

CS341 SYSTEMS BIOLOGY I

LECTURE 7

FEED-FORWARD MOTIFS

On Tuesday, we talked about how single transcription factors could activate or repress transcription. We also began to talk about how two transcription factors might work together to affect transcription. Today, we will talk about the feed-forward motifs described by Mangan & Alon in the 2004 PNAS article.

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

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

If transcription factor u is a repressor, then

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

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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.



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

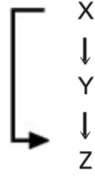
where G is for the AND gate, so

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

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

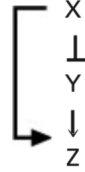
$$\begin{aligned}\frac{dY}{dt} &= B_y + \beta_Y \frac{(X^*/K_{xy})^H}{1 + (X^*/K_{xy})^H} - \alpha_y Y \\ \frac{dZ}{dt} &= B_z + \beta_Z \left(\frac{(X^*/K_{xz})^H + (Y^*/K_{yz})^H}{1 + (X^*/K_{xz})^H + (Y^*/K_{yz})^H} \right) - \alpha_z Z\end{aligned}$$

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

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