Dynamics of Feed Forward Loop Motifs

1 Feed Forward Loop Motif Coherent 1 (C1)

To cope with the complexity of the biological networks we try to understand their behavior in terms of the dynamics of their building blocks. Motifs [1] are parts/building blocks of the biological networks that occur frequently when the latter are compared to random networks. We already discussed during the lectures the claim of Alon et al. [1] that the Feed-Forward Loop (FFL) motif is the only three-node motif that occurs statistically significant more often in biological networks than in random networks. The interesting question is why is this so? One logical way to try to find the answer is to assume that there is some biological function that is favorable for the organisms and that causes that the motif is "invented" and preserved by the evolution.

In the sequel we will give a formal description of some motifs in terms of Boolean regulatory graphs and try to deduce their functions from their dynamics. In Fig. 1 the so called C1 (Coherent 1) FFL is given.
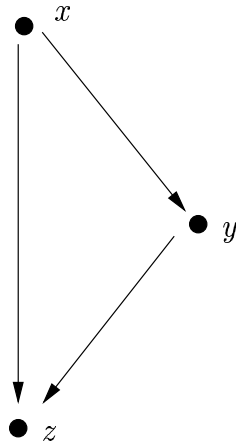

Fig. 1. Motif FFL C1.

The AND variant of the FFL C1 motif can be described by the Boolean regulatory network (G, I, F) where:

- $G = \{x, y, z\}$;
- $I = \{I_x, I_y, I_z\}$, where $I_x = \emptyset$, $I_y = \{x\}$, and $I_z = \{x, y\}$;
- $F = \{f_x, f_y, f_z\}$, where

- $f_x = Id$ (the identity function, so x is a constant determined by its initial value),
- $f_y(0) = 0$, $f_y(1) = 1$, and
- f_z is a logical and function, i.e. $f_z(1,1) = 1$ while for the other combinations of y and z $f_z(x,y) = 0$.

As we saw during the lectures, one possible important function of the C1 FFL AND network is to filter out sudden short changes of the concentrations of the product of gene x. In our discussion we actually made a step outside of our Boolean regulatory graphs formalism by assuming that the influences between genes happen with some time delay. In the case of C1 a sudden jump of the expression level of x from 0 to 1 will make y switching from 0 to 1 but with some delay T_{xy}. During the T_{xy} time interval z remains off since both x and y must be on in order z to become active. Only after another time delay T_{yz}, associated with the interaction between y and z, the latter will switch to an on state. Thus, there is a total time delay of $T_{xy} + T_{yz}$ between the activations of x and y. Such a delay filters out brief changes of the level of x and reacts only on activations of x with duration longer than T_{yz}.

We mentioned during the lectures that this is a solution that occurs quite often in the engineering practice (the example with the elevator door). It is also observed in vivo in E. coli in the system that regulates the use of the sugars glucose and arabinose in the cell [1].

A greater delay occurs only when x switches from on to off. In case the level of x suddenly drops than z will also switch off after time T_{xy} (assuming the same influence time delay), i.e., shorter than when x changes in the opposite direction from off to on. Thus the filtering is sign sensitive - it basically happens only when x goes from 0 to 1.

If we want to describe the OR variant we have to only modify the f_z function: $f_z(0,0) = 0$ and for the other combinations of x and y $f(x,y) = 1$. The function of the OR version of the C1 FFL is in a sense complementary to the one of the AND version. It also filters out small changes but in the opposite direction - when x drops from 1 to 0.

2 Feed Forward Loop Motifs Incoherent 1 (I1) and Incoherent 4 (I4)

The hypothesis that nature has selected certain flavors of the FFL motif because they fulfill some useful function is plausible, but it cannot explain why the FFL I1 is more frequent than FFL I4 (Fig. 2).

We consider here the AND variants of those motifs. The specification of I1 as a Boolean regulatory network differs from the one of the FFL C1 motif, which was given above, only in the definition f_z which is defined as follows: $f_z(0,y) = 0$, $(y = 1,2)$, $f_z(1,0) = 1$, and $f_z(1,1) = 0$. In order to specify FFL I4 we have to change also the f_y function: $f_y(0) = 1$ and $f_y(1) = 0$. For f_z we have: $f_z(0,y) = 0$, $(y = 1,2)$, $f_z(1,0) = 0$, and $f_z(1,1) = 1$.
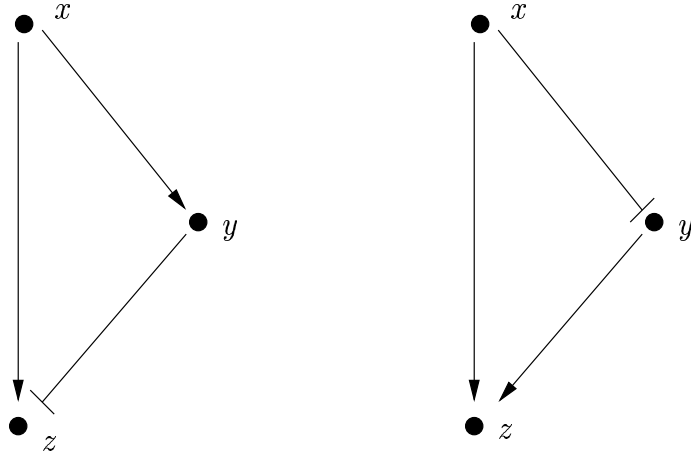
Fig. 2. Motifs FFL I1 (left) and FFL I4 (right).

Specified in such a way, both I1 and I4 can be regarded as pulse generators. For instance, in I1, assuming that initially all genes are off, if x switches on, then with some delay T_{xz}, i.e., the time needed for the interaction between x and z, z will become active too. However, after some delay T_{xy} also y will become active and as a result, after some time T_{yz}, z will go back to 0. In this way the activity of z has a form of a pulse. Similarly, in I4, a simultaneous activation of both x and y after some delay will activate z. However, after some time x will deactivate y. This will further result in deactivation of z and thus again in a pulse-like behavior of z.

One argument in favor of I1 would be that in I1 x plays only a role of an activator, while in I4 x must also act as an inhibitor. However, there exist genes that can occur both in the role of activators and repressors in the same time. An example can be found again in E. coli: the molecule known as CRP, which serves as a signal that there is no sufficient glucose, can both activate and repress genes [1].

Thus to find more convincing arguments we analyze again the dynamics of I1 and I4, but this time the *steady state* version of it. Steady state dynamics means that we consider only stable states, i.e., states from which no transition to another state is possible. In the context of Petri-nets we called them also end states. It can be checked that all combinations of the values of x, y, and z in the definition of f_z for I1 correspond to stable (end) states. On the other hand, the state corresponding to the combination $(1,1,1)$ in the definition of f_z for I4 is not stable, as x will deactivate y causing the system to jump to the state $(1,0,1)$. Since now y is not active also z will switch off and from this state the system will further move to $(1,0,0)$ which is a stable state. Thus, the steady state dynamics of I4 is simpler than the one of I1. Actually, considered as an input, y does not play any role since the stable values of z are dependent only

on x, which is not the case in I1, where both x and y determine the steady state behavior.

References

1. U. Alon, *An Introduction to Systems Biology: Design Principles of Biological Circuits*, Chapman and Hall, 2007.