The energy-speed-accuracy trade-off in sensory adaptation

Ganhui Lan\textsuperscript{1,\ddagger,†}, Pablo Sartori\textsuperscript{2,§}, Silke Neumann\textsuperscript{3}, Victor Sourjik\textsuperscript{3} and Yuhai Tu\textsuperscript{1,*}

Adaptation is the essential process by which an organism becomes better suited to its environment. The benefits of adaptation are well documented, but the cost it incurs remains poorly understood. Here, by analysing a stochastic model of a minimum feedback network underlying many sensory adaptation systems, we show that adaptive processes are necessarily dissipative, and continuous energy consumption is required to stabilize the adapted state. Our study reveals a general relation among energy dissipation rate, adaptation speed and the maximum adaptation accuracy. This energy-speed-accuracy relation is tested in the \textit{Escherichia coli} chemosensory system, which exhibits near-perfect chemoreceptor adaptation. We identify key requirements for the underlying biochemical network to achieve accurate adaptation with a given energy budget. Moreover, direct measurements confirm the prediction that adaptation slows down as cells gradually de-energize in a nutrient-poor medium without compromising adaptation accuracy. Our work provides a general framework to study cost-performance trade-offs for cellular regulatory functions and information processing.

Living systems are highly dissipative, consuming energy to carry out different vital functions. Although it is natural to relate energy consumption to physical functions in a cell, such as biomolecule synthesis and cell motility, the costs of regulatory functions, from maintaining homeostasis to timing of the cell cycle to computing in the brain\textsuperscript{1}, remain poorly understood. Sensory adaptation is an important regulatory function possessed by many living systems. It allows organisms to adjust themselves to maintain their sensitivity and fitness in varying environments. Most sensory adaptations are facilitated by biochemical feedback networks, examples of which, in systems ranging from bacterial chemotaxis\textsuperscript{2} and osmotic sensing in yeast\textsuperscript{3} to olfactory\textsuperscript{4} and light sensing\textsuperscript{5} in mammalian sensory neurons, are shown in Fig. 1. Given the small number of molecules in the underlying chemical reactions and thermal fluctuations, the dynamics of biological networks are inherently noisy. This then raises the questions of what drives accurate adaptation in noisy biological systems and what is the energy cost of the biochemical feedback control mechanisms.

We address these questions by first studying the stochastic dynamics of the core negative feedback control loop (Fig. 1a) shared by various adaptation systems (Fig. 1b–e). We show that despite their varying complexities, negative feedback control mechanisms break detailed balance, and therefore always operate out of equilibrium with energy dissipation. We find that energy dissipation is needed to stabilize the adapted state against noise. A relation between adaptation performance, characterized by its speed and accuracy, and the minimum energy cost is discovered. This energy-speed-accuracy (ESA) relationship is verified in a detailed microscopic model of the \textit{E. coli} chemosensory system. Direct measurements of the adaptation dynamics of starving \textit{E. coli} cells show that adaptation slows down but maintains its accuracy, confirming our predictions. Finally, we discuss the general implications of our study and its comparison with other information processing mechanisms (such as kinetic proofreading).

Breakdown of detailed balance in negative feedback loop

The three-node negative feedback network shown in Fig. 1a represents a minimum network to achieve accurate adaptation\textsuperscript{6}. A stimulus signal (s) causes a fast response in the output activity (a). The change in a triggers a slower change in the negative control element (m), which eventually cancels the effect of s and brings a back to a stimulus-independent level \(a_0\). Owing to the small size of a cell, \textit{in vivo} biochemical reactions are highly noisy. The stochastic dynamics of this feedback network can be described by two coupled Langevin equations\textsuperscript{6}:

\begin{equation}
\dot{a} = F_a(a,m,s) + \eta_a(t); \quad m = F_m(a,m) + \eta_m(t)
\end{equation}

The functions \(F_a\) and \(F_m\) characterize the coarse-grained biochemical interactions, \(\eta_a\) and \(\eta_m\) are the noises, assumed to be white with strengths \(2\Delta_a\) and \(2\Delta_m\) respectively. The detailed balance condition \(\Delta_a \partial_a F_a = \Delta_m \partial_m F_m\) is satisfied in all equilibrium systems\textsuperscript{6}. However, the negative feedback mechanism for adaptation requires the two cross derivatives of the interaction functions, \(\partial F_a / \partial m\) and \(\partial F_m / \partial a\), to have opposite signs. This requirement directly indicates the breakdown of detailed balance in all negative feedback control systems. This means that adaptation is necessarily a non-equilibrium process and it always costs (dissipates) energy.

To understand why energy dissipation is necessary for adaptation, we consider the following forms of \(F_a\) and \(F_m\):

\begin{equation}
F_a(a,m,s) = -\omega_a [a - G(s,m)]
\end{equation}

\begin{equation}
F_m(a,m) = -\omega_m (a - a_0) [\beta - (1 - \beta) C a G(s,m)] / \partial m
\end{equation}

Here, \(F_a\) describes the fast response dynamics of \(a\), with a fast rate \(\omega_a\); \(G(s,m)\) is the mean activity with opposite dependence on \(s\) and \(m\) (\(\partial_a G > 0, \partial_m G < 0\)). \(F_m\) describes the slow adaptation dynamics, with the adaptation speed controlled by \(\omega_m (\ll \omega_a)\). The

\textsuperscript{1}IBM T.J. Watson Research Center, PO Box 218, Yorktown Heights, New York 10598, USA, \textsuperscript{2}Max Planck Institute for the Physics of Complex Systems, Nothnitzer Str. 38, 01187 Dresden, Germany, \textsuperscript{3}Zentrum für Molekulare Biologie der Universität Heidelberg, 69120 Heidelberg, Germany. \textsuperscript{†}Present address: NCI Physical Sciences—Oncology Center, Johns Hopkins University, 3400 N Charles St., Maryland 21218, USA. \textsuperscript{§}These authors contributed equally to this work. *e-mail: yuhai@us.ibm.com.

© 2012 Macmillan Publishers Limited. All rights reserved.
factor \((a - a_0)\) in \(F_m\) is introduced to make accurate adaptation at \(a = a_0\) (independent of \(s\)) possible. A \(\beta\)-dependent term (in brackets) is introduced in \(F_m\) to study both the equilibrium \((\beta = 0)\) and the non-equilibrium \((\beta \neq 0)\) cases within the same model. For \(\beta = 0\), equations (2) and (3) represent an equilibrium model, as the detailed balance condition is satisfied with the constant \(C = \Delta s \omega_2/(\Delta s \omega_0)\). For \(\beta \neq 0\), the model becomes non-equilibrium. For \(\beta = 1\), we have \(F_m = -\omega_2(a - a_0)\), which corresponds to a linearized coarse-grained model for studying adaptation in \textit{E. coli} chemotaxis\(^7\).

From equations (2) and (3), there exists a steady state with a constant activity \(a = a_0\) and an \(m\)-value given by \(G(s, m^*) = a_0\) for all values of \(\beta\). With a stimulus-independent activity \(a_0\), this steady state has the desired characteristic of an accurately adapted state. However, linear stability analysis shows that this steady state is only stable when

\[
\beta > \beta_c \equiv C \partial_m G(s, m^*)/(\partial_s G(s, m^*) + 1) > 0
\]

which clearly shows that stable adaptation can only be achieved in a non-equilibrium system. To further demonstrate this point, an effective potential \(H(m)\) in \(m\)-space can be obtained by averaging over the fast-variable \(a\) (see Supplementary Information for details). As shown in Fig. 2a, for the equilibrium case \(\beta = 0\), the desired adaptation state \((m = m^*)\) is at the maximum of \(H(m)\) and
therefore unstable. As $\beta$ increases, $H(m)$ is deformed, essentially by the increasing amount of energy dissipation. When $\beta > \beta_c$, $m = m^*$ becomes a minimum of $H(m)$ and stable adaptation becomes possible.

The energy cost of adaptation

To calculate the energy cost of adaptation, we first determine the phase-space probability density $P(a,m,t)$ for the stochastic system described by equations (1)–(3). The dynamics of $P(a,m,t)$ is governed by the Fokker–Planck (FP) equation:

$$\frac{\partial P}{\partial t} = - \frac{\partial}{\partial m} \left( F_m P - \frac{\partial}{\partial m} \Delta_m P \right) - \frac{\partial}{\partial a} \left( F_a P - \frac{\partial}{\partial a} \Delta_a P \right)$$

$$= - \frac{\partial J_m}{\partial m} - \frac{\partial J_a}{\partial a}$$

(4)

where $J_m = F_m P - \Delta_m (\partial P/\partial m)$ and $J_a = F_a P - \Delta_a (\partial P/\partial a)$ are the two components of the probability density flux (current) in the $(a,m)$ phase-space. Following previous works, the non-equilibrium system can be characterized by its entropy production rate $S$, which can be computed from $J_m, J_a$ and $P$ (see Supplementary Information for derivation). From $S$, we obtain the rate at which the system dissipates energy by heating its environment, characterized by an effective temperature $T_{\text{eff}}$:

$$W = \int \int \left[ \frac{J_m^2}{\Delta_m P} + \frac{J_a^2}{\Delta_a P} \right] \, \mathrm{d}a \, \mathrm{d}m$$

in units of $kT_{\text{eff}}$, where $k$ is the Boltzmann constant. Note that the energy unit $kT_{\text{eff}}$ for the coarse-grained model can be different from the thermal energy unit $kT$, even though it ultimately originates from thermal fluctuations in the underlying chemical reactions. The average activity $\langle a \rangle$ and the relative adaptation error $\epsilon$ can also be determined by $P(a,m,t)$:

$$\langle a \rangle = \int \int \int \left[ \int a P \, \mathrm{d}a \right] \, \mathrm{d}m$$

$$\epsilon = |1 - \langle a \rangle/\bar{a}_0|$$

As $\omega_a \gg \omega_m$, the steady state solution $P^{(0)}(a,m)$ of the Fokker–Planck equation can be obtained approximately by separation of the fast variable $(a)$ from the slow one $(m)$. From $P^{(0)}(a,m)$, $\epsilon$ and $W$ in the adapted state can be determined. For the biologically relevant case with $\beta = 0$ (ref. 9), we find $\epsilon \approx \epsilon_0 \exp(-c_0 \omega_m/\Delta_m)$, and $W \approx \sigma_a^2 \omega_a/\Delta_m$, with $\sigma_a^2 \equiv \Delta_a/\omega_a$ the variance of the activity.
Figure 3 | The *E. coli* chemotaxis adaptation. **a**, The schematics 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, analogous to the flux cycles shown in Fig. 2d. **b**, The energy dissipation $\Delta W = \int W_i^{m-1}$ per unit of time ($k_i^{m-1}$) (solid lines) and the normalized adaptation error $\epsilon_i/\epsilon_0$ (dotted lines) versus the parameter $\gamma$ for different values of ligand concentration $s$. $\epsilon_i = \epsilon_0= 1$). **c**, The adaptation error versus energy dissipation for different values of background ligand concentration $s$. Solid lines from bottom to top represent $\log_{10}(s/K_i) = \{2, 1, 0.5, -0.5\}$; dashed lines from bottom to top represent $\log_{10}(s/K_i) = \{3, 3.5, 4, 5\}$. $K_i$ is the dissociation constant for the inactive receptor. $\epsilon_i$ is the saturation error at $\Delta W \rightarrow \infty$. $\Delta W_c$ is defined as the $\Delta W$ value when $\epsilon = 0.99\epsilon_i$. **d**, The prefactor $\alpha$ in the error-energy relationship and its dependence on the methyl modification rates $k_b$ and $k_d$.

(a) fluctuation. From these results, a simple relation between the rate of energy dissipation $W$, the adaptation speed $w_m$ and the adaptation error $\epsilon$ emerges:

$$W \approx (\epsilon_0 \sigma_m^x) \times w_m \times \ln(\epsilon_0/\epsilon)$$  

(5)

where $\epsilon_0$ and $\epsilon_0$ are constants depending on the system parameters and details of G. This general ESA relation holds true for other cases ($\beta < \beta < 1$), with only different expressions for $\epsilon_0$ and $\epsilon_0$. Equation (5) shows that higher energy dissipation is needed for more accurate and/or faster adaptation. See Supplementary Information for a detailed derivation of the ESA relation.

For a specific choice of $G(s, m)$ and other parameters, the phase space dynamics can be determined quantitatively by solving the FP equation (4) (see Methods). For the equilibrium model ($\beta = 0$) (Fig. 2b), the system always localizes at one of the corners of the phase space, flux vanishes everywhere ($I_i = I_m = 0$), and there is no adaptation. For the fully adaptive model ($\beta = 1$; Fig. 2c), phase-space fluxes, a trademark of non-equilibrium systems, appear. The flux vectors form a vortex (cycle) that effectively traps the system in the adapted state, which has a constant average activity ($\langle a \rangle$) and an average $m$-value ($m^*$) that increases with the signal $s$ (Fig. 2c and Supplementary Movie).

The energy cost of the negative feedback control can also be understood intuitively from a two-state system that switches between its active ($a = 1$) and inactive ($a = 0$) states with free energies $E_1(m)$ and $E_0(m)$. As illustrated in Fig. 2d, $E_1(m)$ and $E_0(m)$ have different dependencies on $m$ and cross at an intermediate point $m^*$ (a specific form of $E_0(m)$ is given in Methods). If the system operates at equilibrium, it always goes to its lowest energy state (Fig. 2d, left panel) and thus does not adapt. The strategy for adaptation is to trap the system near $m^*$. As the cross-point $m^*$ is not a minimum on either energy line, external free energy is consumed to push the system up the energy ‘hills’ along the $m$-coordinate to stabilize this adapted state (Fig. 2d, right panel).

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

To test the general ESA relation established by the coarse-grained model of adaptation, we turn to *E. coli* chemotaxis, where detailed microscopic models are available15–19. Here, we use such a microscopic model to study the energy cost of adaptation and compare the results with the general ESA relation as well as with direct experimental observations.

As shown in Fig. 3a, the state of a chemoreceptor dimer is characterized by two discrete variables: $a = 0, 1$ for activity; and $m = 0, 1, ..., m_0$ for methylation level ($m_0 = 4$ in this paper). For a given $m$, the transitions between the active ($a = 1$) and inactive ($a = 0$) states are fast, with a characteristic timescale $\tau_i$; the mean activity is determined by the free energy difference $\Delta E(s, m)$ between active and inactive states. On a change in external signal $s$, the mean activity changes quickly. The receptors adapt by changing their methylation levels ($m$ values) to balance the effect of $s$ in $\Delta E(s, m)$. The methylation and demethylation reactions are catalyzed by the methyltransferase CheR and the methylesterase CheB respectively. Here, we approximate the methylation and demethylation processes as one-step reactions, without explicitly modelling the intermediate enzyme–substrate binding/unbinding steps. The one-step reaction rates, $k_b$ and $k_d$, depend on the enzyme and substrate concentrations. This approximation does not affect the energy dissipation rate calculation significantly for Michaelis–Menten type reactions, where the substrate reaches fast chemical equilibrium with the enzyme–substrate complex (see Supplementary Information for details). To achieve accurate adaptation, CheR should preferentially enhance the methylation of the inactive receptors and CheB should preferentially enhance the demethylation of the active receptors15–18. These irreversible effects are described by two parameters $\gamma_1 (\leq 1)$ and $\gamma_2 (\leq 1)$.
that suppress the demethylation rate for the inactive receptors and the methylation rate for the active receptors respectively from their equilibrium values.

We study the stochastic dynamics of the chemoreceptors for different values of $\gamma \leq 1$ ($\gamma_1 = \gamma_2 = \gamma$ for simplicity), where $\gamma = 1$ corresponds to the equilibrium case. The probability of a receptor in a given state $(a, m), P_a(m)$, 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 $\epsilon$ and the energy dissipation rate $W$ (see Methods for details). In Fig. 3b, we show the dependence of $\epsilon$ and $\Delta W \equiv W k_R^{-1}$, which is the energy dissipation by a receptor to its environment in the form of heat during the methylation time $t_R \equiv k_R^{-1}$, on $\gamma$ for different background signals. Smaller $\gamma$ leads to smaller error, but costs more energy. By plotting $\epsilon$ versus $\Delta W$ in Fig. 3c, we find that $\epsilon$ decreases exponentially with $\Delta W$ when $\Delta W$ is less than a critical value $\Delta W_c$: 

$$\epsilon \approx \epsilon_0 e^{-a \Delta W}$$

For $\Delta W > \Delta W_c$, $\epsilon$ saturates to $\epsilon_c$, which depends on key parameters of the system. The exponential energy–error relationship holds true for different choices of the kinetic rates $k_R$ and $k_s$, and the prefactor $a$ is found to be: $a = (k_R + k_s)/2k_R$ (Fig. 3d and Supplementary Fig. S1). With the parameter correspondence $c_{0a} = k_R + k_s, a_0 = k_s/(k_R + k_s), \sigma_0^2 = a_0(1 - a_0) = k_s^2k_R/(k_R + k_s)^2$ and $c_0 = 2$, equation (6) found in $E. coli$ chemotaxis confirms the general ESA relationship (equation (5)).

**Network requirements for accurate adaptation**

The error–energy relation (equation (6)) sets the minimum adaptation error 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 $\Delta E(s, m)$ and activation time $t_R$ in our model. To evaluate these dependencies, we have computed adaptation error and energy dissipation for a large number of models, each with a random parameter set ($\Delta E(m), t_R, s, \gamma$). Figure 4 shows $\epsilon$ versus $\Delta W$ for all these models are shown in Fig. 4a. All the error–energy points are bounded by a 'best performance' (BP) line, which agrees exactly with (equation (6)).

The deviation from this BP line is caused by the finite saturation error $\epsilon_c$, evident from Fig. 3c. Taking the limit of $\gamma = 0$, we can derive the expression for $\epsilon_c$:

$$\epsilon_c = |(1/a_0 - 1)P_1(0) - P_0(m_0)|$$

which shows that the saturation error results mainly from the receptor population at the methylation boundaries ($m = 0$ or $m_0$) where the enzyme (CheB or CheR) fails to decrease or increase the receptor methylation level any further (see Supplementary Information for details). Therefore, having large boundary energy differences ($|\Delta E(0)|, |\Delta E(m_0)|$) and fast activation time ($t_R \ll k_R^{-1}$) can reduce $\epsilon_c$ by decreasing the receptor populations at the methylation boundaries (see Supplementary Figs S2,S3 for details). These requirements for accurate adaptation are met for the aspartate receptor Tar, which has $\Delta E(0) \geq 2kT, \Delta E(4) \leq -6kT$ (ref. 20), and $t_Rk_R < 10^{-3}$ (ref. 2). Our analysis also provides a plausible explanation (smaller $|\Delta E(m_0)|$) for the less accurate adaptation for the serine receptor Tsr (ref. 21).

**The energy sources for adaptation**

An examination of different adaptation networks (Fig. 1) shows that the energy sources are energy-bearing biomolecules such as ATP, GTP and SAM. For example, both the HOG1 feedback loop3,22,23 in yeast osmotic shock adaptation (Fig. 1c) and the

---

**Figure 4 | The cost-performance relationship. a.** Adaptive accuracy versus energy cost for over 10,000 different models (represented by open circles) with random choices of parameters. log($\Delta W$) is randomly picked from $0, -10 \log(\Delta W)$ is randomly picked from $-3, 3$. $\Delta E(0)$ and $\Delta E(m_0)$ are randomly picked from $[11, 22]kT$, log($\Delta E(m_0)$) is randomly picked from $[-10, 10]$. The best performance line is outlined. The case for Tar is shown (dashed line) with the available energies in SAM and ATP (both at 20% efficiency) marked. **b.** The responses to a step stimulus (from $s = 0$ to $s = 10k$) at $t = 1$ for the equilibrium model (black), and non-equilibrium models driven by ATP (red line) and SAM (blue line) at 20% efficiency.

Calmodulin kinase II-dependent feedback control24,25 for olfactory adaptation (Fig. 1d) are fueled by ATP hydrolysis accompanying various phosphorylation–dephosphorylation cycles.

For *E. coli* chemotaxis, adaptation is driven by hydrolysis of SAM, the methyl group donor for chemoreceptors. Because one fuel molecule (SAM) is hydrolyzed during each methylation–demethylation cycle, the adaptation accuracy is controlled by the free energy release in the hydrolysis of one fuel molecule. As shown in Fig. 4b, given the high energy release ($\Delta G^\circ \sim 29kT$) from methylation by SAM (ref. 26), a modest 20% efficiency ($\Delta W/\Delta G^\circ$) leads to a maximum adaptation accuracy of $\sim 99\%$, consistent with the high adaptation accuracy observed in *E. coli* chemotaxis27. At the same efficiency, if adaptation is driven by phosphorylation from ATP ($\Delta G^\circ \sim 12kT$), the accuracy would be $\sim 80\%$, consistent with the less accurate (but adequate) adaptation in the rod cell28.

**Adaptation dynamics of starving cells**

According to the ESA relation, the 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 $k_b$, 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.

We have tested this prediction by direct measurements of E. coli’s adaptation dynamics using fluorescent resonance energy transfer (FRET; ref. 29). As shown in Fig. 5a–c, adaptation to a given stimulus becomes progressively slower (Fig. 5b) for cells that are kept in a medium without an energy source. The background kinase activity (in buffer) decreases with time (Fig. 5a), indicative of the decreasing energy level of the starving cells. Remarkably, the adaptation accuracy remains almost unchanged with time (within experimental resolution), as shown in Fig. 5c, consistent with our prediction.

For an E. coli cell, the methylation levels of its chemoreceptors serve as the memory of the external signals it received.30 After a change in the signal, the adaptation process ‘rewrites’ this memory accordingly. As pointed out by Landauer31, 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 integrity of the memory against noise. For an E. coli cell with \( \sim 10^8 \) chemoreceptors32 and a (linear) adaptation time of \( \sim 10 \) s, the energy consumption rate is \( \sim 3 \times 10^4 kT/s \) (equivalent to \( \sim 10^4\) ATP/s), which is 5–10% of the energy needed to drive a flagellar motor rotating at 100 Hz (ref. 33), even when the cell is not actively sensing or adapting. The total energy budget for regulations in an E. coli cell is 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 seen in Fig. 5a may be seen as a way for the cells to conserve energy for other regulatory functions with higher priorities.

Discussion

In biochemical networks, there are many ‘futile cycles’, in which two pathways run simultaneously in opposite directions dissipating chemical energy with no apparent function34. Here, we show that these cycles, shown in Figs 3a and 2d, are crucial in powering accurate adaptation. In general, cells need to process information accurately under noisy conditions. A well-known example is the kinetic proofreading (KP) scheme for error-correction proposed by Hopfield35. Similar to the sensory adaptation system studied here, energy is also consumed to increase accuracy in the KP scheme36. However, subtle differences exist between adaptation and KP. Whereas energy is consumed in KP to effectively lower the free energy of the already stable ‘correct’ state to reduce error, it is used in the adaptation system to stabilize an originally unstable state (Fig. 2a). It remains an open question whether there are general thermodynamic principles governing cellular information processing, such as proofreading and sensory adaptation. It will also be interesting to establish the ESA relationship in other more complex adaptation systems, such as those mentioned in Fig. 1c–e, and to relate the ESA relationship to the efficiency at maximum power studied in molecular motor systems11,38.

Biological systems consume energy to carry out various vital functions, many of which are related to regulation5, where accuracy and speed are of primary importance. Despite the complexity of biochemical networks responsible for various regulatory functions, it has been suggested that a small set of network motifs are used repeatedly41. The cost–performance tradeoff studied in this paper provides a new perspective, in addition to other general considerations such as robustness15 and evolvability42, to understand the design principles and evolutionary origins of these regulatory circuits and their building blocks.

Methods

A specific case of \( G(s, m) \). A simple sigmoidal form \( G(s, m) = 1/1+ \left( s/K_s(m) \right)^4 \) has been studied in the continuum adaptation model, equations (1)–(3).

$$K_s(m) = K_o e^{-m}$$

and time step \( \Delta t = 5 \times 10^{-4} \). No flux boundary conditions are used:

$$J_t(a, m = 0) = J_t(a, m = 4) = J_r(a = 0, m) = J_r(a = 1, m) = 0.$$ Other parameters used are \( \omega_m = 5, \omega_m = 50(\beta \omega_m), \sigma_m^2 = 10^{-2}, a_0 = 0.5, \) and \( H = 1. \)
The dynamics of $P_a(m)$ is governed by the master equation:
\[
dP_a(m)/dt = -k_{-a}(m + 1)P_a(m + 1) + k_{-a}(m)P_a(m) - k_{-a}(m - 1)P_a(m - 1) + k_{-a}(m)P_a(m),
\]
for $a = 0, 1$ and $m = 0, 1, 2, 3, 4$. No transition flux boundary conditions are used at $m = 0$ and $m = 4$. The methylation (demethylation) rate for inactive (active) receptor is set to be $k_0$ and $k_a$; $k_{-a}(m) = k_{-a}(m)$. Their counter rates are suppressed from their equilibrium values by $\gamma_1$ and $\gamma_2$; $k_{-a}(m) = k_{-a}(m)\exp(-\gamma_1/2)$, $k_{-a}(m) = k_{-a}(m)\exp(-\gamma_2/2)$. The activation rate $\alpha(m)$ and deactivation rate $\alpha(m)$ satisfy $\alpha(m) = \alpha(m)/(\exp(\Delta E(s,m))$. The activation time $\tau_a = \min(\alpha(m))$ is set to be 1, and the methylation flux $\gamma_1$ is taken from the Monod-Chandeux-Wyman (MWC) model of E. coli chemoreceptor complexes, with the ligand concentration. We choose $E_0(s,m) = (a - 1)\Delta E(s,m)$ for simplicity. The parameters in $\Delta E(s,m)$ are from ref. 9 for E. coli chemoreceptor Tar. $K_m = 18.2\mu M$, $K_s = 3.000\mu M$, $\omega_m = 2$, $m = 1$. $N$ is the number of strongly coupled receptor dimers. From the linear dependence of $\Delta E$ on $N$, it can be shown that the energy dissipation rate $W$ scales linearly with $N$. So, only $N = 1$ is studied here and the resulting energy cost is for each receptor dimer. Note that according to ref. 20, the adaptation speed also scales linearly with $N$. Therefore, the ESA relation holds independent of $N$.

The steady-state distribution $P_{ss}(m)$ is solved by $dP_{ss}(m)/dt = 0$. The energy dissipation depends on the fluxes between two states $A$ and $B$. For example, for $A = (m, a)$, $B = (n, a + 1)$, the two counter fluxes are $f_{AB} = k_{-a}(m)P_a(m)$ and $f_{BA} = k_{a}(m + 1)P_a(m + 1)$. The entropy production rate at link AB is $S_{AB} = (J_{AB} - J_{BA}\max)\ln(J_{AB}/J_{BA})$, and the total entropy production rate $S$ of the system is the sum of $S_{AB}$ over all the links (see Supplementary Information for details). The energy dissipation rate $W = kT$ $S$, where $kT$ is the thermal energy unit. The adaptation error can be obtained from the average activity ($\langle a \rangle = \sum P_{ss}(m)$).

**Experiments.**

The adaptation measurement was performed with tryptophan-broth-grown E. coli K-12 strain L1100 $\Delta$ (cheY cheZ) expressing the CheY-YFP (yellow fluorescent protein)/CheZ-CEF (cyan fluorescent protein) FRET pair, a reporter for kinase activity, as described in a previous article $\cite{24}$. During the measurement, cells were kept under a constant flow of nutrient-free terehing buffer (10 mM KPO$_4$, 0.1 mM EDTA, 1 mM methionine, 67 mM NaCl, pH 7.0) at a rate of 300 ml min$^{-1}$ and were stimulated at regular intervals with 50 pmol/μl α-methyl-ω-aspartate (MeAsp), a non-metabolizable aspartate analogue, until adaptation was completed. Data were acquired as in ref. 43.

**Received 9 September 2011; accepted 22 February 2012; published online 25 March 2012**

**References**

1. Niven, J. E. & Laughlin, S. B. Energy limitation as a selective pressure on the evolution of sensory systems. J. Exp. Biol. 211, 1792–1804 (2008).
2. Hazebauer, G. L., Falke, J. J. & Parkinson, J. S. Bacterial chemoreceptors: high-performance signaling in networked arrays. Trends Biochem. Sci. 33, 9–19 (2008).
3. Hohmann, S. Osmotic stress signaling and osmoadaptation in yeasts. Am. Soc. Microbiol. 66, 300–372 (2002).
4. Menini, A. Calcium signalling and regulation in olfactory neurons. Curr. Opinion Neurobiol. 9, 419–426 (1999).
5. Nakatani, K., Tamura, T. & Yau, K. W. Light adaptation in retinal rods of the rabbit and two other nonprimate mammals. J. Gen. Physiol. 97, 413–435 (1991).
6. Ma, W. et al. Defining network topologies that can achieve biochemical adaptation. Cell 138, 760–773 (2009).
7. Sartori, P. & Tu, Y. Noise filtering strategies in adaptive biochemical signaling networks: Application to E. Coli chemotaxis. J. Stat. Phys. 142, 1206–1217 (2011).
8. Kampen Van, N. G. Stochastic Processes in Physics and Chemistry (North-Holland, 1981).
9. Tu, Y., Shimizu, T. S. & Berg, H. C. Modeling the chemotactic response of E. Coli to time-varying stimuli. Proc. Natl Acad. Sci. USA 105, 14885–14890 (2008).
10. Lobevoi, J. L. & Sopha, H. A Gallavotti–Cohen-type symmetry in the large deviation functional for stochastic dynamics. J. Stat. Phys. 95, 333–365 (1999).
11. Parmeggiani, A., Julicher, F., Ajdari, A. & Prost, J. Energy transduction of isothermal ratchets: Generic aspects and specific examples close to and far from equilibrium. Phys. Rev. E 60, 2127–2140 (1999).
12. Seifert, U. Entropy production along a stochastic trajectory and an integral fluctuation theorem. Phys. Rev. Lett. 95, 040602 (2005).
13. Tate, T. Entropy production in nonequilibrium systems described by a Fokker–Planck equation. Brazilian J. Phys. 36, 1285–1289 (2006).
14. Qian, H. Phosphorylation energy hypothesis: Open chemical systems and their biological function. Annu. Rev. Phys. Chem. 58, 113–142 (2007).
15. Barkai, N. & Leibler, S. Robustness in simple biochemical networks. Nature 387, 913–917 (1997).