

# Temperature dependence of the transport coefficients of ions from molecular dynamics simulations

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## Abstract

The force fields employed in molecular dynamics (MD) simulations are determined under ambient conditions but not much attention is paid to their domain of applicability. Whether the current MD force fields have predictive power is an important issue that will affect the future developments in the field. Here, we determine the transport coefficients of ions in water from MD simulations at various temperatures and compare them with the available data. The results reveal that the rigid models used in standard MD force fields have difficulties in reproducing the observed temperature variations in conductivity data.

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Theoretical description of aqueous solutions is one of the most challenging problems in physical chemistry. Analytical approaches developed in the last century have failed to provide an adequate representation of the experimental data – agreement could only be achieved by resorting to phenomenological parameter fitting [1,2]. Computational approaches, and in particular molecular dynamics (MD) simulations, have the potential to provide a more realistic description of aqueous solutions [3]. With increasing computational power, such approaches are rapidly becoming the method of choice when dealing with solutions. This is especially the case in molecular biology, where electrolyte solutions are an integral part of any system and their accurate representation is essential for obtaining reasonable results.

In most applications of MD simulations, a software package such as AMBER [4], CHARMM [5] or GROMACS [6] is employed. The force fields in these packages are determined from fits to the bulk properties of solutions at ambient conditions. An important question that is seldom addressed in literature is the predictive power of these force fields, that is, whether they can be applied

beyond the ambient conditions [7,8]. Such tests are necessary for broadening the range of applications of MD simulations, and thus turning the MD method from a descriptive tool to a predictive one that can motivate new experiments. For example, investigation of the temperature dependence of observables in biomolecular processes could yield valuable information about the dynamics of a system. However, lack of a proper theoretical framework to analyse and interpret the experimental results often hinders and discourages such attempts. Conductance of ion channels is a case in point – despite the clear evidence that channel conductance varies much faster with temperature compared to that of bulk electrolyte [9], very few such experiments have been carried out so far. Perhaps more tellingly, these results have been interpreted as ‘relatively temperature-insensitive’ [10]. Clearly, we need to develop a theoretical basis for understanding the results of such experiments before they will be considered seriously by experimentalists. Investigation of such phenomena via MD simulations might have been unthinkable a decade ago, but they are certainly within the reach of the current generation of computer clusters.

Here we carry out a test of the GROMACS force field to see whether the MD simulations can reproduce

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the temperature dependence of the transport coefficients (conductivity and diffusion) of ions in common salt solutions of biological importance, namely, NaCl, KCl and CaCl<sub>2</sub>. It appears from a survey of literature that such a study has not been undertaken before. There are a few simulations for LiCl, which point to discrepancies in the temperature dependence of diffusion coefficients [11,12]. However, the standard force fields have difficulties in dealing with the anomalous properties of the ‘hard’ Li ions even at ambient conditions, so those results may not necessarily carry over to the softer ions, which are reasonably well described at 25 °C [13].

The choice of electrolyte concentration for the simulations is a critical one. A dilute system would be preferable to minimize cross-correlations which complicates interpretation of the results. However, this has an adverse effect on sampling, requiring much longer simulations. As a compromise, we have used 2773 water molecules and 5 pairs of ions (10 Cl ions in the case of CaCl<sub>2</sub>) in a cubic box of size 43.8 Å at room temperature. This corresponds to a  $c = 0.1$  M solution for monovalent ions. The simulations are carried out in a canonical  $NpT$  ensemble using periodic boundary conditions. Pressure is kept constant at 1 bar and temperature is varied from 0 to 100 °C. Berendsen coupling is used to maintain the temperature and pressure at the chosen values [14]. A damping constant of 1 ps is used in both cases during production runs. The long-range Coulomb forces are calculated using the particle-mesh Ewald summation. A timestep of 2 fs is employed and the trajectory data for ions is written at every timestep. Each system is equilibrated for 0.1 ns before production runs.

Force field parameters for ions are taken from Version 3.1.3 of GROMACS [15]. The SPC/E model is used for water molecules. The parameters of the Lennard-Jones interaction for ions and water are listed in Table 1. The interaction parameters among different species are generated using the Lorentz–Berthelot combination rules [3].

We have tried two different methods to calculate the conductivities of ions:

- (i) Apply an electric field  $E_z$  in the  $z$  direction in non-equilibrium MD simulations, and count the number of ions of species  $v$  ( $n_v$ ) crossing imaginary  $x$ - $y$  planes during a simulation time of  $t_0$ . The con-

ductivity is determined from  $\sigma_v = n_v q_v / A t_0 E_z$ , where  $q_v$  is the charge of ions and  $A$  is the cross-sectional area. Although we have obtained plausible results with this method, we had to use a fairly high electric field (i.e., 10<sup>8</sup> V/m) to achieve reasonable statistics. In a 10 ns test simulation for the NaCl system, the calculated conductivities found to be 15–30% higher compared to those obtained from the Kubo formula (see below). This is presumably due to operating outside the linear response regime. Therefore, we have refrained from using this method in the rest of the work.

- (ii) Use the Kubo formula [16] in equilibrium MD simulations

$$\sigma_v = \frac{1}{3VkT} \int_0^\infty \langle \mathbf{J}_v(0) \cdot \mathbf{J}_v(t) \rangle dt, \quad (1)$$

where  $\mathbf{J}_v = \sum_i q_{vi} \mathbf{v}_{vi}$  is the total current due to the ions of species  $v$  and  $V$  is the volume. Test simulations with the NaCl system reveals that the current–current autocorrelation function quickly converges in the interval [0, 0.2] ps, but beyond that it exhibits fluctuations that varies with the simulation time. Examples of correlation functions obtained after 1 and 10 ns are shown in Fig. 1. The fluctuations die out and the correlation functions become stable after about 5 ns of simulation. While one can use a cutoff in the integration (1) to avoid the contributions from the fluctuations

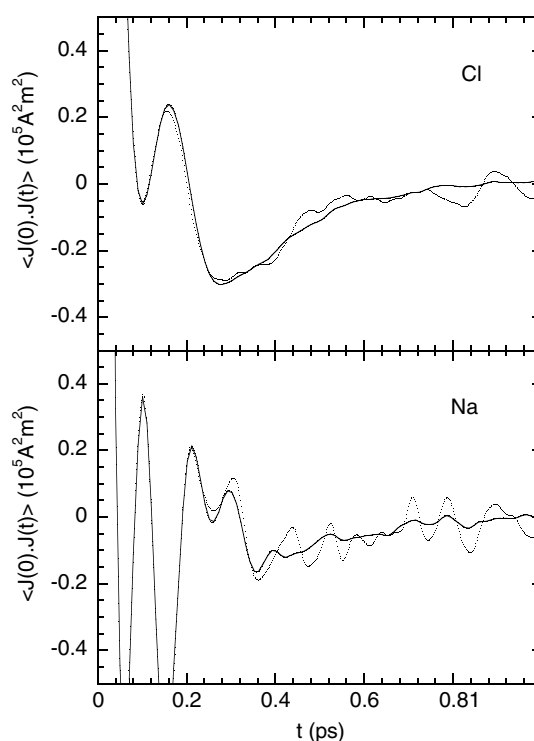


Fig. 1. Current–current autocorrelation functions for Na<sup>+</sup> and Cl<sup>−</sup> ions. The dashed and solid lines are obtained after simulating the system for 1 and 10 ns, respectively.

Table 1  
GROMACS parameters for the Lennard-Jones interaction,  
 $U_{LJ} = c_{12}/r^{12} - c_6/r^6$

Atom	$c_6$ (kJ nm <sup>6</sup> )	$c_{12}$ (kJ nm <sup>12</sup> )
Na <sup>+</sup>	$7.2059 \times 10^{-5}$	$2.1014 \times 10^{-8}$
K <sup>+</sup>	$1.6379 \times 10^{-6}$	$1.1838 \times 10^{-7}$
Ca <sup>2+</sup>	$1.0052 \times 10^{-3}$	$4.9800 \times 10^{-7}$
Cl <sup>−</sup>	$1.3804 \times 10^{-2}$	$1.0691 \times 10^{-4}$
O(W)	$2.6171 \times 10^{-3}$	$2.6331 \times 10^{-6}$

in shorter MD simulations, this will not yield the correct conductivities as an inspection of Fig. 1 shows. Therefore, we have employed a period of 10 ns in all subsequent simulations to ensure the stability of the transport coefficients obtained from the Kubo formula.

Equivalent conductivities,  $\Lambda_v = \sigma_v/c$ , of ions determined from the MD simulations of the NaCl, KCl and CaCl<sub>2</sub> systems are compared to the experimental results in Fig. 2. Simulations are carried out at four different temperatures,  $T = 0, 25, 55,$  and  $100^\circ\text{C}$ , which are indicated by various symbols in the figure. The error bars on the simulation results show the statistical errors, which are estimated from the independent motion of ions in the  $x, y$  and  $z$  directions. The same method is used in estimation of errors in all subsequent simulation results. The experimental data in the range of  $0\text{--}100^\circ\text{C}$  are fitted with polynomials and represented as lines in

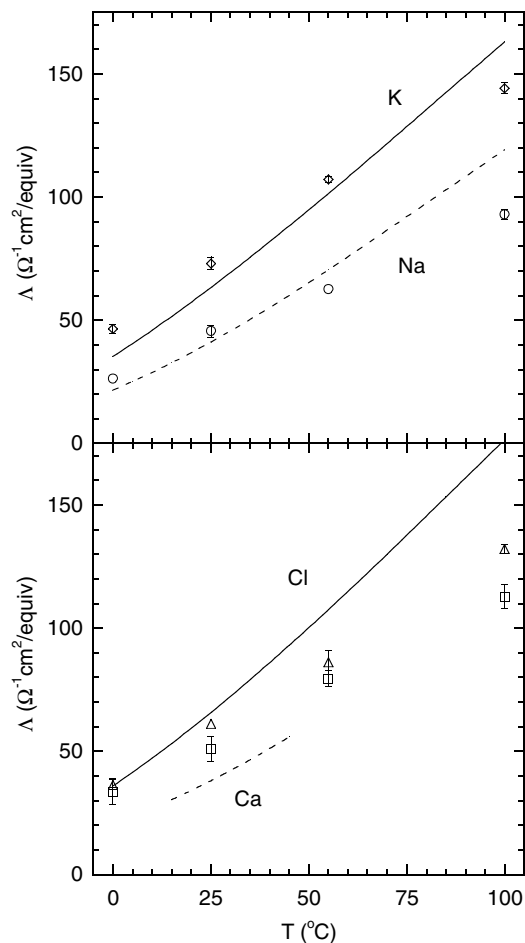


Fig. 2. Comparison of MD simulation results for equivalent conductivities of ions with the experimental data [1,2] in the temperature range of  $0\text{--}100^\circ\text{C}$ . The simulation results for  $\text{Na}^+$  are indicated by circles,  $\text{K}^+$  by diamonds,  $\text{Ca}^{2+}$  by squares, and  $\text{Cl}^-$  by triangles. Error bars are not shown if they are smaller than the marker size. The fits to the experimental data are represented by full and dashed lines as indicated.

the graphs (for  $\text{Ca}^{2+}$  data are available only in the range of  $15\text{--}45^\circ\text{C}$ ). The sharp increase in conductivities with temperature is reproduced with a varying degree of success. Cation results are somewhat better than those for  $\text{Cl}^-$  ions, but in all cases the slopes in the simulation results are smaller than those of the experimental data. As expected, discrepancies increase with temperature as one moves away from the ambient conditions (where the force fields are determined). We note that  $\text{Cl}^-$  ions have a larger polarizability compared to cations. Thus neglect of polarizability in standard force fields may have contributed to the poorer results for  $\text{Cl}^-$  ions.

In the above discussion, we have neglected the contributions from the cross-correlations between cations and anions. The reason is that we are interested in specific conductivity of each ion type, and there is no clear way of distributing the contributions from cross-correlations among individual ion types. For our dilute systems, the contributions of the cross-correlations to the total conductivity are found to be  $4\text{--}8\%$  regardless of the simulation temperature. Thus including them in the calculations would reduce the individual conductivities presented in Fig. 2 by about  $2\text{--}4\%$ . As the focus of our study is the temperature dependence of conductivities, and the relative contribution of the cross-correlations remain more or less independent of temperature, their neglect does not alter our conclusions.

We next discuss the self-diffusion coefficients of water and ions. The diffusion coefficients are determined from the velocity autocorrelation functions (VAF)

$$D_v = \frac{1}{3} \int_0^\infty \langle \mathbf{v}_v(0) \cdot \mathbf{v}_v(t) \rangle dt. \quad (2)$$

The comments about the convergence of the current-current autocorrelation functions similarly apply to VAF. We have also used the mean square displacement to determine the diffusion coefficients of ions. Test calculations in the NaCl system yielded similar but slightly smaller values of  $D$  compared to those obtained from VAF. We have preferred to use VAF in the rest of this work to be consistent with the conductivity calculations.

For water, a separate MD simulation without ions is carried out. Temperature dependence of the water diffusion coefficient is shown in Fig. 3. The MD simulation results appear to track the data reasonably well but the discrepancy remains substantial. To quantify it, we note that  $D$  increases by a factor of 8.6 from  $0$  to  $100^\circ\text{C}$ , whereas the increase in the simulations is only 4.6. We have checked whether simulation artifacts could be responsible for some of this discrepancy. Repeating the calculations in the NVE ensemble, and thus avoiding the effects of the artificial barostat and thermostat, have yielded  $3\text{--}4\%$  smaller diffusion coefficients at all temperatures. The change is too small and also it won't help to rectify the slow rise in the slope. Other potential artifacts such as finite size effects [19] have too small temperature

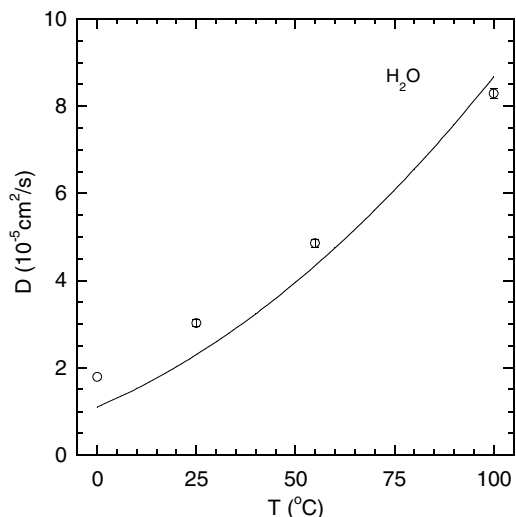


Fig. 3. Temperature dependence of the self-diffusion coefficient of water molecules obtained from VAF (circles). The experimental data [17,18] are represented by the solid line.

dependence to explain such a large discrepancy. Recent MD simulations of water with polarizable force fields [20–22], however, reproduce the rise in the data rather well, indicating that use of a rigid water model is the likely cause of the problem.

Diffusion coefficients of ions are calculated using the same trajectory data as those employed in the conductivity calculations. The temperature dependence of  $D$  for the selected ions are shown in Fig. 4. Unfortunately there are no experimental data on temperature dependence of diffusion coefficients so it is not possible to make a comparison as in Figs. 2 and 3. The available data at room temperature are compared to the simulation results in Table 2. Note that there is a small depen-

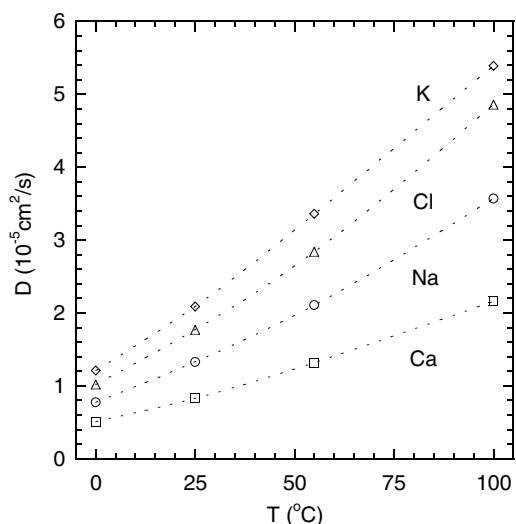


Fig. 4. Temperature dependence of the self-diffusion coefficient of ions obtained from VAFs. The results are indicated by the same symbols as in Fig. 2 and joined by the dotted lines to guide the eye. Error bars are not shown as they are about the size of markers or smaller.

Table 2

Comparison of the self-diffusion coefficients of ions at room temperature (in units of  $10^{-5}\text{cm}^2/\text{s}$ )

Atom	$D_{\text{exp}}$	$D_{\text{sim}}$
$\text{Na}^+$	1.33	$1.33 \pm 0.05$
$\text{K}^+$	1.96	$2.09 \pm 0.01$
$\text{Ca}^{2+}$	0.79	$0.83 \pm 0.04$
$\text{Cl}^-$	2.03	$1.77 \pm 0.01$
O(W)	2.30	$3.03 \pm 0.08$

The data are for infinite dilution [1,2], and the simulation results are for  $c = 0.1$  M.

dence of the diffusion coefficients on concentration, so the simulation results would be slightly higher at infinite dilution. As in the case of conductivity, diffusion coefficient of  $\text{Cl}^-$  ions exhibit the largest discrepancy, and one may again blame lack of polarizability for the problem.

An interesting observation regarding the temperature dependence of conductivity and diffusion coefficients in Figs. 2 and 4 is the similarity of the slopes for a given ion type. To turn this observation into a more quantitative statement, we use the Einstein relation

$$\sigma = \frac{nq^2}{kT} D, \quad (3)$$

which follows from Eq. (1) if we neglect the ion–ion correlations and use Eq. (2) for  $D$ . Here,  $n$  is the density of ions. In Fig. 5, we plot the ratio  $kT\sigma/nq^2D$  for the ions as a function of temperature. At infinite dilution, this ratio would yield 1 at all temperatures. Ion–ion correlations at finite concentration reduces the conductivity more than the diffusion coefficient. Therefore, this ratio is expected to be less than 1 for the MD simulations carried out at  $c = 0.1$  M for monovalent ions, and even smaller for the divalent  $\text{Ca}^{2+}$  ions. These expectations are borne out at room temperature where the the ratio for the monovalent ions are all bunched together. But it is

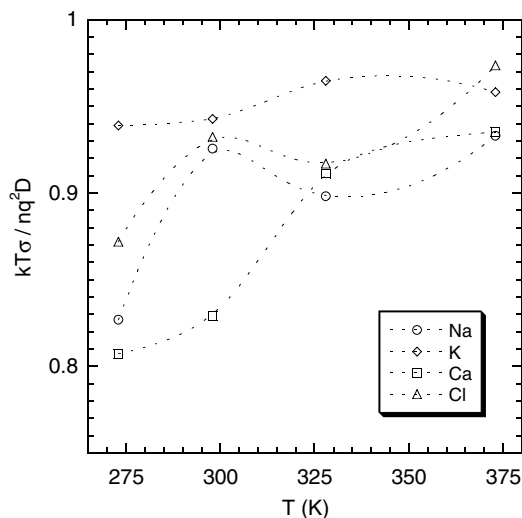


Fig. 5. Comparison of the simulation results for  $kT\sigma/nq^2D$  (symbols joined with dotted lines) with the Einstein relation, which predicts 1 for the ratio at all temperatures.

difficult to account for the substantial variations in this ratio with temperature. Simulation artifacts are expected to cancel out when taking the ratio, so there is no obvious explanation other than that force fields work well at room temperature but have problems at different temperatures. The figure also exposes that things are not that well at the 0 °C end either – a fact that was not so obvious in Fig. 2 due to the much smaller values of the conductivity at 0 °C.

The rapid rise in ion transport coefficients with temperature are obviously related to the likewise behaviour in water. Whether changes in the hydration shell of ions also contribute to this process is of interest. We have determined the hydration numbers of ions in the first shell at all temperatures, but found no perceptible variations from the room temperature values of 5.4 for Na<sup>+</sup>, 6.2 for K<sup>+</sup>, and 7.6 for Cl<sup>-</sup>. Clearly the changes in the temperature range are too small to have much effect in the binding of water molecules in the first shell. Such an effect is more likely to show up in the second hydration shell where the binding energy is much weaker. Unfortunately the second shell is rather loosely defined, and it is very difficult to determine the hydration numbers unambiguously.

In conclusion, our simulation results for ion transport coefficients show that their temperature dependence is not very well described by the traditional force fields. Resolution of this issue is important for future applications of MD simulations to description of temperature dependent processes especially in biomolecules. Recent MD simulations of water with polarizable force fields have resulted in considerable improvement in description of the diffusion coefficient of water. Thus it will be worthwhile to carry out a similar study for ions using a polarizable force field. On the experimental side, we note the lack of data for diffusion coefficients of ions at different temperatures. Such data can be obtained relatively easily using modern techniques such as NMR spin-echo [23], and would be very useful in testing the domain of validity of MD force fields beyond the ambient conditions.

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