

CS341 SYSTEMS BIOLOGY I

LECTURE 7

FEED-FORWARD MOTIFS

On Tuesday, we talked about how single transcription factors could activate or repress transcription. Today, we will talk about two multiple transcription factors can interact when regulating a single gene. Next Tuesday, we will talk about the feed-forward motifs described by Mangan & Alon in the 2003 PNAS article that you will read for HW tonight.

Today's notes are a combination of the material for today and for next Tuesday. I didn't separate them because one is embedded in the other.

Here is the combined story:

A feed-forward motif is one in which transcription factor X regulates production of transcription factor Y and of gene Z. Also, Y regulates Z. This means Z is regulated by X both indirectly (through Y) and directly – an effect the “feeds forward”. There are 8 possible configurations for the regulation (X can up- or down-regulate Y, Y can up- or down-regulate Z, and X can up- or down-regulate Z). And, at Z, X and Y can operate together (with an AND gate) or competitively (with a competitive OR gate). In the homework, I asked you to write about 3 motifs. These notes derive the answers.

Set-up. In general, the model is

$$\begin{aligned}\frac{dY}{dt} &= B_y + \beta_Y f(X^*, K_{xy}) - \alpha_Y Y \\ \frac{dZ}{dt} &= B_z + \beta_Z G(X^*, K_{xz}, Y^*, K_{yz}) - \alpha_Z Z\end{aligned}$$

where f is a regulation function. X^* is active X in the system and Y^* is active Y ($Y^* = Y$ if parameter SY=1 and $Y^* = 0$ if SY=0).

If transcription factor u is an activator, then

$$f(u, K) = \frac{u^H}{K^H + u^H} = \frac{(u/K)^H}{1 + (u/K)^H}$$

1

If transcription factor u is a repressor, then

$$f(u, K) = \frac{K^H}{K^H + u^H} = \frac{1}{1 + (u/K)^H}$$

and AND gate is modeled simply by multiplying the activation functions for the effects of X on Z and Y on Z

$$G(X^*, K_{xz}, Y^*, K_{yz}) = f(X^*, K_{xz})f(Y^*, K_{yz})$$

and a competitive OR gate is more complicated

$$G(X^*, K_{xz}, Y^*, K_{yz}) = fc(X^*, K_{xz}, K_{yz}, Y^*) + fc(Y^*, K_{yz}, K_{xz}, X^*)$$

where fc for an activator is

$$fc(u, K_u, K_v, v) = \frac{(u/K_u)^H}{1 + (u/K_u)^H + (v/K_v)^H}$$

and fc for a repressor is

$$fc(u, K_u, K_v, v) = \frac{1}{1 + (u/K_u)^H + (v/K_v)^H}$$

Coherent Type 1 with AND Gate. The coherent type 1 motif involves only activation.



$$\begin{aligned} \frac{dY}{dt} &= B_y + \beta_Y f(X^*, K_{xy}) - \alpha_Y Y \\ \frac{dZ}{dt} &= B_z + \beta_Z G(X^*, K_{xz}, Y^*, K_{yz}) - \alpha_Z Z \end{aligned}$$

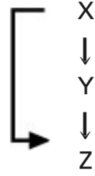
where G is for the AND gate, so

$$\begin{aligned}\frac{dY}{dt} &= B_y + \beta_Y f(X^*, K_{xy}) - \alpha_y Y \\ \frac{dZ}{dt} &= B_z + \beta_Z f(X^*, K_{xz}) f(Y^*, K_{yz}) - \alpha_z Z\end{aligned}$$

and all f 's are for activators, so

$$\begin{aligned}\frac{dY}{dt} &= B_y + \beta_Y \frac{(X^*/K_{xy})^H}{1 + (X^*/K_{xy})^H} - \alpha_y Y \\ \frac{dZ}{dt} &= B_z + \beta_Z \left(\frac{(X^*/K_{xz})^H}{1 + (X^*/K_{xz})^H} \right) \left(\frac{(Y^*/K_{yz})^H}{1 + (Y^*/K_{yz})^H} \right) - \alpha_z Z\end{aligned}$$

Coherent Type 1 with OR Gate. The coherent type 1 motif involves only activation.



$$\begin{aligned}\frac{dY}{dt} &= B_y + \beta_Y f(X^*, K_{xy}) - \alpha_y Y \\ \frac{dZ}{dt} &= B_z + \beta_Z G(X^*, K_{xz}, Y^*, K_{yz}) - \alpha_z Z\end{aligned}$$

where G is for the OR gate with competition, so

$$\begin{aligned}\frac{dY}{dt} &= B_y + \beta_Y f(X^*, K_{xy}) - \alpha_y Y \\ \frac{dZ}{dt} &= B_z + \beta_Z (fc(X^*, K_{xz}, K_{yz}, Y^*) + fc(Y^*, K_{yz}, K_{xz}, X^*)) - \alpha_z Z\end{aligned}$$

and all f 's and fc 's are for activators, so

$$\begin{aligned}\frac{dY}{dt} &= B_y + \beta_Y \frac{(X^*/K_{xy})^H}{1 + (X^*/K_{xy})^H} - \alpha_Y Y \\ \frac{dZ}{dt} &= B_z + \beta_Z \left(\left(\frac{(X^*/K_{xz})^H}{1 + (X^*/K_{xz})^H + (Y^*/K_{yz})^H} \right) + \left(\frac{(Y^*/K_{yz})^H}{1 + (X^*/K_{xz})^H + (Y^*/K_{yz})^H} \right) \right) - \alpha_Z Z\end{aligned}$$

which simplifies slightly to

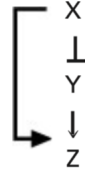
$$\begin{aligned}\frac{dY}{dt} &= B_y + \beta_Y \frac{(X^*/K_{xy})^H}{1 + (X^*/K_{xy})^H} - \alpha_Y Y \\ \frac{dZ}{dt} &= B_z + \beta_Z \left(\frac{(X^*/K_{xz})^H + (Y^*/K_{yz})^H}{1 + (X^*/K_{xz})^H + (Y^*/K_{yz})^H} \right) - \alpha_Z Z\end{aligned}$$

Let's make a truth table for the OR gate, to see if it really acts as one.

X^*	Y^*	$\left(\left(\frac{(X^*/K_{xz})^H}{1 + (X^*/K_{xz})^H + (Y^*/K_{yz})^H} \right) + \left(\frac{(Y^*/K_{yz})^H}{1 + (X^*/K_{xz})^H + (Y^*/K_{yz})^H} \right) \right)$
little	little	$\frac{\text{little}}{1 + \text{little} + \text{little}} + \frac{\text{little}}{1 + \text{little} + \text{little}} = \text{little}$
little	big	$\frac{\text{little}}{1 + \text{little} + \text{big}} + \frac{\text{big}}{1 + \text{little} + \text{big}} = \text{little} + 1 = 1$
big	little	$\frac{\text{big}}{1 + \text{big} + \text{little}} + \frac{\text{little}}{1 + \text{big} + \text{little}} = 1 + \text{little} = 1$
big	big	$\frac{\text{big}}{1 + \text{big} + \text{big}} + \frac{\text{big}}{1 + \text{big} + \text{big}} = \frac{\text{big}}{2\text{big}} + \frac{\text{big}}{2\text{big}} = \frac{1}{2} + \frac{1}{2} = 1$

TABLE 1. Remember, *never* use vertical lines in tables.

Incoherent Type 4 with AND Gate. The incoherent type 4 motif involves X repressing Y, X activating Z, and Y activating Z.



$$\begin{aligned}\frac{dY}{dt} &= B_y + \beta_Y f(X^*, K_{xy}) - \alpha_Y Y \\ \frac{dZ}{dt} &= B_z + \beta_Z G(X^*, K_{xz}, Y^*, K_{yz}) - \alpha_Z Z\end{aligned}$$

where G is for the AND gate, so

$$\begin{aligned}\frac{dY}{dt} &= B_y + \beta_Y f(X^*, K_{xy}) - \alpha_y Y \\ \frac{dZ}{dt} &= B_z + \beta_Z f(X^*, K_{xz}) f(Y^*, K_{yz}) - \alpha_z Z\end{aligned}$$

X represses Y, so

$$\begin{aligned}\frac{dY}{dt} &= B_y + \beta_Y \frac{1}{1 + (X^*/K_{xy})^H} - \alpha_y Y \\ \frac{dZ}{dt} &= B_z + \beta_Z f(X^*, K_{xz}) f(Y^*, K_{yz}) - \alpha_z Z\end{aligned}$$

and X and Y both activate Z

$$\begin{aligned}\frac{dY}{dt} &= B_y + \beta_Y \frac{1}{1 + (X^*/K_{xy})^H} - \alpha_y Y \\ \frac{dZ}{dt} &= B_z + \beta_Z \left(\frac{(X^*/K_{xz})^H}{1 + (X^*/K_{xz})^H} \right) \left(\frac{(Y^*/K_{yz})^H}{1 + (Y^*/K_{yz})^H} \right) - \alpha_z Z\end{aligned}$$