

# Using biophysical models to understand eukaryotic chromatin structure and regulation of gene transcription

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## Abstract

Regulation of gene transcription in eukaryotes is strongly affected by the chromatin structure: DNA packaged into nucleosome core particles is not as readily accessible to transcription factors as naked DNA. Nucleosome positions in eukaryotic genomes are determined by both the free energy of nucleosome formation (DNA sequences tested in the lab exhibit more than a thousand-fold range of binding affinities), and by the dynamic competition of histones with other DNA binding factors for regulatory sequence.

We have developed a DNA mechanics-based model for predicting free energies of nucleosome formation (DNABEND), and used it to predict nucleosome positions in the *Saccharomyces cerevisiae* genome. Our model accurately reproduces available *in vitro* measurements of nucleosome free energies, and provides a simple mechanistic explanation for periodic sequence patterns observed in nucleosome positioning sequences. Genome-wide calculations of nucleosome positions reveal intrinsic nucleosomal organization of the yeast genome, and highlight the role of nucleosomes in facilitating *in vivo* chromosomal functions. We argue that it is the dynamic competition between nucleosomes and TATA binding proteins (TBPs) that determines experimentally observed chromatin structure around transcription/translation start sites. We also find that the nucleosome-induced cooperativity plays an important role in differentiating functional transcription factor binding sites (determined with CHIP-on-chip experiments) from the non-functional sites with similar binding energies.

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