Analysis of Oscillatory Dynamics in Gene Regulatory Networks

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Abstract

Motivation: Understanding oscillatory gene expression is a key to unraveling biological principles of physiological functions.

Result: We have analytically obtained (i) conditions for existence of oscillations, and (ii) oscillation profiles, using feedback control theory for multiple dynamic agents. This analysis has revealed that oscillatory dynamics can be characterized by four essential parameters.

Mathematical model

- Dynamics of cyclic gene regulatory network with \( N \) genes
  
  \[
  \frac{dx_i}{dt} = \left[ \begin{array}{cc} -\alpha & 0 \\ \beta & -\beta \end{array} \right] x_i + \left[ \begin{array}{c} \mu \\ 1 \end{array} \right] u_i \\
  \]

  Activation/Repression by proteins

  \( u_i = f_i(p_{i-1}) := \left\{ \begin{array}{ll} \frac{p_{i-1}}{1 + \alpha p_{i-1}} & (\text{Activation}) \\
  \frac{1}{1 + \beta p_i} & (\text{Repression}) \end{array} \right. \)

  Assumption: The number of repressive interactions is odd.

- Transfer function of each gene: \( h(s) \)
- Interaction between genes: \( f \)

\[
h(s) := \frac{1}{(\tau_s + 1)(\tau_s + 1)} \quad \text{with} \quad \tau_a := \frac{1}{\alpha}, \tau_b := \frac{1}{\beta}
\]

\[
f := [R^2f_1(p_0), R^2f_2(p_1), \ldots, R^2f_N(p_{N-1})]^T
\]

Existence of periodic oscillations

Lemma (Local instability leads to oscillations)

The equilibrium of the system is unique. If the equilibrium is locally unstable, there exist periodic oscillations of protein concentrations.

Theorem (Graphical condition)

If at least one eigenvalue of \( K \) lies in \( \Omega_+ \), the system has periodic oscillations.

Theorem (Analytic condition)

The system has periodic oscillations if

\[
r^2 = \left( \frac{2W(Q, N)}{-2W(Q, N) + Q(1 + \cos(\xi)) + \alpha + \Omega(N, Q) + \alpha Q(1 + \cos(\xi))} \right)^{1/2} \quad \text{and} \quad r > \left( \frac{2W(Q, N)}{Q(1 + \cos(\xi))} \right)^{1/2}
\]

where \( Q := \frac{\sqrt{\beta}}{\alpha + \beta} \), \( R := \frac{\alpha + \Omega(N, Q)}{\alpha} \) and \( \Omega(N, Q) = \frac{2Q(1 + \cos(\xi)) + Q^2(2 + Q^2(2 + \Omega(N, Q)))}{Q^2(2 + \Omega(N, Q))} \)

Note: The conditions in Theorems are necessary and sufficient for local instability of the unique equilibrium.

Oscillation Profiles

Key idea: Harmonic balance method

1. Approximate the oscillations with \( p_i(t) \approx x_i + y_i \sin(\omega t + \phi_i) \)
2. Solve the following bias/harmonic balance equations:

\[
\begin{align*}
\left( \phi(w) K_{\phi}(\phi(w)) \right) &= \mathbf{C} \\
\left( \phi(w) K_{\omega}(\phi(w)) \right) &= \mathbf{W} \\
\end{align*}
\]

Frequency Amplitude and phase

\[
K_{\phi}(\phi(w)) := \text{cyclic}(q_0, q_1, \ldots, q_N) \in \mathbb{R}^{N \times N} \\
K_{\omega}(\phi(w)) := \text{cyclic}(\omega, \ldots, \omega) \in \mathbb{R}^{N \times N}
\]

Oscillation profiles are expected as \( p_i(t) \approx x_i + y_i \sin(\omega t + \phi_i) \)

Theorem (Frequency and phase of oscillations)

The oscillation profiles are expected as \( p_i(t) \approx x_i + y_i \sin(\omega t + \phi_i) \) where \( \omega = \frac{-1 + \sqrt{1 + 4Q_+^2 \tan^2(\phi)}}{2Q_+ \tan(\phi)} \) and \( \phi = \frac{1}{N} \) with \( z_i = \frac{1}{n_{\phi} + \Omega(N, Q) + \alpha} \).

Biological insight

- Essential parameters that characterize the oscillatory dynamics can be obtained from the analytic conditions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Physical meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>( N )</td>
<td>The number of genes</td>
</tr>
<tr>
<td>( Q )</td>
<td>Discrepancy of mRNA and protein degradation rate, or ( \alpha ) and ( \beta ), ( 0 &lt; Q &lt; 1 ), and ( Q = 1 \implies \alpha = \beta )</td>
</tr>
<tr>
<td>( R )</td>
<td>Ratio of degradation and production rates (related to equilibrium concentration)</td>
</tr>
<tr>
<td>( \nu )</td>
<td>Hill coefficient (degree of cooperative binding)</td>
</tr>
</tbody>
</table>

Existence of periodic oscillations

Gene regulatory networks tend to have oscillations as:
- The number of genes \( (N) \) becomes larger
- mRNA and protein degradation rates become closer

Oscillation profiles

- Frequency changes monotonically w.r.t. \((N, Q)\)
- Phase is primarily determined by the activation/repression structure

References