Feed Forward Loops in Biological Systems

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1 Introduction

The next set of lectures opens up interesting paradigms of visualising logic circuits inside organisms like *E. coli* and yeast. We revisit interesting concepts we had simulated in electronics years back and connect them to behaviour in biological networks. Let us remember that the molecular networks inside cells are highly complex and dynamic and hence have to be represented in terms of interaction graphs that combine mathematical methods to interpret biological data.

2 Network Motifs

The transcription regulation networks (that we discussed in lesson 2), as we know, control gene expression patterns in living cells. But their design principles are poorly understood. Recent advances in computing, circuit and network simulations have yielded enormous and unprecedented information from these networks. These transcription networks accommodate recurrent biochemical wiring patterns called Network Motifs**.**

2.1 Feed Forward Loops

In order to understand the general features of such networks and to extract useful information from them, we dissect them at hierarchical levels- into modules and motifs which can explain their functionality, evolution and dynamic behavior. Over the process of evolution, these networks show information processing functions. Interesting investigations on network behaviour have shown that simple switching circuits, amplifiers or oscillators can map to the core process of biological decision making. These have been implemented by two or three gene network motifs and are characterized by how they behave around fixed points in the system. Here the steady state of the system as well as the process of achieving equilibrium in the system reflects the characteristic function performed by the genetic circuit.

Network motifs appear at frequencies much higher than those expected at random and hence imply information processing roles for these motifs. To arrive at such significant patterns, one first identifies the different patterns of these motifs in real and randomized networks and then calculates the number of appearances of these patterns in the real

and random networks. The discussion that follows focuses on patterns with 3 nodes (forming a triangle), **Fig 1**. There are 13 possible 3-node patterns in such arrangement. Of these, only one of them qualifies to be a network motif called the **Feed Forward Loop.**
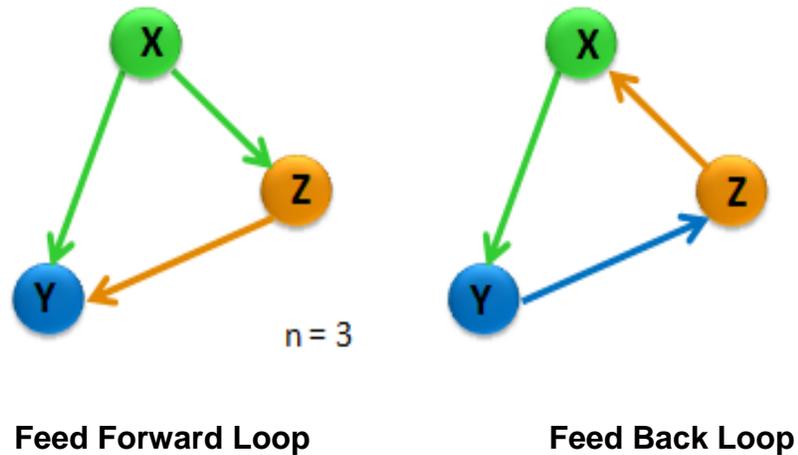

Feed Forward Loop　　　　　**Feed Back Loop**

Fig 1 Representative Feed Forward and Feed Back Loops with nodes n=3 forming a triangle

The most significant of the network motifs in *E. coli* and yeast is the Feed Forward Loop which is defined by a transcription factor X that regulates a second transcription factor Y. X and Y both jointly regulate an operon Z by binding to its regulatory region. Here X is called the general transcription factor, Y the specific transcription factor and Z the effector operon. As described in **Fig 2**, this type of motif occurs in the L-arabinose utilization system where Crp is the general transcription factor and Ara-C is a specific transcription factor. Such a motif characterizes 40 effector operons in 22 different systems in the network database and accommodates 10 different transcription factors.
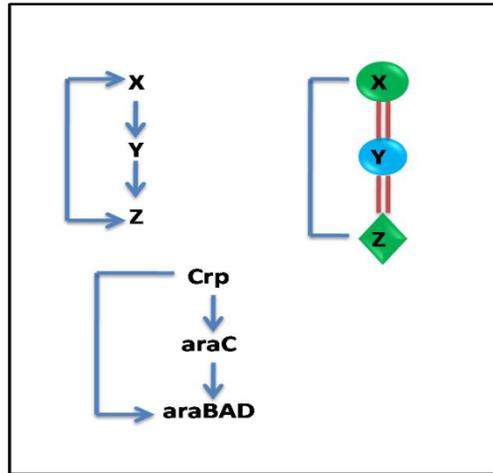
**Fig 2. Diagrammatic representation of FFL with an example of
L-arabinose utilization system**

In order to appreciate the dynamics of the Feed Forward Loop, one needs to study the regulation at each one of its three edges, each of which can represent activation or a repressive interaction. S_X and S_Y are the two input signals to the Feed Forward Loop. The signals could be small molecules, protein partners, biochemical or environmental stimuli or covalent modifications that activate or inhibit the transcription of X and Y. Therefore there are 8 possible types of FFL - 8 structural configurations of activator and repressor interactions.

2.1.1 Coherent Feed Forward Loops

A Feed Forward Loop is termed 'coherent' if the direct effect of the general transcription factor X on the effector operons has the same sign (positive or negative) as its net indirect effect through the specific transcription factor.
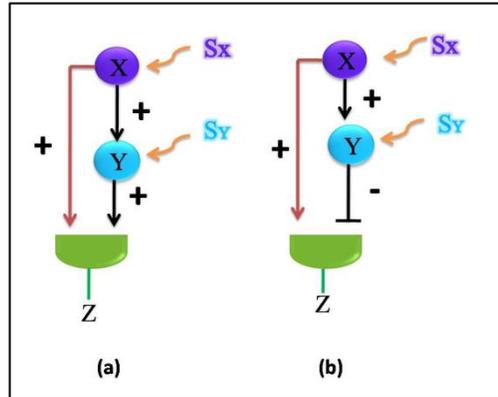
Fig 3. Feed-Forward Loop (FFL) (a) Coherent FFL (type1), X regulates Y and both jointly regulate Z. (b) Incoherent FFL (type1), here Sx and Sy are the signals

In other words, if X regulates Y positively and if X and Y both positively regulate Z, the Feed Forward Loop is coherent. i.e. the sign of the direct path of regulation (X to Z) is the same as the overall sign of the indirect regulation path (X to Z through Y). The overall sign of a path is determined by the multiplication of the sign of each arrow on the path. In **Fig 3 (a)** we see that the sign of the indirect path (X➔Y➔Z) is plus x plus =plus, while the direct path (X➔Z) is already plus. Since both the direct and indirect paths have the same positive sign, this loop is called a Coherent Feed Forward Loop.

2.1.2 Incoherent Feed Forward Loops
The other type of FFL (as in **Fig 3 (b)**) is called **Incoherent FFL** in which the sign of the indirect path of regulation is opposite to that of the direct path. In type-1 Incoherent FFL as denoted the direct path is positive and the indirect path is negative. The Incoherent FFLs show odd number of minus edges.

In both the coherent and incoherent loops, the effects of the general and specific transcription factors X and Y are integrated at the promoter region of gene Z. The expression profile of Z is modulated by the concentrations of X and Y bound to their inducers. The cis regulatory input function of Z describes this modulation. cis regulatory input functions include logic gates like AND which require both X and Y to express Z and OR gates in which either X or Y is sufficient to express Z.

Both Coherent and Incoherent Feed Forward Loops are sign sensitive. Type 1 coherent FFLs (in which all three regulations are positive) are the most abundant type of Feed

Forward Loops which will be discussed in detail in this class. The Incoherent Feed Forward loop type-1 is the second most abundant type of FFL among biological networks. The other types of feedforward loop do not appear more frequently than CFFL I and ICFFL I.

The next two classes will focus on the function of FFLs as logic gates. We will discuss how we can construct AND and OR gates using FFLs under varying conditions and understand gene expression patterns from the output states of the loops.

3 References

3.1 Text Book

1. Uri Alon, An Introduction to Systems Biology: Design Principles of Biological Circuits, 2/e, *CRC Press*, (2006).

3.2 Literature References

1. Shai S. Shen-Orr, Ron Milo, Shmoolik Mangan & Uri Alon, Network motifs in the transcriptional regulation network of *Escherichia coli*, *Nature Genetics*, (2002), 31, 64–69.

2. S. Mangan and U. Alon, Structure and function of the feed-forward loop network motif, *PNAS*, (2003), 100, 11980–11985.