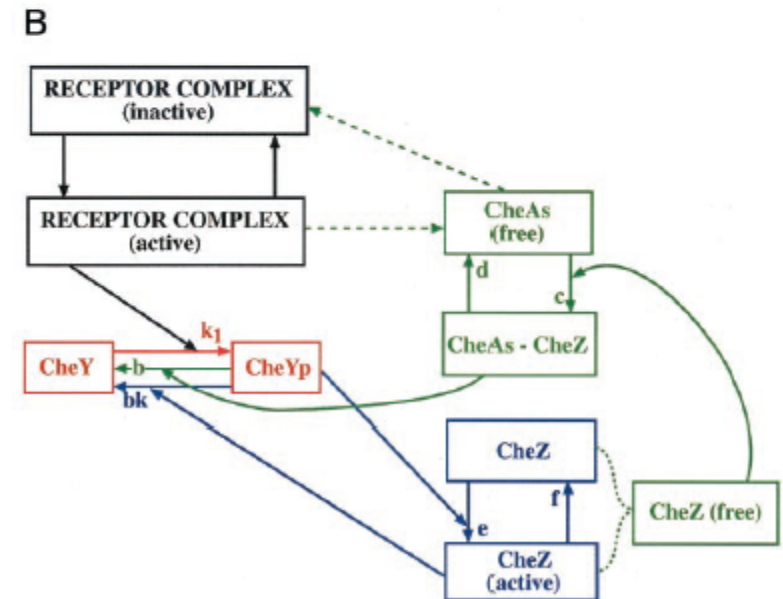
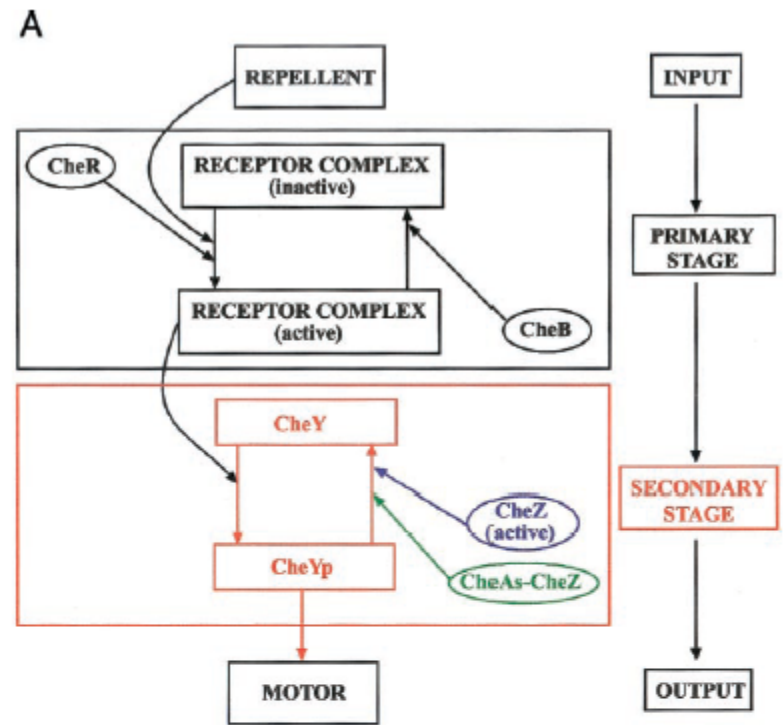
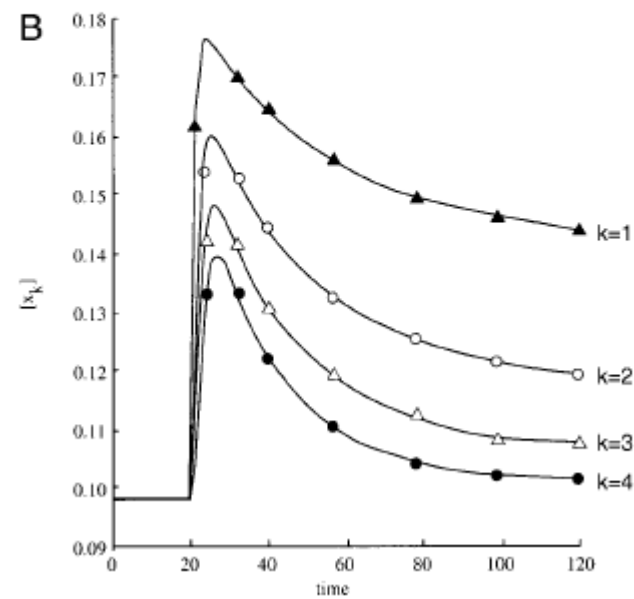
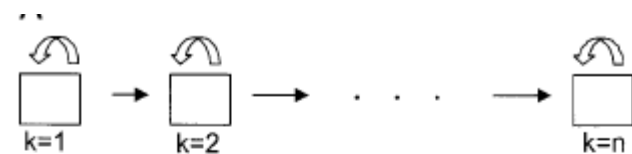
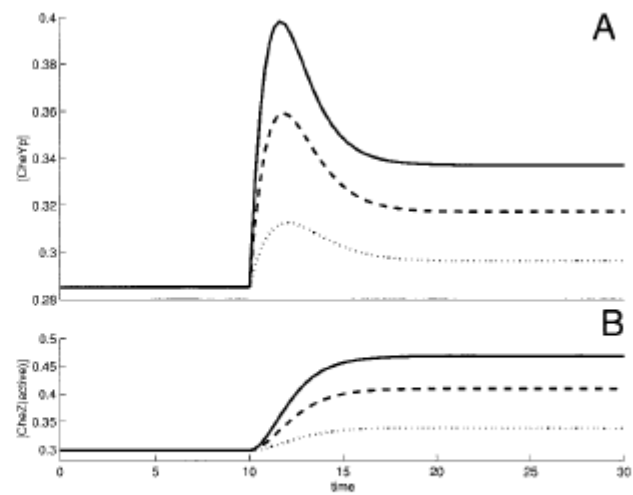
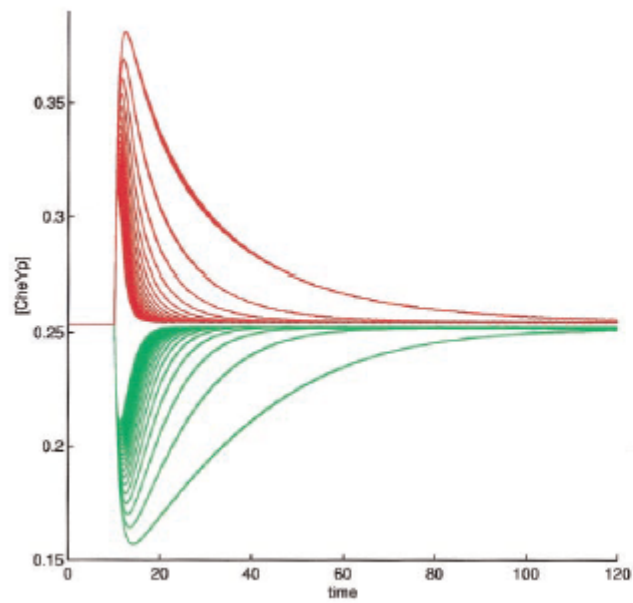


$$\frac{d(\text{CheYp})}{dt} = A(\text{CheY}_{\text{total}} - \text{CheYp}) - b \cdot \text{CheYp}((\text{CheAs}-\text{CheZ}) + k \cdot \text{CheZ}_{\text{active}}),$$

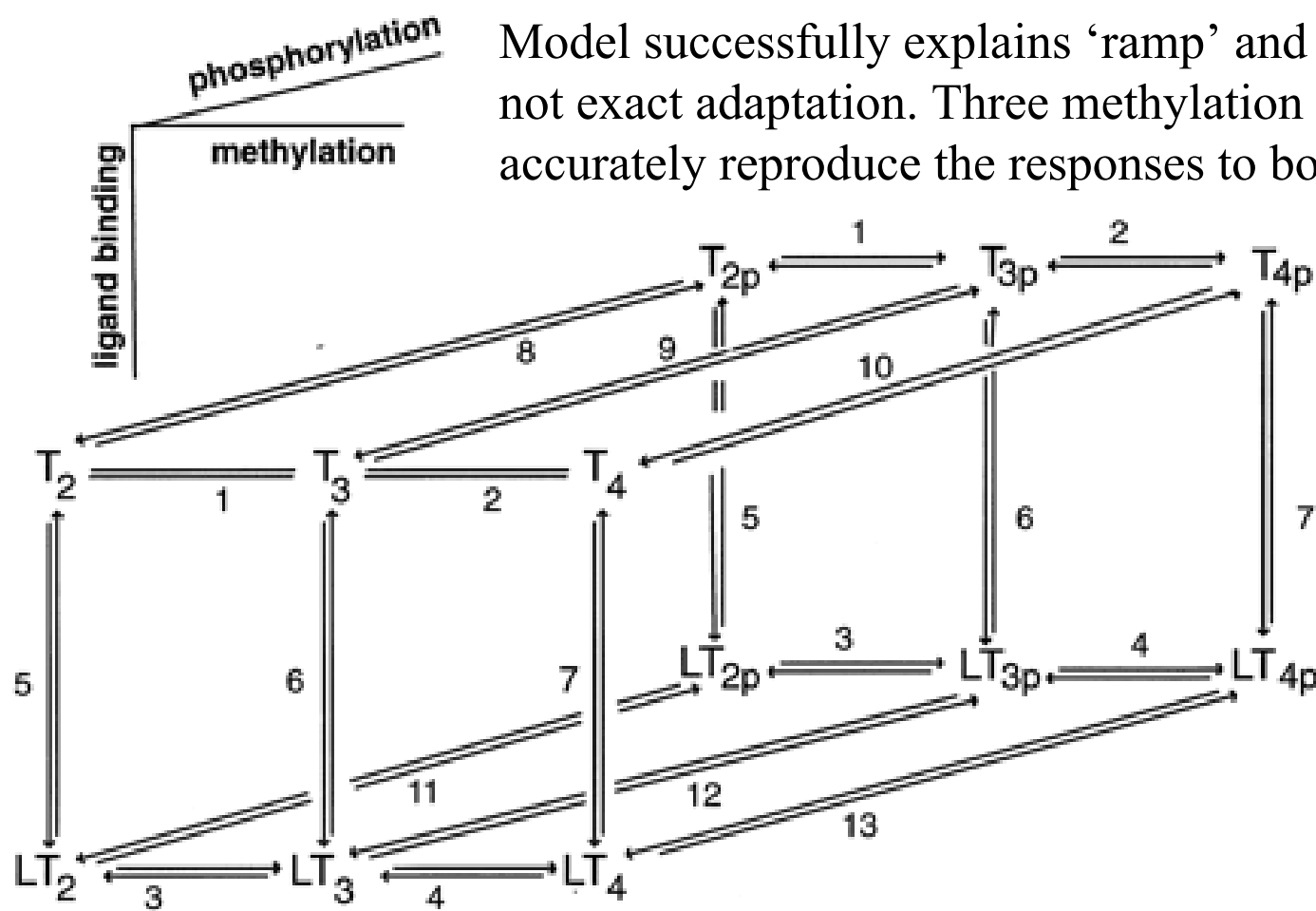
$$\frac{d(\text{CheAs}-\text{CheZ})}{dt} = c(A/k_1 - (\text{CheAs}-\text{CheZ})) \cdot (\text{CheZ}_{\text{total}} - (\text{CheAs}-\text{CheZ})) - d(\text{CheAs}-\text{CheZ}),$$

$$\frac{d(\text{CheZ}_{\text{active}})}{dt} = e(\text{CheZ}_{\text{active}} + \varepsilon)\text{CheYp}(\text{CheZ}_{\text{free}} - \text{CheZ}_{\text{active}}) - f \cdot \text{CheZ}_{\text{active}}.$$





Model successfully explains ‘ramp’ and ‘step’ experiments, but not exact adaptation. Three methylation states are necessary to accurately reproduce the responses to both step and ramp stimuli.



1. So, you either ‘add blocks’, or model ‘everything’.
2. Are there blocks?
3. OK to be an outsider.
4. Explain all, or part?
5. Always, important qualitative punch line.

6. Importance of tables of parameters and variables from as few sources as possible.
7. How to cite.

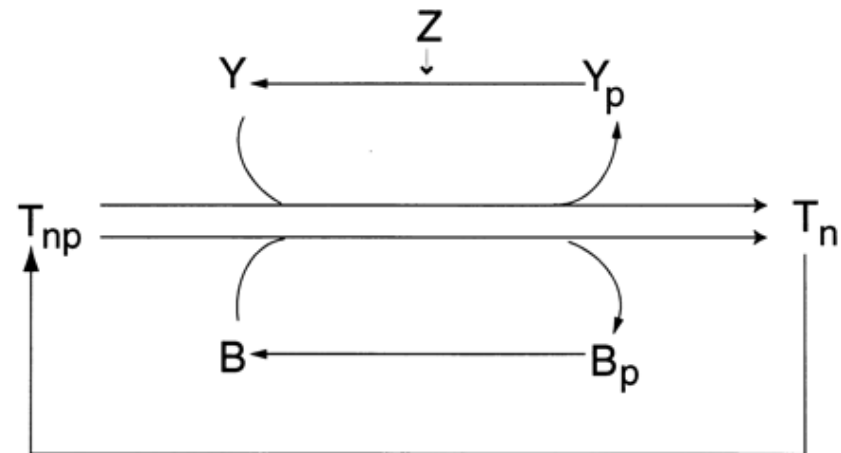


Table 3. Rates used in the model, and corresponding values from the literature

Reaction	Rate constant	Value	Literature value	Ref.
$T_2R \rightarrow T_3 + R$	k_{1c}	0.17 s^{-1}	0.17 s^{-1}	12
$T_3R \rightarrow T_4 + R$	k_{2c}	$0.1k_{1c}$	$>0.02k_{1c}^*$	13
$LT_2R \rightarrow LT_3 + R$	k_{3c}	$30k_{1c}$	$15k_{1c} - 30k_{1c}^\dagger$	13
$LT_3R \rightarrow LT_4 + R$	k_{4c}	$30k_{2c}$	$15k_{2c} - 30k_{2c}^\dagger$	13
$T_n + R \rightleftharpoons T_nR$	$k_{10}/k_{10}, \dots, k_{40}/k_{40}$	$1.7 \mu\text{M}$	$1.7 \mu\text{M}$	12
$T_3 + B_p \rightarrow T_2 + B_p$	k_{-1}	$4 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$	$3 \times 10^4 \text{ M}^{-1}\text{s}^{-1}$	11
$T_4 + B_p \rightarrow T_3 + B_p$	k_{-2}	$3 \times 10^4 \text{ M}^{-1}\text{s}^{-1}$	$>3.0k_{-1}^\ddagger$	13
$LT_3 + B_p \rightarrow LT_2 + B_p$	k_{-3}	k_{-1}	k_{-1}^\S	13
$LT_4 + B_p \rightarrow LT_3 + B_p$	k_{-4}	k_{-2}	k_{-2}^\S	13
$L + T \rightarrow LT$	k_5, k_6, k_7	$7 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$	$7 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$	3 [¶]
$LT \rightarrow L + T$	k_{-5}, k_{-6}, k_{-7}	70 s^{-1}	70 s^{-1}	3 [¶]
$T_2 \rightarrow T_{2p}$	k_8	15 s^{-1}	17 s^{-1}	14
$T_3 \rightarrow T_{3p}$	k_9	$3k_8$		
$T_4 \rightarrow T_{4p}$	k_{10}	$3.2k_8$		
$LT_2 \rightarrow LT_{2p}$	k_{11}	0		
$LT_3 \rightarrow LT_{3p}$	k_{12}	$1.1k_8$		
$LT_4 \rightarrow LT_{4p}$	k_{13}	$0.72k_{10}$	k_{10}	15
$B + T_{np} \rightarrow B_p + T_n$	k_b	$8 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$	$8 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$	11
$Y + T_{np} \rightarrow Y_p + T_n$	k_y	$3 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$	$3 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$	14
$B_p \rightarrow B$	k_{-b}	0.35 s^{-1}	0.35 s^{-1}	14
$Y_p + Z \rightarrow Y + Z$	k_{-y}	$5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$	$5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$	14

*Methylation rates of different methylation sites vary by a factor of up to 50.

[†]Ligand binding increases methylation rates of different methylation sites by a factor of 15–30.

[‡]Demethylation rates of different methylation sites vary by a factor of up to 3.

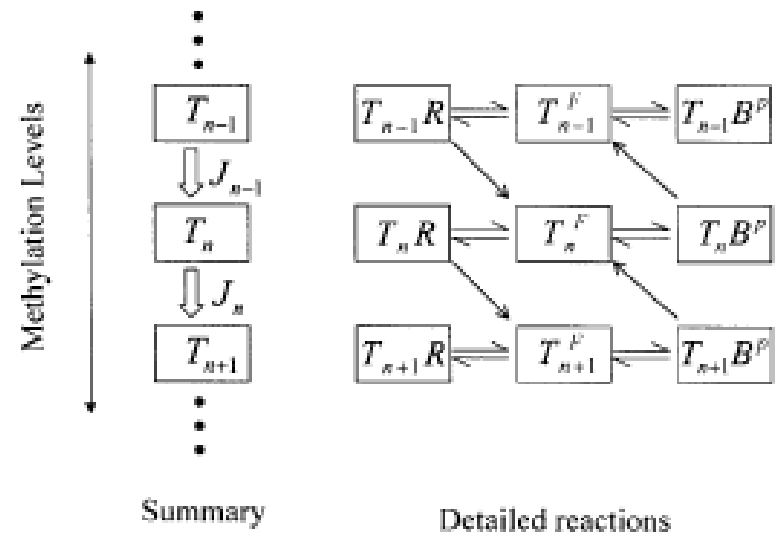
[§]Ligand binding has little effect on demethylation rate.

[¶]Estimated from figure 10 in ref. 3.

^{||}Estimated from figure 3 in ref. 11.

TABLE 2 Chemotaxis signal transduction reactions

Ligand binding	$T_{un} + L \leftrightarrow T_n L (= T_{ms})$	
Methylation	$T_n + R^F \leftrightarrow T_n R$	$T_n R \rightarrow T_{n+1} + R^F$
	$T_n + B^{PF} \leftrightarrow T_n B^P$	$T_n B^P \rightarrow T_{n-1} + B^{PF}$
Phosphorylation	$T_n^U \rightarrow T_n^P$	$Y^P \rightarrow Y^U$
	$T_n^P + Y^U \rightarrow T_n^U + Y^P$	$B^{PF} \rightarrow B^{UF}$
	$T_n^P + B^{UF} \rightarrow T_n^U + B^{PF}$	



Summary

Detailed reactions

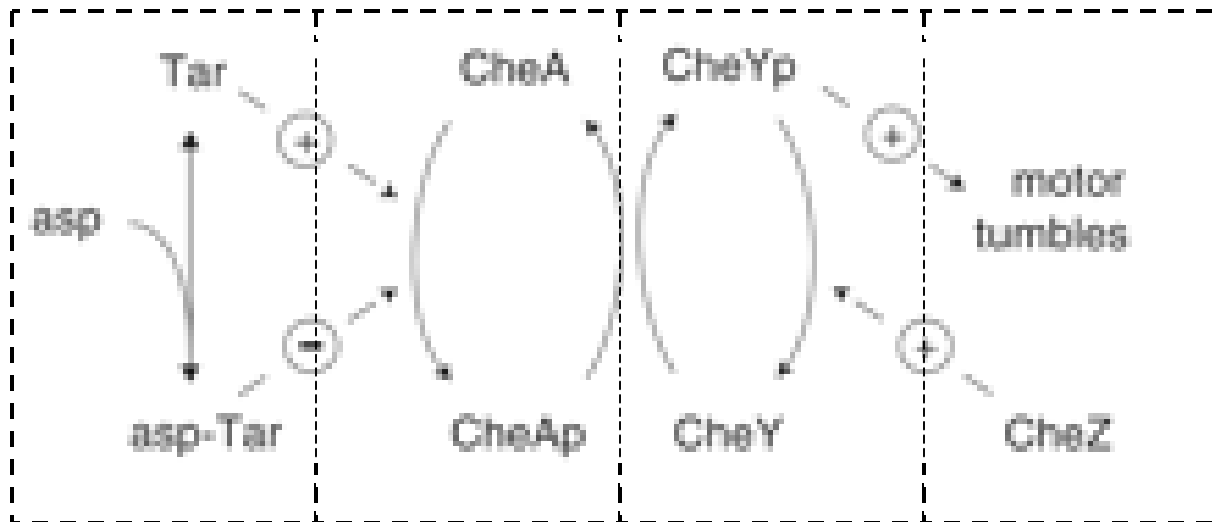
Conditions for perfect adaptation:

1. Ligand binding is very fast.
2. Ligand binding d.n. change dissociation rates of TR and TB.
3. Association rates of T and R,B are linear functions of receptor activity level.
4. Activity of maximally methylated and unmethylated receptor d.n. depend on ligand.
5. Ratios of R to B catalytic rates are the same for all methylated levels.
6. Phosphate transfer rates from A to B and Y are \sim autophosphorylation rate.
7. Ratios of total R and B concentrations to their respective catalytic rates are the same.

This is an excellent example what a mathematician can do. Still have to know biology.

Question of gain: $gain = (\Delta f / f) / (\Delta s / s)$ where f is the tumbling frequency and s is the ligand concentration (signal). There was long standing controversy about what is gain in chemotaxis. The consensus now is that it is $\sim 10-100$. (How it was measured – attention to Materials and Methods.) This is surprisingly high (molecule to molecule signal). The cell can sense increase in just one occupied receptor out of 10,000! Recently, it became clear that the amplification is not on the CheY-motor level, and most likely not CheA to CheY step ('front-end'). So, either receptor itself, or CheA, or both. Also, CheB and CheB-P are essential.

$$gain = \frac{\Delta O}{\Delta S_n} \cdot \frac{\Delta S_n}{\Delta S_{n-1}} \cdots \frac{\Delta S_2}{\Delta S_1} \cdot \frac{\Delta S_1}{\Delta S}$$



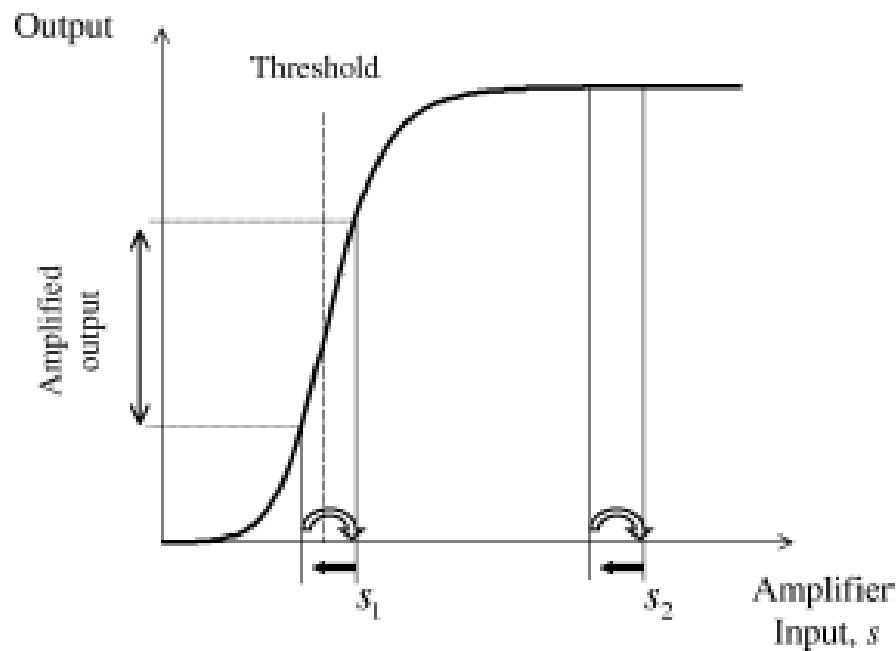


Figure 1. A typical input–output curve for an amplifying system. When the steady state input (s_1) is close to the threshold, a small stimulus (black arrow) leads to a large response. Adaptation (open arrow) resets the input back to the vicinity of the threshold and maintains the ability to respond to further stimuli. When the steady state is away from the threshold (s_2) the ability to respond to small signals is severely reduced. Amplification generally relies on ‘fine tuning’: the biochemical parameters must be carefully adjusted so that the steady state maintained by the adaptation process lies at the threshold of the amplifier.

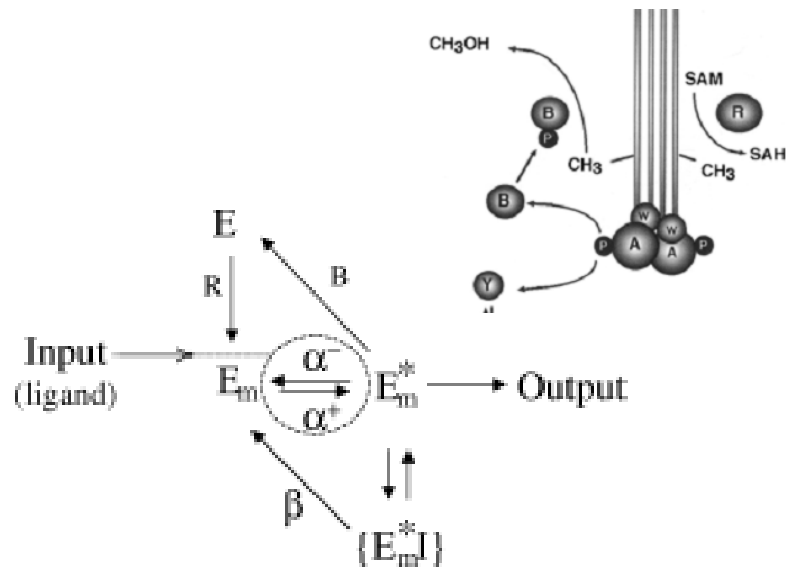
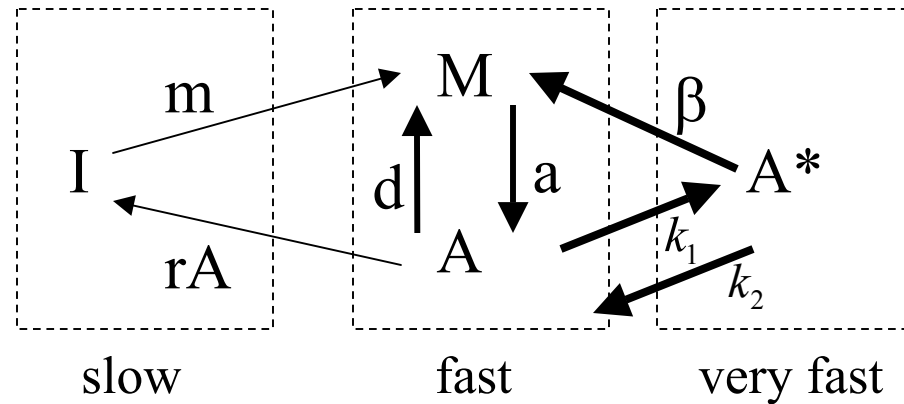
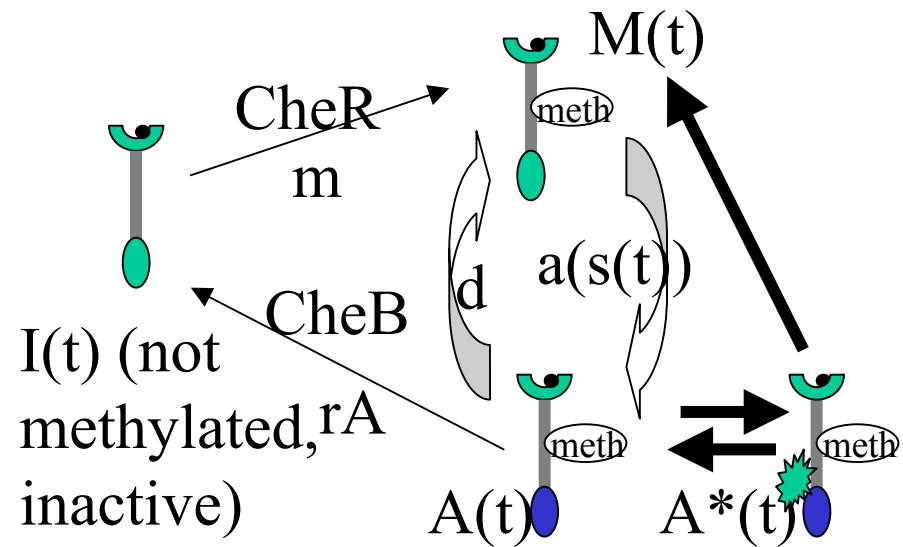


Figure 2. Two-state model exhibiting robust adaptation and amplification. A receptor E is modified by enzyme R , which works at saturation. The modified receptor undergoes transitions between active and inactive states, denoted by E_m^* and E_m respectively, with transition rates α^\pm that depends on the input level ℓ . E_m^* , but not E_m , is the substrate for enzyme B which catalyses the reverse modification reaction. An inhibitor I binds strongly to the active receptor E_m^* . The complex $\{E_m^*I\}$ cannot transmit an output signal. It dissociates with a rate β , releasing an inactive receptor. There are three time scales in the system. Modification reactions are slow, transition between active and inactive receptors are intermediate, while the binding of inhibitor is fast.



$$\frac{dM}{dt} = m + (dA - aM) + [\beta A^*]$$

$$\frac{dA}{dt} = -rA + (aM - dA) - [k_1 A - k_2 A^*]$$

$$\frac{dA^*}{dt} = [k_1 A - k_2 A^* - \beta A^*]$$

$$A^* \approx \frac{k_1}{k_2 + \beta} A, \quad d^* = d + \frac{k_1 \beta}{k_2 + \beta}$$

$$\frac{dM}{dt} = m + (d^* A - aM)$$

$$\frac{dA}{dt} = -rA + (aM - d^* A)$$

$$A = \frac{m}{r}, \quad M = \frac{m(1 + d^*/r)}{a} \approx \frac{md^*}{ra}$$

$$a \rightarrow a - \Delta a, \quad \frac{A - \Delta A}{M + \Delta M} = \frac{a - \Delta a}{d^*},$$

$$A - \Delta A + M + \Delta M = A + M \approx \frac{m}{r} \left(1 + \frac{d^*}{a} \right) \approx const,$$

$$gain = \frac{[\Delta A / (m/r)]}{\Delta a / a} \approx \frac{d^* / a}{1 + (d^* / a)}$$

How do you present the model. Do you start with abstract idea and then look for facts supporting it?

Model in which active receptors induce activity in the neighboring receptors, as in Ising model. The average radius of the activity spread has to be large enough to have amplification effect, but not large enough to ‘jam’ the sensitivity to future changes.

$$r + r + \dots + r + R \leftrightarrow R^*,$$

$$\overline{R} = \frac{r^n}{r_{th}^n + r^n}$$

Chemotaxis is the example of the phenomenon about to be understood completely.

