MAR16-2015-003905

Abstract for an Invited Paper
for the MAR16 Meeting of
the American Physical Society

New insights into chromatin folding and dynamics from multi-scale modeling[1]

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The dynamic organization of chromatin plays an essential role in the regulation of gene expression and in other fundamental cellular processes. The underlying physical basis of these activities lies in the sequential positioning, chemical composition, and intermolecular interactions of the nucleosomes–the familiar assemblies of roughly 150 DNA base pairs and eight histone proteins–found on chromatin fibers. We have developed a mesoscale model of short nucleosomal arrays and a computational framework that make it possible to incorporate detailed structural features of DNA and histones in simulations of short chromatin constructs with 3-25 evenly spaced nucleosomes. The correspondence between the predicted and observed effects of nucleosome composition, spacing, and numbers on long-range communication between regulatory proteins bound to the ends of designed nucleosome arrays lends credence to the model and to the molecular insights gleaned from the simulated structures. We have extracted effective nucleosome-nucleosome potentials from the mesoscale simulations and introduced the potentials in a larger scale computational treatment of regularly repeating chromatin fibers. Our results reveal a remarkable influence of nucleosome spacing on chromatin flexibility. Small changes in the length of the DNA fragments linking successive nucleosomes introduce marked changes in the local interactions of the nucleosomes and in the spatial configurations of the fiber as a whole. The changes in nucleosome positioning influence the statistical properties of longer chromatin constructs with 100-10,000 nucleosomes. We are investigating the extent to which the 'local' interactions of regularly spaced nucleosomes contribute to the corresponding interactions in chains with mixed spacings as a step toward the treatment of fibers with nucleosomes positioned at the sites mapped at base-pair resolution on genomic sequences.

[1]Support of the work by USPHS R01 GM 34809 is gratefully acknowledged.