

APPLICATION OF BROWNIAN MOTION THEORY TO THE ANALYSIS OF MEMBRANE CHANNEL IONIC TRAJECTORIES CALCULATED BY MOLECULAR DYNAMICS

ERIC JAKOBSSON AND SEE-WING CHIU

Department of Physiology and Biophysics; and Program in Bioengineering, University of Illinois Urbana, Illinois 61801

ABSTRACT This paper shows how Brownian motion theory can be used to analyze features of individual ion trajectories in channels as calculated by molecular dynamics, and that its use permits more precise determinations of diffusion coefficients than would otherwise be possible. We also show how a consideration of trajectories of single particles can distinguish between effects due to the magnitude of the diffusion coefficient and effects due to barriers and wells in the potential profile, effects which can not be distinguished by consideration of average fluxes.

INTRODUCTION

Several groups have done molecular dynamics studies on the movement of ions in gramicidin A channels including water. Two studies (Mackay et al., 1984; Kim et al., 1985) did relatively short and localized runs including the complete atomic structure of the gramicidin molecule. Another study (Lee and Jordan, 1984) reduced the degrees of freedom and explored more ion positions. A comprehensive review of theoretical descriptions on the atomic scale of resolution of gramicidine permeation is given in Jordan (1987). Recently, Skerra and Brickmann (1987, *a* and *b*) utilized a rigid-helix approximation of the gramicidin backbone to achieve molecular dynamics simulations of ion movement lasting over 100 ps. Such runs are long enough to permit the statistical evaluation of quantities used as parameters in less detailed descriptions of ion movement, such as electrodiffusion and Brownian dynamics. The equivalence of Brownian motion and diffusion was established by Einstein (1926), Brownian dynamics was first used to describe biomolecular motion by Simon and Zimm (1969), and has recently been introduced to describe the translocation of ions across membrane channels (Cooper et al., 1985; Jakobsson and Chiu, 1987). The theory of doing statistical evaluation of atomic motion in liquids by use of Brownian motion theory is well enough established to be treated in standard texts. (McQuarrie, 1976) One important quantity that can be determined is the diffusion coefficient. The results of Skerra and Brickmann raise the question of whether and how the theory used in liquids to evaluate the diffusion coefficient may be extended to the

case of ions moving through a membrane channel. This is the question dealt with here.

APPLICATION OF BROWNIAN MOTION THEORY TO AN ION MOVING IN A BARRIER-FREE POTENTIAL PROFILE: SODIUM MOVEMENT IN GRAMICIDIN

The first point to establish is whether Brownian motion theory is even applicable. The criterion for this is whether the time scales of interest are long compared with the velocity correlation time for the diffusing species. (For a clear exposition of this and other aspects of Brownian motion theory, See McQuarrie [1976], Ch. 20) The equation for this characteristic time is:

$$\tau = mD/(kT), \quad (1)$$

where m is mass of diffusing species (grams), D is diffusion coefficient of diffusing species (cm^2/s), k is Boltzmann's constant (1.381×10^{-16} erg/ $^\circ\text{K}$), T is temperature, 300 $^\circ\text{K}$ in the Skerra-Brickmann simulations.

The mass and diffusion coefficient of the diffusing species are to be inferred from the Skerra-Brickmann data for sodium permeation of the channel since, judging from the trajectory presented, there are no deep potential wells or high potential barriers in the free energy function for sodium translocation across the channel. (In the special case of periodic boundary conditions and absence of lipid or aqueous phases represented in the Skerra-Brickmann computations. In real life, of course, there are wells and barriers. [Jakobsson and Chiu, 1987, and others before

us.]) In this case, the diffusing species consists of a sodium ion plus eight associated waters, so the mass is $(23 + [8 \times 18]) / (6.023 \times 10^{23})$, or 2.773×10^{-22} g. The diffusion coefficient can be calculated approximately (just how approximately will be seen below) from the overall velocity in an electric field by the equation:

$$D = -v \times kT / [q(dV/dx)], \quad (2)$$

where v is the drift velocity for sodium as measured by Skerra-Brickmann, which is $11 \text{ \AA} / 120 \text{ ps}$, q is the charge on a sodium ion ($1.6 \times 10^{-19} \text{ C}$), and dV/dx is the electric field applied across the channel in the Skerra-Brickmann simulations ($1 \text{ V} / 26 \text{ \AA}$ or $3.9 \times 10^8 \text{ V/m}$). Putting the numbers into Eq. (2) yields a diffusion coefficient of $6.1 \times 10^{-6} \text{ cm}^2/\text{s}$. Finally, putting this diffusion coefficient and the appropriate mass into Eq. (1) yields a velocity correlation time of $4.1 \times 10^{-14} \text{ s}$ or 41 fs . The meaning of this is that as long as we look at the translocation phenomenon on a time scale longer than this, for example 0.1 ps or longer, then the Brownian motion theory should be applicable. (It is worth noting that Skerra and Brickmann implicitly assumed the validity of Brownian motion theory in their analysis by assuming a linear relation between applied field and velocity, since the condition for such a linear relationship to hold is the same as that for Brownian motion theory to be valid; that is, that the time scales of interest are long compared with the velocity correlation time. On the face of it, the Skerra-Brickmann assumption appears valid; after taking the fluctuations into account, the drift of the sodium ion really looks linear with time.)

One relatively easy calculation is to estimate the uncertainty in the value of the diffusion coefficient calculated by the net drift of the sodium-water complex in the electric field. The distance traveled along one spatial coordinate in a time t by a Brownian particle will have a standard deviation of $\sqrt{2Dt}$. For our estimated diffusion coefficient above and for the duration of 120 ps in the Skerra-Brickmann simulations, the standard deviation of the distance traveled in that time is thus 3.8 \AA , or 35% of the 11 \AA observed by Skerra and Brickmann. Thus the standard deviation of the diffusion coefficient determined in this way is 35% of its apparent value, or $2.1 \times 10^{-6} \text{ cm}^2/\text{s}$. Since the distribution of distances randomly walked by a Brownian particle is a Gaussian function, there is an easy translation between standard deviation and confidence level. That is, there is a 68% probability that the actual value differs from the apparent value by no more than the standard deviation. In other words, there is a 68% probability that the true diffusion coefficient predicted by the assumptions embodied in the Skerra and Brickmann computations is between 4.0×10^{-6} and $8.2 \times 10^{-6} \text{ cm}^2/\text{s}$.

There is a way to determine the diffusion coefficient with greater precision from data of the type presented by Skerra and Brickmann, and that is to utilize the information contained in the many small fluctuations in the trajectory, rather than simply the net drift over a relatively

long period of time. The general body of theory for doing this is time-correlation analysis. A particularly straightforward application of the general theory is to look at many small time intervals Δt in a trajectory and use the relationship that:

$$D = \langle \Delta x^2 \rangle / (2\Delta t), \quad (3)$$

where Δx is the displacement in an interval Δt and $\langle \rangle$ is the average over many time intervals Δt . The power of eq. (3) is that one trajectory can in effect yield many independent estimates of D , with a good precision resulting from taking the average of all those estimates. The limitation in precision is that Δt must be large compared with the velocity correlation time. A 200 fs value for Δt would be about five times our estimated correlation time for sodium in gramicidin and provide 600 independent estimates of D during the 120 ps duration of the trajectory computer by Skerra and Brickmann. To illustrate the point, we did simulations with a Brownian dynamics program we had previously used to simulate sodium permeation of gramicidin. (Jakobsson and Chiu, 1987) To create a situation similar to the Skerra and Brickmann computations we set up a channel 11-\AA long, set the diffusion coefficient at $6.1 \times 10^{-6} \text{ cm}^2/\text{s}$, kept a flat free energy profile within the channel (no potential wells or barriers), and imposed an electric field of $3.9 \times 10^8 \text{ V/m}$ across the channel. We also put a very high bath concentration on the high voltage side, so that the channel was essentially continually occupied by an ion that had entered from the high voltage side. For each passage across the channel we calculated D three ways. One was by the passage time across the channel, which corresponds to the methods of Skerra and Brickmann. Because of the absorbing boundary conditions at the ends of the channel, the expression relating the electric field, the passage time, the channel length, and the mobility is not Eq. (2). The correct equation can be obtained by integrating Eq. (6) in Jakobsson and Chiu, 1987, using the condition that the potential in the channel is a linear function of the distance. The expression resulting from this process is:

$$D = (L^2/t_p)[(e^\psi + 1) - (2/\psi)(e^\psi - 1)] / [\psi(e^\psi - 1)], \quad (4)$$

where L = channel length (11 \AA in these calculations), t_p = passage time, and $\psi = (qV)/(kT)$, where V is the trans-channel potential difference. (0.4231 V in these calculations).

In the limit of very large electric fields, Eq. (4) converges to Eq. (2), where L/t_p corresponds to the drift velocity. For the magnitude of the electric field we are putting into these calculations, the expressions differ by $\sim 15\%$.

The second method for calculating D was by time correlation according to Eq. (3), with a Δt of 200 fs . Because Brownian dynamics is less computer intensive than molecular dynamics, we were able to calculate many trajectories, and simply look at the standard deviations of

the two sets of calculated diffusion coefficients as a measure of which method gave higher precision.

Finally, the third method of calculating D was by time correlation corrected for the drift in the electric field according to the relationship:

$$D = \langle [\Delta x + (\Delta t) D_{\text{ass}} q(dV/dx)/(kT)]^2 \rangle / (2\Delta t), \quad (5)$$

where D_{ass} is the value of D put into the Brownian dynamics program, $6.1 \times 10^{-6} \text{ cm}^2/\text{s}$.

There are two reasons for doing the corrected time correlation according to Eq. (5). First, it provides a check on the functioning of our Brownian dynamics program. If the program is operating perfectly, there should be no nonrandom difference between D and D_{ass} . Secondly, the difference between the values of D calculated by Eqs. (3) and (5) provides an indication of the degree of inaccuracy introduced into the determination of D by time correlation when the drift velocity due to a potential gradient is ignored.

To provide data for the above analyses, we ran our Brownian dynamics program for 100 simulated ns, during which time 859 simulated ions crossed the simulated channel. The results are shown in Table I. It is seen that the first method for evaluating D , that of passage times, had about the same precision as the drift velocity method of Skerra and Brickmann, as expected. (It should be noted that our value for D was not the arithmetic mean of the individual D 's, but was the reciprocal of the arithmetic mean of the reciprocals of the individual D 's. This is the appropriate averaging technique because Eq. (4) comes from the original expression for the mean passage time, and the passage time is reciprocally rather than directly proportional to D .) Time correlation on the 200 fs time scale, on the other hand, proved for these runs to be almost six times more precise than the drift method for evaluating

D . Comparison of the corrected and uncorrected time correlation results shows that the uncorrected electric field introduces a small (~2%) systematic error in the determination of D by the method of Eq. (3). The small size of this systematic error reflects the fact that on the 200 fs time scale, the thermal jumps are a much larger component of the motion than is the drift with the electric field, even for such an intense field as we are dealing with here.

The above results suggest strongly that for molecular dynamics results of the type presented by Skerra and Brickmann for sodium movement in gramicidin, time correlation analysis can give much more precise values of the diffusion coefficient than can the value of the overall drift in the electric field. Of course we are applying the method to a Brownian dynamics simulation rather than molecular dynamics output, but in fact time correlation of this sort has been applied successfully to molecular dynamics output for about as long as molecular dynamics has been done. (For an early and very clearly presented example, see Rahman, 1964).

The actual value of D is of interest, as well as methods for determining it. In a previous paper (Jakobsson and Chiu, 1987), fitting of published data (Barrett Russell et al., 1986) using constitutive theory led us to an estimate of D for sodium in gramicidin of $\sim 0.5 \times 10^{-6} \text{ cm}^2/\text{s}$, which might range up to $\sim 1.2 \times 10^{-6} \text{ cm}^2/\text{s}$ based on some higher measured values for single-channel conductance. (Dani and Levitt, 1981) Our analysis was based on neglecting access resistance for diffusion of ions up to the channel mouth. We have more recently done a more complete analysis including access resistance, (S.W. Chiu and E. Jakobsson, manuscript submitted for publication) which has resulted in an increase in our estimate of the most plausible value of D for sodium to a range of values that is in essential agreement with the results of Skerra and Brickmann.

TABLE I
DIFFUSION COEFFICIENTS, STANDARD DEVIATIONS,
AND STANDARD OF THE MEAN FROM ANALYSIS OF
859 BROWNIAN DYNAMICS TRAJECTORIES

Method	D	SD	SEM
	cm^2/s		
Passage times, Eq. (4)	6.126×10^{-6}	2.003×10^{-6}	0.068×10^{-6}
Uncorrected time correlation, 200 fs time intervals, Eq. (3)	6.185×10^{-6}	0.373×10^{-6}	0.013×10^{-6}
Corrected time correlation, 200 fs time intervals, Eq. (5)	6.066×10^{-6}	0.366×10^{-6}	0.012×10^{-6}

The input diffusion coefficient was $6.100 \times 10^{-6} \text{ cm}^2/\text{s}$. The results show that in the event only one or a few trajectories are available for analysis, as in the output of molecular dynamics computations, time correlation can provide much more precise values for the diffusion coefficient than can passage times or drift velocities. Also, only a small systematic error is introduced into the time correlation analysis owing to potential gradients not accounted for in the correlation analysis according to Eq. (3).

APPLICATION OF BROWNIAN MOTION THEORY TO AN ION MOVING IN A POTENTIAL PROFILE WITH BARRIERS: LITHIUM OR POTASSIUM IN GRAMICIDIN

In contrast to the situation for sodium, the molecular dynamics trajectories computed by Skerra and Brickmann (1987b) for potassium and lithium movement in gramicidin show evidence of potential wells and barriers spaced $\sim 2 \text{ \AA}$ apart. For many authors, the existence of such features in the potential profile for ion permeation has made a description of this process in terms of transition state theory (Eyring rate theory) seem natural. However the criteria for transition state theory to provide a physical description of kinetic processes in general are not satisfied in either electrolyte solutions (Wolynes, 1980) or in biomolecular motions. (Frauenfelder and Wolynes, 1985) (See also Laidler, 1987, chapter 4 for an extended discussion of conditions for validity of application of transition state theory.) Therefore transition state theory seems unpromis-

ing as a truly physical description of motion in the electrolytic lumen of a membrane channel protein, despite its widespread use as a phenomenological description. Woodbury (1971) showed that in a channel with a large number of wells and barriers, transition state theory produces exactly the same current-voltage curves as electrodiffusion theory with no wells and barriers, with an effective diffusion coefficient that is a function of the number of barriers and the rate coefficient (probability per unit time) for jumping over each barrier. In the section below, we consider the question of how an electrodiffusion calculation of channel permeation is affected by the inclusion of wells and barriers. We have considered this question from the point of view of the mean passage time and maximum net flux in a single-occupancy channel as a function of the number and depth of potential wells in the channel potential profile.

By rearrangement of Eqs. (6) and (10) in Jakobsson and Chiu (1987) we can write the maximum flux and the inverse of the mean passage time in units of (D/L^2) ,

multiplied by integrals involving the channel potential profile. We evaluated these integrals for the case where we superimposed on a linear potential profile varying numbers of sinusoidal potential wells of varying depth.

Representative results are shown in Fig. 1, for zero and 500 M transmembrane voltage. One clear and expected result is that for a high voltage, the maximum flux and the inverse of the mean passage time are essentially identical. Every ion that comes in the high potential side and spends any significant time in the channel winds up going through. This phenomenon is independent of the number and depth of the potential wells, as shown in Fig. 1, *a* and *b*. At zero applied potential and no potential wells, on the other hand, the ratio between the inverse of the mean passage time and the maximum flux is exactly three. (Fig. 1 *c*) Further, this ratio of three for zero applied potential also pertains for many potential wells—but not for just one or a few wells. (Fig. 1 *c*) In addition, the ratio of three for the many-well case is essentially correct independent of the depth of the wells. (Fig. 1 *d*) Finally, by comparing 1, *b* and *d*, one sees

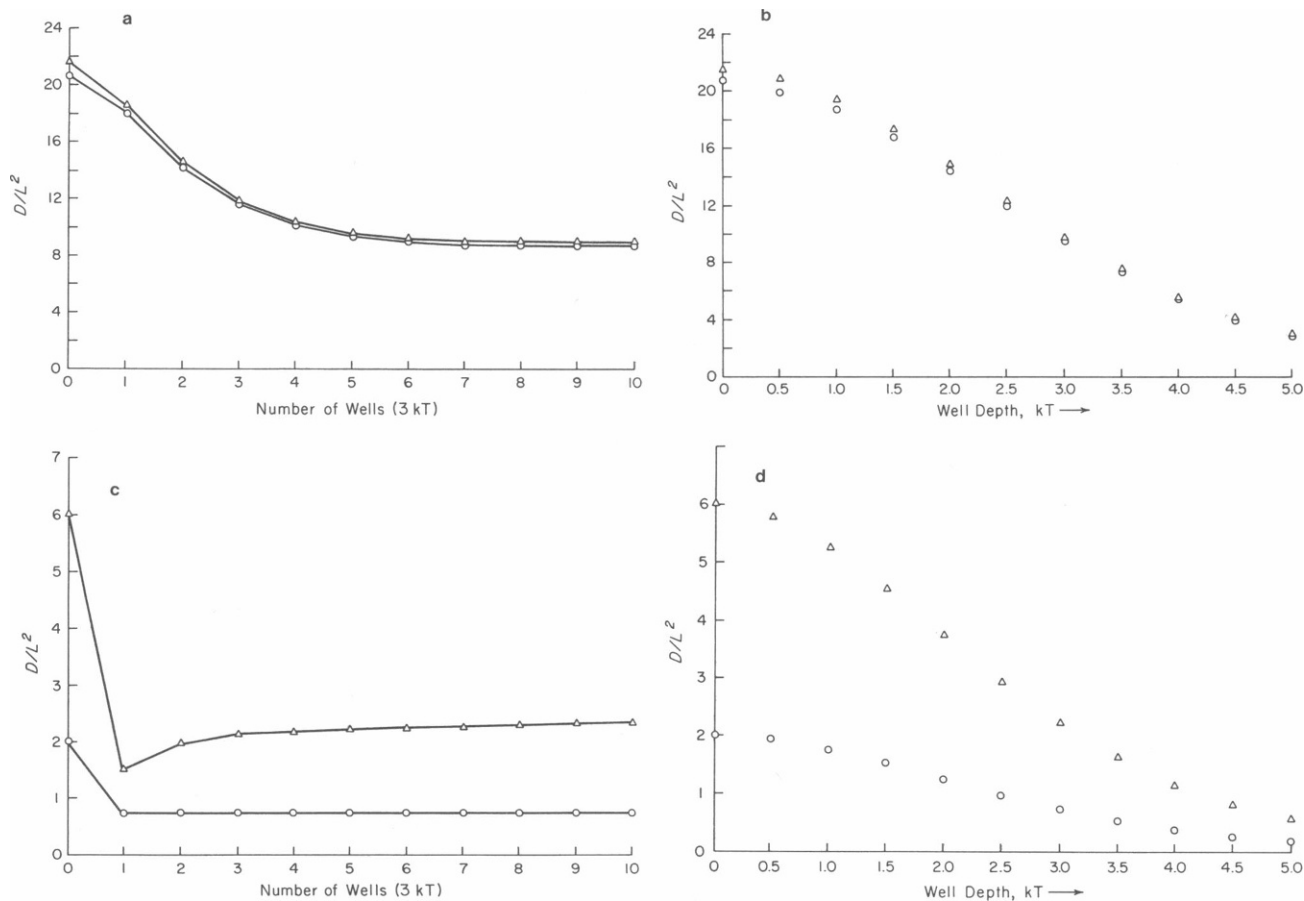


FIGURE 1. Effect of periodic potential wells and barriers on maximum flux and reciprocal of mean passage time in a one-ion channel. Well and barrier shapes are purely sinusoidal and the phase is such that the potential is a relative maximum at each channel mouth. Thus the number of wells in each case is one greater than the number of barriers. Maximum flux and reciprocal of mean passage time are presented as multiples of the quantity (D/L^2) . Symbols are: o, maximum flux; Δ , (mean passage time) $^{-1}$. (a) Retarding effect on permeation as a function of the number of 3 kT potential wells at a high applied voltage (500 mv). (b) Retarding effect on permeation as a function of the depth of five wells at an applied voltage of 500 mv. (c) Retarding effect on permeation as a function of the number of 3 kT wells in the channel at zero applied voltage. (d) Retarding effect on permeation as a function of the depth of five wells at zero applied voltage.

that in the many-well (in this case, five-well) case, the voltage dependences of both the mean passage time and the maximum flux remain unchanged when the depth of the potential wells is changed. For more than ~ 5 wells in the channel, changing the number or depth of the wells in the channel does not change the voltage dependence of, or the ratio between, the inverse of the mean passage time and the maximum flux. Further, these voltage dependences and ratios are the same as if there were no wells in the channel potential profile. The magnitudes of both quantities are changed, however. In other words, for five or more wells in the channel, the effects on ion permeation statistics of changing the number or depth of the wells are indistinguishable from the effects of changing the diffusion coefficient. Zwanzig (1988) has presented an analytical expression, valid for the many-barrier limiting case, of the reduction of the effective diffusion coefficient due to the superimposition of sinusoidal barriers and wells on a smooth potential function. Zwanzig's calculations were specific to a mean first passage time problem with slightly different boundary conditions from ours, but are readily extendable to our situation.

If one considers a finer level of resolution than the statistics and looks at trajectories of individual ions, effects of changing the potential profile are distinguishable from the effects of changing the diffusion coefficient. To show this, we show in Fig. 2 trajectories calculated from a Brownian dynamics computer program, for a situation in which an ion is moving in a channel across which a large voltage has been applied. Trajectory A is for a situation in

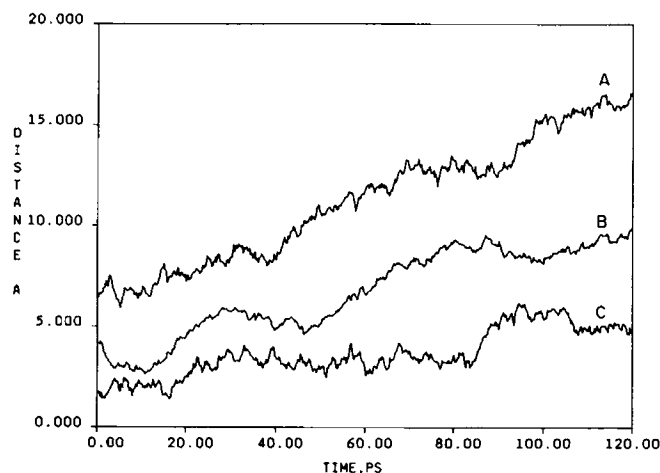


FIGURE 2. Effect on individual ion trajectories of changes in diffusion coefficient and of superposition of wells and barriers in the potential profile. Brownian dynamics simulations were used to generate trajectories for a channel 26 Å long with a potential difference of 1 V applied across it. Trajectory A is for a diffusion coefficient of 6.1×10^{-6} s and a linear potential profile. Trajectory B is for a diffusion coefficient of 2.44×10^{-6} cm²/s and a linear potential profile. Trajectory C is for a diffusion coefficient of 6.1×10^{-6} s and 3 kT sinusoidal potential wells with a periodicity of 2 Å such that the potential minima fall at 1, 3, 5, etc. Å. The trajectories are not chosen to be typical, but rather the first trajectory generated under each set of conditions is displayed.

which the potential profile is linear; there are no potential wells or barriers. Trajectories B and C are for situations for which the statistics of ion permeation would be indistinguishable from each other, since in each case the net average drift velocity would be reduced by a factor of 2.5. However, the ionic trajectories are clearly significantly different from each other, and this is because of the way in which the average drift velocity was reduced. For trajectory B, the diffusion coefficient was set at just 40% of the value of trajectory A. For trajectory C, the diffusion coefficient was set at the same value as for trajectory A but a sinusoidally shaped potential of 2 Å periodicity and 3 kT depth was superposed on the channel potential profile, because we had determined from the analytical electrodiffusion theory that sinusoidally shaped wells of this depth should slow the drift rate down to just a little over 40% of its value with a linear potential profile. The trajectories shown are not selected to be typical. Rather each trajectory is the first one that was calculated at each set of conditions, in order to avoid any bias on our part in possibly selecting trajectories that looked good to us. By the overall drift it appears that the diffusion coefficients for trajectories B and C are about the same as each other and distinctly less than for A. In fact, however, the diffusion coefficient as defined in the equations of Brownian motion and realized in our Brownian dynamics simulation program is the same for trajectories A and C, and both of these are 2.5 times greater than the diffusion coefficient for trajectory B. We did a time-correlation analysis at a 200 fs resolution on the small fluctuations in the three trajectories according to Eq. (3), and found by this method the three diffusion coefficients in the ratio of 1.0/0.412/1.062 for A, B, and C respectively. By this analysis we conclude that for potential profiles with substantial barriers, it is the time-correlation method rather than the drift method that yields the diffusion coefficient as that coefficient is normally defined in Brownian motion theory. The drift method, on the other hand, gives the diffusion coefficient as would be deduced from the statistics of many ions crossing the channel assuming a linear potential profile. (the constant field assumption common in electrophysiology [Goldman, 1943]) Alternatively, the drift method may be said to yield the effective diffusion coefficient, (Zwanzig, 1988) which actually describes barrier crossing rates rather than pure diffusion in a smooth potential.

Interestingly, the characteristic time scales for different types of ion-water motion in an ion channel as reported by Skerra and Brickmann (1987b) and analyzed above are the same as those for a wide variety of protein and nucleic acid simulations as summarized by McCammon and Harvey (1987, page 115). Characteristically the short time (subpicosecond) motions in macromolecules are diffusive, since the many collisions make these motions chaotic. On a longer time scale (tens of picoseconds), there is time for significant movement away from equilibrium positions and thus significant restoring forces are brought into play.

These restoring forces render motions on these longer time scales oscillatory in macromolecules and, according to the results of Skerra and Brickmann, can superimpose an oscillatory component on the ion-water complex moving in a membrane channel.

CONCLUSION

The use of time correlation analysis, derived from Brownian motion theory, was examined for possible application in deriving diffusion coefficients from molecular dynamics simulation of ion permeation of membrane channels. Time correlation analysis was compared specifically with the method of deducing the diffusion coefficient from the average drift in an applied electric field. The analysis was done on trajectories simulated by a Brownian dynamics computer program. For linear potential profiles, it was found that the two methods give essentially the same answer but that the time correlation analysis is much more precise. For potential profiles containing multiple barriers and wells, the two methods give different answers. The answer given by the drift method corresponds to the apparent diffusion coefficient that would be deduced from the average behavior of many ions crossing the channel, in the absence of detailed knowledge of ion-channel interactions and assuming a linear potential profile. The answer given by the time correlation analysis corresponds to the diffusion coefficient as it is normally used in Brownian motion theory, exemplified specifically in the original Einstein description of Brownian motion (Einstein, 1926) and subsequently incorporated into Brownian dynamics simulations of thermally driven processes. Time correlation analysis would seem also relevant to determine the diffusion coefficient of water in membrane channels from trajectories of the sort presented by Mackay and Wilson (1986).

We had useful conversations with Dr. Subramanian Shankar and Dr. John Morgan while doing these calculations and preparing this note. We also benefited by being able to discuss these ideas with Mr. Roger Davenport, Mr. Peter Helfrich, and Mr. Fred Susi in lab meetings at Illinois. Comments by the referees resulted in improvements in the paper.

This work was supported by grant PHS 1 ROS GM32356 from the National Institutes of Health.

Received for publication 6 August 1987 and in final form 17 May 1988.

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