A Regulatory Role for Repeated Decoy Transcription Factor Binding Sites in Target Gene Expression

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***Short Abstract* — Intergenic tandem repeats (TRs) containing transcription factor (TF) binding sites could serve as DNA decoys competitively binding TFs and affecting target gene expression. Using a yeast synthetic system, we demonstrate that repeated decoy sites tightly sequester a transcriptional activator and inhibit the promoter activation, creating a sigmoidal-like dose-response. This altered response can qualitatively change a network behavior by converting a transcriptional positive feedback response from graded to bimodal. Finally, we find that the TR's binding affinity for TF becomes lower with increasing activator level, implying a possibility of anticooperative binding.**

***Keywords* — Tandem Repeats, Transcription Factor Decoy, Bimodality, Anticooperative Binding**

I. Introduction

Repetitive DNA sequences are frequently present in both prokaryote and eukaryote genome and the majority of repeats are concentrated in intergenic regions [1]. Since TRs rapidly expand and contract, they have been regarded as non-functional 'junk' DNA [2]. However, a number of recent studies implicate variable TRs within or close to the gene in phenotypic variation, suggesting those TRs are functional [3, 4]. Whether intergenic TRs can also create a functional consequence is, however, generally not clear. Bioinformatic studies reveal that numerous intergenic TRs include TF binding sites [5]. If these TRs competitively bind TFs and thereby affect gene expression, they could serve as an unappreciated gene regulator. Recent reports, though qualitative, support this hypothesis [6].

To quantitatively understand the effect of repetitive binding sites on target gene expression, we utilize a synthetic system in budding yeast, measure how repeats affect the dose-response between a transcriptional activator and its target promoter, and interpret those results using a mathematical model [7].

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II. Results

We show that intergenic TRs of activator binding sites effectively sequester activators and reduce gene expression [8]. However, unexpectedly, the initially linear dose-response between the activator and the promoter is converted to a sigmoidal-like response in the presence of TRs, indicating that TRs' binding affinity for activator is more than 100 fold higher than the promoter's even though the activator binding sites within the promoter and TRs are identical in sequence. The strong binding is further confirmed in the transcriptional positive feedback system where TRs alter a graded feedback response to bimodal. Finally, we find that this tight TR/activator interaction occurs only when most of the TRs are vacant. Subsequent TR/activator binding is weaker and its affinity is comparable to promoter/activator binding, suggesting that the strength of the activator/TR interaction is anti-correlated with the activator level.

III. Conclusion

Our quantitative study demonstrates that repeated TF binding sites can play an important role for gene regulation leading a qualitative change in dose-response of the target promoter and in gene network behavior.

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