DOI: 10.14529/jsfi220205

Analysis of Ion Atmosphere Around Nucleosomes Using Supercomputer MD Simulations

Nikita A. Kosarim[1], ***Grigoriy A. Armeev***[1], ***Mikhail P. Kirpichnikov***[1,2], ***Alexey K. Shaytan***[1,3]

The nucleosome is the basic unit of eukaryotic DNA compaction. It consists of about 147 base pairs wrapped around an octamer of histone proteins. Nucleosomal dynamics provides the availability of packaged DNA for various factors that carry out the vital processes associated with chromatin. It is not completely known how the structure and dynamics of the nucleosome depends on the ionic environment. The current researches do not give an unambiguous answer and often contradict each other. In this paper, we demonstrate supercomputer molecular dynamics simulations of nucleosome models surrounded by monovalent sodium and potassium cations. Analyzing the trajectories, we have shown the details of the distribution of sodium and potassium ions around the linker DNA, nucleosomal DNA at the sites of nucleosomal opening, and histone residues involved in the process of nucleosomal breathing. We have demonstrated the mobility of DNA linkers and the process of nucleosomal unwrapping in various ionic environments, and also assessed the probable mechanisms of the dependence of nucleosome unwrapping on the type of ions in the system. Our study is intended to emphasize the importance of understanding the role of the ionic environment in the functioning of chromatin.

Keywords: molecular modeling, molecular dynamics simulations, nucleosomes, protein-DNA interactions, monovalent cations, sodium, potassium.

Introduction

The length of DNA in a human cell is about 2 meters, which is 200,000 times the diameter of the nucleus [37]. To fit DNA in the nucleus, it must be packed into a compact structure – chromatin, the elementary unit of which is the nucleosome. The nucleosome is formed by a histone octamer (two H2A-H2B dimers in complex with a tetramer H3-H4/H3-H4), which is wrapped by DNA about 147 base pairs long in a 1.67-turn of a left-handed superhelix (Fig. 1). This structure is also called nucleosome core particle (NCP) [26, 38]. Neighboring nucleosomes are connected by the so-called linker DNA with a length of 10 to 90 bp depending on the type of organism, cell type, stage of the cell cycle, and location in the cell nucleus [2, 21].

The nucleosome is dynamic [4]. Its dynamic plays a key role in the vital processes that take place in the nucleus. An important part of nucleosomal dynamics is nucleosome breathing, which is the unwrapping of up to twenty base pairs from the NCP. The process of nucleosomal breathing is driven by dynamic interactions between neighboring DNA strands, as well as interactions between DNA and histones. The main meaning of nucleosomal breathing is to regulate the availability of DNA for factors that carry out chromatin-associated processes.

The nucleosome is a charged structure [17], and most of the contacts between DNA and histones are electrostatic. This causes the dependence of nucleosome structure and dynamics on the ionic environment. In living systems, the main monovalent ions are Na^+ and K^+. While sodium prevails in the extracellular environment, potassium dominates in the intracellular environment, being an essential element of the DNA environment. One of the hypotheses for such distribution of ions in eukaryotic cells, suggests a more efficient implementation of chromatin-associated

[1]Department of Biology, Lomonosov Moscow State University, Moscow, Russia
[2]Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, Moscow, Russia
[3]Bioinformatics Lab, Faculty of Computer Science, HSE University, Moscow, Russia

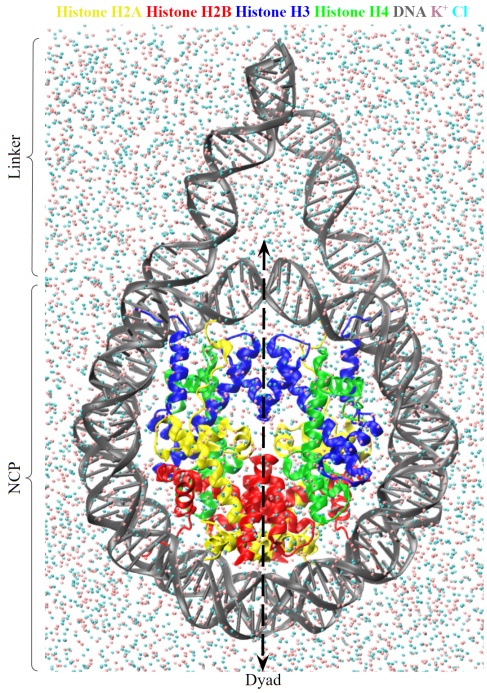


Figure 1. Nucleosome model in simulated system

processes in the potassium environment compared to sodium [21]. Nevertheless, due to the similarity of Na^+ and K^+ ions, most of the experimental work related to the study of nucleosomes is carried out in media containing sodium ions. Some works demonstrated the identity of experimental results obtained in potassium and sodium solutions [7, 22–24]. However, today, more and more researchers are declaring significant differences between these ionic environments. The key difference between sodium and potassium is the diameter of the ions: sodium has a smaller diameter than potassium. At the same time, the diameter of the hydration shell of sodium is larger than that of potassium. This difference can affect the features of ions interactions with the nucleosome and their distribution around it. As a result, structure and dynamics of the nucleosome, which determine the efficiency of various processes associated with chromatin, can be affected.

For example, the question of the comparative affinity of sodium and potassium ions for DNA has not yet been unambiguously resolved. Some computational work suggests a higher affinity for sodium [40]. In turn, the results of experimental work are contradictory. Earlier studies suggest a greater affinity for potassium [47]. More recent studies, including works made with the ion counting method, indicate that the affinity of sodium and potassium ions for DNA does not differ or differs slightly [6, 23, 25].

Molecular dynamics and experiments show that sodium ions pack DNA [47] and polynucleosomal chains [2] more effectively than potassium ions. Thus, sodium ions can suppress the natural dynamics of chromatin. However, at the level of mononucleosomes the opposite effect is observed: the nucleosome acquires a more compact conformation in the potassium environment [28].

The type of ions in the medium can also influence the contacts between DNA and histones. Binding of DNA and histones is primarily due to electrostatic interactions between the negatively charged phosphate groups of DNA and the positively charged side chains of arginine and lysine amino acids through ion pairs [27]. It was shown that in the presence of mono- and

divalent cations, these interactions weaken, and their geometry changes due to the polarization of the phosphate groups charges towards ions [13]. Thus, the main role of cations in interactions between DNA and histones is the regulation of these interactions, in particular, the modulation of the dynamics of nucleosomal DNA opening and closing by weakening intermolecular contacts.

One of the powerful tools for studying the structure and dynamics of nucleosomes is the molecular dynamics (MD) method, which makes it possible to interpret and supplement the results of experimental studies. MD simulations have been applied to study the structure and dynamics of nucleosomal DNA [39], nucleosomal unfolding [3, 12, 18, 44], functions and dynamics of histone tails [9, 11, 15, 32, 36, 41], the role of histone post-translational modifications [14, 35], DNA-DNA and DNA-protein interactions [46], counterion distribution around nucleosomes [30], role of DNA sequence in nucleosome dynamics [42], etc. However, a detailed analysis of the ionic environment of the nucleosome and the dependence of the nucleosomal structure and dynamics on it has not been previously carried out. Due to the complexity and computation time, models often require various approximations such as removing parts of the system (e.g. histone tails), using implicit solvent models, or representing the system as a coarse-grained model to achieve significant simulation times. At the moment, the duration of the longest trajectory of an all-atom nucleosome model with intact histone tails, obtained using supercomputing, is about 15 μs [5]. However, many important dynamic processes of the nucleosome occur in the range from microseconds to milliseconds [16], which requires an increase in speed and efficiency of computational methods.

In this work, motivated by the ambiguity of the available evidence about the effect of the monovalent cations type on the nucleosome structure and dynamics, we aimed to use all-atom supercomputer molecular dynamics simulations to model nucleosome dynamics in different ionic environments. Simulating the time trajectory of such a large all-atom model as the nucleosome with ions requires considerable computing power. Thus, the most efficient way is to carry out MD calculations on supercomputers, which make it possible to achieve significant computational speeds and trajectory lengths. Using the Lomonosov-2 supercomputer, we obtained eight trajectories for nucleosome models (including 20 bp linker DNA segment) in solution with Na^+ and K^+ ionic concentrations of 150 mM and 3 M. In our work, we analyzed the details of the distribution of sodium and potassium ions around DNA of the nucleosome, and assessed the possible effect of ions on the process of nucleosomal breathing.

1. Methods

1.1. Simulation Preparation

The work was carried out using the molecular dynamics simulations method. The systems were based on the initial X-ray structure 1KX5 from the PDB database [10]. The 1KX5 structure was modified by adding 20 bp DNA-linkers with identical sequence and truncating histone tails. Sites of truncation were chosen in order to remove histone tails‘ flexible parts and avoid removing parts near the globular core that make stable contacts with DNA and histones. The final modified structure was placed in rhombododecahedral cell with periodic boundary conditions and minimal distance from nucleosome to cell wall 2 or 3 nm depending on the system. Then water molecules (TIP3P model) and K^+ or Na^+ and Cl^- ions were added to reach the desired concentration for the whole cell volume (150 mM or 3 M) (Fig. 1). In order to avoid possible fraying of base pairs at the ends of DNA, an additional harmonic potential (with a force constant of 1000 kJ

mol^{-1} nm^{-2}) was applied to the distance between glycosidic nitrogen atoms of the terminal base pairs. Simulations were performed with the GROMACS 2020.2 software package [1]. An AMBER ff14SB force field [29] with parmbsc1 DNA parameter correction [20] and CUFIX ion parameter correction [45] was used. The prepared systems were energy minimized and step-by-step equilibrated with a gradual relaxation of harmonic positional restraints imposed on all atoms except hydrogens. Minimization was carried out using the steepest descent gradient method with positional restraints of 500 kJ mol^{-1} nm^{-2}. Then the five stages of equilibration were performed: 1. 100 ps with positional restraints of 500 kJ mol^{-1} nm^{-2} with a step of 0.5 fs; 2. 200 ps with positional restraints of 50 kJ mol^{-1} nm^{-2} with a step of 2 fs (then the step was kept); 3. 200 ps with positional restraints of 5 kJ mol^{-1} nm^{-2}; 4. 200 ps with positional restraints of 0.5 kJ mol^{-1} nm^{-2}; 5. 200 ps free simulation. The systems were modeled in an NPT ensemble with a temperature of 300 K using the velocity rescale scheme [8] and with a 1 bar pressure coupling using Parrinello-Rahman barostat [34]. The molecular dynamics simulation step was 2 fs, and frames in the molecular dynamics trajectory simulation were saved every 1 ns. Detailed simulated systems description and production run protocol files may be found at `https://github.com/intbio/Kosarim_et_al_2022`.

Simulations were performed on the Lomonosov-2 supercomputer [43] using 1 computing node, having 14 CPU cores and one NVidia Tesla K40 GPU. Average speed of simulation was 6 ns per day. For calculation of non-bonded interactions GPU was used.

1.2. Trajectory Analysis

The resulting trajectories were analyzed using Gromacs [1], MDAnalysis [31] and VMD [19] programs, as well as algorithms developed by our scientific group using Python 3.

The unwrapping of nucleosomal DNA during nucleosome breathing was measured as the length of a DNA fragment in which all base pair centers were more than 7 angstroms further from the centers of any base pair in the initial structure.

Radial distribution functions (RDF) of the of sodium and potassium ions were plotted around two regions of the nucleosome DNA, namely, around any atom of DNA linkers (74-92 bp, “linker”) and nucleosomal DNA in the region of the exit from the nucleosome (54-73 bp, “core”). The functions were normalized in such a way as to converge to 1 at large values of the distance.

Survival probability (SP) reflects the probability of finding ions within a given radius from DNA within a certain time. In our case, we considered the probability of detecting sodium and potassium ions at concentrations of 150 mM and 3 M within a radius of 5 angstroms from any DNA atom around DNA linkers (74-92 bp, “linker”) and nucleosomal DNA (54-73 bp, “core”).

For a comparative analysis of the spatial distribution of sodium and potassium ions around DNA, the occupancy of ions near the nucleosomal DNA in the region of the DNA exit from the nucleosome (base pair number 54-73) was plotted. The occupancy values are obtained as follows: the space is divided by a cubic lattice in a certain cell size (in this case, 1 angstrom); during the analysis the lattice nodes are assigned the values 0 or 1 depending on whether one or more of the considered atoms intersect with them; then the results are averaged along all the trajectory. For this analysis, we selected pairs of systems that demonstrate the greatest opening of the DNA in nucleosome (K150/Na150 and K3000a/Na3000a).

2. Results and Discussion

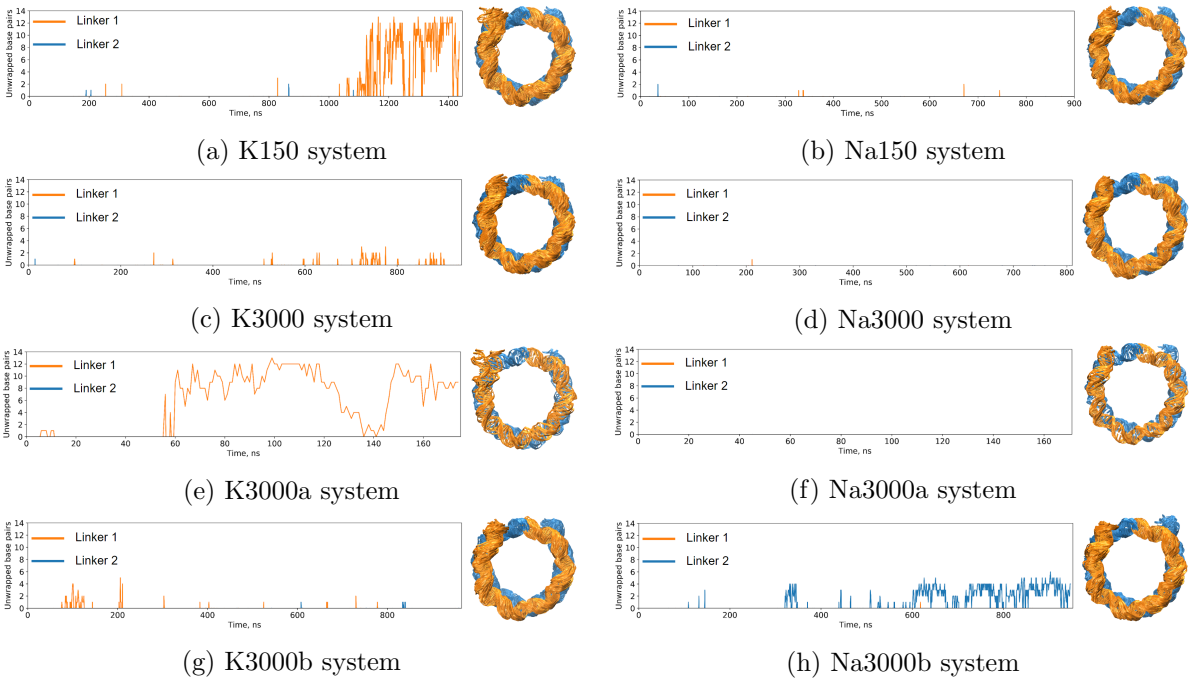
The study of the influence of the monovalent cations type on the process of nucleosome breathing was carried out on eight systems, mainly differing in the type of cations, their concentration and simulation time (Tab. 1).

Table 1. Simulated systems

System	K150	K3000	K3000a	K3000b	Na150	Na3000	Na3000a	Na3000b
Atom number	319435	302890	397389	302890	323520	302890	397389	302890
Water molecules	99490	89184	119461	89184	99490	89184	119461	89184
Cation type	K^+	K^+	K^+	K^+	Na^+	Na^+	Na^+	Na^+
Ions number, cation/Cl	577/271	5723/5417	7557/7251	5723/5417	577/271	5723/5417	7557/7251	5723/5417
Cation concentration, mM	150	3000	3000	3000	150	3000	3000	3000
Distance to the box, nm	2	2	3	2	2	2	3	2
Time, μ s	1.37	0.92	0.94	0.16	0.88	0.80	0.93	0.16

2.1. DNA Unwrapping

DNA unwrapping was observed in trajectories at timescales of greater than 1 microsecond for ion concentrations of 150 mM and at timescales of hundreds of nanoseconds for 3M concentrations (Fig. 2). The obtained results clearly demonstrate the asymmetric nature of nucleosome breathing in our simulations, that was experimentally shown by Ngo and colleagues [33]. Despite the fact that the nucleosome unwrapping in the obtained graphs is observed mainly in the potassium environment, this, unfortunately, cannot serve as unambiguous evidence of the influence of the ions type due to the probabilistic nature of nucleosome breathing and the short duration of simulations.



(a) K150 system (b) Na150 system

(c) K3000 system (d) Na3000 system

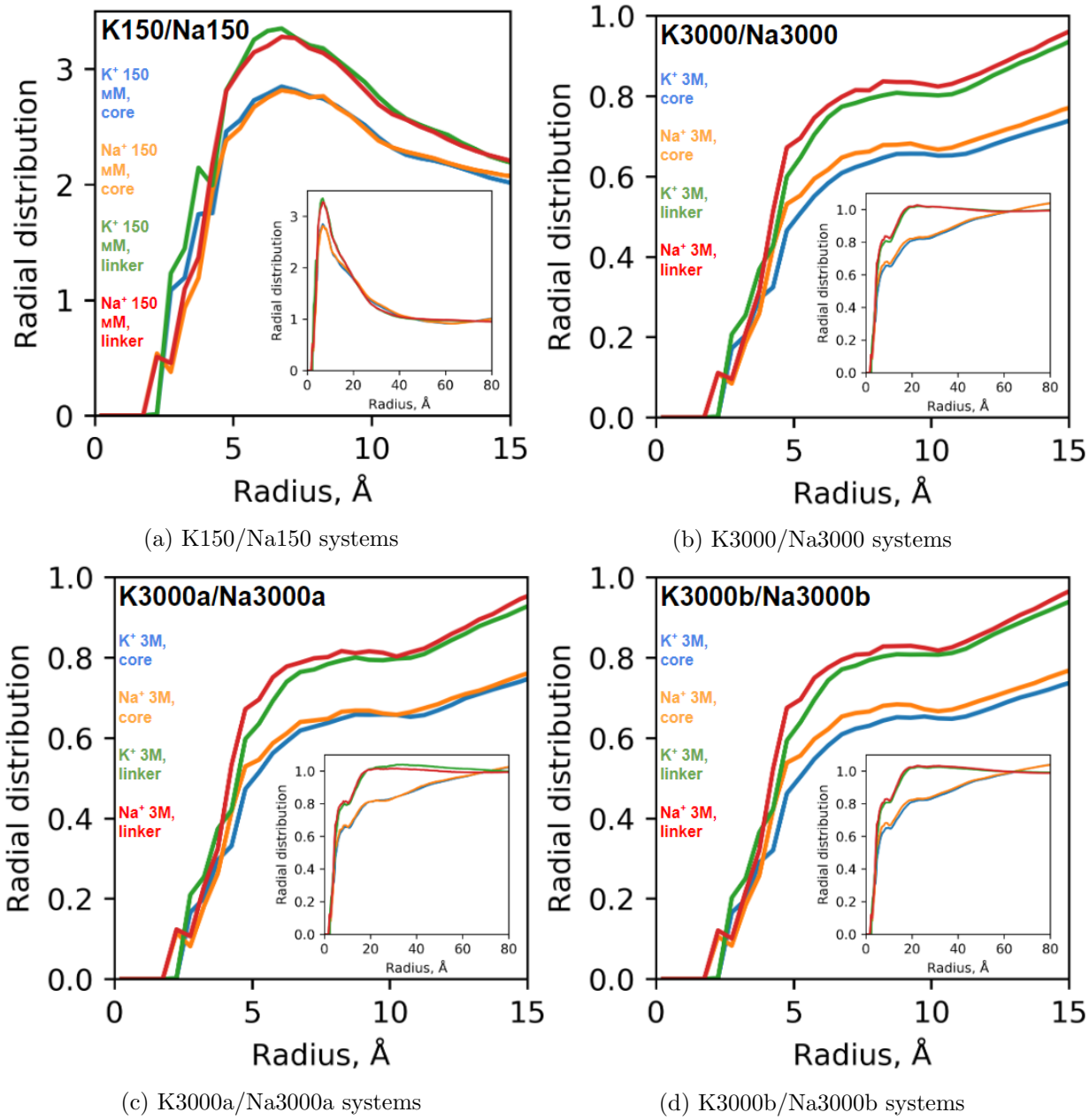
(e) K3000a system (f) Na3000a system

(g) K3000b system (h) Na3000b system

Figure 2. Profiles of the extent of DNA unwrapping during MD simulations and corresponding overlays of MD snapshots spaced 50 ns apart

2.2. Radial Distribution of Ions

According to the radial distribution function (RDF) plots (Fig. 3), several important observations can be made: firstly, the plots of the ionic distribution around DNA linkers are higher than around nucleosomal DNA, which indicates a greater probability of potassium and sodium ions binding to the linker DNA than to the nucleosomal DNA; secondly, the plots for sodium and potassium ions do not differ significantly, which indicates a similar probability of detecting potassium and sodium ions near both linker and nucleosomal DNA.



(a) K150/Na150 systems

(b) K3000/Na3000 systems

(c) K3000a/Na3000a systems

(d) K3000b/Na3000b systems

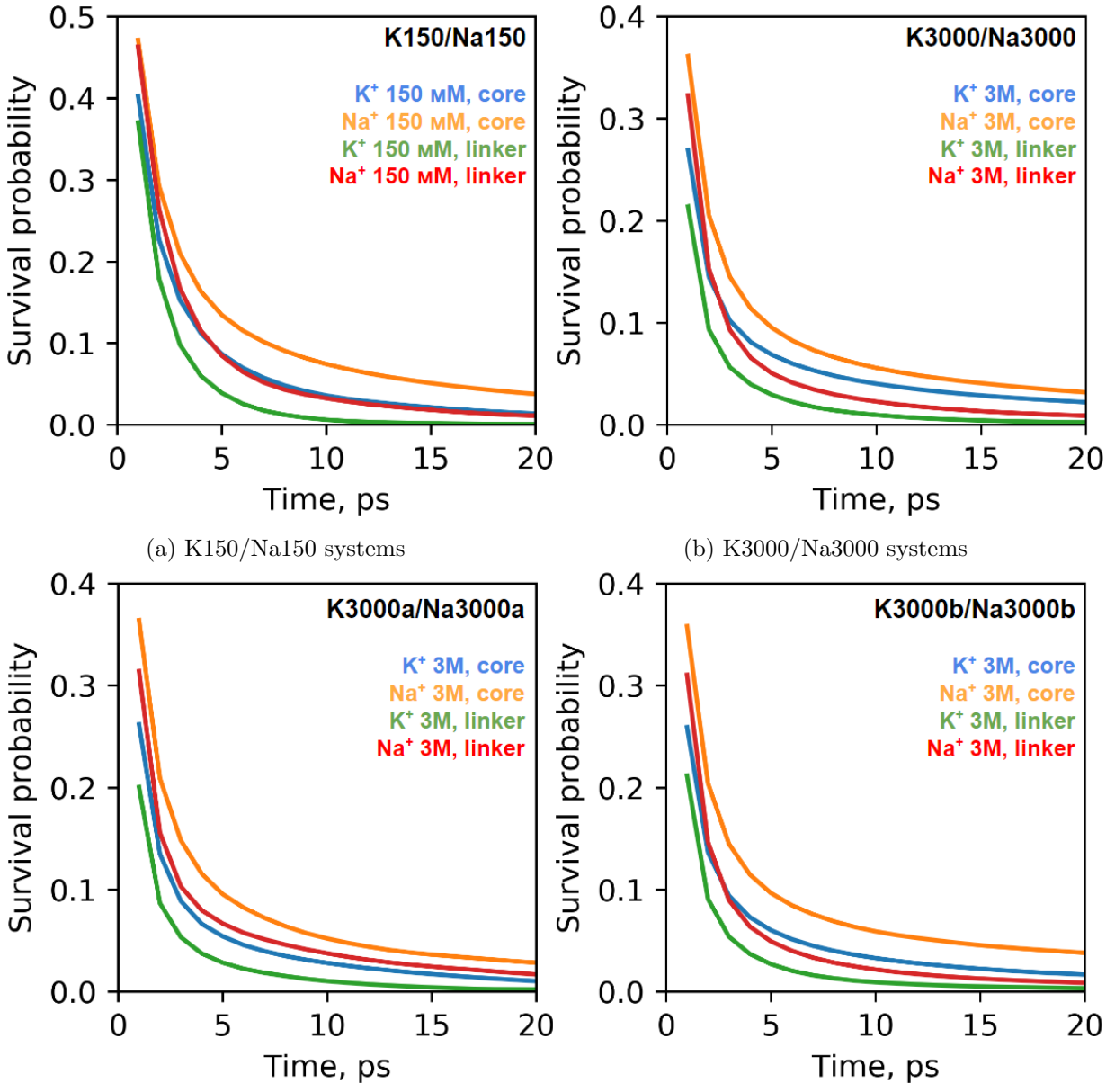
Figure 3. Radial distribution functions of Na^+ and K^+ ions around linker ("linker") and nucleosomal ("core") DNA

The first observation can be explained due to the fact that some of the ion-binding sites on nucleosomal DNA can be occupied by the amino acid residues of the adjacent histones or by

adjacent DNA gyres. The second observation may be a consequence of the fact that both types of ions have similar interaction patterns with the DNA.

2.3. Survival Probability of Ions

The calculated survival probability (SP) plots demonstrate higher values of the SP for sodium ions compared to potassium ions near the linker and nucleosomal DNA, both at a concentration of 150 mM and at 3 M (Fig. 4). This indicates a longer interaction of sodium ions with DNA. We would also like to note the increased SP of both types of ions near nucleosomal DNA compared to the SP near linker DNA. This observation indicates a relatively longer residence time of both types of ions near nucleosomal DNA. This can be explained by the interactions of ions with histones or the neighboring gyres of the nucleosomal DNA, preventing their movement.



(a) K150/Na150 systems

(b) K3000/Na3000 systems

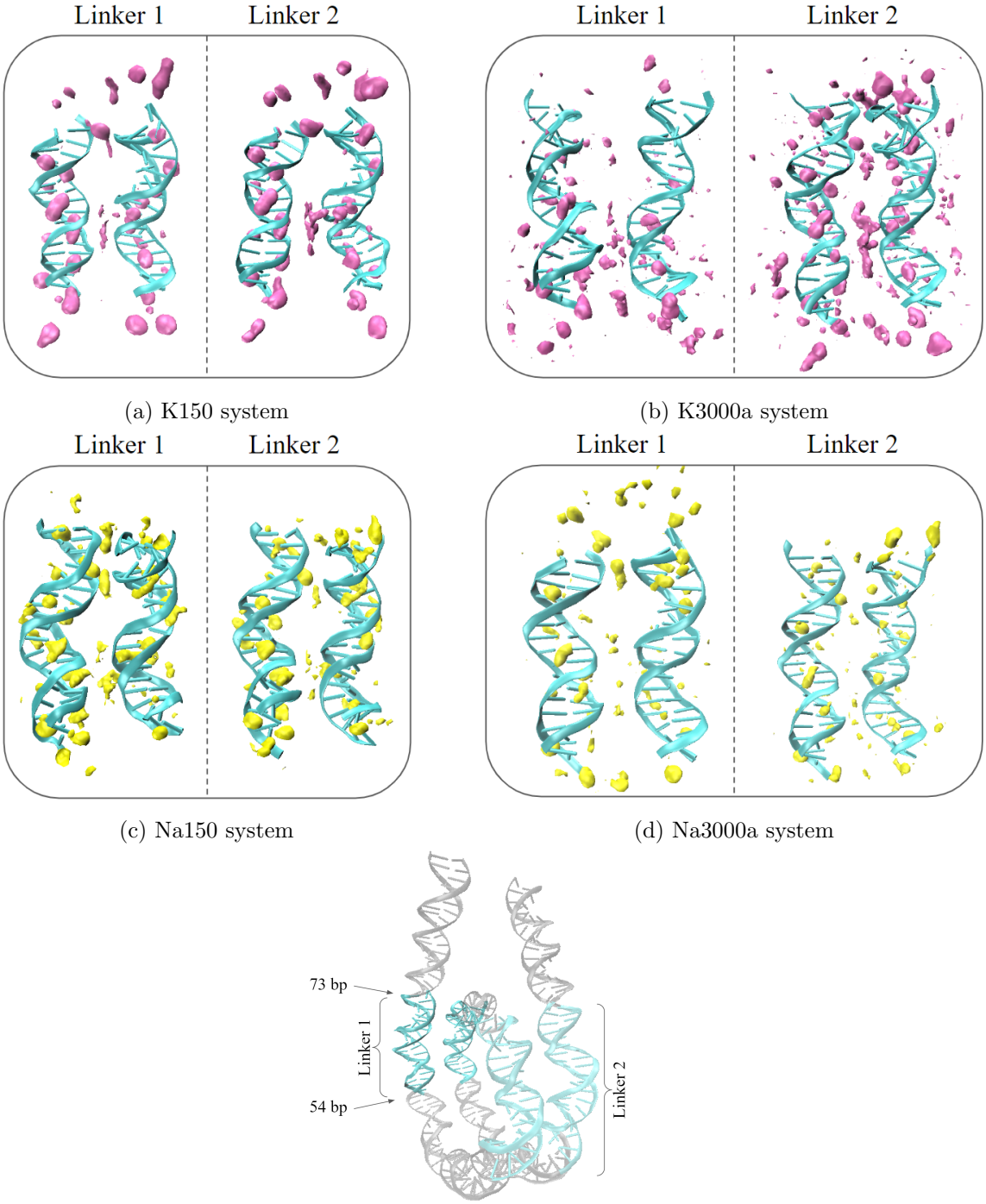
(c) K3000a/Na3000a systems

(d) K3000b/Na3000b systems

Figure 4. Survival probability of Na^+ and K^+ ions in 5 Å around linker ("linker") and nucleosomal ("core") DNA in simulation pairs

2.4. Ionic Occupancy

In systems with a sodium environment, where the nucleosomal DNA is predominantly wrapped on both sides during the entire simulation, the occupancy of sodium ions does not significantly differ (Fig. 5). At the same time, in systems with potassium ions, and especially in the K3000a system, there is a clear difference in the ion occupancy in the space between adjacent DNA gyres.



(a) K150 system

(b) K3000a system

(c) Na150 system

(d) Na3000a system

(e) Scheme of nucleosome

Figure 5. Occupancy of Na^+ and K^+ ions around nucleosomal DNA at entry/exit regions and corresponding scheme of nucleosome

The occupancy is increased on the non-unwrapping side of the nucleosome ("Linker 2"), where the DNA segment of the upper and lower DNA gyre reside closer together throughout the entire trajectory. At the same time, occupancy on the unwrapping side ("Linker 1") is lower. This may indicate both that the approach of DNA segments leads to the accumulation of ions in the intermolecular space, and the opposite – ions, accumulating between and around the adjacent DNA segments, prevent their repulsion and, in this case, the nucleosome breathing.

Conclusion

As a result of this work, we have made important observations concerning the distribution of monovalent sodium and potassium cations around the nucleosomal DNA, as well as their influence on the structure and dynamics of the nucleosome linker region. In particular, plots of nucleosome unwrapping, radial and temporal distribution functions, and populations of both types of ions near linker and nucleosomal DNA were obtained. We showed that the concentration and mobility of both types of ions near the nucleosomal DNA is lower than around the linker DNA, which can be explained by the interactions of DNA with histones and interactions between neighboring DNA gyres. The noted longer residence time of sodium ions near the DNA presumably indicates their greater affinity for DNA compared to potassium ions at least within the force field model used in our simulations. Among other things, it has been demonstrated that ions tend to accumulate in the space between the nucleosomal DNA gyres, probably contributing to their attraction and thus preventing nucleosome breathing. The problem of monovalent cations type effect on nucleosome requires further examination due to its ambiguity. Nevertheless, the use of potassium, which is predominant *in vivo*, may be preferred in computer simulations.

Acknowledgements

This research was funded by the Ministry of Science and Higher Education of the Russian Federation, grant No. 075-15- 2021-1354. This research has been non-profit supported by the Interdisciplinary Scientific and Educational Schools of Moscow University "Molecular Technologies of the Living Systems and Synthetic Biology".

References

1. Abraham, M.J., Murtola, T., Schulz, R., *et al.*: Gromacs: High performance molecular simulations through multi-level parallelism from laptops to supercomputers. SoftwareX 1-2, 19–25 (2015). https://doi.org/10.1016/j.softx.2015.06.001

2. Allahverdi, A., Chen, Q., Korolev, N., Nordenskild, L.: Chromatin compaction under mixed salt conditions: Opposite effects of sodium and potassium ions on nucleosome array folding. Scientific Reports 5 (2015). https://doi.org/10.1038/srep08512

3. Armeev, G.A., Shaitan, K.V., Shaytan, A.K.: Nucleosome structure relaxation during dna unwrapping: Molecular dynamics simulation study. Moscow University Biological Sciences Bulletin 71, 141–144 (2016). https://doi.org/10.3103/S0096392516030020

4. Armeev, G.A., Gribkova, A.K., Pospelova, I., *et al.*: Linking chromatin composition and structural dynamics at the nucleosome level. Current Opinion in Structural Biology 56, 46–55 (2019). https://doi.org/10.1016/j.sbi.2018.11.006

5. Armeev, G.A., Kniazeva, A.S., Komarova, G.A., *et al.*: Histone dynamics mediate DNA unwrapping and sliding in nucleosomes. Nature Communications 12 (2021). https://doi.org/10.1038/s41467-021-22636-9

6. Bai, Y., Greenfeld, M., Travers, K.J., *et al.*: Quantitative and comprehensive decomposition of the ion atmosphere around nucleic acids. Journal of the American Chemical Society 129, 14981–14988 (2007). https://doi.org/10.1021/ja075020g

7. Braunlin, W.H., Nordenskiold, L.: A potassium-39 NMR study of potassium binding to double-helical DNA (1984)

8. Bussi, G., Donadio, D., Parrinello, M.: Canonical sampling through velocity rescaling. Journal of Chemical Physics 126 (2007). https://doi.org/10.1063/1.2408420

9. Chakraborty, K., Kang, M., Loverde, S.M.: Molecular mechanism for the role of the H2A and H2B histone tails in nucleosome repositioning. Journal of Physical Chemistry B 122, 11827–11840 (2018). https://doi.org/10.1021/acs.jpcb.8b07881

10. Davey, C.A., Sargent, D.F., Luger, K., *et al.*: Solvent Mediated Interactions in the Structure of the Nucleosome Core Particle at 1.9 Å Resolution. Journal of Molecular Biology 319(5), 1097–1113 (2002). https://doi.org/https://doi.org/10.1016/S0022-2836(02)00386-8

11. Erler, J., Zhang, R., Petridis, L., *et al.*: The role of histone tails in the nucleosome: A computational study. Biophysical Journal 107, 2911–2922 (2014). https://doi.org/10.1016/j.bpj.2014.10.065

12. Ettig, R., Kepper, N., Stehr, R., *et al.*: Dissecting DNA-histone interactions in the nucleosome by molecular dynamics simulations of DNA unwrapping. Biophysical Journal 101, 1999–2008 (2011). https://doi.org/10.1016/j.bpj.2011.07.057

13. Farca, A.A., Bende, A.: The influence of monovalent and divalent metal cations on the stability of the DNA-protein interaction in the nucleosome core particle. Advances in Quantum Chemistry 81, 269–290 (2020). https://doi.org/10.1016/bs.aiq.2020.05.001

14. Fu, I., Geacintov, N.E., Broyde, S.: Molecular dynamics simulations reveal how H3K56 acetylation impacts nucleosome structure to promote DNA exposure for lesion sensing. DNA Repair 107, 103201 (2021). https://doi.org/10.1016/j.dnarep.2021.103201

15. Furukawa, A., Wakamori, M., Arimura, Y., *et al.*: Characteristic H3 N-tail dynamics in the nucleosome core particle, nucleosome, and chromatosome. iScience 25(3) (2022). https://doi.org/10.1016/j.isci.2022.103937

16. Gansen, A., Felekyan, S., Khnemuth, R., *et al.*: High precision FRET studies reveal reversible transitions in nucleosomes between microseconds and minutes. Nature Communications 9 (2018). https://doi.org/10.1038/s41467-018-06758-1

17. Gebala, M., Johnson, S.L., Narlikar, G.J., Herschlag, D.: Ion counting demonstrates a high electrostatic field generated by the nucleosome. eLife 8, e44993 (2019). https://doi.org/10.7554/eLife.44993

18. Huertas, J., Cojocaru, V.: Breaths, twists, and turns of atomistic nucleosomes. Journal of Molecular Biology 433 (2021). https://doi.org/10.1016/j.jmb.2020.166744

19. Humphrey, W., Dalke, A., Schulten, K.: VMD: Visual Molecular Dynamics (1996)

20. Ivani, I., Dans, P.D., Noy, A., *et al.*: Parmbsc1: A refined force field for DNA simulations. Nature Methods 13, 55–58 (2015). https://doi.org/10.1038/nmeth.3658

21. Korolev, N.: How potassium came to be the dominant biological cation: of metabolism, chemiosmosis, and cation selectivity since the beginnings of life. BioEssays 43 (2021). https://doi.org/10.1002/bies.202000108

22. Korolev, N., Lyubartsev, A.P., Rupprecht, A., Nordenskild, L.: Competitive binding of $Mg2^+$, Ca^{2+}, Na^+, and K^+ ions to DNA in oriented DNA fibers: Experimental and Monte Carlo simulation results. Biophysical Journal 77, 2736–2749 (1999). https://doi.org/10.1016/S0006-3495(99)77107-9

23. Korolev, N., Lyubartsev, A.P., Rupprecht, A., Nordenskild, L.: Experimental and Monte Carlo simulation studies on the competitive binding of Li^+, Na^+, and K^+ ions to DNA in oriented DNA fibers. Journal of Physical Chemistry B 103, 9008–9019 (1999). https://doi.org/10.1021/jp9913517

24. Korolev, N., Nordenskild, L.: Influence of alkali cation nature on structural transitions and reactions of biopolyelectrolytes. Biomacromolecules 1, 648–655 (2000). https://doi.org/10.1021/bm000042f

25. Kuznetsov, I., Gorshkov, V., Ivanov, V., *et al.*: Ion-exchange properties of immobilized DNA (1984)

26. Luger, K., Der, A.W.M., Richmond, R.K., *et al.*: Crystal structure of the nucleosome core particle at 2.8 Å resolution (1997)

27. Luscombe, N.M., Laskowski, R.A., Thornton, J.M.: Amino acid-base interactions: a three-dimensional analysis of protein-DNA interactions at an atomic level (2001)

28. Lyubitelev, A.V., Studitsky, V.M., Feofanov, A.V., Kirpichnikov, M.P.: Effect of sodium and potassium ions on conformation of linker parts of nucleosomes. Moscow University Biological Sciences Bulletin 72, 146–150 (2017). https://doi.org/10.3103/S0096392517030075

29. Maier, J.A., Martinez, C., Kasavajhala, K., *et al.*: ff14SB: Improving the accuracy of protein side chain and backbone parameters from ff99SB (2015)

30. Materese, C.K., Savelyev, A., Papoian, G.A.: Counterion atmosphere and hydration patterns near a nucleosome core particle. Journal of the American Chemical Society 131, 15005–15013 (2009). https://doi.org/10.1021/ja905376q

31. Michaud-Agrawal, N., Denning, E.J., Woolf, T.B., Beckstein, O.: MDAnalysis: A toolkit for the analysis of molecular dynamics simulations. Journal of Computational Chemistry 32, 2319–2327 (2011). https://doi.org/10.1002/jcc.21787

32. Morrison, E.A., Bowerman, S., Sylvers, K.L., *et al.*: The conformation of the histone H3 tail inhibits association of the BPTF PHD finger with the nucleosome . https://doi.org/10.7554/eLife.31481.001

33. Ngo, T.T., Zhang, Q., Zhou, R., *et al.*: Asymmetric unwrapping of nucleosomes under tension directed by DNA local flexibility. Cell 160, 1135–1144 (2015). https://doi.org/10.1016/j.cell.2015.02.001

34. Parrinello, M., Rahman, A.: Polymorphic transitions in single crystals: A new molecular dynamics method. Journal of Applied Physics 52, 7182–7190 (1981). https://doi.org/10.1063/1.328693

35. Peng, Y., Espiritu, D., Li, S., *et al.*: Deciphering the effects of post-translational modifications and mutations on histone tail dynamics and interactions. Biophysical Journal 121, 361a (2022). https://doi.org/10.1016/j.bpj.2021.11.931

36. Peng, Y., Li, S., Landsman, D., Panchenko, A.R.: Histone tails as signaling antennas of chromatin. Current Opinion in Structural Biology 67, 153–160 (2021). https://doi.org/10.1016/j.sbi.2020.10.018

37. Razin, S.V., Ulianov, S.V.: Gene functioning and storage within a folded genome. Cellular & Molecular Biology Letters 22, 18 (2017). https://doi.org/10.1186/s11658-017-0050-4

38. Richmond, T.J., Davey, C.A.: The structure of DNA in the nucleosome core (2003)

39. Roccatano, D., Barthel, A., Zacharias, M.: Structural flexibility of the nucleosome core particle at atomic resolution studied by molecular dynamics simulation. Biopolymers 85, 407–421 (2007). https://doi.org/10.1002/bip.20690

40. Savelyev, A., Papoian, G.A.: Electrostatic, steric, and hydration interactions favor Na^+ condensation around DNA compared with K^+. Journal of the American Chemical Society 128, 14506–14518 (2006). https://doi.org/10.1021/ja0629460

41. Shaytan, A.K., Armeev, G.A., Goncearenco, A., *et al.*: Coupling between histone conformations and DNA geometry in nucleosomes on a microsecond timescale: Atomistic insights into nucleosome functions. Journal of Molecular Biology 428, 221–237 (2016). https://doi.org/10.1016/j.jmb.2015.12.004

42. Sun, R., Li, Z., Bishop, T.C.: TMB library of nucleosome simulations. Journal of Chemical Information and Modeling (2019). https://doi.org/10.1021/acs.jcim.9b00252

43. Voevodin, V.V., Antonov, A.S., Nikitenko, D.A., *et al.*: Supercomputer Lomonosov-2: Large scale, deep monitoring and fine analytics for the user community. Supercomputing Frontiers and Innovations 6, 4–11 (2019). https://doi.org/10.14529/jsfi190201

44. Winogradoff, D., Aksimentiev, A.: Molecular mechanism of spontaneous nucleosome unraveling. Journal of Molecular Biology 431, 323–335 (2019). https://doi.org/10.1016/j.jmb.2018.11.013

45. Yoo, J., Aksimentiev, A.: New tricks for old dogs: Improving the accuracy of biomolecular force fields by pair-specific corrections to non-bonded interactions. Physical Chemistry Chemical Physics 20, 8432–8449 (2018). https://doi.org/10.1039/c7cp08185e

46. Yoo, J., Winogradoff, D., Aksimentiev, A.: Molecular dynamics simulations of DNADNA and DNAprotein interactions. Current Opinion in Structural Biology 64, 88–96 (2020). https://doi.org/10.1016/j.sbi.2020.06.007

47. Zinchenko, A.A., Yoshikawa, K.: Na^+ shows a markedly higher potential than K^+ in DNA compaction in a crowded environment. Biophysical Journal 88, 4118–4123 (2005). https://doi.org/10.1529/biophysj.104.057323