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Information Processing in Bacteria: Memory, Computation, and Statistical Physics: a Key Issues Review

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Outline

Living systems have to constantly sense their external environment and adjust their internal state in order to survive and reproduce. Biological systems, from as complex as the brain to a single *E. coli* cell, have to process these information in order to make appropriate decisions. How do biological systems sense the external signals? How do they process the information? How do they respond to the signals? Through years of intense study by biologists, many key molecular players and their interactions have been identified in different biological machineries that carry out these signaling functions. However, an integrated, quantitative understanding of the whole system is still lacking for most cellular signaling pathways, not to say the more complicated neural circuits.

To study signaling processes in biology, the key thing to measure is the input-output relationship. The input is the signal itself, such as chemical concentration, external temperature, light (intensity and frequency), and more complex signal such as the face of a cat. The output can be protein conformational changes and covalent modifications (phosphorylation, methylation, etc.), gene expression, cell growth and motility, as well as more complex output such as neuron firing patterns and behaviors of higher animals. Due to the inherent noise in biological systems, the measured input-output dependence is often noisy. These noisy data can be analysed by using powerful tools and concepts from information theory such as mutual information, channel capacity, and maximum entropy hypothesis. This information theory approach has been successfully used to reveal the underlying correlations between key components of the biological networks, to set bounds for the network performance, and to understand possible network architecture in generating the observed correlations. Many such examples appear in recent literature [1, 2, 3, 4, 5, 6]. See [7] for a recent review and references therein.

Although information theory approach provides a general tool in analysing noisy biological data and may be used to suggest possible network architectures in preserving information, it does not reveal the underlying mechanism that leads to the observed input-output relationship, nor does it tell us much about which information is important for the organism and how biological systems use these information to carry out specific functions. To do that, we need to develop models of the biological machineries, e.g., biochemical networks and neural networks, to understand the dynamics of biological information processes. This is a much more difficult task. It requires deep knowledge of the underlying biological network – the main players (nodes) and their interactions

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(links) – in sufficient details to build a model with predictive power, as well as quantitative input-output measurements of the system under different perturbations (both genetic variations and different external conditions) to test the model predictions to guide further development of the model. Due to the recent insurgency of biological knowledge thanks in part to high throughput methods (sequencing, gene expression microarray, etc.) and development of quantitative *in vivo* techniques such as various fluorescence technology, these requirements are starting to be realized in different biological systems. The possible close interaction between quantitative experimentation and theoretical modeling has made systems biology an attractive field for physicists interested in quantitative biology.

In this review, we describe some of the recent work in developing a quantitative predictive model of bacterial chemotaxis, which can be considered as the Hydrogen atom of systems biology. Using statistical physics approaches, such as Ising model and Langevin equation, we study how bacteria, such as *E. coli*, sense and amplify external signals, how they keep a working memory of the stimuli, and how they use these information to compute the chemical gradient. In particular, we will describe how *E. coli* cells avoid cross-talk in a heterogeneous receptor cluster to keep a ligand-specific memory. We will also study the thermodynamic costs of adaptation for cells to maintain an accurate memory. The statistical physics based approach described here should be useful in understanding design principles for cellular biochemical circuits in general.

1 Introduction: The *E. coli* chemo-sensory circuit

One of the best studied signaling systems in biology is the bacterial chemosensory pathway, which serves as a model system for understanding general principles of sensory signal transduction in biology [8, 9, 10, 11, 12, 13]. In *Escherichia coli*, extracellular chemical information is sensed by several types of transmembrane chemoreceptors, each binding to a different set of chemical ligands and converting this binding interaction to the regulation and control of intracellular pathway activities. Tar and Tsr receptors are the two most abundant chemoreceptors in *E. coli*, specific for aspartate and serine, respectively [14]. Experiments showed that the receptors form hetero-trimers of homo-dimers in bacterial cytoplasmic membrane [15, 16, 17], and these receptor trimers-of-dimers (TOD) interact to form clusters together with the cytoplasmic adapter protein CheW and the histidine kinase CheA [18, 19]. Recent advances in Cryo-EM technology have revealed the fine structure of the chemoreceptor cluster (with CheW and CheA) in intact bacterial cells [20, 21, 22, 23]. It is now known that the basic functional unit consist of 2 TOD's connected by two CheW molecules and one CheA dimer [24]. These basic units can connect with each other through interactions between CheW and CheA into a regular two dimension lattice with 6-fold symmetry [24]. Ligand binding to receptors in this highly connected regular network of proteins changes the autophosphorylation activity of the CheA's in the network, which in turn affects phosphorylation of the response regulator protein CheY and eventually regulates cell's swimming behavior.

In this section, we will introduce the *E. coli* chemotaxis pathway as a biochemical circuit that process chemical information. Given the structure of the circuit, we can now ask the questions of how the circuit works, how it encodes a memory, and what it computes. These subjects will be discussed in the subsequent sections.

1.1 Signal amplification: Cooperativity in a mixed receptor cluster

To explain the large signal amplification and high sensitivity in bacterial chemotaxis, receptor cooperativity in the cluster was first proposed by Dennis Bray [25, 26]. This important insight has since been confirmed by *in vitro* [27, 28] and *in vivo* [29, 30] experiments as well as by subsequent quantitative modeling. In particular, *in vivo* measurements of pathway activity using fluorescence resonance energy transfer (FRET) [29, 31] and the corresponding modeling work [32] demonstrated strong interactions between different types of chemoreceptors, such as Tar and Tsr. Cooperativity among different types of receptors allows them to act together (globally) in the mixed cluster to amplify the response to any specific signal.

There are different mathematical models, in particular the Ising model [32, 33, 34, 35, 36] and the Monod-Wyman-Chandeux (MWC) model [30, 37, 38, 39, 40, 41, 42, 43], which have been developed to describe cooperativity in a receptor cluster. The elementary building block of these models is the receptor functional unit, which is comprised of the receptor TOD, CheW, and CheA. These are two-state models where the elementary units can be either active or inactive [25]. Each receptor dimer can also bind with a ligand molecule [44]. For a given receptor unit, the free energy difference between the active and inactive states is controlled by its ligand-binding status (vacant or bound) and an internal variable – its methylation level (see the next subsection). Receptor-receptor interactions are incorporated differently in different models. In the Ising-type model, receptor units sit in an extended lattice (network) and cooperative interactions with finite strength are introduced between nearest neighbors in this lattice. In the MWC model, the receptor units form tightly coupled functional cluster with a finite size (number of receptor units) N . Within the tightly coupled MWC cluster, the receptor units act in an all-or-none fashion, i.e., they can be either all active or all inactive. There is no correlation between different MWC clusters.

Both models have been used successfully to describe signal amplification in *E. coli* chemotaxis. The MWC model [40, 42, 43] can be considered as a special case of the Ising model with an infinite coupling strength between members of a MWC cluster and zero coupling between units from different MWC clusters. The MWC model can be solved analytically and thus has been the favorite among modelers. However, as we will see later, the MWC model is not suitable to describe the adaptation dynamics of a mixed receptor cluster with different types of receptors.

1.2 Adaptation encodes a working memory for computing gradient

As all biological systems, bacteria can adapt to changes in their environment. For chemotaxis, after a fast initial response to a step increase of a certain stimulus, the activity of the cell can slowly relax back to its pre-stimulus level even though the stimulus is still there [45]. At the molecular level, sensory adaptation in *E. coli* chemotaxis is carried out by receptor methylation and demethylation, mediated by two cytoplasmic enzymes: methyltransferase (CheR) and methylesterase (CheB), which add and remove methyl group (CH_3^+) at specific methylation sites on the receptor, respectively [13, 46, 47]. This covalent modification of the receptor modulates the activity of the attached histidine kinase CheA, which phosphorylates both CheY and CheB [46, 47]. Since CheB methylesterase activity

dramatically increases upon phosphorylation, the overall (global) kinase activity can control the methylation process through CheB phosphorylation. In addition, receptors undergo reversible conformational changes upon ligand binding and methylation [21]. These local conformational changes also affect the methylation/demethylation processes, allowing the cell to adapt.

Essentially, the cell changes its internal state, i.e., its receptor methylation level to balance the external stimulus, in order to adapt to the environment. At the adapted state, the cell's internal state variable – the receptor methylation level – balances the external input (stimulus) [48, 49]. Therefore, when the cell adapts to a given level of external stimulus, the adapted receptor methylation level provides a measure (an internal representation) of the external stimulus. Given the long adaptation time as compared with the response time, the receptor methylation level thus serves as a working memory of the external signal. We will describe the dynamics of this working memory in this section.

1.3 The “standard model” of bacterial chemotaxis pathway

When we put the fast response dynamics and the slower adaptation of the receptor together, we develop a model for describing the response of the chemosensory circuit to arbitrary time dependent signals:

$$\begin{aligned} a &= G([L], m), \\ dm/dt &= F(a, m, [L]), \end{aligned} \quad (1)$$

with a the average activity, m the average receptor methylation level, and $[L]$ the ligand concentration. Since the response is fast, here we have used the quasi-static approximation to describe the dynamics of the activity.

The activity function $G([L], m)$ describes the average activity of the receptor cluster, and can be obtained from the Ising model or the MWC model. For example, by using the simpler MWC model, we have an analytical expression for $G(m, [L])$ [13]:

$$G([L], m) = \frac{L(1+[L]/K_i)^N}{L(1+[L]/K_i)^N + (1+[L]/K_a)^N}, \quad (2)$$

where $L = \exp(-Nf_m(m))$ is the equilibrium constant with $f_m(m)$ the methylation level dependent free energy difference between the active and the inactive states and N the number of receptor units within an MWC sensory cluster unit. K_i and K_a are the dissociation constants for ligand binding to the inactive and active receptors, respectively. The methylation free energy function $f_m(m)$ and the values of the dissociation constants can be determined experimentally. In particular, $f_m(m)$ is found to depend approximately linearly on m [50, 51].

The methylation rate function $F(a, m, [L])$ determines the adaptation dynamics, and the methylation process represents a biological realization of the “state-dependent inactivation”

mechanism [52]. From the fact that *E. coli* can adapt accurately, i.e., the adapted activity a_{ad} in steady state is independent of the ligand concentration $[L]$, we can guess that the function $F(a, m, [L])$ should have weak dependence on m or $[L]$. This can be seen easily by looking at the steady state when $dm/dt = 0$, which leads to $F(a) = 0$. Provided that $F'(a) < 0$ for all a , the steady state activity will always go to the root (a_0) of the function F : $F(a_0) = 0$. Since a_0 is constant, this means that the activity always adapt to the same level independent of $[L]$, i.e., perfect adaptation. $F(a)$ can be approximated by a linear expansion around $a = a_0$, which works well for a wide range of activity around a_0 . For fitting very large stepwise MeAsp removal experiments, a nonlinear dependence of F on a is needed [53].

The standard *E. coli* chemotaxis model (Eq. (1)) can be used to study response of the system to an arbitrary time dependent signals. In fact, the form of the methylation rate function $F(a)$ can be directly determined (reverse-engineered) experimentally by measuring the response of the system to exponential ramps with different ramp rates [51]. In these experiments, it was found that there is a large region near $a = a_0$ where F is linearly dependent on a [51]. From analysis of the model and the experimentally measured responses to signals with different frequencies, it was shown that the signaling pathway computes time derivative of the signal at low frequency regime where the memory variable m has enough time to record the external stimulus [54]. Evidently, the working memory of the system as encoded in the methylation level m is crucial for the system to carry out its key function, i.e., computing the gradient of the external stimulus [36].

In the rest of this article, we review some of the recent work in understanding how the system maintains the specificity of its memory and how much it costs to maintain an accurate memory by using the modeling framework described here.

2 The memory is signal specific: Local adaptation prevents contamination

2.1 Challenges, attempts, and problems

2.1.1 Memory contamination predicted by MWC model—Experiments have shown that *E. coli* is capable of distinguishing different chemical signals, processing the mixed information and making decisions to follow the favorable gradient [55]. More recent results also demonstrated that the chemo-receptors undergo selective methylation process when exposed to different ligands, suggesting that the working memory is signal specific [56, 57, 58]. However, the traditional MWC model fails short in explaining these simple facts. Since the receptors within the tightly coupled MWC cluster are either all active (on) or all inactive (off), the sensing and methylation dynamics of different types of receptors are completely synchronized [36]. In other words, when a heterogeneous receptor system is exposed to one type of ligand, all receptors, regardless their ligand-binding type, will become permanently methylated due to the strong coupling (termed “permanent methylation”). Consequently, the MWC cluster converts the binding of different types of ligands into largely amplified but identical intracellular signal, causing memory contamination.

More severely, if one type of ligand is saturated, all receptors in the MWC cluster will be methylated to the highest methylation level. Therefore, when the concentration of another type of ligand changes, the cluster will completely lose its ability to sense and respond to the change, even though a large portion of its receptors are not bound with any ligand molecule. This poisoning effect can arise from the permanent methylation crosstalk, and is not desirable for the *E. coli* chemotaxis network to sense a complex environment with mixed signals.

2.1.2 Cooperative sensing vs. ligand-selective methylation—The apparent paradox in the problem is that signal amplification requires receptor cooperativity at the kinase activity level, which, according to the “standard model” Eq. (1), would cause crosstalk in the methylation process, leading to non-selective methylation. Several approaches have been used to address this issue.

Hansen *et al.* proposed a “dynamic-signaling-team” mechanism [59], in which different types of receptors form signaling-teams and each signaling-team still switches under the “all-or-none” rule as the MWC model. However, the receptors are allowed to switch between different MWC clusters. The switching events are governed by the energy states of the receptors depending on their ligand occupancies, activities and methylation levels. By encouraging active receptors to form signaling-teams, the heterogeneous receptor system are divided into different “dynamic-signal-teams” in which ligand-occupied receptors tend to cluster together. This “dynamic-signal-team” model inherits the high cooperativity from the MWC model and at the same time reduces memory contamination by effectively inhibiting different types of receptors to form signaling-teams. However, although the selective methylation process is incorporated in this model, it still predicts relatively high level of permanent methylation crosstalk between different types of receptors [59].

An alternative approach was developed by Goldman *et al.* based on the Ising-type model to eliminate the methylation crosstalk [60]. In this approach, a lattice of CheA dimer is considered separately from the heterogeneous receptor cluster, and the direct receptor-receptor interaction is replaced by the CheA-CheA interactions within this extended CheA lattice. The absence of direct receptor-receptor interaction nicely avoids permanent methylation crosstalk, but it also eliminates the transient crosstalk. As predicted by Goldman *et al.*, the Tsr methylation level does not change at all in response to aspartate, which is inconsistent with known experimental measurements [57]. Moreover, there has been no direct experimental evidence in support of a direct interaction between CheA dimers in the cluster.

2.2 The local adaptation model

To capture the accurate methylation dynamics at both the short and long time scales (i.e. transient and permanent methylation crosstalk), we proposed a local adaptation (LA) model [36]. As illustrated in Figure 1A, Tar and Tsr receptors form a mixed network with nearest neighbor interactions. Each individual receptor, R_{qlam} , is characterized by 4 state variables (written as subscripts): q represents the type of receptor with $q = 1$ for Tar and $q = 2$ for Tsr; $l = 0, 1$ indicates ligand occupancy state of the receptor to be either vacant or occupied; $a =$

0, 1 represents inactive or active conformation of the receptor; $m \in [0, 4]$ is the receptor methyl level (Figure 1B). Neighboring receptors in the connected network can interact and affect each other's activity-related conformational states (Figure 1C).

2.2.1 The Ising-type energy description—Following the Ising-model used in describing collective behaviors in physical systems, such as ferromagnetism [61], we can write down the free energy of a given receptor in a particular state (q, l, a, m) :

$$H(q, l, a, m) = \mu_q l + a (E_q^L l + E_{q,m}^M + E_q^C), \quad (3)$$

where $\mu_q = \ln K_q^I / [L]_q$ and $\mu_q + E_q^L = \ln K_q^A / [L]_q$ are the chemical potentials of the inactive and active ligand-occupied receptors, respectively, and are set to be q -dependent constants; $E_{q,m}^M$ is the methylation-dependent free energy contribution; E_q^C is the coupling interaction strength between neighboring receptors; K_q^I and K_q^A are the dissociation constants for the inactive and active type- q receptors, and $[L]_q$ is the concentration of ligand that binds with type- q receptor. All energies in Eq. (3) are in units of the thermal energy $k_B T$.

As mentioned previously in this review, experiments have indicated that the methylation energy $E_{q,m}^M$ is roughly a linear function of the methylation level m [51]:

$$E_{q,m}^M = E_{q,0}^M + \alpha_q m, \quad (4)$$

where $E_{q,0}^M$ is the base methylation energy with $m = 0$ and $\alpha_q (< 0)$ the amount of energy change by adding one methyl group to a type- q receptor.

Like the Ising model, the coupling energy E_q^C is assumed to depend linearly on the activity of its nearest neighbors (nn):

$$E_q^C = \sum_{(nn)} C_{qq'} (a_{q'} - 0.5) \quad (5)$$

Eq. (5) shows that activity of a receptor ($a = 0$ or 1) is influenced by its neighbor's activity with a coupling constant (strength) $C_{qq'}$.

For *E. coli* chemotaxis, the time scales for ligand binding ($l = 0, 1$) and activity switching ($a = 0, 1$) are much faster than that of receptor methylation/demethylation. Therefore, any individual receptor in the cluster is approximated to be at quasi-equilibrium among its four (a, l) states: (0, 0), (0, 1), (1, 0) or (1, 1), with the probabilities given by the Boltzmann distribution function based on the free energy function Eq. (3). So for any given methylation level m , the average activity of type- q receptor $\langle a \rangle_{q,m}$ is determined by $H(q, l, a, m)$. The average activity over all methylation levels is then $\langle a \rangle_q = \sum_m P_{q,m} \langle a \rangle_{q,m}$, where $P_{q,m}$ is the population of type- q receptors with methylation level m .

2.2.2 The local adaptation dynamics—To complete the description of the signaling pathway, we need to model the (slow) dynamics of receptor methylation level distribution $P_{q,m}$. According to the “standard” model, the methylation process has to depend on the receptor activity in order to explain the observed accurate adaptation [45]. One obvious way of receptor activity dependence comes from the fact that the methylesterase protein CheB becomes active when it is phosphorylated by the histidine kinase CheA, which is controlled by the integrated global activity of all the chemoreceptors [62]. However, accurate adaptation occurs even in the absence of CheB phosphorylation with a constitutively active CheB [63]. A more subtle but perhaps more important way of receptor activity dependence comes from individual receptor’s conformational changes (local activity, Figure 1C), which can control the accessibility of its methylation sites and/or affinity of the enzymes to the receptor [64, 65]. Thus, in the local adaptation (LA) model, the dynamics of the receptor population $P_{q,m}$ is given by:

$$\frac{P_{q,m}}{dt} = k_R (1 - a_{q,m-1}) P_{q,m-1} + k_B a_{q,m+1} P_{q,m+1} - [k_R (1 - a_{q,m}) + k_B a_{q,m}] P_{q,m} \quad (6)$$

where k_B and k_R are rates of methylation and demethylation (assumed to be the same for different types of receptors). Different terms on the right hand side of Eq. 6 represent the methylation and demethylation dynamics between adjacent methylation states.

2.3 LA model predicts distinct behaviors of heterogeneous receptor clusters

2.3.1 Local adaptation prevents permanent methylation crosstalk within the perfect-adaptation regime—Using the LA model, the adaptation dynamics of Tar and Tsr in a heterogeneous cluster can be quantified [36]. As summarized in Figure 2, in response to a step increase of the chemo-attractant MeAsp, the activity of Tar is suppressed immediately by ligand binding, similar to the MWC model behavior. Owing to the heterogeneous receptor-receptor interactions (E^C), the activity of Tsr in the mixed receptor cluster also decrease quickly. After the initial activity drop, the system starts to recover (adapt) by increasing the receptor methylation levels, which restores the receptor activities to their initial pre-stimulus levels. However, unlike the MWC model, the LA model predicts that only the average methylation level $\langle m \rangle_1$ of Tar receptor, which directly bind the external ligand (MeAsp), increases monotonically and reaches a higher methylation level in the final adapted state; whereas the average methylation level $\langle m \rangle_2$ of the Tsr receptors increases only transiently before returning back to its pre-stimulus level when the system reaches its adapted steady state. Thus the LA model predicts only transient methylation interference (crosstalk) but no permanent (steady state) methylation crosstalk.

It is known that the *E. coli* chemo-receptors can adapt accurately to a certain range of ligand concentration by adjusting its methylation level [66, 67]. A mixed receptor cluster made of Tar and Tsr has the ability of adapting to both MeAsp and serine stimuli, but with different adaptation ranges [68, 69]. Since LA model connects the methylation dynamics of Tar and Tsr solely to their own activity levels and their specific ligands (Eq (6)), the steady-state methylation levels (memories) of the two receptors will be ligand (signal) specific. In other

words, Local adaptation prevents permanent methylation crosstalk as long as the system can adapt perfectly (accurately).

Another interesting prediction from the LA model is that the average kinase activity does not always stay below the adapted value and recovers monotonically as it would be in the MWC model. If Tsr is more abundant than Tar and Tsr adapts slower than Tar, the transient nonmonotonic Tsr activity recovery dynamics in response to addition of aspartate or MeAsp can bring the overall kinase activity above its adapted level (i.e., an overshoot) before the system reaches its final steady state. This predicted behavior from the LA model is consistent with the overshoot in the transient response (in terms of the rotational bias of the flagellar motor) of *E. coli* to a large step chemotactic stimuli observed by Berg and Tedesco [70]. This agreement strongly supports the LA model.

What happens when adaptation becomes imperfect? Figure 3A&B shows the post-stimulus steady-state activity and methylation level of Tar and Tsr as function of added MeAsp concentration $[L]_1$. When stimulus strength is low ($[L]_1 < K_1^A$), the system adapts perfectly (i.e. activity level is independent of $[L]_1$, Figure 3A, left to the dashed line), and the methylation level of Tsr remains constant (red line in Figure 3B, left to the dashed line).

However, when stimulus strength keeps increasing beyond K_1^A , the effect of ligand binding may no longer be balanced by the covalent modification (methylation) of Tar, therefore the system fails to adapt accurately (blue line in Figure 3A, right to the dashed line). This permanent change in activity (imperfect adaptation) is felt by Tsr in the heterogeneous

cluster through receptor-receptor interaction $\sum C_{q_i q_i'} \times (a_{i'} - 0.5)$, which depends on the activity (red line in Figure 3A, right to the dashed line). The changes in receptor-receptor interaction strength drive the methylation of the non-binding receptors and eventually leads to permanent changes of their methylation levels, i. e., methylation crosstalk (red line in Figure 3B, right to the dashed line). Similar results can be obtained if MeAsp is replaced with serine (Figure 3C&D). The differences between these two stimuli indicate the different adaptation ranges of Tar and Tsr. Figure 3E summarizes the causal relation between the absolute adaptation error, $\langle a \rangle = \langle a \rangle - \langle a \rangle_0$, and the level of permanent methylation crosstalk, m .

2.3.2 Imperfect adaptation caused by boundary effects—What causes imperfect adaptation? We can answer this question by deriving the dynamical equation for the average

methylation level $\langle m \rangle_q (\equiv \sum_{m=0}^4 P_{q,m} m)$ by summing over the dynamical equations (Eq. (6)) for receptor populations $P_{q,m}$ in different methylation levels:

$$\frac{d\langle m \rangle_q}{dt} = k_R (1 - \langle a \rangle_q) - k_B \langle a \rangle_q + k_B \langle a \rangle_{q,0} P_{q,0} - k_R (1 - \langle a \rangle_{q,4}) P_{q,4} \quad (7)$$

The last two terms in the above equation represent the contributions from the boundary methylation values $m = 0$ and $m = 4$. If the receptor population at these boundary methylation levels are small, i.e., $P_{q,0}, P_{q,4} \ll 1$, these boundary terms can be neglected from Eq. (7), which will lead to $\langle a \rangle_q = k_R / (k_R + k_B)$ in steady state independent of ligand

concentration, i.e., perfect adaptation. Otherwise, as first pointed out by Mello and Tu [71], these two “boundary terms” are responsible for imperfect adaptation of the system.

There are two factors contributing to imperfect adaptation: finite receptor populations at the methylation boundaries ($P_{m=0} = 0$ or $P_{m=4} = 0$); and the existence of activity “gaps” at these methylation boundaries (defined as $\langle a \rangle_{q,0} \equiv \langle a \rangle_{q,0}$ and $\langle a \rangle_{q,4} \equiv 1 - \langle a \rangle_{q,4}$). If the activity gaps are not closed, i.e., $\langle a \rangle_{q,0} = 0$ or $\langle a \rangle_{q,4} = 0$, CheB or CheR would still attempt to demethylate or methylate MCP receptors at the methylation boundaries ($m = 0$) or ($m = 4$) in order to achieve perfect adaptation. However, the finite range of receptor methylation levels (boundaries) prohibits these enzymatic reactions. Therefore the two boundary activity gaps affect the adaptation accuracy by controlling the catalytic deficiency at the two boundaries. As the receptor activity “gap” is normally very small ($\langle a \rangle_{q,0} \sim 0$) at $m = 0$, the dominant contribution for imperfect adaptation comes from the receptor population at the highest methylation level $m = 4$.

2.3.3 Comparison of theoretical predictions to experiments—Theoretical modeling allows us to study the detailed dynamics of receptor population $P_{q,m}$ in each individual methylation state ($m = 0, 1, \dots, 4$) and for different types of receptors ($q = 1, 2$). When there is no MeAsp present, the Tar receptors mostly populate the low-methylation states ($m = 0, 1$). After adding 1mM MeAsp, the Tar population shifts from low-methylation states to high-methylation states with monotonic decreases of $P_{1,0}$ & $P_{1,1}$, and monotonic increases of $P_{1,2}$, $P_{1,3}$ & $P_{1,4}$ (Figure 4A). However, for the Tsr receptors that do not bind MeAsp, methylation level distributions remain unchanged upon adaptation to MeAsp. Transiently, we observe a decrease-then-increase trend of the low-methylation state probabilities $P_{2,0}$, $P_{2,1}$ & $P_{2,2}$ for Tsr, whereas the probabilities of the high-methylation states $P_{2,3}$ & $P_{2,4}$ show opposite transient behaviors due to the conservation of the total receptor population (Figure 4B).

The relative population of receptors with different number of methyl groups can be measured by gel electrophoresis due to their different motilities in the gel at different time points after the addition of a stimulus (Figure 4C&D, also see [36]). The dynamics of receptor populations in different methylation levels can then be compared with our model predictions (Figure 4E&F), which show good quantitative agreement. In particular, experiment and theory both show that, after addition of 1mM MeAsp, the $m = 1$ & 2 states of Tsr receptors (i.e. $P_{2,1}$ & $P_{2,2}$) first decrease to lower levels and then recover back to the pre-stimulus level; whereas the $m = 3$ state (i.e. $P_{2,3}$) exhibits an opposite increase-then-decrease transient dynamic trajectory (Figure 4E). Furthermore, the overall methylation dynamics also confirms that only Tar that binds with MeAsp gets methylated permanently (Figure 4F).

On the other hand, when the heterogeneous receptor cluster is exposed to 1mM of serine, Tsr receptors are unable to balance the high serine concentration, leading to an imperfect adaptation. As a result, methylation crosstalk of Tar persists permanently (Figure 5). Overall, the experimental measurements support the LA model, in which individual receptor activity has an important role in regulating its own methylation level to achieve adaptation. The observations are inconsistent with the MWC models, including the “dynamic-signaling-

team” model, where methylation is solely controlled by the total activity of the mixed receptor cluster. It also disagrees with Goldman’s multi-layer model that predicts the absence of any (even transient) methylation crosstalk. Both the LA model and the experimental measurements show that when a mixed receptor cluster is exposed to a mixture of external chemo-stimuli, different types of receptors adapt to different methylation levels, depending on the composition of the mixed stimuli. This LA mechanism suggests that bacteria can distinguish and encode complex external ligand information through methylation levels of their corresponding receptors [36].

2.4 Encoding ligand information to working memory

The ability to adapt to complex environments is essential for organisms to survive [72]. For *E. coli* chemotaxis, the adaptation dynamics after a given environment change can be illustrated by the two-dimensional trajectories of the average Tar and Tsr methylation levels. For the LA model, as shown in Figure 6A, adding MeAsp leads to a methylation level trajectory that ends to the right of the starting point, whereas adding serine gives rise to a trajectory that ends above the starting point. When perfect adaptation is achieved, the methylation coordinate of the end point in the non-binding direction is the same as that of the starting point, indicating no permanent methylation crosstalk [36]. However, when the trajectories approach the maximum methylation level ($m = 4$), perfect adaptation fails, and the end (steady state) point has finite changes in both methylation coordinates even for additions of one single type of stimulus, indicating the start of methylation crosstalk. Contrarily, for the MWC-type adaptation models, the methylation dynamics always follows the same trajectory independent of the details of the environment changes. As shown in Figure 6B, the end points only depend on an overall strength of the environment changes integrated over all stimuli, and the methylation level trajectories for different ligand perturbations all collapse onto a single line, indicative of severe permanent methylation crosstalk [36].

The relevant information about the external chemical environment for an *E. coli* cell can be specified by the ligand concentrations ($[L]_1, [L]_2$) for MeAsp and serine, respectively. From the methylation trajectory analysis, it is clear that the LA mechanism encodes this information distinctively in the methylation levels of Tar and Tsr ($\langle m \rangle_1, \langle m \rangle_2$) in a unique one-to-one manner without loss of information, as shown in Figure 6C. However, for the MWC model, the mapping from the chemical information to its intracellular record is not unique (many-to-one). In fact, as shown in Figure 6D, a whole line of different combinations of concentrations are mapped to a single point in the methylation space, representing a severe loss of information. The precise encoding of the environmental ligand information may play a role in mediating *E. coli* cells’ long-term adaptation in changing environments. Experiments have shown that *E. coli* cells can adjust the ratio of their Tar and Tsr receptors according to changes in the environmental nutrient condition [73, 74]. In principle, environment information such as nutrient composition, which is stored in the receptor methylation levels of different receptors, may be used somehow to trigger syntheses of proteins (e.g., receptors) that can help enhance the cells’ sensitivity towards specific nutrient gradients.

3 The thermodynamic cost of maintaining an accurate memory

Adaptation is a fundamental function of living systems. For *E. coli*, it encodes a working memory, which is crucial for gradient sensing in chemotaxis. However, despite its well-known benefits, the cost of accurate adaptation in a noisy environment (both internal and external) has been elusive. It was not clear how much, if any, energy needs to be consumed for a given level of adaptation accuracy; and what is the thermodynamic limit of such dissipative living system?

3.1 *E. coli* chemotaxis network is intrinsically dissipative

From the network topology point of view, the standard *E. coli* chemotaxis model, Eq. (1), describes the behavior of a 3-node regulatory motif called “Negative- Feedback-Loop” (NFL), in which $[L]$, a and m are the nodes for *input*, *output* and *controller*, respectively (Figure 7A). This motif represents a minimum network to achieve accurate adaptation [76]. A stimulus signal ($[L]$) causes a fast response in the output activity (a). The change in a triggers a slower encoding process in the negative control element (m), which precisely balances the effect of $[L]$ and brings a back to a stimulus-independent level a_0 (Figure 7B). Due to the small size of a cell, *in vivo* biochemical reactions are highly noisy. Based on the deterministic standard model, the stochastic dynamics of this feedback network can be described by two coupled Langevin equations [54]:

$$da/dt = \dot{G}([L], m) + \eta_a(t); \quad dm/dt = F(a, m, [L]) + \eta_m(t), \quad (8)$$

where the functions $\dot{G}$ and F characterize the network interactions, which may be mediated by multiple intermediate nodes. η_a and η_m are the noises assumed to be white with strength 2_{-a} and 2_{-m} respectively. The negative feedback mechanism for adaptation requires the two cross derivatives of the interaction functions, $\dot{G}/m$ and F/a , to have opposite signs. This requirement immediately leads to the observation:

$$\Delta_m \partial \dot{G} / \partial m \neq \Delta_a \partial F / \partial a, \quad (9)$$

which indicates the breakdown of detailed balance that is obeyed by all equilibrium systems [77]. This general observation suggests that all negative feedback control systems, including the *E. coli* chemotaxis network, are nonequilibrium and dissipative. Consequently, adaptation always costs energy.

3.2 The energy-speed-accuracy tradeoff in *E. coli* chemotaxis

3.2.1 A reversible microscopic model of *E. coli* chemotaxis—Based on the molecular details of *E. coli* chemotaxis discussed in the previous sections, we can construct a microscopic model to study the energy cost of adaptation through the *E. coli* chemotaxis network [36, 43, 45, 51, 71, 75, 78, 79].

Similar to the LA model, we use discrete variables to characterize a chemoreceptor dimer: $a = 0, 1$ for activity, and $m = 0, 1, \dots, 4$ for methylation level (Figure 7C). However, unlike the

LA model in which the activity switching process is omitted by using the quasi-equilibrium approximation [36], we consider the full dynamic process explicitly in this microscopic model [75]. For a given m , the transition between the active ($a = 1$) and inactive ($a = 0$) states are fast, with a characteristic timescale τ_a . The methylation and demethylation reactions are catalyzed by the methyltransferase CheR and the methylesterase CheB, with one-step reaction rates k_R and k_B , respectively.

Another distinct feature of the microscopic model is the reversibility in all reaction steps [75]. It is known that to achieve accurate adaptation, CheR should preferentially enhance the methylation of the inactive receptors and CheB should preferentially enhance the demethylation of the active receptors [13, 36, 43, 45, 46, 47, 51, 71, 78, 79]. The degree of irreversibility is quantified by a parameter γ ($\gamma = 1$) that suppresses the methylation rate for the active receptors and the demethylation rate for the inactive receptors from their equilibrium values (Figure 7C). Therefore, $\gamma = 1$ represents an equilibrium reaction network with full reversibility; whereas $\gamma = 0$ represents a fully irreversible chemotaxis network.

3.2.2 Quantitative evaluation of energy dissipation and adaptation accuracy

—We study the stochastic dynamics of the chemoreceptor within the 2-dimensional phase-space of (a, m) for different values of γ . The probability of a receptor to be at a given state in the phase-space, $P_a(m)$, can be determined by solving the master equation. From $P_a(m)$ and the transition rates between different states, we can compute the adaptation error ε defined as (Figure 7B):

$$\varepsilon \equiv \left| 1 - \frac{\langle a \rangle}{a_0} \right|, \quad \langle a \rangle = \sum_m P_1(m). \quad (10)$$

The energy dissipation rate $\dot{W}$ is given by:

$$\dot{W} = k_B T \sum (J_{AB} - J_{BA}) \ln \frac{J_{AB}}{J_{BA}}, \quad (11)$$

where A & B are any two connected states of the receptor; J_{AB} and J_{BA} are the two counter fluxes between A & B , respectively; and the sum is taken over all the reactions (transitions) in the (a, m) phase space.

Figure 8 shows the dependence of ε and $\Delta W \equiv \dot{W} k_R^{-1}$, which is the energy dissipation by a receptor to its environment in the form of heat during the methylation time $\tau_R \equiv k_R^{-1}$, on γ for different background signals. Smaller γ leads to smaller error, but costs more energy. By plotting ε versus ΔW (Figure 9A), we find that ε decreases exponentially with ΔW when ΔW is less than a critical value ΔW_c :

$$\varepsilon \approx \varepsilon_0 e^{-\alpha \Delta W} = \varepsilon_0 e^{-\alpha \dot{W} \tau_R} \quad (12)$$

For $W > W_c$, ε saturates to ε_c , which depends on key parameters of the system. The exponential error-energy relationship holds true for different choices of the kinetic rates k_R and k_B , and the prefactor α is found to be (Figure 9B):

$$\alpha = \frac{k_R + k_B}{2k_B}.$$

Eq. (12) indicates a tradeoff relationship among the Energy Dissipation, the Adaptation Speed and the Adaptation Accuracy (the ESA tradeoff relation) [75].

3.3 Network requirements for accurate adaptation

From the previous section, adaptation error is caused by the boundary effects in the m dimension (Eq. (7)): the boundary population $P_{m=0\&4}$ and the activity “gap” $\langle a \rangle_{m=0\&4}$. From the energetic point of view, the error-energy relation (Eq. (12)) sets the minimum adaptation error (i.e. the highest possible adaptation accuracy) for a given energy dissipation. To approach this optimum performance, proper conditions on the key components and parameters of the network are required. In particular, adaptation accuracy depends on the energetics and kinetics of the receptor activity, parameterized by $E^M(m)$ and activation time τ_a in the microscopic model.

Figure 10 summarizes the computed adaptation error and energy dissipation for a large number of models, each with a random parameter set ($E^M(m)$, τ_a , $\gamma[L]$). All the error-energy points are bounded by a “best performance” (BP) line, which agrees exactly with Eq. (12), indicating that the Energy-Speed-Accuracy tradeoff relation defines the thermodynamic limit of any NFL-facilitated adaptation networks.

The deviation from this BP line is caused by the finite saturation error ε_c . Taking the limit of $\gamma = 0$, ε_c can be derived:

$$\varepsilon_c = |(1/a_0 - 1)P_{a=1}(m=0) - P_{a=0}(m=4)|,$$

which reconfirms that the saturation error results mainly from the receptor population at the methylation boundaries where the enzyme (CheB or CheR) fails to decrease or increase the receptor methylation level any further [36, 71]. Therefore, having large boundary energy differences ($E(0)$, $E(4)$) and fast activation time ($\tau_a \ll k_R^{-1}$) can reduce ε_c by decreasing the receptor populations at the methylation boundaries [75]. These requirements for accurate adaptation are met for the aspartate receptor Tar, which has $E(0) \approx 2k_B T$, $E(4) \approx -6k_B T$, and $\tau_a k_R < 10^{-3}$ [12]. The network requirements obtained from the dynamic analysis and the energetic analysis are in line with each other.

3.4 Experimental evidence: Adaptation dynamics of starved *E. coli* cells

According to the ESA relation, adaptation accuracy is controlled by the dissipated free energy, which comprises two parts: the internal energy of the fuel molecule and an entropic contribution. As the entropic energy depends only on the logarithm of the fuel molecule concentration, the adaptation accuracy is not very sensitive to the change in abundance of

the fuel molecule. However, the kinetic rates, for example the methylation rate k_R , depend strongly on the concentration of the fuel molecule. Therefore, if a cell's fuel molecule pool becomes smaller owing to deficient metabolism or starvation, the adaptation should slow down whereas its accuracy should stay relatively unaffected.

This prediction was tested by direct measurements of *E. coli*'s adaptation dynamics using fluorescent resonance energy transfer (FRET) [48]. As shown in Figure 11A, adaptation to a given stimulus becomes progressively slower (Figure 11B) for cells that are kept in a medium without any energy source. The background kinase activity (in buffer) decreases with time, indicative of the decreasing energy level of the starving cells. Remarkably, the adaptation accuracy remains almost unchanged with time (within experimental resolution, Figure 11C), consistent with the prediction from the ESA tradeoff relation [75].

For an *E. coli* cell, the methylation levels of its chemoreceptors serve as the memory of the external signals it received [36]. After a change in the signal, the adaptation process “rewrites” this memory accordingly. As pointed out by Landauer [80], only erasure of information (for example, memory) is dissipative owing to phase space contraction and the resulting entropy reduction. As changing the methylation level does not necessarily shrink the phase space, the adaptation response to a signal change does not have to cost extra energy. Instead, energy is consumed continuously to maintain the stability of the adapted state or, equivalently, the accuracy of the memory against noise. For an *E. coli* cell with $\sim 10^4$ chemoreceptors [81] and a (linear) adaptation time of ~ 10 s, the energy consumption rate is $\sim 3 \times 10^4 k_B T/s$ (equivalent to $\sim 10^3$ ATP/s), which is 5–10% of the energy needed to drive a flagellar motor rotating at 100 Hz [82], even when the cell is not actively sensing or adapting. The total energy budget for regulations in an *E. coli* cell is likely much higher, given the many regulatory functions needed for its survival. During starvation, *E. coli* cells are likely to have different priorities for different energy consuming functions. Thus, the slowing down of adaptation in starved cells may be seen as a way for the cells to conserve energy for other regulatory functions with higher priorities.

3.5 The cost-performance relation in biological regulatory processes

Biological systems are dissipative and consume energy to carry out various vital functions. Most of these functions are related to intracellular regulation, where temporal, spatial and intensity information about the external environment are transduced into molecular signals to control downstream cellular events such as gene expression, cell division, and motility. Given the relatively small number of molecules involved in cellular processes, the information flow is exposed to high levels of noise. To maintain the integrity of information, different biological circuits (networks), fueled by metabolic energy, are used to reduce the effects of noise. The improvement of the performance (functionality) comes with the price of free energy cost. The cost-performance relationship has been studied in the context of ultra-sensitive switch [83], sensory adaptation [75, 84, 85], kinetic proofreading [86], bacterial cell division regulation [87], eukaryotic cell gradient sensing [88], and biochemical oscillations [89].

In this review, we describe the Energy-Speed-Accuracy (ESA) tradeoff relationship (Eq. (12)) in *E. coli* negative feedback network for adaptation [75]. The same ESA relationship

was also found in an Incoherent-Feedforward-Loop (IFFL) network for adaptation [85], and it represents a general cost-performance relation of maintaining the information flow through sensory adaptation networks. Here, the network's performance is evaluated quantitatively by the accurate and speed of adaptation; whereas the cost is given by the free energy dissipation rate (i.e. the power of the biochemical circuit). As information intrinsically relates to entropy change of the system, the ESA tradeoff relation can be regarded as a representation of the second law of thermodynamics in sensory adaptation processes [90].

From an information processing standpoint, biological regulation can be treated as the learning of an internal representation of an external process [3, 91, 92, 93, 94, 95, 96, 97]. The regulatory performance can therefore be defined by the learning accuracy and the learning rate (i.e., rate of mutual information), and the energetic cost is characterized as the rate of thermodynamic entropy production. For example, The original work of Berg and Purcell was extended to show that effective sensing of external concentrations necessitates energy consumption and the certainty of the learning outcome can be enhanced by increased power consumption [94].

The rate of mutual information between the internal states and the external processes has also been investigated in models with and without feedbacks [91, 95, 96, 97, 98, 99, 100, 101]. Interestingly, it is found that for a sensing process without feedback, the rate of mutual information can be nonzero even for an equilibrium system [95, 96]. However, for sensory adaptation processes that include feedback (Fig. 7AC), the rate of mutual information is shown to be bounded by the thermodynamic cost that combines both the dissipation through the internal process and the chemical work done by the external process [97]. In fact, the external chemical work can serve as the energy source to power adaptation through "equilibrium" networks with feed-forward topologies [102, 103]. Similar to the results reported in [75], Barato *et al.* also found that the feedback induced methylation dynamics increases the concentration range within which a substantial learning rate can be maintained [97].

Besides the sensory adaptation network, mutual information analyses have also been carried out in the context of the genetic regulation. The information transmission through transcriptional networks have been characterized and the networks' information capacity, under high level of biological noises, have been estimated both theoretically and experimentally [1, 2, 4, 6, 104, 105, 106, 107, 108, 109]. It has been pointed out that, although the mutual information between the input and steady-state (static) output is quite small (~ 1 bit)[4], the network can potentially achieve unlimited information capacity if the network's output is read out and utilized dynamically [109]. The optimal information processing strategies in small genetic networks has also been investigated in different network topologies [110, 111, 112, 113]. However, all these works have focused on the information transmission aspect of the transcriptional networks and only very limited efforts have been devoted to analyze the networks' energetic cost[114]. It would be of great interests to further establish the quantitative connection between the networks' dissipative properties and their functions, especially to demonstrate whether the genetic regulatory networks would share similar tradeoff principles as the sensory adaptation networks.

The performance-to-cost analysis provides a general framework to determine the optimal operating regimes of the networks by balancing their economy and effectiveness. It has been reported that, for an integral feedback network, the best-compromised systems always have particular combinations of biochemical parameters that control the network's performance and the optimal systems fall on a hypercurve in the parameter space [115]. As discussed here, the size of the regulatory system also sets a limit to which performance saturates even with excess amount of energy consumption. Other factors that can limit the conversion of thermodynamic energy to biological functions have also been reported. By investigating the sensing process of coupled receptors, Skoge *et al.* found that although nonequilibrium coupling within 2 dimensional receptor cluster can improve the receptors' signal-to-noise ratio under high gain conditions, the energy dissipation cannot completely circumvent the tradeoff between gain and intrinsic noise [116]. More recently, Govern and ten Wolde reported that the amount of receptors and their integration time, the number of downstream readout molecules, and the energy dissipation are the 3 classes of resources for sensing, each of which sets its fundamental sensing limit that cannot be compensated by other recourses [117]. Overall, considerations of these performance-to-cost tradeoffs may provide insights for understanding evolution of regulatory networks and for designing efficient synthetic biochemical circuits.

Discussion

Biological systems need to sense and process information from their environment in order to make decisions vital for their survival and growth. Like a computer, a cell not only needs to take the input information, it also has the ability to store information (memory) and to use the memory together with the input to compute an output (decision) that will enhance its survival and/or growth. In this review, we use the simple *E. coli* chemotaxis signaling system as an example to demonstrate the ability of a cell to maintain an accurate memory and to compute. In a loose sense, the *E. coli* chemotaxis pathway can be considered as a probabilistic Turing machine [118, 119, 120], see Figure 12. The external information, i.e., the ligand concentration $[L]$, is arranged on a TAPE in the order of space or time. An *E. coli* cell has a HEAD with receptors, which can read (sense) the information on the TAPE. The cell also has an internal state variable m , the receptor methylation level or the memory. At a given time, the information $[L]$ read from the TAPE together with the current internal variable m determine the internal state variable at the next time m' , and a probability P or $1 - P$ of moving either left or right on the TAPE. For a general Turing machine, the HEAD can also writes (or erases) information on the tape. For cells that do not produce or consume ligand molecules, the HEAD simply leaves the information on the TAPE ($[L]$) unchanged (or equivalently copy the information exactly). The updating rules of a Turing machine, typically given in a TABLE, are given here by the biochemical reaction kinetics described in the standard model (Eq. 1) for *E. coli* chemotaxis.

However, despite the analogy to the universal Turing machine, the cell is not under any selection pressure to be a general purpose computer. The main function of the chemotaxis Turing machine is specific, i.e., to compute the gradient of the ligand concentration so the cell can follow the gradient to reach places with more favorable conditions (e.g., higher attractant concentrations). But this specific computing task does not make it a simple one

because the computation needs to be carried out by chemical reactions among a small number of molecules. Nonetheless, the cell has developed ingenious ways of accurate computation using these primitive noisy components. Unlike electronic circuits where dedicated wiring prevents cross-talk, components of the biochemical networks (circuits) are connected (“wired”) by biochemical reactions that are subject to non-specific chemical interactions, i.e., chemical cross-talks, which can degrade the specificity of the signals, contaminate the memory, and eventually lead to “bad” decision (output). In bacterial chemotaxis, interactions between different types of chemoreceptors, such as Tar and Tsr, within a mixed receptor cluster are known to amplify the signal. But, how do cells achieve ligand specific memory in the presence of these heterogeneous receptor-receptor interactions? Here, in combining theoretical modeling based on the well known Ising model from statistical physics and quantitative experiments, we show that *E. coli* uses a local adaptation mechanism to prevent memory contamination. The basic idea is that the receptor-receptor interaction energy depends on the difference between the average activities of the two interacting receptors. If each receptor can adapt to the same activity level, then the effect of receptor-receptor interaction vanishes in the adapted state, and therefore the methylation level (memory) of a given receptor only depends on the strength of the signal it directly senses, i.e., the memory is signal specific.

Computation costs energy. At the molecular level, the fundamental thermodynamic cost of information processing was studied by Landauer, who showed that erasure of one bit of information costs at least $kT \ln 2$ amount of free energy, the so called Landauer’s principle [121]. Here, we show that the chemotaxis Turing machine operates out of equilibrium. The internal state of chemotaxis Turing machine – characterized by its methylation level m – is maintained by feedback mechanism that is powered by a constant rate of free energy consumption. This energy dissipation rate can be considered as the cost of constantly writing and erasing a bit, i.e., a receptor continuously going through the methylation/demethylation cycle even in the steady state. Without this energy-consuming feedback mechanism, the adapted state is unstable. Furthermore, we found that there is a tradeoff relationship between the power consumption and the performance of adaptation as measured by adaptation speed and accuracy. The *E. coli* chemotaxis circuit is found to be highly efficient in achieving high accuracy in adaptation with relatively small energy expenditure [75]. In general, we argue that considering biological systems as information processing machines may provide one unifying perspective in studying dynamics of biochemical networks, their physical limits, and the underlying design principles.

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Figure 1.

Illustration of the Ising-type Local Adaptation model (reproduced from Figure 1 in Reference [36]). (A) The heterogeneous receptor cluster, in which neighboring receptors interact with a finite coupling strength to favor (but not absolutely enforce) same activities. (B) Schematic illustration of a single receptor that can bind with ligand ($I = 1$: bound, $I = 0$: vacant) and be in different methylation states ($m \in [0, 4]$). The water level inside the receptor represents the activity (a). (C) The local adaptation model, in which the methylation of individual receptor is controlled by its own conformational changes.

Figure 2.

Local Adaptation model prevents permanent methylation crosstalk (reproduced from Figure 2 in Reference [36]). **(A)** Adding modest amount (180 mM) of MeAsp induces immediate activity drops for both Tar and Tsr receptors. Afterwards, Tar activity recovers monotonically (blue line), whereas Tsr activity (red line) first increases to a higher level (overshoot) and then returns back to its initial level. Black line is the averaged activity recovery trajectory of the entire heterogenous receptor cluster. **(B)** Tar and Tsr exhibit different methylation dynamics after MeAsp addition: Tar increases its methylation level monotonically to a higher level (blue line), whereas Tsr is first methylated then demethylated before returning to its pre-stimulus level (red line). **(C)** Schematic illustration of methylation dynamics after MeAsp addition under local (upper row) and MWC (bottom row) adaptation schemes. The blue color represents the Tar-related components and red color labels the Tsr-related components. The water level inside each receptor represents activity of that particular receptor. In Figures 2–6, the Tar/Tsr ratio is chosen to be 1/2 [55]; $K_I^1 = 18.1 \mu M$, $K_I^2 = 6.0 \mu M$ and $E_1^L = 8$, $E_2^L = 3$ reflect the estimated ligand binding affinities for inactive and active receptors [34, 40]; $\alpha_1 = -1.875$ & $\alpha_2 = -1.0$ and $E_{1,0}^M = 1.875$ & $E_{2,0}^M = 2.5$ are taken from previous experimental measurements and estimates [51, 36]; $C_{1,1} = -5.5$, $C_{1,2} = -6.0$, $C_{2,1} = -6.0$ & $C_{2,2} = -6.0$ are designed to be symmetric, meanwhile provide high sensitivity [32, 34]; $k_R = 1$ & $k_B = 2$ are set to be the same for both receptors and the timescale is set by having $k_R = 1$.

Figure 3.

The steady-state activities, receptor methylation levels and their relationship in different (MeAsp or serine) backgrounds (reproduced from Figure 3 in Reference [36]). **(A)** The steady-state kinase activities and **(B)** the receptor methylation levels for different background MeAsp levels. The system can adapt perfectly to very high concentrations of MeAsp (up to $[L]=10^2 K_1^L$). As the Tar methylation level approaches its maximum (boundary) value of 4, adaptation becomes inaccurate (labeled by the dotted line), and the Tsr methylation level starts to increase. **(C)** The steady-state kinase activities and **(D)** the receptor methylation levels for different background serine levels. The perfect adaptation range for serine is much smaller than that for MeAsp, but the general relationship between kinase activity and receptor methylation still holds. As the adaptation becomes inaccurate (labeled by the dotted line), the Tar methylation level starts to increase. **(E)** The relationship between permanent methylation crosstalk and adaptation accuracy. The blue line is calculated from panels **A**, **B** for MeAsp responses, and red line from panels **C**, **D** for serine response. The near-linear curves demonstrate strong correlation between permanent methylation crosstalk and adaptation error.

Figure 4.

Quantitative comparison between the LA model prediction and experimental measurements with 1mM MeAsp (reproduced from Figure 2, 4 & 5 in Reference [36]). (A, B) The predicted dynamics of the receptor populations in each methylation level for Tar and Tsr, respectively, after adding 1mM MeAsp. (C) Mobility images of the Tar-Tsr two receptor system on the SDS-PAGE gel after addition of 1mM MeAsp. Different columns show the results at specified time points after ligand addition: $t = 0$ s (dark), $t = 30$ s (red), $t = 60$ s (orange), $t = 180$ s (yellow), $t = 360$ s (light blue) and $t = 600$ s (blue). Results from pure Tar and pure Tsr receptors in fixed modification (amidation) states on the same gel are shown in the first two columns for calibration purpose. (D) Relative receptor populations in different methylation states measured from C: colored curves corresponds to the time columns with the same color-label. The inset shows calibration profiles of mixtures of Tar (green) and Tsr (black) receptors. Numbers 0, 1, 2, 3 and 4+5 (in black) show the positions of Tsr receptor with corresponding number of modifications (methylation levels), and numbers 0, 1, 2+3 and 4 (in green) are the positions of Tar receptor with corresponding number of modifications. (E) Comparison of theoretical predictions and experimental observations of the dynamic of Tsr receptor populations in $m = 1, 2$ and 3 states after addition of 1mM MeAsp. The LA model predicts non-monotonic transient behaviors for $P_{2,m}$, which always return back to the pre-stimulus level (solid blue lines), in agreement with experiments (red dots). The experimental values of $P_{2,m}$ are determined from D. All receptor populations shown are normalized by their values at $t = 0$. (F) Relative change of the population of a subset of receptor methylation levels (shaded areas in D) at different time points after addition of 1mM MeAsp. The black dots are for Tsr methylation level from 1 to 3, and the green dots are for Tar methylation levels from 2 to 4. Solid blue lines are simulation results from the LA model.

Figure 5. Quantitative comparison between the LA model prediction and the experimental measurement with 1mM of serine (similar to Figure 4C & F, reproduced from Figure 4 & 5 in Reference [36]).

Figure 6.

The adaptation trajectories and the mapping from external chemical signal to internal memory (reproduced from Figure 4 & 5 in Reference [36]). **(A)** The adaptation dynamics in response to additions of different stimuli, as represented by the (average) methylation level trajectories in the 2D plane spanned by $(\langle m \rangle_1, \langle m \rangle_2)$, are shown for the local adaptation model. Each line, started from the same original pre-stimulus state at the lower left corner, represents one trajectory after adding certain amount of stimuli (labeled besides the end point of each curve). **(B)** The adaptation trajectories from the MWC-type model. Trajectories for different stimuli fall onto a single line in the $(\langle m \rangle_1, \langle m \rangle_2)$ plane. **(C)** The ligand concentration space $(\langle [L] \rangle_1, \langle [L] \rangle_2)$ is organized by the constant adapted activity contour lines shown in the left panel; the corresponding (average) receptor methylation levels $(\langle m \rangle_1, \langle m \rangle_2)$ adapted to the external stimuli $(\langle [L] \rangle_1, \langle [L] \rangle_2)$ can be determined from the local adaptation model and are shown in the right panel with the same color as the corresponding ligand concentrations. The mapping from the external stimuli $(\langle [L] \rangle_1, \langle [L] \rangle_2)$ to the internal memory $(\langle m \rangle_1, \langle m \rangle_2)$ is unique (one-to-one) in the local adaptation model, and there is no loss of information. **(D)** In the MWC model, each constant kinase activity line in the $(\langle [L] \rangle_1, \langle [L] \rangle_2)$ space, shown on the left, is mapped onto a single point in the methylation space, shown on the right. This represents a drastic reduction of information from external chemical signal to the internal memory.

Figure 7. Negative-Feedback-Loop and the 10-state microscopic model for *E. coli* sensory adaptation (reproduced from Figure 1 & 3 in Reference [75]). **(A, B)** The 3-node feedback topology and its general adaptive behaviour. **(C)** The schematic 10-state microscopic model of the *E. coli* chemoreceptor adaptation process. The red and blue cycles represent the receptor methylation/demethylation cycles for low and high attractant concentrations, respectively.

Figure 8.

The energy dissipation $\Delta W = \dot{W} k_R^{-1}$ per unit of time (k_R^{-1}) (solid lines) and the normalized adaptation error $\varepsilon/\varepsilon_0$ (dotted lines) versus the parameter γ for different values of ligand concentration $[L]$. $\varepsilon_0 \equiv \varepsilon(\gamma)$. (Reproduced from Figure 3 in Reference [75]).

Figure 9.

Energy dissipation reduces adaptation error (reproduced from Figure 3 in Reference [75]).

(A) The adaptation error versus energy dissipation for different values of background ligand concentration $[L]$. Solid lines from bottom to top represent $\log_{10}([L]/K_I) = 1.2, 1.0, 0.5, -3.0$; dashed lines from bottom to top represent $\log_{10}([L]/K_I) = 3, 3.5, 4, 6$. K_I is the dissociation constant for the inactive receptor. ϵ_C is the saturation error at $W \rightarrow \infty$. W_C is defined as the W value when $\epsilon = 0.99\epsilon_C$. (B) The prefactor α in the error-energy relationship, i.e. Eq. (12), and its dependence on the methyl modification rates k_R and k_B .

Figure 10.

Adaptive accuracy versus energy cost for over 10,000 different models (represented by open circles) with random choices of parameters. $\log_{10} \gamma$ is randomly picked from $[-10, 0]$, $\log_{10} \tau_a$ is randomly picked from $[-3, 3]$, $E(0)$ and $-E(m_0)$ are randomly picked from $[11, 22]k_B T$, $\log_{10}([L]/K_I)$ is randomly picked from $[-10, 10]$. The best performance line is outlined. The case for Tar is shown as dashed line. (Reproduced from Figure 3 in Reference [75]).

Figure 11.

Adaptation dynamics of starved *E. coli* cells (reproduced from Figure 3 in Reference [75]).

(A) Response of *E. coli* cells to successive addition and removal of a saturating stimulus ($50\mu\text{M}$ MeAsp) over a 7-hour period in a medium without nutrition (stimulus time series shown at top). Changes in kinase activity were measured using FRET (based on a YFP fusion to the chemotaxis response regulator CheY and a CFP fusion to its phosphatase CheZ). The grey line is the monitored fluorescence signal (ratio of YFP to CFP). The baseline YFP/CFP ratio at zero FRET is shown by the black dashed line. The black solid line indicates the adapted activity without any stimuli. The drift in the zero-FRET baseline is primarily due to the differences in the photobleaching kinetics of YFP and CFP. The inset plot shows the normalized FRET signal in response to $50\mu\text{M}$ MeAsp addition at 1,442s (blue), 10,761s (red) and 23,468s (black), as indicated by arrows of the same colours in the main plot. The response amplitude weakens as cells de-energize. Adaptation takes longer, but activity always returns to its pre-stimulus level with high accuracy. (B) The adaptation half-time, defined as the time needed to recover half of the maximum response on MeAsp addition, increases by a factor of about 3 (from $\sim 130\text{s}$ to $\sim 410\text{s}$). (C) The relative adaptation accuracy remains unchanged (95%). The symbols in B and C are from measurements and the red lines are a guide for the eye.

E. coli chemotaxis as a probabilistic Turing machine

Figure 12.
E. coli chemotaxis as a probabilistic Turing machine.