Proc. Nat. Acad. Sci. USA
Vol. 72, No. 8, pp. 3111-3113, August 1975
Biophysics

Brownian motion in biological membranes

(diffusion)

P. G. SAFFMAN AND M. DELBRÜCK

Department of Applied Mathematics and Division of Biology, California Institute of Technology, Pasadena, Calif. 91125

Contributed by M. Delbrück, June 9, 1975

ABSTRACT Brownian motion (diffusion) of particles in membranes occurs in a highly anisotropic environment. For such particles a translational mobility (independent of velocity) can be defined if the viscosity of the liquid embedding the membrane is taken into account. The results of a model calculation are presented. They suggest that for a realistic situation translational diffusion should be about four times faster in relation to rotational diffusion than in the isotropic case.

Rotational and translational diffusion of protein and lipid molecules in biological membranes has recently become accessible to experimental study (1–4). The problem can be studied theoretically by applying the classical analysis of Brownian motion to a hydrodynamic model. A simple model is one in which the membrane is taken as an infinite plane sheet of viscous fluid (lipid) separating infinite regions of less viscous liquid (water). The protein molecule is regarded as a cylinder, with axis perpendicular to the plane of the sheet, moving about in the sheet under the action of Brownian motion (Fig. 1).

Diffusion of a particle due to Brownian motion is described by diffusion coefficients, D_T and D_R, for translational and rotational displacements. For motion in a plane and rotation about a perpendicular axis,

$$\overline{r^2} = 4D_Tt, \qquad \overline{\theta^2} = 2D_Rt, \qquad [1]$$

where $\overline{r^2}$ and $\overline{\theta^2}$ are the mean square displacement and angular rotation in time t, respectively.

The diffusion coefficients are related to the mobilities of the particle by the Einstein relations

$$D_T = k_BTb_T; \qquad D_R = k_BTb_R \qquad [2]$$

where k_B is Boltzmann's constant, T is the absolute temperature, and b is the mobility (independent of force or torque) defined as the velocity (or angular velocity) produced by steady unit force (or torque) (5).

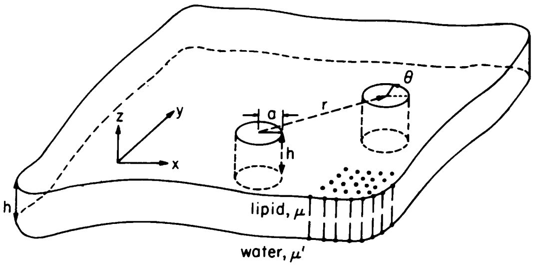

FIG. 1. The hydrodynamic model. A cylindrical particle embedded in a lipid bilayer membrane bounded by aqueous phases on both sides. The particle is permitted to move laterally in the x-y plane, and to rotate around the z-axis.

For a sphere in an unbounded fluid of viscosity μ it is well known that

$$b_T = \frac{1}{6\pi\mu a}, \qquad b_R = \frac{1}{8\pi\mu a^3}. \qquad [3]$$

The ratio between these two mobilities is independent of the viscosity:

$$b_T/b_R = \frac{4}{3}a^2 \qquad [4]$$

where a denotes the particle radius, it being assumed that the Reynolds number is small so that the equations of slow viscous motion (inertial terms neglected) apply.

For our model of the protein in the membrane, matters are not so simple. We denote by μ the viscosity of the fluid representing the membrane and by μ' the viscosity of the exterior liquid. It is supposed that $\mu' \ll \mu$. If μ' is neglected completely, there is no viscous stress transmitted across the surfaces of the sheet and the hydrodynamical problem is that of the motion of a cylinder through a viscous fluid in directions perpendicular to its generators. Finding the rotational mobility is a trivial calculation, giving

$$b_R = \frac{1}{4\pi\mu a^2 h}, \qquad [5]$$

where h denotes the thickness of the sheet and a now stands for the radius of the cylindrical particle. However, the translational mobility does not exist, for there is no solution of the slow viscous flow equations for steady translational motion in two dimensions (the so-called Stokes paradox) (6).

A finite translational mobility b_T can be obtained by taking account of the inertia of the viscous fluid, replacing the slow viscous flow equations by the Oseen equations (6). It is then found that

$$b_T = \frac{1}{4\pi\mu h}\left(\log \frac{4\mu}{\rho U a} + \frac{1}{2} - \gamma\right) \qquad [6]$$

where ρ denotes the density of the fluid, U is the (steady) translational velocity, and γ is Euler's constant (0.5772). But the mobility is now not independent of force and the argument leading to Einstein's relation (Eq. 2) fails. One can replace U by an average value, $(k_BT/m)^{1/2}$ say, where m = particle mass, but this is conceptually unsatisfactory.

There are three alternative ways to proceed.

(*i*) Give the membrane a finite size.

(*ii*) Take account of the viscosity μ' of the outer liquid.

(*iii*) Calculate the mean square displacement from the Langevin equation (ref. 7) using the drag as given by the slow viscous flow equations for unsteady flow. This approach is sometimes referred to as irreversible thermodynamics.

We shall now state the results for these three approaches. It may be kept in mind that although in principle any two or all three effects can be incorporated at the same time, analytical difficulties render this impractical. On the other hand, the methods of calculation imply that the effects add reciprocally (like resistances in parallel), so it is sufficient to treat them separately. Also, these effects are minor corrections for the rotational mobility which is given to sufficient accuracy by Eq. 5.

Eqs. 3, 5, 7, and 8 are obtained by using the traditional boundary condition of no slip on the surface of the particle. Recently doubts have been raised about the universal appropriateness of this boundary condition (8). It has been found that in organic solvents rotational relaxation of small molecules is better described by a boundary condition implying perfect slip (no tangential stress) between solvent and solute, while in aqueous solutions the behavior of small molecules is intermediate, depending on the number of hydrogen bonds formed between solvent and solute (9). In real membranes it is not obvious which condition is appropriate. In our model it turns out that the translational mobility is changed little by the choice of boundary condition, and these changes will be given. The rotational mobility, however, could be very high for a very symmetrical particle and a slip boundary condition. For an asymmetric molecule the rotational mobility may be quite similar for "slip" or "stick," but model calculations would be very complicated.

(*i*) Finite membrane size

This is modeled by supposing that the particle is at the center of a circular sheet of radius R, where $R \gg a$. Then

$$b_{T^{(i)}} = \frac{1}{4\pi\mu h}\left(\log \frac{R}{a} - \frac{1}{2}\right). \qquad [7]$$

This result is calculated using a no-slip boundary condition on the surface of the particle. The condition of zero tangential stress simply deletes the term $-\frac{1}{2}$.

(*ii*) Finite viscosity of the outer liquid

For the calculation of this effect, we note that the membrane is composed of amphiphilic molecules (lipids with polar head groups) whose structure does not permit shear across the membrane. Thus, the velocity field inside the sheet is exactly two-dimensional. (This is accomplished formally by having an anisotropic viscosity with one coefficient infinite.) A no-slip boundary condition is imposed at the surfaces of the sheets, so the external liquid is dragged into motion by the flow in the sheet, and directly by the area of particle in direct contact with the outer liquid. The outer liquid exerts a surface traction on the fluid in the sheet, adding an extra term to the equation of motion for the fluid in the sheet. The mathematical problem can be reduced to the solution of a pair of dual integral equations (8). But for $\mu' \ll \mu$, singular perturbation techniques (9) can be applied directly and lead (after a difficult calculation) to the result

$$b_{T^{(ii)}} = \frac{1}{4\pi\mu h}\left(\log \frac{\mu h}{\mu' a} - \gamma\right) \qquad [8]$$

with zero slip on the surface of the particle. With the alternative zero tangential stress, a term $+\frac{1}{2}$ is added inside the bracket. These results are independent of the amount by which the particle sticks out of the sheet.

(*iii*) Irreversible thermodynamics

The drag on a cylinder moving with arbitrary, but not identically zero, acceleration through a viscous fluid is calculated from the unsteady slow viscous flow equations. This information is fed into the Langevin equation (ref. 7), and it is found by standard methods of irreversible thermodynamics that the diffusion coefficient corresponds to an effective mobility

$$b_{T^{(iii)}} = \frac{1}{4\pi\mu h}\left(\log \frac{4\mu t}{\rho a^2} - \gamma - 1\right), \qquad [9]$$

where $\mu t/\rho a^2 \gg 1$. Note that this is a time-dependent mobility. This result is for a no-slip boundary condition on the particle. The alternative zero stress condition now requires that the lengthy calculation leading to **9** be repeated *ab initio*, and has not been carried out.

As mentioned previously, when all three effects are present, the effective mobility for insertion into Eq. **2** for the diffusion coefficient is the smallest of **7**, **8**, and **9**. The detailed calculations for (*ii*) and (*iii*) are of mathematical interest and will be published elsewhere. For motions of particles in biological membranes expected values of the parameters are

$$a \approx h \approx 10^{-7}\ \text{cm}, \qquad R \approx 10^{-3}\ \text{cm},$$
$$\mu \approx 1\ \text{poise}, \qquad \mu' \approx 10^{-2}\ \text{poise},$$
$$\rho \approx 1\ \text{g/cm}; \qquad k_BT \approx 4 \times 10^{-14}\ \text{ergs}$$
$$t \approx 10\ \text{sec}.$$

Then case (*ii*) is appropriate. Thus, we predict

$$D_T = \frac{\overline{r^2}}{4t} = \frac{k_BT}{4\pi\mu h}\left(\log \frac{\mu h}{\mu' a} - \gamma\right),$$
$$D_R = \frac{\overline{\theta^2}}{2t} = \frac{k_BT}{4\pi\mu a^2 h} \qquad [10]$$

yielding a ratio between the two mobilities depending logarithmically on the viscosity ratio:

$$b_T/b_R = \left(\log \frac{\mu h}{\mu' a} - \gamma\right)\cdot a^2. \qquad [11]$$

Comparing this result with the corresponding ratio obtained for diffusion in a homogeneous isotropic fluid (Eq. **2**) we see that in membranes the translational mobility (and diffusion) is increased, relative to the rotational one, by a factor of about 4. Perhaps this result can be rationalized intuitively as follows: the velocity field generated by rotation falls off as $1/r^2$ in 3 D and as $1/r$ in 2 D. The energy dissipated is, therefore, highly localized. In contrast, the velocity field generated by translation falls off more slowly as $1/r$ in 3 D and as $\log r$ in 2 D. This energy dissipation is, therefore, spread over a greater environment. Thus, in a membrane of high viscosity between aqueous layers of much lower viscosity the *rotational* drag is almost entirely determined by the membrane, while the *translational* drag is reduced because of the low dissipation in the aqueous phases.

We may compare our result **11** to the only case for which both translational and rotational diffusion coefficients have been reported, the rhodopsin molecule of the frog retina's rod outer segment. Cone (1) finds $D_R = 5 \times 10^{+4}\ s^{-1}$ (within a factor of two) and Poo and Cone (3) find $D_T = 3.5 \pm 1.5$

$\times 10^{-9}\ \mathrm{cm}^2\ s^{-1}$. The radius of the rhodopsin molecule must be very close to 2×10^{-7} cm. Thus, we obtain

$$\begin{aligned} & \overset{\text{expt.}}{=} \frac{2\text{-}5 \times 10^{-9}}{2.5\text{-}10 \times 10^{+4}}\,\mathrm{cm}^2 = 2\text{-}20 \times 10^{-14}\ \mathrm{cm}^2 \\ D_T/D_R = b_T/b_R & \\ & \overset{\text{theor.}}{=} 4 \times (2 \times 10^{-7}\ \mathrm{cm})^2 = 16 \times 10^{-14}\ \mathrm{cm}^2 \end{aligned} \qquad [12]$$

In view of the large experimental error limits, the simplifying assumptions of the model (including the assumption of infinite thickness of the aqueous phases) and the uncertainty regarding the viscosity of these phases, the agreement can be considered encouraging and perhaps susceptible to refined tests.

1. Cone, R. A. (1972) *Nature New Biol.* **236,** 39–43.
2. Poo, M. & Cone, R. A. (1973) *Exp. Eye Res.* **17,** 503–510.
3. Poo, M. & Cone, R. A. (1974) *Nature* **247,** 438–441.
4. Edidin, M. (1974) *Annu. Rev. Biophys. Bioeng.* **3,** 179–201.
5. Landau, L. D. & Lifshitz, E. M. (1959) in *Fluid Mechanics* (Pergamon Press, Elmsford, N.Y.), sect. 59.
6. Lamb, H. (1932) in *Hydrodynamics* (Cambridge University Press, New York), sect. 343.
7. Wax, N., ed. (1954) *Selected Papers on Noise and Stochastic Processes* (Dover Press, New York).
8. Hu, C. & Zwanzig, R. (1974) *J. Chem. Phys.* **60,** 4354.
9. Bauer, D. R., Brauman, J. I. & Pecora, R. (1974) *J. Am. Chem. Soc.* **96,** 6840–6843.
10. Titchmarsh, E. C. (1973) in *Theory of Fourier Integrals* (Oxford Univ. Press, New York), chap. XI.
11. Van Dyke, M. (1964) *Perturbation Methods in Fluid Mechanics* (Academic Press, New York).