Effects of molecular sequestration on stochastic gene expression

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Short Abstract **— Transcription factors (TFs) interact with a multitude of binding sites on DNA and partner proteins inside cells. We investigate how nonspecific binding/unbinding to such "decoy binding sites" affects the magnitude of random fluctuations in TF copy numbers. We find that increasing the number of decoy sites can considerably reduce stochasticity in free TF copy numbers. Moreover, TF noise impacts the expression levels of target genes. Intriguingly, we find that noise in the expression of the target gene decreases with increasing decoy sites for linear TF-target protein dose-responses, even in regimes where decoy sites do not change noise in TF level.**

I. Introduction

Noise in the gene expression process manifests as stochastic fluctuations in protein copy numbers inside individual cells. Cells use a variety of regulatory mechanisms, such as incoherent feedforward circuits and negative feedback loops [1] to minimize randomness in essential protein levels, including TFs. Here we explore an alternative noise-buffering mechanism in TFs: nonspecific binding of TFs to the large number of sites on DNA, referred to as *decoy binding sites*.

Studies have found that TF sequestration by decoy binding sites can considerably affect gene network dynamics by slowing response times [2], converting graded TF-target protein dose-responses to binary responses [3], and reducing the magnitude of random fluctuations in TF levels using numerical simulations [4-5].

To understand how unspecific binding affects stochastic expression of TF and downstream target protein, statistical moments of the TF and target protein population count are derived in the presence of decoy sites. Our analysis reveals that while decoy sites reduce the extent of random fluctuations, they can both shorten or lengthen the time-scale of fluctuations in the levels of the free TF.

II. Model

Our model of TF expression and sequestration at decoy binding sites is based on the stochastic formulation of a gene network in which, consistent with measurements inside the cell [6], TF is produced in geometrically distributed bursts.

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The TFs which are bound to decoy sites are assumed to be protected from degradation. As a consequence, the average number of free TF molecules at steady-state is independent of number of decoy sites.

Moreover, we assume that the interaction between TFs and decoy binding sites is fast. Thus, at any given time, binding and unbinding interactions are in quasi steady-state.

III. Results

Our calculations show when burst size is one with probability one, free TF has Posisson statistics, and the noise level is independent of the number of decoy sites. Interestingly, noise in the target protein decreases with increasing number of decoy sites. This is because adding decoy sites causes the time-scale of free TF fluctuations to become faster, and the variability in target protein expression decreases due to the efficient time averaging of upstream TF fluctuations.

For large mean burst sizes, noise in both free TF and target protein populations decrease with increasing number of decoy sites. However, because the addition of decoy sites makes TF fluctuations longer and more permanent, the ratio of noise from target protein to noise of TF increases.

IV. Conclusion

In summary our results show that nonspecific TF binding to the large number of sites on DNA plays a critical role in regulating TF copy number fluctuations inside individual cells. Moreover, noise attenuation is also achieved in target proteins for linear TF-target gene dose-responses. Future efforts will focus on experimentally verifying these results using synthetic genetic circuits.

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