Evolution of Robustness to Noise and Mutation in Phenotypic Dynamics

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***Short Abstract* — We demonstrate the relevance of phenotype fluctuations of isogenic organisms to evolution. From the analysis of evolutionary stability in population distribution, derived is a general inequality between the phenotype variance due to genetic variation and the intrinsic phenotype variance of clones, as well as proportionality between the two through evolution. Based on this analysis, "error catastrophe" is shown to appear as a result of the decrease in the phenotypic noise. These counter-intuitive theoretical predictions are confirmed by numerical evolution of a gene-network model. The results reveal how noise itself shapes networks' robustness to stochasticity in gene expression, which in turn shapes networks' robustness to mutation.**

***Keywords* — Evolution, Noise, Phenotype-Genotype mapping, fluctuation-response relationship**

Robustness is ability to function against changes in the parameter of a system. In a biological system, the changes have two distinct origins, genetic and epigenetic. The former concerns with genetic robustness, i.e., rigidity of phenotype against mutation, which is necessary to maintain a high fitness state. The latter concerns with fluctuation in number of molecules, i.e., stochasticity in gene expression and external environment**.** Phenotype that is concerned with fitness is expected to keep some robustness against such stochasticity in gene expression in 'developmental' dynamics, and against mutation, as well.

Whether such "developmental'' and "genetic'' robustness emerge under natural selection have long been debated in the context of developmental dynamics and evolution theory, as Schmalhausen's stabilization selection and canalization by Waddington[1]. Are developmental robustness to noise and genetic robustness to mutation related? Is phenotypic noise relevant to attain robustness to mutation? Here, we answer these questions quantitatively with the help of stability analysis of distribution function and dynamical network model of gene expression[2-4].

Under the presence of noise in gene expression, phenotype as well as fitness, of isogenic organisms is distributed. When the phenotype is less robust to noise, this distribution is broader. Hence, the variance of this distribution, i.e., variance of isogenic phenotypic fluctuation denoted as V_{ip}, gives an index for robustness to noise in developmental dynamics. On the other hand, robustness to mutation is measured from the fitness distribution over individuals with different genotypes, given by variance of phenotypic fluctuation arising from diversity of genotypes in a population, denoted here as V_g. This variance V_g increases as the fraction of low-fitness mutants increases.

Here we show that robust evolution is possible only when the inequality $V_{ip} \geq V_g$ is satisfied, from the stability assumption of distribution function of genotypes and phenotypes[2-4]. Since the isogenic phenotypic fluctuation V_{ip} increases with noise, this means that evolution of robustness is possible only when the amplitude of phenotypic noise is larger than some critical value, implying a positive role of noise to evolution.

Through simulations of a simple stochastic gene expression network that undergoes mutation and selection, we confirm all the relationship between V_{ip} and V_g [4]. We demonstrate that both the two variances decrease in the course of evolution, while keeping the proportionality between the two. This proportionality is consistent with an observation in a bacterial evolution experiment [5]. Existence of the critical noise strength, supported from the inequality, is also demonstrated, below which the network cannot acquire both types of robustness. We explain the origin of this critical noise strength, by noting that smooth dynamical behavior free from a rugged potential landscape evolves as a result of phenotypic noise. When the noise amplitude is smaller than the threshold, we observe that low-fitness mutants are accumulated, so that robustness to mutation is not achieved. Generality and relevance of our results to biological evolution are briefly discussed.

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