Maxwell’s demon in biochemical signal transduction with feedback loop

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Signal transduction in living cells is vital to maintain life itself, where information transfer in noisy environment plays a significant role. In a rather different context, the recent intensive research on ‘Maxwell’s demon’—a feedback controller that utilizes information of individual molecules—have led to a unified theory of information and thermodynamics. Here we combine these two streams of research, and show that the second law of thermodynamics with information reveals the fundamental limit of the robustness of signal transduction against environmental fluctuations. Especially, we find that the degree of robustness is quantitatively characterized by an informational quantity called transfer entropy. Our information-thermodynamic approach is applicable to biological communication inside cells, in which there is no explicit channel coding in contrast to artificial communication. Our result could open up a novel biophysical approach to understand information processing in living systems on the basis of the fundamental information–thermodynamics link.
A crucial feature of biological signal transduction lies in the fact that it works in noisy environment\(^4\)–\(^11\). To understand its mechanism, signal transduction has been modelled as noisy information processing\(^4\)–\(^11\). For example, signal transduction of bacterial chemotaxis of Escherichia coli (E. coli) has been investigated as a simple model organism for sensory adaptation\(^12\)–\(^16\). A crucial ingredient of E. coli chemotaxis is a feedback loop, which enhances the robustness of the signal transduction against environmental noise.

The information transmission inside the feedback loop can be quantified by the transfer entropy, which was originally introduced in the context of time series analysis\(^17\), and has been investigated as a simple model organism for sensory adaptation\(^12\)–\(^16\). The transfer entropy is the conditional mutual information representing the directed information flow, and gives an upper bound of the redundancy of the channel coding in an artificial communication channel with a feedback loop\(^21\). This is a fundamental consequence of Shannon’s second theorem\(^22,23\). However, as there is not any explicit channel coding inside living cells, the role of the transfer entropy in biological communication has not been fully understood.

The transfer entropy also plays a significant role in thermodynamics\(^24\). Historically, the connection between thermodynamics and information was first discussed in the thought experiment of ‘Maxwell’s demon’ in the nineteenth century\(^25\)–\(^27\), where the demon is regarded as a feedback controller. In the recent progress on this problem in light of modern non-equilibrium statistical physics\(^28\),\(^29\), a universal and quantitative theory of thermodynamics feedback control has been developed, leading to the field of information thermodynamics\(^24,30\)–\(^48\). Information thermodynamics reveals a generalization of the second law of thermodynamics and the Shannon’s information theory\(^22,23\). We numerically studied the information-thermodynamics efficiency of the signal transduction of E. coli chemotaxis, and found that the signal transduction of E. coli chemotaxis is efficient as an information-thermodynamic device, even when it is highly dissipative as a conventional heat engine.

**Results**

**Model.** The main components of E. coli chemotaxis are the ligand density change \(l\), the kinase activity \(a\) and the methylation level \(m\) of the receptor (Fig. 1). A feedback loop exists between \(a\) and \(m\), which reduces the environmental noise in the signal transduction pathway from \(l\) to \(a\) (ref. 49). Let \(l_0\), \(a_0\) and \(m_0\) be the values of these quantities at time \(t\). They obey stochastic dynamics due to the noise, and are described by the following coupled Langevin equations\(^24\)–\(^16\):

\[
\begin{align*}
\dot{a}_t &= -\frac{1}{C_2} [a_t - a_t(m_t, l_t)] + \zeta_1^n, \\
\dot{m}_t &= -\frac{1}{C_1} m_t + \frac{\gamma}{C_1} a_t + \zeta_1^m,
\end{align*}
\]

where \(a_t(m_t, l_t)\) is the stationary value of the kinase activity under the instantaneous values of the methylation level \(m_t\) and the ligand signal \(l_t\). In the case of E. coli chemotaxis, we can approximate \(a_t(m_t, l_t)\) as \(2m_t - \beta l_t\) by linearizing it around the steady-state value\(^14\)–\(^16\): \(\langle \zeta_1^n \rangle = 0\) and \(\langle \zeta_1^m \zeta_1^n \rangle = 2T_a^1 \delta_{xx}(t - t')\), where \(\langle \cdots \rangle\) describes the ensemble average. \(T_a^1\) describes the intensity of the environmental noise at time \(t\), which is not necessarily thermal inside cells. The noise intensity \(T_a^1\) characterizes the ligand fluctuation. The time constants satisfy \(t^m \gg t^e > 0\), which implies that the relaxation of \(a\) to \(a_0\) is much faster than that of \(m\).

The mechanism of adaptation in this model is as follows (Fig. 2; ref. 14,16). Suppose that the system is initially in a stationary state with \(l_t = 0\) and \(a_t = a_t(m_0, 0) = 0\) at time \(t < 0\), and \(l_t\) suddenly changes from 0 to 1 at time \(t = 0\) as a step function. Then, \(a_t\) rapidly equilibrates to \(a_t(m_1, 1)\) so that the difference \(a_t - a_0\) becomes small. The difference \(a_t - a_0\) plays an important role, which characterizes the level of adaptation. Next, \(m_t\) gradually changes to satisfy \(a_t(m_t, 1) = 0\), and thus \(a_t\) returns to 0, where \(a_t - a_0\) remains small.

**Robustness against environmental noise.** We introduce a key quantity that characterizes the robustness of adaptation, which is defined as the difference between the intensity of the ligand noise \(T_a^1\) and the mean square error of the level of adaptation \(\langle (a_t - a_0)^2 \rangle\):

\[
I_T^a := \frac{1}{t^a} \left[ T_a^1 - \frac{1}{t^e} \langle (a_t - a_0)^2 \rangle \right].
\]

The larger \(I_T^a\) is, the more robust the signal transduction is against the environmental noise. In the case of thermodynamics, \(I_T^a\) corresponds to the heat absorption in \(a\) and characterizes the
violation of the fluctuation–dissipation theorem. Since the environmental noise is not necessarily thermal in the present situation, $J_t^a$ is not exactly the same as the heat, but is a biophysical quantity that characterizes the robustness of adaptation against the environmental noise.

Information flow. We here discuss the quantitative definition of the transfer entropy. The transfer entropy from $a$ to $m$ at time $t$ is defined as the conditional mutual information between $a_t$ and $m_t + m_{t-1}$ under the condition of $m_t$:

$$dI_t^a := \int dm_{t+dt} da_t dm_t p[m_{t+dt}, a_t, m_t] \ln \frac{p[m_{t+dt}, a_t | m_t]}{p[m_{t+dt} | m_t]},$$

where $p[m_{t+dt}, a_t, m_t]$ is the joint probability distribution of $(m_{t+dt}, a_t, m_t)$, and $p[m_{t+dt} | m_t]$ is the probability distribution of $m_{t+dt}$ under the condition of $(a_t, m_t)$. The transfer entropy characterizes the directed information flow from $a$ to $m$ during an infinitesimal time interval $dt$ (refs 17,50), which quantifies a causal influence between them. From the non-negativity of the conditional mutual information, that of the transfer entropy follows: $dI_t^a \geq 0$.

Second law of information thermodynamics. We now consider the second law of information thermodynamics, which characterizes the entropy change in a subsystem in terms of the information flow (Fig. 3). In the case of equation (1), the generalized second law is given as follows (see also Methods section):

$$dS_t^{\text{info}} + dS_t^{\text{ therm}} \geq \frac{dI_t^a}{T_t^a} dt. \tag{4}$$

Here, $dS_t^{\text{info}}$ is the conditional Shannon entropy change defined as $dS_t^{\text{info}} := S[a | m_t + m_{t-1}] - S[a | m_t]$ with $S[a | m_t] := -\int da_t dm_t p[a_t | m_t] \ln p[a_t | m_t]$, which vanishes in the stationary state. The transfer entropy $dI_t^a$ on the left-hand side of equation (4) shows the significant role of the feedback loop, implying that the robustness of adaptation can be enhanced against the environmental noise by the feedback using information. This is analogous to the central feature of Maxwell’s demon.

To further clarify the meaning of inequality (equation (4)), we focus on the case of the stationary state. If there was no feedback loop between $m$ and $a$, then the second law reduces to $\langle \dot{a}_t \rangle \geq \frac{\varepsilon_t T_t^a}{a}$, which, as naturally expected, implies that the fluctuation of the signal transduction is bounded by the intensity of the environmental noise. In contrast, in the presence of a feedback loop, $\langle \dot{a}_t \rangle$ can be smaller than $\varepsilon_t T_t^a$ owing to the transfer entropy $dI_t^a$ in the feedback loop:

$$\langle \dot{a}_t \rangle \geq \frac{\varepsilon_t T_t^a}{a} \frac{dI_t^a}{\varepsilon_t}.$$  \tag{5}

This inequality clarifies the role of the transfer entropy in biochemical signal transduction; the transfer entropy characterizes an upper bound of the robustness of the signal transduction in the biochemical network.

In general, the information-thermodynamic bound becomes tight if $\varepsilon_t \sim \varepsilon_t^a$ are both small. The realistic parameters of the bacterial chemotaxis are given by $\varepsilon_t \sim 0$ and $\varepsilon_t^a \sim 0$ (refs 7,14,16), and therefore the real adaptation process is accompanied by a finite amount of information-thermodynamics dissipation.

Our model of chemotaxis has the same mathematical structure as the feedback cooling of a colloidal particle by Maxwell’s demon, where the feedback cooling is analogous to the noise filtering in the sensory adaptation. This analogy is a central idea of our study; the information-thermodynamic inequalities (equation (5) in our case) characterize the robustness of adaptation as well as the performance of feedback cooling.

Numerical result. We consider the second law (equation (4)) in non-stationary dynamics, and numerically demonstrate the power of this inequality. Figure 4 shows $f_t^a dt / T_t^a$ and $\Xi_t^{\text{info}} := dI_t^a + dS_t^{\text{info}}$ in six different types of dynamics of adaptation, where the ligand signal is given by a step function (Fig. 4a), a sinusoidal function (Fig. 4b), a linear function (Fig. 4c), an exponential decay (Fig. 4d), a square wave (Fig. 4e) and a triangle wave (Fig. 4f). These results confirm that $\Xi_t^{\text{info}}$ gives a tight bound of $f_t^a$, implying that the transfer entropy characterizes the robustness well. In Fig. 4b,f, the robustness $f_t^a dt / T_t^a$ is nearly equal to the information-thermodynamics bound $\Xi_t^{\text{info}}$ when the signal and noise are decreasing or increasing rapidly (for example, $t \simeq 0.008$ and $t = 0.012$ in Fig. 4f).

Conventional second law of thermodynamics. For the purpose of comparison, we next consider another upper bound of the robustness, which is given by the conventional second law of thermodynamics without information. We define the heat absorption by $m$ as $J_t^m := -\langle \dot{a}_t \rangle \langle \varepsilon_t \rangle$, and the Shannon entropy change in the total system as $dS_t^{\text{ therm}} := S[a | m_t + m_{t-1}] - S[a | m_t]$ with $S[a | m_t] := -\int da_t dm_t p[a_t | m_t] \ln p[a_t | m_t]$, which vanishes
in the stationary state. We can then show that

$$\Xi_{\text{SL}}^t := - \frac{f^m}{T^m_t} \, dt + dS^m_t$$  \hspace{1cm} (7)

is an upper bound of $f^m_t \, dt / T^m_t$, as a straightforward consequence of the conventional second law of thermodynamics of the total system of $a$ and $m$ (refs 28,29). The conventional second law implies that the dissipation in $m$ should compensate for that in $a$ (Fig. 3). Figure 4 shows $f^m_t \, dt / T^m_t$ along with $\Xi_{\text{info}}^m$ and $\Xi_{\text{SL}}^m$. Remarkably, information-thermodynamic bound $\Xi_{\text{info}}^m$ gives a tighter bound of $f^m_t$ than the conventional thermodynamics bound $\Xi_{\text{SL}}^m$ such that

$$\Xi_{\text{SL}}^t \geq \Xi_{\text{info}}^m \geq \frac{f^m_t}{T^m_t} \, dt,$$  \hspace{1cm} (8)

for every non-stationary dynamics shown in Fig. 4. Moreover, we can analytically show inequalities (equation (8)) in the stationary state (Supplementary Note 4).

To compare the information-thermodynamic bound and the conventional thermodynamics one more quantitatively, we introduce an information-thermodynamic figure of merit based on the inequalities (equation (8)):

$$\chi := 1 - \frac{\Xi_{\text{info}}^m - f^m_t \, dt / T^m_t}{\Xi_{\text{SL}}^t - f^m_t \, dt / T^m_t},$$  \hspace{1cm} (9)

where the second term on the right-hand side is given by the ratio between the information-thermodynamic dissipation $\Xi_{\text{info}}^m - f^m_t \, dt / T^m_t$ and the entire thermodynamic dissipation $\Xi_{\text{SL}}^t - f^m_t \, dt / T^m_t$. This quantity satisfies $0 \leq \chi \leq 1$, and $\chi \approx 1$ ($\chi \approx 0$) means that information-thermodynamic bound is much tighter (a little tighter) compared with the conventional thermodynamic bound. We numerically calculated $\chi$ in the aforementioned six types of dynamics of adaptation (Supplementary Figs 1–6). In the case of a linear function (Supplementary Fig. 3), we found that $\chi$ increases in time $t$ and approaches $\chi \approx 1$. In this case, the signal transduction of _E. coli_ chemotaxis is highly dissipative as a thermodynamic engine, but efficient as an information transmission device.

**Comparison with Shannon’s theory.** We here discuss the similarity and the difference between our result and the Shannon’s information theory (refs 22,23; Fig. 5). The Shannon’s second
Robustness of signal transduction against noise $J^R_t$

$$\text{d}I^R_t = \frac{\text{d}I^A}{\text{d}t} \text{dt}$$

in the stationary state

Achievable information rate

Figure 5 | Analogy and difference between our approach and Shannon’s information theory. (a) Information thermodynamics for biochemical signal transduction. The robustness $J^R_t$ is bounded by the transfer entropy $dI^R_t$ in the stationary states, which is a consequence of the second law of information thermodynamics. (b) Information theory for artificial communication. The achievable information rate $R$, given by the redundancy of the channel coding, is bounded by the channel capacity $C = \max dI^R_t$, which is a consequence of the Shannon’s second theorem. If the noise is Gaussian as is the case for the E. coli chemotaxis, both of the transfer entropy and the channel capacity are given by the power-to-noise ratio $C = dI^R_t = (2)^{-1} \ln (1 + \text{d}P_t / N_t)$, under the condition that the initial distribution is Gaussian (see Methods section).

The analytical expression of the transfer entropy. In the case of E. coli chemotaxis, we have $a_t = z_m - \beta \ell_t$, and equation (1) become linear. In this situation, if the initial distribution is Gaussian, we can analytically obtain the transfer entropy up to the order of $d_t$ (Supplementary Note 4): $dI^R_t = (2)^{-1} \ln (1 + \text{d}P_t / N_t)$, where $N_t = \sum a_t$ describes the intensity of the environmental noise, and $d_t := (1 - \langle a \rangle^2) \langle \text{d}P_t / d_t \rangle$ describes the intensity of the signal from a to $m_t$ per unit time with $d_{m_t} := (1 - \langle a \rangle^2) (\text{d}P_t / d_t)^{\langle a \rangle^2}$. We note that $d_{m_t}$ for the Gaussian case is greater than that of the non-Gaussian case, if $V^2$ and $\rho^m$ are the same. Therefore, the above analytical expression of $dI^R_t$ is the same as the Shannon–Hartley theorem.

Methods

The outline of the derivation of inequality (4). We here show the outline of the derivation of the information-thermodynamic inequality (equation (4); see also Supplementary Note 2 for details). The heat dissipation $\text{d}S_t^{\text{th}} / \text{d}t$ is given by the ratio between forward and backward path probabilities as $\text{d}S_t^{\text{th}} / \text{d}t = \int \text{d}a \text{d}b \text{d}c \text{d}N \text{p}(a, b, c, N) p(a, b, c, N) / p(a, b, c, N)$ (refs 24,28,29), where the backward path probability $p(a, b, c, N) := p(c, b, a, N) / p(c, b, a, N)$ can be calculated from the forward path probability $p(a, b, c, N) := p(c, a, b, N) / p(c, a, b, N)$. Thus, the difference $dI^R_t + dS_t^{\text{th}} / \text{d}t$ is given by the Kullback–Leibler divergence. From its non-negativity, we have $dI^R_t + dS_t^{\text{th}} / \text{d}t \geq dI^F_t$. This inequality can be derived from the general inequality of information thermodynamics (see Supplementary Note 3 and Supplementary Fig. 7). As discussed in Supplementary Note 3, this inequality gives a weaker bound of the entropy production.

The analytical expression of the transfer entropy. In the case of E. coli chemotaxis, we have $a_t = z_m - \beta \ell_t$, and equation (1) become linear. In this situation, if the initial distribution is Gaussian, we can analytically obtain the transfer entropy up to the order of $d_t$ (Supplementary Note 4): $dI^R_t = (2)^{-1} \ln (1 + \text{d}P_t / N_t)$, where $N_t = \sum a_t$ describes the intensity of the environmental noise, and $d_t := (1 - \langle a \rangle^2) \langle \text{d}P_t / d_t \rangle$ describes the intensity of the signal from a to $m_t$ per unit time with $d_{m_t} := (1 - \langle a \rangle^2) (\text{d}P_t / d_t)^{\langle a \rangle^2}$. We note that $d_{m_t}$ for the Gaussian case is greater than that of the non-Gaussian case, if $V^2$ and $\rho^m$ are the same. Therefore, the above analytical expression of $dI^R_t$ is the same as the Shannon–Hartley theorem.

References

1. Phillips, R., Kondev, J. & Theriot, J. Physical Biology of the Cell (Garland Science, 2009).
2. Korobkova, E., Emonts, T., Vilar, J. M., Shimizu, T. S. & Cluzel, P. From molecular noise to behavioural variability in a single bacterium. Nature 428, 574–578 (2004).
3. Lestas, I., Vinnicombe, G. & Paulsson, J. Fundamental limits on the suppression of molecular fluctuations. Nature 467, 174–178 (2010).
4. Andrews, B. W. & Iglesias, P. A. An information-theoretic characterization of the optimal gradient sensing response of cells. Proc. Natl Acad. Sci. USA 104, 21810–21815 (2007).
5. Skerker, J. M. et al. Rewiring the specificity of two-component signal transduction systems. Cell 133, 1043–1054 (2008).
6. Mehta, P., Goyal, S. L., Tong, J., Bassler, B. L. & Wingreen, N. S. Information processing and signal integration in bacterial quorum sensing. Mol. Syst. Biol. 5, 325 (2009).
7. Tostevin, F. & ten Wolde, P. R. Mutual information between input and output trajectories of biochemical networks. Phys. Rev. Lett. 2, 218101 (2009).
8. Tu, Y. The nonequilibrium mechanism for ultrasensitivity in a biological switch: Sensing by Maxwell’s demons. Proc. Natl Acad. Sci. USA 105, 11737–11741 (2008).
9. Cheong, R., Rhee, A., Wang, C. J., Nemenman, I. & Levchenko, A. Information transduction capacity of noisy biochemical signaling networks. Science 334, 354–358 (2011).
10. Uda, S. et al. Robustness and compensation of information transmission in signaling pathways. Science 341, 558–561 (2013).
11. Gavrilova, C. C. & ten Wolde, P. R. Optimal resource allocation in cellular sensing networks. Proc. Natl Acad. Sci. USA 111, 17486–17491 (2014).
12. Barkai, N. & Leibler, S. Robustness in simple biochemical networks. Nature 387, 913–917 (1997).
13. Alon, U., Surette, M. G., Barkai, N. & Leibler, S. Robustness in bacterial chemotaxis. *Nature* **397**, 168–171 (1999).
14. Tu, Y., Shimizu, T. S. & Berg, H. C. Modeling the chemotactic response of Escherichia coli to time-varying stimuli. *Proc. Natl Acad. Sci. USA* **105**, 1485514860 (2008).
15. Shimizu, T. S., Tu, Y. & Berg, H. C. A modular gradient-sensing network for chemotaxis in Escherichia coli revealed by responses to time-varying stimuli. *Mol. Syst. Biol.* **6**, 382 (2010).
16. Lan, G., Sartori, P., Neumann, S., Sourjik, V. & Tu, Y. The energy-speed-accuracy trade-off in sensory adaptation. *Nat. Phys.* **8**, 422–428 (2012).
17. Schreiber, T. Measuring information transfer. *Phys. Rev. Lett.* **85**, 461 (2000).
18. Vicente, R., Wibral, M., Lindner, M. & Pipa, G. Transfer entropy - a model-free measure of effective connectivity for the neurosciences. *J. Comput. Neurosci.* **30**, 45–67 (2011).
19. Bauer, M., Cox, J. W., Caveness, M. H., Downs, J. J. & Thornhill, N. F. Finding the direction of disturbance propagation in a chemical process using transfer entropy. *IEEE Trans. Control Syst. Technol.* **15**, 12–21 (2007).
20. Lunarella, M. & Sporns, O. Mapping information flow in sensorimotor networks. *PLoS Comput. Biol.* **2**, e144 (2006).
21. Maslov, S. Causality, feedback and directed information. *Proc. Int. Symp. Inf. Theory Appl.* 303–305 (1990).
22. Shannon, C. E. A mathematical theory of communication. *Bell Syst. Tech. J.* **27**, 379 (1948).
23. Cover, T. M. & Thomas, J. A. *Element of Information Theory* (John Wiley and Sons, 1991).
24. Ito, S. & Sagawa, T. Information thermodynamics on causal networks. *Phys. Rev. Lett.* **111**, 180603 (2013).
25. Maxwell, J. C. *Theory of Heat* (Appleton, 1871).
26. Szlacid, L. On the decrease of entropy in a thermodynamic system by the intervention of intelligent beings. *Z. Phys.* **53**, 840–856 (1929).
27. Lef, H. S. & Rex, A. F. (eds) *Maxwell’s Demon 2: Entropy, Classical and Quantum Inference Computing* (Princeton University Press, 2003).
28. Sekimoto, K. *Stochastic Energetics* (Springer, 2010).
29. Seifert, U. Stochastic thermodynamics, fluctuation theorems and molecular machines. *Rep. Prog. Phys.* **75**, 126001 (2012).
30. Allahverdyan, A. E., Janzing, D. & Mahler, G. Thermodynamic efficiency of information and heat flow. *J. Stat. Mech.* P09011 (2009).
31. Sagawa, T. & Ueda, M. Generalized Jarzynski equality under nonequilibrium feedback control. *Phys. Rev. Lett.* **104**, 090602 (2010).
32. Toyabe, S., Sagawa, T., Ueda, M., Muneyuki, E. & Sano, M. Experimental demonstration of information-to-energy conversion and validation of the generalized Jarzynski equality. *Nat. Phys.* **6**, 988–992 (2010).
33. Horowitz, J. M. & Vaikuntanathan, S. Nonequilibrium detailed fluctuation theorem for repeated discrete feedback. *Phys. Rev. E* **82**, 061120 (2010).
34. Fujitani, Y. & Suzuki, H. Jarzynski equality in the linear feedback system. *J. Phys. Soc. Jpn.* **79**, 104003–104007 (2010).
35. Horowitz, J. M. & Parrondo, J. M. Thermodynamic reversibility in feedback processes. *Eur. Phys. Lett.* **95**, 10005 (2011).
36. Ito, S. & Sano, M. Effects of error on fluctuations under feedback control. *Phys. Rev. E* **84**, 021123 (2011).
37. Sagawa, T. & Ueda, M. Fluctuation theorem with information exchange: role of correlations in stochastic thermodynamics. *Phys. Rev. Lett.* **109**, 180602 (2012).
38. Kundu, A. Nonequilibrium fluctuation theorem for systems under discrete and continuous feedback control. *Phys. Rev. E* **86**, 021107 (2012).
39. Mandal, D. & Jarzynski, C. Work and information processing in a solvable model of Maxwell's demon. *Proc. Natl Acad. Sci. USA* **109**, 1164111645 (2012).
40. Berut, A. et al. Experimental verification of Landauer’s principle linking information and thermodynamics. *Nature* **483**, 187189 (2012).
41. Hartich, D., Barato, A. C. & Seifert, U. Stochastic thermodynamics of bipartite systems: transfer entropy inequalities and a Maxwell’s demon interpretation. *J. Stat. Mech.* P02016 (2014).
42. Munakata, T. & Rosinberg, M. L. Entropy production and fluctuation theorems for Langevin processes under continuous non-Markovian feedback control. *Phys. Rev. Lett.* **112**, 180601 (2014).
43. Horowitz, J. M. & Esposito, M. Thermodynamics with continuous information flow. *Phys. Rev. X* **4**, 031015 (2014).
44. Barato, A. C., Hartich, D. & Seifert, U. Efficiency of cellular information processing. *New J. Phys.* **16**, 103024 (2014).
45. Sartori, P., Granger, L., Lee, C. F. & Horowitz, J. M. Thermodynamic costs of information processing in sensory adaption. *PLoS Comput. Biol.* **10**, e1003974 (2014).
46. Lang, A. H., Fisher, C. K., Mora, T. & Mehta, P. Thermodynamics of statistical inference by cells. *Phys. Rev. Lett.* **113**, 148103 (2014).
47. Horowitz, J. M. & Sandberg, H. Second-law-like inequalities with information and their interpretations. *New. J. Phys.* **16**, 125007 (2014).
48. Shiraiishi, N. & Sagawa, T. Fluctuation theorem for partially masked nonequilibrium dynamics. *Phys. Rev. E* **91**, 012130 (2015).
49. Sartori, P. & Tu, Y. Noise filtering strategies in adaptive biochemical signaling networks. *J. Stat. Phys.* **142**, 1206–1217 (2011).
50. Kaiser, A. & Schreiber, T. Information transfer in continuous processes. *Physica D* **166**, 43–62 (2002).
51. Hlavackova-Schindler, K., Palu, M., Vejmelka, M. & Bhattacharya, J. Causality detection based on information-theoretic approaches in time series analysis. *Phys. Rep.* **441**, 1–46 (2007).
52. Barnett, L., Barrett, A. B. & Seth, A. K. Granger causality and transfer entropy are equivalent for Gaussian variables. *Phys. Rev. Lett.* **103**, 238701 (2009).
53. Collins, D. et al. Verification of the Crooks fluctuation theorem and recovery of RNA folding free energies. *Nature* **437**, 231–234 (2005).
54. Ritott, F. Single-molecule experiments in biological physics: methods and applications. *I. Phys. Condens. Matter* **18**, R531 (2006).
55. Toyabe, S. et al. Nonequilibrium energetics of a single F1-ATPase molecule. *Phys. Rev. Lett.* **104**, 198103 (2010).
56. Hayashi, K., Ueno, H., Ino, R. & Noji, H. Fluctuation theorem applied to F1-ATPase. *Phys. Rev. Lett.* **104**, 218103 (2010).