

Analysis of the relationship between noise in gene expression and regulatory structure in amino acid biosynthesis pathways

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Abstract

Gene regulatory dynamics involves several processes of stochastic chemical reactions. As a consequence, the copy number of given protein varies greatly among cells, even within genetically identical cell population. In recent studies^{1,2}, the characteristics of noise in gene expression were well studied by using simple artificial gene networks. Also, there are some studies^{3,4} showing comprehensive analysis of noise amplitude at the proteomics scale. However, the characteristics of noise in natural regulatory networks, such as the relationship between the noise property and structure of regulatory interactions, still remain unclear. In this study, we focused on the noise in natural regulatory network to understand such characteristics of noise. Here the expressions of genes related to amino acid biosynthesis (AAB) were targeted, because of their well known regulatory structures.

To quantify the noise in the target gene expression related to AAB networks, we construct 31 reporter strains of *Escherichia coli*. Each reporter strain has *gfp* gene which is controlled by the promoter of AAB target gene. These reporter strains were firstly grown in defined medium M9A (M9 medium containing 20 amino acids). Then, we inoculated the strains from the cultures into M9A without a given amino acid (containing 19 amino acids) to perturb target promoter regulation. After the perturbation, the noise in the gene expression was measured by flow cytometry every 15 minutes until the target promoter activity reached next steady state.

By measuring noise in the expression of these AAB genes using flow cytometry, we found that the amplitude of noise in AAB genes depends on the structure of regulatory network. In general, expressions of AAB genes are regulated by negative feedbacks, and we categorized these feedback regulatory networks into two cases (Figure 1). One is the case that the expression of AAB gene is negatively regulated by the final products of the AAB pathway, such as amino acid (case1). Another is the case that the expression of AAB gene is negatively regulated as a result of depletion of substrate which is located upstream of target AAB pathway and activates the expression of the target gene (case2). Our data revealed that the noise amplitude of AAB genes in case1 is significantly smaller than those of genes in case2 (Figure 2). We expect that the relationship between noise amplitude in gene expressions and regulatory structures provides a basis for better understanding of natural regulatory networks.

References

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Figures in the Abstract

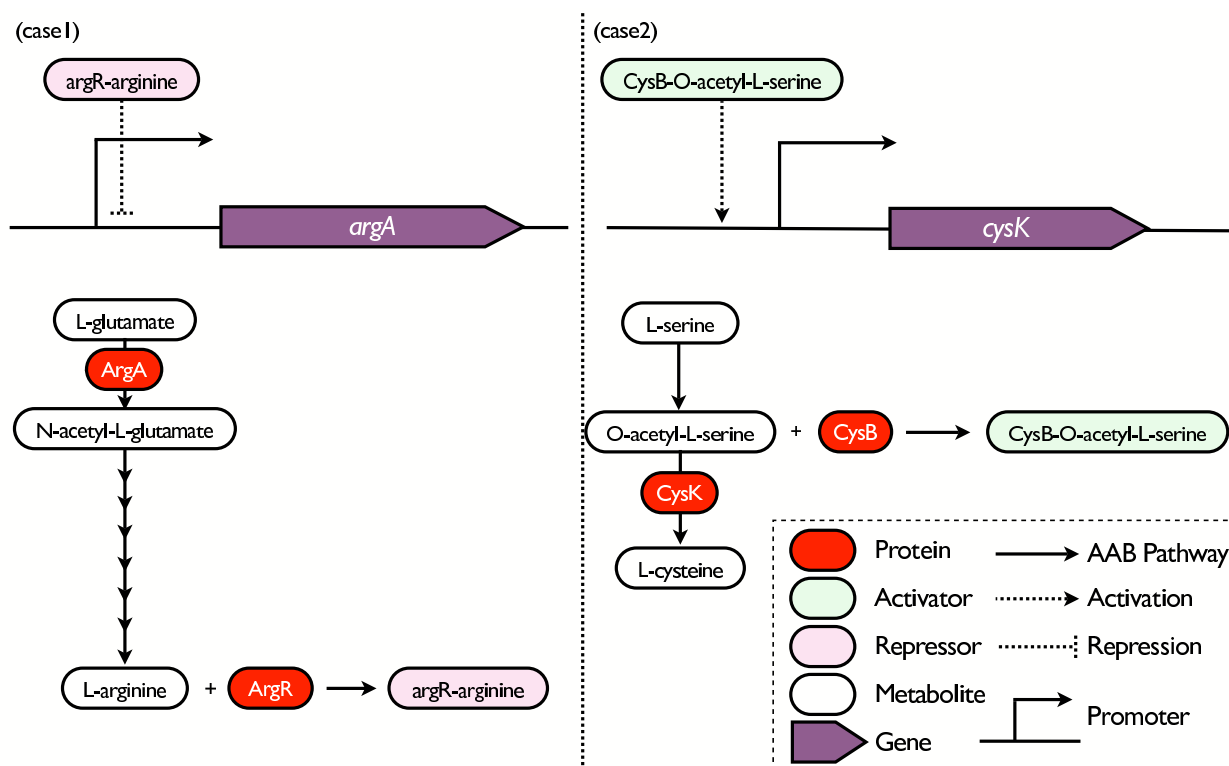


Figure 1: Two examples of negative feedback regulation in AAB genes. Upper figures show the gene regulation of AAB gene, and lower figures show the location of gene in AAB pathway. In the case1, the expression of AAB gene (*argA*) is negatively regulated by the final products (arginine) of the AAB pathway. In the case2, the expression of AAB gene (*cysK*) is negatively regulated as a result of depletion of substrate (O-acetyl-L-serine) which is located upstream of target AAB pathway and activates the expression of target gene.

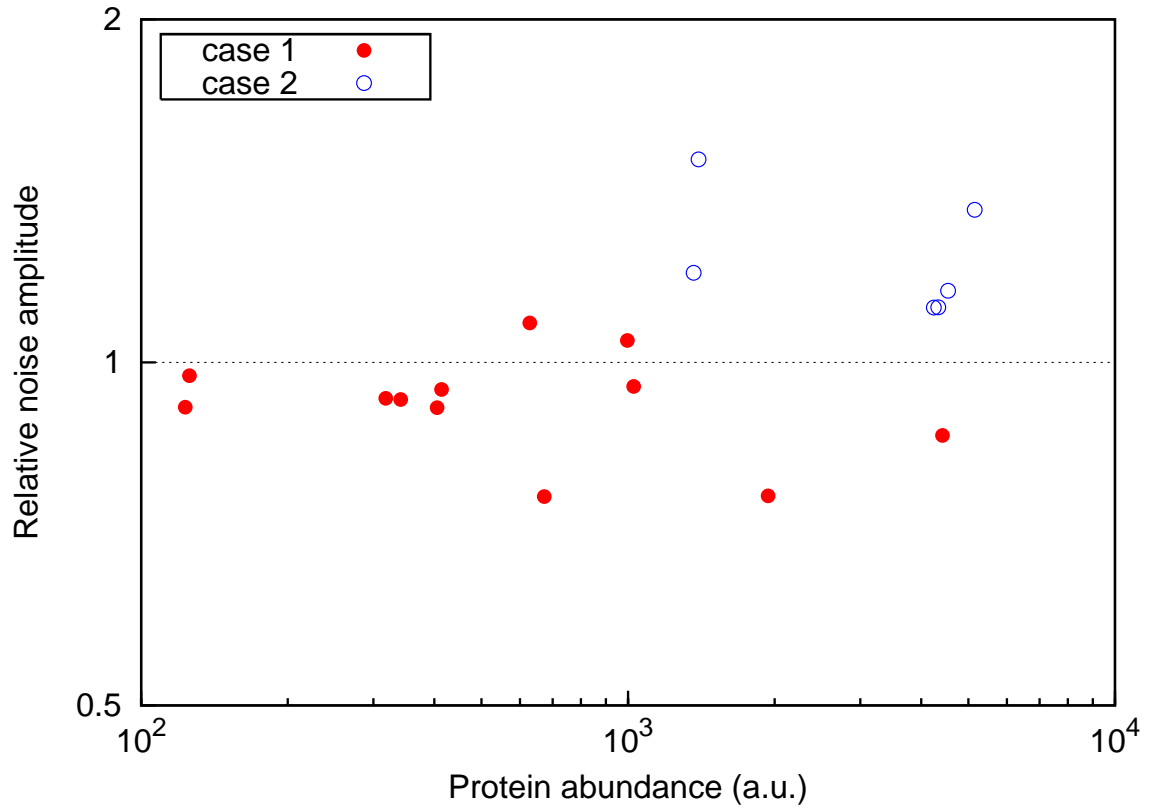


Figure 2: Relationship between noise amplitude and regulatory structures. In the figure, the horizontal axis indicates the protein abundance estimated by fluorescence intensity of GFP. The vertical axis shows the relative noise amplitude obtained by the ratio of observed noise amplitude of a protein to the median of noise amplitude among similar abundant proteins. Each point represents the protein abundance and relative noise amplitude of AAB gene, which is categorized in case1 or case2. As shown, the relative noise amplitude of AAB genes in case1 is significantly smaller than those of genes in case2.