EE430
Introduction to Systems Biology

Week 4 Course Notes

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Topics

• Regulation of gene transcription
  – Regulation in a biomolecular network
  – Primary regulation mechanisms
    • Autoregulation
    • Feed-forward loops
Regulation in a Biomolecular Network

- **Selection promotes**
  - efficiency
    - Cells operate in an environment with limited resources
    - The resources must be spent on supplying the mechanisms that are of higher priority than others
  - adaptability
    - The extracellular environment and the conditions it imposes on the cells change in time
    - The cells must be able to respond to these changes by adjusting their priorities
  - rapid response
    - The quicker the cells adapt to the changing conditions the better for maintaining efficiency
  - robustness
    - At the same time, the cellular operations must also be shielded from random fluctuations in the environmental conditions
Regulation in a Biomolecular Network

• Tightly controlled regulation of gene transcription is a result of natural selection
  – Genetic variability produces diverse organisms with slightly different regulatory skills
  – The organisms possessing the regulatory skills that endow them with a higher fitness undergo positive selection

• Several primary regulatory mechanisms for gene transcription are present “conspicuously” across different species
  – Autoregulation
  – Feed-forward loop
Autoregulation

- Regulation of a gene Y by another gene X is indicated by an edge in the network graph between the nodes X and Y
  - If the regulation is activation, the edge is an arrow
    \[ X \rightarrow Y \]
  - Conversely if X represses Y, the edge ends with a line stop
    \[ X \rightarrow\!
    \]
- In autogenous regulation, a gene’s product acts as its own transcription factor
  - Such cases are indicated by a self-edge
  - The edge can be activation or repression as any other edge in the regulatory network
Production Rates of Autogenously Regulated Genes

• Positive autoregulation
  – This situation refers to the case where the gene’s own protein product acts as a transcription factor activating its expression
  – The input function governing a positively autoregulated gene $X$ is given by the usual Hill function
    \[
    \text{rate of production of } X = f([X^*]) = \frac{\beta [X^*]^n}{\kappa^n + [X^*]^n}
    \]
• Negative autoregulation
  – The gene’s product represses its expression
  – The input function is given by
    \[
    \text{rate of production of } X = f([X^*]) = \frac{\beta}{1 + ([X^*]/\kappa)^n}
    \]
• Note that these functions do not characterize a static system
  – By definition, a positive production rate increases $[X]$
  – Since we assume that the signal $S_X$ is always present, all $[X]$ is readily transformed into the active state $[X^*]$
  – Thus, the graph does not remain on the initial value of $[X^*]$
• Instead, they represent instantaneous production rates
Transients of Autoregulation

• Dynamic response in negative autoregulation
  – The equation governing the temporal variation of a gene product is
    \[ \frac{d([X])}{dt} = f([X^*]) - \alpha [X] \]
    where the production rate follows the relationship
    \[ f([X^*]) = \frac{\beta}{1 + ([X^*/\kappa]^n)} \].
  – Combining the equations above with \([X^*] = [X] (S_X \text{ always present})\) produces
    \[ \frac{d([X])}{dt} = \frac{\beta}{1 + ([X]/\kappa)^n} - \alpha [X] \].
  – For manual analysis, the logic function approximation provides
    \[ \frac{d([X])}{dt} \approx \beta \ 1([X] < \kappa) - \alpha [X] \]
    • For \([X] < \kappa\), \([X]\) is simply regulated with \(\frac{d([X])}{dt} = \beta - \alpha [X]\) resulting in an exponential rise towards the \(\frac{\beta}{\alpha}\) with \(T_{1/2} = \frac{\log(2)}{\alpha}\)
    • For \([X] > \kappa\), the production ceases and exponential decay starts
      \(\Rightarrow\) stability around \([X] = \kappa\)
Dynamic Response in Negative Autoregulation

\[ [X] \]

\[ \kappa \]

- blue: negative autoregulation
- red: logic approximation
- dotted blue: simple regulation

[diagram showing the response over time]
Dynamic Response in Negative Autoregulation

- Negative autoregulation alters the response time of gene activation
  - The time to half steady state (around kappa) is given by
    \[ \kappa/2 = \beta/\alpha (1 - \exp(-\alpha T_{1/2})) \]
    \[ \{ \kappa < \beta/\alpha \} \]
    \[ \Rightarrow T_{1/2} = \log(2\beta/(2\beta - \kappa\alpha))/\alpha \]
  (For \( \kappa << \beta/\alpha \), \( T_{1/2} \approx \kappa/2\beta \).)
  - Compare that to \( \log(2)/\alpha \) in a simple regulation alternative with
    \[ \beta' = \kappa \alpha \]
    that achieves the same steady state level
Dynamic Response in Negative Autoregulation

\[ \kappa = \frac{\beta_0}{\alpha}, \quad \beta_1 \gg \beta_0 \]

- Simple regulation (\( \beta = \beta_0 \))
- Negative autoregulation (\( \beta = \beta_1 \))
Dynamic Response in Negative Autoregulation

• In addition to a faster rise, negative autoregulation provides robustness in gene expression against random fluctuations in the production rate $\beta$
  – Twin bacterial cells show variations in their respective production rates
    • Differences in capacity leads to variations from a few percents to tens
  – The production rate also varies in time due to random effects
  – The steady state level in simple regulation is directly affected by the production rate fluctuations
    • Note that the steady state level is given by $\beta/\alpha$
  – The threshold $\kappa$ on the other hand is a biochemical property of the input function, and is much more stable across individuals and in time

$\Rightarrow$ The steady state expression level in negative autoregulation is stable even though the production rate may fluctuate
Dynamic Response in Positive Autoregulation

• In positive autoregulation, a gene product improves the expression rate of its own gene
  – Using the Hill function and positive autoregulation transient equation provides
    \[ \frac{d([X])}{dt} = \frac{\beta [X]^n}{\kappa^n + [X]^n} - \alpha [X] \]
  – The logic function approximation leads to
    \[ \frac{d([X])}{dt} = \beta \mathbf{1}([X] > \kappa) - \alpha [X] \]
  – This suggests that
    • If [X] is low, it stays low
    • If [X] is high (at the steady state level), it stays high
      \( \Rightarrow \) Bi-stability in gene expression
Dynamic Response in Positive Autoregulation

\[ \frac{\beta}{\alpha} \]

\[ \frac{\beta}{2\alpha} \]
Dynamic Response in Positive Autoregulation

• Bi-stability represents permanent decision making
  – Once a gene is activated, it remains active
  – Such decisions are frequently made in the early stages of development
    • In cellular differentiation, identical stem cells are set to grow into different tissues and organs
  – The state of positively autoregulated genes thus represents a bar-code for the cell’s identity
    • This set would naturally include the genes that are governed by positive autoregulation cascades

• Delay represents timing priorities
  – The genes that produce proteins required at a specific stage of a process are delayed to wait for the completion of the preceding stages
Another common regulation mechanism in gene transcription networks is the feed-forward loop

- Consists of three nodes
  - First node regulates the other two
  - The second is regulated by the first and regulates the third
  - The third is regulated jointly by the first two
- The regulatory mechanism consists of the effects of the signals to the first two nodes onto the expression of the third
The Feed-Forward Loop

- Depending on the functionality on the edges, the regulatory function of the feed-forward loop changes
  - Coherent type: The regulatory effects of both paths are the same
  - Incoherent type: The regulatory effects conflict with each other

- An additional control mechanism is in the integration of the regulatory inputs from both paths at the third node
  - AND or OR (SUM is not particularly interesting and will not be considered)
Coherent Type-1 Feed Forward Loop with AND Integration

- Characteristics of the regulatory mechanism:
  - All regulatory edges are activations
    - $X \rightarrow Y$ with $\kappa_{XY}$
    - $X \rightarrow Z$ with $\kappa_{XZ}$
    - $Y \rightarrow Z$ with $\kappa_{YZ}$
  - Two alternate paths with the same regulatory function on gene Z
  - Activation signals from both paths are required to express Z
    - AND integration
Coherent Type-1 Feed Forward Loop with AND Integration

- **Kinetic model**
  - **Premises:**
    - $S_Y$ is present, $S_X$ becomes present at time $t = 0$
    - $[X]$ is constant at steady state, $[Y]$ is initially zero
      
      $([X])(0^-) = [X]_{st}$, $([Y])(0^-) = 0$

  - **$X \rightarrow Y$:**
    - Simply regulated
    - The expression of $Y$ begins at time $t = 0$ when $[X]$ is activated into $[X^*]$
    - The dynamics are governed by
      
      $d([Y])/dt = \beta_Y - \alpha_Y([Y])(t)$

  - **$X$ AND $Y \rightarrow Z$:**
    - Both are simply regulated as well
    - The expression of $Z$ begins after ($[X]$ crosses the threshold $\kappa_{XZ}$ and) $[Y]$ crosses the threshold $\kappa_{YZ}$

      production rate of $Z = \beta_Z [Y]^{nYZ}/(\kappa_{YZ}^{nYZ} + [Y]^{nYZ})$
    - The dynamics are thus governed by
      
      $d([Z])/dt = \beta_Z ([Y])^{nYZ(t)}/(\kappa_{YZ}^{nYZ} + ([Y])^{nYZ(t)}) - \alpha_Z([Z])(t)$
Coherent Type-1 Feed Forward Loop with AND Integration

- Dynamic evaluation:
  - The expression of Y is turned on when $S_X$ is switched on at time $t = 0$
    - The activated transcription factor $X^*$ binds the promoters of Y and Z
  - [$Y$] (and hence [$Y^*$]) starts to build up toward its steady state value following an exponential rise
  - As activated [$Y$] crosses the threshold $\kappa_{YZ}$, it starts binding the promoter of Z in large amounts, initiating the transcription of Z
Coherent Type-1 Feed Forward Loop with AND Integration

\[ s_x 1 \]
\[ s_y 1 \]
\[ \beta_Y/\alpha_Y \]
\[ \kappa_{YZ} \]
\[ \beta_Z/\alpha_Z \]

\[ 0 - \log(1 - \kappa_{YZ} \alpha_Y / \beta_Y) / \alpha_Y \]

\( t \)
Coherent Type-1 Feed Forward Loop with AND Integration

• The coherent type-1 FFL network element with AND integration acts as a sign-sensitive delay element
  – A delay of $-\log(1-\kappa_{YZ}\alpha_{\gamma}/\beta_{\gamma})/\alpha_{\gamma}$ is present at the initiation of the Z transcription
  – No such delay exists when either $S_X$ or $S_Y$ is turned off

• This mechanism protects the gene transcription against spurious activations
  – Spurious activations cause the cell both energy and raw materials
    • Hence, there is no reason to start Z transcription unless it really is required
  – In C1-FFL w/ AND, the Z transcription is activated only when the signal $S_X$ persists for a sufficiently long time
    • Indicating that Z transcription really is required
Coherent Type-1 Feed Forward Loop with OR Integration

- **Premises:**
  - $S_Y$ is present
  - $S_X$ becomes present at time $t = 0$
  - $[X]$ is constant at steady state, $[Y]$ is initially zero
    \[
    ([X])(0^-) = [X]_{st}, \ ([Y])(0^-) = 0
    \]

- **Dynamic evaluation:**
  - As soon as $S_X$ becomes present at time $t = 0$, the transcriptions of both $Y$ and $Z$ begin
    - Only one of $X$ or $Y$ is sufficient to initiate $Z$ transcription
  - When $S_X$ is turned off again, the transcription of $Y$ ceases and the $[Y]$ level drop exponentially
  - The transcription of $Z$ ceases only when the $[Y]$ level is below $\kappa_{YZ}$
Coherent Type-1 Feed Forward Loop with OR Integration

\[ S_X \]
\[ S_Y \]
\[ \beta_Y/\alpha_Y \]
\[ \kappa_{YZ} \]
\[ \beta_Z/\alpha_Z \]
\[ t \]
Coherent Type-1 Feed Forward Loop with OR Integration

• The coherent type-1 FFL network element with OR integration also acts as a sign-sensitive delay element
• However, in contrast with the same element with AND integration, the delay is observed at the cessation of the gene transcription
• This mechanism thus protects the transcription of gene Z against spurious loss of signal $S_X$
  – The process requiring Z should not be shut off accidentally due to a noise in $S_X$
  • Accidental shut off’s are costly
Incoherent Type-1 Feed Forward Loop with AND Integration

- In this feed forward loop, the two paths are antagonistic
  - X directly activates Z
  - X also represses Z indirectly through Y

- Dynamic evaluation:
  - Premises:
    - $S_Y$ is present
    - $S_X$ becomes present at time $t = 0$
    - $[X]$ is constant at steady state, $[Y]$ is initially zero
  - Immediately as $S_X$ is turned on at time $t = 0$, the transcriptions of both Y and Z begin following the exponential curve
  - Gradually as $[Y]$ builds up, it crosses the threshold $\kappa_{YZ}$, causing Y to repress Z
  - As Z is repressed, $[Z]$ decays
Incoherent Type-1 Feed Forward Loop with AND Integration

- **Kinetic model:**
  - With the activation of $X \rightarrow X^*$ at time $t = 0$ ($S_X(t) = u(t)$), $[Y]$ increases via
    \[
    \frac{d([Y])}{dt} = \beta_Y - \alpha_Y([Y])(t)
    \]
  toward its steady state level $[Y]_{st} = \beta_Y/\alpha_Y$
  - The transcription of $Z$ follows the transient equation
    \[
    \frac{d([Z])}{dt} = \frac{\beta_Z}{1+([Y](t)/\kappa_{YZ})^n} - \alpha_Z([Z])(t)
    \]
  - Initially, $[Z]$ rises according to the exponential curve of simple regulation towards $[Z]_{st} = \beta_Z/\alpha_Z$
  - Around time $t \approx -\log(1 - \kappa_{YZ}\alpha_Y/\beta_Y)/\alpha_Y$, increasing $[Y]$ starts to repress the $Z$ transcription
  - Eventually, $[Y]$ attains its steady state level $[Y]_{st}$, and $[Z]$ decays toward a different steady state level $[Z]_{st}'$
    \[
    [Z]_{st}' = \frac{\beta_Z}{\alpha_Z(1+([Y]_{st}/\kappa_{YZ})^n)}
    \]
  - The repression coefficient $F$ is defined as the ratio of the two levels:
    \[
    F = \frac{[Z]}{[Z]_{st}' = (1+([Y]_{st}/\kappa_{YZ})^n)}
    \]
Incoherent Type-1 Feed Forward Loop with AND Integration

\[
\begin{align*}
S_X &= 1 \\
S_Y &= 1 \\
\beta_Y/\alpha_Y &= -\log(1 - \kappa_{YZ} \alpha_Y / \beta_Y) / \alpha_Y \\
\kappa_{YZ} &= 0 \\
\beta_Z/\alpha_Z &= -\log(1 - \kappa_{YZ} \alpha_Y / \beta_Y) / \alpha_Y \\
\end{align*}
\]
Incoherent Type-1 Feed Forward Loop with AND Integration
Incoherent Type-1 Feed Forward Loop with AND Integration

• The incoherent type-1 feed forward loop with AND integration acts as a pulse generator
  – In the absence of repression from Y, Z undergoes an exponential rise towards $[Z]_{st}$
  – Eventually $[Y]$ rises sufficiently, and represses $[Z]$
  – Under repression, $[Z]$ declines toward $[Z]'_{st}$

• The response time of $[Z]$ is dramatically improved as well (assuming $[Z]'_{st}$ is the desired steady-state level)
  – Instead of rising towards $[Z]'_{st}$ via simple regulation, $[Z]$ is shot up towards $[Z]_{st} \gg [Z]'_{st}$ and brought down to $[Z]'_{st}$ later
  – Rise towards $[Z]_{st}$ is much faster than towards $[Z]'_{st}$ via simple regulation and crosses the $[Z]'_{st}$ level much sooner
Summary

• Gene transcription networks are endowed with specific network elements that carry out critical functions
  – Autoregulation
    • Negative autoregulation: Rapid response
    • Positive autoregulation: Delayed response and bistability
  – Feed-forward loop
    • C1-FFL: Sign-sensitive delay protection against spurious signals (with AND integration) and signal losses (with OR integration)
    • I1-FFL: Pulse generation and rapid response
• Such critical network elements are observed “abundantly” in gene transcription networks
• The statistical significance of this “abundance” is crucial to derive a functional understanding of gene transcription regulation