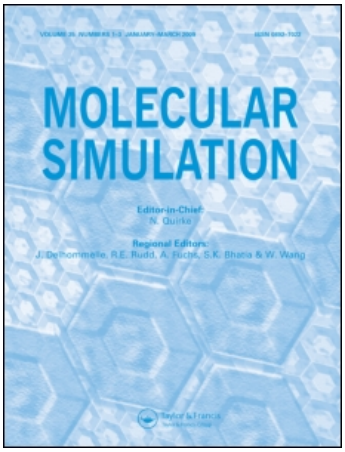

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DNA deformability and hydration studied by molecular dynamics simulation

Y. Yonetani[a]; H. Kono[bc]; S. Fujii[d]; A. Sarai[d]; N. Go[b]

[a] CREST, JST, Japan Atomic Energy Agency, Kyoto, Japan [b] Computational Biology Group, Neutron Biology Research Center, Japan Atomic Energy Agency, Kyoto, Japan [c] PRESTO, Japan Science and Technology Agency, Saitma, Japan [d] Department of Biosciences and Bioinformatics, Kyushu Institute of Technology, Fukuoka, Japan

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DNA deformability and hydration studied by molecular dynamics simulation

Y. YONETANI†, H. KONO‡¶*, S. FUJII§, A. SARAI§ and N. GO‡

†CREST, JST, Japan Atomic Energy Agency, 8-1 Umemidai, Kizu-cho, Soraku-gun, Kyoto 619-0215, Japan
‡Computational Biology Group, Neutron Biology Research Center, Japan Atomic Energy Agency, 8-1 Umemidai, Kizu-cho, Soraku-gun, Kyoto 619-0215, Japan
¶PRESTO, Japan Science and Technology Agency, 4-1-8 Kawaguchi, Saitma 332-0012, Japan
§Department of Biosciences and Bioinformatics, Kyushu Institute of Technology, Iizuka, Fukuoka 820-8502, Japan

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DNA tetramer sequences AATT and TTAA are known to be conformationally more rigid and flexible, respectively. In this study, we carry out molecular dynamics (MD) simulations of these two sequences and investigate the characteristic hydration pattern. The rigid AATT is found to be more likely to construct the hydration spine in the minor groove, than the flexible TTAA. The result suggests that the hydration water molecules play a critical role, for determining the sequence dependent deformability of DNA conformation.

Keywords: DNA; Deformability; Hydration; Molecular dynamics simulation; Water molecules

1. Introduction

DNA conformation and deformability depend on sequence composition. For example, it is known that a sequence containing contiguous AT steps is more deformable. The variability in DNA conformation and deformability has been believed to be one of the important factors in specific recognition of DNA sequence by regulatory proteins [1]. Several factors can be considered to yield the difference in DNA conformation and deformability among distinct DNA sequences. One is the mechanical stiffness inherent in the DNA itself, which is originated from base-pairing hydrogen interactions and base-stacking interactions. Another important factor affecting the DNA conformation and deformability is the hydration. The hydration effect is inevitable when discussing the structural properties of DNA, since DNA is physiologically surrounded by water molecules and the structure cannot be maintained without water.

A characteristic hydration pattern observed for DNA is the spine of water [2,3], which is composed of highly ordered water molecules aligned along the floor of the minor groove. In the first hydration shell, ordered water molecules form a bridge between the bases of two strands, where each hydrogen atom of the bridge water makes a hydrogen bond with the acceptor atom (N3 or O2) of the bases (figure 1). A bridge between the two adjacent bridge water molecules in the first hydration shell is further constructed, which composes the second hydration shell. The hydration spine was first found by Drew and Dickerson [2] in the single crystal structure of a sequence of 5′CGCGAATTCGCG3′, where a sequence dependent deviation from the canonical B-DNA structure was observed. A regular hydration spine was observed at the central region of AATT, whereas not observed at the both end regions of CGCG. Thus, the hydration pattern in DNA as well as the conformation of DNA is also a sequence dependent property. Consequently, the following question arises: How and to what extent does the hydration affect the sequence-dependent deformability of DNA? To address this question, a comparative study of various DNA sequences is required.

Molecular dynamics (MD) simulation is particularly suited to make such a systematic investigation compared to X-ray and neutron experiments, because it is easy to prepare many kinds of DNA samples composed of distinct sequences. Furthermore, the MD simulation has an advantage in providing the information not only about the average structures of DNA and hydrated water molecules, but also about their fluctuation, which is directly related to the DNA deformability. Recently, the

*Corresponding author. Email: kono.hidetoshi@jaea.go.jp

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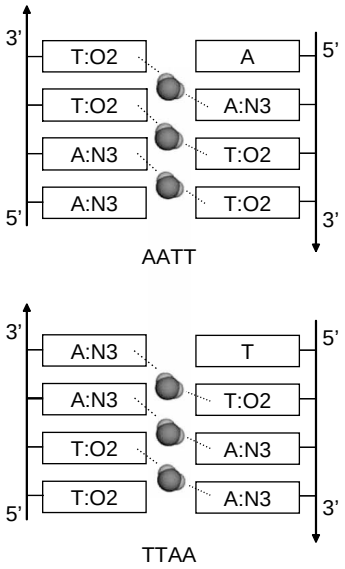

Figure 1. A schematic drawing of possible water hydration patterns in DNA minor grooves. Here, each of the water molecules forms a bridge between two bases. Bases (A and T) and acceptor atoms (O2 and N3) belonging to the bases are shown in the rectangular boxes. This hydration pattern is less likely to be observed in TTAA, as suggested by the result in figure 2.

sequence dependence of DNA conformation and deformability has been studied by MD simulations, where all possible 136 patterns for tetramer were examined [4,5]. As a result, the sequences AATT and TTAA were found to be the most rigid and flexible, respectively, among all possible tetramer sequences. In this work, we carry out MD simulations of these two extreme sequences and analyze characteristic hydration patterns observed in the distinct sequences. Our current analysis is focused on the behavior of the bridge water in the first hydration shell of DNA (figure 1). This is because such water molecule is a major component of hydration spine and thus expected to play an important role in determining the structural properties of DNA. On the basis of MD results of the two sequences AATT and TTAA, we discuss a possible relationship between the hydration and the deformation of DNA.

2. Details of MD simulations

MD simulations of DNA are carried out using a program AMBER [6] with the parm99 force field [7], which is known as a proper force field for simulating the B-form DNA [8]. A truncated octahedral box of size $60 \times 60 \times 60\,\text{Å}^3$ is prepared, in which the 12mer DNA

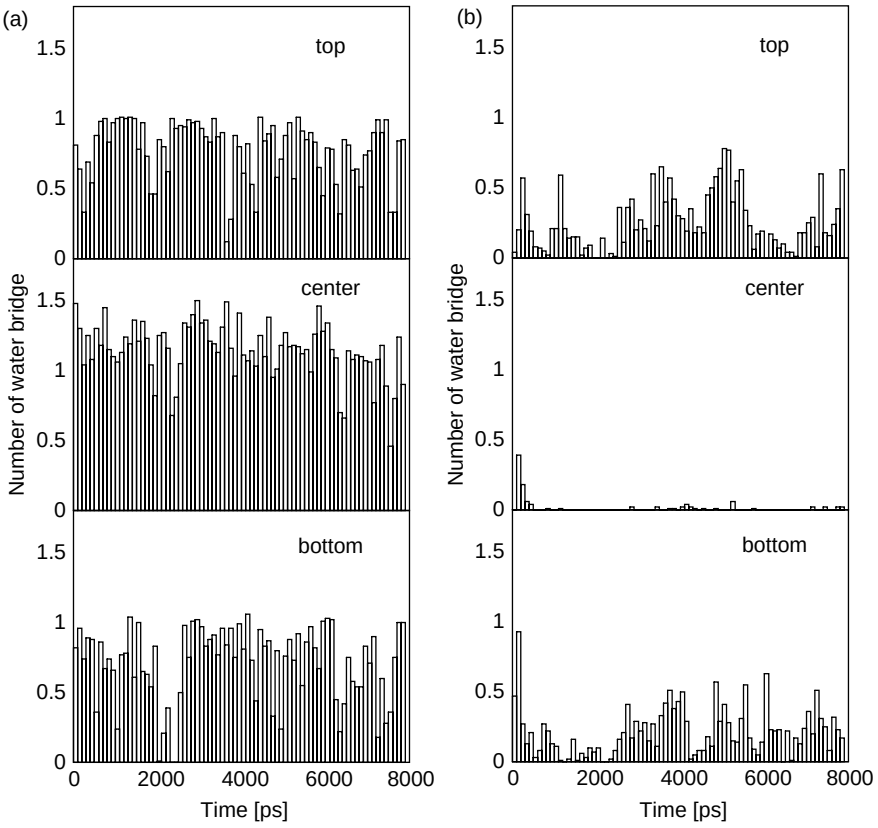

Figure 2. Probability of formation of a water bridge: (a) AATT, (b) TTAA. Each panel (top, center, and bottom) shows the number of water molecules forming the bridge at each hydration site in figure 1, where its average value within every 100 ps period is represented by a bar. The water bridge is accomplished by formation of the two hydrogen bonds connecting the two bases across the bridge water molecule. The hydrogen bonds are identified according to the following criterion: the distance between the hydrogen atom of a water molecule and its acceptor atom (O2 or N3) is shorter than 3.1 Å and the angle between the hydrogen–acceptor connection and the O—H covalent bond of the water molecule is over 90°.

of the sequence 5′CGCGAATTCGCG3′ or 5′CGCGTTA-ACGCG3′, TIP3P water molecules [9] and ions (39 K^+ and 17 Cl^-) are included. A periodic boundary condition is imposed on the simulation box. In addition to the 22 K+ ions for neutralization, 17 K^+ and 17 Cl^- ions are added to mimic the physiological salt condition 0.15 M. The electrostatic interactions are calculated by the particle mesh Ewald [10] and the van der Waals interactions are calculated by cutoff scheme with the cutoff length of 9 Å. The temperature and pressure are controlled to be 300 K and 1 atm, respectively, by the Berendsen weak coupling method [11]. For each system of AATT and TTAA sequences, a 10 ns-long MD simulation is carried out, and the last 8 ns trajectory is analyzed.

3. Results and discussion

The probability of observing a water molecule at each hydration site (figure 1) is shown in figure 2. The results from the two different sequences AATT and TTAA are significantly different. In AATT, the water bridge is found with a high probability throughout the simulation. The number of water bridges at the central site frequently surpasses 1.0. This is because more than one water molecule can make a bridge between the same pair of acceptor atoms of bases. On the other hand, in the TTAA case, the bridge-forming rate is relatively low and in particular, the bridge formation at the central site is very rare. This tendency is in accordance with a previous experimental observation by Mack *et al.* [3]. Their X-ray analysis showed that a clearly visible spine is formed in AATT, while in TTAA the water bridge is broken at the central T-A step and a spine is not formed.

The difference in bridge forming rate can be explained in terms of the distance between two acceptor atoms (O2 or N3). At the central site of AATT with a high probability of bridge formation, the average distance of T:O2–T:O2 is 3.64 ± 0.35 Å (one standard deviation). It is a proper distance for the bridge formation when considering the geometry of hydrogen bonds participating in the bridge. On the other hand, the distance of A:N3–A:N3 at central site of TTAA is 5.74 ± 1.19 Å, which is too long to make bridge-constructing hydrogen bonds. Therefore, a bridge is likely to be formed at the AATT central site whereas is not at the TTAA site. In this way, the bridge formation is nearly determined by the acceptor-acceptor distance.

The feature of the hydration we have confirmed in figure 2 can be recognized also as the spatial distribution of the water molecules. The density of the DNA surrounding water is shown in figure 3, where the regions having three times higher density than that of the bulk water are shown. In AATT, the high density regions are aligned along the minor groove. They correspond to the water bridge forming sites (figure 1). On the other hand, in the TTAA minor groove, the high density regions of the bridge water sites does not appear. Instead, smaller high density regions can be observed for each acceptor site of

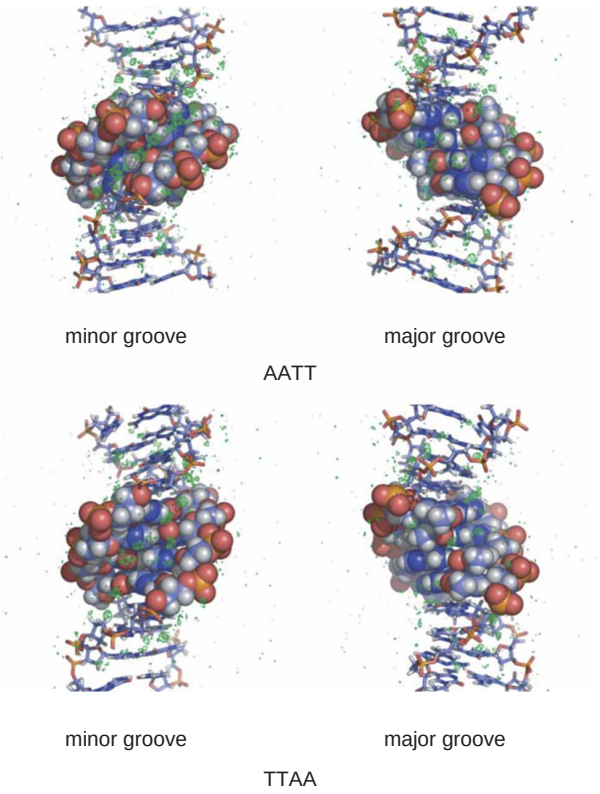

Figure 3. Graphical views of water hydration in minor and major grooves of AATT and TTAA sequences. Regions having a three times higher density than that of the bulk water (0.997 g/cm^3) are represented by the green mesh. The trajectory of 1 ns (3.5–4.5 ns in figure 2) is used for the density calculation. A typical simulation snapshot of DNA is also shown.

bases, implying that the minor groove bases of TTAA are hydrated only by individual (not spine forming) water molecules. As for major grooves, such high density regions are scarcely observed regardless of the sequence. Therefore, the major groove is not favored for localizing water molecules compared to the minor groove.

According to some previous works [12,13], the formation of water bridges in the minor groove is correlated with the DNA groove width. This tendency has also been confirmed by our results. Figure 4 shows the minor and major groove width observed in our simulations. In TTAA, the minor groove width changed largely during the simulation and it is about 5 Å in a narrow state, but it occasionally reaches over 10 Å. The comparison with the behavior of the bridging water (figure 2) confirms us that the narrow state is favorable for the formation of the water bridge and as the groove width increases, it has less chance to construct the water bridge. To the contrary, the change of the minor groove of AATT is not so large and it remained narrow. Consequently, the formation of water bridges is more likely.

This study reported that the conformational characteristics of DNA are highly correlated with the hydration pattern. The rigid AATT sequence favors the formation of water bridges, while the flexible TTAA does not. This observed tendency agrees with the previous experimental observation. As mentioned before, the bridging water

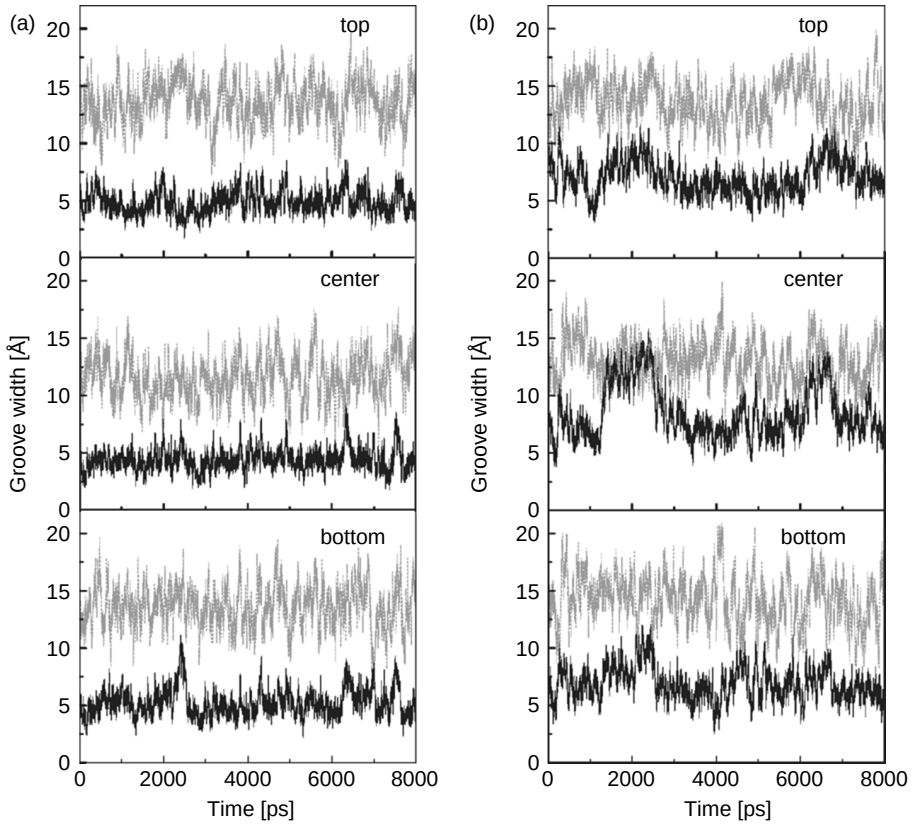

Figure 4. Width of minor groove (black solid line) and major groove (gray dashed line): (a) AATT, (b) TTAA. Each panel (top, center and bottom) shows the groove width given for the base step of each hydration site in figure 1. The width of the minor and major grooves is calculated as phosphorous–phosphorous distance, according to the definition by Hassan and Calladine [14].

observed in the minor groove is the primary component constructing the hydration spine of DNA. Thus it would be an important factor to determine the structural properties of DNA. Although our current result is not enough to thoroughly understand the relationship between DNA hydration and deformability, it will be revealed from a further systematic investigation of various sequences.

Finally, we propose a plausible mechanism linking the DNA hydration and the deformability. As we have shown, hydration patterns in DNA minor grooves are determined by the distance between two acceptor atoms. Such hydration patterns further determine DNA conformation and deformability in the following way: the deformability of DNA is suppressed when the water bridge is formed, but DNA becomes deformable with breaking the bridge. In this manner, the DNA deformability may be partly slaved to the water hydration. This hypothesis will be thoroughly examined by the on-going, extended investigation on various DNA sequences.

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