doi 10.18699/bgrs2024-3.1-34

Epigenetic regulation through nucleosome plasticity: insights from MD simulations

Fedulova A.S.[1]*, Motorin N.A.[1], Shariafetdinova A.S.[1], Armeev G.A.[1], Shaytan A.K.[1, 2]

[1] *Department of Biology, Lomonosov Moscow State University, Moscow, Russia*

[2] *Bioinformatics Lab, Faculty of Computer Science, HSE University, Moscow, Russia*

** a.kniazeva@intbio.org*

Key words: nucleosomes; chromatin; molecular dynamics simulations

Motivation and Aim: Eukaryotic DNA exists within a structure called chromatin. Chromatin and its basic unit, the nucleosome, are highly dynamic structures. The nucleosome core particle is formed by an octamer of histone proteins and 145–147 base pairs of wrapped DNA. Nucleosome dynamics regulate the accessibility of DNA to molecular machines and facilitate nuclear protein interactions. While experimental studies of nucleosome dynamics provide a static snapshots of dynamically stable states, additional methods, such as molecular modeling, are essential to interpret the indirect data. We use molecular dynamics (MD) simulations to describe nucleosome dynamics and mechanisms underlying its epigenetic regulation. Recent rapid improvements in computational capabilities have enabled the modeling of atomistic nucleosome dynamics on a multi-microsecond timescale.

Methods and Algorithms: We used all-atom MD simulations of nucleosomes whose initial structures were derived from the Protein Data Bank. Due to the nucleosome's substantial size and the presence of intrinsically disordered regions, MD simulations are particularly challenging. The study of nucleosomal DNA and protein (histone) globular core dynamics has been carried out on nucleosome X-ray structures with truncated disordered regions (histone tails) and using the TIP3P water model. For the histone tails simulations, different water models had to be tested. MD simulations were performed using the Gromacs, Amber ff14SB with parmbsc1 and CUFIX corrections. The NVT ensemble was used with a reference temperature and pressure of 300 K and 1 bar. Ion concentration of 150 mM NaCl was used.

Results: MD simulations in the multi-microsecond time scale allowed to simulate the partial unwinding of nucleosomal DNA from the histone core (both for nucleosomes with full-length and truncated tails) [1–3]. Additionally, DNA sliding coupled with histone-DNA contact reorganization was observed [2]. Detailed analysis showed that nucleosomal DNA dynamics are accompanied by bending motions of the H2A-H2B histone dimer. Such bending dynamics were characterized by principal component analysis as a general dynamic mode of H2A-H2B dimers (within the nucleosome and intact dimer) [4]. We hypothesize that epigenetic factors, such as histone variant incorporation or peptide binding, influence nucleosome dynamics through these histone core dynamic modes. Further MD simulations demonstrated that nucleosomes containing the variant histone H2A.Z exhibited a greater degree of bending in H2A-H2B dimers compared to canonical nucleosomes [4]. This observation aligns with findings from other studies that reported more pronounced DNA unwinding in variant

nucleosomes [5]. In another example, binding of the viral peptide LANA to the histone surface of the nucleosome stabilizes a more bent H2A-H2B dimer [6].

The influence of histone tail modifications (a major source of epigenetic marks) remains poorly understood. The MD studies should take into account recent findings on the use of various water models. Previously, the study by colleagues presented the comparison of NMR data (R1 and R2 relaxation rates) with the MD-derived analogue parameters and stated that the TIP4P-D water model is the most suitable for such studies [7]. In our latest simulations, the closest values of the R1/R2 relaxation parameters were obtained in the OPC water model.

Conclusion: MD simulations have provided mechanistic insights into the interplay between DNA dynamics and histone core dynamics within nucleosomes. The role of histone bending in DNA sliding and unwinding has been described, as well as how the presence of histone variants or peptide binding can influence nucleosome dynamics. These findings enhance our understanding of the structural and dynamic complexity of nucleosomes, particularly in the context of epigenetic regulation.

Funding and Acknowledgements: The study is supported by the Russian Science Foundation grant #23-74-10012 (https://rscf.ru/en/project/23-74-10012/). The research is carried out using the equipment of the shared research facilities of HPC computing resources at Lomonosov Moscow State University.

References

1. Winogradoff D., Aksimentiev A. Molecular Mechanism of Spontaneous Nucleosome Unraveling. *J Mol Biol*. 2019;431(2):323-335. doi 10.1016/j.jmb.2018.11.013
2. Armeev G.A., Kniazeva A.S., Komarova G.A., Kirpichnikov M.P., Shaytan A.K. Histone dynamics mediate DNA unwrapping and sliding in nucleosomes. *Nat Commun*. 2021;12(1):2387. doi 10.1038/s41467-021-22636-9
3. Huertas J., Schöler H.R., Cojocaru V. Histone tails cooperate to control the breathing of genomic nucleosomes. *PLoS Comput Biol*. 2021;17(6):e1009013. doi 10.1371/journal.pcbi.1009013
4. Kniazeva A.S., Armeev G.A., Shaytan A.K. H2A-H2B Histone Dimer Plasticity and Its Functional Implications. *Cells*. 2022;11(18):2837. doi 10.3390/cells11182837
5. Li S., Wei T., Panchenko A.R. Histone variant H2A.Z modulates nucleosome dynamics to promote DNA accessibility. *Nat Commun*. 2023;14(1):769. doi 10.1038/s41467-023-36465-5
6. Oleinikov P.D., Fedulova A.S., Armeev G.A. et al. Interactions of Nucleosomes with Acidic Patch-Binding Peptides: A Combined Structural Bioinformatics, Molecular Modeling, Fluorescence Polarization, and Single-Molecule FRET Study. *IJMS*. 2023;24(20):15194. doi 10.3390/ijms242015194
7. Rabdano S.O., Shannon M.D., Izmailov S.A. et al. Histone H4 Tails in Nucleosomes: a Fuzzy Interaction with DNA. *Angew Chem Int Ed*. 2021;60(12):6480-6487. doi 10.1002/anie.202012046