Ion effects of Sr$^{2+}$, Cs$^+$ and I$^-$ on DNA in aqueous solutions

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Molecular dynamics simulations of B-DNA in aqueous solution containing Na$^+$ and K$^+$ ions, or Na$^+$, K$^+$ and one kind of $^{90}$Sr$^{2+}$, $^{137}$Cs$^+$ or $^{137}$I$^-$ are investigated at 298 K. For the ions in the minor groove, K$^+$ ions are dispersed as Sr$^{2+}$ or Cs$^+$ added, but Na$^+$ ions dominate the minor groove when I$^-$ ions are added. For the ions in the major groove, the interaction of K$^+$ and DNA becomes stronger as I$^-$ added. As for the DNA conformation, Cs$^+$ ions affect most while Sr$^{2+}$ ions the least.

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1. Introduction

After the Three Mile Islands, Chernobyl and Fukushima accidents in the last thirty years, $^{90}$Sr, $^{137}$Cs and $^{131}$I raise attention of the radioactive hazards on human beings [1,2]. $^{137}$Cs and $^{90}$Sr can gather in the skeleton without discharging for their medium life (the half lifes of $^{137}$Cs and $^{90}$Sr reach 30 and 28.79 years, respectively) [2]. $^{131}$I enters into the circulatory system in a very short period, though the half life of it is just 8.3 days. These radionuclides participate in the physical and chemical processes and induce the loss of the hematopoietic system, the regulatory dysfunction of the nervous system, even the increasing risk of cancer in the bodies [2].

The underlying primary mechanisms may perhaps be attributed to the damage caused by these radionuclides to DNA [3]. The storing, duplication, realization and transcription of the genetic information of DNA are closely-related with the environment around and the conformation of the DNA [4,5]. Furthermore, the ions provide electroneutrality to the system and mitigate the electrostatic repulsion between anionic phosphates of the B-DNA, the most prominent form in the cell [6], via the ion atmosphere and sequence-dependent contact or water-mediated structures [7–10]. Due to the polyanionic nature of DNA, the radionuclide ions can locate closer to B-DNA than the radionuclide atoms. Though being less, the ionized $^{90}$Sr, $^{137}$Cs and $^{131}$I may damage the B-DNA more powerful and more valuable to study in the solution.

Ionic effects act faster than radiation damages and have been studied many times with B form self-complementary Dickerson-Drew dodecamer d (CGCGAATTCCG), affecting DNA conformations, even the physiological functions [11–13]. The closer inspection [14] showed that Na$^+$ ions appeared at the ApT steps are located in the minor groove. K$^+$ ions bind to the electronegative sites of DNA bases in the major and minor groove and interact with most sites of the DNA bases strongly [15]. It seems that electrostatic, steric and hydration interactions favor Na$^+$ condensation a little around DNA when competing K$^+$ ions [16]. However, K$^+$ ions have more affinity than Na$^+$ at the A tract in the minor groove when they co-exist in the solution [17,18] without DNA conformation changing.

$^{90}$Sr$^{2+}$ and $^{137}$Cs$^+$ ions are also studied for their influence on the function of DNA. The interaction of Sr$^{2+}$ and Cs$^+$ with nucleobases were explored using a density functional based approach [19]. The preferential attack to the bases in the order: G > C > T > U > A and these two ions prefer the mono-coordination in almost all more likely complexes. Nevertheless, the density function theory is limited by the simulation atom numbers and time. These deficiencies can be overcome by molecular dynamics simulation and the simulation results can gain some interesting and subtle results about the exact distribution of $^{90}$Sr$^{2+}$, $^{137}$Cs$^+$, $^{131}$I$^-$ and the physiological ions around DNA and the DNA conformation change. The incident energy of decay products (Alpha, Beta particles or Gamma radiation) coming from radionuclide ions mainly depends on the distance between the initial position of decay products and target materials, which means the position of radionuclide ions is one of the crucial factors on the radiation-induced genomic instability.

There still are several questions about ionic effects waiting for answering, (1) the affinity of Sr$^{2+}$ and Cs$^+$ ions with DNA, (2) the affinity of Sr$^{2+}$, Cs$^+$ and I$^-$ ions on DNA, (3) the energy of Sr$^{2+}$ and Cs$^+$ ions, (4) the energy of Sr$^{2+}$, Cs$^+$ and I$^-$ ions.

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distribution of Na\textsuperscript{+} and K\textsuperscript{+} ions as different ions added and (3) the change of DNA structure. If there are structure changes, are they pre-existing intrinsic property of DNA favoring ion binding [20,21]. We try to catch on the mechanisms about ion competitions and structure change behind.

2. Methods

The NMR structure of a synthetic B form duplex d (CGCCATTCGCCG) named 171d is chosen from Protein Data Bank (PDB) [22] as the starting structure. The Amber 94 force fields are implemented [23] for DNA, solvent and ions with the parameters of Na\textsuperscript{+}, K\textsuperscript{+}, Sr\textsuperscript{2+}, Cs\textsuperscript{+}, I\textsuperscript{−} and Cl\textsuperscript{−} ions being selected as $€_{\mathrm{Na^+}} = 0.358 \text{kJ/mol, } €_{\mathrm{K^+}} = 2.73 \text{Å, } €_{\mathrm{Sr^{2+}}} = 0.568 \text{kJ/mol, } €_{\mathrm{Cs^+}} = 3.36 \text{Å, } €_{\mathrm{I^-}} = 0.495 \text{kJ/mol, } €_{\mathrm{Cs^+}} = 3.10 \text{Å, } €_{\mathrm{Cl^-}} = 2.132 \text{kJ/mol, } €_{\mathrm{Cs^+}} = 3.92 \text{Å, } €_{\mathrm{Cl^-}} = 1.68 \text{kJ/mol, } €_{\mathrm{Cl^-}} = 4.86 \text{ Å,}$ and $€_{\mathrm{I^-}} = 0.408 \text{kJ/mol, } €_{\mathrm{I^-}} = 5.40 \text{Å}$ [24,25], respectively. The solvent is derived from the widely used flexible simple point charge (SPC) water molecule model. These ion parameters are checked compatibly with SPC [26], and different DNAs with SPC [27,28].

The intermolecular energy consists of two parts: $E = E_C + E_{\text{vdw}}$. The flexibility of SPC model is considered with a Morse type of potential for its covalent bonds [29]: $V_{\text{vdw}} = D(1 - \exp(-\rho (r - r_{eq})))$. The package we use to perform molecular dynamics simulations is M.DynaMix [30,31]. The double time-step algorithm by Tuckerman et al. [32] is implemented and short time step is 0.2 fs for the interactions between ions and solvent, and 2.0 fs for the other interactions.

The stereo views are present along the DNA helix axis with the major groove at the upper half and the minor groove at the lower half. SDFs of ions are drawn for densities $>10$ particles/nm$^3$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3. Results and discussion

The stability of DNA structure and the ion convergence on DNA are examined (data is not shown). Spatial distribution functions (SDFs) of the ions around averaged 171d structures in the grooves are presented in Figure 1 at 10 ns, 20 ns and 30 ns, respectively. For CTR (Figure 1(a)), K\textsuperscript{+} ions stably distribute in the minor and major groove as Na\textsuperscript{+} ions dispersed from the A tract steps of the minor groove, locating in the major groove and around the backbone of DNA within 10 ns. It indicates that K\textsuperscript{+} ions have higher affinity than Na\textsuperscript{+} ions in the minor groove while Na\textsuperscript{+} ions prefer to distribute around the peripheries. However, neither of them can control the whole groove. When Sr\textsuperscript{2+} ions are added (Figure 1(b)), the distributions of Na\textsuperscript{+} and K\textsuperscript{+} ions are affected by Sr\textsuperscript{2+} ions although low concentration of Sr\textsuperscript{2+} ions locate widely around backbone. Na\textsuperscript{+} ions still screen out of the minor groove while K\textsuperscript{+} ions are released from the A tract, just locate around the G tract after 10 ns evolution. The distributions are stabilized after 20 ns evolution that neither of Na\textsuperscript{+} and K\textsuperscript{+} ions co-exist in the A tract. However, the affinity of K\textsuperscript{+} ions becomes lower. It seems that the competition between Na\textsuperscript{+} and K\textsuperscript{+} ions are stronger in the minor groove that the minor groove can not be dominated by either of ions. For CS (Figure 1(c)), though just permeating into the peripheries of the minor groove, Cs\textsuperscript{+} ions release K\textsuperscript{+} ions away from the A tract and screen Na\textsuperscript{+} ions from coordinating within 10 ns. Consequently, neither of Na\textsuperscript{+} and K\textsuperscript{+} ions can locate at the A tract. K\textsuperscript{+} ions scatter around CpG and GpC steps and most of Na\textsuperscript{+} ions bind with backbone. After 30 ns evolution, Cs\textsuperscript{+} ions firmly occupy the A tract and both Na\textsuperscript{+} and K\textsuperscript{+} ions are totally dispersed of the minor groove. Cs\textsuperscript{+} ions prevent both of Na\textsuperscript{+} and K\textsuperscript{+} ions from entering into the A tract. In the major groove, Cs\textsuperscript{+} can not totally screen Na\textsuperscript{+} and K\textsuperscript{+} that Na\textsuperscript{+} ions prefer to distribute around the peripheries while K\textsuperscript{+} ions are dispersed out from the G tract. Because of the influencing of Cs\textsuperscript{+} ions, the competitions happen at the G tract that K\textsuperscript{+} ions dominate the sites of minor groove while Na\textsuperscript{+} ions occupy the site of

![Figure 1. SDFs of Na\textsuperscript{+} (orange), K\textsuperscript{+} (dark grey), Sr\textsuperscript{2+} (light blue) (SR) and Cs\textsuperscript{+} (dark blue) (CS) around averaged DNA at 10 ns, 20 ns and 30 ns. I\textsuperscript{−} and Cl\textsuperscript{−} are not shown. The stereo views are present along the DNA helix axis with the major groove at the upper half and the minor groove at the lower half. SDFs of ions are drawn for densities $>10$ particles/nm$^3$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)](image)
major groove. As for I (Figure 1(d)), the distributions of K\(^+\) and Na\(^+\) ions are completely changed though I\(^-\) ions uniformly distribute around DNA in the evolution. K\(^+\) ions are dispersed from the minor groove and locate in the major groove. In the meanwhile, Na\(^+\) ions occupy the G tract of the minor groove and scatter in the major groove. The distributions of Na\(^+\) and K\(^+\) are affected strongest by I\(^-\) that Na\(^+\) ions win the competitive with K\(^+\).

It can be seen that the systems reach the equilibrium in less than 20 ns. A stabler K-DNA interaction is in the minor groove while Na-DNA interaction stronger in the major groove. Although coordinating with DNA at different positions, both of Sr\(^{2+}\) ions and Cs\(^+\) screen K\(^+\) ions from the A tract in the minor groove and change the distribution of K\(^+\) and Na\(^+\) ions in the major groove, then influence the competition between K\(^+\) and Na\(^+\) ions. However, K\(^+\) ions still interact with DNA stabler and Na\(^+\) ions affinity with DNA higher as I\(^-\) ions added. It shows that anions are more influential than cations to increase the competitive of Na\(^+\) with K\(^+\) ions. The added I\(^-\) ions affect the competition between Na\(^+\) and K\(^+\) ions more than Sr\(^{2+}\) and Cs\(^+\) ions.

To check the underlying causes of the effect of different ions in the vicinity of DNA more closely, the radial distribution functions (RDFs) of ions around atoms in the minor groove and major groove are calculated in Figures 2 and 3, respectively. Figure 2 presents the RDFs of the ions around minor groove that the maxima of RDF appear right at the strongest cation-DNA interaction sites described above. As for CTR, Na\(^+\) ions just locate around the backbone (Figure 2(a)) and K\(^+\) ions directly bind to AN3 and TO2 with the first peaks of g (r) reaching 5.2 and 5.1 at 2.9 Å, respectively (Figure 2(b)). For SR, Sr\(^{2+}\) ions interact with base pairs through hydration for maxima of g(r)_{Sr} not appearing within 5 Å (Figure 2(c (i))). K\(^+\) ions are dispersed out of the adenine and thymine but the first peaks of g(r)_{CO2} and g(r)_{GN3} reach 9.2 and 9.4, respectively (Figure 2(d)). The strongest Cs-DNA interaction site appears at GN3 with g(r)_{GN3} about 1.1 in Figure 2(e (i)). As to Na\(^+\) and K\(^+\), both ions are dispersed from the A tract, K\(^+\) ions reside around G tract that the maxima of g(r)_{CO2} and g(r)_{GN3} are 3.9 and 5.4, respectively (Figure 2(e) and (f)), smaller than that in SR. RDFs of Na\(^+\) and K\(^+\) ions for I (Figure 2(g) and (h)) are completely different with that of other cases. Na\(^+\) ions dominate the G tract that the maxima of g(r)_{CO2} and g(r)_{GN3} reach 11.9 and 13.1, respectively.

In Figure 3, K\(^+\) ions enter into the whole major groove and K-DNA interactions are stronger than Na-DNA interaction that the first peak of g(r)_{KGO6} exceeds 16 at 3 Å, while the interaction between Na\(^+\) with GO6 is relatively weaker (the first peak of g(r)_{NaGO6} is 12 (Figure 3(a) and (b)) in CTR. For SR, both of K\(^+\) and Na\(^+\) ions exist in the major groove that all of the maximum values of g(r) exceed 1.5 (Figure 3(c) and (d)). However, K-DNA interaction is not strong enough. Some Sr\(^{2+}\) ions enter into the A tract

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**Figure 2.** RDFs of Na\(^+\) (a), (c), (e) and (g)), K\(^+\) (b), (d), (f) and (h)), Sr\(^{2+}\) (c (i)) and Cs\(^+\) (e (i)) ions with O2 of the thymine, N3 of the adenine, N3 of the guanine, and O2 of the cytosine in the minor groove, respectively.
that \( g(r) \) reach 1.1 at 3.2 Å (Figure 3(c(i))). \( \text{Cs}^+ \) ions strongly interact with the whole major groove that \( g(r) \) \( \text{Cs}^+/\text{Go6} \) and \( g(r) \) \( \text{Cs}^+/\text{To4} \) exceed 4.5 and 2.8, respectively (Figure 3(e(i))). \( \text{K}^+ \) ions are dispersed from the A tract that no distinct peak of \( g(r) \) \( \text{To4} \) appears within 4 Å (Figure 3(f)). Meanwhile, the first peak of \( g(r) \) \( \text{Na}^+/\text{Go6} \) is 22 at 2.9 Å for \( \text{Na}^+ \) ions locating in the major groove (Figure 3(g) and (h)). Different with that in the minor groove, the RDFs of \( \text{K}^+ \) ions become larger than that of \( \text{Na}^+ \) ions that the maximum of \( g(r) \) \( \text{K}^+/\text{Go6} \) reaches 15 while the first peak of \( g(r) \) \( \text{Na}^+/\text{Go6} \) is just 6.7 for I (Figure 3(g) and (h)).

The coordination numbers (abbreviated as \( CN \)) of cations around the A and G tract in the minor groove are presented in Table 1. For \( CN_{\text{Na}^+} \), the high affinities distribute around G tract (0.13, 0.22, 0.24, 1.27) but lower at A tract, close to 0, except that in I. \( CN_{\text{Na}^+} \) exceeds 0.2 at A tract when I’ ions are added in. \( CN_{\text{K}^+} \) keeps around 0.5 at G tract for all cases except I. \( CN_{\text{K}^+} \) reaches 1.24 at A tract for CTR and the decreasing in \( CN_{\text{K}^+} \) s are also observed in the center part as radionuclide ions adding in with \( CN_{\text{K}^+} \) being 0.16, 0.11, 0.05 for SR, Cs, I, respectively. \( CN_{\text{Sr}^{2+}} \) is only observed at G tract with the value 0.22 since \( \text{Sr}^{2+} \) ions are screened from the grooves. In contrast, the values of \( CN_{\text{Cs}^+} \) are much higher than that of the other ions, reaching 0.45 and 0.2 at A and G tract, respectively.

These phenomena can be further traced from variation of self-diffusion coefficient \( (D) \) of \( \text{Na}^+ \) and \( \text{K}^+ \) ions around DNA. In our calculations, \( D_{\text{Na}^+} \) is the smallest for I and largest for CTR and conversely, \( D_{\text{K}^+} \) smallest for CTR and largest for I. \( D_{\text{Na}^+} \) and \( D_{\text{K}^+} \) are 1.764 \( \times 10^{-9} \) m²/s and 0.985 \( \times 10^{-9} \) m²/s for CTR, respectively. The values of \( D_{\text{Na}^+} \) for SR and CS are close to that for CTR. In the meanwhile, some \( \text{Na}^+ \) ions are constrained at the G tract when I’ ions are added in, reflecting on the smallest \( D_{\text{Na}^+} \) (1.291 \( \times 10^{-9} \) m²/s).

As for \( \text{K}^+ \) ions, they are dispersed from the grooves when radionuclide ions are added in, \( D_{\text{K}^+} \)s increase to 1.173 \( \times 10^{-9} \) m²/s, 1.343 \( \times 10^{-9} \) m²/s and 1.578 \( \times 10^{-9} \) m²/s for SR, CS and I, respectively.

It can be concluded that the competition and distribution of \( \text{K}^+ \) and \( \text{Na}^+ \) ions displays strongly sensitivity to the intruding radioactive ions around the DNA. RDFs of \( \text{K}^+ \) and \( \text{Na}^+ \) ions are influenced most by I’. For cations, it seems that a group of elements with similar

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<td>0.06 (0.22)</td>
<td>0.42 (0.24)</td>
<td>0.21 (1.27)</td>
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<tr>
<td>K⁺</td>
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<td>0.16 (0.57)</td>
<td>0.11 (0.52)</td>
<td>0.05 (0.12)</td>
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<tr>
<td>Sr²⁺</td>
<td>– (-)</td>
<td>0.01 (0.22)</td>
<td>– (-)</td>
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<tr>
<td>Cs⁺</td>
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<td>0.45 (0.23)</td>
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chemical properties can be replaced by each other around DNA (Cs\(^+\) ions replace K\(^+\)) and this direct interactions with base pairs influence the ion atmosphere around DNA more. The order influencing the distributions and competitions of K\(^+\) and Na\(^+\) are as following: I\(^-\) > Cs\(^+\) > Sr\(^{2+}\).

Since influencing the distributions of ions, whether the radionuclide ions can affect the structure of DNA or not. To evaluate the DNA conformation changes in detail, eight distinct structure parameters are calculated and compared with the parameters of standard A- and B-form DNA during 30 ns in Figure 4. The inner eight base pairs are present with their values over 3000 average structures of every 10 ps. The results show that the DNA in simulations of CTR preserves the B-form that most features such as Inc, Xdp, Dy, mW and mD just fluctuate around values around the B-form line. Phi and Dy are changed at GpA steps close to 125\(^\circ\) and −0.1 Å, respectively. Nevertheless, the structure of the DNA dose not correlate with the presence of Na\(^+\) and K\(^+\) ions in the vicinity of the groove. For SR, all of parameters keep close to B values at G tract, similar with that for CTR. As for the A tract, some parameters deviate away from B values into the values between A and B. Phi and MW are 103\(^\circ\) and 6.4 Å at ApT steps, respectively. Though Sr\(^{2+}\) do not permeate into the grooves, the structure of grooves are still affected.

The structures of A tract are completely affected by Cs\(^+\) ions. All of parameters are close to the values between A and B form at G tract. Inc increases to 12\(^\circ\). Meanwhile, Phi and Dy decrease to 84\(^\circ\) and −1.2 Å, respectively. Comparing with that in SR, the structures of groove changes strongly that the maxima of mW and mD reach 11.8 Å and −1.1 Å at TpC steps, respectively. For I, Dy and mW are changed to the middle area between A and B form, reaching −1.0 Å and 8.9 Å at the peripheries, respectively. In the mean while, the other parameters are close to B value. As the conclusions before, Na\(^+\) ions enter into the minor groove of DNA and influence the structure of DNA from B value to the value between A and B form, which indicates that Na\(^+\) ions are more capable of significant modulation of DNA conformation than K\(^+\) ions. Furthermore, it seems that the structure of DNA is sensitive to the ions entering into the grooves. Though I\(^-\) ions completely changed the distribution of K\(^+\) and Na\(^+\) around DNA, the structures of DNA are influenced by Cs\(^+\) ions most in these three radionuclide ions, forcing preferred DNA structure changing to the state between A and B form. Since Sr\(^{2+}\) ions are inability to intrude into the grooves and change the

Figure 4. Eight structure parameters of inner eight base pairs of DNA for CTR, SR, CS and I. The (a) to (d) are sugar pucker angle (Phi), inclination angle (Inc), the X-displacement (Xdp), the Slide (Dy), (e) to (h) show parameters of minor (mW and mD) and major (MW and MD) groove. The horizontal dashed lines indicate the reference values of typical A (orange or light gray) and B (cyan or dark gray) forms. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
distributions of K+ and Na+ little, DNA mainly keep stable at the B form. The order influencing DNA conformations are in the following way: Cs+ > I- > Sr2+.

4. Conclusions

In the present letter, we investigated the competition between Na+ and K+ ions and the ionic effect of Sr2+, Cs+ and I- on a typical B form duplex d (CCCGAATTCGG) in solution. For the CTR, K+ ions have a slightly higher affinity than Na+, which is similar with experiment [35], but different with molecular dynamic simulations [17] for the totally different sequence they used. It seems that the DNA sequence influence the affinity of ions and ionic competitions for DNA strongly. As different radionuclide ions added into the solution with Na+ and K+ ions, the order of the capability of three ions influence the distributions of K+ and Na+ ions and the structures of DNA with the following ways: I- > Cs+ > Sr2+ and Cs+ > I- > Sr2+, respectively.

The equilibrium time of 137Cs+, 90Sr2+ and 131I- ions around DNA is far less than their half life, which means that after the ionic effects, the radiation effect of these radionuclide ions may break DNA strands or produce a variety of pyrimidine photoproducts more directly and irreparably since close relationship with DNA. Furthermore, for the preferred locations of Sr2+ and Cs+ ions, the decay products (Beta particles or Gamma radiation) from Sr2+ and Cs+ ions may damage the backbones and base pairs more, respectively. Though not breaking the strands or the bonds of DNA, these ionic effects may influence the key functions of DNA, induce DNA mutation or deformation, then change the radiation effect on DNA.

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