Regulation Revealed by Correlations in Gene Expression Noise

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Short Abstract — **Gene regulatory interactions are context–dependent, active in some cellular conditions but not in others. We present a method for determining when a regulatory link is active given temporal measurements of gene expression. Correlations in time series data are used to determine how genes influence each other and their causal relationships. Natural stochastic noise is shown to aid in the process of network identification by perturbing the expression of genes; the speed and direction at which the noisy signal propagates shows how the network is connected. We present results from a synthetic gene circuit and a natural feed-forward loop responsible for galactose regulation.**

***Keywords* — network inference, extrinsic and intrinsic noise, synthetic biology, feed-forward loop**

I. Extended Abstract

Recent work has shown that noise in gene expression can generate fluctuations, leading to substantial cell-cell variability [1-4]. Noise has now been measured systematically across many genes [5, 6]. In the context of a transcriptional regulatory circuit, noise in the concentration of a transcription factor can only propagate through one or more active regulatory links. Thus noise may provide information about active regulatory connections without explicit perturbation of cellular components.

However, noise propagation through active regulatory links is not the only factor affecting expression correlations between genes. The expression of many or all genes in the organism may be correlated due to global variations, or 'extrinsic noise,' in the overall rate of gene expression [2, 3]. For example, fluctuating numbers of ribosomes, polymerase components, and cell size can affect the expression of all genes in a cell. At the same time, a target gene can fluctuate independently of its regulator due to stochasticity, or 'intrinsic noise,' in its own expression, reducing its correlation with other genes.

Gene regulation occurs with a delay; it takes time for protein concentrations to build up sufficiently to have a regulatory effect on the downstream genes they control [7]. The sign of the delay provides information about the direction of the link. Such a delay does not occur for extrinsic noise, which affects all genes simultaneously. Similarly, intrinsic noise is uncorrelated at all time scales. Thus, dynamic measurements, in which one can follow the expression of multiple genes over time, can be used to decouple noise from regulatory correlations. This effect can be analyzed using the temporal cross correlation function, which describes how well two signals are correlated when one of them is shifted in time relative to the other. Similar approaches have been used to infer connectivity of *in vitro* networks [9-10].

We present results from a three-color synthetic gene circuit that validate the method on a circuit with known topology. In addition results from a natural feed-forward loop that is involved in the galactose regulatory pathway are discussed [11].

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