A generic mechanism for adaptive growth rate regulation by noise

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Short Abstract — **How can a microorganism adapt to a variety of environmental conditions despite there exists a limited number of signal transduction machineries? We show that for any growing cells whose gene expression is under stochastic fluctuations, adaptive cellular state is inevitably selected by noise, even without specific signal transduction network for it. The results suggest a general form of adaptation that has never been brought to light - a process that requires no specific machineries for sensory adaptation.**

Keywords — **Adaptation, Noise, Gene Regulatory Network**

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. 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.

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) isdetached from the original regulatory system, expression of the gene is regulated adaptively in response to environmental demands [1]. Furthermore, Kashiwagi et al. demonstrated that *E. coli* cells select an appropriate intra-cellular state according to environmental conditions without the help of signal transduction machineries [2].

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. Using a cell model consisting of a regulatory network of protein expressions and a metabolic reaction network, we show that selection of cellular state with high growth rates can be achieved without complicated regulatory machineries, which is only mediated by stochastic fluctuations of molecular consternations. The fundamental assumption therein is that synthesis and degradation of proteins are proportional to the cell growth rate, and that the protein expression dynamics is influenced by stochastic noise. In such cases, cellular state with lower growth rate is more influenced by concentration fluctuations, since in such state the deterministic part of the dynamics (i.e., synthesis and degradation) becomes small and the stochastic noise part is relatively dominant in the protein expression dynamics. As a result, the probability to escape the cellular state due to stochastic fluctuation becomes large. In contrast, when the growth rate is large, the magnitude of the deterministic part of expression dynamics is larger than that of the stochastic part, resulting in small probability to escape such state. With this growth rate dependency of the escape probability from a cellular state, the states with large growth rates can be selected by stochastic fluctuation, without any sophisticated regulatory machinery, as long as the strength of stochastic fluctuation is adequate.

The result here provides a clue to understand flexible adaptation process in a cell. For example, Palsson et al. [3] demonstrated that the metabolic reaction profiles in a cell are organized to achieve optimal growth in various environmental conditions. Our result provides a possible mechanism for selecting cellular states with optimal or close to optimal growth rate for a variety of environmental conditions, without assuming sophisticated machineries of gene regulations.

References

[1] Stolvicki E, Dror T, Brenner N, and Braun E (2006) Synthetic Gene Recruitment Reverals Adaptive Reprogramming of Gene Regulation in Yeast. *Genetics* **173**, 75-85

[2] Kashiwagi A, Urabe I, Kaneko K, and Yomo T (2006) Adaptive Response of a Gene Network to Environmental Changes by Fitness-Induced Attractor Selection. *PLoS ONE* **1**(1), e49

[3] Edwards JS, Ibarral RU, Palsson BO, (2001) In Silico Predictions of E.coli Metabolic Capabilities are Consistent with Experimental Data. *Nature Biotech*.**19**, 125-130

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