

## Structure and dynamics of chromatin at nucleosome level: integrating experiments and simulations

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Recent decades have witnessed tremendous progress in DNA sequencing and availability of complete genomic sequences for many living organisms. The digital-like discrete encoding of the genetic information within the primary sequence of the DNA opened many possibilities for bioinformatic analysis. However, understanding the functioning of the genomes ultimately requires the understanding of the 3D structural interactions between the DNA/RNA, proteins and their dynamics. In eukaryotic organisms, chromatin – the complex of DNA, RNA, histone and non-histone proteins – provides a complex framework for genome functioning and regulation. Deciphering the mechanisms of eukaryotic chromatin operation starts with understanding the structure and dynamics of the nucleosomes – the basic units of chromatin. Nucleosomes comprise an octamer of eight histone proteins and around 150 DNA base pairs wrapped around it. The canonical structure of the nucleosome was revealed by X-ray crystallography 25 years ago. It has since become apparent that at physiological conditions nucleosomes are highly dynamic and this dynamics is instrumental for genome functioning at epigenetic level [1]. However, despite recent progress in structural biology techniques we are still facing conceptual and methodological challenges in describing and understanding how large dynamic macromolecular such as nucleosomes function.

In this report I will showcase how combination of atomistic and coarse-grained supercomputer simulations supplemented with data from various biophysical and biochemical experiments can be used to study the structure and dynamics of chromatin at nucleosome and supranucleosome levels. Based on our works I will first discuss data analysis and modeling approaches that may be used to reconstruct the structures of arbitrary nucleosomes based on hydroxyl-radical footprinting experiments [2, 3]. In such experiments the DNA is cleaved within the nucleosome at solvent-accessible sites. Modeling of this process combined with pseudosymmetry of the nucleosome core allows for the reconstruction of the exact rotational and translational positioning of the DNA in nucleosomes. I will next discuss the application of atomistic supercomputer molecular dynamics (MD) simulations to decipher the functional motions of histones and DNA in nucleosomes [4]. Record long MD simulations at a timescale exceeding 10 microseconds allowed us to analyze the interplay between histone and DNA dynamics that facilitates nucleosome sliding along the DNA and regulates access of transcription machinery to the genetic information. I will conclude with showing how coarse-grained modeling and integrative modeling approaches may be used to model the structure of nucleosome complexes with chromatin proteins and the structure of chromatin fibrils.

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## References

1. Armeev G.A. et al. Linking chromatin composition and structural dynamics at the nucleosome level. *Curr Opin Struct Biol.* 2019;56:46-55.
2. Shaytan A.K. et al. Hydroxyl-radical footprinting combined with molecular modeling identifies unique features of DNA conformation and nucleosome positioning. *Nucleic Acids Res.* 2017;45(16):9229-9243.
3. Shaytan A.K. et al. Structural interpretation of DNA–protein hydroxyl-radical footprinting experiments with high resolution using HYDROID. *Nat Protoc.* 2018;13(11):2535-2556.
4. Armeev G.A. et al. Histone dynamics mediate DNA unwrapping and sliding in nucleosomes. *Nat Commun.* 2021;12:2387.