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A computational genomics approach to identify cis-regulatory modules from chromatin immunoprecipitation microarray data – a case study of E2F1

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Short Abstract: We have developed a computational genomics approach (ChIPModules), to identify transcriptional regulatory modules using data obtained from chromatin immunoprecipitation microarrays. We have used E2F1 in cancer cells as a study case to demonstrate our approach has identified five regulatory modules for E2F1 and verified one module by another ChIP-chip.

Long Abstract:
Advances in high-throughput technologies such as ChIP-chip and the completion of human and mouse genomic sequences now allow analysis of the mechanisms of gene regulation on a systems level. In this study, we have developed a computational genomics approach (termed ChIPModules), which integrates positional weight matrices constructed from transcription factor binding sites, a comparative genomics approach, and statistical learning methods to identify transcriptional regulatory modules using data obtained from chromatin immunoprecipitation microarrays. We have used E2F1 binding site information obtained from ChIP-chip analyses of ENCODE regions, from both HeLa and MCF-7 cells. Our approach not only distinguished targets from non-targets with a high specificity, but it also identified five regulatory modules for E2F1. One of the identified modules predicted a co-localization of E2F1 and AP-2α on a set of target promoters with an intersite distance of less than 270 bp. We tested this prediction using ChIP-chip assays with arrays containing ~14,000 human promoters. We found that both E2F1 and AP-2α bind within the predicted distance to a large number of common human promoters, demonstrating the strength of our sequence-based, unbiased and universal protocol. Finally, we have used our ChIPModule approach to develop a database of thousands of computationally identified and experimentally verified E2F1 target promoters.