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Strategy of tuning gene expression ratio in prokaryotic cell from perspective of noise and correlation

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HIGHLIGHTS

- Strategy of tuning gene expression ratio from perspective of noise and correlation is discussed.
- Analytical results of genes expression noise and correlation for the two-state and the constitutive promoter are given.
- Noises and correlation of gene expressions in operon with the two-state promoter are higher than in operon with the constitutive promoter.
- Polar effect obviously lowers the correlation between genes in operons.
- Tuning translation rates is the optimal strategy to tune gene expression ratio in operon.

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ABSTRACT

Genes are organized into operons in procaryote, and these genes in one operon generally have related functions. However, genes in the same operon are usually not equally expressed, and the ratio needs to be fine-tuned for specific functions. We examine the difference of gene expression noise and correlation when tuning the expression level at the transcriptional or translational level in a bicistronic operon driven by a constitutive or a two-state promoter. We get analytic results for the noise and correlation of gene expression levels, which is confirmed by our stochastic simulations. Both the noise and the correlation of gene expressions in an operon with a two-state promoter are higher than in an operon with a constitutive promoter. Premature termination of mRNA induced by transcription terminator in the intergenic region or changing translation rates can tune the protein ratio at the transcriptional level or at the translational level. We find that gene expression correlation between promoter-proximal and promoter-distal genes at the protein level decreases as termination increases. In contrast, changing translation rates in the normal range almost does not alter the correlation. This explains why the translation rate is a key factor of modulating gene expressions in an operon. Our results can be useful to understand the relationship between the operon structure and the biological function of a gene network, and also may help in synthetic biology design.

1. Introduction

An operon is a unit of genomic DNA containing a cluster of genes under the control of a single promoter (Jacob and Monod, 1961). Genes in an operon generally belong to the same function class (Salgado and Moreno-Hagelsieb, 2000; Dandekar et al., 1998), and they are transcribed together into a mRNA strand. Their expressions can be regulated coordinately, which is one of the reasons that genes are organized into operons (Price et al., 2005).

Gene expression is noisy, which can influence its function (Eldar and Elowitz, 2010; Hao et al., 2011a; Paulsson et al., 2000; Ray and Igoshin, 2012; Chalancon et al., 2012). Noise from the stochasticity of transcription and translation process is recognized as the intrinsic noise. Noise introduced by other factors such as different concentrations of RNA polymerase, ribosome or transcription factors is recognized as the extrinsic noise. The extrinsic noise is relatively slow in the same environment (Taniguchi et al., 2010; Rosenfeld et al., 2005). Intrinsic and extrinsic noises together determine the gene expression profile (Taniguchi et al., 2010; Rosenfeld et al., 2005; Paulsson, 2004).

Proteins work together to execute specific functions in the cell. Different components in the same pathway need to be coordinated

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to get the robust result. For example, protein complex formation is most efficient when subunits of a protein complex are expressed with the needed ratio (Carmi et al., 2006, 2009; Swain, 2004). Expressions of enzymes in a metabolism pathway usually need to be correlated to avoid intermediate product cumulation (Ray and Igoshin, 2012) which may be toxic. Experiment shows that gene expressions in the same operon are more correlated together than those in the separated operons even with identical promoters, especially when gene expression levels are low (Tabor et al., 2008). The strengthened correlation can be explained by co-transcription (Sneppen et al., 2010; Swain, 2004; Ray and Igoshin, 2012; Iber, 2006) or in some cases also by co-translation (Swain, 2004; Iber, 2006). Statistics from *Escherichia coli* genomics indicate that for genes with products in linear metabolic pathways, with physical interactions and in covalent modification modules, they are more likely to be organized into operons (Ray and Igoshin, 2012). Noise of the genes expression from one operon can be further attenuated by different mechanisms, for example, transcriptional or translational feedback (Swain, 2004). Sometimes subunits of macromolecular complex are produced from different operons. Swain (2004) shows that both translational and transcriptional feedback can increase the correlation between these subunits, but translational feedback is more efficient.

However, even in the same operon, genes are not expressed at the equivalent level. The cell needs to fine-tune the gene expression ratio to fit their biological functions. The tuning can be executed at the transcriptional or the translational level. In this work, we try to study the difference of noise and correlation when the cell takes distinct tuning strategies.

Tuning transcription rate or stability of mRNA can change the mRNA level, which will be passed to the protein levels by translation. Lifetime of mRNAs in bacteria is relatively short. Most mRNAs will be degraded by various ribonucleases (Condon, 2007) and live only several minutes (Selinger et al., 2003; Bernstein et al., 2002; Kristoffersen et al., 2012). Different transcription rates can be introduced by the internal promoter or terminator. Intergenic Rho-dependent or Rho-independent (Lesnik et al., 2001) terminator can introduce the polar effect which means genes in the promoter-proximal region are transcribed more compared with the promoter-distal ones. Recently, transcriptome sequencing of *Mycoplasma pneumoniae* (Güell et al., 2009) and synthetic biology studies in *E. coli* (Nishizaki et al., 2007; Hiroe et al., 2012) indicate that this effect might be a global phenomenon even for an operon without an obvious termination signal in the intergenic region. As for mRNA degradation rate, although distinct regions in one operon may have different degradation rates (Selinger et al., 2003; Kristoffersen et al., 2012), for those genes with close function relationship, their transcripts seem to have the similar degradation rates (Bernstein et al., 2002; Kristoffersen et al., 2012; Quax et al., 2013). Previous works indicate that co-transcription of genes in one operon is the main source of correlation (Sneppen et al., 2010; Swain, 2004; Ray and Igoshin, 2012; Iber, 2006), so it can be expected that tuning gene expression ratio at transcriptional level would lower the correlation.

Although it cannot be ruled out that tuning translation degradation would be one of the mechanisms to adjust the protein expression level, it is well known that most proteins in the prokaryotic cell are not degraded to avoid wasting (Gur et al., 2011). It is more likely that cells tune a protein level by adjusting protein synthesis rate. Many features embedded in coding and non-coding regions of the mRNA sequence can influence the translation initiation and elongation rate. The Shine–Dalgarno sequence and its distance to translation initiation codon will affect the assembling of translation complex (Vellanoweth and Rabinowitz, 1992; Chen et al., 1994). The structure of 5′-UTR will affect the accessibility of the ribosome binding site (Goodman et al., 2013; Bentele et al., 2013; Hao et al., 2011b). Codon usage will influence translation elongation (Tuller et al., 2010; Cannarrozzi et al., 2010; Klumpp et al., 2012). The internal Shine–Dalgarno like sequence may induce translation pausing (Li et al., 2012; Wen et al., 2008).

In this work, we use stochastic models to describe the transcription and translation processes of a bicistronic operon driven by a constitutive or a two-state promoter (Fig. 1A) respectively. We get analytical results of intrinsic noise and correlation of gene expressions. We utilize termination efficiency of terminator to characterize the stiffness of polar effect, i.e., the ratio of transcripts that are prematurely terminated. Stochastic simulations confirm our analytical results. Our results show that the correlation between proteins decreases monotonously as termination efficiency increases and the correlation almost does not vary as the translation rate changes in the normal range. It may help to understand gene organization and its evolution in prokaryotes.

2. The bicistronic operon with the constitutive promoter

In our analysis, we focus on the statistics when the system is in the steady state. We use $\langle q\rangle$ and δq^2 to denote the mean and variance of numbers of species q, the Fano factor $\nu=\delta q^2/\langle q\rangle$ and coefficient of variance $\eta=\sqrt{\delta q^2}/\langle q\rangle$ to characterize noise. The Fano factor can be a measurement for deviation from the Poisson behavior. It takes the value of 1 for a Poisson process. We use the Pearson correlation coefficient $\rho=\langle(q_1-<q_1>)(q_2-<q_2>)\rangle/\sqrt{\delta q_1^2\delta q_2^2}$ to denote the correlation of the numbers of two species q_1 and q_2.

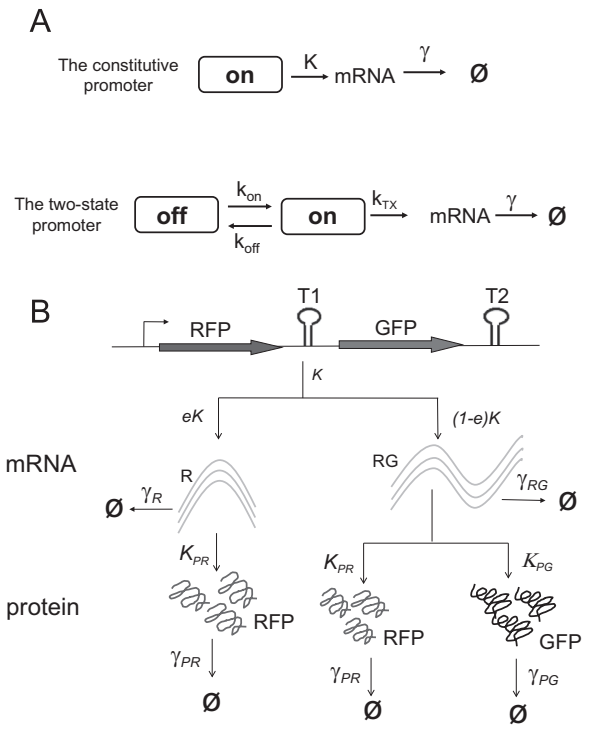

Fig. 1. (A) Two kinds of promoters used in our study. (B) Gene expression process of the bicistronic operon with the constitutive promoter. T1 represents any kind of polar effect mechanism: Rho-dependent or Rho-independent terminator in intergenic region of operon or other possible mechanisms (Güell et al., 2009). The termination efficiency of T1 is e, the transcription rate of promoter is K, the translation rates of RFP and GFP are K_{PR} and K_{PG}, the degradation rates of R, RG, RFP and GFP are respectively γ_R, γ_{RG}, γ_{PR} and γ_{PG}. For the two-state promoter, K should be replaced with k_{TX}, and transcription happens only when the promoter is in the on state.