L3.2: Simple Models of Gene Expression

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In this lecture

• Mathematical representation of gene expression
  • Gene Activation
  • Gene Repression
• Gene Product Production
  • Hill function model
  • Logic model
• Gene Product Decay
  • Degradation
  • Dilution
• Steady state response & response time for turning genes ON and OFF
Effect of Transcription Factor X on Gene Y

**Activation**

- Increases probability of RNAp binding
- Increases probability of transcription

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>[X] = high</td>
<td>ON</td>
</tr>
<tr>
<td>[X] = 0</td>
<td>OFF (or low)</td>
</tr>
</tbody>
</table>

**Repression**

- Reduces probability of RNAp binding
- Reduces probability of transcription

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simple deterministic model

Rate of change of Y = \[ \frac{dy}{dt} = in - out + \text{generation} - \text{consumption} \]

\( y \) : [Y] conc. protein Y inside cell
\( in \) : rate of transport of Y into cell from outside
\( out \) : rate of transport of Y out of the cell
\( gen \) : rate of transcription / translation of Y
\( cons \) : rate of degradation or dilution

Assume no transport in or out
\[
\frac{dy}{dt} = \text{generation} - \text{consumption}
\]
\[
\frac{dy}{dt} = \beta f(x) - (\alpha_{\text{dilution}} + \alpha_{\text{degradation}})y
\]

**Generation**

- basal expression rate in ON state, $\beta$
- depend on transcription factor $[X] = x$
- $x$ modifies the probability of transcription

**Consumption**

degradation: passive or active

- $\alpha_{\text{degradation}}$ small for a stable protein
- $\alpha_{\text{degradation}}$ large for rapidly degraded protein

dilution: cell division

- $\alpha_{\text{dilution}} = \text{growth rate}$
Generation: Hill function model

activator

probability of transcription

\[ f(x) = \frac{x^n}{x^n + K^n} \]

Repressor

probability of transcription

\[ f(x) = \frac{1}{1 + \left(\frac{x}{K}\right)^n} \]
Hill function model of gene activation

\[ f(x) = \frac{x^n}{x^n + K^n} \]

- \( K \): units conc.
  - defines functional concentration range of X
  - may correlate with (but is not formally) the binding affinity of X to the DNA
  - other factors contribute to K

- \( n \): Hill coefficient
  - increases nonlinearity of function
  - increases steepness of sigmoidal
  - greater n, more on/off switch-like

<table>
<thead>
<tr>
<th>[X]</th>
<th>prob.</th>
<th>rate</th>
<th>gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>( x \gg K )</td>
<td>( \Rightarrow 1 )</td>
<td>( \Rightarrow \beta )</td>
<td>ON high</td>
</tr>
<tr>
<td>( x = K )</td>
<td>( 0.5 )</td>
<td>( \beta/2 )</td>
<td>ON mod</td>
</tr>
<tr>
<td>( x \ll K )</td>
<td>( \Rightarrow 0 )</td>
<td>( \Rightarrow 0 )</td>
<td>OFF</td>
</tr>
</tbody>
</table>
Hill function model of gene activation

In the extreme of $n \rightarrow \infty$

approximate hill function with logic model

$$f(x) = \theta(x > K)$$

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<tr>
<th>$x/K$</th>
<th>$\theta$</th>
<th>generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$x &gt; K$</td>
<td>= 1</td>
<td>= $\beta$</td>
</tr>
<tr>
<td>$x &lt; K$</td>
<td>= 0</td>
<td>= 0</td>
</tr>
</tbody>
</table>

- Activation is switch like
- $K$ becomes threshold concentration
- Increasing the stoichiometry of binding one way to increase $n$

Note: In reality $n$ is rarely $> 4$. However logic model approximation is still useful in dynamic analysis of large circuits & for building intuition regarding circuit behavior.
general equation for gene activation

\[
\frac{dy}{dt} = \beta f(x) - (\alpha_{\text{dilution}} + \alpha_{\text{degradation}})y
\]

dynamics to turn ON

System is initially OFF
\[x(t<0) = 0\]
Gene expression turns on at \(t = 0\)
\[x(0) = x \gg K\]

governing rate equation for protein Y

\[
\frac{dy}{dt} = \beta \frac{x^n}{x^n + K^n} - \alpha y
\]

dynamics to turn OFF

System is initially ON
\[x(t<0) = x \gg K\]
Gene expression turns OFF at \(t = 0\)
\[x(0) = 0\]

What is the steady state response?
What is the response time to turn ON or OFF?
\[ \frac{dy}{dt} = \beta \frac{x^n}{x^n + K^n} - \alpha y \]  

governing equation for simple activation

\[ \frac{dy}{dt} = \beta \theta(x > K) - \alpha y \]  

logic model approximation

\[ \frac{dy}{dt} = \beta - \alpha y \]  

strong activation \((x \gg K, \text{assume } f(x) = 1)\)

steady state solution

\[ y_{ss} = \frac{\beta}{\alpha} \]

trajectory of \(y(t)\) to turn on

system initially off - no expression, turn on at \(t = 0\)

\[ y(0) = 0 \]

\[ y(t) = \frac{\beta}{\alpha} (1 - e^{-\alpha t}) \]
Response time to turn ON

\[
y(t) = \frac{\beta}{\alpha} (1 - e^{-\alpha t})
\]

\[
y(t_{1/2}) = \frac{\beta}{\alpha} (1 - e^{-\alpha t_{1/2}}) = \frac{1}{2} y_{ss} = \frac{1}{2} \frac{\beta}{\alpha}
\]

\[
(1 - e^{-\alpha t_{1/2}}) = \frac{1}{2}
\]

\[
t_{1/2} = \frac{\ln 2}{\alpha}
\]

steady state expression level depends on expression strength (\(\beta\)) & degradation/dilution rate (\(\alpha\))

response time depends only on degradation/dilution rate (\(\alpha\))
OFF kinetics

\[ \frac{dy}{dt} = \beta - \alpha y \]

system initially fully ON

turns off at \( t = 0 \)

\[ \frac{dy}{dt} = \beta - \alpha y \]

\[ \frac{dy}{dt} = -\alpha y \quad \text{simple exponential decay} \]

\[ y(0) = y_{ss} = \frac{\beta}{\alpha} \]

\[ y(t) = \frac{\beta}{\alpha} (e^{-\alpha t}) \]

\[ t_{1/2} = \frac{\ln 2}{\alpha} \]
1. Work out the ON and OFF kinetics for a repressor using the same approach.

2. Work out the ON and OFF kinetics for an activator without making the logistic approximation of the hill function
   • Does it make much of a difference? Qualitatively? Quantitatively?
   • Use numerical integration (e.g. matlab)
   • Vary n, K, β, & α. How do the curves change?
Next up

• Take a closer look at the gene product (protein) consumption rate, $\alpha$

• Start looking at dynamics when we put together activators/repressors to make simple circuits