

Histone variants and tail dynamics in chromatin organization

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Nucleosomes are the fundamental repeating unit of eukaryotic chromatin. Experimental evidence suggests a direct role of histone tails and core histone variants in mediating chromatin stability, thereby modulating gene expression. However, how dynamics of histone tails and variant histones influences chromatin organization is not clearly understood. We have constructed a high-resolution model of the nucleosome core particle using simplified interaction potentials and performed Discrete Molecular Dynamics simulations of the model nucleosome core. We identify key histone-DNA interactions, termed *cold sites*, essential for nucleosome stability. We observe histone tails bind to nucleosomal DNA via strong salt-bridge interactions over a wide range of simulated temperatures. This suggests a mechanism of chromatin structural organization, whereby histone tails regulate inter- and intra-nucleosomal assemblies via binding with nucleosomal DNA. Simulations at multiple effective salt concentrations show that histone tails have a direct functional role in stabilizing higher order chromatin structure, mediated by salt bridge interactions with adjacent DNA. To investigate the role of histone variants in chromatin organization, we constructed a homology model of centromere-specific nucleosome. A major paradox in centromere biology is accumulation of cohesin rings at regions of separated sister DNA strands. We propose that pericentric chromatin is held together via intramolecular cohesion. Equilibrium between intra- vs. inter-molecular cohesion results in oscillations in the position of the centromere relative to the chromosome axis, resulting in a *C-loop* cruciform topology of the kinetochore junction.

References:

1. Bloom, K., S. Sharma, and N. V. Dokholyan. 2006. The path of DNA in the kinetochore. *Curr. Biol.* 16:R276-R278.
2. Sharma, S., F. Ding, and N. V. Dokholyan. 2006. Multiscale modeling of nucleosome dynamics. *Biophys. J.* Submitted.