



Memory effects in Brownian dynamics simulations of ion transport

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Abstract

Brownian dynamics simulations of ion transport are often carried out using the Langevin equation with the Markovian assumption for random forces. We investigate whether memory effects play any role in the ion transport processes by comparing the results of simulations obtained using the Langevin and generalized Langevin equations. As expected, the two methods yield similar transport coefficients in bulk simulations but differences appear when ions have to cross potential energy barriers.

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Recent determination of the crystal structures of several ion channel proteins [1–3] have generated a great deal of interest in modeling of the structure-function relations ion channels (see [4–6] for recent reviews). Several methods ranging from molecular and Brownian dynamics simulations to the continuum Poisson–Nernst–Planck equations have been used for this purpose. Of these, molecular dynamics (MD) offers the most fundamental approach. However, it is too slow to enable computation of conductance, which is the primary observable in ion channels. The Poisson–Nernst–Planck approach, on the other hand, suffers from the break down of the mean field approximation in a nanopore environment, and hence it is not suitable for modeling of ion channels [7]. This leaves Brownian dynamics (BD) as the most viable alternative for investigation of structure-function relations in ion channels. Indeed, since the appearance of the crystal structure of the KcsA potassium channel in 1998 [1], there have been many studies of its conductance properties using BD simulations [8–12]. The success of BD in the KcsA channel has, in turn, spurred its application to other ion channels, for example, calcium [13], porin [14], gramicidin [15], chloride [16], and acetylcholine receptor [17].

While the BD simulations of ion channels have yielded promising results so far, there are several issues with the formalism that require clarification – an important one being the use of the Langevin equation with Markovian random forces. Strictly speaking, the Markovian assumption is justified when the Brownian particles are much heavier than the solvent molecules. This condition is obviously not satisfied for ions in water. In such cases, correlations may be important and can be taken into account by using the generalized Langevin equation. Previously, the Langevin and generalized Langevin equations were compared for ions in bulk electrolytes [18], and the memory effects were found to be unimportant for description of self-diffusion and ion-pair properties. However, ion transport in channels involves, besides self-diffusion, conductance under an applied electric field and barrier crossing. So far there has been no systematic assessment of the influence of the Markovian assumption on ion conductivity and barrier crossing. Here we investigate the role of memory effects on these aspect of ion transport by comparing the results of BD simulations that employ Langevin and generalized Langevin equations in otherwise identical electrolyte systems.

The generalized Langevin equation for N interacting ions is given by

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$$m_i \dot{v}_i = -m_i \int_0^t dt' \zeta_i(t-t') v(t') + R_i + F_i, \quad i = 1, \dots, N, \quad (1)$$

where m is the mass of ions, and R and F are the random and systematic forces acting on them (for convenience, we suppress the x, y, z indices). In Eq. (1) the frictional force depends on the previous velocities through the integral over the memory function ζ_i , which also quantifies the correlations in random forces via the fluctuation–dissipation theorem

$$\langle R_i(0) R_j(t) \rangle = kT m_i \zeta_i(t) \delta_{ij}. \quad (2)$$

When the Brownian particle is much heavier than the solvent molecules, correlations in its velocities persist much longer than those in the random forces specified by ζ_i in Eq. (2). Then the velocity term can be taken as approximately constant in the integral for the frictional force in Eq. (1), yielding a constant friction coefficient: $\gamma_i = \int \zeta_i(t) dt$. This is equivalent to using a delta function for the memory function, $\zeta_i(t) = 2\gamma_i \delta(t)$ in Eq. (1), which results in the Langevin equation

$$m_i \dot{v}_i = -m_i \gamma_i v_i + R_i + F_i, \quad i = 1, \dots, N. \quad (3)$$

With this choice of ζ_i , the Markovian property of the random forces also becomes explicit in the fluctuation–dissipation theorem in Eq. (2)

$$\langle R_i(0) R_j(t) \rangle = 2kT m_i \gamma_i \delta(t) \delta_{ij}. \quad (4)$$

An important consequence of the Markovian assumption is that the velocity autocorrelation functions (VACF) exhibit an exponential decay

$$\langle v(0)v(t) \rangle = \langle v^2 \rangle e^{-\gamma t} = \frac{kT}{m} e^{-\gamma t}, \quad (5)$$

with a relaxation time constant γ^{-1} (values of γ^{-1} determined from the experimental diffusion coefficients using the Einstein relation, $D = kT/m\gamma$ with $T = 298$ K are listed in Table 1). It is well known from MD simulations of electrolytes that VACF of ions exhibit damped oscillations due to the caging effect in their hydration shells, and this effect can be reproduced in generalized Langevin dynamics using appropriate memory functions [19]. The memory functions determined from MD simulations of NaCl solutions broadly follow the pattern of an exponential decay with a small dip [19]. Since our aim here is an investigation of the memory effects in a simple setting rather than an exact reproduction of the

MD simulations, we choose the more convenient exponential form for ζ_i

$$\zeta_i(t) = \zeta_{0i} e^{-t/\tau_i}. \quad (6)$$

The parameters ζ_0 and τ are determined from fits to the MD results in [19] and listed in Table 1. Comparison of the velocity and force relaxation times in Table 1 (γ^{-1} and τ) shows that the two timescales, far from being separated, overlap with each other. Note that there are differences among the memory functions obtained from MD simulations, so the τ values are not uniquely determined. The similarity between γ^{-1} and τ should thus be seen as a coincidence.

The above discussion makes it clear that the Langevin equation is not suitable for description of the short timescale properties of ions such as VACFs. However, as indicated earlier [18], it may still be useful for studying the long timescale properties such as diffusion and lifetimes of ion pairs. Here we investigate whether this extends to conductivity and barrier crossing of ions, which is necessary to justify the application of the Langevin equation to ion channels. Although ion channels are the primary motivation of this study, the issues raised are quite general and, therefore, will be addressed in the broader setting of a bulk-like system. This will also help to increase the statistical accuracy of the results, which is a significant consideration in simulation of barrier crossing events.

The Langevin equation (3) is integrated using the third order Gunsteren–Berendsen algorithm [20], which allows arbitrary timesteps to be employed in the simulations. Indeed, timesteps varying from 2 to 100 fs have been employed in BD simulations of ion channels in the past. Therefore, it is pertinent to check the sensitivity of the simulation results to the timestep employed. We stress that there is no a priori justification for using timesteps smaller than the relaxation times of ions γ^{-1} in the Langevin equation. Hence justification of these smaller timesteps is an outstanding issue in applications of BD. For the generalized Langevin equation (1), we use the leap-frog algorithm developed by Nilsson and Padró [21]. In this case, only a short timestep of 2 fs is considered as it is necessary for a correct integration of the friction integral in Eq. (1). Because we are interested in single-ion properties, the concentration of the NaCl solution is kept relatively low at $c = 0.1$ M, which corresponds to an average ion–ion distance of 20 Å. Although it is not important for this study, we mention that the ion–ion interactions are modeled realistically using the potential of mean force results from MD simulations [22]. Besides the Coulomb, they contain the $1/r^9$ short-range and hydration interactions in the form of damped oscillations (see [13] for the parameters). Unlike MD simulations, we need not worry about long-range forces here because water is implicit and the Coulomb

Table 1
Parameters used in simulations of ions with the Langevin and generalized Langevin equations

Ion	m (10^{-26} kg)	D (10^{-9} m ² /s)	γ^{-1} (fs)	τ (fs)	ζ_0 (10^{27} s ⁻²)
Na ⁺	3.8	1.33	12	33	2.6
Cl ⁻	5.9	2.03	29	28	1.3

forces among ions are attenuated by dielectric and Debye screening effects.

In order to demonstrate that both methods are properly calibrated, we first calculate the self-diffusion coefficients of ions. The results in Table 2 are obtained by simulating 500 Na⁺ and 500 Cl⁻ ions in a cubic box with a sidelength of 200 Å. In each case, the system is equilibrated for 0.1 ns and the trajectory data are collected for 1 ns. Diffusion coefficients are obtained from the mean-square displacement of ions using the Einstein equation. The slight reduction in the calculated D values from the input values given in Table 2 (at infinite dilution) may be attributed to the increased concentration. Thus both methods can reproduce the self-diffusion properties of ions fairly accurately. Perhaps a surprising aspect of the results in Table 2 is that the BD simulations with the Langevin equation yield accurate results even when $\Delta t \ll \gamma^{-1}$, way beyond its expected domain of validity. As indicated above, this is important for justification of recent applications of BD simulations to ion channels.

We next compare the conductivities of ions obtained by applying a uniform electric field E_z in the z direction. The conductivity is determined from the measured current density J_z via $\sigma = J_z/E_z$. The current densities of ions are obtained from two fundamental definitions:

- (i) The net number of ions N_i crossing imaginary x - y planes (spaced at 1 Å intervals) are measured during a simulation period of T . The current density at each plane is given by $J_{iz} = N_i q / TA$, where A is the cross-sectional area. Averaging the results over all the planes, a mean value of J_z is determined.

- (ii) The drift velocity v_d of ions of each type is calculated from time and ensemble average of the z -component of ion velocities. The current density is determined from $J_z = nqv_d$, where n is the number density of ions.

The two methods yield consistent results for conductivity, but the statistical errors are much smaller in the first method. Therefore, we quote only the conductivity results obtained with the first method in Table 3.

Simulations are carried out for 125 Na⁺ and 125 Cl⁻ ions in a box with dimensions $100 \times 100 \times 200$ Å. A smaller system is chosen here in order to run longer simulations and thereby improve statistics (the run time scales with the square of the number of ions). Each conductivity result in Table 3 is obtained from a 20 ns production run after 0.1 ns of equilibration. The statistical errors are estimated by dividing the 20 ns data to 2 ns segments and calculating the standard deviation in the resulting sample of 10. Two sets of conductivities are obtained using electric fields of 2×10^7 and 10^8 V/m. The chloride conductivity exhibits some dependence on Δt employed in the BD simulations at the lower field strength, which disappears for higher E_z . Otherwise the results are consistent with those obtained from the Einstein relation, $\sigma = nq^2 D/kT$. The similarity of the results with fivefold different electric fields suggests that the linear response regime is achieved. For a more rigorous test of this assertion simulations with a lower electric field and/or calculation of the conductivity using the Green–Kubo formula is desirable. The deviation of the simulation results from the experimental ones is due to the electrophoretic effect, which can be described by including the hydrodynamic interactions [24]. As ion channels are typically charge selective, this is not a significant issue for such applications. Going back to our main focus of memory effects, there is a discernible reduction in the conductivities obtained with the generalized Langevin equation. However, the effect is rather small to have much impact in practical applications.

The most critical test of the memory effects involves barrier crossing. For this purpose, we erect a Gaussian potential energy barrier centered at the $z = 0$ plane

Table 2
Diffusion coefficients of ions (in units of 10^{-9} m²/s) obtained from simulations with the Langevin and generalized Langevin equations (the last column denoted by GLE)

Δt (fs)	100	30	10	2	GLE
$D(\text{Na}^+)$	1.32	1.32	1.32	1.32	1.32
$D(\text{Cl}^-)$	1.99	2.02	2.00	1.99	2.02

The timestep employed in each simulation is given in the first row.

Table 3
Conductivities of ions (in units of $\Omega^{-1} \text{m}^{-1}$) obtained from simulations with the Langevin and generalized Langevin equations (the last column)

Ion	Δt (fs)						
	Exp.	ER	100	30	10	2	GLE
Na ⁺	0.41	0.51	0.50	0.50	0.49	0.50	0.49
Na ⁺			0.52	0.52	0.51	0.51	0.49
Cl ⁻	0.66	0.79	0.78	0.75	0.73	0.80	0.72
Cl ⁻			0.79	0.79	0.79	0.79	0.74

The timestep employed in each simulation is given in the first row.

$E = 2 \times 10^7$ V/m is applied in the top rows for Na⁺ and Cl⁻, and $E = 10^8$ underneath.

The associated statistical errors are about ± 0.01 in the first case and ± 0.003 for the higher electric field.

Experimental results [23] and predictions of the Einstein relation (ER) are quoted in the second and third columns, respectively.

$$U = U_0 \exp(-z^2/2b^2), \quad (7)$$

where U_0 is the barrier height and b is its width. The ions can be driven across the barrier either by an electric field or a concentration gradient. When an electric field is applied, ions form a double layer across the barrier which complicates the interpretation of the results. We, therefore, choose the simpler second method. The presence of a barrier severely reduces the number of ions crossing the $z = 0$ plane. To increase the statistics, we use a box with larger x and y dimensions; $200 \times 200 \times 40$ Å. The number of Na^+ (and Cl^-) ions in the lower ($z < 0$) and upper ($z > 0$) part of the box are 200 and 20, respectively. The ionic concentrations in each part are held constant during the simulations by using a stochastic boundary condition [8]. That is, whenever an ion crosses the barrier, a similar ion closest to the boundary is transported to the other side keeping the concentrations fixed in their initial values.

As our aim here is to demonstrate the magnitude of the memory effects rather than a comprehensive systematic study, we will consider only a limited range of barrier parameters. In a first study, the barrier height is kept fixed at $U_0 = 3$ kT and the width is varied from $b = 1$ –5 Å. The current densities of ions, determined from the net number of ions that cross the $z = 0$ plane, are plotted in Fig. 1. Each data point in the figure is obtained from the average of 10 simulations, each lasting 100 ns. Such long simulations are necessary to reduce the statistical fluctuations. The main message of Fig. 1 is that inclusion of the memory effects increases the probability of barrier crossing as one would expect intuitively. Perhaps more surprisingly, the discrepancy between the Langevin (with $\Delta t = 2$ fs) and generalized Langevin equation results is not that large. The largest discrepancy occurs for the sharpest barrier (at $b = 1$ Å, 48% for Cl and 30% for Na), which steadily decreases as the barrier gets smoother (at $b = 5$ Å, 36% for Cl and 17% for Na). Comparison of the $\Delta t = 2$ and 100 fs results shows that using smaller timesteps in the Langevin simulations leads to a better agreement with those of GLE. The observed minima in flux may appear intriguing. From Kramers theory, one would expect a $1/b$ dependence, which is seen for small b . The rise in flux for larger b is the unintended consequence of using a fixed volume, which leads to higher effective concentrations of ions as the central barrier is expanded.

In a similar study, the barrier width is kept fixed at $b = 4$ Å and the height is varied from $U_0 = 2$ –4 kT. The barrier crossing events become very rare at higher U_0 values and do not lead to statistically meaningful results within the simulation time of 1 μ s. The general trend deduced from the limited amount of data is that the discrepancy between the Langevin and generalized Langevin equation results grows with increasing barrier

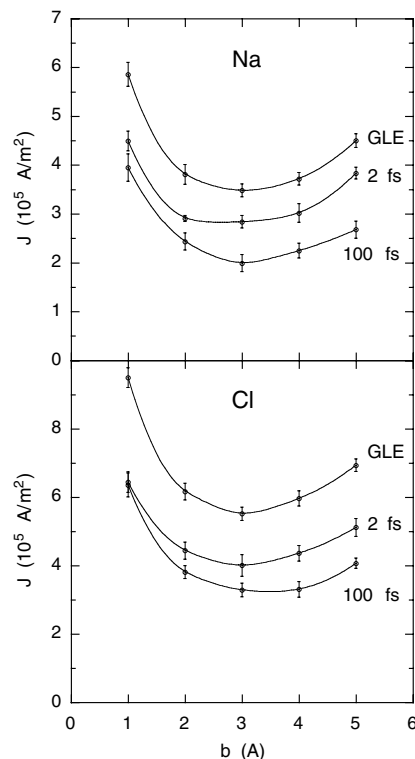


Fig. 1. Current densities of Na^+ and Cl^- ions crossing the Gaussian barrier of height $U_0 = 3$ kT at $z = 0$ are plotted as a function of the barrier width b . Results obtained from the Langevin equation (with $\Delta t = 2$ and 100 fs) are compared with those obtained from the generalized Langevin equation.

height. For example, the discrepancy for Cl ions is 25%, 35% and 49% for $U_0 = 2$ –4 kT, respectively.

In conclusion, our results indicate that the memory effects in ion transport are negligible in bulk simulations of electrolytes. Only when ions have to cross energy barriers, inclusion of the memory effects via the generalized Langevin equation becomes an issue. Such energy barriers are a common feature of ion channels. Therefore, in future BD simulations of ion channels, we recommend switching from the Langevin to the generalized Langevin equation for ions inside the pore region. Our results also provide justification for the use of smaller time steps in BD simulations. Using a timestep of $\Delta t = 2$ fs is shown to yield similar or better results than those of the larger timesteps. This is a curious result and understanding its microscopic origins is a future challenge for MD simulations.

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