Published in final edited form as:

Annu Rev Biophys. 2013 ; 42: 337–359. doi:10.1146/annurev-biophys-083012-130358.

Quantitative modeling of bacterial chemotaxis: Signal amplification and accurate adaptation

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Abstract

We review the recent developments in understanding bacterial chemotaxis signaling pathway by using quantitative modeling methods. The models are developed based on structural information of the signaling complex and the dynamics of the underlying biochemical network. We focus on two important functions of the bacterial chemotaxis pathway: signal amplification and adaptation. We give in-depth description of the structure and the dynamics of the mathematical models and their comparison with existing experiments, with emphasis on the predictability of the models. Finally, we point out several directions for future development of the modeling approach in understanding the bacterial chemo-sensory system.

Keywords

Bacterial Chemotaxis; Gradient Sensing; Receptor Clustering; Adaptation; Modeling

1 Introduction

Bacterial chemotaxis is the phenomenon in which bacterial cells sense their chemical environments and direct their motion towards attractants and away from repellents. It is one of the best studied sensory signal transduction systems in biology. It also serves as a model system for studying two-component signaling pathways that are ubiquitous in the bacterial kingdom and plants (for a recent review, see (16)).

As illustrated in Figure 1, the major players in the *E. coli* chemotaxis signal transduction pathway are the transmembrane methyl-accepting chemotaxis protein (MCP) receptors and 6 cytosolic proteins: CheA, CheB, CheR, CheW, CheY and CheZ. 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 increase the motor's clock-wise (CW) bias and the cells tumble probability. Like other biological sensory systems, the bacterial chemotaxis pathway enables the cell to adapt to persistent chemical stimuli. The chemotaxis adaptation in *E. coli* is facilitated by the methylation and demethylation of the chemoreceptors, catalyzed by CheR and CheB-P, respectively.

Despite its simplicity, bacterial chemotaxis exhibits rich biological behaviors such as robust adaptation, signal amplification, and ultra-sensitivity. Thus, it serves as an ideal model system, like the Hydrogen atom in the early days of quantum mechanics to advance systems biology by allowing us to test new theoretical ideas and develop system-level models to unravel general principles in biological information processing.

In this review, we describe some of the recent developments in quantitative modeling of *E. coli* chemotaxis. We first consider the two most important aspects of bacterial chemotaxis signaling, signal amplification and adaptation, followed by the description of an integrated model that captures both of these features, with emphasize on direct comparison with experimental data. We conclude by outlining some of the remaining challenges for future investigation.

2 Signal amplification

2.1 Receptor clustering and the Bray hypothesis

In bacterial chemotaxis, the membrane bound chemoreceptors can bind to chemo-effector ligand molecules and trigger down-stream response. There are a few tens of thousands of chemoreceptors in a single *E. coli* cell, depending on its physiological conditions and growth phase (25). In 1993, It was first discovered by Maddock and Shapiro that the chemoreceptors form large clusters near the cell pole with other cytoplasmic proteins, in particular CheA and CheW (26).

What may be the function of such large cluster of receptors? In 1998, it was first proposed by Bray and his coworkers that cooperativity due to the receptor clustering can lead to signal amplification in bacterial chemotaxis (8). It was hypothesized that the conformational change of a chemoreceptor in the cluster is not only induced by binding of its cognate ligand, its conformational state and henceforth its kinase activity can also be modulated by the conformational changes of the neighboring receptors in the cluster. This “infection” model, as Bray et al argued, can give rise to increased sensitivity as the binding of a ligand molecule to one receptor in the cluster can induce responses in many other receptors.

2.2 The two-state Ising model for the chemoreceptor cluster

The chemoreceptors form homo-dimer, each homo-dimer can bind with one lig-and molecule. In this paper, we use the term “(chemo)receptor” to represent such a chemoreceptor homo-dimer. The simplest model for describing the kinase activity of a chemoreceptor assumes that it has two discrete conformations: one active and the other inactive. This two-state model of the chemoreceptor maps onto the well-known Ising model in physics nicely: an active receptor corresponds to an up-spin and an inactive receptor corresponds to a down-spin. The cooperative receptor-receptor interactions between nearest neighbors in the receptor cluster can then be modeled as the Ising ferromagnetic spin-spin interaction that favors the neighboring receptors to have the same conformations (see sidebar for description of the Ising model).

Sidebar

A simple primer on the Ising model (to appear near section 2.2)

The Ising model describes a system of spins interacting between nearest neighbors in a graph (usually a regular lattice). First proposed for modeling ferromagnetism, the Ising model has become a powerful paradigm in studying collective phenomena and phase transitions. The energy function (Hamiltonian) of the system can be written as:

$$H(\vec{s}) = - \sum_{\langle ij \rangle} J s_i s_j - \sum_i h s_i,$$

where $s_i = 1, -1$ represents the up or down state of the spin at site i ; $\langle ij \rangle$ represents the nearest neighbor pair of spins at site i and j . J is the interaction (coupling) strength; h

represents the external magnetic field. The probability in a given spin configuration $\vec{s} \equiv (s_1, s_2, \dots)$ follows the Boltzmann distribution: $P(\vec{s}) = \exp[-H(\vec{s})/(K_B T)]/Z$, with K_B the Boltzmann constant and T the temperature; $Z = \sum_{\vec{s}} \exp[-H(\vec{s})/(K_B T)]$ is the partition function.

In the absence of spin-spin interaction ($J = 0$), the average spin $\langle s \rangle$ has a simple sigmoidal dependence on the external field h : $\langle s \rangle = \tanh[h/(K_B T)]$. In the presence of ferromagnetic interaction ($J > 0$), the spins are correlated with each other, which gives rise to more sensitive dependence of $\langle s \rangle$ on h near $h = 0$. Quantitatively, the susceptibility $\chi \equiv d\langle s \rangle/dh|_{h=0}$ 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.

In the Ising model, a magnetic field h favors the up-spin state over the down-spin state by introducing an energy difference h between the two states. To determine the effective “magnetic” field for the receptor cluster, we study the 4-state model of the chemoreceptor by considering the receptor’s ligand binding status explicitly. As shown in Fig. 2, the state of a receptor can be characterized by two 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 in each of the four state is given by $P(a, l)$. The ligand dissociation constants for the active ($a = 1$) and inactive ($a = 0$) receptor are defined as 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 state only depends on the receptor methylation level m . In equilibrium steady state, the probabilities in the four states satisfy the following relations:

$$\frac{P(0, 1)}{P(0, 0)} = \frac{[L]}{K_i}, \quad \frac{P(1, 1)}{P(1, 0)} = \frac{[L]}{K_a}, \quad \frac{P(0, 0)}{P(0, 1)} = e^{-f_m(m)}, \quad (1)$$

where $[L]$ is the ligand concentration. Together with the normalization condition $\sum_{a,l} P(a, l) = 1$, the steady state probabilities can be fully determined and the average activity can be obtained:

$$\langle a \rangle = P(1, 0) + P(1, 1) = \frac{e^{f_m(m)}(1 + [L]/K_a)}{1 + [L]/K_i + e^{f_m(m)}(1 + [L]/K_a)}. \quad (2)$$

Let Δf be 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 $\langle a \rangle = (1 + e^{-\Delta f})^{-1}$. From Eq. (2), we obtain the expression for Δf , which plays the role of magnetic field in analogy to the Ising model:

$$\Delta f(m, [L]) = f_m(m) + f_L([L]), \quad \text{with} \quad f_L([L]) \equiv \ln \frac{1 + [L]/K_a}{1 + [L]/K_i}. \quad (3)$$

From Eq. (3), Δf has two contributions: an “internal” term $f_m(m)$, which depends on the receptor’s internal state, i.e., its methylation level m ; and an “external” term f_L , which depends on the “external” environment, i.e., the ligand concentration $[L]$. The form of $f_L([L])$ given in Eq. (3) is also quite informative. f_L goes from 0 to $\ln(K_i/K_a)$ as $[L]$ increases from 0 to ∞ . The two dissociation constants K_a and K_i essentially set the range of signal to which the system responds sensitively.

Taken together, we can describe the kinase activity of a chemoreceptor cluster with total number of receptor N_t by using an Ising-type model. The activity of each receptor $i \in [1, N_t]$

in the cluster is characterized by a two-state variable $a_j = 0, 1$. Each neighboring receptor pair in the cluster interact with each other with an interaction strength J , which favors the neighboring pair to have the same activity (0 or 1). The activity of an individual receptor is also affected by an effective magnetic field Δf . The free energy for a given activity pattern $\vec{a} \equiv (a_1, a_2, \dots, a_{N_p})$ is given by:

$$H_i(\vec{a}) = - \sum_{(i,j)} J \times (2a_i - 1) \times (2a_j - 1) - \sum_i \Delta f(m_i, [L]) \times a_i, \quad (4)$$

where m_i is the methylation level of the receptor i , and Δf is given by Eq. (3).

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 $P(\vec{a}) = \exp(-H(\vec{a}))/Z$, where the thermal energy $k_B T$ 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 (MFT) approximation.

The basic Ising-type model described here can be easily extended to describe mixed receptor cluster. There are five different types of MCP receptors in *E. coli*. The serine sensing receptor Tsr and the aspartate sensing receptor Tar are the most abundant, which together constitute ~90% of the total MCP population in a cell. For a given receptor i , $[L]$ in Δf in Eq. (4) should be understood as the concentration of the ligand that can bind with receptor i . The receptor-receptor interaction strength J can also be different between different types of receptors. Other complications include the dependence of J , K_a , and K_i on the methylation level m , which needs to be considered to obtain quantitative agreements with experimental data (30,31,33,45).

2.3 The all-or-none Monod-Wyman-Changeux (MWC) model

An alternative approach for describing receptor cooperativity in the cluster is to divide it into smaller sub-clusters. Within each sub-cluster, all the receptors are tightly coupled and always in the same state (either active or inactive); whereas the receptors from different sub-clusters do not correlate with each other at all. This is essentially the all-or-none model proposed by Monod, Wyman, and Changeux (MWC) to describe allosteric protein interaction in protein complex with multiple subunits (35). The MWC model corresponds to the Ising model with infinite interaction strength $J = \infty$ between receptors within the same sub-cluster, and no interaction $J = 0$ between receptors from different sub-clusters. The difference between the MWC model and the Ising model is illustrated in Figure 3.

In the MWC model, the degree of cooperativity is given explicitly by N , the size of the all-or-none sub-cluster. In comparison, the degree of cooperativity in the Ising model can be described by a correlation length which increases with the receptor interaction strength J . This simplification makes the MWC model analytically solvable. From Eq. (4), in an all-or-none MWC cluster with N receptors, the free energy difference between the all-active and the all-inactive state is simply $N\Delta f(m, [L])$. Therefore, the average activity can be obtained analytically:

$$\langle a \rangle = (1 + \exp(-N\Delta f))^{-1}, \quad (5)$$

which together with the expression for $\Delta f(m, [L])$ leads to the explicit expression for $\langle a \rangle$:

$$\langle a \rangle = \frac{L(1+[L]/K_i)^N}{L(1+[L]/K_i)^N + (1+[L]/K_a)^N}, \quad (6)$$

where $L = \exp(-Nf_m(m))$ is the equilibrium constant. Eq. (6) is the familiar expression for average activity of an all-or-none MWC complex (12,35).

2.4 Comparison with experiments

The Ising-like model was first used to describe receptor cooperativity by Duke and Bray (13). However, quantitative modeling of *E. coli* chemotaxis took off later when quantitative data became available, in particular the in vivo measurements of the kinase activity of the intact receptor cluster developed in the Berg lab by using the Förster resonance energy transfer (FRET) technique (47). These FRET measurements were done for different stimuli in wild type cells and different mutant strains. They have generated a rich set of quantitative data to test and refine the idea of high cooperativity enabled by receptor clustering.

The first quantitative explanation of the FRET data was done using a Ising-type model by Mello and Tu (30), who showed that the input-output data (measured by FRET) for both wt cells and various CheRB (adaptation disabled) mutants can be explained when and only when receptor-receptor interactions, including those between different types of receptors (such as Tar and Tsr), are included in the model. In Figure 4, quantitative agreements between model (dotted lines) and data (symbols) are shown for six mutant strains in which Tar and Tsr are fixed in different methylation states.

In later experiments, Sourjik and Berg measured the chemotaxis input-output responses for cells with different expression levels of MCP, CheA, and CheW (48); and they first used the classical MWC model to describe the cooperativity of a cluster of identical receptors. Rao et al (39) also applied the MWC model to describe the activity of *E. coli* receptor cluster, but with independent energy parameters for different mixed receptor clusters. A rigorous extension of the classical MWC model for clusters with identical subunits to a heterogeneous cluster is developed by Mello and Tu (32). This heterogeneous MWC model was used to explain the experimental data quantitatively and to infer the functional receptor cluster size N and its dependence on the MCP expression level. Keymer et al (in the Wingreen lab) developed the same MWC model for mixed receptor cluster and pointed out the different regimes of the model as the energy parameters change (14,19,45).

Due to its simplicity, the MWC model has been popular and quite successful in describing the receptor cooperativity. However, because of the all-or-none assumption made in the MWC model, it fails to describe processes that depend on activities of individual receptors in the cluster, in which case the microscopically more accurate Ising-type model has to be used (24). We discuss this limitation of the MWC model later in this paper.

3 Adaptation in bacterial chemotaxis

Bacterial chemotaxis, like other biological sensory systems, can adapt to permanent changes in the environment. Due to its relative simplicity, *E. coli* chemotaxis has become a model system to study sensory adaptation.

3.1 Robustness versus fine-tuning: the Barkai-Leibler model

It was observed by Berg and Brown some 40 years ago that upon a sudden increase in the concentration of chemo-attractant aspartate, a cell's tumbling frequency first decreases before it recovers and eventually returns back to its pre-stimulus level (5). The adapted value of the tumbling frequency remains the same for a wide range of the stimulus strength

(aspartate concentration). This accurate adaptation, which has been observed in individual cells, is remarkable given the large variations in the concentrations of the key biomolecules among individual cells (22). How can such accurate adaptation occur in a biochemical network whose components can have large cell to cell variations? This question motivated Barkai and Leibler (4) to study the mechanism for *E. coli* chemotaxis adaptation in particular and the robustness of biochemical networks in general.

At the molecular level, *E. coli* chemotaxis adaptation is carried out by receptor methylation and demethylation, catalyzed by the enzymes CheR and CheB respectively. The state of each receptor can thus be represented by three variables: its activity a , its ligand occupancy I , and its methylation level m . A general dynamic model of a receptor in the phase space spanned by (a, I, m) was studied by Spiro et al (49). As pointed out by Barkai and Leibler (4), accurate adaptation can only be achieved in such a general model for receptor dynamics by fine-tuning some of the key parameters of the model. Such fine tuning, however, is unrealistic in noisy biological systems.

Instead of fine-tuning the kinetic parameters and various enzyme concentrations to account for the accurate adaptation, Barkai and Leibler (BL) made two key assumptions in their model: 1) the methylation enzyme CheR works at saturation with the maximum catalytic speed V_{max}^2 ; 2) the demethylation enzyme only works on active receptor with the maximum catalytic speed V_{max}^B and a Michaelis-Mentum constant (per receptor) K_b . With these two simple assumptions, the BL model allows accurate adaptation even when the concentrations of various key components, such as CheR and CheB, in the network change by orders of magnitude.

Intuitively, the accurate adaptation in the BL model can be understood by looking at the rate of change of the receptor methylation level m :

$$\frac{dm}{dt} \approx V_{max}^R - \frac{V_{max}^B \langle a \rangle}{K_b + \langle a \rangle}, \quad (7)$$

where $\langle a \rangle$ is the average receptor activity. When the system adapts, it reaches a steady state with $dm/dt = 0$, leading to the adapted value of $\langle a \rangle = \frac{K_b V_{max}^R}{V_{max}^B - V_{max}^R}$, which is independent of the ligand concentration. Thus, accurate adaptation is achieved without fine-tuning any parameters of the system and the ability to adapt accurately is a robust property of the underlying biochemical network.

The robustness of the accurate adaptation in *E. coli* chemotaxis was subsequently tested experimentally by varying the expression levels of the key chemo-taxis genes, such as CheR, CheB, and CheZ. As shown in the work by Alon et al (2), although the CW bias of the adapted state (CW bias) and the adaptation time vary with the gene expression changes, the adaptation accuracy remains high for more than ten-fold changes in the expression levels of these key proteins.

It was first pointed out by Yi et al (54) that the way *E. coli* maintains its adapted state accurately, as demonstrated in Eq. (7), is similar to the well known integral control mechanism in control theory. In another study with detailed analysis of a generic model (36) of the underlying biochemical reactions, a full set of conditions for achieving perfect or near-perfect adaptation were derived (29). The two key assumptions in the BL model were found to be sufficient, but not necessary. For example, the methyltransferase enzyme CheR does not have to work at saturation (in fact, it indeed does not), as long as it favors the active receptors as its substrate, accurate adaptation can be achieved. Additional conditions beyond

those discussed by Barkai and Leibler were also found (24,28, 29, 54). Violations of these conditions can explain the inaccuracy in adaptation (5,28).

Generally, the study on adaptation accuracy in *E. coli* chemotaxis has led to the idea of robustness as a fundamental property of cellular biochemical networks. Specifically for bacterial chemotaxis, it raises the question of why the system needs to have accurate adaptation in the first place.

3.2 The effect of accurate adaptation: maintaining the high gain

What is the benefit of accurate adaptation? To answer this question, we first look at the sensitivity of the receptor cluster in response to a change in ligand concentration by using the MWC model, i.e., Eq. (6). At a background ligand concentration $[L]_0$, the receptors have an average methylation level m_i and the (average) activity of the system is a_0 :

$$a_0 = \frac{L_0(1+[L]_0/K_i)^N}{L_0(1+[L]_0/K_i)^N + (1+[L]_0/K_a)^N}, \quad (8)$$

where $L_0 = \exp(Nf_m(m_i))$ is the equilibrium constant for the MWC receptor cluster that has adapted to $[L]_0$.

Upon a ligand concentration change from $[L]_0$ to $[L] \equiv [L]_0 + \Delta[L]$, the immediate activity change Δa is:

$$\Delta a = \frac{L_0(1+([L]_0+\Delta[L])/K_i)^N}{L_0(1+([L]_0+\Delta[L])/K_i)^N + (1+([L]_0+\Delta[L])/K_a)^N} - a_0, \quad (9)$$

where we have used the fact that receptor methylation level (m) changes slowly and therefore the equilibrium constant $L \approx L_0$ remains unchanged at the time scale of the fast activity response. For relatively small ligand concentration change $\Delta[L] \ll [L]_0$ and by using the expression for a_0 from Eq. (8), we have:

$$\Delta a \approx -N \times a_0(1-a_0) \times \frac{(K_i-K_a)\Delta[L]}{(K_i+[L]_0)(K_a+[L]_0)}. \quad (10)$$

The first term in the above expression for Δa indicates that the size N of the all-or-none MWC receptor cluster directly amplifies the response. The second term $a_0(1-a_0)$ on the right hand side of Eq. (10) shows that the response also depends on the adapted pre-stimulus activity a_0 . Specifically, the response vanishes near the two extreme values $a_0 = 0, 1$ and is maximum when a_0 is close to its mid-point value $a_0 \approx 1/2$.

However, as shown in Eq. (8), a_0 depends on $[L]_0$ and only remain near 1/2 for a small range of $[L]_0$ if L_0 is fixed. Therefore, accurate adaptation is needed to restore the activity a to a_0 in order to maintain the high signal amplification (gain). Essentially, adaptation drives a (slow) change in m and consequently a change in the equilibrium constant L_0 , which balances the change of the stimulus and restore the activity back to a_0 . As shown in Fig. 5a, adaptation corresponds to a shift of the response curve so that the adapted activity at the new ligand concentration returns to a_0 .

From this intuitive picture of accurate adaptation, the adapted equilibrium constant becomes

$L_0 = \frac{a_0}{1-a_0} \times \frac{(1+[L]_0/K_a)^N}{(1+[L]_0/K_i)^N}$ when the system adapts to the ambient ligand concentration $[L]_0$. The value of L_0 can then be used to predict the immediate response of the system upon a change

of ligand concentration from $[L]_0$ to $[L]$. Let us define $a([L], [L]_0)$ as the activity right after the ligand concentration change from $[L]_0$ to $[L]$, we have:

$$a([L], [L]_0) = \frac{a_0(K_a + [L]_0)^N (K_i + [L])^N}{a_0(K_a + [L]_0)^N (K_i + [L])^N + (1 - a_0)(K_a + [L]_0)^N (K_i + [L])^N}. \quad (11)$$

This somewhat complicated looking expression only contains 4 essential parameters: N , a_0 , K_a , K_i , each with a clear biological definition. Eq. (11) can be used to fit a set of FRET measurements of responses of cells in different ambient concentration of MeAsp (47). The agreement as shown in Fig. 5b is quite impressive considering the few number of parameters used in the model and the large amount of data fitted (33). The parameters obtained from the fitting are also quite revealing. N is found to be ~ 6 , which means there are approximately 6 Tar dimers in the MWC cluster; $K_i \approx 18 \mu M$ and $K_a \approx 3 mM$ spans more than 2 orders of magnitude; and $a_0 \approx 1/3$ is near the mid-point of the response curve.

3.3 Putting the two pieces together: the standard model for *E. coli* chemotaxis signaling

Based on the simplified dynamics of receptor methylation/demethylation (as illustrated in Fig. 6a), we developed a coarse-grained model, where the *E. coli* chemosensory circuit can be described by three dynamic variables: the ligand concentration $[L](t)$ is the input, the average kinase activity $a(t)$ is the output, and the average methylation level of the receptors $m(t)$ is the controller, as shown in Fig. 5b. The kinase activity is inhibited by binding of attractant ligand, the system adapts by receptor covalent modification (methylation/demethylation), which is itself controlled by the receptor activity through a negative feedback. Here, we focus on studying pathway kinetics at the methylation time scale, the most relevant time scale for bacterial motion (run time ~ 1 sec). Since the time scales for ligand binding and kinase response are much faster than the receptor covalent modification time, we can treat the receptor kinase activity and ligand binding with a quasi-equilibrium approximation. Specifically, we can ignore the dynamics of a and express it as a function of m and $[L]$. Here, we use the MWC model as given in Eq. (5) to describe the average activity of the highly cooperative chemoreceptors. Denoting the rate of change of the average receptor methylation level m by a general function F , we can write the full model of the chemotaxis circuit as:

$$\frac{dm(t)}{dt} = F(a), \quad a = \left[1 + \exp(N(f_m(m) + \ln \frac{1 + [L]/K_i}{1 + [L]/K_a})) \right]^{-1}. \quad (12)$$

The net methylation rate F (methylation rate minus the demethylation rate) depends on the details of the methylation/demethylation kinetics in vivo, which are not well understood quantitatively at present. In principle, F can depend on m and $[L]$ directly. However, from the observed near perfect adaptation (at least to MeAsp) (4, 5, 29, 54), the function F should only have strong dependence on a . To see this, let us assume F only depends on a in a monotonically decreasing fashion, i.e., $F'(a) < 0$. Then, in steady state, we have $dm/dt = F(a) = 0$, which leads the system to a single fixed point at $a = a_0$, where a_0 is the root of the $[L]$ -independent function F : $F(a_0) = 0$. This $[L]$ -independent fixed point is globally stable as $F'(a) < 0$ and $da/dm > 0$. This means that the kinase activity always adapts to the same level independent of $[L]$, i.e., perfect adaptation.

Despite its simplicity, our model captures the essential features (receptor cooperativity, effects of receptor methylation on kinase activity, perfect adaptation) of the underlying pathway at the appropriate time resolution for studying system-level properties of bacterial

chemotaxis. We call it the standard model of *E. coli* chemotaxis. The validity of the model is tested by direct experimental measurements described in the next section.

4 Responses to time-varying stimuli: testing the standard model

In their natural environment, cells need to extract useful information from complex temporal signals that can vary widely in intensity and time scale. The standard model Eq. (12) provides a quantitative system-level description of the chemotaxis signaling pathway dynamics. It can be used to predict *E. coli* chemo-taxis responses to arbitrary temporal signals and to reveal the way a *E. coli* cell processes time-varying signals.

4.1 Responses to exponential ramps: measuring the methylation rate function $F(a)$

During an ramp stimulus, the ligand concentration $[L]$ increases (or decreases) continuously, which triggers the increase (or decrease) of the receptor methylation level as the system tries to adapt to the preferred activity level a_0 . However, due to the slow adaptation dynamics, the methylation lags behind the signal and the activity settles to a level different from a_0 .

The ramp response can be determined quantitatively by the standard model (Eq. 12). For an exponential ramp: $[L] = [L]_0 e^{rt}$ with r the ramp rate and in the region where $K_i \ll [L] \ll K_a$, we have $f_L \approx \ln([L]/K_i) = rt + \ln([L]_0/K_i)$, which varies linearly with time. To reach a steady state with a constant activity $a = a_c$, the total free energy difference $f_t = N(f_m + f_L)$ should be a constant independent of time, i.e., $df_t/dt = 0$, which means $df_m/dt = -df_L/dt = -r$. Given that $f_m(m) = -\alpha(m - m_0)$ depends on m linearly, we deduce that m should change linearly with time $\dot{m} = r/\alpha$. From the standard model, in the steady state with activity a_c , the receptor methylation level varies with a rate $F(a_c)$: $\dot{m} = F(a_c)$. Combining these two expressions for $\dot{m}$, we obtain a relation between the steady state activity a_c and the ramp rate r :

$$F(a_c) = r/\alpha, \quad \text{or} \quad \alpha_c = F^{-1}(r/\alpha) \quad (13)$$

where F^{-1} is the inverse function of F .

From this simple analysis of the standard model, we see that in response to an exponential ramp, the kinase activity, after an initial transient, settles to a constant level $a_c = F^{-1}(r/\alpha)$ that depends on the ramp rate r . Since the function $F(a)$ is a monotonically decreasing function of a , a up-ramp (down-ramp) with $r > 0$ ($r < 0$) leads to a down (up) shift in a , which agrees with the ramp experiments by Block et al (7), where the responses to ramps were observed by measuring the motor bias.

The dependence of the steady-state activity a_c on the ramp rate r , discovered by the analytical solution Eq. (13), provides a remarkable connection between the ("microscopic") methylation kinetics and the ("macroscopic") exponential ramp responses (7). The measured responses (shifted activity) for the different ramp rates can thus be used to determine the full functional form of $F(a)$. Indeed, the theoretical results from the standard model have motivated a thorough study of the ramp response by using FRET (43). The measured constant activity shifts in response to exponential stimuli, as shown in Figure 7 a&b, not only confirm the standard model, they also determined the quantitative form of the methylation rate function $F(a)$.

The form of $F(a)$ is quite informative of the underlying receptor methylation (demethylation) dynamics. As shown in Fig. 7 b&c, $F(a)$ has a large linear regime near its fixed point $a = a_0$ with a small slope, indicating a weak control or high sensitivity near the preferred activity level. Near the two extreme values $a = 0$ and $a = 1$, F changes much faster, indicating a much stronger control there. We note that the assumptions used in the Barkai and Leibler

model (4) would lead to a form of $F(a)$ expressed in Eq. (7), which is inconsistent with Fig. 7c. Regardless of the molecular details of the adaptation process, however, we now have all the parameters and functions determined in the standard model to predict the response to any time-varying signal without adjustable parameters.

4.2 Responses to oscillatory signals: how does *E. coli* compute time derivative?

To understand the response to signals that varies with different time scales, we study the standard model with an oscillatory signal $[L](t) = [L]_0 \exp[A_L \sin(2\pi \nu t)]$. We consider the case where the range of the ligand concentration is well within the most sensitive regime of the sensory system: $K_a \gg [L]_0 \exp(\pm A_L) \gg K_i$. The exponentiated sine-wave form for $[L]$ leads to a simple form for $f_L \approx \ln([L]/K_i) = \ln([L]_0/K_i) + A_L \sin(2\pi \nu t)$.

The kinase responses as well as the corresponding methylation dynamics can be obtained by linearizing the standard model around $a = a_0$:

$$\frac{d\Delta m}{dt} = F'(a_0)\Delta a, \quad \Delta a = Na_0(1-a_0)[\alpha\Delta m - A_L \cos(2\pi \nu t)], \quad (14)$$

where $\Delta a \equiv a - a_0$ and $\Delta m \equiv m - m_i$ with $m_i = m_0 + (\alpha N)^{-1} \ln[a_0/(1-a_0)] + \alpha^{-1} f_L([L]_0)$. Expressing $\Delta m(t)$ and $\Delta a(t)$ as: $\Delta m = \text{Re}(A_m \exp(2\pi i \nu t))$, $\Delta a = \text{Re}(A_a \exp(2\pi i \nu t))$, where $i = \sqrt{-1}$ and "Re" stands for real part, we can solve for A_m and A_a :

$$A_a = \frac{i\nu c_a}{i\nu + \nu_m} A_L, \quad A_m = \frac{\nu_m c_m}{i\nu + \nu_m} A_L, \quad (15)$$

where $c_a \equiv -Na_0(1-a_0)$, $c_m \equiv \alpha^{-1}$, and the characteristic frequency $\nu_m \equiv -(\alpha F'(a_0)Na_0(1-a_0))/2\pi$ are all pre-determined constants. The kinase activity response can be characterized by its amplitude $|A_a|$ and its phase lag φ_a :

$$|A_a| = \frac{\nu c_a}{\sqrt{\nu^2 + \nu_m^2}} A_L; \quad \varphi_a = \pi/2 + \tan^{-1}(\nu/\nu_m). \quad (16)$$

To test these theoretical predictions, kinase activity responses to exponentiated sine-waves were measured directly by using FRET (43), as shown in Figure 8. Both the amplitude and the phase shift of the measured kinase response for different frequency ν are in agreement with the theoretical predictions from Eq. (16) without any fitting parameters.

What do Eq. (16) and the experiments shown in Fig. 8 tell us about the cell's signal processing dynamics? For low frequency signals with $\nu \ll \nu_m$, we have: $A_a \approx \frac{c_a}{\nu_m} (i\nu A_L)$, $A_m \approx c_m A_L$, which means that the adaptation dynamics can keep up with the temporal variation of the signal and the kinase activity is proportional to the time-derivative of the signal ($i\nu A_L$ in frequency space). Thus, the cell computes the derivative of $\ln[L]$ for $\nu \ll \nu_m$. For high frequency signals with $\nu \gg \nu_m$, we have: $A_a \approx c_a A_L$, $A_m \approx c_m \nu_m (A_L/i\nu)$, which means that the methylation kinetics can no longer keep up with the fast signal and the kinase activity is determined by the instantaneous signal. The cell loses its ability to compute the time-derivative of the signal for $\nu \gg \nu_m$.

4.3 The Weber-Fetchner law and logarithmic sensing in *E. coli* chemotaxis

The Weber-Fetchner (WF) law, which was first proposed in the study of human response to a physical stimulus (like weight), holds that the just noticeable difference between two stimuli is approximately proportional to the average stimuli, and the perceived sensation is proportional to the logarithm of the stimulus intensity. The WF law applies (approximately)

in many sensory systems, including vision and sound. The WF law was first suggested to describe bacterial chemotaxis phenomenologically by Mesibov et al in their classical capillary assay experiments (34). It was shown by Tu et al (51) that the WF law in *E. coli* chemotaxis comes out naturally from the standard model of the underlying signaling pathway.

The response of a cell to a sudden, small change in stimulus $\Delta [L]$ after it has adapted to a stimulus $[L]_0$ can be calculated from the standard model. By using $K_i \ll [L]_0 \ll K_a$ in Eq. (10), we derive the WF law:

$$\Delta a = -k \times \frac{\Delta [L]}{[L]_0}, \quad (17)$$

with the Weber-Fechner constant k given analytically: $k = Na_0(1 - a_0)$, which depends on the receptor cluster size N and the adapted activity a_0 .

In a wide range of ligand concentration $K_i \ll [L] \ll K_a$, the total free energy difference $f_t = N(-\alpha(m - m_0) + \ln([L]/K_i))$, and the standard model Eq. (12) is invariant under the following transformation:

$$[L](t) \rightarrow \gamma [L](t), \quad m(t) \rightarrow m(t) + \alpha^{-1} \ln \gamma, \quad a(t) \rightarrow a(t), \quad (18)$$

for any positive constant $\gamma (> 0)$. This invariance is only valid when the free energy difference varies linearly with the methylation level m . This scaling invariance of the standard model makes a general prediction that the response to an arbitrary time-varying signals $[L](t)$ is the same as that to the globally rescaled signal $\gamma [L](t)$ with arbitrary constant γ . This prediction was verified by a recent experiments by Lazova et al (23). It is easy to see that the prediction can be extended for motile cells moving in ligand concentration profiles that vary in both space and time. The chemotactic motion of *E. coli* cells should be statistically the same in ligand concentration profiles $[L](x, t)$ and $\gamma [L](x, t)$. The phenomenon of logarithmic tracking has also been called “fold change detection” by Shoval et al (44).

Previous explanation for the WF law in *E. coli* chemotaxis was based on the assumption that the response depends directly on the time rate-of-change of receptor ligand occupancy (6, 11, 34, 50). Our model shows that the fundamental origin for the WF law is the perfect adaptation kinetics and the specific characteristics of the free-energy function. The logarithmic form of the ligand-dependent free energy, $f_L([L]) \sim \ln[L]$ ensures that Weber’s law holds and the additional linear form of the methylation-dependent free energy, $f_m(m) \sim -\alpha m$ leads to the scaling invariance.

The balance of the two free energies (achieved by adaptation) implies a logarithmic mapping between ligand concentration and methylation: $m \sim \alpha^{-1} \ln[L]$ — the methylation level of the receptors, as the memory of the system, records and tracks the ligand concentration on a logarithmic scale. This view is supported by recent *in vivo* experiments (42,47) showing that increasing the receptor methylation level shifts the kinase dose-response curve to higher ligand concentrations in a semi-log plot. Furthermore, recent microfluidic experiments (18) showed that *E. coli* chemotaxis behaviors remain the same for an overall rescaling of linear spatial attractant profiles, thus directly demonstrate that the system senses the gradient of the logarithm of the attractant concentration $[L]$ in the range $K_i \ll [L] \ll K_a$.

Functionally, this logarithmic transformation of the external signal condenses the range of the input significantly, which could be beneficial for the cells as they need to function in a wide range of environmental conditions with only a finite number of memory (methylation)

levels. This desirable ability of logarithmic sensing may provide a clue as to why *E. coli* has evolved to have the observed linear methylation energy.

5 Some current challenges and possible future directions

The recent progress in both theory and experiment has lead to a much deeper, more quantitative understanding of the bacterial chemo-sensory system. They also expose several significant gaps in our knowledge of the pathway. We describe some of the open questions and possible solutions in this section.

5.1 Mixed receptor cluster: the Ising model revisited

The main assumption made in the MWC model is that all receptors within the functional cluster turn on and off synchronously. If we are only concerned with the total kinase activity of the whole receptor cluster, such assumption does not make any qualitative difference. However, in order to adapt accurately, an individual receptor's conformational change, which is responsible for its kinase activity, also affects its methylation/demethylation dynamics. Thus, the all-or-none assumption made in the MWC model may lead to incorrect receptor methylation dynamics.

In a wt *E. coli* cell, different types of chemoreceptors form mixed clusters (3). Time series of the methylation levels of Tar and Tsr were measured after exposure to different stimuli (serine and MeAsp) was first measured by Sanders and Koshland (41), and it was found that receptor methylation dynamics is ligand specific. More recently, it was reported in (24) that upon exposure to persistent MeAsp, the receptors change their methylation levels permanently in the adapted steady state; but the Tsr receptors only increase their methylation levels during the transient adaptation process before returning to their pre-stimulus values in the adapted steady-state. These experiments on the methylation dynamics are inconsistent with any "global" model, such as the MWC model, where the overall activity of a mixed cluster is used to control the individual receptor's methylation dynamics. Instead, a "local" adaptation model, such as the Ising-type model, where each receptor has its own activity, which is used to control its own methylation dynamics, was able to explain the adaptation dynamics of the mixed receptor cluster (24).

5.2 Receptor cluster: structure and function

Recent advances in Cryo-EM technology have started to reveal the detailed structure of the chemoreceptor cluster in intact bacterial cells (10,21,55). These structural information has profound impact on modeling the structure and function of the chemoreceptor cluster.

The current models are based on either coarse grained (MWC model) or highly simplified (Ising-type model) descriptions of the chemoreceptor clusters. As more structural information becomes available, these models need to be improved in order to understand the functional implication of the detailed receptor cluster structure.

For example, in the standard Ising-type model, receptors form a regular lattice. In an intact cell, the receptors form an extended cluster by both direct interactions (to form trimer) and indirect interactions mediated by CheW and CheA. The resulting cluster structure in vivo can be highly variable, depending on factors such as the expression levels of the receptor, CheW and CheA. Indeed, a recent study showed that the growth condition of the cells can affect the tightness of the receptor cluster by controlling the expression levels of CheW and CheA; and the different receptor cluster structures lead to different response sensitivities of the cells grown in different growth conditions (20). Therefore, the Ising-type model needs to be defined on an irregular and possibly variable network rather than a rigid regular lattice.

A more fundamental change is needed in reconsidering the homogeneous nearest neighbor interaction used in the Ising-type models. From a recent study on the local crystalline structure of the MCP cluster in *E. coli* (9), there are at least four types of interactions: receptor-receptor (within the trimer of dimer); receptor-CheW; receptor-CheA; and CheW-CheA. Therefore, heterogeneous receptor-receptor interactions—the direct one within the trimer and the indirect ones that are mediated by CheA and CheW—need to be considered explicitly in the model. Furthermore, given the functional importance of CheA, a separate two-state variable may be defined to describe the activity of the CheA molecules in the cluster. Together with the two-state variable for the receptor conformation, we can envision a two-level Ising model in which receptors and CheA dimers form an intercalating network with different interactions between nearest neighbors depending on whether the interaction is direct or mediated by CheW.

5.3 Sensing non-chemical signals

Besides chemical signals, the chemotaxis pathway can also react to other non-chemical signals, such as osmotic pressure (52), temperature (27) and pH (1).

How does the chemo-sensory system sense a non-chemical signal? Within the framework of the standard model for chemotaxis, the response of the chemotaxis pathway to these non-chemical signals can be understood and characterized by the dependence of the free energy difference (Δf) on the external parameters, such as temperature or osmotic pressure. In the case of chemical sensing, a detailed model of binding and activation of the receptor leads to a specific dependence of Δf on the ligand concentration $[L]$, as shown in Eq. (3). For non-chemical signals, which are typically global factors, a mechanistic derivation is difficult but an empirical determination of Δf may be possible (17). Another complication is that other than affecting the free energy difference Δf , these global factors, such as temperature can also affect kinetic constants. How the cell compensates for these global factor dependent changes in reaction rates has been addressed in a recent study (37).

In most cases, there is a qualitative difference between chemical sensing and the sensing of these global factors. While chemical sensing allows the cells to seek out ever higher concentrations of the attractants, cells use the chemotaxis pathway to go to a preferred level of these external factors. Since the former is a form of gradient-sensing behavior; we call the latter a “precision-sensing” behavior (17). How could chemotaxis pathway, a gradient-sensing pathway, be used to perform precision sensing? One possible answer is that the global factor can act as either an attractant or a repellent depending on its absolute value. This sensory reversal may be achieved if the dependence of Δf on the global factor is non-monotonic in comparison to its monotonic dependence on $[L]$. In the case of temperature sensing, the reversal seems to be caused by changes in the receptor methylation (27,38); in the case of pH sensing, the reversal is caused by the fact that the activities of Tar and Tsr have opposite dependence on pH (46). Overall, the mechanisms of precision sensing through a gradient sensing pathway are still not well understood.

5.4 Chemotaxis in bacteria other than *E. coli*

The molecular basis for chemotaxis is highly universal for different species of bacteria (53). Recent cryo-EM studies show that chemoreceptors in different types of bacteria all form tight polar clusters with conserved structure (10). However, the adaptation processes in other bacteria are in general more complex than that of *E. coli*. For example, in *Bacillus subtilis*, there are two extra adaptation mechanisms enabled by additional chemotaxis proteins that are not found in *E. coli* (40). So far, it is not clear whether these multiple adaptation mechanisms are redundant or have their own specific functions. It is thus highly desirable to extend the general modeling framework developed for *E. coli* to include these extra

adaptation mechanisms, which could shed light on the possible functions of the different adaptation mechanisms.

For most other bacteria, their bacterial chemosensory systems are more complex with multiple homologues of the chemotaxis proteins found in *E. coli*. For example, in the case of *Rhodobacter sphaeroides*, there are two clusters of the MCP complex: one localized at the cell pole as in *E. coli*; the other localized in the cytoplasm (15). There are also multiple response regulators, homologues of CheY and CheB, each of which can be phosphorylated by either one or both of the two MCP clusters. The functions of the two MCP clusters and the multiple response regulators are not clear. Given the complexity of the highly nested network with multiple chemotaxis protein homologues, mathematical models become necessary in testing system-level hypothesis and in understanding the possible origin and advantages of the highly nontrivial network design.

Definitions and Acronyms

Ising model	see Sidebar
MWC model	The “Monod-Wyman-Changeux” model proposed to describe cooperativity caused by allosteric interactions among subunits of a large protein complex
Signal amplification	The ratio of the response change over the signal change, also called the gain
FRET	Förster resonance energy transfer. In <i>E. coli</i> chemotaxis, FRET is used to measure the level of CheY-P/CheZ complex, from which the CheY-P level can be inferred

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Summary Points

1. Both receptor cooperativity and accurate adaptation can be described quantitatively by simple mathematical models.
2. An integrated model (the “standard model”), which contains both signal amplification and adaptation, is developed to predict responses of *E. coli* cells to any time-dependent stimuli quantitatively.
3. Exponential ramps induce activity shifts, which depend on the ramp rate through the methylation rate function $F(a)$.
4. Responses to oscillatory signals reveal that *E. coli* computes time-derivative in the low-frequency regime.
5. *E. coli* memorizes the logarithm of the ligand concentration and the Weber-Fetcher law holds in *E. coli* chemotaxis.

Figure 1.
Illustration of the *E. coli* chemotaxis signaling pathway.

Figure 2.
The relative free energy levels of the four states of a receptor dimer.

Figure 3.

The difference between the MWC-type model and the Ising-type model. In the MWC model, receptors within a functional cluster (shaded) are synchronized, while those from different functional clusters are independent of each other. In the Ising model, receptors are coupled through nearest neighbor couplings.

Figure 4.

The response curves for 6 CheRB-mutant strains as measured by the FRET experiments (symbols, from ref. (47)) and computed from an Ising-type model for mixed receptor clusters (lines, from ref. (30)). The fixed methylation levels of the Tar and Tsr receptors for the 6 different mutant strains are given in the shaded legend box.

Figure 5.

The receptor adaptation dynamics. (a) Illustration of the adaptation process. A sudden change in stimulus induces a quick and strong response from state A to B . Over longer time, the response curve shifts to higher attractant concentration as the system adapts until it reaches the adapted state C with the same activity as the pre-stimulus state A . More importantly, the adapted state C in the new environment has the same high response sensitivity as that of state A . The corresponding time series of the activity is shown in the right panel. (b) The response curves for cells that are pre-adapted to different backgrounds $[L]_0$. The symbols are experimental data (47) and the lines are from a MWC model with adaptation (33).

Figure 6.

Illustration of receptor adaptation models. (a) A microscopic model where only active (inactive) receptor demethylates (methylates) as represented by the blue arrows. The receptor activity, which is determined by the ratio of the activation and deactivation rates represented by the red and green arrows respectively, is higher for higher methylation level. The receptor activity also depends on the attractant concentration, which decreases (increases) the activation (deactivation) rate. (b) A coarse-grained model abstracted from the microscopic model shown in (a). The input $[L]$ suppresses the output a , which suppresses the controller (or memory) m , which enhances the output.

Figure 7.

The responses to exponential ramps (regenerated from Fig. 2&3 in ref. (43)). (a) An exponential ramp induces a shift in the steady-state activity away from a_0 . (b) The steady-state activity a_c for different ramp rate r . The inset shows the linear regime near $a = a_0$. (c) The functional form of the methylation rate function is determined by using the relation $r = \alpha F(a_c)$.

Figure 8.

The responses to oscillatory signals (regenerated from Fig. 4 in ref. (43)). (a) The measured response to an oscillatory signal is measured by its amplitude $|A|$ and phase shift ϕ . (b) The dependence of $|A|$ (upper panel) and ϕ (lower panel) on the frequency of the signal ν . For $\nu \ll \nu_m$, $|A| \propto \nu$ and $\phi \approx \pi/2$, which means that system computes time derivative of the signal. This is confirmed by looking at $H \equiv A(i\nu)$, whose amplitude (the green line in the upper panel) is roughly constant for $\nu \ll \nu_m$.