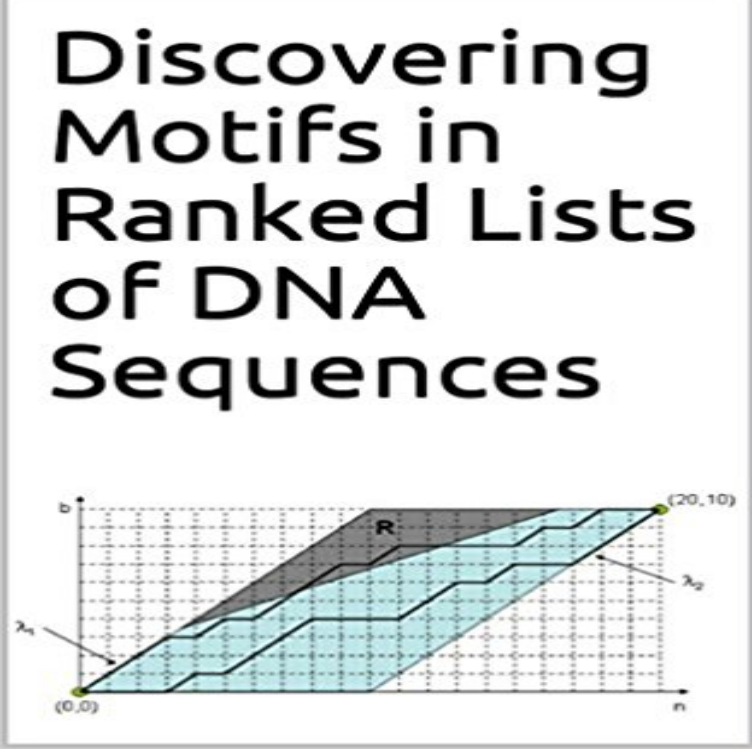


# Discovering Motifs in Ranked Lists of DNA Sequences



Computational methods for discovery of sequence elements that are enriched in a target set compared with a background set are fundamental in molecular biology research. One example is the discovery of transcription factor binding motifs that are inferred from ChIPchip (chromatin immuno-precipitation on a microarray) measurements. Several major challenges in sequence motif discovery still require consideration: (i) the need for a principled approach to partitioning the data into target and background sets; (ii) the lack of rigorous models and of an exact p-value for measuring motif enrichment; (iii) the need for an appropriate framework for accounting for motif multiplicity; (iv) the tendency, in many of the existing methods, to report presumably significant motifs even when applied to randomly generated data. In this paper we present a statistical framework for discovering enriched sequence elements in ranked lists that resolves these four issues. We demonstrate the implementation of this framework in a software application, termed DRIM (discovery of rank imbalanced motifs), which identifies sequence motifs in lists of ranked DNA sequences. We applied DRIM to ChIPchip and CpG methylation data and obtained the following results. (i) Identification of 50 novel putative transcription factor (TF) binding sites in yeast ChIPchip data. The biological function of some of them was further investigated to gain new insights on transcription regulation networks in yeast. For example, our discoveries enable the elucidation of the network of the TF ARO80. Another finding concerns a systematic TF binding enhancement to sequences containing CA repeats. (ii) Discovery of novel motifs in human cancer CpG methylation data. Remarkably, most of these motifs are similar to DNA sequence elements bound by the Polycomb complex that promotes histone

methylation. Our findings thus support a model in which histone methylation and CpG methylation are mechanistically linked. Overall, we demonstrate that the statistical framework embodied in the DRIM software tool is highly effective for identifying regulatory sequence elements in a variety of applications ranging from expression and ChIPchip to CpG methylation data. DRIM is publicly available at <http://bioinfo.cs.technion.ac.il/drim>.

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