Fluctuation-Driven Adaptation and Symbiosis in Cellular Dynamics

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Abstract. Biological systems can generally adapt environmental changes and to create symbiotic relationship with other species, by changing their intra-cellular states flexibly. However, the mechanisms for such flexible adaptation and creation of symbiotic relationship remain unclear. In this study, by using simple computer models of cells, we show that for cells whose gene expression fluctuate stochastically, the adaptive cellular state is inevitably selected by noise, even without sophisticated mechanisms. Furthermore, by the fluctuation-induced adaptation mechanism, we show that symbiotic relationships naturally appear in systems of interacting cells. This mechanism can provide clues to understand flexible adaptation and creation of symbiotic relationship. Applications of this mechanism for designing artificial systems are also discussed.

Keywords: fluctuation, attractor, adaptation, symbiosis.

1 Introduction

Cells adapt to a variety of environmental conditions by changing the pattern of gene expression and metabolic flux distribution. Furthermore, the flexible changes in intra-cellular states of cells make it possible to create symbiotic relationship between different species through cell-cell interactions. Although these adaptation and creation of symbiotic relationship are ubiquitous in nature, the mechanisms for the flexible changes in intra-cellular state are not yet fully understood. In contemporary molecular biology, these adaptive responses are generally explained by signal transduction mechanisms, where external events are interpreted by gene regulatory networks. 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 [1]. However, such program-like descriptions of adaptive response are not always able to explain the flexible adaptive behavior and creation of symbiotic relationship, since such program-like responses require evolution of regulatory network, and the program for adaptation to novel environmental changes and creation of symbiotic relationship that the species has not experienced cannot be programmed in advance through evolutionary process.

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Furthermore, a recent study indicated the possibility that cells can respond to environmental changes adaptively without pre-programmed signal transduction mechanisms. Kashiwagi et al. demonstrated that *E. coli* cells select an appropriate intra-cellular state according to environmental conditions without the help of signal transduction mechanisms [2]. 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 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 our previous study [3], using an abstract cell model we demonstrated that cells can select states most favorable for their survival among a large number of other possible states as an inevitable outcome. By studying a model that consists of a protein regulatory network and a metabolic reaction network, we showed 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 [4,5,6]. 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 showed 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. The results indicated the possibility that cells can respond to environmental changes adaptively without finely-tuned preprogrammed signal transduction mechanisms.

In this study, we analyze the possibility that this fluctuation-driven flexible adaptation mechanism can explain flexible formation of symbiotic relationship among cells. We construct a model of interacting cells in which each cell has gene expression dynamics with stochastic fluctuation within. Using this model of interacting cells, we show that the cell-cell interactions can cause mutually adaptive response of cells by fluctuation of gene expression, that eventually results the formation of symbiotic relationship. In the first part of this paper, we briefly present the mechanism of fluctuation-driven adaptation using a single cell model. In the latter part, we show the result of the interacting cell model to show the mechanisms of emergence of symbiotic relationship. The application of the noise-based mechanisms for adaptation and formation of symbiotic relationship are also discussed.

2 Fluctuation-Driven Adaptation

2.1 Cell Model

A schematic representation of the single cell model is shown in Fig.1. The cell includes two networks, i.e., a gene regulatory network which controls expression levels of proteins through each other, and a metabolic reaction network whose

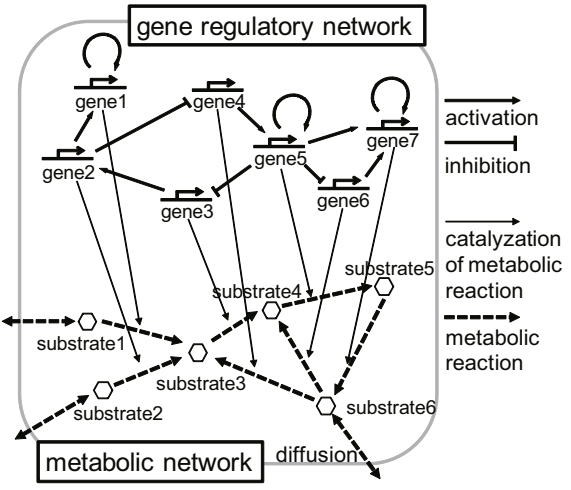

Fig. 1. A cell model with gene-metabolic networks

fluxes are regulated by the expression levels of the proteins. The internal state of a cell is represented by a set of expression levels of n proteins $(x_1, x_2, \cdots, x_n)$ and concentrations of m metabolic substrates $(y_1, y_2, \cdots, y_m)$. The time development of protein expression 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. The dilution of proteins is proportional to the growth rate of cell volume v_g, which is determined by the metabolic fluxes. 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 [7], which suggests that the change of protein dilution rate was compensated by changing protein synthesis rate. 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:

$$\frac{dx_i(t)}{dt} = f(\sum_{j=1}^{n} W_{ij}x_j(t) - \theta)v_g(t) - x_i(t)v_g(t) + \eta(t) \tag{1}$$

The first and second terms in r.h.s. represent synthesis, dilution of the protein i, respectively. In the first term, the regulation of protein expression levels by other proteins are indicated by regulatory matrix W_{ij}, which takes 1, 0, or -1 representing activation, no regulatory interaction, and inhibition of the i-th protein expression by the j-th protein, respectively. The synthesis of proteins is given by the sigmoidal regulation function $f(z) = 1/(1 + exp(-\mu z))$, where

$z = (\sum W_{ij} x_j(t) - \theta)$ is the total regulatory input with the threshold θ for activation of synthesis, and μ indicates gain parameter of the sigmoid function. The regulatory interactions are determined randomly with the rate ρ_a, ρ_i, indicating the connection rate of excitatory paths and inhibitory paths, respectively. 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

Temporal changes in concentrations of metabolic substrates are given by metabolic reactions and transportation of substrates from the outside of the cell. Each metabolic reaction is catalyzed by a corresponding protein. Some nutrient substrates are supplied from the environment by diffusion through the cell membrane, to ensure the growth of a cell. Here, the dynamics of i-th substrate concentration y_i is represented as:

$$\frac{dy_i}{dt} = \epsilon \sum_{j=1}^{n} \sum_{k=1}^{m} Con(k, j, i) x_j y_k - \epsilon \sum_{j'=1}^{n} \sum_{k'=1}^{m} Con(i, j', k') x_{j'} y_i + D(Y_i - y_i) \quad (2)$$

where ϵ indicates the coefficient for the metabolic reactions, and $Con(i, j, k)$ represents the reaction matrix of the metabolic network, which takes 1 if there is a metabolic reaction from i-th substrate to k-th substrate catalyzed by j-th protein, and 0 otherwise. The first and second terms of r.h.s. correspond to synthesis and consumption of i-th substrate by metabolic reactions, respectively. The third term of r.h.s. represents the transportation of the substrate through the cell membrane, which is approximated by the linear term in the diffusion process with a diffusion coefficient D. Y_i is a constant representing the concentration of i-th substrate in the environment. The concentration Y_i is nonzero only for nutrient substrates.

The cellular growth rate v_g is determined by the dynamics in the metabolic reactions. We assume that some of metabolic substrates are necessary for cellular growth, and the growth rate v_g is determined as a function of the concentrations of them. Several choices of the function are possible, and the results to be discussed are generally observed as long as the growth rate varies drastically depending on the concentrations. Here we assume that the growth rate is proportional to the minimal concentration among these necessary substrates. In other words, among m metabolic substrates there are r substrates $(y_1, y_2, \cdots, y_r)$ required for cellular growth, and the growth rate is represented as $v_g \propto \min(y_1, y_2, \cdots, y_r)$.

We carried out numerical experiments with the model using several sets of parameter values obeying the above constraints that allows for multiple attractors, and evaluated thousand of different randomly generated reaction networks. We found that the adaptation processes triggered by noise shown below are generally observed, as long as the intra-cellular dynamics has multiple attractors. In the next section, we present the typical behaviors obtained by using networks consisting of n $\sim$ 96 proteins and m $\sim$ 32 metabolic substrates.

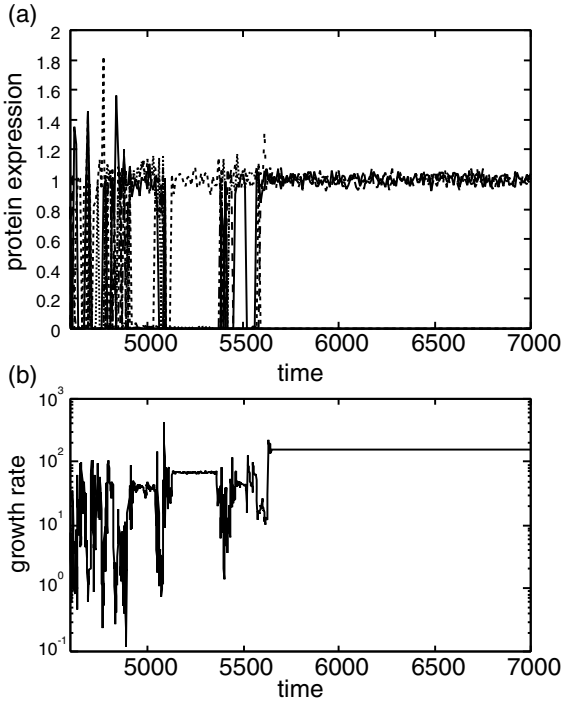

Fig. 2. Time series of .protein expressions and growth rate. Randomly generated gene regulatory network and metabolic network with n=96 and m=32 were used for the simulation. (a) Time series of protein expressions. The vertical axis show the expression levels of proteins, and the horizontal axis represents time. Six out of 96 protein species are displayed. (b) Time series of growth rate observed during the time interval shown in (a). Initially, the growth rate of the cell is relatively low and it fluctuates due to the highly stochastic time course of protein expressions. After a few short-lived nearly optimal states (c.f. 4800 and 5600 time steps), the cell finds a state of protein expression that realize a relatively high growth rate. The parameters are θ=0.5, μ=10, ϵ=0.1, D=0.1. In addition, we enhanced the rate of positive autoregulatory paths, so that the regulatory network has multiple attractors. In the simulations, 30% of activating paths are chosen as autoregulatory paths.

2.2 Simulation Results

In Fig.2, 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 2(a) and 2(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

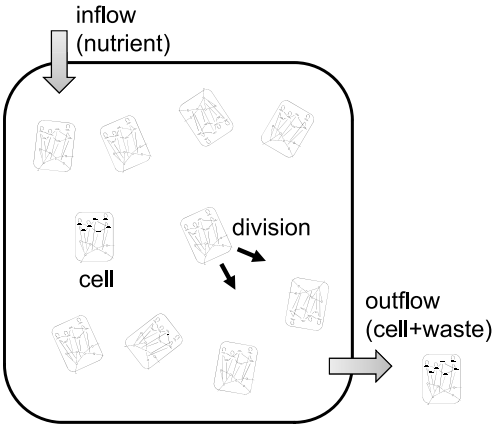

Fig. 3. A model of interacting cells. Each cell has gene-metabolic networks as shown in Fig.1. The cells interact with each other through the transport of metabolites into and out of the surrounding medium. A certain amount of fresh medium containing nutrient metabolites is continuously supplied from outside the environment, and the same amount of medium with cells is discarded to keep the total amount of medium constant. A cell divides in a time interval which is inversely proportional to the growth rate.

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 independently of initial conditions. Note that once one of the expression patterns is selected as an attractor, the flux pattern on the metabolic network is uniquely determined. As a result, the cellular growth rate v_g is also fixed, which in turn affects the protein expression dynamics. Here the influence of noise depends on the growth rate v_g for each attractor. When v_g is small, the deterministic part of protein expression dynamics (i.e., the first and second terms of r.h.s. in 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 due to fluctuation 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 larger than that of the stochastic part. As a result, the probability to escape the state becomes small.

3 Emergence of Symbiotic Relationship by Cell-Cell Interactions

In the previous section, we show that cells can change their internal state to achieve higher growth rate by stochastic fluctuation, even without sophisticated signal transduction machinery. The next question addressed here is what happens when cells with such fluctuation-driven adaptation mechanism interact each

other? We can expect that, cells adapt to environment that is maintained by other cells, which can result mutual adaptation and formation of symbiotic relationship without finely-tuned preprogram. To study this fluctuation-driven symbiotic formation, we constructed an interacting cell model in which each cell has internal expression dynamics with fluctuation as in the previous section and they interact each other through environment.

3.1 Interacting Cell Model

A schematic representation of the interacting cell model is shown in Fig.3. Each cell has gene regulatory network and metabolic network, which are identical to those in the previous section. We assume that some metabolites can penetrate the cell membrane, and each cell communicates with its environment through the transport of metabolic substrates. Thus, interactions between cells occur throughout the environment. Also, e assume that the medium is well stirred by neglecting the spatial variation of the concentration, so that all cells interact with each other through an identical environment. In this model, we consider only diffusion processes through the cell membrane. Thus, the rates of chemicals transported into a cell are proportional to differences of chemical concentrations between the inside and the outside of the cell. The cells are cultured in a tank with a fixed volume, where fresh medium containing nutrient metabolite are continuously supplied and the same amount of medium including the cells are discarded. Thus, when the number of cells in the medium is q, the concentration of i-th substrate in the medium Y_i obeys the following differential equation:

$$\frac{dY_i}{dt} = -\sum_{j=1}^{q} D(Y_i - y_i^j) + \hat{D}(\hat{Y}_i - Y_i) \tag{3}$$

where y_i^j represents the concentration of i-th substrate in j-th cell. The first term in r.h.s. represents consumption and production of i-th substrate by the cells. The second term represents the flow of the substrate from/to the environment, in which $\hat{D}$ and $\hat{Y}_i$ are constants. As an initial condition, we take a single cell, with randomly chosen expression pattern. The number of cells increases due to cell divisions, where the doubling time of a cell is inversely proportional to its growth rate v_g. As a result of increase of cell number, the concentrations of nutrients in the tank decrease, which result a decrease of the growth rate v_g.

3.2 Simulation Results

In this interacting cell system, cells can adapt the dynamically changing environmental condition by the fluctuation-driven adaptation mechanism discussed in the previous section. That is, the transition between attractor is driven by the fluctuation in the expression dynamics, only when the growth rate v_g is small. In Fig.4, we show a typical example of such adaptation process of interacting cells, in which time evolutions of the number of cells in different attractors are

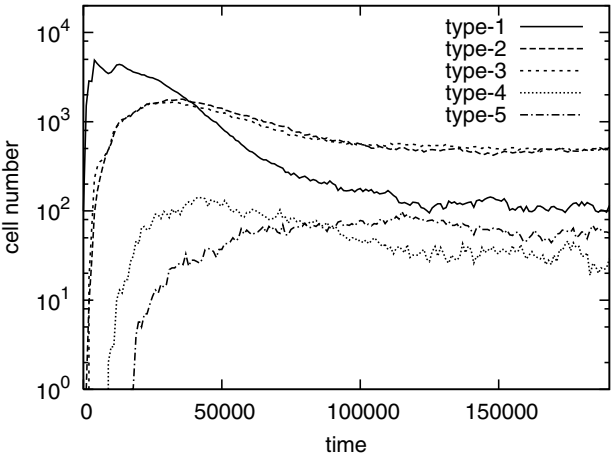

Fig. 4. The emergence of symbiotic system driven by noise in cellular dynamics. Each line represents the number of cells in each cell type. Here, the cell type is defined as a cellular state which falls into a certain attractor. The noise amplitude σ=0.1.

plotted. In this simulation, the amplitude of noise $\sigma = 0.1$, while other parameters of intra-cellular dynamics are identical to those used in Fig.2. In this example, the initial cell falls into a fixed cellular state (denoted by "type-1" in Fig.4), and the number of cells having type-1 state increases by cell divisions. As the result of increase of type-1 cells, the nutrients in the environment which are required for the growth of type-1 cell are consumed and the concentrations of these nutrients decrease. Then, the growth rate v_g of type-1 cells decrease, and the stochastic fluctuation starts to dominate the cellular dynamics of type-1 cells. By this fluctuation, the intra-cellular states of some cells are kicked out of the type-1 state, and fall into different cellular states. The cells appeared after this transition (e.g., type-2 and type-3) consume the waste products of type-1 cells in the environment as nutrients. Furthermore, after the increase of type-2 and type-3 cells, other cell types emerge by the fluctuation. The network of production and consumption of substrates in the medium by the cells with different states can form symbiotic relationships, for example, type-2 and type-5 cells supply the nutrients for their growth to each other. In this simulation, even though the gene regulatory and metabolic networks are identical for all cells, complex parasitic and symbiotic dynamics emerges by fluctuation-driven adaptive mechanism. Important point here is that, by this emergence of complex eco-system, the cells can utilize the nutrient supplied from outside the environment more efficiently than without such symbiotic relationship. In Fig.5, we plot how the total cell number at the steady state depends on the amplitude of the noise. As shown in the figure, when the amplitude of noise is small, the cellular state of the cells is homogeneous and the total number of cells is relatively small. In contrast, when the noise amplitude exceeds a threshold, the total cell number increases. In this phase, cells start to change their intra-cellular state by noise,

and parasitic and symbiotic relationships appear. Here, the cell-cell interactions through production and consumption of metabolic substrates make it possible use the nutrient from outside the environment more efficiently in total, even though each cell does not have sophisticated sensory machineries and preprogrammed regulatory machineries for such formation of ecosystem. This spontaneous emergence of complex ecosystem driven by the noise provides clues to understand the emergence and maintenance of real complex ecosystems including networks of parasitic and symbiotic relationships.

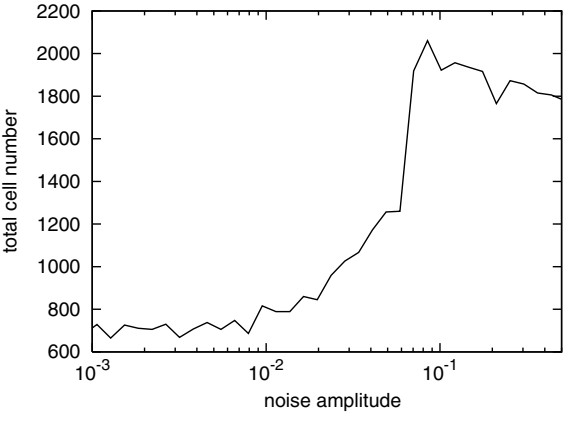

Fig. 5. The relationship between the noise amplitude and cell number in the steady state. When the noise amplitude is small, the state of cells are homogeneous, and the total cell number is relatively small. With the increase of the noise amplitude, a symbiotic relationship as shown in Fig.4 emerges, and the exchange of metabolites among cells with different states can realize efficient utilization of nutrient, which result total cell number in a steady state.

4 Discussion

We have carried out numerical experiments with our models 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 emergence of adaptation and symbiotic processes 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. 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 flexible adaptation and formation of symbiotic relationship. Although symbiotic relationship is quite ubiquitous in nature [8], the mechanism of formation of symbiotic relationship, that is, how species maximizing their growth can create a cooperative relationship, still remains unclear. This study show that, even when each cell in a cell society maximizes the growth rate, as the result of transitions of cellular states by the noise and selection of adaptive state, the cells with the cooperative relationship naturally emerges.

The noise-driven symbiotic formation process presented in this study might provide a novel control mechanism of multi-unit artificial systems in the field of engineering. Modern artificial systems are generally controlled complicated computer programs and interactions among units are precisely designed. However, in general, such control mechanism by complicated programs and precisely designed interactions cannot respond adequately to circumstances for which no response is pre-programmed and the system never faced. For example, if an unpredictable interaction with other units occurs, to response adequately is difficult for such elaborate artificial systems. Thus, a control mechanism that can respond to unexpected condition is desirable for the robust control mechanism for artificial systems. The noise-driven adaptive and symbiotic process presented in this study can be applied to such robust control mechanism. For example, recently based on this noise-driven adaptive mechanism, a method for virtual topology controls of internet traffic was proposed [9]. In this study, it was shown that the noise-driven topology control method can successfully adapt changes of traffic around twice higher variance comparing with conventional control method. For more complex traffic networks, such as interacting multiple overlay networks, the noise-driven mechanisms for the formation of symbiotic relationship we proposed in this study might be applicable to robust traffic control method, since this mechanism enables multi-unit systems to response unexpected condition with aid of stochastic fluctuation in internal dynamics, as discussed throughout this paper. We expect that this noise-driven robust control mechanism will be applied for controlling multi-unit artificial systems in future.

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