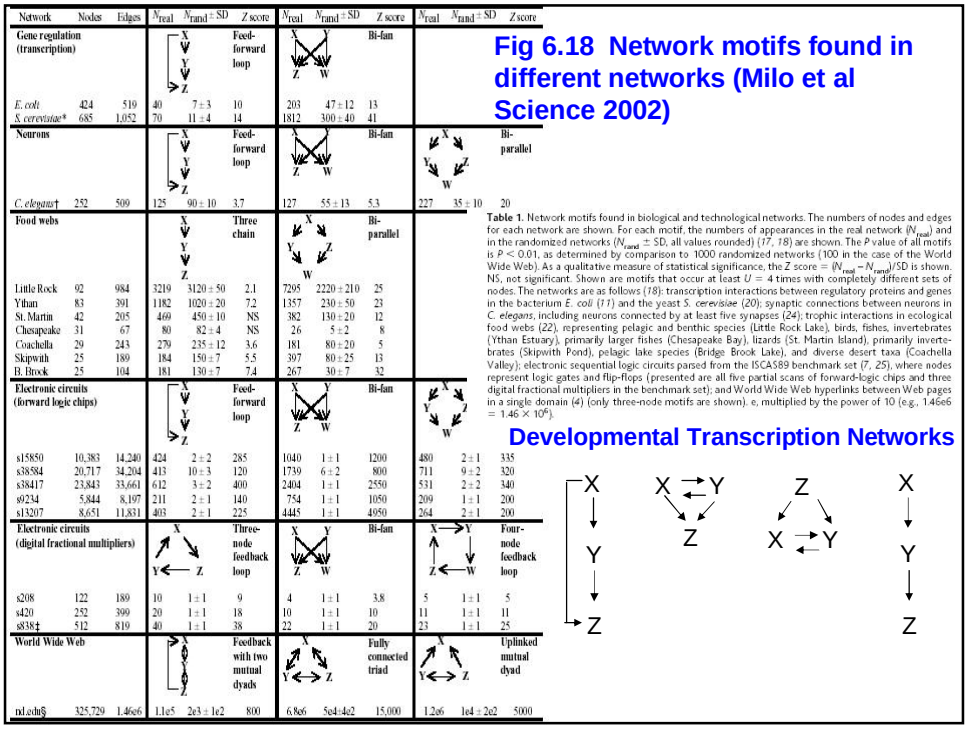
Fig 6.17 (a) A network motif found in many biological oscillatory systems, composed of a composite negative feedback loop and a positive auto-activation loop. In this motif, X activates Y on a slow timescale, and also activates itself. Y inhibits X on a rapid timescale.
(b) A repressilator made of three cyclically linked inhibitors shows noisy oscillations In the presence of noise in the production rates for a wide range of biochemical parameters.

6.6 Network motifs in the neuronal network of C. elegans

1) Most real-world networks contain a small set of network motifs

2) The motifs in different types of networks are generally different

- Fig 6.18
- Subgraph profiles: statistical significance of various subgraphs (Fig 6.19)



Network	Nodes	Edges	N_{real}	$N_{rand} \pm SD$	Z score	N_{real}	$N_{rand} \pm SD$	Z score	N_{real}	$N_{rand} \pm SD$	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			
Electronic circuits (forward logic chips)					**Feed-forward loop**			**Bi-fan**			
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

Table 1. Network motifs found in biological and technological networks. The numbers of nodes and edges for each network are shown. For each motif, the numbers of appearances in the real network (N_{real}) and in the randomized networks ($N_{rand} \pm SD$, all values rounded) (*17*, *18*) are shown. The *P* value of all motifs is $P < 0.01$, as determined by comparison to 1000 randomized networks (100 in the case of the World Wide Web). As a qualitative measure of statistical significance, the *Z* score = $(N_{real} - N_{rand})/SD$ is shown. NS, not significant. Shown are motifs that occur at least $U = 4$ times with completely different sets of nodes. The networks are as follows (*18*): transcription interactions between regulatory proteins and genes in the bacterium *E. coli* (*11*) and the yeast *S. cerevisiae* (*20*); synaptic connections between neurons in *C. elegans*, including neurons connected by at least five synapses (*24*); trophic interactions in ecological food webs (*22*), representing pelagic and benthic species (Little Rock Lake), birds, fishes, invertebrates (Ythan Estuary), primarily larger fishes (Chesapeake Bay), lizards (St. Martin Island), primarily invertebrates (Skipwith Pond), pelagic lake species (Bridge Brook Lake), and diverse desert taxa (Coachella Valley); electronic sequential logic circuits parsed from the ISCAS89 benchmark set (*7*, *25*), where nodes represent logic gates and flip-flops (presented are all five partial scans of forward-logic chips and three digital fractional multipliers in the benchmark set); and World Wide Web hyperlinks between Web pages in a single domain (*4*) (only three-node motifs are shown). e, multiplied by the power of 10 (e.g., 1.46e6 = 1.46×10^6).

Fig 6.18 Network motifs found in different networks (Milo et al Science 2002)

Developmental Transcription Networks

Text of Fig 6.18

Table 1. Network motifs found in biological and technological networks. The numbers of nodes and edges for each network are shown. For each motif, the numbers of appearances in the real network (N_{real}) and in the randomized networks ($N_{rand} \pm SD$, all values rounded) (*17*, *18*) are shown. The *P* value of all motifs is $P < 0.01$, as determined by comparison to 1000 randomized networks (100 in the case of the World Wide Web). As a qualitative measure of statistical significance, the *Z* score = $(N_{real} - N_{rand})/SD$ is shown. NS, not significant. Shown are motifs that occur at least $U = 4$ times with completely different sets of nodes. The networks are as follows (*18*): transcription interactions between regulatory proteins and genes in the bacterium *E. coli* (*11*) and the yeast *S. cerevisiae* (*20*); synaptic connections between neurons in *C. elegans*, including neurons connected by at least five synapses (*24*); trophic interactions in ecological food webs (*22*), representing pelagic and benthic species (Little Rock Lake), birds, fishes, invertebrates (Ythan Estuary), primarily larger fishes (Chesapeake Bay), lizards (St. Martin Island), primarily invertebrates (Skipwith Pond), pelagic lake species (Bridge Brook Lake), and diverse desert taxa (Coachella Valley); electronic sequential logic circuits parsed from the ISCAS89 benchmark set (*7*, *25*), where nodes represent logic gates and flip-flops (presented are all five partial scans of forward-logic chips and three digital fractional multipliers in the benchmark set); and World Wide Web hyperlinks between Web pages in a single domain (*4*) (only three-node motifs are shown). e, multiplied by the power of 10 (e.g., 1.46e6 = 1.46×10^6).

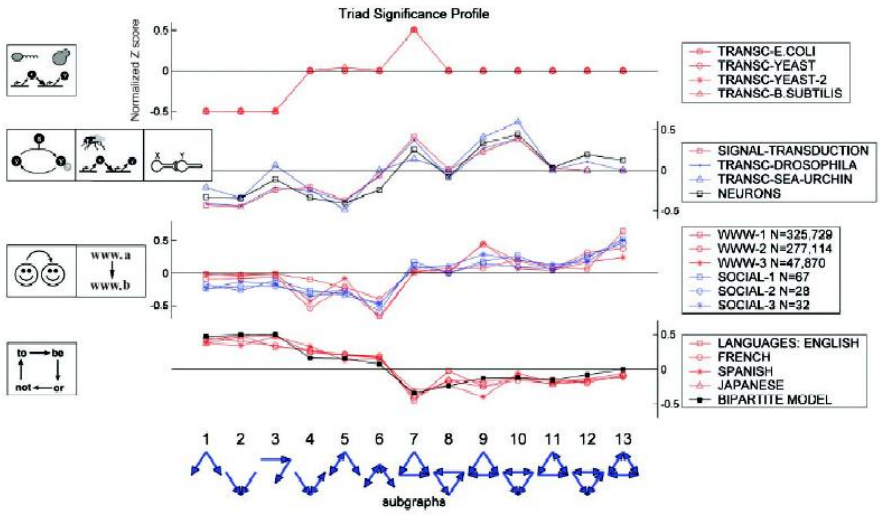
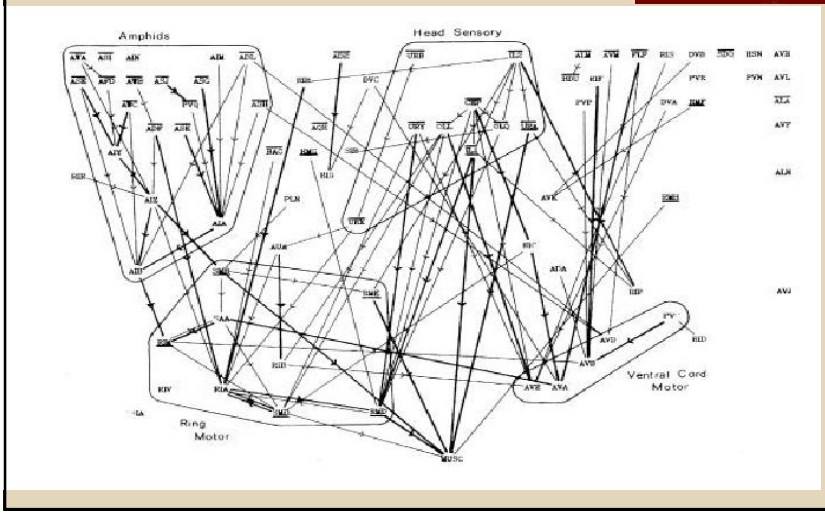


Fig 6.19 Significance profiles of three-node subgraphs found in different networks. The significance profile allows comparison of networks of very different sizes ranging form tens of nodes (social networks where children in a school class select friends) to millions of nodes (world-wide-web networks). The y-axis is the normalized Z-score (N_{real}-N_{rand}) / std(N_{rand}) for each of the thirteen three-node subgraphs. Language networks have words as nodes and edges between words that tend to follow each other in texts. The neural network is from *C. elegans* (chapter 6), counting synaptic connections with more than 5 synapses. For more details, see Milo et al Science 2004.

Neuronal network of C. elegans (cont)

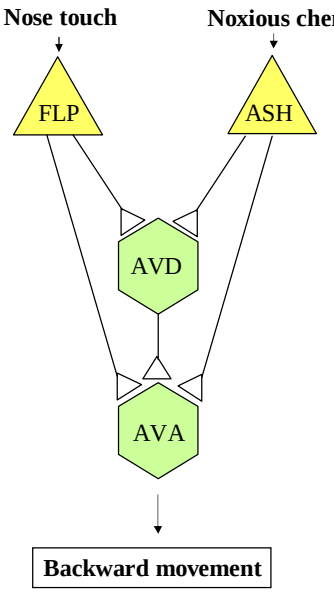
- Unrelated networks can sometimes share smilar motifs: example – the neuronal network of C. elegans (Fig 6.20)
- Many of the motifs found in transcription and signal transduction networks are also present in neuronal network of C. elegans
- FFL is the most significant
- Why? **Similarity in function needs similar regulators**:
  - Both networks need to convey information between sensory components that receive the signals and motor the components that generate the responses
  - Neurons process information between sensory neurons and motor neurons
  - Transcription factors process information between factors receiving signals from the expternal world and structural genes that act on the internal or outer environment

6.20 Map of synaptic connections between C. elegans neurons. Shown are connections between neurons in the worm head. Source: R. Durbin PhD Thesis, www.wormbase.org



6.6.1 The multi-input FFL in neuronal networks

- **Multi-input FFL** = FFL with input X multiplied:
  - Most common FFL generalization in C. elegans neural network: Fig 6.21
- Neurons act primarily by transmitting electrical signals to other neurons via synaptic connections:
  - Each neuron has a time-dependent transmembrane voltage difference ~ neurons' activity
  - C. elegans neurons: graded voltages X(t), Y(t), Z(t)
- Classic **integrate-and-fire model**: summation of synaptic inputs from input neurons



Sensory neurons

Interneurons

Thomas & Lockery 1999

6.21 Feed-forward loops in *C. elegans* avoidance reflex circuit. Triangles represent sensory neurons, hexagons Represent inter-neurons. Lines with triangles represent synaptic connections between neurons.

Multi-input FFL (cont)

- Classic **integrate-and-fire model**: summation of synaptic inputs from input neurons:
  - The change in voltage of Y is activated by a step function

    $$dY/dt = \beta\Theta(w_1X_1 + w_2X_2 > K_Y) - \alpha Y$$

    where:
    - α = the relaxation rate related to the leakage of the current through the neuron cell membrane
    - The weights w_1 and w_2 correspond to the strengths of the synaptic connections from input neurons X_1 and X_2 to neuron Y
  - Depending on weights w_1 and w_2, the weighted sums can generate either AND or OR gates

Multi-input FFL (cont)

- Fig 6.22: Z is controlled by X_1 and X_2, and receives an additional input from Y:

  $dZ/dt = \beta'\Theta(w_1'X_1 + w_2'X_2 + w_3'Y > K_Z) - \alpha'Z$

- Experiments suggest that Z is activated by (X_1 OR X_2) AND Y
- Multi-input FFL can perform coincidence detection of brief input signals (Fig 6.22 c)

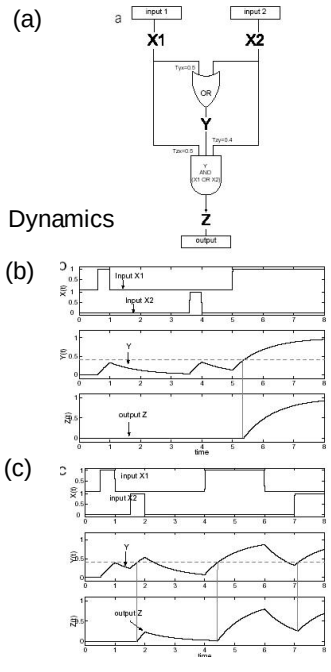


Fig 6.22: Dynamics in a model of a *C. elegans* multi-input FFL following pulses of input stimuli.

a) A double input FFL, input functions and thresholds are shown.

b) Dynamics of the two-input FFL, with well-separated input pulses for X_1 and X_2, followed by a persistent X_1 stimulus

c) Dynamics with short X_1 stimulus followed rapidly by a short X_2 stimulus. The dashed horizontal line corresponds to the activation thresholds for Y. α=1 was used.

Source: Kashtan et al, PRE 2004 70: 031909

6.6.2 Multi-layer perceptron in the C. elegans neuronal network

- Fig 6.23: Among patterns with four or more nodes, the most abundant motifs in the synaptic wiring of C. elegans are multi-layer perceptrons. These are similar to the motifs in signal transduction networks, the main difference being that C. elegans multi-layer perceptrons have more connections between nodes in the same layer
- Note that the motifs in neuronal networks can, of course, perform many additional functions. Each neuron is a sophisticated cell able to perform computations and adapt over time. The present discussion considered only the simplest scenario of these network motifs

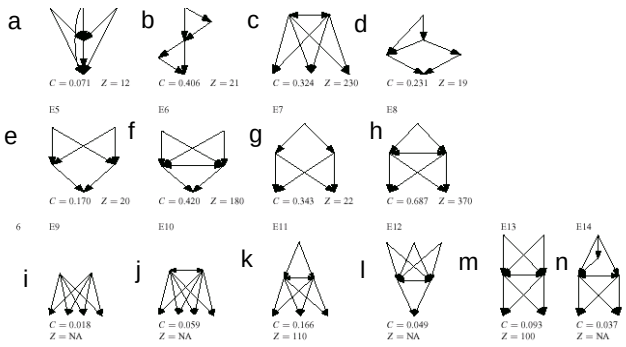


Fig 6.23 Five and six node network motifs in the neuronal synaptic network of C. elegans. Note the multi-layer perceptron patterns e, f, g, h, k, l, m, and n, many of which have mutual connections within the same layer. The parameter C is the concentration of the subgraph relative to all subgraphs of the same size in the network (multiplied by 10^-3), Z is the number of standard deviations it exceeds randomized networks with the same degree sequence (Z-score). These motifs were detected by an efficient sampling algorithm suitable for large subgraphs and large networks. Source: N. Kashtan, S. Itzkovitz, R. Milo, U. Alon, *Efficient sampling algorithm for estimating subgraph concentrations and detecting network motifs.* Bioinformatics. 2004 Jul 22;20(11):1746-58.

6.7 Summary

- Networks are a convenient approximation to the complex set of biological interactions
- The network presentation masks a great deal of the detailed mechnisms at each node and edge
- Such a simplified network representation helps highlight the similarity in the circuit patterns in different parts of the network and between different networks.
- The dynamics of the networks at this level of resolution lend themselves to analysis with rather simple models: we care only that X activates or inhibits Y, not precisely how it does it on biochemical level.
- This abstraction helps to define network motifs as specific functional building blocks of each type of network.