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Epigenetic Ratchet: Spontaneous Adaptation via Stochastic Gene Expression

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Adaptation to unforeseen environmental changes is one of the most prominent features that characterize the living system. Although signal transduction and gene regulation networks evolved to adapt specific environmental conditions that they frequently experience, it is also reported that bacteria can modify their gene expression patterns to survive a huge variety of environmental conditions even without such pre-designed networks to adapt specically to each environment. Here we propose a general mechanism of cells for such "spontaneous" adaptation, on the basis of stochastic gene expression and epigenetic modication. First, a variety of gene expression states that are marginally stable states are generated by epigenetic modication. Then by taking advantage of stochastic gene expression and dilution by cellular growth, it is shown that, a gene expression pattern that achieves greater cell growth is generically selected, as conrmed by simulations and analysis of several models. The mechanism does not require any design of gene regulation networks. General relevance of the mechanism to cell biology is also discussed.

Cells can adapt to a variety of environmental conditions to achieve a higher growth state. This adaptation is attained by changing the gene expression pattern, with which cells can grow upon different environmental conditions. According to the seminal work by Jacob and Monod[1], such a response of a gene expression pattern is implemented through a signal transduction network that translates environmental conditions to the actions on the promoter of the genes responsible for adaptation. In spite of the importance of such an adaptation mechanism, there remains a question to be addressed: In order to adapt to a variety of environmental conditions, cells have to prepare signal transduction networks corresponding to all of them, for which a huge variety of chemicals and genes would be needed, which may exceed the capacity of a cell. Besides, with such a mechanism, cells would not be able to adapt to the environmental changes that they have never experienced.

Indeed, recent experiments suggest that cells can adapt even to a novel, unforeseen environment by changing a gene expression pattern[2–6]. In this case there is no room to evolve signal networks for such environment. In addition, some experiments have revealed that bacterial cells with an artificial gene network without corresponding signal transduction networks can show an adaptive response[4,7–9].

Accordingly, a possible theoretical mechanism for the selection of the adaptive state has been proposed[4,10,11]: When a cell has multiple attractors with different growth rates, the attractor with faster growth is less perturbed by stochasticity in gene expression dynamics, and cells tend to be kicked out from slow-growth attractors and attracted to those with faster growth. For this attractor selection mechanism by noise to work, however, gene regulation networks (GRNs) have to be prepared to have multiple attractors allowing for a higher growth rate under given environmental conditions. This situation will strongly limit the applicability of the mechanism. Can selection of adaptive states with higher growth rates be generally achieved without designing the GRN to have multistability?

Indeed, epigenetic modifications based on several factors, including DNA or histone modification, and their interplay with higher-order chromatin structure are known to play key roles to modify the gene expression patterns of cells[12,13]. These modifications can be fixed to various levels, via which, gene expression levels can be fixed continuously, rather than at a discrete set of values as in attractors. As will be shown, the expression level, in terms of dynamical systems, are not given as a fixed-point attractor but are given as a continuous state. Now, the growth

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rate depends on the expression level, and cellular states with different growth rates are generated depending on modification levels.

In the present paper, we demonstrate that adaptation to achieve faster growth for given environmental conditions is generally attained only by noise and the growth-induced dilution, without preparing specific gene expression networks with multiple attractors. We will provide a general concept of selection from and discuss their relevance to cell biology.

Model

Here, we study a simple cell model consisting of proteins and the degree of epigenetic modification levels of genes. In the model, we take into account the following processes: (i) Each protein is synthesized at a certain rate according to the expression level of genes; (ii) proteins are spontaneously degraded; (iii) Some specific proteins determine the growth rate of the cell, whereas proteins are diluted due to the volume growth of the cell (the cell division is incorporated in the dilution process). (iv) For specific genes, epigenetic modifications are taken into account and can alter the expression levels of genes, whereas the modification changes need specific molecular machinery.

Now, we introduce a simple model consisting of the expression level of two types of genes and the corresponding proteins: target (t) and sensor (s) genes and proteins. Here, each expression variable does not necessarily represent a single gene or protein but can be regarded as a collective variable representing the average behavior of genes or proteins that share similar functions.

The target protein contributes to the growth of the cell, whose rate μ, thus, μ is the function of its concentration. As the simplest example, we suppose that the synthesis rate of the target protein is determined by an epigenetic modification level, while the sensor protein is produced in a constant rate, v_s.

Although the molecular mechanisms that regulate the epigenetic modification have not yet been fully elucidated, it is natural to assume that the epigenetic modification is regulated some other genes, which we call here as the sensor gene. If the concentration of the sensor protein exceeds a threshold value, it facilitates the synthesis of some proteins that modify the epigenetic state of the target gene. By means of the rate equations, the dynamics of the above model are given as

$$\frac{dE_t}{dt} = H(P_s)(l_+ - l_- E_t),$$ (1)

$$\frac{dP_t}{dt} = v_t E_t - d_t P_t - \mu P_t,$$ (2)

$$\frac{dP_s}{dt} = v_s - d_s P_s - \mu P_s,$$ (3)

with where E_t, P_t, and P_s represents the level of the epigenetic modification, the concentration of the target protein, and the concentration of the sensor protein, respectively. P_t is produced in proportional to the epigenetic modification level, with a rate $v_t E_t$ (the proportionality is not essential to the present study, as long as the production rate depends on E_t. For example, the mechanism works when $v_t E_t$ is replaced by $v_t E_t/(1 + E_t)$ or $v_t/(1 + E_t)$, as shown in Supplement). d_s and d_t represent the degradation rate of the corresponding protein. l_+ and l_- is the activation and inhibition rate of the epigenetic state E_t, respectively.

The modification by the sensor protein is represented by $H(P_s)$ given by a sigmoidal function, $H(P_s) = 1/(1 + \exp(-\beta(P_s - \theta)))$, where θ is the threshold for the induction, and β is steepness of this increase, corresponding to the Hill coefficient (If H is replaced by a Hill function, the results are not altered qualitatively, as shown in Supplement). This form is adopted as a natural consequence of binding–unbinding kinetics between a DNA molecule and transcription factors, with the inclusion of the effect of cooperativity.

The target protein is synthesized at the rate proportional to the epigenetic state of the gene. Here we set specific growth rate μ to $\mu = \mu_{\max}/(1 + (P_t - P_t^*)^2)$ (i.e., there is an optimal concentration of the target protein to maintain the cell growth). The results shown below, however, do not change qualitatively if we choose other forms of μ (see Supplement). Note that any specific input to increase the growth rate is not introduced here. In the Eqs. (2) and (3), a gene and corresponding protein to modify the epigenetic state are not explicitly included to the model for simplicity's sake. We have also studied a model in which the modifier gene and protein are implemented, and have confirmed that the simplification is not necessary to obtain the main results.

To study the influence of stochasticity on chemical reactions, we employed stochastic simulations of the reactions corresponding to Eqs. (1–3), via the Gillespie algorithm[14] (i.e., in the continuous limit with a large number of molecules Eqs. (1–3) is regained). The master equation which we used for the simulation is shown in the Supplement.

Results

Spontaneous adaptation via stochastic gene expression. In Fig. 1(a), examples of the time course of the growth rates and the variables are plotted for two different values of threshold θ, where the initial value of E_t and P_t at the steady-state values of Eqs. (1–3) with $\theta = 0$, so that the growth rate is low initially. The time courses show that the growth rate of a cell switches to a high value when θ is large, whereas for small θ (black curve), it remains at the initial low value. In the former case, the epigenetic state of the target gene is modified so that the cell achieves a high growth rate. Dependence of the averaged growth rate on θ is plotted in Fig. 1(b), which shows that the growth rate starts to rise at approximately $\theta \approx 150$ and reaches the maximal value at $\theta \approx 200$. Note that
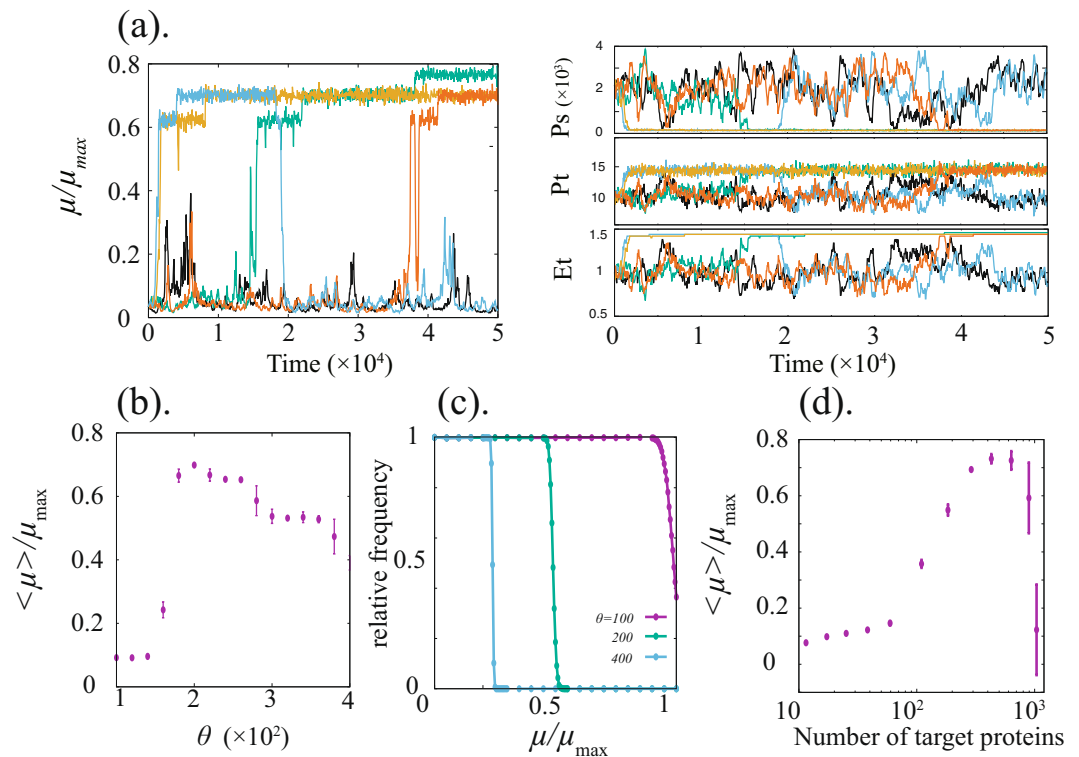
Figure 1. Simulation of our model via adaptation by stochastic reactions. (**a**) left: Time courses of the growth rate relative to its maximum value for $\theta = 0$ (black curve) and 200 (other curves). Although the time course with $\theta = 0$ fails to increase the growth rate, other time courses with $\theta = 200$ sequentially increase the growth rate. right: The behavior of the three variables, P_s, P_t, and E_t. The colors corresponds to the left panel. While the concentration of the sensor protein fluctuates around $P_s \approx 2$, it settles down at low concentration once E_t and P_t reach the target level. (**b**) The average growth rate as a function of θ. (**c**) Relative frequency of a modification event plotted against the growth rate $\mu/\mu_{\max}$. The relative frequency is obtained by dividing by that at $\mu = 0$. Data resulting from different values of θ are plotted with different colors. The frequency is obtained for a given growth rate at the moment. (**d**) Dependence of the average growth rate on the number of molecules in the reaction system. The number of reacting molecules is changed by changing the volume of the system Ω. For (**b**) and (**c**), each point is computed by averaging 50 samples of a time-averaged growth rate. Error bars indicate standard deviation. The samples were obtained by simulations with different seeds of random numbers, whereas E_t and P_t were set to the attractor value initially. The growth rate is averaged from $t = 10^5$ to $t = 10^6$. Parameters are set as $v_s = v_t = 10^2$, $d_s = 10^{-2}$, $d_t = 10$, $l_\pm = 10^{-3}$, $\mu_{\max} = 1$, $P_t^* = 15$, and $\theta = 200$ for (**d**). Different Ω values are employed to reduce the computation time, the respective values are (**a**) 20, (**b**) 50, and (**c**) 10.

even if we start from a fast-growth state, the cell cannot maintain the fast growth when $\theta \approx 0$. Thus, the failure of this adaptation at $\theta \approx 0$ is not due to the choice of the initial state.

When we set θ and the noise level appropriately, the adaptation mechanism works. It is intuitively explained as follows (referring the right panel of Fig. 1(a) might be useful): If the growth rate of the cell is low (i.e., P_t is far from P_t^*), then the sensor protein accumulates and P_s exceeds the threshold value for $H(P_s)$, θ, and then the epigenetic state of the target gene is modified. If the epigenetic state of the target gene reaches an appropriate value to allow for the increase in the growth rate, then all proteins are strongly diluted accordingly. Then, the concentration of the sensor protein hardly exceeds the threshold value because of the strong dilution by rapid growth, so that the modification of the epigenetic variable takes place at a low probability. As shown in Fig. 1(c), the probability of the change in the epigenetic variable suddenly drops to almost zero when μ is increased. Thus, the epigenetic state of the target gene remains at a certain value which supports high-growth rate. If the cell remains at a slow-growth state, however, then the epigenetic modification state keeps on being changed by noise. Hence, the system sooner or later reaches a fast-growth state and stays there.

Three conditions are essential for this adaptation mechanism to the fast-growth state work.

(i). **the noise level**, due to the finiteness of the molecule number in a cell. With the decrease in the number, the noise level due to a stochastic reaction process is increased. In Fig. 1(d), the average growth rate is plotted against the average number of molecules. If the number is too small, noise dominates over the average gene expression dynamics, so that the cellular state fluctuates almost randomly. On the other hand, when the number is too large, the noise level is so small that the state is hardly kicked out from the initial low-growth attractor of the deterministic equation (Eqs. (1–3)). At an intermediate noise level, the noise is dominant for a slow-growth state, and
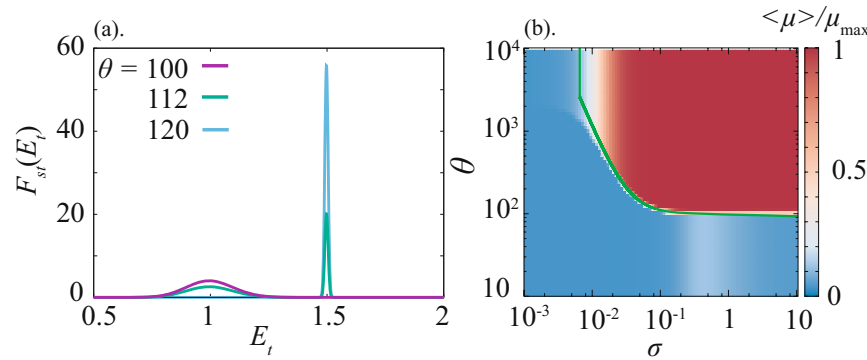
Figure 2. A distribution and the average growth rate obtained from the Fokker–Planck equation. (**a**) A stable distribution of E_t plotted for $\theta = 100,\ 112$ and 120. The peak of distribution moves from the steady-state value of Eq. (4) without a noise term to the neighbor of the target value E_t^*, as θ increases. (**b**) The average growth rate plotted as a function of the noise amplitude σ and threshold θ. The green line is the boundary which separates the adaptive and non-adaptive region. Parameter values are $l_+ = l_- = 10^{-2}$, $v = 10$, $d_t = 1$, $\tilde{\beta} = 5.0$, $\mu_{\max} = 1$, $P_t^* = 15$, and $\sigma = 0.1$ for (**a**).

once a fast-growth state is reached by the fluctuation, the deterministic change via Eqs. (1–3) dominates over the stochasticity, and the state remains therein. Thus, selection of a fast-growth state then occurs.

(ii). **"line attractor"**. Here, the reached states with high growth rates are not given as a unique fixed point but rather on a line of marginal stable states (termed as line attractor). The state can take any value on the line continuously, whereas it is attracted across the line: Recalling that the dynamics of the averaged concentration of the target molecule is written as $dE_t/dt = H(P_s)(l_+ - l_-E_t)$, E_t relaxes to l_+/l_- if P_s constantly exceeds the threshold ($H \neq 0$). Here, however, H becomes vanishingly small if P_s is far below the threshold. Then, E_t can stay at an arbitrary value. Hence the points along the line with arbitrary value of E_t and $H(P_s) = 0$ are marginally stable attractors. The solution of $dP_s/dt = 0$ and $dP_t/dt = 0$ under a given E_t value corresponds the unique fixed point of (P_s, P_t) system at which the Jacobi matrix always has negative eigenvalues.

(iii). **timescale separation between the epigenetic variable and other variables**. First of all, the change in the E_t value must be quickly reflected in the concentration of the target protein concentration P_t. If the dynamics of P_t are considerably slower than those of E_t, then P_t would not reach the value giving rise to the high growth rate, even if E_t reached the value corresponding to the fast growth. Additionally, the dynamics of P_s have to be faster than those of E_t. Otherwise, the reached steady-state value of E_t cannot afford a high growth rate.

From Eqs. (1–3), E_t and P_n ($n = s, t$) exponentially relaxes to its steady state solution with the rate approximately l_-, and $d_n + \mu_{\mathrm{st}}$, respectively, where μ_{st} is the mean growth rate near the steady state. Hence, the relation $l_- \ll d_n + \mu_{\mathrm{st}}$ is the condition for the adaptation mechanism to work.

An analytic exploitation of the mechanism. Noting the time-scale difference among the variables, we can analyze the conditions for this adaptive growth, by deriving the Fokker–Plank equation of E_t. Under the assumption that the number of the proteins is sufficiently large, we obtain the Langevin equations corresponding to Eqs. (1–3). We then assume that the timescales in the change of P_t and P_s are sufficiently smaller than that of E_t and apply the quasi-steady-state approximation: we solve the steady-state of the deterministic equation of Eqs. (2) and (3), and plug the solutions into $H(P_s)$. The noise terms for P_t, P_s, and E_t are integrated into multiplicative noise to Eq. (1)[15,16]. We thus obtain a one-variable Langevin equation, which is transformed to the Fokker–Planck equation for E_t. In addition, for the ease of analysis, we study the cases in which $d_t \gg \mu_{\max}$ while $\mu_{\max} \gg d_s$ hold. The Fokker–Planck equation for the probability density function for $F(E_t, t)$ for the epigenetic variable E_t at time t is now derived as

$$\frac{\partial}{\partial t}F(E_t, t) = -\frac{\partial}{\partial E_t}\tilde{H}(E_t)(l_+ - l_-E_t)F(E_t, t)$$

$$+\frac{\sigma^2}{2}\frac{\partial^2}{\partial E_t^2}\tilde{H}(E_t)(l_+ + l_-E_t)F(E_t, t)$$

$$\tilde{H}(E_t) = \frac{1}{1 + \exp[-\tilde{\beta}((E_t - E_t^*)^2 - \tilde{\theta})]} \tag{4}$$

The parameters are given by $\tilde{\beta} = \beta(v_t/d_t)^2 v_s/\mu_{\max}$, $\tilde{\theta} = (\theta\mu_{\max}/v_s - 1)(d_t/v_t)^2$, and $E_t^* = P_t^*d_t/v_t$, while σ represents the noise strength (A rigorous derivation of Eq. (4) and its analysis are given in Supplement). The steady solution $F_{\mathrm{st}}(E_t)$ is obtained, as is plotted for several values of θ in Fig. 2(a). The peak of the steady distribution shows a transition from the trivial value corresponding to the stable fixed point value of E_t in the noiseless limit to the adaptive value $E_t \sim E_t^*$. The average growth rate thus obtained is plotted as a function of σ and θ in Fig. 2(b). Accordingly, a boundary which separates the adaptive and non-adaptive regimes is analytically estimated (see Supplement). The estimate well captures the transition between two regimes. The growth rate remains at the high
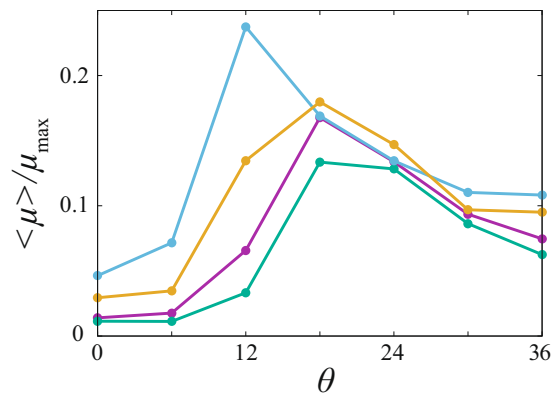
Figure 3. The averaged growth rates computed from three metabolic networks are overlaid. The growth rates are enhanced in the intermediate value (10 ~ 20) of θ. Each point is computed by averaging 5 samples of a time-averaged growth rate. Details of the simulations, and parameter values are given in Supplement.

values even if σ increases further as long as θ is sufficiently large, whereas in the infinitely large noise region, our assumption that the effect of stochasticity can be neglected for P_s and P_t is no longer valid.

To verify the robustness of the presented results, we confirmed that the adaptation mechanism works independently of the specific form of the growth rate and parameter values. Furthermore, even if the epigenetic modification state changes spontaneously, a fast-growth state is selected and sustained, as long as the modifications triggered by the sensor protein dominates the epigenetic modification. The detailed set-ups and the results are presented in Supplement.

In addition, we tested the reliability of our adaptation mechanism in chemical reaction network systems in which metabolites are converted into growth factors via several enzymatic reactions. In the model, the epigenetic variable is implemented to each enzyme, whereas one sensor protein triggers the changes of all the epigenetic variables. As shown in Fig. 3, the proposed mechanism works also in the chemical reaction network model. Details of the model are given in the Supplement.

The achieved growth rate here is still lower than μ_{max} (e.g., 20% of it), the possible maximal value. Recall, however, that initially the growth rate is ~0, and it is enhanced in the orders of magnitude, just by the fluctuations in the epigenetic modication level. The growth rate is then sustained at a high level. Note also that just a random reaction network is chosen here, without tuning the parameter values, either. Optimizing parameter values or network structures would further increase the growth rate.

Discussion

To sum up, numerical simulations and analytic calculation of our model revealed that the epigenetic regulation and stochasticity of chemical reactions lead to an increase in the growth rate of the cell, starting from the stable attractor with a low growth rate. Even though there is no pre-designed gene-regulation or signal transduction network to achieve the high growth rate, the cell reaches a high-growth state, and stays therein driven by stochastic noise and dilution by cell-volume increase.

If the growth rate is high, the dilution is large, so that the protein concentrations relax fast, and the perturbation by noise has little influence. For the slow-growth state, the protein concentrations fluctuate more under the action of noise, whereas the epigenetic state is frequently modified due to the accumulation of the sensor protein, which enables reaching a fast-growth state. This directional epigenetic change driven by noise may be reminiscent of thermal ratchet[17–21], but here it is due to noise in the reaction and epigenetic process. Given that this "epigenetic ratchet" does not require any tuned design by evolution, it can explain the robust adaptation observed experimentally[2–4].

Here we briefly review the key features for the present mechanism to work. (i). Protein concentrations are diluted due to volume growth of the cell. This is simply because the concentration is the number divided by the volume. (ii). The rate of epigenenetic modification increases with the sensor protein level, in a sigmoidal manner. This type of sigmoidal dependence is ubiquitous in biochemical reactions, and can be derived, for example, by assuming that the epigenetic modification takes place with the dissociation-association kinetics between DNA and epigenetic modification protein. Then, as in the Hill equation, the sigmoid function is a natural consequence. (iii). The epigenetic level of the target gene determines the production rate of the target protein. While we assumed that the production rate increases linearly with the epigenetic level for most part in the text, the mechanism works with the Michaelis-Menten-type production rate, and even with the decreasing function of E_t (see Supplement). (iv). The concentration of target protein determines the growth rate. Taking into account an experimental report that the expression levels of metabolic proteins are tuned to optimise the resource allocation[22], the existence of the optimal concentration of the target protein will be reasonable, whereas this assumption can be relaxed as discussed in Supplement. (v). The sensor protein needs to be constitutively produced. This point needs further experimental confirmation in bacteria. In some other organisms, however, it is verefied. For example, in one of the mammalian oxidative stress response systems, Nrf2-Keap1 system, a pluripotent transcription factor Nrf2 is continuously produced. Further, it is suggested that the transcriptional regulation by Nrf2 leads to a chromatin remodeling[23].

Although we need further experimental evidences to support the present model, we should also note that the importance of the epigenetic regulatory mechanisms has been confirmed both for prokaryotes and eukaryotes by a number of studies[24–26]. It is also reported theoretically that the epigenetic modifications allow for compatibility between evolutionary robustness and plasticity[27]. Although factors that provoke epigenetic modification events remain to be elucidated, some evidence suggests that epigenetic modifications are incuded by environmental changes[26]. Besides, the epigenetic modification contains noise because of the inherent stochasticity of gene expression levels and chemical reactions. Indeed, switches between the two epigenetic states in the *lac* systems are reported to be stochastic[28,29]. Furthermore, epigenetic modifications are inherited over generations as "epigenetic memory"[30], which may indicate slow dynamics of epigenetic modifications. These experimental reports support the assumptions on the epigenetic modifications required in the present study.

Recently, Rocco *et al.*[31] proposed a possible scenario for the bacterial persistence[32,33], based on the transcriptional noise and slow relaxation of the protein concentration (instead of the epigenetic change in our model). We hope that the adaptive mechanism proposed here could also shed light on persistence.

Note that the three adaptation mechanisms, i.e., designed signal transduction[1], attractor selection[4,10,11], and the present epigenetic mechanism are not mutually exclusive. Using these three adaptation mechanisms properly according to the situations, cells may realize the flexible adaptation.

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Author contributions

Y.H. conceived of the present idea and carried out the calculations and computations. K.K. supervised the project. Y.H. and K.K. wrote the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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