The Feed-Forward Regulation 2
(Continued)

02/02/2012
Three ways to speed up response

- Under the simple X->Y regulation, the response time can be slow, usually on the order of the cell generation.
- We have learned so far that there are three ways to speed up the response time:

  1. To increase degradation rate:

     \[ T_{1/2} = \frac{\ln 2}{\alpha}, \text{ where } \alpha = \alpha_{\text{deg}} + \alpha_{\text{dil}} \]

     **Benefit:** The response times for both turn-ON and turn-OFF gene expression are increased

     **Disadvantage:** this strategy creates a futile cycle, where the protein is rapidly produced and rapidly degraded.

When benefit of speeding the response time surpasses the cost of increased production, this design can still be selected by evolution in some system.
Three ways to speed up response

2. Negative autoregulation: Speeding-up is achieved by a strong promoter to give rapid initial production, which is then turned off by the production itself, thereby achieving a steady state.

\[
\frac{T_{1/2}^{(n.a.r)}}{T_{1/2}^{simple}} = \frac{\beta_{simple}}{2 \beta \ln 2}.
\]

**Benefit:** can greatly decrease response time for protein production.

**Disadvantage:** it does not affect on turn-OFF gene expression, and the gene itself needs to be a regulator.
Three ways to speed up response

3. Incoherent FFL: I1-FFL can speed up ON responses, which is achieved by a strong promoter to give rapid initial production that is later turned off by a delayed repressor.

\[ T_{1/2} = \frac{\ln \frac{2F}{2F - 1}}{\alpha Z} \]

**Benefit:** can greatly decrease response time for turn-ON gene expression for any gene.

**Disadvantage:** it does not affect on turn-OFF gene expression.

- Design 2 and 3 can be combined with 1 to further speed up the response times of negative autoregulation and I1-FFL.
Why are some FFL type rare?

> Distribution of the 8 types of FFL in real gene transcriptional regulatory networks.

From Alon Fig 4.4
Why are some FFL types rare?

To address this question, let’s consider the computation of steady state $Z_{st}$ performed by these rare FFLs.

The difference between incoherent type-1 FFL and type-4 FFL

From Alon Fig 4.16:
Dynamics of I4-FFL

There are four functional states of an I4-FFL with an AND gate:

1. None binding
2. Y* binding
3. X* binding
4. Both X* AND Y* binding

From Alon Fig 4.17
Dynamics of I4-FFL

- I4-FFL has very similar dynamics as I1-FFL, and is also an sign sensitive accelerator for an ON step of $S_X$.

From Alon Fig 4.17:
**The difference between I1-FFL and I4-FFL**

- In I1-FFL, in the absence of $S_Y$, the expression of $Z$ is high: $\beta/\alpha_Z$
- When both $S_X$, $S_Y$ are present, at steady state, $Z = \beta'/\alpha_Z$.

From Alon Fig 4.16
The difference between I1-FFL and I4-FFL

- In an I4-FFL, when both $S_X$, $S_Y$ are present, at steady state, $Z_{st} = \beta'/\alpha_Z$.
- When $S_X$ is present, but $S_Y$ is not, at steady state, we have the same steady state $Z_{st} = \beta'/\alpha_Z$.

From Alon Fig 4.17: Time

I4-FFL

\[ S_X \]

\[ Y^* \]

\[ Z \]

AND

\[ Z \]

\[ S_Y \text{ absent} \]

\[ \frac{\beta'}{\alpha_Z} \]
The difference between I1-FFL and I4-FFL

- Therefore, we conclude that, $S_Y$ has no effect on the steady state of $Z$ in an I4-FFL.

- Thus, one source of information is not utilized by an I4-FFL.

- This might be at least the partial reason that I4-FFL is not frequently selected by evolution.

- The same conclusion can be drawn for the other rare coherent as well as incoherent FFLs.

- The failure to utilize one source of information is probably the major reason for these FFLs not to be selected frequently during evolution.
Evolution of FFLs

- If gene $Z$ has to respond to signal $S_X$ and $S_Y$, then a V-shaped structure should be first selected.

- Then the third edge $X-Y$ is selected for the special properties that confer to the circuit.

A possible scenario of C1-FFL evolution

A possible scenario of I1-FFL evolution

I4 is less frequently selected

I3 and C2 are less frequently selected

C4 is less frequently selected
Convergent evolution of FFLs

It was found that TFs that regulate two homologous genes Z and Z’ are not always conserved, however the gene circuit are more often conserved, suggesting that evolution had converged independently on the same regulatory circuit to control the homologous genes.
Temporal programs and the global structure of sensory transcription networks
Types of network motifs in sensory transcription networks

- Gene transcription networks that are coupled/connected to environmental changes are called sensory transcription networks (STNs).

- We have so far discussed two types of network motifs found in sensory transcription networks. These are small motifs with fixed number of nodes:
  1. Autoregulation;
  2. Feed forward loop;

- In addition, there are motif families with varying number of nodes fund in STNs. Each member in the family shares the same architectural pattern.

- The first of motif families we want to discuss is
The SIM network motif family

- The common feature of SIM family is that a master TF X regulates multiple genes \((Z_1, Z_2, \ldots, Z_n)\), which do not receive any other regulation.

- The sign of regulation is the same for all these target genes, and often the master regulator X is auto-regulatory.

An inhibitory SIM motif

\[ X \]

\[ Z_1 \quad Z_2 \quad \ldots \quad Z_n \]

A stimulatory SIM motif

\[ \text{argR} \]

\[ \text{argCBH} \quad \text{argD} \quad \text{argE} \quad \text{argF} \quad \text{argI} \]

The arginine biosynthesis regulatory system
The SIM network motif family

- The SIM family is determined by a free parameter, the number of target genes $n$. The larger the $n$, the stronger the SIM is a network motif.

- This is because it is rare to find in a random network having a node with a large out-degree of $n$.

- The functions of SIMs: To control a group of genes with coordinated functions in response to a signal sensed by the master regulator:
  1. Genes that work sequentially to synthesize or break down a molecule;
  2. Genes that encode subunits of a molecular machine;
  3. Genes that the cell uses to respond to a specific stress;
  4. Genes that are involved in global responses.
A SIM regulating a three-step metabolic pathway

- These enzymes catalyze the conversion of substrate S0 to S1, S1 to S2, and S2 to S3, resulting in the culmination of the product S3.
- The product S3 binds to the regulator R, and increases the probability that R is in its active state R*, which binds the promoters to repress the production of enzymes.

From Alon Fig 5.2.
SIM can generate temporal expression program

- The most important dynamical property of a SIM is that it can generate temporal programs of expression, in which genes are activated one by one in a defined order according to their activation thresholds, and genes are turned off in a reverse order of their activation.

![Diagram showing gene activation](image)

X is an activator

X → Z1 → Z2 → Z3

The graphs show the temporal expression of genes X, Z1, Z2, and Z3 over time with threshold levels indicated.
SIM can generate temporal expression program

- Thus, the temporal expression program generated by a SIM is in last-in-first-out (LIFO) order.

- The temporal order of genes match their functional order in the pathway: in general, the earlier the protein functions in the pathway, the earlier its gene is activated.

- This is an economical design, proteins are not produced before they are needed ----- a just-when-needed design.

- The temporal order of a SIM is selected by evolution by changing the binding affinity between the TF and cis-regulatory binding sites, and their relative positions.

- This also explains the degenerate nature of cis-regulatory binding sites of a TF----to achieve different affinity to the TF----$k_d$. 
Temporal order in arginine biosynthesis system with minutes between genes

Zaslaver et al Nature genetics 2004
Robustness of SIMs in global response systems

- In addition to biosynthesis and degradation pathways, SIMs are mainly found in global cellular responses where timing is important:
  1. SOS DNA repair system;
  2. Genes controlling the cell cycle;
  3. Circadian clock;

- In these cases, target genes may also receive regulation from other regulators responsible to local subsystems. Thus, the network is not strictly a SIM.

- However, the temporal program can still be generated as long as the master regulator is the only active regulator during the interval of interest.
Many target genes of a SIM are shared by evolutionarily distant species, however, the masters regulator are often not conserved, though the same SIM architecture are maintained, suggesting a convergent evolution of SIMs.
The drawback of the LIFO dynamics of SIMs

- The LIFO dynamics generated by a SIM is useful for some systems, however, this dynamics may waste resource in some situation where proteins that are produced earlier are not needed in the later stage when later genes are OFF.