The magnitude and color of noise in genetic negative feedback systems

Margaritis Voliotis[1], Clive G. Bowsher[2]

***Short Abstract* — Negative feedback control is a widespread mechanism of gene regulation. How effectively do different negative feedback systems suppress fluctuations? Is a mechanism involving small RNAs often better than self-repression of mRNA production (transcription) by the protein itself? We consider how best to measure biochemical fluctuations, characterize the minimal levels of noise that are achieved by common systems, and compare to the theoretical limit of optimal control. Transcriptional autorepression controls noise more robustly, reduces the lifetime of fluctuations, and is usually less costly. However, the sRNA-based system can achieve more extreme noise suppression.**

***Keywords* — noise, gene expression, sRNA, negative feedback, autocorrelation, autorepression.**

I. Introduction

In order to understand life at the level of individual cells we must understand how cells control and exploit the stochasticity inherent in biochemical mechanisms [1]. It is often proposed that negative feedback control is an important means of suppressing biochemical fluctuations [2,3]. Recent work [4] has derived limits on the extent to which biochemical feedback control mechanisms could suppress fluctuations by characterizing their magnitude when the control is mathematically optimal. However, very little is known about how close biochemical systems come in practice to achieving such lower bounds.

Negative feedback control is a widespread mechanism of gene regulation in both bacteria and eukaryotes [5]. Such regulation occurs both transcriptionally (at the level of mRNA synthesis) and post-transcriptionally due to the action of small non-coding RNAs (termed sRNAs in bacteria and microRNAs in eukaryotes). Here, we compare the ability of these two feedback mechanisms to control fluctuations or 'noise' in gene expression. We analyze the noise properties of the two systems for a broad, biologically plausible range of rate parameters, and compare them with the noise properties of the system which is identical except for the absence of the feedback loop.

II. Results

We find that negative transcriptional autoregulation (NTAR) and translational, small RNA-mediated autoregulation (NSAR) affect noise properties very differently. Transcriptional autorepression robustly reduces both the relative variance and persistence (or lifetime) of fluctuations. Autorepression via small RNA can achieve more extreme noise reduction and typically has less effect on the mean expression level. However, it is often more costly to implement and is more sensitive to rate parameters.

Both NTAR and NSAR usually suppress protein variance strongly enough compared to the reduction in the mean to reduce the relative variance or Fano factor but not enough to reduce the coefficient of variation. Also, we find that the relative variance is rarely reduced below one and often substantially exceeds a theoretical lower limit for feedback control [4].

We consider the dynamic properties of protein fluctuations, in particular their autocorrelation properties. We explain analytically how beneficial reductions in both the autocorrelation time ('noise whitening') and in the relative variance of a transcription factor combine to control the noise in downstream gene expression. We find that NTAR whitens noise more substantially and reliably, compared to NSAR.

Finally, we find that for transcriptional autorepression, substantial reductions in the relative variance of both the autoregulated protein and of a downstream gene are very frequently observed with little increase in the average cost per molecule of mean expression.

The disparate signatures on protein noise properties suggest different functional roles for the two feedback architectures. Our results challenge preconceptions concerning the strength and costliness of noise suppression by autoregulation in genetic networks. Also, they caution against comparing systems using any single, summary measure of biochemical noise.

[1] School of Mathematics, University of Bristol. E-mail: M.Voliotis@bristol.ac.uk

[2] School of Mathematics, University of Bristol. E-mail: C.Bowsher@bristol.ac.uk

References

[1] Eldar A, Elowitz, MB (2010) Functional roles for noise in genetic circuits. Nature, **467**, 167–173.

[2] Savageau MA (1974) Comparison of classical and autogenous systems of regulation in inducible operons. Nature, **252**, 546–549.

[3] Alon U (2007) Network motifs: theory and experimental approaches. Nat Rev Genet, **8**, 450– 461.

[4] Lestas I, Vinnicombe G, and Paulsson J (2010) Fundamental limits on the suppression of molecular fluctuations. Nature, **467**, 174–178.

[5] Lee TI, Rinaldi NJ, Robert F, Odom, DT, et al (2002) Transcriptional regulatory networks in Saccharomyces cerevisiae. Science, **298**, 799–804.