PS #2 corrections

1. Tomorrow recitation 10/19/05 topic ‘PS #2 support’

2. PS #2 due Thursday 10/20/05

3. Tuesday Lecture 10/25/05 cancelled

Organizational remarks

Main points of last 2 lectures:

L9: Biological background

what is the function of the individual molecules?

L10: modeling of all possible chemotactic reactions

why doesn’t this model reproduce experimentally observed perfect adaptation?

L10-11: 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\textsubscript{p} decreases

low CheA\textsubscript{p}, low CheY\textsubscript{p}, tumble suppression

Higher methylation states autophosphorylate easier, so slowly CheA\textsubscript{p} adapts to its initial level

high CheA\textsubscript{p}, high CheY\textsubscript{p}, tumbling

The complete route

time ~ 50 s, slowly the complex methylates. Note that demethylation is switched off because of low levels of CheA\textsubscript{p} (low CheB\textsubscript{p}).

also low CheA\textsubscript{p}, low CheY\textsubscript{p}, tumble suppression
The key to adapting perfectly is to return the level of phosphorylated receptor to its pre-stimulus level, and this occurs because CheA autophosphorylates more rapidly the more highly methylated the receptor!
First reduction

\begin{align*}
\alpha &= \frac{[3]}{[2]+[3]} \\
\text{in steady state:} \\
\kappa_{\text{phos}} &= (1-\alpha)\kappa_{\text{eff1}}(L) + \alpha\kappa_{\text{eff2}}(L)
\end{align*}

fine-tune: net phosphorylation rate and \(\kappa_{\text{eff1}}\) and \(\kappa_{\text{eff2}}\) 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:
- \([\text{CheR}] \ll \text{[receptors]},\) methylation operates at saturation \((r_\text{in} \text{ is independent of receptor concentrations})\)

experimental backup:
- Michaelis constant of CheR binding \(\ll \text{[receptors]}\)
  so \(R_{\text{tot}} \approx R_{\text{bnd}}\)

Fourth reduction

additional assumption:
- demethylation is identical for bound and unbound receptors, so \(k_{\text{eff}4}\) 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 \(L\).

\[
\left[3p\right] = \frac{2r_{\text{in}}}{k_{\text{eff}4}}
\]
Stability Analysis:

\[ \dot{C}^* = (-k_{pt} - k_{eff4})C^* + k_{eff2}C + r_{in} \]
\[ \dot{C} = k_{pt}C^* - k_{eff2}C + r_{in} \]

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

\[ x = C^* \]
\[ y = C \]
\[ a = (-k_{pt} - k_{eff4}) \]
\[ b = k_{eff2} \]
\[ c = k_{pt} \]
\[ d = -b \]

Nullclines:

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

\[ y = \frac{-r_{in} - a}{b} x = \frac{-r_{in} + k_{pt} + k_{eff4}}{k_{eff2}} x \]

**fixed point (stable or unstable?)**
increased ligand concentration

\[ \dot{y} = 0 \]

\[ x + y = C_{\text{TOT}} \]

\[ \dot{x} = 0 \]

\[ C_{\text{TOT}} \]

\[ C_{\text{TOT}} \]

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

Guestimated response

\[ C^* \]

\[ \text{activity} \]

(phosphorylation level)

\[ \text{time} \]

\[ \text{methylaion level} \]

\[ \text{time} \]

Dynamical response of switches, chemotactic network and oscillators

'switch'

adaptation

(differentiator, at least for small frequencies)

oscillator

two stable fixed points

one stable fixed point

unstable fixed point

Dynamical response of switches, chemotactic network and oscillators
nullclines: \[
\frac{du}{dt} = \frac{\alpha_1 - u}{1 + \beta} = \frac{\alpha_2 - v}{1 + \gamma} = 0
\]

Adaptation (one stable fixed point):
\[
(x^*, y^*) = \left( \frac{2r_{\text{in}}}{k_{\text{eff}4} k_{\text{eff}2}(L)}, \frac{k_{\text{eff}4} + 2r_{\text{in}} k_{\text{eff}2}(L)}{k_{\text{eff}4} k_{\text{eff}2}(L)} \right)
\]

\[
\begin{align*}
\dot{x} &= - (k_{\text{pt}} + k_{\text{eff}4}) x + k_{\text{eff}2} y + r_{\text{in}} \\
\dot{y} &= k_{\text{pt}} x - k_{\text{eff}2} y + r_{\text{in}}
\end{align*}
\]

Oscillator (unstable fixed point):
\[
(x^*, y^*) = \left( \frac{2r_{\text{in}}}{k_{\text{eff}4} k_{\text{eff}2}(L)}, \frac{k_{\text{eff}4} + 2r_{\text{in}} k_{\text{eff}2}(L)}{k_{\text{eff}4} k_{\text{eff}2}(L)} \right)
\]

\[
\begin{align*}
\dot{x} &= 0 \\
\dot{y} &= (k_{\text{pt}} + k_{\text{eff}4}) x + k_{\text{eff}2} y + r_{\text{in}}
\end{align*}
\]

increased ligand concentration
\[
\begin{align*}
\dot{x} &= \frac{2r_{\text{in}}}{k_{\text{eff}4} k_{\text{eff}2}(L)} x \\
\dot{y} &= k_{\text{pt}} x - k_{\text{eff}2} y + r_{\text{in}}
\end{align*}
\]

- switch -

two stable fixed points.

\(x > 0, y < 0\)
L11-12: 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