Positively and negatively hydrated counterions in molecular dynamics simulations of DNA double helix

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December 30, 2019

Abstract

The effects of positive and negative hydration of counterions (Na\(^+\), K\(^+\), and Cs\(^+\)) incorporated into the hydration shell of the DNA double helix have been studied using molecular dynamics approach. The results show that the dynamics of the hydration shell of counterions depends on region of ion localization around the macromolecule. The longest residence times have been observed for water molecules near the counterions that are localized in the minor groove of the double helix: about 30 ps in the case of Na\(^+\) counterions and about 7 ps in the case of K\(^+\) and Cs\(^+\) counterions. In the major groove and outside the double helix it is essentially lower. The counterions constrain water molecules too strong, and as the result the effect of negative hydration for K\(^+\) and Cs\(^+\) counterions was not observed in the simulations. The analysis show that the effects of counterion hydration may be described better by using the water models with lower dipole moments.

1 Introduction

The DNA is a polycationic macromolecule with the double helix structure that under the natural conditions is stabilized by water molecules and metal ions (counterions) forming the ion-hydration shell [1]. The ion-hydration shell has different physical properties in different regions of the macromolecule: inside the minor and major grooves of the double helix, and outside DNA [2-5]. The counterions, which are metal ions (Na\(^+\), K\(^+\)) and organic positively charged molecules (polyamines), neutralize the negatively charged atomic groups of DNA, making disorder or stabilizing the waters structure inside the macromolecule. The interplay between water molecules and counterions is shown to be important for counterion distribution around the DNA double helix [6,7]. To understand the role of counterions in mechanisms of DNA biological functioning the effects of ion hydration should be studied.

The ions organize water molecules into the hydration shells with the structure that depends on ion type. With this regard metal ions are usually classified as positively hydrated and negatively hydrated ions [8]. In the case of positively hydrated ions (Li\(^+\), Na\(^+\), and Mg\(^{2+}\)) the water molecules in the hydration shells are highly ordered, and the mean residence time of the molecule in the hydration shell of the ion is much higher than in the bulk, where a water
molecule is surrounded by the other water molecules. Therefore, these ions are also known as the structure making ions [9]. In the case of negatively hydrated ions (K\(^+\), Rb\(^+\), and Cs\(^+\)) the mean residence time of a molecule in hydration shell of the ion is lower than in the bulk, and the structure of the hydration shell is more friable as in the bulk water. Therefore, these ions are also known as the structure braking ions [9].

The structure of hydration shell of DNA is essentially different form the structure of liquid water and depends on a region of the double helix [2, 3, 5, 10]. In particular, in the minor groove of the double helix the mean residence time of water molecule is characterized by the highest values that may reach to about 100 ps [10]. In some cases of nucleotide sequence the water molecules can bridge in the minor groove the atoms of different nucleotides that was observed in crystallographic experiments as a spine of hydration [2, 11]. In the major groove the hydration shell is friable and the dynamics of water molecules are characterized by several times lower values of the residence times than in the minor groove, and in the regions near the phosphate groups of the DNA backbone even less [5, 10]. The hydration shell of DNA macromolecule is an important component that may be considered as the integral part of the double helix structure.

The intrusion of counterions into the hydration shell of DNA rebuilds its structure and influences the dynamics. The structure of water solutions of metal ion may be described within the framework of statistical theory of electrolytes [12] that may be extended for the consideration of the ion-hydrate shell of DNA. There also exist some polyelectrolyte models that qualitatively describe the distribution of counterions around the double helix [13, 14]. In the such models the macromolecule is presented as a chain of charged beads or as a uniformly charged cylinder immersed into the charged continuum. These models explain the effect of counterion condensation on DNA that was observed experimentally [15–18]. From another side, the structure of DNA with counterions may be presented as the ionic lattice [19, 20]. The existence of the lattice-like structure of DNA with counterions has been proved by the observation of the modes of ion-phosphate vibrations in the low-frequency Raman spectra of DNA (< 200 cm\(^{-1}\)) [19–24]. The concept of ion-phosphate lattice has been proven to be useful for the description of different effects of DNA-counterion interaction [25, 26].

Despite the success of already existed approaches, which allow a general outline of some structural and dynamical properties of the DNA-counterion systems, they are not enough to describe the effects of counterions hydration. In this regard the method of classical molecular dynamics seems the most appropriate in the present time for the development of problem understanding. The molecular dynamics studies [4, 6, 7, 27–31] show that the character of counterion distribution around the double helix and their localization in characteristic binding sites of DNA depend on sequence of nucleotide bases and region of the double helix. These features of DNA-counterion localization are governed by the interplay between counterions and water molecules in many respects [6, 7, 29]. In particular, the study of counterion hydration [7] show that the interaction of structure making ions with DNA occurs via water molecules of the hydration shell mostly, while the structure breaking ions may squeeze through DNA hydration shell to the groove bottom and form long lived complexes with the atoms of nucleotide bases. Thus, for the understanding the interplay between water molecules and counterions in the hydration shell of DNA double helix the molecular dynamics simulations of positively and negatively hydrated counterions should be carried out.

The goal of the present work is to study the character of hydration of positively and negatively hydrated counterions that are localized in different regions of the DNA double helix. To solve this problem the atomistic molecular dynamics simulations of DNA with positively hydrated (Na\(^+\)) and negatively hydrated (K\(^+\), Cs\(^+\)) counterions have been studied. The radial
distribution functions of water molecules with respect to the ions were built, and the potentials of mean force were derived. The residence times of water molecules in the hydration shell of counterions have been estimated. The results show that the dynamics of the hydration shell of counterions depends on a region of the double helix, where the ion is localized. The effects of counterion hydration have been shown to be better described with the use of the water models having lower dipoles moments.

2 Materials and methods

The analysis of the structure and dynamics of the hydration shells of counterions, localized in different regions of the double helix, has been done through molecular dynamics simulations [7]. The simulations [7] were carried out for the DNA double helix with the nucleotite sequence d(CGCGAATTCGCG) that is known as the Drew-Dickerson dodecamer [2]. This fragment of DNA is characterized by the narrowed minor groove in the region with AATT nucleotide sequence (Fig. 1a). The major groove is visibly wider comparing to the minor groove. The DNA macromolecule was immersed into the water box 64×64×64 Å with the metal ions of defined type: Na⁺, K⁺ or Cs⁺. The number of counterions was 22 that was equal to the number of the DNA phosphate groups, making the system electrically neutral. As a result three systems of DNA water solution with the counterions of different type were studied: Na-DNA, K-DNA, and Cs-DNA.

The computer simulations [7] were performed using NAMD software package [32] and CHARMM27 force field [33, 34]. The length of all bonds with hydrogen atoms was taken rigid using SHAKE algorithm [35]. The TIP3P water model [36] and the Beglov and Roux parameters of ions have been used [37]. The total lengths of the trajectory for each system was more than 200 ns. The simulation data were analyzed after 100 ns of equilibration. The details of the simulation process are described in [7].

In the present work the VMD software [38] was used for the analysis and visualization. Using the plug-in [39] implemented to VMD, the radial distribution functions (RDFs) have been calculated by the following formula:

\[
g(r) = p(r)(4\pi r^2\Delta r N_p/V), \tag{1}
\]

were \( p(r) \) is the average number of atom pairs, found at the distance within \( (r \div r + \Delta r) \); \( N_p \) is the number of pairs of selected atoms; \( V \) is the total volume of the system; \( \Delta r \) is the width of histogram bins which in the present work was taken equal to 0.5 Å. The average number of atomic pairs has been calculated every 10000 time steps that is 500 frames per the nanosecond. The RDFs have been built for each nanosecond of simulation trajectory and than the mean RDFs have been obtained.

The RDFs have been built for oxygen atoms of water molecules with respect to the ions localized in different regions of the double helix: in the minor and major grooves (RDF\textsubscript{minor}\text{Ion} and RDF\textsubscript{major}\text{Ion}), near the phosphate groups (RDF\textsubscript{ph}\text{Ion}), and in the bulk (RDF\textsubscript{bulk}\text{Ion}). The counterion has been considered to be localized in some region of the double helix if it was within 5 Å of one of the reference atoms. The reference atoms of DNA that have been used in the present study are shown on the Figure 1b and indicated in the Table 1. The same radial distribution functions have been calculated for water molecules with respect to other water molecules, localized in different regions of DNA macromolecule (RDF\textsubscript{minor}\text{W}, RDF\textsubscript{major}\text{W}, RDF\textsubscript{ph}\text{W}, and RDF\textsubscript{bulk}\text{W}). The reference water molecules were not in direct contact with the atoms of the DNA macromolecule.
Figure 1: a) The structure of the Drew-Dickerson dodecamer d(CGCGAATTCGCG) [2]. The minor and major grooves are indicated. Nucleotide colour scheme: Cytosine (orange), Guanine (yellow), Adenine (blue), Thymine (purple). b) Thymine-Adenine and Guanine-Cytosine nucleotide pairs and the reference atoms shown as enlarged spheres with the names of atoms that were used as reference points for the construction of the radial distribution functions.

Table 1: The reference atoms of DNA macromolecule for the radial distribution functions.

| DNA region   | Adenine | Guanine | Thymine | Cytosine |
|--------------|---------|---------|---------|----------|
| Minor groove | N₃, C₂  | N₃, N₂  | O₂      | O₂       |
| Major groove | N₆, C₅, | O₆, C₅, | O₄, C₅m,| N₄, C₅,  |
|              | N₇, C₈  | N₇, C₈  | C₆      | C₆       |
| Phosphates   | PO₁,₂   | PO₁,₂   | PO₁,₂   | PO₁,₂    |
3 Results

Radial distribution functions. The obtained averaged radial distribution functions of water molecules with respect to the counterions (ion-water RDFs) are characterized by two maxima: the first is intensive and the second is weak (Fig. 2a). The position of maxima are governed by the size of counterion and water molecule, therefore the shifting of the maxima to larger distances is observed as counterion size increases. The intensity of the first and the second maxima depends on a region of the double helix where the counterion is localized. The only exception is observed in the case of the first maximum for RDFs of Na\(^+\) counterions that have approximately the same height for all considered regions of counterion localization. In the same time, in the case of K\(^+\) and Cs\(^+\) counterions the difference is essential in the case of the both the first and the second maxima.

The RDFs of water molecules with respect to water molecules (water-water RDFs) are characterized by strong first maximum and flat curve after (Fig. 2b). The second maximum is very weak and hardly visible. The obtained shape of the RDFs is characteristic for the TIP3P water model \[36,40\]. The difference between water-water RDFs for the case of different regions of the double helix is observed only for the first peak that has always lower intensity in the case of water molecules in the minor groove.

Potential of mean force. A water molecule in the hydration shell of the ion is trapped in the potential well that is characterized by the potential barrier (Fig. 3). In the present work the potential barrier is estimated using the potential of mean force (PMF) derived from the radial distribution functions:

\[
E(r) = -k_B T \ln (g(r)),
\]

\(k_B\) is the Boltzmann constant, \(T\) is the temperature.

The calculated potentials of mean force are shown on the Figure 3. The obtained potential functions are characterized by two potential wells. In the present work the dynamics of water molecule in the first hydration shell is in the scope of interest, therefore the first potential well and the potential barrier (\(\Delta E\)) between the first and the second potential wells have been studied.

It is seen that in the case of ion-water PMF their shape and depth are different in the case of different counterions. In the case of Na\(^+\) the potential well is the deepest, while in the case of Cs\(^+\) it is the smallest (Fig. 4a). The difference of ion-water PMFs is also observed for different regions of the double helix, where the counterion may be localized. In the same time, the water-water PMF are rather similar, and the difference is hardly visible for different regions of the double helix.

Using the obtained PMFs, the parameters describing the energy of counterion hydration were calculated using the formula (2). The resulted values of the potential barriers for water molecule in the hydration shell of the ion (\(\Delta E_{ion}\)) are the highest in the case of Na\(^+\) ions, while in the case of K\(^+\) and Cs\(^+\) ions the values of \(\Delta E_{ion}\) are about two times lower. Such behaviour is the result of different size of the ions. The potential barrier \(\Delta E\) is the highest in the case of counterions in the minor groove, and it is the lowest in the case of counterion near the oxygen atoms of the phosphate groups and in the bulk (Table 2). The energy barrier of water molecule in the hydration shell of counterion in the bulk is essentially higher than the energy of water molecule (\(\Delta E_{ion} < \Delta E_w\)).

The calculated values of the potential barrier in the Table 2 has been compared with the results of molecular dynamics simulations for the ions in aqueous solutions at 25 °C \[11\]: 2.3 kcal/mol, 1.3 kcal/mol, and 0.9 kcal/mol for water in the hydrations shell of Na\(^+\), K\(^+\), and Cs\(^+\).
Figure 2: The radial distribution functions (RDFs) for the oxygen atoms of water molecules with respect to Na$^+$, K$^+$, Cs$^+$ counteions (a) and with respect to the other oxygen atoms of water molecules (b) in different regions of the double helix: minor groove (RDF$^{\text{minor}}_{\text{Ion}}$ and RDF$^{\text{minor}}_{W}$), major groove (RDF$^{\text{major}}_{\text{Ion}}$ and RDF$^{\text{major}}_{W}$), and near the phosphate groups of DNA backbone (RDF$^{\text{ph}}_{\text{Ion}}$ and RDF$^{\text{ph}}_{W}$).
Figure 3: The schematic structure of mean field potential energy of water molecule, derived from a radial distribution function. $\Delta E$ is the potential energy barrier; $E_a$ and $E_b$ are the energy values in the minimum ($r_a$) and maximum ($r_b$), respectively.

Table 2: Parameters of the potentials of mean force. The positions of minimum and maximum of the potential well $r_a$ and $r_b$, respectively (in Å). The values of the potential barriers in kcal/mol for water molecules in the hydration shell of the ion ($\Delta E_{ion}$) and for water molecule surrounded by the other water molecules ($\Delta E_w$).

| System       | Na-DNA | K-DNA | Cs-DNA |
|--------------|--------|-------|--------|
| **Ion-water**|        |       |        |
| Minor gr.    | 2.36   | 3.20  | 3.00   |
| Major gr.    | 2.36   | 3.20  | 2.85   |
| Phosph.      | 2.36   | 3.20  | 2.78   |
| Bulk         | 2.32   | 3.15  | 2.82   |
| $r_a$ $r_b$ $\Delta E_{ion}$ | $r_a$ $r_b$ $\Delta E_{ion}$ | $r_a$ $r_b$ $\Delta E_{ion}$ |
| Minor gr.    | 2.75   | 3.60  | 1.77   |
| Major gr.    | 2.75   | 3.60  | 1.65   |
| Phosph.      | 2.75   | 3.60  | 1.45   |
| Bulk         | 2.71   | 3.55  | 1.58   |
| $r_a$ $r_b$ $\Delta E_{ion}$ | $r_a$ $r_b$ $\Delta E_{ion}$ | $r_a$ $r_b$ $\Delta E_{ion}$ |
| Minor gr.    | 3.15   | 4.10  | 1.20   |
| Major gr.    | 3.16   | 4.10  | 1.03   |
| Phosph.      | 3.17   | 4.10  | 0.97   |
| Bulk         | 3.10   | 4.05  | 1.03   |

| **Water-water**|        |       |        |
| $r_a$ $r_b$ $\Delta E_w$ | $r_a$ $r_b$ $\Delta E_w$ | $r_a$ $r_b$ $\Delta E_w$ |
| Minor gr.    | 2.85   | 4.20  | 0.68   |
| Major gr.    | 2.85   | 4.30  | 0.64   |
| Phosph.      | 2.85   | 4.25  | 0.68   |
| Bulk         | 2.79   | 4.05  | 0.67   |
| $r_a$ $r_b$ $\Delta E_w$ | $r_a$ $r_b$ $\Delta E_w$ | $r_a$ $r_b$ $\Delta E_w$ |
| Minor gr.    | 2.85   | 4.20  | 0.68   |
| Major gr.    | 2.85   | 4.20  | 0.68   |
| Phosph.      | 2.85   | 4.20  | 0.66   |
| Bulk         | 2.84   | 4.20  | 0.67   |
Figure 4: The potentials of mean force of water molecules (PMFs). a) The PMFs for water molecules with respect to Na\(^+\), K\(^+\), Cs\(^+\) in different regions of the double helix. b) The PMF for water molecules with respect to the oxygen atoms of water molecules in different regions of the double helix. The lines correspond to curves fitted to PMFs: solid, dashed and dotted lines correspond to the cases of the counterion minor groove, in the major groove, and near the phosphate group of DNA, respectively.
ions, respectively. It is seen that the barriers $\Delta E_{\text{ion}}$, obtained in the present work, are rather close to the values [41], but in general overvalued. The reason is may be that in the work [41] water model and ion parameters were different from that have been used in the present work.

The difference of the energy barriers for water molecule in the hydration shell of counterion and in the bulk ($dE = \Delta E_{\text{ion}} - \Delta E_w$) determines the character of counterion hydration. The structure making (positively hydrated) ions have $dE > 0$, while the structure braking (negatively hydrated) ions are characterized by $dE < 0$. From the Table 2 follows that the values of $dE$ are positive for all counterions. For example, in the case of ions in the bulk water the values of $dE$ are 2.15 kcal/mol, 0.91 kcal/mol, and 0.34 kcal/mol for Na$^+$, K$^+$, and Cs$^+$ counterions, respectively. In the same time, the experimental data reveal that among considered counterions only sodium is positively hydrated, $dE = 0.25$ kcal/mol [8], while potassium and cesium are negatively hydrated ions, $dE = -0.25$ kcal/mol and $dE = -0.33$ kcal/mol, respectively [8].

The reason of the difference of obtained energy values and experimental data may be related to the parametrization of water models that will be discussed in the following section.

**Residence time.** The potential barrier $\Delta E$ determines the average residence time of water molecule $\tau$ that is usually described by the equation of Arheniuns type [8]. In the present work it is presented in the following form:

$$\tau = 2\tau_0 \exp \left( \frac{\Delta E}{k_B T} \right),$$

(3)

where $\tau_0$ is the characteristic time of approaching of the molecule to the potential barrier $\Delta E$. The coefficient 2 in the formula (3) appears because in our approach we consider that being at the top of the potential barrier the water molecule may leave the hydration shell or return back to the ion with the equal probability. The value of $\tau_0$ is estimated from the law of energy conservation for the finite motion:

$$\tau_0 = \sqrt{\frac{1}{2\mu} \int_{x_{\text{min}}}^{x_{\text{max}}} \frac{dx}{\sqrt{E_0 - E(x)}}},$$

(4)

where $\mu$ is the mass of a water molecule; $x = r - r_a$ is the displacement for the equilibrium position; $x_{\text{min}}$ and $x_{\text{max}}$ are the amplitude displacements of the mass of water molecule from the equilibrium position $r_a$; $E_0$ is the amplitude energy that may have a water molecule by vibrating in the potential well (Fig. 3). The potential function $E(x)$ is determined from the potential of mean force as the approximation by the polynomial function:

$$E(x) \approx E_a + C_2 x^2 / 2 + C_3 x^3 / 3 + C_4 x^4 / 4,$$

(5)

where $E_a$ is the depth of the potential well; $C_2$, $C_3$, $C_4$ are the fitting parameters. The amplitude displacement ($x_{\text{min}}$ and $x_{\text{max}}$) were determined from the condition: $E(x) = E_0$ (Fig. 3). Taking into consideration the Boltzmann law of equidistribution of energy by the degrees of freedom the value of amplitude energy of vibration has been determined as follows: $E_0 = E_a + k_B T$. By substituting (3) to the equation (4) the elliptic integral in the resulted equation is obtained, which has been calculated numerically.

The calculated residence times of water molecules in the hydration shell of the ion are within the range from about 2 ps to 30 ps (Table 3). The longest residence time is observed for the case of sodium counterions, while in the case of potassium and cesium ions it is several times lower. The dependence of $\tau$ values on the region of counterion localization is also observed. The largest values of the residence time are in the case of the ion localization in the minor groove.
Table 3: The residence times ($\tau$) and the half-period of vibration ($\tau_0$) in ps for water molecules in the hydration shell of counterion and surrounded by other water molecules.

| System     | Na-DNA | K-DNA | Cs-DNA |
|------------|--------|-------|--------|
| Ion-water  | $\tau$ | $\tau_0$ | $\tau$ | $\tau_0$ | $\tau$ | $\tau_0$ |
| Minor gr.  | 29.58  | 0.10  | 6.53   | 0.17  | 6.82   | 0.46  |
| Major gr.  | 23.48  | 0.10  | 5.59   | 0.18  | 5.82   | 0.52  |
| Phosph.    | 20.92  | 0.10  | 3.87   | 0.17  | 5.57   | 0.55  |
| Bulk       | 22.20  | 0.10  | 4.79   | 0.17  | 5.48   | 0.98  |
| Water-water| $\tau$ | $\tau_0$ | $\tau$ | $\tau_0$ | $\tau$ | $\tau_0$ |
| Minor gr.  | 1.80   | 0.29  | 2.11   | 0.34  | 2.17   | 0.35  |
| Major gr.  | 1.89   | 0.32  | 2.10   | 0.34  | 2.17   | 0.36  |
| Phosph.    | 2.07   | 0.34  | 2.11   | 0.35  | 2.35   | 0.43  |
| Bulk       | 2.30   | 0.27  | 1.64   | 0.27  | 2.43   | 0.39  |

of the double helix ($\tau_{\text{minor}}$), while in the major groove they are shorter ($\tau_{\text{major}}$), and the lowest values near the phosphate group of the macromolecule backbone ($\tau_{\text{ph}}$): $\tau_{\text{minor}} > \tau_{\text{major}} > \tau_{\text{ph}}$.

The comparison of our results with the results of molecular dynamics simulations of alkali metal ions in water solutions [41] show the obtained residence times have qualitatively the same dependence on the ion size. However, the $\tau$ values in the Table 3 are much lower than in the work [41]. The reason is that the values of residence times have been determined by different methods. In the method that was used in the present work the residence times have been calculated directly from the mechanistical approximation of the motion of water molecule in the potential well that was obtained from on the basis of the potential of mean force. In the work [41] the residence time is calculated using time correlation functions. These two approaches are not equivalent and the additional analyzes should be done to find where these two approaches meet each other.

Thus, the results for DNA with the positively hydrated Na$^+$, and negatively hydrated K$^+$ and Cs$^+$ counterions show that the dynamics of water molecules in the hydration shells of counterions depends on their localization around the double helix. In particular, the longest residence time was observed for a water molecule near the counterion that is localized inside the minor groove of the double helix, and it is longer than for the case of a water molecule near the same ion but in a bulk water. This difference may be due to the confined space inside the double helix and due to the structured system of water molecules that is formed in DNA grooves. In the same time, the results clearly show that the obtained energy barriers for water molecules near the ions are too high, making the hydration shell too rigid. The counterions Na$^+$, K$^+$, and Cs$^+$ in the simulated systems are positively hydrated, and the effect of negative hydration for K$^+$, and Cs$^+$ was not observed.

4 Discussion

To explain the reason of high values of the potential barriers the possible influence of water model should be analyzed. The TIP3P water model that was used in the simulations is characterized by the dipole moment value 2.35 D, while the experimental value for water molecule in gas phase is 1.86 D and in liquid phase is 2.95 D [44]. In this regard, let us analyze the
potential barrier as a function of dipole moment. For this purpose the potential of mean force has been estimated as the change of free energy of water molecule after its replacement from the hydration shell of the ion to the bulk water as follows:

\[ \Delta E \equiv \Delta G = \Delta H - T \Delta S + \Delta G_0, \]  

where \( \Delta H \) and \( T \Delta S \) are the enthalpy and entropy contributions, and \( \Delta G_0 \) is some constant part of the free energy change.

The enthalpy contribution is featured mostly by the interaction of water molecule with the ion. In the work [42] the energy of water molecule near the ion was successfully described by presenting the water molecule as a dipole in the field of the ion. In our model the repulsion between water molecule and ion at small distances is also taken into consideration. As the result the enthalpy change may be presented as a sum of average dipole-dipole \((U_{i-d}(r))\) and repulsion \((U_{rep}(r))\) terms:

\[ \Delta H = U_{i-d}(r) + U_{rep}(r). \]  

Under the room temperatures the direction of dipole vector in the electric field of the ion may be described by the Boltzmann distribution. Taking this into consideration an average ion-dipole interaction may be presented in the following form:

\[ U_{i-d}(r) = -k_B T L(\alpha) \alpha(r), \]  

where \( L(\alpha) = \coth \alpha - \alpha^{-1} \) is the Langevin function, and

\[ \alpha(r) = \frac{1}{k_B T} \cdot \frac{qd}{4\pi \varepsilon \varepsilon_0 r^2}. \]

Here \( q \) is the charge of the ion; \( \varepsilon \) is the dielectric constant of the media near the ion; \( \varepsilon_0 \) is the dielectric constant of vacuum; \( d \) is the dipole moment of water molecule.

The repulsion between water molecule and ion is described by the potential in Born-Mayer form that is often used for the description of interaction of the ions in ionic crystals [43] and the energy of DNA ion-phosphate lattice [23]:

\[ U_{rep}(r) = Ae^{-r/b}, \]  

where \( A \) and \( b \) are the parameters describing repulsion between ion and water molecule as hard cores.

To determine the entropy contribution to the change of the free energy we take into consideration that the motions of dipole moments of water molecules around the ion are hindered and due to the electrostatic field the molecules are highly oriented. Therefore, we assume that the entropy increases with ion-water distance the same as the average direction of water dipole that is described in our model by the Langevin function \( L(\alpha) \). As a result the change of entropy is presented as follows:

\[ \Delta S = -s_0 L(\alpha), \]  

where \( s_0 \) is the entropy of water molecule in the bulk. The parameters \( A \) and \( s_0 \) we derive from the condition for maximum and minimum at the distances \( r_a \) and \( r_b \): \( \frac{d\Delta G}{dr}|_{r=r_a} = 0, \frac{d\Delta G}{dr}|_{r=r_b} = 0 \).

The energy contribution \( \Delta G_0 \) is featured by the interaction energy with other water molecules of the system that includes the both enthalpy and entropy contributions. The estimation of
Figure 5: a) The distance dependence of the energy of water molecule in the first hydration shell of the ion. b) The dependence of the potential barrier $\Delta E$ on the dipole moment of water molecule. The values of dipole moments that correspond to different water models and experimental data are shown as the figured points. The lines on the both (a) and (b) figures made in solid, dashed, and dotted style correspond to Na$^+$, K$^+$, and Cs$^+$ ions, respectively.

This contribution is a complex problem and it is not essential for the study of the potential barrier. In the present work it is determined from the condition $\Delta G(r_c) = 0$, here $r_c$ is some point where the potential of mean is equal to zero. Taking this into consideration and using the equations (7) – (12), the change of the potential of mean force may be written in the following form:

$$E(r) = -k_BT L(\alpha) [\alpha(r) + s_0] + Be^{-\frac{r-a}{b}} + \Delta g_0,$$

where $B = -A/k_BT$; $\Delta g_0 = -L(\alpha_c) (\alpha_c + s_0) + Be^{-(r_c-r_a)/b}$, and $\alpha_c = \alpha(r_c)$.

For the estimations the repulsion parameter is taken the same as in the case of the crystals of alkali metal ion that is $b \approx 0.3\text{Å}$. The temperature is taken the same as in the molecular dynamics simulations $T = 300^\circ\text{K}$. The dipole moment $d = 2.35\text{D}$ was taken the same as in TIP3P model of water molecule. The values of equilibrium distances ($r_a$) and the barrier distance ($r_b$) were taken from the Table 2. The distance $r_c$ is defined as: $r_c = (r_a + r_b)/2$. The dielectric constant has been determined using the dielectric function [45], developed for the description of the electrostatic interactions in nucleic acids: $\varepsilon(\tilde{r}) = 78 - 77(0.0128\tilde{r}^2 + 0.16\tilde{r} + 1)e^{-0.16\tilde{r}}$, where $\tilde{r}$ is the distance between charges in Angstroms. At the distance about $(2 \div 4) \text{Å}$ this function gives the value within the range $\varepsilon \approx (1.3 \div 3)$.

The estimations performed by the formula (12) show that due to the competition of the electrostatic and entropy contributions to the potential barrier occurs (Fig. 5a). The value of the potential barrier decreases as the size of the counterion increases. The same character of the energy dependence for the case of the first hydration shell is obtained in our molecular dynamics simulations (Figure 4 and Table 2). The potential barrier $\Delta E = g(r_b) - g(r_a)$ have been calculated by the formula (12) for different values of the dipole moment (Fig. 5b). The values of the potential barriers that correspond to the dipole moments of different water models [46–50] are shown by points. The results show that the potential barrier for water molecule in the hydration shell of the ion increases linearly as the value of dipole moment. Taking this into consideration it is expected that the models of water molecule with lower dipole moments should give more accurate description of the hydration effects of counterions.
5 Conclusions

The dynamics of water molecule in the hydration shell of the positively (Na$^+$) and negatively (K$^+$ and Cs$^+$) hydrated counterions around the DNA double helix has been studied using molecular dynamics approach. The potential barriers and the residence times of water molecules near the counterions have been calculated. The results show that the dynamics of water molecules in the hydration shell of counterions depends on their localization around the double helix that is the manifestation of the interplay between water molecules in the hydration shell of DNA and counterion. The longest residence time of water molecule has been observed for the case of counterion in the minor groove of the double helix. It is about 30 ps for the positively hydrated Na$^+$ counterion and about 7 ps for negatively hydrated K$^+$ and Cs$^+$ counterions. In the major groove and outside the double helix it is essentially lower. In the simulations the considered counterions constrain water molecules too strong in the hydration shell making them positively hydrated, and the effect of negative hydration in the case of K$^+$ and Cs$^+$ counterion was not obtained. The analysis, performed within the framework of the developed phenomenological model, has been showed that the strength of the hydration shell is proportional to the value of dipole moment of water model. The water models with lower dipole moments are expected to give better description of the effects of counterion hydration.

Acknowledgement. The present work was partially supported by the Project of the Department of Physics and Astronomy of the National Academy of Sciences of Ukraine (0117U000240).

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