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Dissecting transcription factor networks using high-throughput sequencing and quantitative genetics

In this talk I will describe our recent efforts to elucidate the molecular interactions underlying the behavior of gene regulatory networks. I will first demonstrate how deep sequencing of interactions between DNaseI and naked DNA uncovers a strong dependence of cleavage rate on nucleotide sequence, which can be related to the width of the minor groove; an additional, equally striking dependence on CpG methylation status exists, allowing us to predict methylation status from in vivo DNaseI profiles. Next, I will show how SELEX-seq, a novel methodology for quantifying in vitro interactions between transcription factor complexes and DNA, allowed us to discover that heterodimerization with the cofactor Extradenticle gives rise to large differences in DNA binding specificity between Hox proteins that are absent when these proteins bind as monomers. Finally, I will demonstrate how linear modeling of genetic variation in mRNA expression levels combined with prior information about the DNA binding specificity of transcription factors can be used to map the loci ("aQTLs") whose allelic variation modulates their regulatory activity.