A noise-driven mechanism for adaptive growth rate regulation

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ABSTRACT

How can a microorganism adapt to a variety of environmental conditions despite there exists a limited number of signal transduction mechanisms? We show that for any growing cells whose gene expression fluctuate stochastically, adaptive cellular state is inevitably selected by noise, even without specific signal transduction network for it. In general, changes in protein concentration in a cell are given by its synthesis minus dilution and degradation, both of which are proportional to the rate of cell growth. In an adaptive state with a higher growth speed, both terms are large and balanced. Under the presence of noise in gene expression, the adaptive state is less affected by stochasticity since both the synthesis and dilution terms are large, while for a non-adaptive state both the terms are smaller so that cells are easily kicked out of the original state by noise. Hence, escape time from a cellular state and the cellular growth rate are negatively correlated. This leads to a selection of adaptive states with higher growth rates, and model simulations confirm this selection to take place in general. The results suggest a general form of adaptation that has never been brought to light - a process that requires no specific mechanisms for sensory adaptation. The result here provides a clue to understand flexible adaptation process in a cell, and also may provide a novel control mechanism useful in the field of engineering.

Keywords

Gene Network, Noise, Growth Rate Regulation

1. INTRODUCTION

Adaptation of living systems to various environmental conditions is one of the most universal phenomena in biology. Cells can adapt to a variety of environmental conditions by changing the pattern of gene expression and metabolic flux distribution. These adaptive responses are generally explained by signal transduction mechanisms, where extracellular events are translated into intracellular events through regulatory molecules. For example, the Lac operon of *Escherichia coli* encodes proteins involved in lactose metabolism, and expression of the operon is controlled by a regulatory protein so that, when lactose is available, these proteins are expressed in an efficient and coordinated manner [8]. In general, adaptive responses are depicted by a pre-wired logic circuit that takes an environmental condition as an input and gene expression as an output.

However, such program-like descriptions may not always apply, since the number of possible environmental conditions to which a cell must adapt is so large compared to the limited repertoire of gene regulatory mechanisms. For example, experiments using phenotype microarrays [1] revealed that when *E. coli* cells grow in hundreds of environmental conditions, including different carbon and nitrogen sources and stress environments, in which they are distinctly altered states of gene expression [18]. Considering that the number of *E. coli* genes categorized as 'signal transduction mechanisms' in the genome is less than a few hundred [3], it is less plausible that cells have gene regulatory programs to adapt to such a variety of environmental conditions.

Furthermore, two recent studies indicated the possibility that cells can respond to environmental changes adaptively without pre-programmed signal transduction mechanisms. Braun and colleagues demonstrated using yeast cells that even when the promoter of the essential gene (HIS3) is detached from the original regulatory system, expression of the gene is regulated adaptively in response to environmental demands [17, 16]. Furthermore, Kashiwagi et al. demonstrated that *E. coli* cells select an appropriate intracellular state according to environmental conditions without the help of signal transduction mechanisms [9]. There, an artificial gene network composed of two mutually inhibitory operons was introduced into *E. coli* cells, so that states of gene expression are bistable. These authors found that the cells shift to the adaptive cellular state by expressing the gene required to survive in the environment. They also

Bionetics '08, November 25-28, 2008, Hyogo, Japan

demonstrated that the selection of the adaptive attractor between bistable states by noise is possible by introducing phenomenological activity that governs the synthesis and degradation of protein.

In the present study, using an abstract cell model we demonstrate that cells can select states most favorable for their survival among a large number of other possible states as an inevitable outcome of the very fact that cells grow and that gene expression is inherently stochastic [11, 15, 12, 14, 6]. By studying a model that consists of a protein regulatory network and a metabolic reaction network, we show that cellular states with high growth rates are selected among a huge number of possible cellular states, and this selection is only mediated by fluctuations of gene expressions. This selection of a higher growth state is theoretically explained by noting that a state with lower growth speed is more influenced by stochasticity in gene expression, so that it is easily kicked away triggering a switch to a state with a higher growth rate. we show that there is generally a negative correlation between the rate of noise-driven escape from a given state and the cellular growth rate. Due to this negative correlation, an optimal growth state is selected spontaneously. Noting the generality of this selection mechanism, we provide a possible answer to the question how cells generally adapt to a larger variety of environmental conditions by changing their gene expression pattern even without a specific signal transduction mechanism. The application of this adaptation mechanism triggered by noise are also discussed.

2. RESULT

2.1 Cell Model

Suppose that the internal state of a cell is represented by a set of concentrations of n proteins $\mathbf{x} = (x_1, x_2, \cdots, x_n)$, which are regulated by each other. The change in concentrations of proteins over time is determined by (i) the synthesis of proteins, (ii) the dilution of proteins by the growth in cell volume, and (iii) fluctuations in protein expressions arising from stochasticity in chemical reactions [1]. The dilution of proteins is proportional to the growth rate in cell volume v_g, which is determined by expression profiles of proteins and the environmental conditions. Also, it is natural to assume that the rates of protein synthesis are proportional to the growth rate v_g, since the decrease in protein concentration by dilution due to the cell growth has to be compensated by synthesis to maintain a steady state. In fact, some experimental studies showed that the total protein concentration is relatively unchanged with the growth rate [10, 13], which suggests that the change of protein dilution rate was compensated by changing protein synthesis rate. Still, the adaptation mechanism presented below works, even if the rigorous proportionality of protein synthesis and dilution rate to the growth rate is replaced by just a positive correlation between the synthesis rate and the cell volume growth rate. Following this argument, the dynamics of concentration of the i-th protein is chosen as follows:

$$\frac{dx_i(t)}{dt} = f(\mathbf{x}(t))v_g - x_i v_g + \sigma\eta_i(t). \quad (1)$$

The first and second terms in the right hand side (r.h.s.) represent synthesis and dilution of the proteins, respectively, where $f(\mathbf{x}(t))$ indicates the regulation of protein expressions by other proteins represented by sigmoidal function as Hopfield neural-net model. The third term represents the noise in protein concentration with a certain amplitude σ satisfying $< \eta_i(t)\eta_j(t') >= \delta(t-t')\delta_{ij}$, where i and j represent different proteins. For simplification, we assume that the amplitude of the noise is independent of the growth rate v_g, whereas the inclusion of v_g dependence does not alter our results qualitatively [2]. (For the details of the model equation, see [5].)

Let us consider the case that the expression dynamics represented by eq.(1) has multiple possible states (i.e., attractors) and the growth rate v_g is determined by the expression dynamics. In this case, the influence of noise depends on the growth rate v_g for each attractor. When the cellular dynamics state falls into an attractor that has a small v_g, the deterministic part of protein expression dynamics (i.e., the first and second terms of the r.h.s. of eq.(1)) is small, so that the stochastic part in the dynamics is relatively dominant in the protein expression dynamics. Then, the probability to escape the attractor by noise is large. In contrast, when the growth rate v_g is large in the attractor, the magnitude of the deterministic part of expression dynamics is much larger than that of the stochastic part. Thus, the probability to escape the state becomes small. As the result of this negative correlation between the cellular growth rate v_g and the probability to escape a state, the cells can select a state with a relatively higher growth rate, under the presence of an appropriate noise level of gene expression.

2.2 Simulation results

In this section, we present an example of simulation of a noise-driven selection process. In this simulation, we adopt a cell model with two networks. One is a regulatory network that controls the expression levels of proteins acting through each other. The other is a metabolic network whose fluxes are regulated by the concentrations s of the proteins. The growth rate v_g is determined by the profile of metabolic fluxes and the environmental conditions. We assume that some metabolites are required for cellular growth and a metabolite having minimum concentration among these metabolites limits the growth rate. Thus, we use the simple rule that the growth rate v_g is determined to be proportional to the minimum concentration of these metabolites. Also, we assume that the synthesis of proteins is given by the sigmoidal regulation function with regulatory inputs (activation or inhibition) from other proteins [3]. As the result of these regulations, the gene expression dynamics have multi-

[1]There could also be a process of degradation of proteins besides dilution. However, the inclusion of protein degradation does not change the result for adaptation qualitatively, as long as the growth-dependent dilution dominates the decrease of protein concentrations.

[2]Even if the noise amplitude depends on the growth rate v_g, the noise-driven adaptation will work as long as the noise amplitude does not vanish with the growth rate: in other words, as long as a certain amplitude of the noise is maintained in the nonadaptive state

[3]The form of the single sigmoidal regulation function with regulatory inputs was adopted here for simplification. However, the behavior of the model was unchanged when other forms of regulations are adopted, as long as there is multiple attractors in the gene regulatory dynamics.

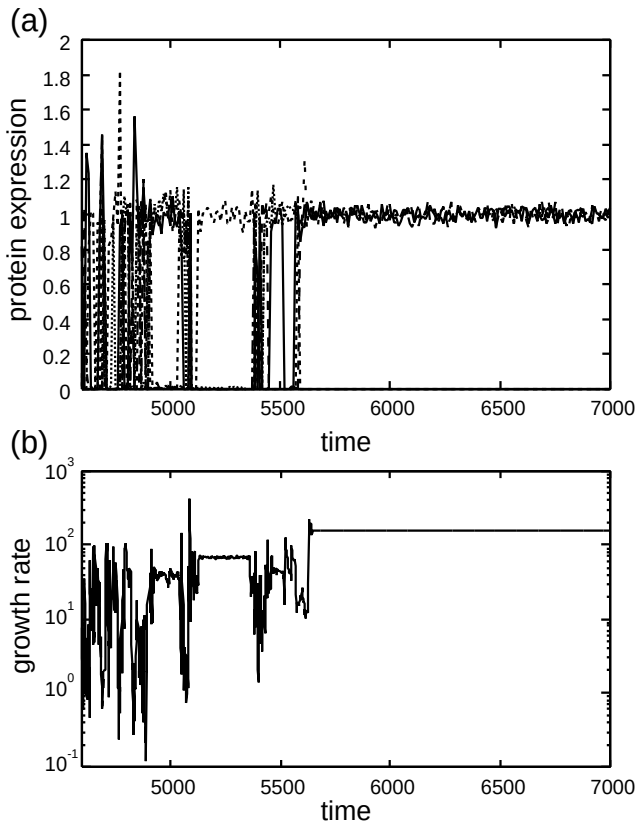

Figure 1: (a) Time series of protein expression levels $x_i(t)$; 10 of 96 protein species are displayed. The vertical axis represents the expression levels of proteins and the horizontal axis represents time. (b) Change in growth rate v_g observed during the time interval shown in (a). Initially, the growth rate of the cell fluctuates owing to the highly stochastic time course in protein expression. After a few short-lived nearly optimal states ($4800 \sim 5600$ time steps), the cell finds a state of protein expression that realizes a high rate of growth.

ple attractors. For a specific form of the noise term, we add a Gaussian white noise term with an amplitude of σ to the expression dynamics.

In Fig.1, an example of the selection process of rapidly growing states, starting from randomly chosen initial expression state, is shown by taking an adequate noise amplitude in expression dynamics. Time series of concentrations of arbitrarily chosen proteins and growth rate of the cell v_g are plotted in 1(a) and 1(b), respectively. In the example, cells are set initially at a state with a low growth rate. In such a state, stochasticity dominates the evolution of protein concentrations with time. After itinerating among various expression patterns, the cellular dynamics arrive at a state with a higher growth rate. Such a transition repeats until the growth rate becomes sufficiently high. Once a gene expression pattern supporting the optimal growth is reached, the system maintains it over time.

This selection of higher growth states was observed for all of the one thousand networks we simulated. It also worked

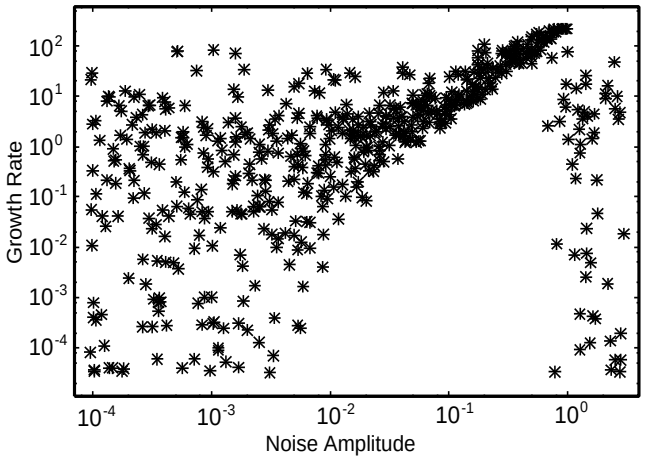

Figure 2: The relationship between the noise amplitude σ and the growth rate v_g. Starting from randomly chosen initial conditions against noise amplitudes σ values ranging over $10^{-4} < \sigma < 3$, the growth rates v_g after 10^5 time steps have been plotted. In the intermediate range of noise strength, $10^{-2} < \sigma < 1$, cellular states with high growth rates are selected among many possible cellular states, as depicted in Fig.1.

independently of initial conditions. As the final state depends on the initial condition, we have computed the distribution of the final growth rate reached from randomly chosen initial conditions. The distribution of the final growth rate thus obtained is plotted in Fig.2. In the case without noise, the cellular state converges rapidly and deterministically into an attractor. In such a case, the final growth rates exhibit a broad distribution as shown in Fig.2, representing a wide variety of the final cellular states. In contrast, in the presence of noise ($\sigma = 0.2$), the final growth rates exhibit a relatively sharp distribution because of the selection of faster growth states, as we have seen in Fig.1.

The relationship between the noise amplitude σ and the final growth rate v_g is plotted in Fig.3. For a small noise amplitude ($\sigma < 10^{-2}$), the final growth rates are distributed broadly, as the cells cannot escape from the first attracting state they encounter. On the other hand, when the noise amplitude is larger ($\sigma > 1$), the final growth rates again exhibit a broad range distribution, because the cellular state continues to change without settling into any attractor. In the intermediate range of the noise strength $10^{-2} < \sigma < 1$, cellular states are selected that are associated with significantly higher growth rates than those found in the other noise ranges. This shift of the final growth rate is caused by the selection of cellular states by fluctuations, as shown in Fig.1.

3. DISCUSSION

We have carried out numerical experiments with our model using several sets of parameter values that allow for multiple attractors in expression dynamics, and have evaluated thousands of different randomly generated reaction networks. The adaptation process triggered by noise is observed generally, independently of the details of the model. In fact, it emerges as long as the following four requirements are

satisfied: i) the coexistence of multiple attractors; ii) the dependence of growth rate on attractors; iii) an increase of cellular reaction processes with the speed of growth; and iv) the presence of stochasticity in reaction dynamics. We have confirmed the robustness of our results against changes in model parameters and rules. For example, the results did not change when the model parameters such as coefficients of reactions were changed, provided the above requirements were satisfied. The robustness of the results against changes in the properties of reaction networks, such as the path density or distributions of numbers of paths is confirmed [5]. Also, the specific form on how the growth rate depends on the expression dynamics is not important for the result, instead the same results are obtained as long as the growth rate is somehow determined by the expression dynamics.

This study provides a possible explanation for the establishment of the optimal growth rate in metabolic reaction networks, proposed by Palsson and colleagues[2, 7, 4]. These studies suggested that a metabolic network is organized so that the growth rate is optimized under given conditions. For example, it was shown that *E. coli* strains with the deletion of a single metabolic gene can adapt to several environmental conditions, and that the value of the final growth rate is consistent with that calculated as an optimal growth rate in such perturbed metabolic networks and environmental conditions[4]. Their results suggest that these bacteria can adjust their intracellular state to optimize their growth rate, even against an environment they have never experienced. Indeed, by the adaptation mechanism we propose here, a cellular state with an optimal growth rate is selected among a variety of environmental conditions. Provided the cellular states are perturbed sufficiently by stochasticity in gene expressions, there will be a negative correlation between the growth rate and the probability of escape from the corresponding cellular state. Thus, we propose that adaptive attractor selection may be at work behind the observed regulations of metabolic fluxes leading to optimal growth rates.

Even though such adaptive attractor selection by noise is relatively slow, it works generally without the requirement of a finely tuned signal transduction network. Hence, for the environmental conditions that an organism encounters frequently, cells have likely developed a sophisticated sensory and signal transduction network, whereas the present mechanism enables adaptation of cells even to environments that they have never faced.

The noise-driven adaptation process proposed in this study might provide a novel control mechanism useful in the field of engineering. Modern artificial systems are generally controlled a complicated computer programs, which are similar with the control of cellular behavior by a huge set of signal transduction mechanisms in a cell. However, in general, such control mechanism by complicated programs cannot respond adequately to environments that the system never faced. For example, in the control mechanism of Internet traffic in a huge network, unexpected failure of some Internet nodes can affect the overall traffic and the recovery from such irregular condition might be difficult for the preprogrammed control mechanisms. Such irregular environmental changes might have often occurred in artificial systems, as in the history of biological systems. Thus, a control mechanism that can respond to unexpected condition is desirable for the robust control mechanism for artificial systems. The adaptation process we proposed in this study can be a candidate for such robust control mechanism, since this adaptation process enables us to respond unexpected condition with aid of stochastic fluctuation in internal dynamic, as discussed throughout this paper. We expect that this noise-driven robust control mechanism will be applied for controlling artificial systems in future.

4. ACKNOWLEDGMENTS

This work was supported in part by a grant from the Global COE (Centers of Excellence) Program and a grant of special coordination funds for promoting science and technology, Yuragi Project, in Osaka University from the Ministry of Education, Culture, Sports, Science and Technology, Japan. This work was also supported by Grant-in-Aid for Young Scientists (B) to CF from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We would like to thank T. Yomo, S. Sawai, and K. Ijichi for stimulating discussions.

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