Tae J. Lee, School of Biology & School of Physics, Georgia Institute of Technology, Atlanta, GA, USA
Joshua S. Weitz, School of Biology & School of Physics, Georgia Institute of Technology, Atlanta, GA, USA
Harold D. Kim, School of Physics & School of Biology, Georgia Institute of Technology, Atlanta, GA, USA

Quantifying the interaction between neighboring gene circuits in *Saccharomyces cerevisiae*

Gene regulation is typically described in terms of the recruitment of transcriptional machinery to genes in order to transcribe RNA from DNA. In this view, transcriptional rates depend on the availability of specific biomolecules called transcription factors, which help recruit and stabilize RNA polymerase, the enzyme responsible for transcription, to the start site of genes. However, recent experimental observations have noted that gene regulation can also be affected by the spatial location of genes in the genome[1,2]. Indeed, adjacent genes in the eukaryotic genome interact to give rise to unique properties. For example, adjacent genes often show stronger correlation in temporal dynamics and higher gene expression level than when they are expressed alone[3,4]. Recent studies in prokaryotes have demonstrated various modes of interaction between adjacent genes (e.g. transcriptional interference), but they cannot account for the unique properties of adjacent genes in eukaryotes. In addition, genome-wide studies in eukaryotes have proposed potential mechanisms for interaction between adjacent genes, but a quantitative understanding of gene-gene interaction remains unclear.

In this study we utilized a combined experimental and theoretical approach to study the interaction between adjacent genes in eukaryotes. We synthesized manipulable genetic circuits comprised of the constitutive KlURA3 promoter (pURA) juxtaposed to the inducible GAL1 promoter (pGAL1) in various arrangements. pGAL1 undergoes a change in chromatin state upon induction, while the chromatin state of pURA is expected to be fixed. Taking advantage of these properties, we quantified how pURA activity is affected by the chromatin state of pGAL1 when the two promoters are oriented in various arrangements.

Our experimental results showed distinct patterns in pURA activity between uninduced and induced conditions, but only when the two promoters are juxtaposed in a bidirectional manner. We observed that the activity of bidirectionally oriented pURA was significantly repressed when pGAL1 was uninduced. Similarly, we observed a drastic increase in pURA activity when pGAL1 was induced. In contrast, our results showed that pGAL1 activity remained constant regardless of the relative arrangements, suggesting that the chromatin state of pGAL1 (but not pURA) is well protected from the neighboring chromatin domains. Our results together demonstrate that functionally unrelated genes that are juxtaposed can be transcriptionally coupled, providing an explanation for the unique properties of adjacent genes. Based on these results, we build a rate-equation based model of transcriptional interactions along the genome. This rate equation model considers multiple states of individual promoters. State transitions within a promoter are then governed by the state of promoter itself and that of adjacent promoters. We utilize this rate equation based model to highlight possible mechanisms and consequences of promoter interaction.

1. Bai Flagfeldt, D., Siewers, V., Huang, L. & Nielsen, J. Characterization of chromosomal integration sites for heterologous gene expression in Saccharomyces cerevisiae. *Yeast* 26, 545–551 (2009).
2. Jansen, A., Van Der Zande, E., Meert, W., Fink, G. R. & Verstrepen, K. J. Distal Chromatin Structure Influences Local Nucleosome Positions and Gene Expression. *Nucl. Acids Res.* (2012).doi:10.1093/nar/gkr1311
3. Lin, J. M. *et al.* Transcription factor binding and modified histones in human bidirectional promoters. *Genome Research* 17, 818 –827 (2007).
4. Trinklein, N. D. *et al.* An Abundance of Bidirectional Promoters in the Human Genome. *Genome Research* 14, 62 –66 (2004).