Organizational remarks

1. Tomorrow recitation 10/25/06 topic ‘Stochastic chemical kinetics’
2. PS#3 has been posted (due 11/02/06)
3. Grades available online (registration required)
4. Collaboration web-site Moderator: Kamal Jaffrey

http://stellar.mit.edu/S/project/systemsbio/index.html

Main points of last 2 lectures:

L11: Biological background
what is the function of the individual molecules?

L12: modeling of all possible chemotactic reactions
why doesn’t this model reproduce experimentally observed perfect adaptation?

L12-13: strip down full model to essentials based on assumptions that are experimentally justified (or sometimes not)
Ligand bound states generally have lower autophosphorylation rates. CheR methylates ligand-bound states more rapidly.

Consider step in aspartate concentration. Time ~ 1 ms, increase in ligand bound complex. Time ~ 5 s, total # of phosphorylated complexes decreases gradually because ligand bound complexes do not autophosphorylate very well. Also: CheB decreases, low CheA_p, low CheY_p, tumble suppression.
time ~ 50 s, slowly the complex methylates. Note that demethylation is switched off because of low levels of CheA_p (low CheB_p). Also low CheA_p, low CheY_p, tumble suppression.

Higher methylation states autophosphorylate easier, so slowly CheA_p adapts to its initial level.

The complete route.

Secondary step:
- Auto phosphorylation reduced for occupied receptors, but phosphorylation continues. Effect is to decrease the fraction of receptors phosphorylated and hence decrease CheY_p.

Third step:
- Methylation and adaptation
  - Effect is to push states from left to right.
  - Ligand binding
    - (Time scale: fraction of a second)
    - Response to a step is to push states down in the network.

The key to adapting perfectly is to return the level of phosphorylated receptor to its pre-stimulus level, and this occurs because CheA autoprophosphorylates more rapidly the more highly methylated the receptor!
First reduction

\[ \alpha \equiv \frac{[3]}{[2]+[3]} \]

in steady state:

\[ k_{\text{phos}} = (1-\alpha) k_{\text{eff1}}(L) + \alpha k_{\text{eff2}}(L) \]

fine-tune: net phosphorylation rate and \( k_{\text{eff1}} \) and \( k_{\text{eff2}} \) so that \( \alpha \) falls in safe zone

Second reduction

additional assumption:
- CheB only demethylates phosphorylated receptors

experimental backup:
- not possible to directly measure if CheB demethylates only active receptors
- rate of methylation drops immediately after addition of ligand indicates that CheB works on active receptors
Third reduction

additional assumption:
- [CheR] << [receptors],
methylation operates at saturation
($r_n$ is independent
of receptor concentrations)

experimental backup:
- Michaelis constant of CheR binding << [receptors]
so $R_{tot} \sim R_{bnd}$

Fourth reduction

additional assumption:
- demethylation is identical for
bound and unbound receptors, so $k_{eff4}$ is independent of $L$.

experimental backup:
- kinetics of demethylation almost independent of
level of methylation and ligand binding.

This final module obeys
perfect adaptation for any
value of $L$.

Stability Analysis:

\[ \dot{x} = ax + by + r_{in} \]
\[ \dot{y} = cx + dy + r_{in} \]

\[ 3 \equiv \frac{2r_{in}}{k_{eff4}} \]
Nullclines:

\[ \dot{x} = 0 \]
\[ \dot{y} = 0 \]

\[ y = \frac{-r_{\text{in}} - \alpha}{b} x = \frac{-r_{\text{in}} + k_{\text{pt}} + k_{\text{eff}}}{k_{\text{eff}}^2} x \]
\[ y = \frac{-r_{\text{in}} - c}{d} x = \frac{r_{\text{in}} + k_{\text{pt}}}{k_{\text{eff}}^2} x \]

fixed point (stable or unstable?)

\[ \dot{x} = (k_{\text{pt}} + k_{\text{eff}})x + k_{\text{eff}}^2 y + r_{\text{in}} \]
\[ \dot{y} = k_{\text{pt}} x - k_{\text{eff}}^2 y + r_{\text{in}} \]

increased ligand concentration

\[ (x^*, y^*) = \left( \frac{2r_{\text{in}}}{k_{\text{eff}}^4} \frac{r_{\text{in}}k_{\text{eff}}^4 + 2r_{\text{in}}k_{\text{pt}}}{k_{\text{eff}}^2 k_{\text{eff}}^2 (L)} \right) \]
Guestimated response

\[ C^* \]

'activity' (phosphorylation level)

\[ C_{TOT} \]

(methylation level)

Dynamical response of switches, chemotactic network and oscillators

'Switch'

adaptation (differentiator, at least for small frequencies)

oscillator

Dynamical response of switches, chemotactic network and oscillators

Two stable fixed points

One stable fixed point

Unstable fixed point

\[
\begin{align*}
\frac{du}{dt} &= 0 \\
\frac{dv}{dt} &= 0
\end{align*}
\]

nullclines:

\[
\begin{align*}
u &= \frac{a_1}{1 + v^\beta} \\
v &= \frac{a_2}{1 + u^\beta}
\end{align*}
\]

\[
\begin{align*}
\frac{du}{dt} &= \frac{a_1}{1 + v^\beta} - u \\
\frac{dv}{dt} &= \frac{a_2}{1 + u^\beta} - v
\end{align*}
\]
Adaptation (one stable fixed point)

$$(x^*, y^*) = \left( \frac{2r_{in} r_{eff 4} + 2r_{in} k_{pt}}{k_{eff 4} k_{eff 2} (L)}, \frac{-k_{pt} x - k_{eff 2} y + r_{in}}{k_{eff 4}} \right)$$

$\dot{x} = -(k_{pt} + k_{eff 4}) x + k_{eff 2} y + r_{in}$

$\dot{y} = k_{pt} x - k_{eff 2} y + r_{in}$

Oscillator (unstable fixed point)

$$(x^*, y^*) = \left( \frac{2r_{in} r_{eff 4} + 2r_{in} k_{pt}}{k_{eff 4} k_{eff 2} (L)_4}, \frac{-k_{pt} x - k_{eff 2} y + r_{in}}{k_{eff 4}} \right)$$

increased ligand concentration

$$(x^*, y^*) = \left( \frac{2r_{in} r_{eff 4} + 2r_{in} k_{pt}}{k_{eff 4} k_{eff 2} (L)}, \frac{-k_{pt} x - k_{eff 2} y + r_{in}}{k_{eff 4}} \right)$$
L13-14: Stochastic Chemical Kinetics

Figure 1: The implications of discreteness

Figure 3: The large number limit

Figure 4: A stochastic bistable system

Figure 5: Stochastic transitions and escape times