1 Intro

In the previous lecture we analyzed transcriptional networks and significant motifs in those networks. Several significant motifs found:

- Auto Regulation (AR).
- Feedback Loop (FBL).
- Feed Forward Loop (FFL).

In this lecture we analyze these motifs and try to explain their functionality.

2 Network Motifs

2.1 Background

The simple edge from X to Y (see Figure 1) means that X regulate Y. We can think of it as an enzyme and substrate reaction. Therefore we get the following function (see Figure 2). But we will work with simpler model, 0,1 model, i.e. Above a certain concentration of X we have activation/deactivation of Y. (see Figure 3).

![X-regulates-Y](image.png)

Figure 1: X-regulates-Y.
2.2 Auto Regulation (AR)

First we think of a simpler case. X with No edges. so we get these 2 grapes.(see Figure 4). Now we add auto regulation. There is a point in time, where the protein concentration gets to a significant level, that the regulation will start work. i.e. if we look at the red line (see Figure 4) we can see that X-transcription rate will stop, and if we define a short life time for mRNA we get a constant level of X protein. This mechanism is good to keep constant level of X protein.

- Protein concentration : $X(t)$
- mRNA production rate : $X_{(mRNA)}(t)$
- Degradation coefficient : $\alpha(t)$

\[
\frac{dx}{dt} = X_{(mRNA)}(t) - \alpha(t)X(t)
\]

We get a differential equation :

\[
\frac{dx}{dt} = \beta - \alpha(t)X(t)
\]

We can see that when $X(t)$ is constant i.e. the change is 0, the production rate is equal to the degradation rate. If we don’t have the AR this will also happens, and we will get constant concentration. (since the production rate is constant and the degradation rate is increasing). So why do we need the AR mechanism?? In order to get a quick responds. With this mechanism we get a faster switch from one state to the other.
2.2.1 sometimes X can be both Auto activator and Auto deactivator. in low level of X we get activation, But in higher levels we get deactivation. when the concentration level is too high we the transcription is stopped. (see Figure 5).

2.3 Feedback Loop (FBL)

We consider this case X activates Y, and Y deactivate X.(see Figure 6) now we explain the process described in Figure 7

1. X in some constant transcription level, protein X increasing. Y transcription rate and protein is 0.
2. X protein reaches critical level. Y transcription rate activates, Y protein increasing.
3. Y protein reaches critical level. X transcription rate deactivates.
4. X degradation. X going down below critical level. Y transcription rate deactivates.
5. Y degradation.

this mechanism gives us a delay of X protein concentration, because the deactivation is linked through Y and not from X to itself. we can activate/deactivate Y and control X.

2.3.1 B-stable

now we change the game a little bit. (see Figure 8) in this case we get 2 possible states:
1. X active. Activates itself and deactivates Y.
2. Y active. Activates itself and deactivates X.

This mechanism allows the cell to "remember" states. Like flip-flop in computers. the "memory" can also be passed to the next generation.(Epigenetic).
The FFL is composed of a transcription factor X, which regulates a second transcription factor Y. The two transcription factors, X and Y, regulate a gene Z. The proportion of each of the transcription factors determines the transcription rate of Z. (see Figure 9) Each one of the 3 edges can be activator or deactivator. So we get 8 possible conformation. (see Figure 10) we can divide the 8 conformation to 2 groups:

1. Coherent
2. Incoherent

**Definition 2.1** A coherent FLL is a motif in which the direct effect of X on Z is similar to the indirect effect of X on Z through Y.

**Definition 2.2** An incoherent FLL is a motif in which the direct effect of X on Z is of opposite nature to the indirect effect of X on Z through Y.

When analyzing the occurrences of the eight structural types in E.coli it seems that two of them appear in transcriptional networks much more frequently than others. The two most frequent types are marked by a rectangle in Figure 10. We shall now analyze the function of these two forms.

**2.4.1 Coherent FFL**

This type of effect can be described as an AND-gate. In this case, Z responds only to persistent stimuli from X and not to short pulses of it. On the other hand, Z responds strongly to off pulses of X (see Figure 11). This type of regulation may be effective if, for example, Z is an energy consuming process.

A few remarks:
• If X pulse is too short so Y is pulse is to low and we don’t get activation of Z.

• This mechanism works as a noise filter.

• Also in real systems (not 0/1) we get the noise filter behavior.

2.4.2 Incoherent FFL

This type of effect can be described by this table:

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

In this case, Z responds quickly to stimuli from X, but responds slowly to off pulses (see Figure 12). We can see that Z is brought to a steady state by the repressing effect of Y, compensating the quick response to X.

3 How can we check this?

In order to check the protein level of Z, we need a system that measure Z protein without dismantle the cell. One way of doing this is by fluorescent marking. Using fluorescent protein (GFP) we can measure the level of protein expression as a function of time. (see Figure 13). The derivative is the production rate.
Figure 11: Coherent FFL. The combined effect of X and Y on Z. (1) X is stimulated. (2) Z is stimulated after the amounts of X and Y reach a critical level. (3) Z is shut off with Y, at an exponential rate. (4) Z is unaffected from a short pulse of X.
Figure 12: [Graph showing transcription rates and protein levels over time for X, Y, and Z genes.]

Figure 13: [Graph showing GFP expression over time.]