L3.6: Feed-forward Loops (FFLs) part 2

Prof Rickus
This lecture …

Type 1 Coherent FFL with AND Logic
  • ON kinetics

• Features
  • Coincidence Detector
  • Filters flicker noise

• Real System – Arabinose Utilization in \textit{E. coli}
Type 1 Coherent FFL with AND logic

COHERENT FFL (C-FFL): Direct and Indirect Paths have the same sign

INCOHERENT FFL (I-FFL) – Direct and Indirect Paths have the opposite sign

Uri Alon. An Introduction to Systems Biology: Design Principles of Biological Circuits
Many transcription factors are regulated. Rendered active or inactive by other signals. e.g. phosphorylation OR small molecule binding.
Naturally Occurring Example of 1C-FFL

Arabinose Utilization Control

Mangan et al 2003 - JMB
**AND integration at Molecular Level**

**Coherent:** Direct and Indirect Effect of gene product X on gene product Z are both activation

**AND Logic:** Promotor region for gene Z requires both X* AND Y* be bound

Ref. Alon. Intro to Systems Biology
Logic Model and Truth Table View

Coincidence detector of 2 signals, $S_x$ and $S_y$:
- Both $S_x$ and $S_y$ must be around & at high enough levels to get enough $X^*$ and $Y^*$

Logic Model of Expression

$$\frac{dY}{dt} = \beta_Y \theta_1(X^* > K_{XY}) - \alpha_Y$$
Usual simple activation

$$\frac{dZ}{dt} = \beta_Z \theta_2(X^* > K_{XZ}) \theta_3(Y^* > K_{YZ}) - \alpha_Z$$
AND integration

<table>
<thead>
<tr>
<th>$X^* &gt; K_{XZ}$</th>
<th>$Y^* &gt; K_{YZ}$</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Z on</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>Z off</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>Z off</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>Z off</td>
</tr>
</tbody>
</table>

Both $X$ and $Y$ must be in their active form at a sufficiently high level.
ON & OFF Kinetics of 1C-FFL with AND Logic

System is initially OFF
\[ x(t<0) = 0 \]
Gene expression turns on at \( t = 0 \)
\[ x(0) = x \gg K_{xy} \]
\[ x(0) = x \gg K_{xz} \]

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

What is the response time for Y and Z to turn ON or OFF?

Assume lots of Sx around. So all X is in active (X* form)
Y Response Time

How long until Y reaches 0.5 $Y_{ss}$?

$y_{ss} = \frac{\beta_y}{\alpha_y}$

$\frac{1}{2} y_{ss}$

$y(t) = \frac{\beta_y}{\alpha_y} (1 - e^{-\alpha_y t})$

$t_{1/2, y} = \frac{\ln 2}{\alpha_y}$

typical simple response time
Y Time to Threshold

How long until we build up enough Y to turn on Z?
How long until Y reaches $K_{YZ}$?
Call this time, $t = T_{ON}$

Usual equation for strong activation

$$y(t) = \frac{\beta_y}{\alpha_y} (1 - e^{-\alpha_y t})$$

![Graph showing time to threshold](image)

To find $T_{ON}$
Plug in and solve for $T_{ON}$

$$T_{ON} = \frac{1}{\alpha_y} \log \left( \frac{1}{1 - \left[ K_{YZ} / \beta_y / \alpha_y \right]} \right)$$
Look at $X$, $Y$ and $Z$ across time

Alon. Intro to Systems Biology
Total Z response time = delay + simple activation response time
Why would a delay be useful?

Short input signal, X
No output signal, Z

Persistent input signal, X
Get output signal, Z

Acts as a Persistence detector
Filters flicking noise

How could we tune the filter/persistence detector?
Design Equation
For tuning the delay in a C1-FFL with AND integration

Delay to turn Z on $\rightarrow$

$$T_{ON} = \frac{1}{\alpha_y} \log \frac{1}{1 - \left[ \frac{K_{YZ}}{Y_{ss}} \right]}$$

Have 3 tuning parameters to set the delay
- Protein half-life
- Threshold for transcription activation
- State state response

Dimensionless Delay
delay relative to Y decay rate

$$\alpha_y T_{ON} = \log \frac{1}{1 - \left[ \frac{K_{YZ}}{Y_{ss}} \right]}$$

Dimensionless threshold

Note: What happens if $K_{YZ} > Y_{ss}$?
if $K_{YZ} > Y_{ss}$

$Y^*$ never reaches the threshold and $Z$ never turns on.

$\alpha_y T_{ON} = \log \frac{1}{1 - [K_{YZ}/Y_{ss}]}$
C1-FFL w/AND integration has simple off dynamics

- Inactivate X
- Y turns off
- Z turns off
- No delay
- Requires Y & X

Fig 4.8b from Alon. Intro to Systems Biology
Coherent FFL in a real system

Coincidence Detector

- glucose

+ arabinose

Arabinose Utilization

- *E. coli* prefer glucose as a carbon source
- But can use arabinose
- Only want to turn on arabinose machinery when glucose is unavailable AND arabinose is available

Mangan et al 2003 - JMB
Coincidence Detector

<table>
<thead>
<tr>
<th>Glucose</th>
<th>cAMP</th>
<th>Arabinose</th>
<th>Arabinose Operon</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>-</td>
<td>-</td>
<td>OFF</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>-</td>
<td>OFF</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>+</td>
<td>OFF</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>+</td>
<td>ON</td>
</tr>
</tbody>
</table>

arabinose operon
arabinose transporters
arabinose catabolism
Does the real system behave like we expect?
Compare 1C-FFL w/AND to a simple AND

- What does the model predict?
- How does the bacteria’s behavior compare to the model behavior?

Mangan et al 2003 - JMB
Levels of Z over Time

model

a) Delay

b) No Delay

Mangan et al 2003 - JMB
Levels of Z over Time

**model**

- **ON**
  - Simple FFL
  - delay

- **OFF**
  - Simple FFL
  - no delay

**experiment**

- **araBAD**
- **lacZYA**

*Mangan et al 2003 - JMB*
Coherent FFL
With AND logic

Sign Sensitive Delay

ON (introduce Sx) $\rightarrow$ delay

OFF (Sx goes away) $\rightarrow$ no delay

Protects against fluctuations / temporary introduction of Sx

Useful when
Cost of turning ON in error is high
Coherent FFL with OR logic

Sign Sensitive Delay

ON (introduce $S_x$) $\rightarrow$ no delay

OFF ($S_x$ goes away) $\rightarrow$ delay

Protects against fluctuations / temporary loss of $S_x$

Useful when
Cost of turning OFF in error is high
Coming Up …

• Cell Dynamics
  • Oscillations
  • Switches