A generic mechanism for adaptive growth rate regulation

Chikara Furusawa\textsuperscript{1,3} and Kunihiko Kaneko\textsuperscript{2,3}

\textsuperscript{1} Department of Bioinformatics Engineering, Graduate School of Information Science and Technology, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565-0871, Japan

\textsuperscript{2} Department of Pure and Applied Sciences, University of Tokyo, Komaba, Meguro-ku, Tokyo 153-8902, Japan

\textsuperscript{3} Complex Systems Biology Project, ERATO, JST, Komaba, Meguro-ku, Tokyo 153-8902, Japan

\textbf{Corresponding Author:} Chikara Furusawa

Department of Bioinformatics Engineering,
Graduate School of Information Science and Technology, Osaka University,
2-1 Yamadaoka, Suita, Osaka 565-0871, Japan

Tel/FAX: +81-6-6879-7432

E-mail: furusawa@ist.osaka-u.ac.jp
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 present scheme may help explain a wide range of cellular adaptive responses including the metabolic flux optimization for maximal cell growth.
Non-technical Summary

Adaptation of living systems to various environmental conditions is one of the most universal phenomena in biology. As is well known from the paradigmatic case in the E. coli lac-operon system, cellular adaptation is generally understood as a physiological shift that is elicited by regulation of genes with a specific signal transduction machinery. However, here is an unsolved paradox. If such strategy is the only means by which cells can adapt to different environment, cells cannot survive novel environment before a signal transduction apparatus has a chance to evolve. Some form of non-specific adaptation must have allowed cells to grow robustly in the novel environment, as is also suggested by recent experiments. This is natural considering that a huge set of signal transduction mechanisms would otherwise be needed for all potential environmental conditions that they may face. Our theoretical study demonstrates that, in fact, changes in gene expression pattern can be adaptive; i.e. a state most favorable for cells’ survival is selected without explicit hard-wired regulatory circuits. This occurs inevitably for any cells that grow under stochastic gene expression. Our mechanism is generic and explains why cells adapt and grow optimally in a variety of environment, taking advantage of stochasticity.
1 Introduction

Cells 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 \textit{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]. 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 [2] revealed that when \textit{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 [3]. Considering that the number of \textit{E. coli} genes categorized as ‘signal transduction mechanisms’ in the genome is less than a few hundred [4], it is less plausible that cells have gene regulatory programs to adapt to such a variety of environmental conditions. Indeed, in case of bacterial growth, a general adaptation process that occurs over generations seems to exist in addition to adaptation through gene regulation by signal transduction mechanisms [5, 6].

Recent two 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 [7, 8]. Furthermore, Kashiwagi et al. demonstrated that \textit{E.}}
coli cells select an appropriate intra-cellular 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. They 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 the present study, we demonstrate that cells 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 [10, 11, 12, 13, 14]. 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 to switch to a state with a higher growth rate. It is generally shown that there is 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 huger variety of environmental conditions by changing their gene expression pattern even without a specific signal transduction mechanism.
2 Result

2.1 Cell Model

Fig. 1 represents the schematic representation of our model. It consists of two networks, i.e., a regulatory network which controls expression levels of proteins through each other, and a metabolic reaction network whose fluxes are regulated by expression levels of the proteins. The internal state of a cell is represented by a set of expression levels of n proteins \((x_1, x_2, \ldots, x_n)\) and concentrations of \(m\) metabolic substrates \((y_1, y_2, \ldots, y_m)\). The change in expression levels of proteins over time is determined by (i) the synthesis of proteins, (ii) dilution of proteins by the cell volume growth, and (iii) molecular fluctuation 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, we assume that the rates of protein synthesis are proportional to the growth rate \(v_g\). This assumption is natural and is necessary to maintain a steady state, since the decrease in protein concentration by dilution due to the cell growth has to be compensated by synthesis (The biological plausibility of the assumption will be discussed in the section Discussion). Thus we write the dynamics of expression level of the \(i\)-th protein 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 \(\theta\) for activation of synthesis, and \(\mu\) indicates gain parameter of the sigmoid function. The regulatory interactions are determined.
randomly with the rate $\rho_a$, $\rho_i$, indicating the connection rate of excitatory paths and inhibitory paths, respectively.

The last term of r.h.s. in eq.(1) represent the molecular fluctuation. For a specific form of the noise, we assume that there are fluctuations in the order of $\sqrt{N}$ for reaction involving $N$ molecules, then we add a noise term $\eta = \xi(t)\sqrt{x_i(t)}$, where $\xi(t)$ denotes Gaussian white noise with the amplitude $\sigma$. In this model, we assume that the amplitude of the noise is independent of the synthesis and dilution terms of proteins, since the inclusion of noise source that depend on the rates of synthesis or dilution does not change the simulation results qualitatively.

Temporal change 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:

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

where $\epsilon$ 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 $v_g \propto \min(y_1, y_2, \cdots, y_r)$.

The basic requirements of our model are summarized in the first column of Table I. In our model, we use specific forms to realize these requirements, as summarized in the second column of Table I and eqs.(1) and (2), while some generalizations are possible as long as they do not harm the requirements, as given in the third column of the Table I.

This requirement of multiple attractors set some range in parameter values. The parameter values of network connectivity (e.g., $\rho_a \sim .03$ and $\rho_i \sim .03$) are thus chosen, which may correspond to Kauffman’s ordered regime [17]. Also, some positive auto-regulation paths ($W_{ii} = 1$) are included, which facilitate coexistence of multiple attractors (In fact, there is a sufficient number of auto-regulation paths even for E. Coli[18]).

We carried out numerical experiments with the model using several different sets of parameter values and choosing thousand of different randomly generated reaction networks. As results, we found that the adaptation processes triggered by noise are generally observed, as long as the requirements in the Table I is satisfied. In the next section, we present the typical behaviors obtained by using networks consisting of $n = 96$ proteins and $m = 32$ metabolic substrates.

### 2.2 Simulation Results

In Fig.2, an example of such selection process of states is shown by taking the noise amplitude $\sigma = 0.2$. Time series of expression levels of arbitrarily chosen proteins and growth rate of the cell are plotted in Fig.2(a) and (b), respectively. In the example, cells are initially put at a state with a low growth rate. In such state, stochasticity dominates the time evolution of protein
levels.

After itinerating among various expression patterns, the cellular dynamics finds itself in a state with a higher growth rate. Such transition repeats until the growth rate becomes sufficiently high. Once a gene expression pattern supporting the optimal growth is reached, the system maintained it over time.

This selection of higher growth states is observed for all of a thousand networks we simulated. It also works 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 final growth rate thus obtained is plotted in Fig.3(a). In the case without noise, i.e., the noise amplitude $\sigma = 0$, the cellular state rapidly converges deterministically into an attractor. In such case, the final growth rates exhibit a broad distribution as shown in Fig.3(a), representing a wide variety of the final cellular states. In contrast, under presence of noise ($\sigma = 0.2$), the final growth rates exhibit a relatively sharp distribution, due to the selection process of faster growth states as we have seen in Fig.2.

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 (Even if the attractor of regulatory dynamics is not a fixed point but oscillatory, our argument follows by considering the minimal (or average) growth rate of each oscillatory state). It should be noted that, all the protein concentrations are not necessarily higher for an adaptive
state. Some proteins increase the concentrations, while some do not. For an adaptive attractor, the overall synthesis rate of proteins is increased, but the overall concentration is not necessarily so since the dilution of proteins by cell growth is also increased.

In Fig. 3(b), the relationship between the growth rate $v_g$ and the probability of an escape to an attractor within a period of time is displayed. The probability is higher as the growth speed of cell is lower. It follows naturally from this relationship that cells drift with a directional bias toward a higher growth rate. Hence, as long as the deterministic part of gene expression (i.e., synthesis minus dilution) increases with the growth rate $v_g$ while the noise amplitude has a $v_g$-independent part, the selection of attractors with higher growth rates generally follows.

The emergence of the selection process as presented in Fig. 2 is not restricted to a specific environmental condition. Instead, the mechanism is a general one ensured by the physical limitation of the replicating system. The mechanism makes it inevitable for the cells to seek states with (nearly) optimal growth independently of environmental context. To show the adaptation process over several environmental conditions, we have computed the temporal evolution of our model, by changing nutrient conditions i.e., by updating a set of substrates having nonzero $Y_i$, successively. We have plotted in Fig. 4, a time series of protein expressions and the growth rate, while environmental conditions are changed at the time points indicated by arrows. After the environmental changes, the fluctuation in expression dynamics is observed. This increase in fluctuation continues, until the cell finally finds a state that ensures a high growth rate. Adaptation to a novel environment is thus possible.

Next, we investigate how this noise-driven adaptation depends on the noise amplitude. In Fig. 5, the final growth rate $v_g$ is plotted against the noise amplitude $\sigma$. For small noise amplitude ($\sigma < 10^{-2}$), the final growth rates are broadly distributed, since cells cannot escape from the first attracting state that 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 $10^{-2} < \sigma < 1$, such cellular states are selected that have significantly higher growth rates than those found in the other noise ranges. This shift of the final growth rate is due to the selection of cellular states by fluctuations, as shown in Fig.2.

Stability of a given attractor against noise is estimated by whether the first two terms in eq.(1) are larger than the noise term. One can roughly estimate that the stability changes at around $v_g \times O(x) \sim \sigma^2$, where $x$ represents the protein expression represented in eq.(1). If the former term is larger for attractors with higher growth rates, and smaller for other attractors with lower growth rates, then the former attractors will be selected. Considering that the term $O(x)$ is about $0.1 \sim 1$, higher growth rates are selected when $\sigma^2$ exceeds $\min(v_g)(0.1 \sim 1)$, while the selection no longer occurs when $\sigma^2 > \max(v_g)(0.1 \sim 1)$ where all the states are visited randomly (Here max and min represent the maximum and minimum of $v_g$ over attractors, respectively). The selection works within the range of noise amplitude $\min(v_g) < \sigma^2/(0.1 \sim 1) < \max(v_g)$.

This estimate is consistent with the numerical simulation.

3 Discussion

Numerical simulation and analysis of our model demonstrated how stochasticity in cellular reaction dynamics results in the gene expression pattern supporting higher growth rates. The selection works for any initial cellular states and environmental conditions. The results presented in this paper generally appear as long as the conditions in Table I are satisfied, i.e., coexistence of multiple attractors, dependence of growth rate on attractors, increase of cellular reaction process with the growth speed, and stochasticity in reaction dynamics.

As long as these requirements are satisfied properly, our results on adaptation are obtained, independently of the details of the model, such as parameters and model equations. To be specific, we have confirmed the robustness of our result against the following change in the model.
Parameter values of reaction dynamics: The results presented in this paper are robust with respect to parameter changes in reaction dynamics, as long as the basic requirements in Table I are satisfied. For example, if the reaction coefficient of metabolic reactions changes from $\epsilon = 0.1$ to 10, the selection of higher growth states still occurs, although the time necessary to approach the final high-growth states may depend on the parameter values.

Determination of growth rate by metabolites: Determination of growth rate by metabolites: In the present model, 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 a simple rule that the growth rate $v_g$ is determined to be proportional to the minimum concentration of these metabolites. However, such specific form on how the growth rate depends on metabolites is not important for our results, instead the same results are obtained as long as the growth rate is somehow determined by metabolite concentrations.

Network properties: We confirmed robustness of our result against the change in the properties of regulatory and metabolic networks, such as the path density or distribution of number of paths (including scale-free distribution). The adaptation by noise generally appears when there are multiple attractors in the regulatory dynamics.

Stochasticity in metabolic reactions: In our model, the fluctuation of metabolites concentrations is ignored, considering that the numbers of metabolite molecules are sufficiently large. However, inclusion of fluctuations of metabolite concentrations does not alter the adaptation process presented here.

Regulation of protein expression by metabolite: Some metabolites are known to regulate the protein expression dynamics, such as lactose and galactose, to transmit information on environmental conditions to regulatory dynamics. However, we do not incorporate such
feedback regulations from metabolites into the model, since the essence of our results is to demonstrate that the adaptation process to any environmental conditions is possible by stochastic nature of regulatory dynamics even without such feedback regulations. Of course, the inclusion of such feedback from metabolite does not alter the adaptation process we proposed, as long as the requirements in Table I are satisfied. Also, inclusion of different types of proteins, such as regulatory factors, catalysts of metabolic reactions, and building blocks does not harm the adaptation process.

The selection of an attractor with higher growth rates works when the cellular states are switched by stochasticity in protein expressions and there is negative correlation between the growth speed and residence time of each cellular state. In our model, the negative correlation is introduced, since both the synthesis and dilution of proteins are proportional to the growth rate, while the noise amplitude is independent of it.

The rigorous proportionality of protein synthesis and dilution rate to the growth rate can be relaxed. Indeed, the present adaptation mechanism works as long as there is a positive correlation between the synthesis rate and the cell volume growth rate. As for such correlation, there are some experimental supports. For example, the positive correlation between the rate of protein synthesis and the growth rate were demonstrated in some microorganisms [19, 20]. Furthermore, the fact that the intra-cellular protein concentrations are relatively unchanged in cells against the change in the cell growth rate [19, 21] indicates that the synthesis and dilution of proteins in a cell are balanced. As the dilution of proteins is proportional to the growth rate, this also supports the proportionality between the protein synthesis and the cell growth rate. Of course, one can include the degradation process of proteins besides the dilution. Even though the growth-rate dependence of the degradation process is not clear, the present adaptation mechanism still works as long as the growth-dependent dilution dominates the decrease of protein concentrations.

Even if the noise form in gene expression is varied, the attractor selection works as long as
the noise amplitude does not vanish with the growth rate, or in other words, as long as a certain amplitude of the noise is maintained in the non-adaptive state. For example, we have simulated a model with another noise term $\sqrt{v_g \eta(t)}$ in addition to the noise in eq.(1), and confirmed that the present adaptive attractor selection still works.

On the other hand, if the variance of total noise decreased linearly with the growth rate $v_g$ and vanished at $v_g = 0$, the present selection would not work. When the noise is originated only in the growth-dependent reaction, one might think that this might be the case. However, as long as there is basal process for the protein synthesis (and degradation) even when a cell does not grow, there should exist a growth independent part in the noise as in eq.(1). Although such part of noise has not been measured separately, the fact that the synthesis of mRNAs, proteins and metabolites are maintained even in the stationary phase of a cell [22] suggests that there exists a growth-independent part in the noise term. As long as such growth-independent part exists in the noise, the present mechanism works.

As for the description of stochastic dynamics in cells, there are two major methods, i.e., continuous dynamics (Langevin description) as adopted here and discrete particle dynamics. An efficient algorithm for the latter description is Gillespie method [23]. To confirm the validity of our result, we have also simulated a stochastic model by adopting the Gillespie method. Due to technical limitation in the computational speed, we have simulated a simpler model with a few degrees of freedom that allows only for two attractors in the regulatory dynamics. As results, we observed that the attractor with a higher growth rate is selected, in agreement with the simulation of the Langevin equation (eq.(1)), as long as the noise does not vanish with the rates of synthesis and degradation of proteins. This suggests that the present attractor selection works if the number of molecules in a cell is not so large.

The magnitude of protein expression noise quantified by coefficient of variation could be in the order of $0.1 \sim 0.01$, as shown in Ref.[24]. In some cases it is suggested that the fluctuation is large enough to force cells back and force between discrete states [25]. This magnitude of noise is
within the estimated range required for the attractor selection, although separate measurement of the basal noise is necessary to complete the estimate. In recent studies on stochasticity in gene expression (e.g. [10, 13]), intrinsic and extrinsic noises are distinguished. However, these studies investigate only the absolute level of fluctuation amplitude in the actively growing state. To examine the validity of our theory, one needs to measure the change in the fluctuation amplitude between adapted and non-adapted state, and how it depends on the growth-rate.

The present study provides a possible explanation for the establishment of the optimal growth rate in the metabolic reaction networks, proposed by Palsson and his colleagues [26, 27, 28]. Their study 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 a 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 these perturbed metabolic networks and environmental conditions [28]. The observed adjustments of metabolic fluxes often occur within several days, suggesting that such adaptation process is not caused by selection of mutants having a higher growth rate under the given condition. These bacteria adjust their intra-cellular state to optimize the growth rate, even though they have never experienced with such environment.

In fact, the attractor selection presented in this paper provides a mechanism for selecting a cellular state with an optimal growth rate, over a variety of environmental conditions. An important point here is that the presented mechanism requires no fine tuning of regulatory mechanisms. As long as the cellular states are perturbed sufficiently by the stochasticity in gene expressions, a negative correlation between the growth rate and the escape probability from the corresponding cellular state is established. Thus we propose that the adaptive attractor selection be at work behind the observed regulations of metabolic fluxes leading to optimal growth rate.

The merit of the present adaptive attractor selection induced by, and optimizing, growth lies in its generality. The mechanism can work without fine-tuning through evolution. Indeed, it
makes adaptation possible to novel environment that the species has not experienced through the course of evolution. Note that organisms have to survive by adapting to new environment even before specific signal transduction network has been developed. Our mechanism provides such general and non-specific ‘proto-adaptation’.

Of course, there are demerits in our mechanism also. If the difference in the growth rates between the two adaptive states is small, the present mechanism cannot distinguish them. Either of these states can be selected. Hence it does not work for very fine selection. Also, the selection process proposed here is not so efficient. The time required for the adaptation can be long. For example, in the case shown in Fig. 2, a large number of generations is needed to reach the adapted state with the optimal growth rate. This long adaptation time is a demerit of the present noise-driven attractor selection, compared with the fine-tuned signal transduction mechanisms. However, such long adaptation time for novel environments may not be fatal for organisms in nature, since not every cell has to adapt such environment. For example, let us consider the case that a population of a large number of cells encounters a novel environment. Even when the average time required for noise-driven adaptation is long, some of cells in the population are able to find an adapted state within a single or few generations, as the present mechanism is stochastic in nature. Then these cells start to increase their population. Adaptive response at population level progresses rather fast, even when each adaptation at a single cell level is inefficient.

The reason that the present adaptation process takes so long time is that we have considered selection process over a thousand of attractors, to demonstrate how it work clearly. On the other hand, if the number of attractors is few for each given environment, the selection process is generally completed within a generation or a few. Indeed the selection over a few attractors may be sufficient to explain adaptation to most novel environment.

Also, the time required for adaptation depends on the choice of network. Here we used regulatory networks generated randomly. By using an organized network, the attractor land-
scape, such as ruggedness, will be changed, so that the adaptation time can be radically reduced. For example, it is interesting to study the evolution of attractor landscape under the present noise-driven adaptation. We expect that some non-trivial characteristics in attractor landscapes (e.g., funnel structures) would emerge to enhance fast and accurate response to environmental changes, which may help us understanding how existing signal transduction mechanisms have evolved. The relationship between adaptation dynamics and the characteristics of attractor landscape is an important future topic.

In the adaptation process proposed here, existence of multiple attractors is necessary. However, there are only a few evidences that the regulatory network within a cell has multiple attractors, so far [29, 30, 25, 31]. With regards to the gene regulatory network, there is a certain amount of (positive) feedback regulatory interactions [18], which can result in multistability of regulatory dynamics. On the other hand, experimental confirmation of the existence of multiple attractors in regulatory dynamics is still difficult, since simultaneous and single-cell level measurements of multiple genes/proteins are necessary for such study. Furthermore, if the adaptation process proposed here works, we can observe only the adaptive attractor, even if there are potentially multiple attractors (Note that the adaptation time is short if the number of attractors is not huge). The experimental/theoretical verification of the existence of multiple attractors in the regulatory dynamics remains to be a future study.

The present noise-induced selection of a higher growth state has not been directly confirmed in real biological systems so far. Standard experimental data concern only for adaptation process based on the signal transduction networks, so that we need novel experimental setups to verify the proposed adaptation mechanism. There are two possibilities. One is the use of artificial gene networks, as demonstrated in Ref.[9]. In this approach, one can introduce a gene network disconnected from the existing signal transduction networks, and investigate whether the artificial gene network exhibits selection of a higher growth state. Another possibility is the study of cellular response against environmental changes that the cells have never faced, or response
of cells in which known regulatory mechanisms are destroyed. In both cases, by investigating
the response of cells, one can examine if cells show adaptive behavior to environmental change,
without the sophisticated regulatory mechanisms, but by utilizing the fluctuation based selection
of a higher growth state, as presented in this paper.

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References


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Basic assumptions necessary for our adaptation mechanism | Representation in the present model | Possible generalizations
---|---|---
Multiple stable states in a cell | multiple attractors in gene regulatory dynamics in eq.(1) | the number of attractors can be arbitrary; attractors can be periodic or chaotic
Growth rate of a cell $v_g$ depends on cell state | dependence of growth rate on metabolic state ($v_g \propto \min(y_1,\ldots,y_r)$) while metabolic process is controlled by gene regulatory dynamics (eq.(2)) | other forms on growth rate dependence on $(y_1,\ldots,y_m)$; feedback from metabolic process to gene regulatory dynamics can be included in eq.(1)
Synthesis of protein increases with $v_g$ to compensate the dilution by the volume increase | Rates of both the synthesis and dilution of proteins are proportional to $v_g$ | rigorous proportionality can be relaxed
Stochasticity in expression dynamics | noise term in gene regulatory dynamics in eq.(1) | other forms are adopted as long as the noise amplitude does not vanish for a state without cellular growth; stochasticity in metabolic process can be included

Table I: Summary of basic requirements for our adaptation mechanism. Each of basic assumptions is natural as long as the growth rate depends on the cell state, and each cell state is a result of protein expression dynamics and dilution of chemical concentrations by the cell growth.
Figure Legends

**Fig.1.** Schematic representation of our cell model. The model consists of two networks, i.e., a gene regulatory network and a metabolic network. As a schematic example, simple networks consisted of $n = 7$ genes and $m = 6$ metabolic substrates are shown. The red arrows in the regulatory network represent activation of expressions, while green lines with blunt ends represent inhibition. The arrows from a gene to itself mean autoregulation of expressions. As a result of these regulatory interactions, the dynamics of expression levels of proteins have multiple attractors. The metabolic reactions, represented by blue arrows, are controlled by expression levels of corresponding proteins. The correspondence between metabolic reactions and gene products (proteins) are shown by the black thin arrows. The regulatory matrix $W_{ij}$ of the presented network takes $W_{21} = W_{32} = W_{33} = W_{45} = W_{56} = W_{67} = W_{77} = 1$, $W_{24} = W_{53} = W_{57} = -1$, and 0 otherwise. The reaction matrix $Con(i, j, k)$ metabolic network takes a value 1 for the elements $(1, 3, 1)(2, 3, 2)(3, 4, 3)(6, 3, 4)(4, 5, 5)(6, 4, 6)(5, 6, 7)$, and 0 otherwise. The choice of $n=7$ in the figure is only for schematic illustration, and in the actual simulation, we used much larger networks with $n = 20 \sim 100$. In the present paper, we adopt a much larger network with $n = 96$ genes and $m = 32$ substrates.

**Fig.2.** (a): Time series of protein expressions $x_i(t)$. 10 out 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 due to highly stochastic time course of protein expression. After a few short lived nearly optimal states (c.f. 4800 $\sim$ 5600 time steps), the cell finds a state of protein expression that realizes a high rate of growth. The parameters are $\theta = 0.5$, $\mu = 10$, $\rho_a = \rho_i = 0.03$, $\epsilon = 0.1$, and $D = 1.0$. In addition, we enhanced the rate of positive autoregulatory paths, i.e., $W_{ii} = 1$ for $i$-th gene, so that the regulatory network has multiple
attractors. In the simulations, 30% of activating paths are chosen as autoragulatory paths.

**Fig.3.** (a): The distribution of growth rate. Starting from randomly chosen $10^5$ initial conditions, the distribution of growth rates after $10^5$ time steps are computed with and without noise ($\sigma = 0.2$). (b): Relationship between the growth rate $v_g$ and the probability to escape an attractor with a certain period of time. The probability is computed by $10^5$ trials starting from randomly chosen initial conditions. After a cell reaches a stable state, noise ($\sigma = 0.2$) is added and the time it takes the cell to escape from the corresponding attractor is measured. The y-axis represents the probability that the cellular state is kicked out of the original state within $10^3$ time steps, and the horizontal axis shows the growth rate $v_g$ of the original state.

**Fig.4.** (a): Time series of protein expressions $x_i(t)$ when the environmental condition is altered. The environmental conditions, i.e., substrates having nonzero $Y_i$, are changed at time points indicated by arrows. (b): Change of growth rate $v_g$ in the same time interval as (a). After the environmental changes, both expression levels of all proteins and the growth rate start to fluctuate until the cell finds a state of protein expression that realizes a high growth rate. In the simulation, the noise amplitude $\sigma = 0.2$.

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