A Systems Approach to Biology

MCB 195

Lecture 5
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BISTABILITY

in

GENETIC REGULATION
NONLINEAR SYSTEM
\[ \frac{dx}{dt} = f(x) \]

line to linearise

LINEARISED SYSTEM
\[ \frac{dy}{dt} = (Df)|_{a}(y) \]

hyperbolic steady state
\( \text{Re} (\lambda) \neq 0 \)

node

spiral

eigenvalues
\( \text{exp}(Df) \) matrix exponential

saddle
\[ \text{det} > 0, \text{Tr} > 0 \]

- **saddles**
  \[ \Delta < 0, \text{Tr} < 0 \]

- **spirals**
  \[ \Delta < 0, \text{Tr} < 0 \]

- **nodes**
  \[ \Delta > 0, \text{Tr} < 0 \]

- **sources**
  \[ \Delta > 0, \text{Tr} > 0 \]

- **centers**
  \[ \Delta < 0, \text{Tr} = 0 \]

- **saddles**
  \[ \Delta > 0, \text{Tr} < 0 \]

- **sinks**
  \[ \Delta > 0, \text{Tr} > 0 \]

- **det < 0**

- **det > 0**

- **Tr > 0**

- **Tr < 0**

**Diagram:**

- \( \Delta > 0 \)
- \( \Delta > 0 \)
- \( \Delta > 0 \)
- \( \Delta = 0 \)

**Axes:**

- Determinant
- Trace
GENETIC AUTOREGULATORY LOOP

POSITIVE FEEDBACK

protein coding region

mRNA translation

transcription

mRNA

positive autoregulation

protein
\[ x = \text{protein concentration} \]
\[ y = \text{mRNA concentration} \]

\[ \frac{dx}{dt} = \lambda y - ax \]

\[ \frac{dy}{dt} = ? - by \]

\[ \lambda \quad \text{mRNA translation rate} \quad \text{(time)}^{-1} \]
\[ a \quad \text{protein degradation rate} \quad \text{(time)}^{-1} \]
\[ b \quad \text{mRNA degradation rate} \quad \text{(time)}^{-1} \]
PHAGE LAMBDA

lysis

lysogeny
**lambda repressor**

- **Cl coding region**
- **Cro coding region**
- **Repressor**
- **Dimerisation**
- **Binds to operator sites**

**OR1, OR2, OR3**

- OR1 > OR2 > OR3
- OR2 is highly favoured if OR1 is already bound
- OR3 is independent of OR1 and OR2

- OR1: cl transcribed at low basal rate
- OR2: 10x increase in transcription of cl
- OR3: cl transcription turned off
\[ X + X \leftrightarrow X_2 \text{ fast} \]

\[ [X_2] = K [X]^2 \]

equilibrium constant

\[ \{ \text{D}_0, \text{D}_1, \text{D}_2, \text{D}_3 \} \text{ slower} \]

very slow

RNA polymerase
steady state
occupation histogram

Markov chain

\[ k_1[X_2] \quad k_2[X_2] \quad k_3[X_2] \]
\[ d_i = \text{probability of state } D_i \text{ at equilibrium} \]

\[
d_i = \left( \frac{k_i[X_2]}{k_{-i}} \right) d_{i-1} = K_i [X_2] d_{i-1}
\]

\[
d_1 = K_1 [X_2] d_0 \quad d_2 = K_1K_2[X_2]^2 d_0 \quad d_3 = K_1K_2K_3[X_2]^3 d_0
\]

\[
d_0 + d_1 + d_2 + d_3 = 1
\]
if \( r_i \) = transcription rate in state \( D_i \) then

the average transcription rate \( r \) is

\[
    r = r_0 d_0 + r_1 d_1 + r_2 d_2 + r_3 d_3
\]

\[
    r = \frac{r_0 + r_1 (K_1 K) x^2 + r_2 (K_1 K_2 K^2) x^4 + r_3 (K_1 K_2 K_3 K^3) x^6}{1 + (K_1 K) x^2 + (K_1 K_2 K^2) x^4 + (K_1 K_2 K_3 K^3) x^6}
\]
Effect of lambda repressor on expression of cl

\[
\frac{r_0 + r_1 (K_1) x^2 + r_2 (K_1 K_2^2) x^4}{1 + (K_1) x^2 + (K_1 K_2^2) x^4 + (K_1 K_2 K_3^3) x^6}
\]

Chaos 11:207-220 2001
The Principle of Detailed Balance

_in a system at equilibrium each individual loop is at equilibrium_

The linear Markov chain satisfies detailed balance

\[ d_i = \frac{k_i [X_2]}{k_{i-1}} d_{i-1} \]

Katchalsky & Curran, “Nonequilibrium Thermodynamics in Biophysics”

“(detailed balance) ... is not based on any previous notion and constitutes an additional principle of physical chemistry ... closely related to one of the fundamental principles of statistical mechanics ... microscopic reversibility”

Tolman, “The Principles of Statistical Mechanics”

“Under equilibrium conditions, any molecular process and the reverse of that process will be taking place, on the average, at the same rate”
x = protein concentration
y = mRNA concentration

\[ \frac{dx}{dt} = \lambda y - ax \]

\[ \frac{dy}{dt} = \frac{\alpha x}{k + x} - by \]

\[ \lambda \text{ mRNA translation rate (time)}^{-1} \]
\[ a \text{ protein degradation rate (time)}^{-1} \]
\[ b \text{ mRNA degradation rate (time)}^{-1} \]
\[ a \text{ maximal gene expression rate (mols)(time)}^{-1} \]
\[ k \text{ “Michaelis-Menten” constant (mols)} \]
\[ \frac{dx}{dt} = 0 \text{ nullcline} \]

\[ \frac{dy}{dt} = 0 \text{ nullcline} \]
\[
\begin{align*}
\frac{dx}{dt} &= f(y) - ax \\
\frac{dy}{dt} &= g(x) - by
\end{align*}
\]

\[a, b > 0\]

\[
\begin{pmatrix}
-a & \frac{df}{dy} \\
\frac{dg}{dx} & -b
\end{pmatrix}
\]

\[\text{Jacobian}\]

\[\text{Tr} = -(a+b) < 0\]

\[\text{det} > 0\]

\[\text{stable (node or spiral)}\]