Identifying factors that control the fundamental noise limit of gene expression in *Escherichia coli*

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***Short Abstract* —Gene expression is a stochastic process, thus random cell-to-cell variations, or noise, occur even in genetically identical cells. Recent system-wide studies have shown that the noise amplitude in any particular gene has a common lower limit in *Escherichia coli* although why remains unclear. To identify molecular factors that relate to this limit, we analyzed correlations between expression levels of randomly-selected gene pairs in *E. coli*. We found that the expression levels of all tested gene pairs are positively correlated. Interestingly, pairs with factors related to transcription and translation showed stronger positive correlations. In addition, using a bacterial artificial chromosome, we revealed that chromosomal effects on gene expression variation are little in high-expression genes. In future studies, we plan to test other potential causes of the global noise limit such as heterogeneity of protein degradation rates.**

***Keywords* — single cell, stochastic gene regulation, extrinsic noise**

I. Background

STOCHASTIC gene expression causes random cell-to-cell variations in genetically identical cells in both prokaryotes and eukaryotes [1]. In low-expression genes, this variation is mainly caused by the inevitable stochasticity of biochemical processes during gene expression (intrinsic noise). In contrast, in high-expression genes, the variation is dominated by additional factors that originate from fluctuations in other cellular components (extrinsic noise) [2]. Recent system-wide proteome analysis of *Escherichia coli* has revealed that the noise amplitude in any particular high-expression gene has a global limit [3]. However, the underlying mechanism determining this limit is unclear. We aim to clarify how the global noise limit originates at the single cell level using *E. coli* as a model organism.

II. Results

We have constructed strains in which *Venus* and *mKate2* are fused chromosomally to two randomly selected high-expression genes at their C-termini. Single cell measurements gave correlations between the expression levels of the selected gene pairs. We found that all 18 gene pairs measured showed a positive correlation at different levels (r = 0.2-0.8), indicating that the fluctuations of all protein levels in a cell are correlated. Interestingly, any gene paired with genes of RNA polymerase, σ factor or a ribosomal protein show relatively higher positive correlations (r = 0.6-0.8), suggesting that protein noise is controlled by noise from global mechanisms involving transcription or translation. We are now preparing correlation profiles for all combinations of 8 randomly selected genes, which include those from RNA polymerase, σ factor and the ribosomal protein to quantitatively analyze expression correlations of high-expression genes.

Next, to test the effects of global regulation by chromosomal structures on the positive correlation levels, we analyzed the expressions of gene pairs embedded on a bacterial artificial chromosome (BAC) [4], which exists as a single-copy episome free of the endogenous chromosome. We found that gene pairs show similar positive correlations of their expressions in BAC as they do in chromosome, suggesting that the global noise is insensitive to the chromosomal states of a cell.

III. Conclusion

Our results suggest that the concentrations of cellular components related to transcription and translation are strongly associated with the expression levels of high-expression genes. We are now considering other possible causes of the global noise limit such as the heterogeneity of protein degradation rates. We also plan to observe long-term cellular component fluctuations in a microfluidic device and control the global noise by artificial modification, for example, by adding a negative feedback loop to the transcriptional and translational processes.

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