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Using DNA mechanics to predict intrinsic and extrinsic nucleosome positioning signals[1]

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In eukaryotic genomes, nucleosomes function to compact DNA and to regulate access to it both by simple physical occlusion and by providing the substrate for numerous covalent epigenetic tags. While nucleosome positions in vitro are determined by sequence alone, in vivo competition with other DNA-binding factors and action of chromatin remodeling enzymes play a role that needs to be quantified. We developed a biophysical, DNA mechanics-based model for the sequence dependence of DNA bending energies, and validated it against a collection of in vitro free energies of nucleosome formation and a nucleosome crystal structure; we also successfully designed both strong and poor histone binding sequences ab initio. For in vivo data from S.cerevisiae, the strongest positioning signal came from the competition with other factors rather than intrinsic nucleosome sequence preferences. Based on sequence alone, our model predicts that functional transcription factor binding sites tend to be covered by nucleosomes, yet are uncovered in vivo because functional sites cluster within a single nucleosome footprint and thus make transcription factors bind cooperatively. Similarly a weak enhancement of nucleosome binding in the TATA region becomes a strong depletion when the TATA-binding protein is included, in quantitative agreement with experiment. Our model distinguishes multiple ways in which genomic sequence influences nucleosome positions, and thus provides alternative explanations for several genome-wide experimental findings. In the future our approach will be used to rationally alter gene expression levels in model systems through redesign of nucleosome occupancy profiles.

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