ETH zürich

Lecture 10: Chemotaxis: Patterning & Signalling

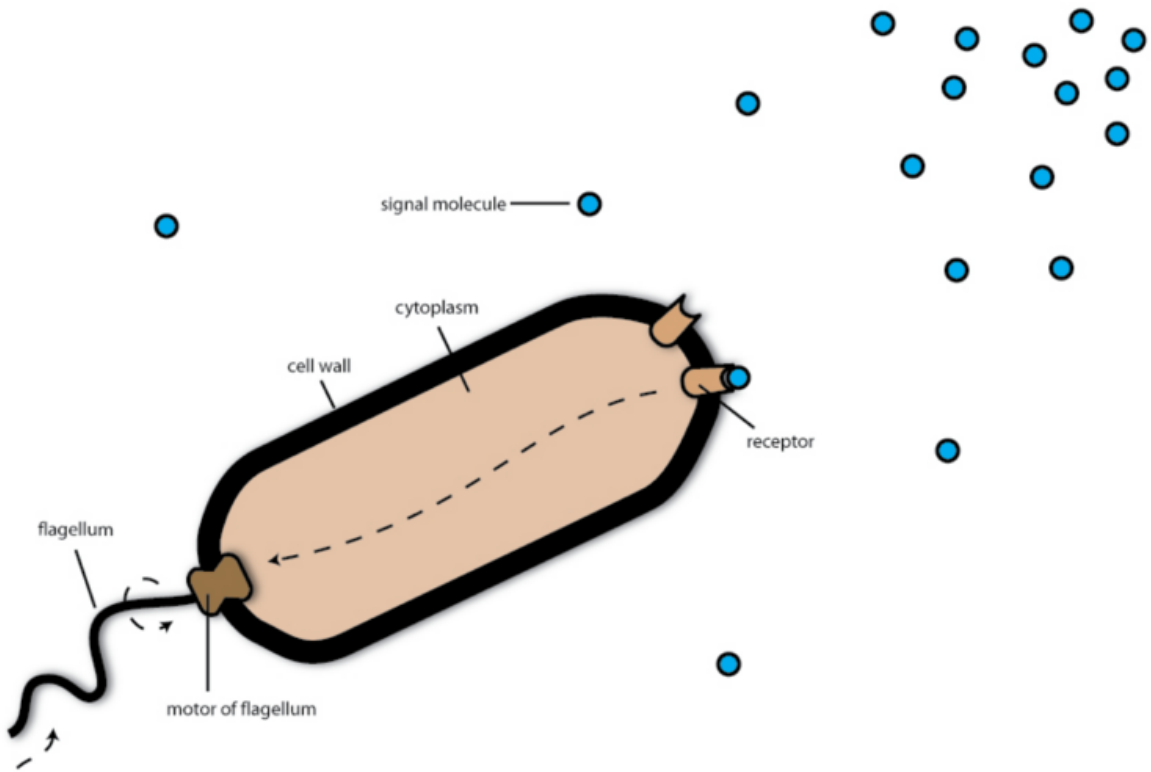
Prof Dagmar Iber, PhD DPhil

MSc Computational Biology 2019/20

Computational Biology Group (CoBi), D-BSSE, ETHZ

Contents

Chemotaxis



http://2008.igem.org/Team:Heidelberg/Project/General_information

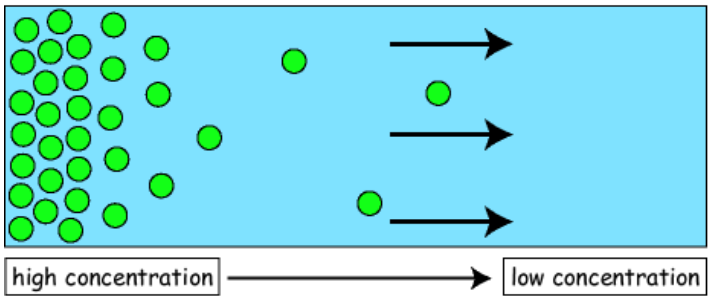
Chemotaxis

The presence of a gradient in a chemoattractant $a(x,t)$ gives rise to movement of a species, density $n(x,t)$, up the concentration gradient.

Continuous Models of Chemotaxis

Chemotaxis

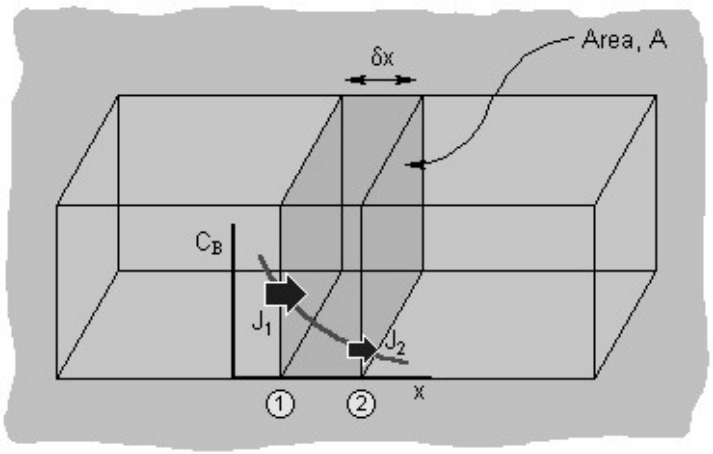
Consider cells with density $n(x,t)$ and a gradient of a chemorepellent $r(x,t)$. How does the cell density change with time?



1. Random Walk of Cells == Diffusion

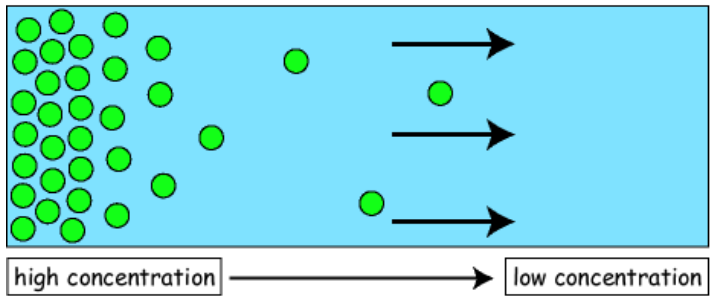
$$J_D = -D\frac{\partial n}{\partial x}; \quad 0 \leq x \leq L$$

$$\frac{\partial n}{\partial t} = -\frac{\partial J_D}{\partial x} = D\frac{\partial^2 n}{\partial x^2}; \quad 0 \leq x \leq L$$



2. Chemotactic Flux

$$J_C = -\chi n \frac{\partial r}{\partial x}; \qquad J_C = \chi n \frac{\partial a}{\partial x}$$



The chemotactic flux J_C, is directed. The magnitude of J_C is proportional to:

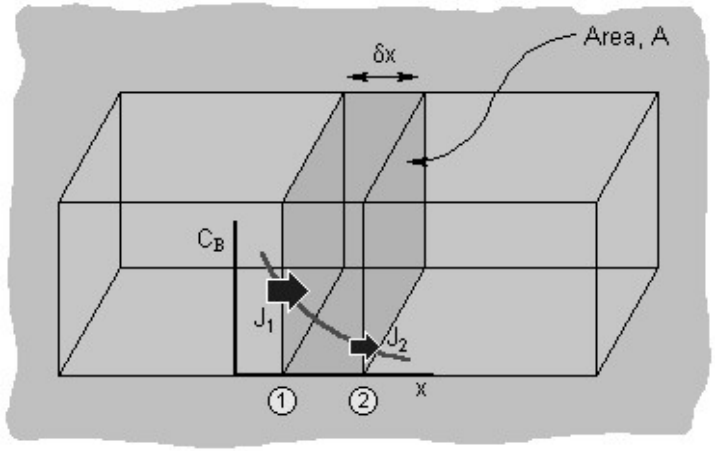
- the chemotactic sensitivity, χ
- the slope of the gradient in the chemoattractant, $\frac{\partial a}{\partial x}$, or repellent, $\frac{\partial r}{\partial x}$
- the local cell density, $n(x, t)$

The sign of J_C depends on whether cells are repelled or attracted.

Cell Dynamics as a result of random walk and chemotaxis

Fick's Second Law

$$\frac{\partial n}{\partial t} = -\frac{\partial J}{\partial x}$$



Fick's Second Law follows from the conservation of mass:

$$\begin{aligned} \text{Chemotactic Flux:} \quad & J_C = n\chi(a)\nabla a \\ \text{Diffusional Flux:} \quad & J_D = -D\nabla n \\ \text{Total Flux:} \quad & J = J_C + J_D \end{aligned}$$

$$\frac{\Delta n}{\Delta t} = -\frac{J(x+\Delta x, t) - J(x,t)}{\Delta x}$$

$$\frac{\partial n}{\partial t} = -\frac{\partial}{\partial x}\left(-D\frac{\partial n}{\partial x} - \chi n\frac{\partial a}{\partial x}\right)$$

Keller-Segel Model (1971)

Fluxes in Keller-Segel Model

$$\text{Chemotactic Flux:} \quad J_C = n\chi(a)\nabla a$$
$$\text{Diffusional Flux:} \quad J_D = -D\nabla n$$
$$\text{Total Flux:} \quad J = J_C + J_D$$

Keller-Segel Model (1971)

$$\text{Cells:} \quad \frac{\partial n}{\partial t} = \nabla(D_n(a)\nabla n - \chi(a)n\nabla a)$$
$$\text{Chemoattractant:} \quad \frac{\partial a}{\partial t} = D_a\nabla^2 a - n\delta(a)$$

Diffusion $D_n(a)$

Diffusion

$$\text{Enhancement of Motility:} \quad D_n(a) = D\left(1 + \alpha \frac{aK}{(a+K)^2}\right)$$

$$\text{Constant Motility:} \quad D_n(a) = D$$

Chemoattractant Degradation $\delta(a)$

Chemoattractant Degradation

$$\begin{aligned} \text{Typically neglected:} \quad & \delta(a) = 0 \\ \text{Nonlinear:} \quad & \delta(a) \propto \frac{a}{(a+K)} \\ \text{Linear:} \quad & \delta(a) \propto a \end{aligned}$$

Chemotactic Sensitivity $\chi(a)$

Experiments: The chemotactic effect increases as the chemoattractant concentration $a(x,t)$ decreases.

Chemotactic Sensitivity

$$\text{Log Law:} \qquad \chi(a) = \frac{\chi_0}{a}$$

$$\text{Receptor Law:} \qquad \chi(a) = \chi_0 \frac{k^2}{(k+a)^2}$$

Interesting qualitative Behaviours

Interesting qualitative Behaviours

$$\text{Travelling Waves:} \quad \chi(a) = \chi_0 \frac{1}{a}$$

$$\text{Aggregation:} \quad \chi(a) = \chi_0$$

.

Work this out as part of your homework!

General Model:

$$\text{Cells:} \quad \frac{\partial u}{\partial t} = D_u \nabla^2 u - \alpha \nabla (u \chi(v) \nabla v) + f(u, v)$$

$$\text{Attractant:} \quad \frac{\partial v}{\partial t} = D_v \nabla^2 v + g(u, v)$$

Parameters: α, χ, D_u, $D_v > 0$.

Conditions for Patterns to emerge: require unstable steady state $\Rightarrow$ carry out linear stability analysis

Linearization about the steady state

We now linearise the system about the steady state(u^*, v^*) by setting

$$u \approx u^* + \epsilon u_1, \qquad v \approx v^* + \epsilon v_1; \qquad 0 < \epsilon \ll 1.$$

$$\begin{aligned} f(u,v) &\approx f(u^*,v^*) + f_u^* \cdot (u-u^*) + f_v^* \cdot (v-v^*) = f_u^* \epsilon u_1 + f_v^* \epsilon v_1 \\ g(u,v) &\approx g(u^*,v^*) + g_u^* \cdot (u-u^*) + g_v^* \cdot (v-v^*) = g_u^* \epsilon u_1 + g_v^* \epsilon v_1 \\ \chi(v) &\approx \chi(v^*) + \chi_v^* \cdot (v-v^*) = \chi(v^*) + \chi_v^* \cdot \epsilon v_1 \end{aligned}$$

We then obtain the linearised system

$$\text{Cells:} \qquad \frac{\partial u_1}{\partial t} = D_u \nabla^2 u_1 - \alpha u^* \chi^* \nabla^2 v_1 + f_u^* u_1 + f_v^* v_1$$

$$\text{Chemoatttractant:} \qquad \frac{\partial v_1}{\partial t} = D_v \nabla^2 v_1 + g_u^* u_1 + g_v^* v_1$$

Vector Form

We write the linear system in vector form

$$\begin{pmatrix} \frac{\partial u_1}{\partial t} \\ \frac{\partial v_1}{\partial t} \end{pmatrix} = \underbrace{\begin{pmatrix} D_u & -\alpha u^* \chi(v^*) \\ 0 & D_v \end{pmatrix}}_{D} \nabla^2 \begin{pmatrix} u_1 \\ v_1 \end{pmatrix} + \underbrace{\begin{pmatrix} f_u^* & f_v^* \\ g_u^* & g_v^* \end{pmatrix}}_{J} \begin{pmatrix} u_1 \\ v_1 \end{pmatrix}.$$

For the perturbation, $\vec{w} = \begin{pmatrix} u_1 \\ v_1 \end{pmatrix} - \begin{pmatrix} u_1^* \\ v_1^* \end{pmatrix} = \epsilon \begin{pmatrix} u_1 \\ v_1 \end{pmatrix}$, about the steady state, we then obtain

$$\frac{\partial \vec{w}}{\partial t} = D\Delta\vec{w} + J\vec{w}. \quad (1)$$

Ansatz: Separable Solution

$$\vec{w_i}(x,t) \propto \Phi_i(t) W_i(x)$$

Time-dependent Solution

$$\dot{\Phi}_i = J\Phi_i \quad \Rightarrow \quad \Phi_i(t) \propto exp(\lambda_i t)$$

where λ_i are the eigenvalues and $\vec{e_i}$ the eigenvectors of J.

Spatial Solution

$$\vec{0} = JW_i + D\Delta W_i \quad \Rightarrow \quad W_i(x) \propto \exp(ik_i x)$$

k_i are referred to as wavenumber.

$$\vec{w_i}(x,t) = \sum_i \alpha_i \vec{e_i} \exp(\lambda t + ikx)$$

Ansatz: Separable Solution

Substituting

$$\vec{w_i}(x,t) = \sum_i \alpha_i \vec{e_i} \exp\left(\lambda t + ikx\right)$$

into Eq. 1, we obtain

$$\lambda \vec{w} = J\vec{w} - k^2 D\vec{w}.$$

We can rewrite this as

$$H\vec{w} = \lambda\vec{w} \qquad H = J - k^2 D.$$

$$H = \begin{pmatrix} f_u^* - D_u k^2 & f_v^* + \alpha\chi u^* k^2 \\ g_u^* & g_v^* - D_v k^2 \end{pmatrix}$$

Stability to temporal perturbations, $k = 0$

To obtain $\mathrm{Re}(\lambda(0)) < 0$ we require

$$tr(J) = (f_u^* + g_v^*) < 0$$

$$\det(J) = h(k^2 = 0) \quad = \quad f_u^* g_v^* - f_v^* g_u^* > 0$$

Eigenvalues of H

$$H\vec{w} = \lambda\vec{w} \qquad H = J - k^2 D.$$

We then have

$$tr(H) = -(D_u + D_v)k^2 + (f_u^* + g_v^*) < 0$$

$$\begin{aligned} \det(H) = h(k^2) &= D_u D_v k^4 - (D_u g_v^* + D_v f_u^* + \alpha u^* \chi^* g_u^*)k^2 \\ &\quad + f_u^* g_v^* - f_v^* g_u^* \end{aligned}$$

Dispersion Relation

The steady state is stable for $\det(H) = h(k^2) > 0$. For patterns to emerge, we require $\det(H) = h(k^2) < 0$. Accordingly, we solve

$$\begin{aligned} \det(H) = h(k^2) &= D_u D_v k^4 - (D_u g_v^* + D_v f_u^* + \alpha u^* \chi^* g_u^*) k^2. \\ &\quad + f_u^* g_v^* - f_v^* g_u^* = 0 \end{aligned}$$

In general, for each set of parameter values there are two, one or zero values of k^2 that satisfy this relation. At bifurcation, i.e. where $\mathrm{Re}(\lambda) = 0$, there is one value, the critical wavenumber,

$$k_c^2 = \frac{D_u g_v^* + D_v f_u^* + \alpha u^* \chi^* g_u^*}{2 D_u D_v};$$

Critical Wavenumber

Replacing

$$k_c^2 = \frac{D_u g_v^* + D_v f_u^* + \alpha u^* \chi^* g_u^*}{2 D_u D_v}$$

in

$$\begin{aligned} h_c(k^2) &= D_u D_v k^4 - (D_u g_v^* + D_v f_u^* + \alpha u^* \chi^* g_u^*) k^2 \\ &\quad + f_u^* g_v^* - f_v^* g_u^* = 0 \end{aligned}$$

yields

$$\begin{aligned} \alpha &= \frac{-(D_u g_v^* + D_v f_u^* + 2\sqrt{D_u D_v (f_u^* g_v^* - f_v^* g_u^*)})}{u^* \chi^* g_u^*} \\ k_c^2 &= \sqrt{\frac{f_u^* g_v^* - f_v^* g_u^*}{D_u D_v}}. \end{aligned}$$

Critical Wavenumber

$$k_c^2 = \sqrt{\frac{f_u^* g_v^* - f_v^* g_u^*}{D_u D_v}} = \sqrt{\frac{\det(J)}{D_u D_v}}$$

defines a critical boundary set in parameter space which separates the two regions of positive and negative $\mathrm{Re}(\lambda)$.

Example: Chemotactic Aggregation

Aggregation of *Dictyostelium discoideum*

Model for the aggregation of the amoebae state of the slime mold *Dictyostelium discoideum*.

http://www.youtube.com/watch?v=bkVhLJLG7ug

The population $n(x,t)$ secretes a chemical attractant, cyclic-AMP, $a(x,t)$, that attracts the amoebae.

$$\text{Cells:} \qquad \frac{\partial n}{\partial t} = D_n \nabla^2 n - \xi \nabla (n \nabla a)$$

$$\text{Chemoattractant:} \qquad \frac{\partial a}{\partial t} = D_a \nabla^2 a + hn - \delta a$$

Parameters: h, δ, ξ, D_n, $D_a > 0$

Linear stability of the steady state

The stability of the steady states can be determined by studying the long-term behaviour of perturbations of the steady state

$$\mathbf{w} = \begin{pmatrix} n - n^* \\ a - a^* \end{pmatrix}$$

$$\dot{\mathbf{w}} = J\mathbf{w} + D\Delta\mathbf{w}$$

$$J = \begin{pmatrix} f_n & f_a \\ g_n & g_a \end{pmatrix}^* = \begin{pmatrix} 0 & 0 \\ h & -\delta \end{pmatrix}; \qquad D = \begin{pmatrix} D_n & -\zeta\, n^* \\ 0 & D_a \end{pmatrix}$$

Dispersion Relation

For patterns to emerge we require

$$\det(H) = h(k^2) = D_n k^2(\delta + D_a k^2) - h\xi n^* k^2 < 0$$

We thus want $h_{min} < 0$. The critical case occurs for

$$h_c(k^2) = D_n k^2(\delta + D_a k^2) - h\xi n^* k^2 = 0$$

and thus

$$k_c^2 = \frac{h\xi n^* - \delta D_n}{D_n D_a}$$

In the **infinite domain** we thus only require $k_c^2 > 0$, i.e. $h\xi > \delta D_n$ for pattern to emerge.

Finite Domain

In the finite domain $[0, 1]$ solutions are with zero flux boundary conditions

$$\mathbf{w} \propto \exp(\lambda t)\cos(kx), \qquad k = n\pi$$

For $n = n^*$ to be unstable, we thus require

$$k_c^2 = \frac{h\chi n^* - \delta D_n}{D_n D_a} \geq \pi^2.$$

The critical wavelength is the first to go unstable.

Dimensional Conditions

In the finite domain $[0, L]$ solutions are with zero flux boundary conditions

$$\mathbf{w} \propto \exp(\lambda t)\cos(kx), \qquad k = \frac{n\pi}{L}$$

We thus require

$$k_c^2 = \frac{\chi h n^* - \delta D_n}{D_n D_a} > \frac{\pi^2}{L^2}$$

for $n = n^*$ to be unstable. The critical wavelength is the first to go unstable.

Minimal Domain Size

In the finite domain $[0, L]$ solutions are with zero flux boundary conditions, domain size L must meet the following condition

$$L^2 > \frac{\pi^2 D_n D_a}{\chi h n^* - \delta D_n}$$

Note that higher expression rate h facilitates the emergence of pattern.

Conditions for Chemotaxis

χ measures aggregation, D_a, D_n dispersion. For pattern to emerge aggregation has to defeat dispersion.

Minimal domain size

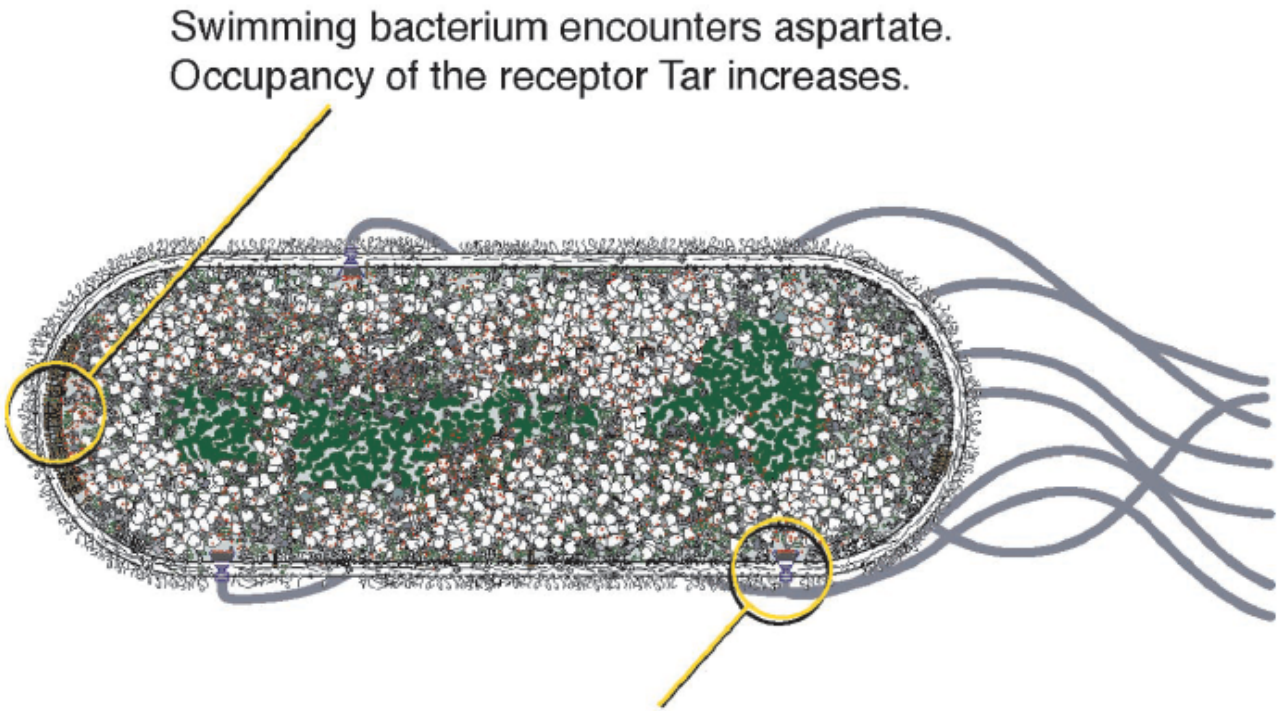
Higher chemoattractant production facilitates pattern formation.

Slime mold solving a maze in the lab

http://www.youtube.com/watch?v=F3z_mdaQ5ac&feature=related

Chemotaxis Signalling & Adaptation

Chemotaxis by *Escherichia coli*

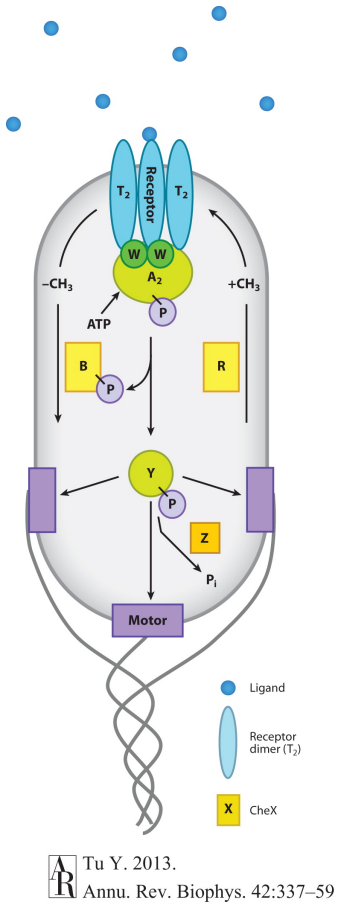


Bray (2002) PNAS

Properties of chemotaxis response in *E. coli*

- E. coli can swim up a gradient, sensing the attractant concentration over at least five orders of magnitude. $\Rightarrow$ Adaptation over at least five orders of magnitude
- High Sensitivity: Bacteria can detect a change in occupancy of their aspartate receptors of 0.1-0.2%, corresponding to the binding of one or two molecules per cell
- Large Gain = change in bias divided by the change in occupancy ~ 60

E. coli chemotaxis signaling pathway

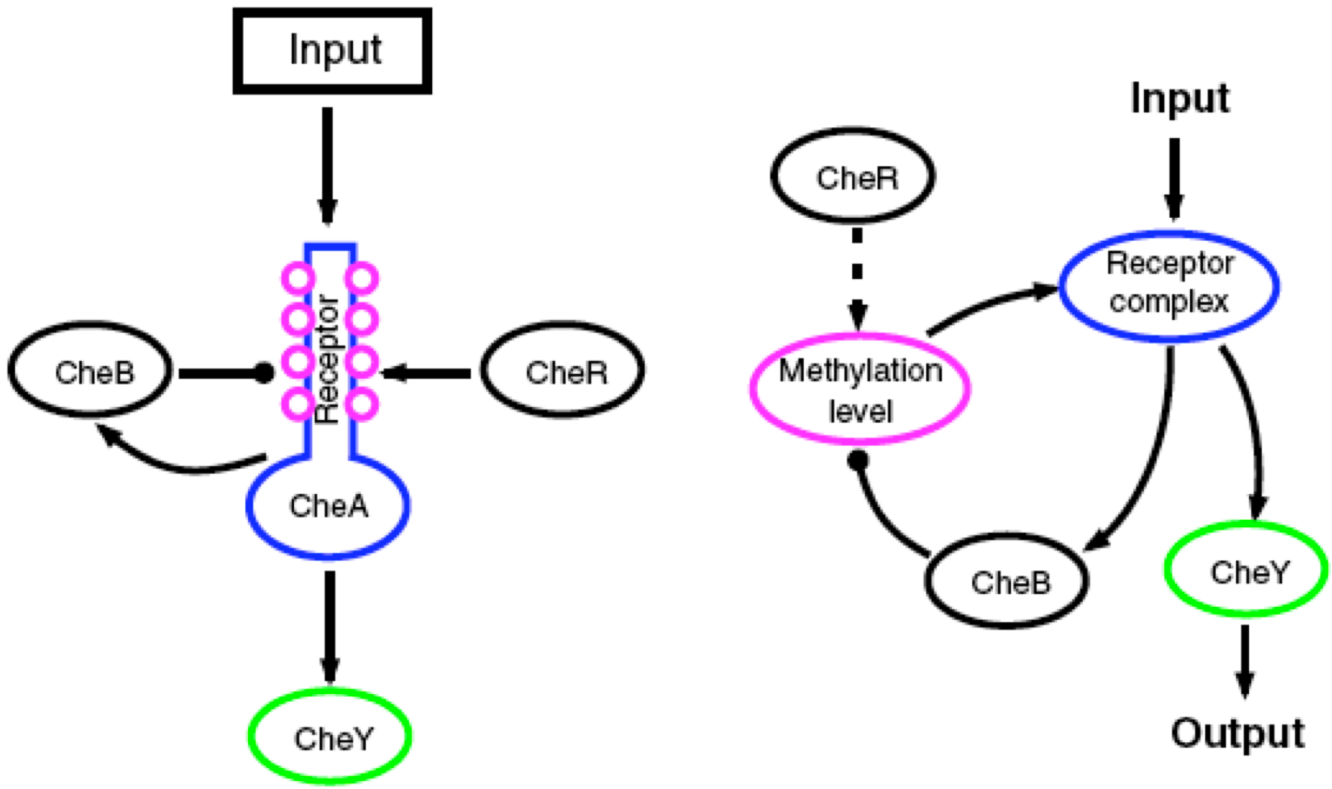


Tu Y. 2013.
Annu. Rev. Biophys. 42:337–59

Tu, Y. (2013). Annu Rev Biophys 42: 337-359.

- The receptors form a complex with the histidine kinase CheA through the adaptor protein CheW.
- The autophosphorylation activity of CheA is suppressed (enhanced) when chemoattractant (repellent) binds to the receptor.
- The activated histidine kinase CheA acquires a phosphate group through autophosphorylation and subsequently transfers it to the response regulator CheY or the demethylation enzyme CheB.
- The phosphorylated CheY can bind with the flagellar motor and can increase the motor's clockwise (CW) bias and the cell's tumble probability.
- Increased receptor methylation reduce the receptor affinity and make it less responsive (negative feedback).

Escherichia coli chemotaxis signaling pathway



Ma et al (2009) Cell, 138, 760-773

Signal Amplification by Receptor Clustering

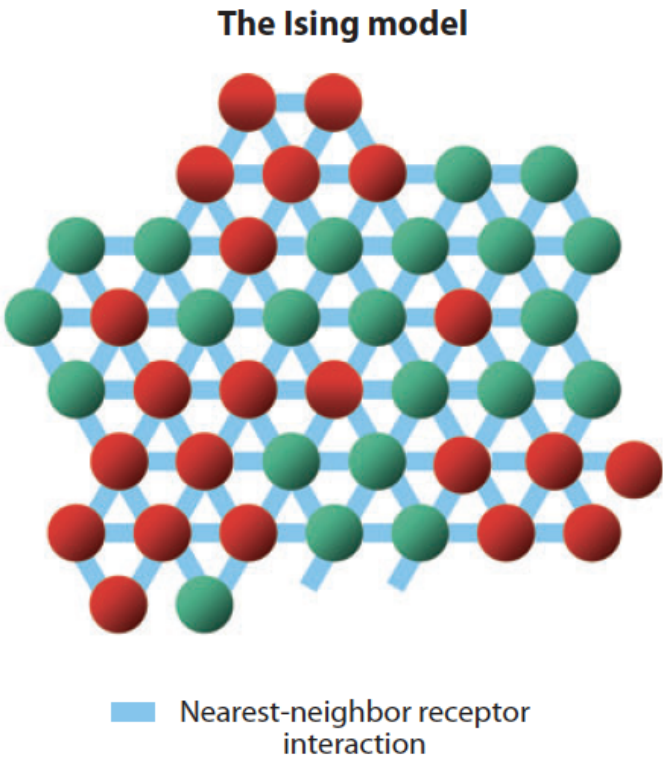
Signal Amplification by Receptor Clustering

- There are a few tens of thousands of chemoreceptors in a single *E. coli* cell, depending on its physiological conditions and growth phase.
- Bacteria can detect a change in occupancy of their aspartate receptors of 0.1-0.2%, corresponding to the binding of one or two molecules per cell.
- Chemoreceptors form large clusters near the cell pole with other cytoplasmic proteins, in particular CheA and CheW.
- Cooperativity due to receptor clustering can lead to signal amplification in bacterial chemotaxis as binding of a ligand molecule to one receptor in the cluster can induce responses in many other receptors

The Two-State Ising Model for the Chemoreceptor Cluster

- The simplest model for describing the kinase activity of a chemoreceptor assumes that it has two discrete conformations: one active and the other inactive.
- Ising model in physics: An active receptor corresponds to an up-spin and an inactive receptor corresponds to a down-spin.
- The cooperative receptor-receptor interactions between nearest neighbours in the receptor cluster can then be modelled as the Ising ferromagnetic spin-spin interaction that favours the neighbouring receptors to have the same conformation.

The Ising Model



The Ising model describes a system of spins interacting between nearest neighbours in a graph (usually a regular lattice).

First proposed for modelling ferromagnetism, the Ising model has become a powerful paradigm in studying collective phenomena and phase transitions.

Tu, Y. (2013). Annu Rev Biophys 42: 337-359.

The Ising Model

The energy function (Hamiltonian) of the system can be written as:

$$H(\vec{s}) = -\sum_{<ij>} J s_i s_j - \sum_i h s_i \tag{2}$$

- $s_i = \{1, 1\}$ represents the up or down state of the spin at site i.
- $< ij >$ represents the nearest-neighbour pair of spins at sites i and j.
- J is the interaction (coupling) strength.
- h represents the external magnetic field: a positive magnetic field $h > 0$ favours the up-spin state over the down-spin state by introducing an energy difference $2h$ between the two states.

The Ising Model

The probability in a given spin configuration $\vec{s} = (s_1, s_2, \ldots)$ follows the Boltzmann distributiuon

$$P(\vec{s}) = \frac{\exp\left(-\frac{H(\vec{s})}{kT}\right)}{Z} \tag{3}$$

k is the Boltzmann constant, T the temperature, and

$$Z = \sum_{\vec{s}} \exp\left(\frac{-H(\vec{s})}{kT}\right) \tag{4}$$

is the partition function.

$$H(\vec{s}) = -\sum_{<ij>} J s_i s_j - \sum_i h s_i$$

The Ising Model

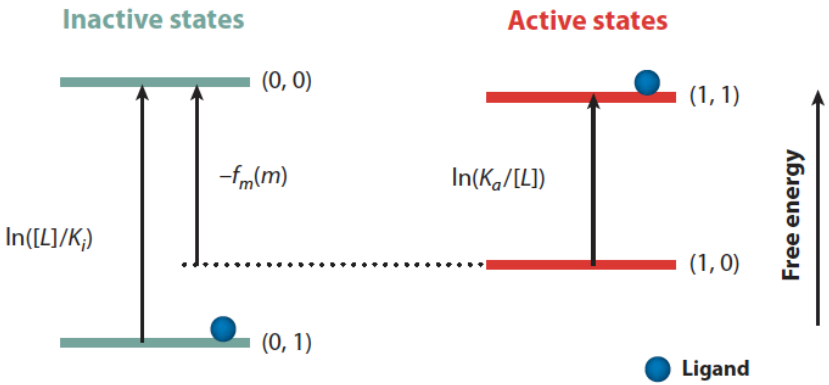
In the absence of spin-spin interaction ($J = 0$), the average spin $< s >$ has a simple sigmoidal dependence on the external field h:

$$< s >= \tanh\left(\frac{h}{kT}\right). \tag{5}$$

In the presence of ferromagnetic interaction ($J > 0$), the spins are correlated with each other, which gives rise to more sensitive dependence of $< s >$ on h near $h = 0$.

Quantitatively, the susceptibility $\chi = \left.\frac{d<s>}{dh}\right|_{h+0}$ increases with J. In an infinite system, χ diverges as J approaches a critical value J_c, which defines the onset of a phase transition.

The Ising Model: application to Chemotaxis



The state of a receptor can be characterized by a pair of binary variables (a, l):
$a = 0, 1$ for inactive and active forms of the receptor, respectively;
$l = 0, 1$ for vacant and ligand-bound receptors, respectively.

The probability for each of the four states is given by $P(a, l)$.

The ligand dissociation constants for the active (a = 1) and inactive (a = 0) receptors are K_a and K_i, respectively.

In the absence of ligand, we have $l = 0$, and the free energy difference, $f_m(m)$, between the active and inactive states depends only on the receptor methylation level m.

The Ising Model: application to Chemotaxis

The equilibrium probabilities in the four states satisfy the following relations with $[L]$ the ligand concentration:

$$\frac{P(0,1)}{P(0,0)} = \frac{[L]}{K_i}, \qquad \frac{P(1,1)}{P(1,0)} = \frac{[L]}{K_a}, \qquad \frac{P(1,0)}{P(0,0)} = \exp\left(-f_m(m)\right)$$

Given the normalisation condition

$$\sum_{a,l} P(a,l) = 1,$$

the average activity, $< a >$, can be obtained as

$$\begin{aligned} < a > &= \sum_{a=0}^{1}\sum_{l=0}^{1} aP(a,l) = P(1,0) + P(1,1) \\ &= \frac{\exp\left(-f_m(m)\right)(1+[L]/K_a)}{1+[L]/K_i + \exp\left(-f_m(m)\right)(1+[L]/K_a)}. \end{aligned}$$

Average Activity

We notice that the average activity,

$$< a > \quad = \quad \frac{\exp\left(-f_m(m)\right)(1 + [L]/K_a)}{1 + [L]/K_i + \exp\left(-f_m(m)\right)(1 + [L]/K_a)}$$

depends in a hyperbolic fashion on the ligand concentration $[L]$.

The affinity of binding and the methylation state determine the ligand concentration at which the half-maximal average activity is achieved.

The Ising Model: application to Chemotaxis

If Δf is the free energy difference between the active state $(P(1,0) + P(1,1))$ and the inactive state $(P(0,0) + P(0,1))$, we have

$$< a > \quad = \quad \frac{1}{1 + \exp(-\Delta f)}. \tag{6}$$

Accordingly,

$$\Delta f(m, [L]) = -f_m(m) - f_L([L]), \quad \text{with} \quad f_L([L] = \ln\left(\frac{1 + [L]/K_i}{1 + [L]/K_a}\right). \tag{7}$$

$$H(\vec{a}) = -\sum_{<i,j>} J \times (2a_i - 1)(2a_j - 1) - \sum_i \Delta f(m_i, [L])a_i$$

The Ising Model: application to Chemotaxis

The steady-state properties of the system, such as its average activity for a given stimulus, can be determined by the probability $P(\vec{a})$ of a given microscopic state $\vec{a}$, which is given by

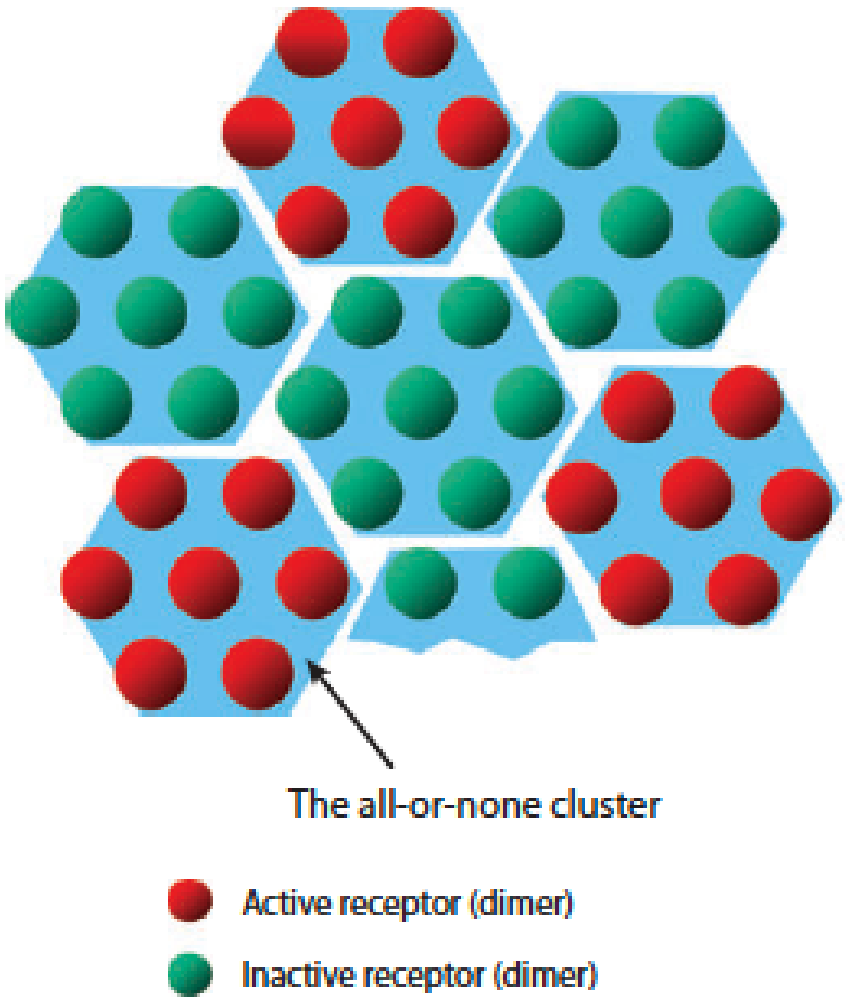
$$P(\vec{a}) = \frac{\exp\left(H(\vec{a})\right)}{Z}$$

where the thermal energy $kT = 1$ is set to unity, and

$$Z = \sum_{\vec{a}} P(\vec{a})$$

is the normalization factor. Technically, the Ising model can be solved numerically by Monte Carlo (MC) simulation methods or analytically by using the mean field theory approximation.

The All-or-None Monod-Wyman-Changeux Model

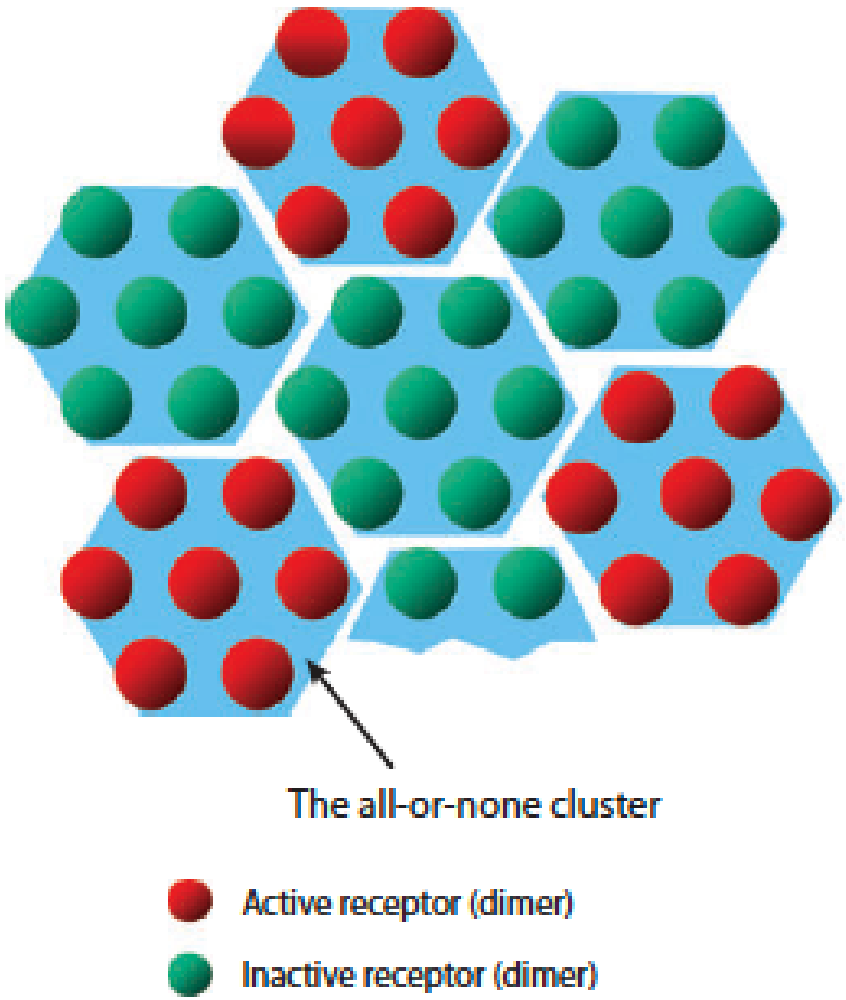


Tu, Y. (2013). Annu Rev Biophys 42: 337-359.

An alternative approach for describing receptor cooperativity in the cluster is to divide it into smaller subclusters.

Within each subcluster, all the receptors are tightly coupled and always in the same state (either active or inactive), whereas the receptors from different subclusters do not correlate with each other at all.

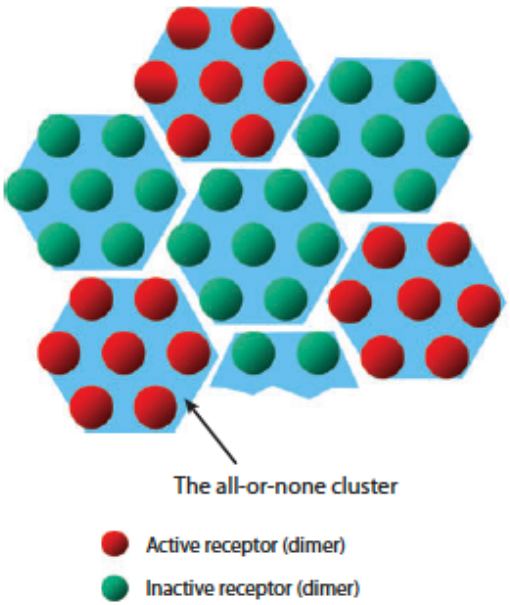
The All-or-None Monod-Wyman-Changeux Model



Tu, Y. (2013). Annu Rev Biophys 42: 337-359.

This is essentially the all-or-none model proposed by Monod, Wyman, and Changeux (MWC) to describe allosteric protein interactions in protein complex with multiple subunits.

The All-or-None Monod-Wyman-Changeux Model



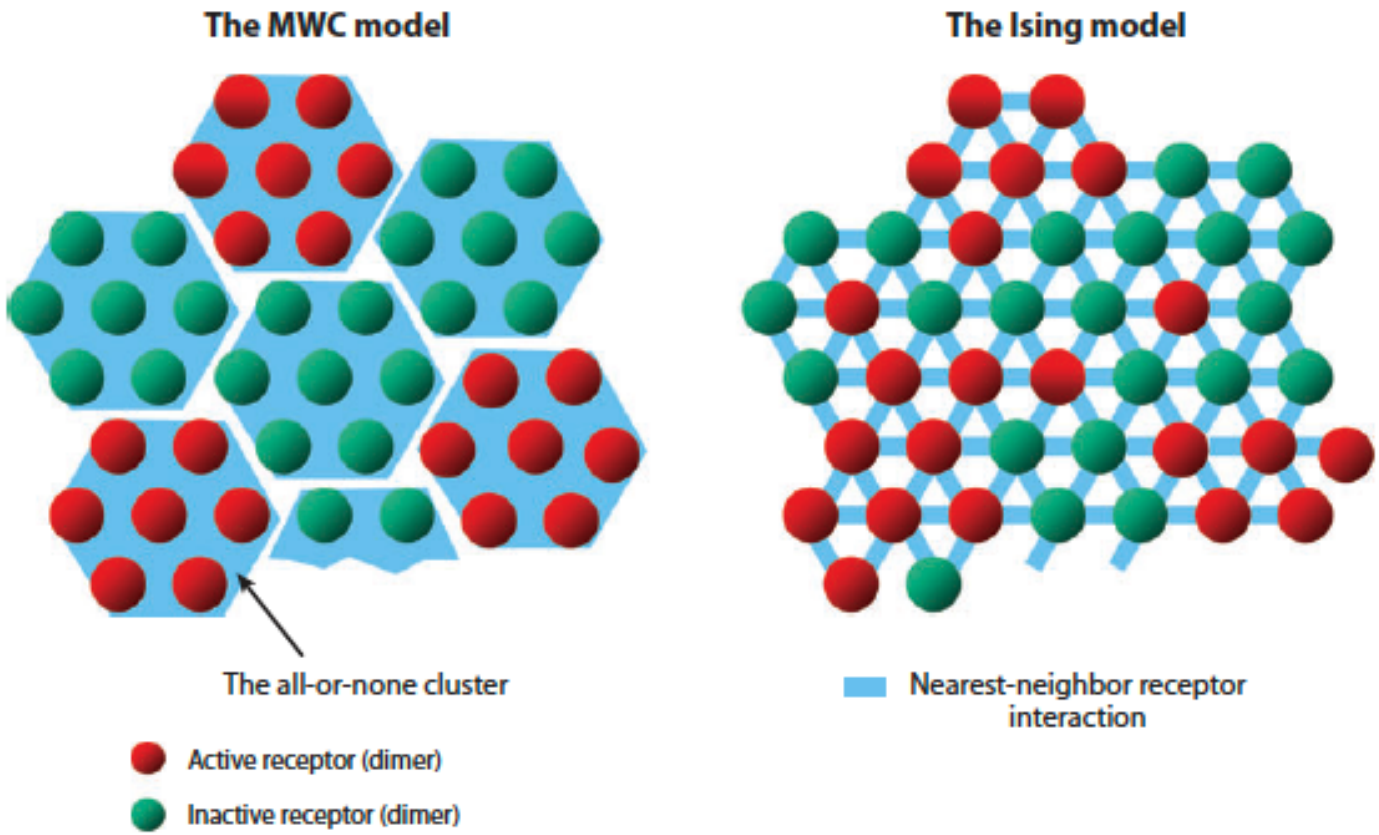
The MWC model corresponds to a special case of the Ising model, in which there is

- an infinite interaction strength $J = \infty$ between receptors within the same subcluster
- no interaction strength $J = 0$ between receptors from different subclusters.

$$H(\vec{a}) = -\sum_{<i,j>} J \times (2a_i - 1)(2a_j - 1) - \sum_i \Delta f(m_i, [L])a_i$$

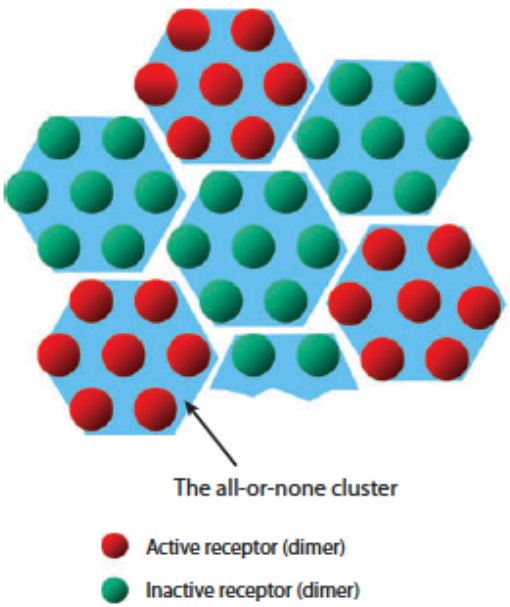
Tu, Y. (2013). Annu Rev Biophys 42: 337-359.

Difference between the MWC model and the Ising model



Tu, Y. (2013). Annu Rev Biophys 42: 337-359.

The All-or-None Monod-Wyman-Changeux Model



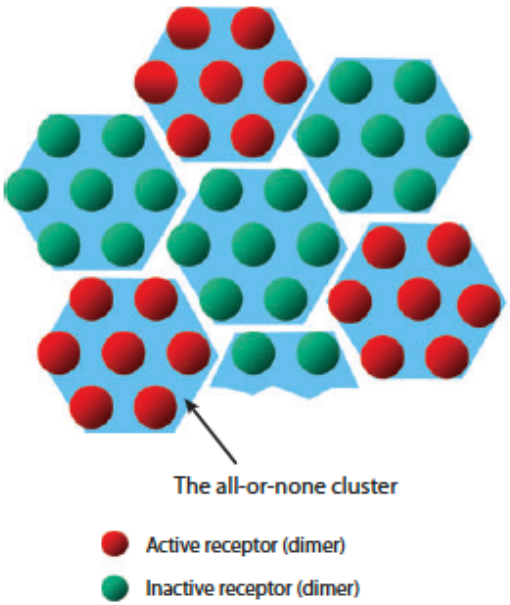
In the MWC model, the degree of cooperativity is given explicitly by N, the size of the all-or-none subcluster.

In comparison, the degree of cooperativity in the Ising model can be described by a correlation length that increases with the receptor interaction strength J.

This simplification makes the MWC model analytically solvable.

Tu, Y. (2013). Annu Rev Biophys 42: 337-359.

The All-or-None Monod-Wyman-Changeux Model



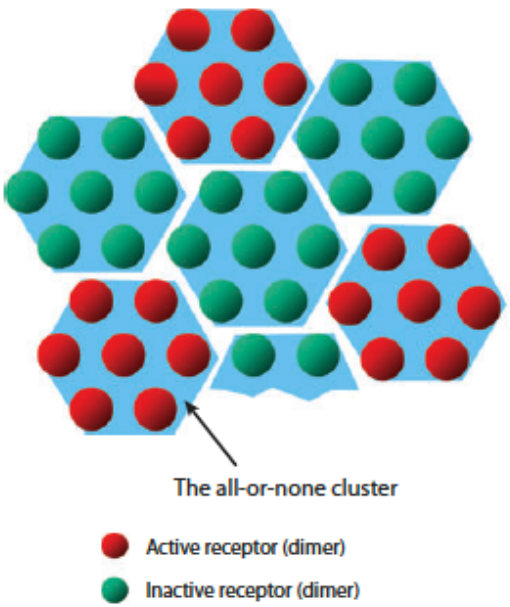
$$H(\vec{a}) = -\sum_{<i,j>} J \times (2a_i - 1)(2a_j - 1) - \sum_i \Delta f(m_i, [L])a_i$$

In an all-or-none MWC cluster with N receptors, the free energy difference between the all-active state and the all-inactive state is simply $Nf(m, [L])$. Therefore, the average activity can be obtained analytically as

$$< a > = (1 + \exp(-N\Delta f))^{-1}$$

Tu, Y. (2013). Annu Rev Biophys 42: 337-359.

The All-or-None Monod-Wyman-Changeux Model



With

$$\Delta f(m,[L]) = -f_m(m) - \ln\left(\frac{1+[L]/K_i}{1+[L]/K_a}\right)$$

we obtain

$$< a > \quad = \quad \frac{K_{eq}(1+[L]/K_a)^N}{(1+[L]/K_i)^N + K_{eq}(1+[L]/K_a)^N}$$

where $K_{eq} = \exp(-Nf_m(m))$ is the equilibrium constant.

Tu, Y. (2013). Annu Rev Biophys 42: 337-359.

Comparison of Models

Ising Model

$$< a > \quad = \quad \frac{K_{eq}(1 + [L]/K_a)}{1 + [L]/K_i + K_{eq}(1 + [L]/K_a)}$$

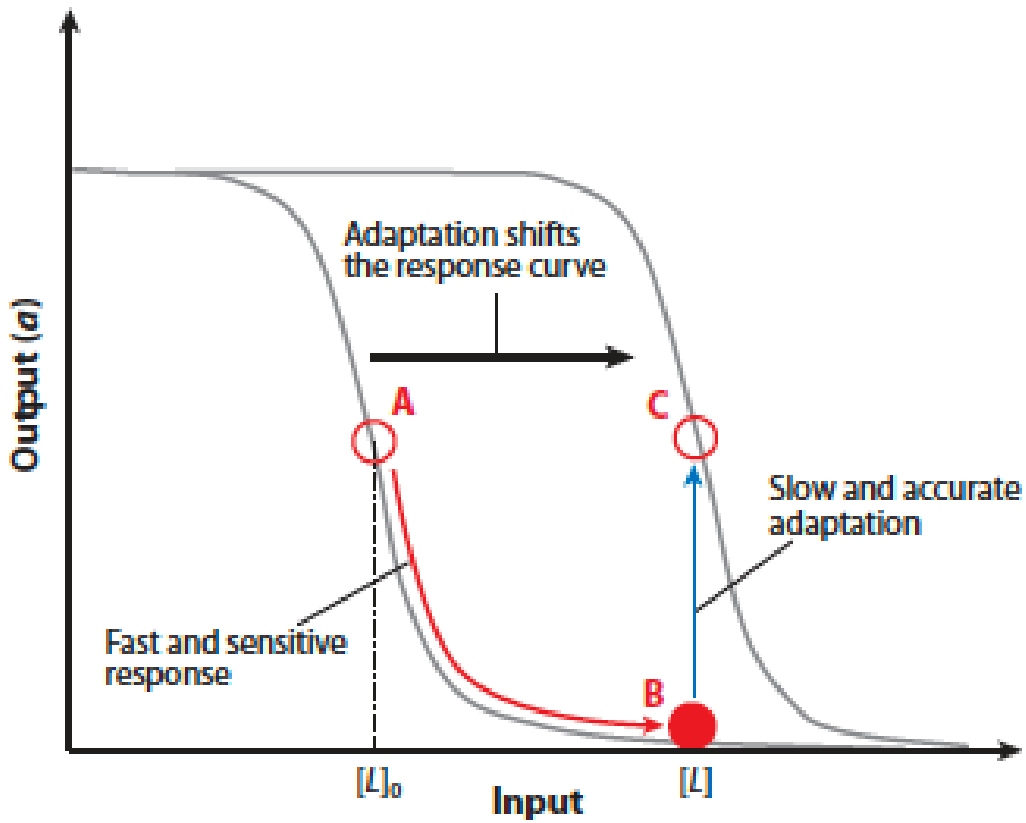
All-or-None Monod-Wyman-Changeux Model

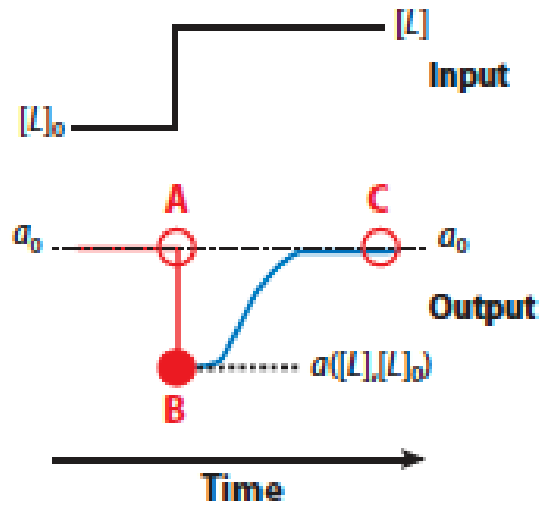
$$< a > \quad = \quad \frac{K_{eq}^{N}(1 + [L]/K_a)^{N}}{(1 + [L]/K_i)^{N} + K_{eq}^{N}(1 + [L]/K_a)^{N}}$$

$K_{eq} = \exp(-f_m(m))$ is the equilibrium constant.

Adaptation

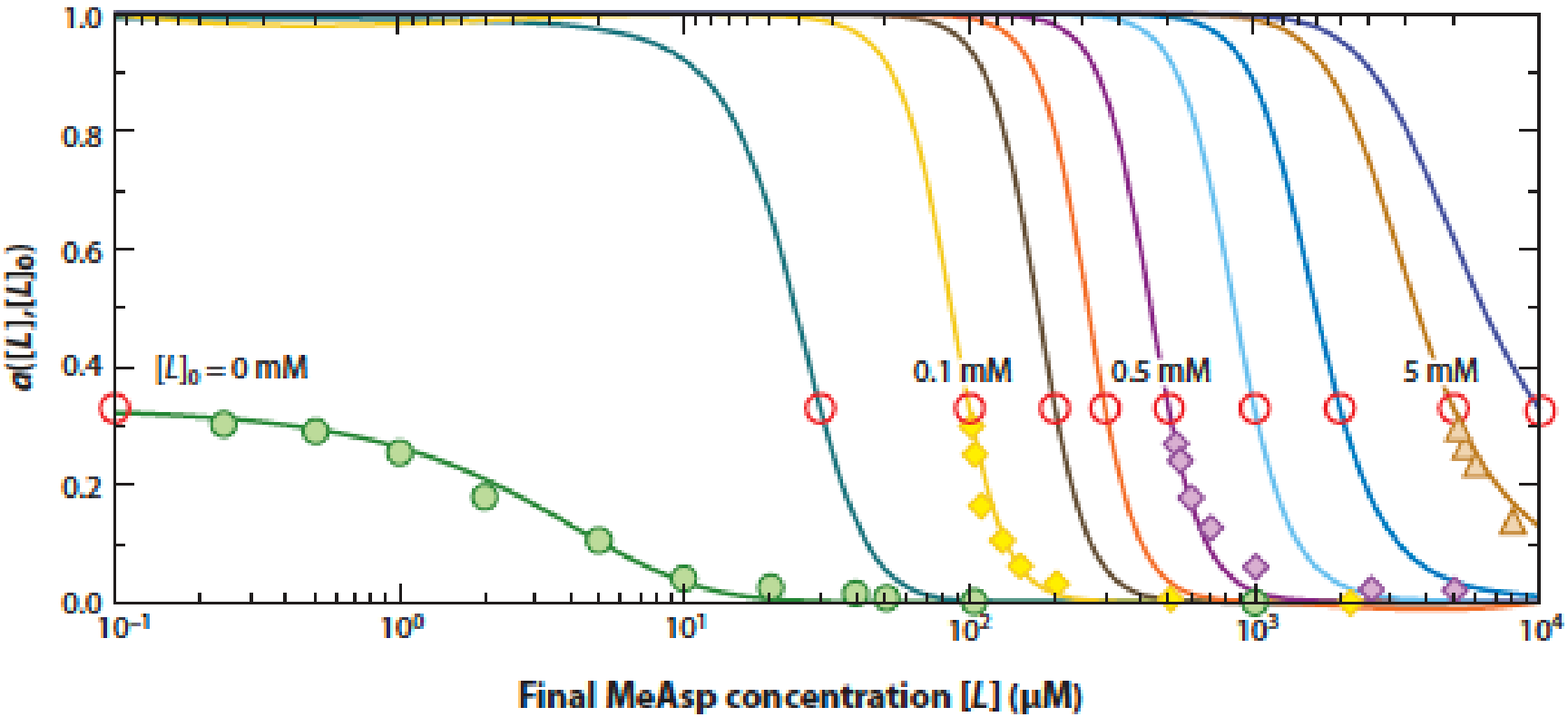
Adaptation





Tu, Y. (2013). Annu Rev Biophys 42: 337-359.

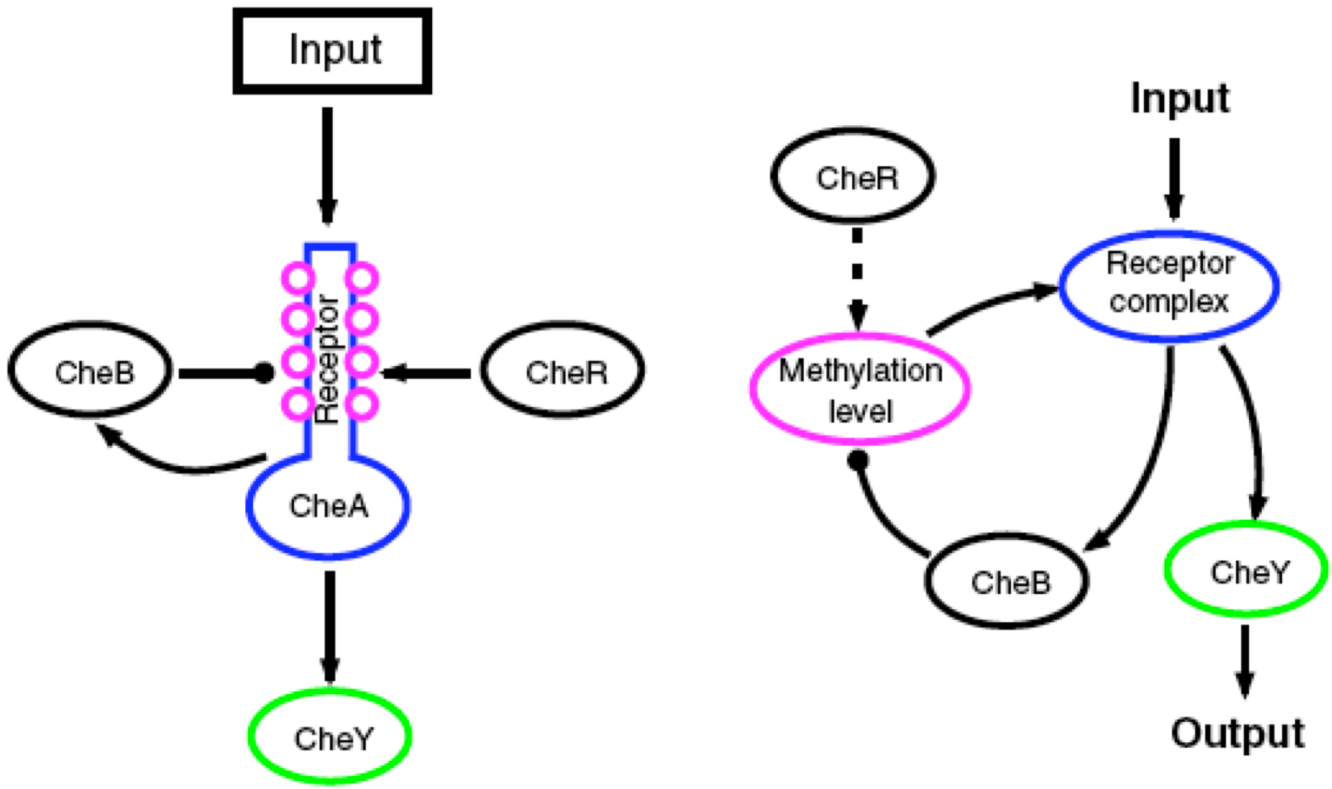
Adaptation in the *E. coli* chemotaxis pathway



The immediate response $a([L], [L]_0)$ to the presence of a (final) ligand (MeAsp) concentration $[L]$ for cells that are pre-adapted to background (initial) ligand (MeAsp) concentration $[L]_0$ as indicated in the figure.

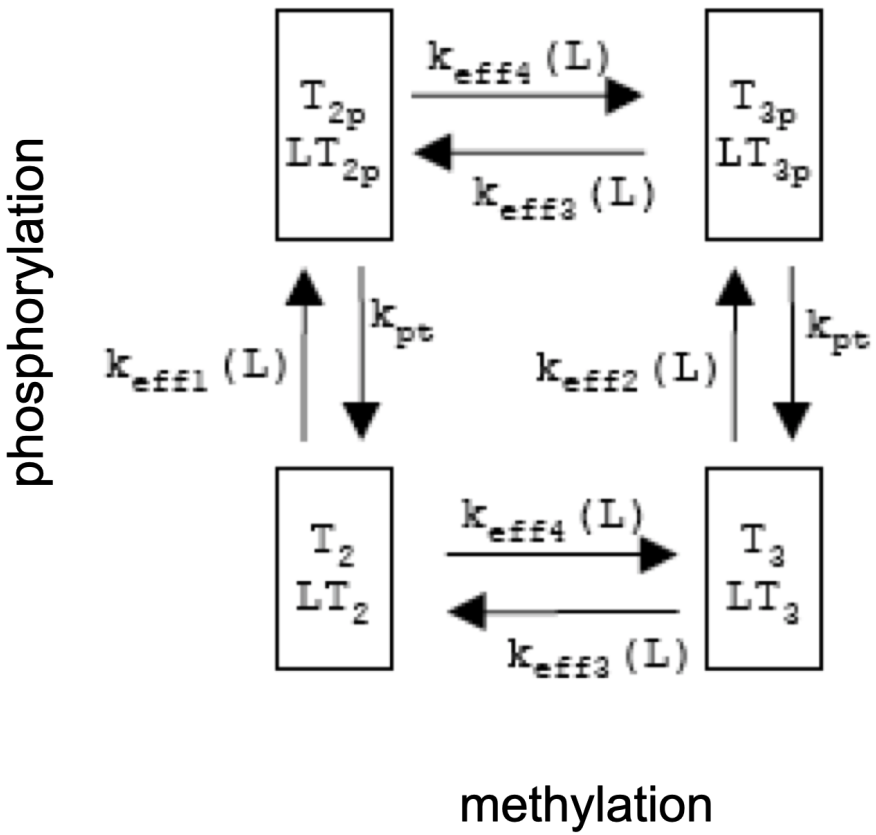
Tu, Y. (2013). Annu Rev Biophys 42: 337-359.

Escherichia coli chemotaxis signaling pathway



Ma et al (2009) Cell, 138, 760-773

Chemotaxis Signaling Models: Spiro Model

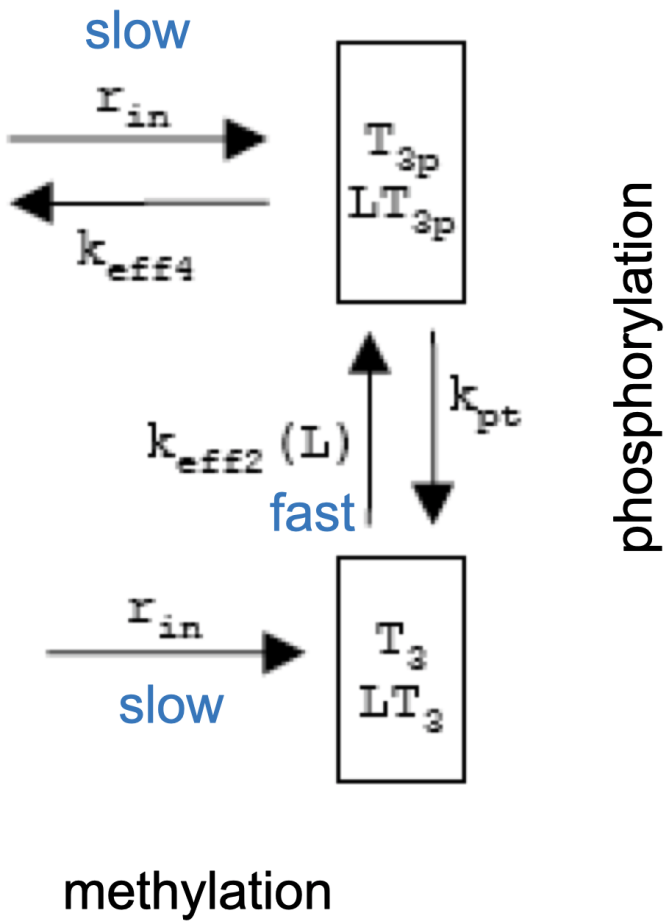


Perfect adaptation is observed only for small part of parameter space in Spiro model, i.e.

- Demethylation only of phosphorylated receptor [T3p, LT3p] (but not of [T3, LT3])
- Methylation at saturation, i.e. independent of [T2], [T2p] and ligand binding

Spiro et al. (1997), PNAS

Chemotaxis Signaling Models: Leibler Model



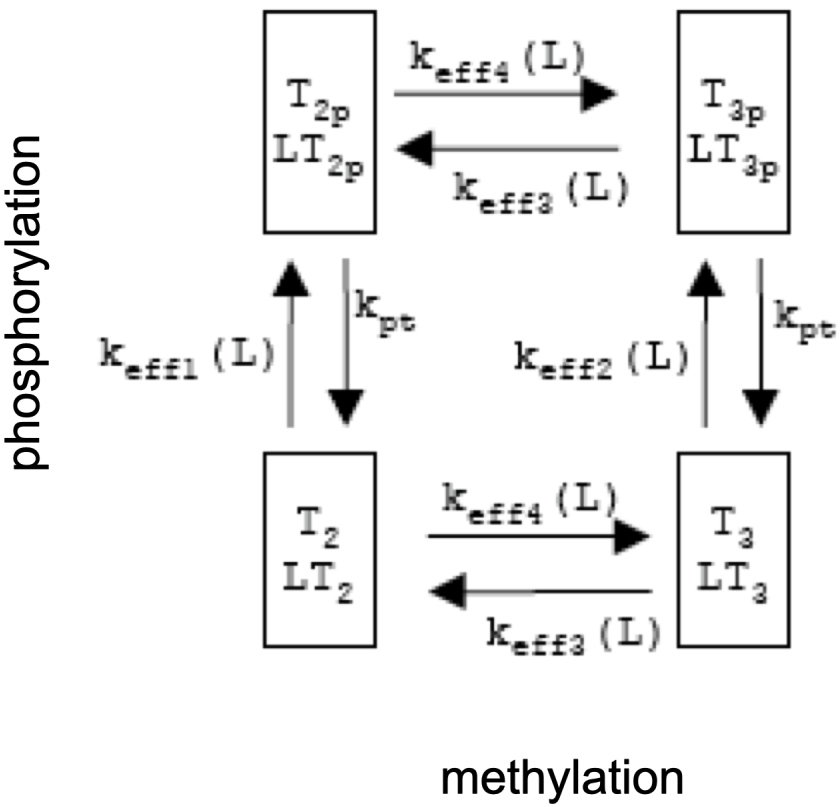
Barkai & Leibler (1997), Nature

Perfect adaptation is observed only for small part of parameter space in Spiro model, i.e.

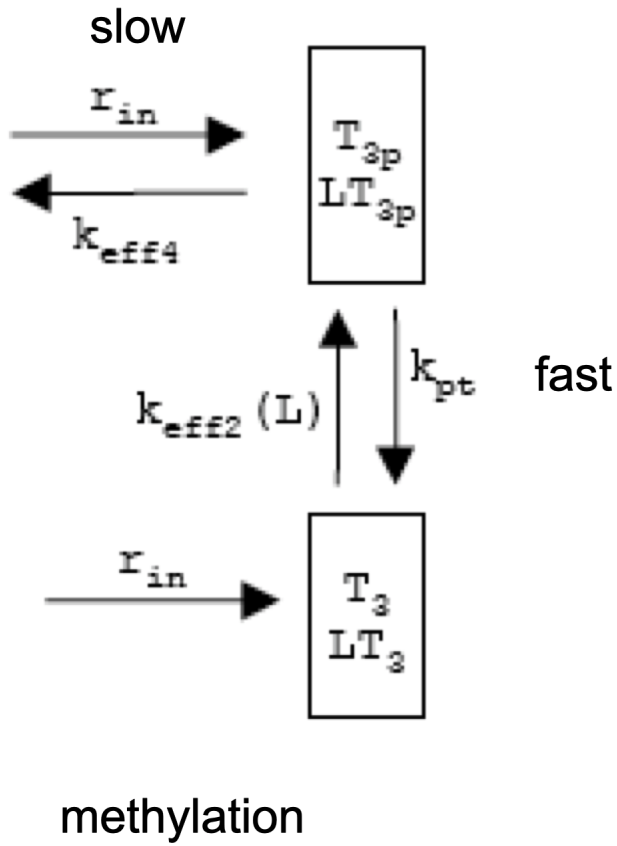
- Demethylation only of phosphorylated receptor [T3p, LT3p] (but not of [T3, LT3])
- Methylation at saturation, i.e. independent of [T2], [T2p] and ligand binding

Chemotaxis Signaling Models

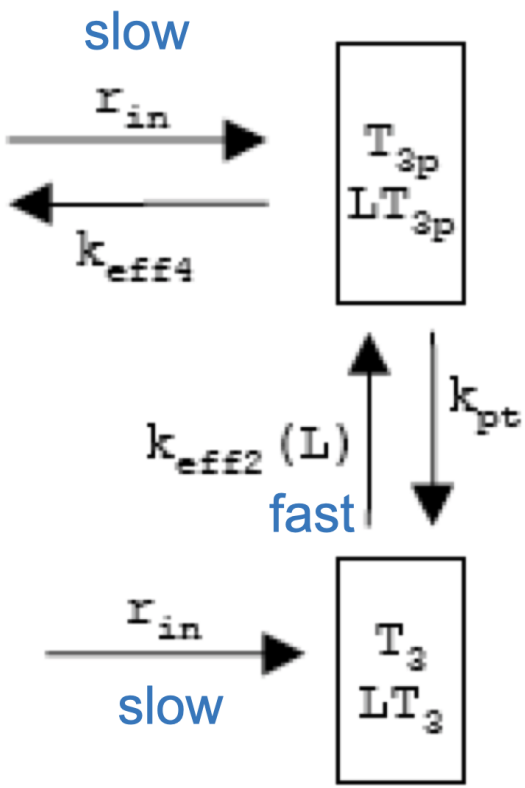
Spiro et al. (1997), PNAS



Barkai & Leibler (1997), Nature

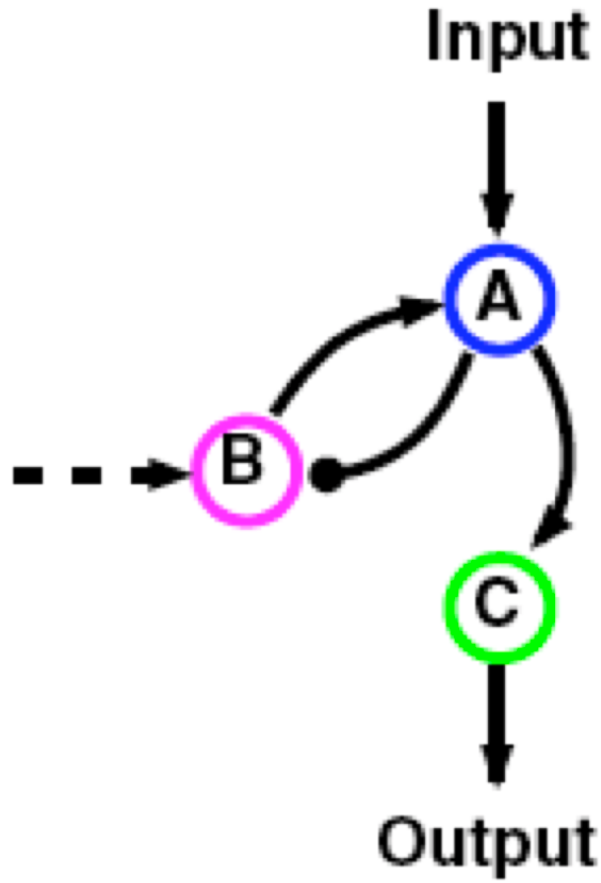


Negative Feedback with a buffering Node



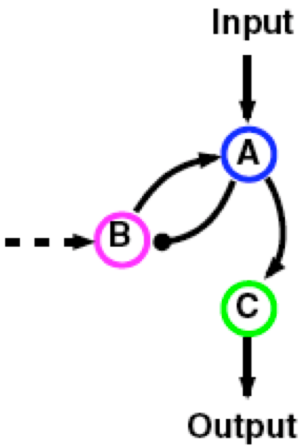
Barkai & Leibler (1997), Nature

phosphorylation



Ma et al (2009) Cell, 138, 760-773

The importance of saturation

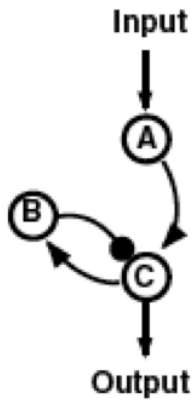


According to the Barkai-Leibler model, CheR works at saturation with a constant methylation rate for all receptor/CheA complexes, independent of the methylation level M.

On the contrary, CheB binds only to the active receptor/CheA complexes, resulting in a demethylation rate that is dependent only on the system's output (CheA activity).

Ma et al (2009) Cell, 138, 760-773

Negative Feedback with a buffer node



$$\frac{dA}{dt} = Ik_{IA}\frac{(1-A)}{(1-A)+K_{IA}} - F_A k'_{F_A A}\frac{A}{A+K'_{F_A A}}$$

$$\frac{dB}{dt} = Ck_{CB}\frac{(1-B)}{(1-B)+K_{CB}} - F_B k'_{F_B B}\frac{B}{B+K'_{F_B B}}$$

$$\frac{dC}{dt} = Ak_{AC}\frac{(1-C)}{(1-C)+K_{AC}} - Bk'_{BC}\frac{C}{C+K'_{BC}}$$

Consider saturating conditions for enzymes acting on node B (K_{CB}, $K'_{FBB} \ll 1$): $\frac{dB}{dt} = Ck_{CB} - F_B k'_{FBB}$

Negative Feedback with a buffer node

$$\frac{dB}{dt} = Ck_{CB} - F_B k'_{FBB} \tag{8}$$

In steady-state we then have

$$C^* = \frac{F_B k'_{FBB}}{k_{CB}} \tag{9}$$

allowing us to write

$$\frac{dB}{dt} = k_{CB}(C - C^*) \tag{10}$$

$$B = B^*(I_0) + k_{CB} \int_0^t (C - C^*) d\tau \tag{11}$$

Integral Control

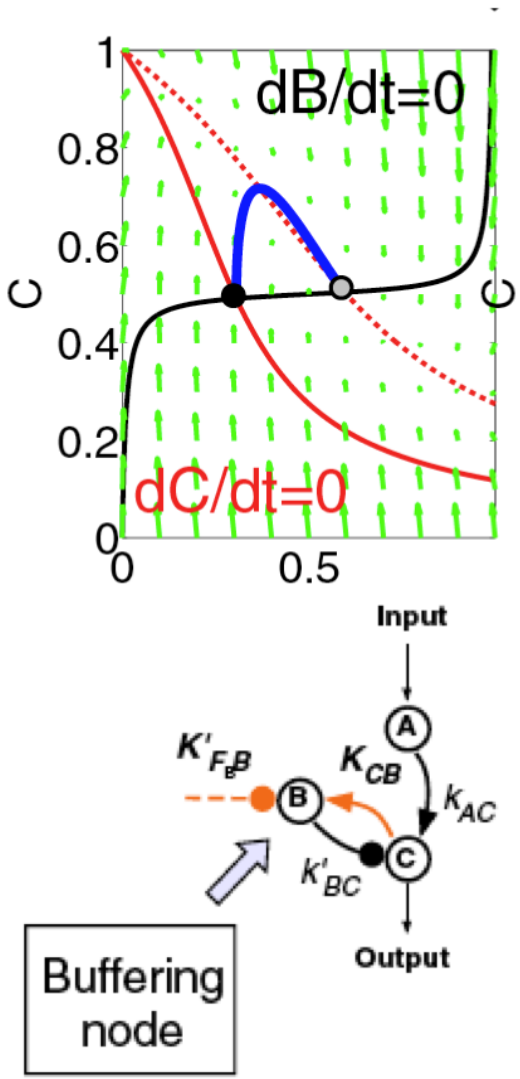
$$B = B^*(I_0) + k_{CB} \int_0^t (C - C^*) d\tau \tag{12}$$

Integral Control

This network design leads to adaptation by **integral control**.

All minimal negative feedback topologies with buffering node follow this integral control mechanism to achieve adaptation.

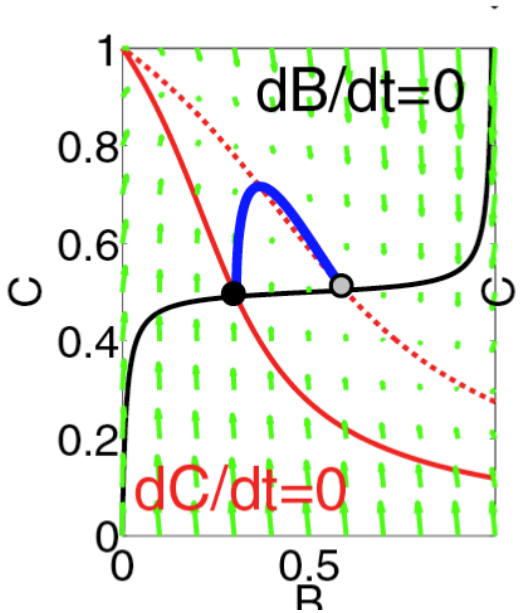
Sensitivity

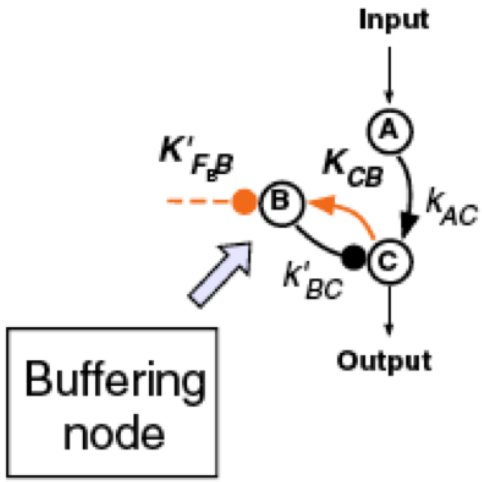


The ability to mount an appropriate transient response to the input change before achieving steady-state adaptation depends on the vector fields (dB/dt, dC/dt) in the phase plane.

A large excursion (large sensitivity) requires large initial $|dC/dt|$ and a small initial $|dB/dt|$ near the pre-stimulus steady-state.

Sensitivity

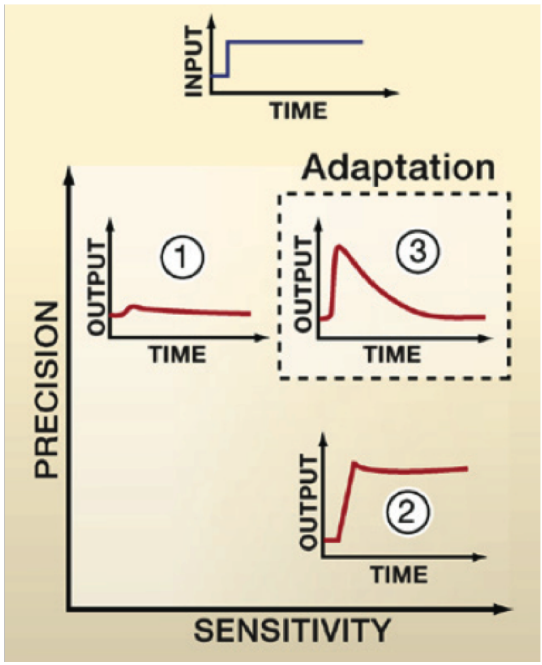




A large excursion (large sensitivity) requires that the response time of node C to the input change is faster than the adaptation time.

Slower adaptation time would require smaller rate constants in the C-B loop.

Summary



Precision

- Determined by Michaelis-Menten constants
- Need to be tuned to achieve operation in saturated regimes

Sensitivity

- Determined by timescales of the system

These two objectives can be tuned independently.

Thanks!!

Thanks for your attention!

Slides for this talk will be available at:
`http://www.bsse.ethz.ch/cobi/education`