Integrative modeling methods for understanding nucleosome dynamics.

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Nucleosomes are elementary building blocks of chromatin, which play crucial role in genome organization, DNA damage and repair. Every nucleosome core particle consists of 147 bp of DNA wrapped around an octamer of histones. Many factors (such as DNA sequence, histone variants, post-translational modifications, etc.) can affect the stability and dynamics of nucleosomes, which in turn provide key mechanisms for epigenetic regulation of gene expression. Nucleosomes are dynamic entities with conformational plasticity at various levels and timescales, which is necessary to fulfill their functions. Hence, both modeling and experimental data analysis at different levels of detail and timescales is necessary to understand nucleosomes. We have developed a range of modeling and experimental data analysis methods to address this problem.

A number of computational experiments with nucleosomal particles using a wide range of modeling methods has been performed. In particular, we used molecular dynamics to study the dynamics of DNA linkers at times up to 1 microsecond, studied the interaction of histone tails with nucleosomal DNA [1]. The distribution of ions and electrostatic potential around the nucleosomes was calculated and the process of reversible DNA unwrapping from nucleosomes was modeled [2]. We also used an MM/PBSA method to calculate free energy profile of DNA unwrapping from histone octamer, which is in good agreement with experimental data [3].

Methods of experimental data integration with molecular modelling techniques were developed. For instance, we proposed a molecular model of FACT induced structural reorganization of nucleosomes based on single-particle Förster Resonance Energy Transfer data [4]. We used hydroxyl DNA footprinting data in conjunction with atomistic structures of nucleosomes enhanced by molecular dynamics simulations to develop a computational method for precise determination of DNA positioning in nucleosomes with the single base pair resolution. An integrative modelling approach based on empirical force field potential for DNA in the internal DNA variables space [5] combined with rigid body docking of histone dimers bound to local DNA regions in conjunction with distance restraints taken from

spFRET experiments and DNA footprinting was used to created a model of DNA conformation in chromatosome [6].

Experimental methods are indispensable but alone often not sufficient to understand the intricate aspects of chromatin function and regulation. We believe that employing multi-scale molecular modeling in conjunction experimental data will allow for detailed understanding of nucleosome dynamics, which is important for unraveling the mechanisms of transcriptional regulation in chromatin.

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