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Noise suppression in auto-regulatory gene networks

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Short Abstract — **Auto-regulatory negative feedback loops, where the protein expressed from a gene inhibits its own expression are common gene network motifs within cells. We present results that predict the level of stochastic fluctuations in protein numbers as a function of quantities that can be experimentally determined, such as the response time of the protein and the level of feedback. This theoretical analysis shows that there is an optimal level of feedback that minimizes protein noise levels and we provide explicit analytical expressions that characterize the smallest level of noise that is inherent to this type of auto-regulation. These theoretical results are shown to be consistent and explain recent experimental observations.**

Keywords — **Auto-regulatory gene networks, noise suppression, feedback strength, response time, intrinsic noise, extrinsic noise.**

I. Purpose

Gene expression and regulation is inherently a noisy process. The origins of this stochasticity lie in the probabilistic nature of transcription and translation and low copy numbers of RNAs and proteins within cells, which can lead to large statistical fluctuations in molecule numbers [1,2,3]. However, various gene network motifs found within cells can decrease these stochastic fluctuations. A common such motif is an auto-regulatory gene network where the protein expressed from the gene inhibits its own transcription [4]. In these networks, the rate at which the protein is produced from the gene is a function of the number of protein molecules present in the cell. We refer to this function as the *transcriptional response* of the gene network. Our goal is to understand how the functional form of the transcriptional response affects stochastic fluctuations in protein numbers and to quantify the limits of noise suppression in these networks.

II. Main results

We develop analytical formulas that relate the functional form of the transcriptional response with the intrinsic noise (i.e., the noise associated with random protein expression and degradation events) and the extrinsic noise (i.e., the noise associated with fluctuations in the reaction rates due to correspondent fluctuations in cellular enzyme levels). We also relate the protein noise levels in these auto-regulatory gene networks with the *response time* of the protein. In particular, we show that for a fixed average number of protein molecules, decreasing (increasing) response times leads to attenuation (magnification) of both protein intrinsic and extrinsic noise, with the extrinsic noise being more sensitive to changes in the response time. However, when the average number of protein molecules in not fixed, we identify scenarios in which one can have an opposite effect : decreasing (increasing) response times leads to magnification (attenuation) of protein noise.

The above-developed formulae allow us to characterize how proteins noise levels change as we vary the *feedback strength* in the transcriptional response. We show that in these auto-regulatory gene networks, protein noise levels are always minimized at *specific intermediate levels* of feedback strength. The noise resulting from these optimal levels of feedback characterizes the smallest level of noise that can be achieved in these networks through the use of feedback. We provide analytical expression for this highest level of noise suppression and the amount of feedback that achieves this minimal noise. These results explain recent experimental observations that reported that protein noise in minimized at some optimal feedback strength and that decreasing or increasing feedback strength away from this optima causes an increase in the protein noise [5]. Our results have implications for the design of synthetic auto-regulatory gene networks with minimal protein noise. They also raise the question of whether these widely occurring network motifs have naturally evolved to operate at the optimal feedback strength.

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