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 on 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 (though 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 an 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

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

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

\[
 f(u, K) = \frac{u^H}{K^H + u^H} = \frac{(u/K)^H}{1 + (u/K)^H}
\]
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
\[ fc(u, K_u, K_v) = \frac{(u/K_u)^H}{1 + (u/K_u)^H + (v/K_v)^H} \]
and $fc$ for a repressor is
\[ fc(u, K_u, K_v) = \frac{1}{1 + (u/K_u)^H + (v/K_v)^H} \]

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

\[
\begin{align*}
\frac{dY}{dt} &= B_y + \beta_Y f(X^*, K_{xy}) - \alpha_y Y \\
\frac{dZ}{dt} &= B_z + \beta_Z G(X^*, K_{xz}, Y^*, K_{yz}) - \alpha_z Z 
\end{align*}
\]
where $G$ is for the AND gate, so
\[
\frac{dY}{dt} = B_y + \beta_Y f(X^*, K_{xy}) - \alpha_y Y \\
\frac{dZ}{dt} = B_z + \beta_Z f(X^*, K_{xz}) f(Y^*, K_{yz}) - \alpha_z Z
\]

and all \(f\)'s are for activators, so

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

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

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

where \(G\) is for the OR gate with competition, so

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

and all \(f\)'s and \(fc\)'s are for activators, so
\[
\frac{dY}{dt} = B_y + \beta_y \left( \frac{(X^*/K_{xy})^H}{1 + (X^*/K_{xy})^H} \right) Y - \alpha_y Y \\
\frac{dZ}{dt} = B_z + \beta_z \left( \frac{(X^*/K_{xz})^H + (Y^*/K_{yz})^H}{1 + (X^*/K_{xz})^H + (Y^*/K_{yz})^H} \right) - \alpha_z Z
\]

which simplifies slightly to
\[
\frac{dY}{dt} = B_y + \beta_y \left( \frac{(X^*/K_{xy})^H}{1 + (X^*/K_{xy})^H} \right) Y - \alpha_y Y \\
\frac{dZ}{dt} = B_z + \beta_z \left( \frac{(X^*/K_{xz})^H + (Y^*/K_{yz})^H}{1 + (X^*/K_{xz})^H + (Y^*/K_{yz})^H} \right) - \alpha_z Z
\]

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

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>( \frac{1}{1 + (X^<em>/K_{xz})^H + (Y^</em>/K_{yz})^H} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>little</td>
<td>little</td>
<td>( \frac{1 + \text{little} + \text{little}}{\text{little}} ) = little</td>
</tr>
<tr>
<td>little</td>
<td>big</td>
<td>( \frac{1 + \text{little} + \text{big}}{\text{big}} ) = little + 1 = 1</td>
</tr>
<tr>
<td>big</td>
<td>little</td>
<td>( \frac{1 + \text{big} + \text{little}}{\text{little}} ) = 1 + little = 1</td>
</tr>
<tr>
<td>big</td>
<td>big</td>
<td>( \frac{1 + \text{big} + \text{big}}{\text{big}} ) = ( \frac{1 + 1}{2} = 1 )</td>
</tr>
</tbody>
</table>

**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.

\[
\frac{dY}{dt} = B_y + \beta_Y f(X^*, K_{xy}) - \alpha_y Y \\
\frac{dZ}{dt} = B_z + \beta_Z G(X^*, K_{xz}, Y^*, K_{yz}) - \alpha_z Z
\]
where \( G \) is for the AND gate, so

\[
\frac{dY}{dt} = B_y + \beta_y f(X^*, K_{xy}) - \alpha_y Y
\]
\[
\frac{dZ}{dt} = B_z + \beta_Z f(X^*, K_{xz}) f(Y^*, K_{yz}) - \alpha_z Z
\]

\( X \) represses \( Y \), so

\[
\frac{dY}{dt} = B_y + \beta_y \frac{1}{1 + \left(\frac{X^*}{K_{xy}}\right)^H} - \alpha_y Y
\]
\[
\frac{dZ}{dt} = B_z + \beta_Z f(X^*, K_{xz}) f(Y^*, K_{yz}) - \alpha_z Z
\]

and \( X \) and \( Y \) both activate \( Z \)

\[
\frac{dY}{dt} = B_y + \beta_y \frac{1}{1 + \left(\frac{X^*}{K_{xy}}\right)^H} - \alpha_y Y
\]
\[
\frac{dZ}{dt} = B_z + \beta_Z \left( \frac{(X^*/K_{xz})^H}{1 + (X^*/K_{xz})^H} \right) \left( \frac{(Y^*/K_{yz})^H}{1 + (Y^*/K_{yz})^H} \right) - \alpha_z Z
\]