BRIEF COMMUNICATION

NOTE ON THE INTERPRETATION OF LATERAL DIFFUSION COEFFICIENTS

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ABSTRACT It is suggested that interpretation of lateral diffusion coefficients measured in membranes should include the effect of forces.

INTRODUCTION

Molecular motion in biological membranes is a subject of considerable current attention (1). One aspect of this subject is the difference in lateral diffusion rates of lipids and membrane proteins in the same system (2, 3), where the lipids generally diffuse much faster than the membrane proteins. According to the current description of size effects in membranes (4), these differences in the measured diffusion coefficients are too large to be explained on the basis of size differences alone. The purpose of this paper is to offer an explanation of the discrepancies by correctly measuring diffusion coefficients in the presence of an external periodic force field, and by explicitly calculating several examples that involve representative, periodic forces.

Inasmuch as lateral diffusion measurements correspond to one-dimensional motion, consider a specific example (motion in one dimension in the lateral direction in a membrane) in which the position r of a specific kind of molecule is followed as a function of time t. These molecules move about both because of the random, dissipative forces from frequent collisions with the thermally agitated surroundings, and because of specific directional forces that may be characterized by a potential energy function $V(r)$. The classic dynamics of such molecules are governed by the Langevin equation, which is equivalent to the Smoluchowski equation (5)—the diffusion equation with an external force field—in the overdamped limit of large frictional coefficient (i.e., small diffusion coefficient).

DIFFUSION COEFFICIENT

The Smoluchowski equation describes the variation of the concentration $\rho(r, t)$ with position and time and has the one-dimensional form

$$\frac{\partial \rho}{\partial t} = D \frac{\partial}{\partial r}\left(\frac{\partial \rho}{\partial r} + \beta \rho \frac{\mathrm{d}V}{\mathrm{d}r}\right) \tag{1}$$

with $\beta = 1/k_BT$ (k_B is the Boltzmann constant and T the absolute temperature); D is the diffusion coefficient that characterizes the motion of the particular molecule in the medium, and is to be determined experimentally.

D is defined in the following equation:

$$D \equiv \lim_{t \to \infty} \overline{(r - \bar{r})^2}/2t, \tag{2}$$

where the bar indicates an average of the quantity over the diffusion space weighted with the (normalized) concentration. The signature of diffusion is then the existence of D as defined by Eq. 2. When $V(r)$ is not constant, and goes to infinity at some point in the space, there is no true diffusional motion. If, however, the potential energy function is both periodic and finite everywhere, Eq. 2 exists (in fact, $\bar{r} = 0$ in the limit) and true diffusion takes place. The diffusion coefficient, however, is renormalized from the value it has for free lateral motion in the membrane (4) and is, in fact, reduced in size from the free value D_0.

The exact form for the renormalized D may be derived by solving the Smoluchowski equation using Bloch's theorem in a manner analogous to problems in the quantum theory of solids (6). The result that is relevant to this discussion is that in a one-dimensional periodic potential,

$$D = \frac{D_0}{\langle e^{\beta V}\rangle \langle e^{-\beta V}\rangle}. \tag{3}$$

$\langle\ \rangle$ indicates the average over one lattice spacing of the periodic potential that has lattice spacing a, that is, for example,

$$\langle e^{\pm\beta V}\rangle \equiv (1/a) \int_0^a \mathrm{d}r\, e^{\pm\beta V}. \tag{4}$$

A simplified derivation of Eq. 3 is given in the Appendix. Note that the potential energy function is not necessarily symmetrical, but it must be periodic and the motion must be one dimensional for this expression for D to be valid.

For a cylindrical particle of radius R embedded to a depth h in a membrane the appropriate expression for D_0 is (4, 7)

$$D_0 = \frac{k_\mathrm{B} T}{4\pi\eta h}\left[\ln\left(\frac{\eta h}{\eta_\mathrm{w} R}\right) - \gamma\right] \tag{5}$$

where η_w is the viscosity of the aqueous phase, η is the viscosity in the membrane, and γ is Euler's constant (0.5772). As estimated by Cherry (1), $D_0 \simeq 6(10)^{-8} - 6(10)^{-9}$ cm^2/s. To obtain estimates for D, several specific choices for $V(r)$ will be made and the integrals in Eq. 3 evaluated analytically.

Potential *a*

Square Barrier. $V = V_0$ for $0 \leq r \leq l$ and $V = 0$ for $l \leq r \leq a$, repeating with a spacing of a. Then

$$D = D_0/\{1 + 2l(a - l)/a^2 [\cosh(V_0/k_\mathrm{B}T) - 1]\} \tag{6}$$

For a barrier height that is large compared with $k_\mathrm{B}T$,

$$D \simeq \frac{a^2 D_0}{l(a - l)} e^{-V_0/k_\mathrm{B}T}. \tag{7}$$

Potential *b*

Sinusoidal Barrier. $V = (V_0/2)\{1 - \cos(2\pi/a)r\}$ for $0 \leq r \leq a$. In this case the diffusion coefficient is

$$D = D_0/\{[I_0(V_0/2k_\mathrm{B}T)]^2\}, \tag{8}$$

where I_0 is the modified Bessel function (8). Because I_0 has the asymptotic form for large argument (8) of

$$I_0(V_0/2k_\mathrm{B}T) \simeq \frac{e^{V_0/2k_\mathrm{B}T}}{\sqrt{\pi V_0/k_\mathrm{B}T}}, \tag{9}$$

Eq. 8 in the limit of a barrier height V_0 that is large compared with $k_\mathrm{B}T$ and becomes

$$D \simeq \pi \frac{V_0}{k_\mathrm{B}T} D_0 e^{-V_0 k_\mathrm{B}T}. \tag{10}$$

Potential *c*

Sawtooth Barrier. $V = (V_0/k_\mathrm{B}T)r/l$ for $0 \leq r \leq l$ and $V = (V_0/k_\mathrm{B}T)(a - r)/(a - l)$ for $l \leq r \leq a$. From Eq. 3, the diffusion coeffent in this potential is

$$D = \left(\frac{V_0}{2k_\mathrm{B}T}\right)^2 \frac{D_0}{\sinh^2(V_0/2k_\mathrm{B}T)}. \tag{11}$$

Looking at the limit in which $V_0 \gg k_\mathrm{B}T$, one obtains the result

$$D \simeq \left(\frac{V_0}{k_\mathrm{B}T}\right)^2 D_0 e^{-V_0/k_\mathrm{B}T}. \tag{12}$$

These potentials give an impression of the effect of a periodic potential energy function in the lateral direction on the diffusion coefficient. Several points are clear. First, from Eq. 3, the measured diffusion coefficient D is always smaller than or equal to D_0. Second, the temperature dependence of D always has an Arrhenius-like temperature dependence multiplied by the temperature dependence of D_0 as well as additional factors that depend on the specific shape of the potential function. In fact, as Eq. 10 shows, the potential may mask the explicit temperature dependence of D_0 (see Eq. 5) and leave only the implicit dependence inherent in the viscosity terms. Thus, over small temperature ranges, the exponential temperature dependence may very well dominate. Third, D is not as strongly dependent on the length parameters of the potential, as there are no exponential terms depending on length.

DISCUSSION

This paper makes two main points. (*a*) Molecules moving laterally in membranes do not necessarily diffuse freely. (*b*) A correct description of the external periodic forces gives Eq. 3 as the equation for the diffusion coefficient. Thus, measurements of the diffusion coefficient in the sense of Eq. 2 ought to yield Eq. 3 as the result. Explicitly, a potential energy barrier height V_0 of ~2.3 $k_\mathrm{B}T$ gives a reduction of a factor of 10 in D compared with D_0. The other terms in Eqs. 7, 10, and 12 tend to increase D to a lesser extent than the exponential term, the net result being the requirement of a somewhat larger value of V_0 (perhaps ~5 $k_\mathrm{B}T$) to effect a factor of 10 reduction of D with respect to D_0.

Recently, a model of lateral diffusion based on steric hindrance by a labile matrix was presented (9) that treats D^{-1} as a sum of two terms, the first of which is D_0^{-1} and the second of which depends explicitly on the cytoplasmic protein matrix. The analysis of reference 9 is different from the one presented in this paper in the sense that differences in diffusion coefficients between proteins and lipids are attributed to the proteins diffusing in two media rather than to potential barrier effects in a single medium (in addition to the aqueous phase). In this paper, differences in D values are determined by different potential barrier effects, although the analysis of reference 9 can probably be carried out by ascribing a potential to the cytoplasmic protein matrix crosslinking interactions and perhaps offers an explanation for $V(r)$.

An alternative to the above "simple" model for the diffusion coefficient would be to have D_0 depend on position with the same periodicity as the potential $V(r)$. In that case

$$D = 1/(\langle e^{\beta v}/D_0\rangle\langle e^{-\beta V}\rangle) \tag{13}$$

For example, in the square barrier case, suppose that the coefficient D_0 has one constant value, D_0, when $V = 0$ and another constant value D_v when $V = V_0$. Then one gets

$$\begin{aligned}\frac{1}{D} = \frac{1}{D_0}\Bigg\{1 + \frac{2l(a-l)}{a^2}\left[\cosh\left(\frac{V_0}{k_B T}\right)^{-1}\right] \\ \frac{-l(a-l)}{a^2}e^{V_0/k_BT} - \frac{l}{a^2}\Bigg\} \\ + \frac{1}{D_v}\left[\frac{l(a-l)}{a^2}e^{V_0/k_BT} + \frac{l^2}{a^2}\right] \qquad (14) \\ \xrightarrow{V_{0\rightarrow 0}} \frac{(1 - l/a)}{D_0} + \frac{l/a}{D_v} \qquad (15)\end{aligned}$$

Eq. 15 reproduces the expression for the diffusion coefficient corresponding to motion perpendicular to the "ridges" in the analysis of lateral diffusion in inhomogeneous membranes by Owicki and McConnell (10).

APPENDIX

Instead of Eq. 2, it is simpler in some cases to consider an alternative definition of D that coincides with Eq. 2 in all cases of interest in this study. The definition is (11) made in terms of the average time $\bar{t}$ to travel by diffusion a fixed square distance, in this case one lattice spacing squared. Then,

$$D \equiv a^2/2\bar{t}. \tag{A1}$$

This corroborates reports in the literature on first - passage times (12–16) of which $\bar{t}$ is an example; in this case, $\bar{t}$ is the average time, starting from $r = 0$, for diffusion, in either the positive or negative direction, over one lattice spacing a. The result for $\bar{t}$ in this case (see reference 11 for a detailed description of the method) is

$$\bar{t} = \frac{a^2}{2D_0}\langle e^{\beta V}\rangle\langle e^{-\beta V}\rangle \tag{A2}$$

from which Eq. 3 follows using the definition of Eq. A1.

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