LATERAL DIFFUSION IN AN ARCHIPELAGO

Effects of Impermeable Patches on Diffusion in a Cell Membrane

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ABSTRACT Lateral diffusion of molecules in lipid bilayer membranes can be hindered by the presence of impermeable domains of gel-phase lipid or of proteins. Effective-medium theory and percolation theory are used to evaluate the effective lateral diffusion constant as a function of the area fraction of fluid-phase lipid and the permeability of the obstructions to the diffusing species. Applications include the estimation of the minimum fraction of fluid lipid needed for bacterial growth, and the enhancement of diffusion-controlled reactions by the channeling effect of solid patches of lipid.

INTRODUCTION

Since the classic paper of Singer and Nicolson (1972) on the fluid mosaic model of the lipid bilayer, the membrane has been pictured as a "lipid sea" in which "protein icebergs" are free to diffuse, unless bound to cytoskeletal elements or cross-linked into large patches. But if the membrane contains proteins or domains of gel-phase lipid, diffusion will be obstructed, and the effective diffusion constant will be reduced. In this case, lateral motion of membrane components will resemble the motion of an iceberg in an archipelago. In this paper, we present a theory of the effect of impermeable domains on the lateral diffusion constant, and discuss their effect on the rate of diffusion-controlled reactions. (For examples of such reactions in cells, see Kahn et al., 1978, and Rimon et al., 1978.)

Several authors have discussed this effect qualitatively. In their study of the rate of intermixing of surface antigens on fused cells, Petit and Edidin (1974) suggested that "islands of solid lipid" can "canalize" diffusion, causing more rapid intermixing. Galla, Sackmann, and co-workers obtained lateral diffusion rates from the rate of formation of pyrene excimers. They found that the pyrene aggregates as the lipids solidify (Galla and Sackmann, 1974), and estimated the size of the solid domains (Sackmann et al., 1977). They suggested that lateral motion is enhanced in the channels between solid protein-lipid domains (Galla et al., 1979), but that long-distance diffusion may be hindered (Kapitza and Sackmann, 1980). The only quantitative treatment of this effect is a recent paper by Owicki and McConnell (1980), who evaluated the direction-dependent diffusion constants for alternating stripes of fluid and solid lipid, and found the appropriate average diffusion constant for measurements of diffusion in multilamellar systems by fluorescence photobleaching recovery. The recent work of Freire and Snyder (1980) is discussed in the theory section.

We consider a random arrangement of solid domains of lipid or protein in a fluid membrane. We assume two-dimensional steady-state diffusion in a finite system. (The conceptual problems with two-dimensional steady-state diffusion are discussed in the appendix.) The diffusion equation then reduces to the Laplace equation, and the problem is equivalent to the evaluation of the electrical conductivity, the dielectric constant, the magnetic permeability, or the thermal conductivity of a composite medium. In the limit as the solid phase becomes impermeable to diffusing molecules, the problem can be treated by percolation theory. As we shall see, both approaches are needed for a complete description.

As will be discussed in more detail later, we assume that the domains are not elongated or branching. (See Hui, 1981 for direct observations of domain geometry by electron microscopy.)

We assume a static system: The lifetime of the impermeable domains is assumed to be long compared with the characteristic time for lateral diffusion. (See Laguës, 1979*a*, *b*.)

For simplicity, we neglect specific interactions between the diffusing species and the impermeable domains. The partition coefficient is assumed to be either zero (corresponding to complete exclusion of the diffusing species from the impermeable domains) or unity (corresponding to equal concentrations of the diffusing species in the two phases).

Lateral phase separation into solidlike and fluidlike regions has been measured by ESR (Shimshick et al., 1973; Shimshick and McConnell, 1973) and by calorimetry (see, for example, Taylor et al., 1973; van Dijck et al.,

1977). Our treatment of diffusion in a composite two-dimensional medium will account for the reduction in diffusion rates due to the presence of impermeable patches of lipid, but lateral phase separation may have another important effect: increasing the lateral compressibility of the membrane, thus facilitating lateral diffusion (Shimshick et al., 1973; Shimshick and McConnell, 1973; Linden et al., 1973. For theoretical treatments of the effect of lateral phase separation on permeability, see Doniach, 1978; Nagle and Scott, 1978; Marcelja and Wolfe, 1979).

Note that the three-dimensional analogues of the theories presented here could be used to describe diffusion in porous polymers, and diffusion of cytoplasmic components in a network of impermeable cytoskeletal elements. (For experimental results, see Keith et al., 1977, 1979.)

First, we shall discuss effective-medium theory, and then percolation theory. Both theories are needed in order to describe diffusion in membranes. As shown by Pike et al. (1974) and Webman et al. (1975) in their treatments of electrical conductivities of composite media, which theory is applicable to a particular system depends on the area fraction of conducting material and the ratio of the conductivities of the two materials. After we present the two theories, we shall discuss how they are to be combined. In the last section, we shall summarize the theoretical results and consider the biological applications.

THEORY

Because most of the references in the section treat the electrical conductivity of composite media, it is often convenient to refer to regions of high and low conductivity, instead of regions of high and low diffusivity, or fluid and solid domains of lipid.

Effective-medium Theory

Effective-medium theories have long been used to evaluate the electrical conductivity of composite materials. These theories have been reviewed by Landauer (1978). (See also Milton, 1980.)

Rayleigh, and later Runge, used a multipole expansion to obtain the conductivity σ_c of an infinite square array of perfectly conducting cylinders in a matrix of conductivity σ_0 (Keller and Sachs, 1964). From this result and a theorem of Keller (1963), the conductivity of an array of perfectly insulating cylinders in a matrix of conductivity σ_0 is

$$\sigma_c^* = \frac{\sigma_c}{\sigma_0} = \frac{1 - (1 - x) - 0.30584(1 - x)^4 - 0.013363(1 - x)^8}{1 + (1 - x) - 0.30584(1 - x)^4 - 0.013363(1 - x)^8}, \quad (1)$$

where x is the area fraction of matrix. Note that this expression could be used to estimate the diffusion constant of a lipid in a regular array of proteins such as that found in *Halobacterium halobium* or in patches of acetylcholine receptors (Jackson and Sturtevant, 1978).

The treatments of Rayleigh and Runge assume that the nonconducting particles are circular, but the results are insensitive to the detailed shape of the particles. Bell and Crank (1974) showed that the diffusion constant in a regular array of impermeable squares is very close to that of a similar array of disks of equal area. The shape is important only if the nonconducting particles are elongated or branching. If, for example, the domains were arranged in alternating stripes of solid and fluid, the treatment would have to take into account that geometry (Owicki and McConnell, 1980; see also Crank, 1975, and references cited there).

For our purposes, the most useful form of the effective-medium theory is that of Bruggeman (1935) and of Landauer (1952, 1978), who showed that for a two-dimensional random distribution of disks of conductivity σ_1, in a medium of conductivity of σ_0,

$$\sigma_c^* = (x - \tfrac{1}{2})(1 - r) + \sqrt{(x - \tfrac{1}{2})^2(1 - r)^2 + r}, \quad (2)$$

where x is the area fraction of component 0 and $r = \sigma_1/\sigma_0$. This expression treats the two materials symmetrically. If component 1 is nonconducting, $r = 0$, and the conductivity of the composite is

$$\sigma_c^* = \begin{cases} 2x - 1 & (x > \tfrac{1}{2}) \\ 0 & (x < \tfrac{1}{2}) \end{cases} \quad (3)$$

To derive Eq. 2, one finds the exact local field around an element embedded in an effective medium, and requires that the deviations of the local field from the effective value cancel out, on the average. This self-consistency requirement determines the conductivity of the effective medium (Granqvist and Hunderi, 1978; Kirkpatrick, 1971).

Percolation Theory

If the diffusion rate through the obstructions is negligible compared with the rate through the matrix, the diffusion constant can be obtained from percolation theory. (For reviews of percolation theory, see Shante and Kirkpatrick, 1971; Kirkpatrick, 1973; de Gennes, 1976; Zallen, 1978; Stauffer, 1979; and Essam, 1980.)

There are two types of percolation problems: lattice and continuous percolation. Lattice percolation is well illustrated by the experiments of Watson and Leath (1974). They measured the electrical conductivity of a wire mesh as a function of the fraction $1 - x$ of sites removed at random. The conductivity decreased and went to zero at a critical value $x_c = 0.587$. They treated the site problem, in which the nodes are cut out; one could also treat the bond problem, in which the cuts are made between nodes. Continuous percolation can be visualized in terms of raindrops falling on an initially dry square of pavement; after a certain time, a continuous wet path will be formed across the pavement (Swann, 1914, quoted in Morris and Coutts, 1977). The key result in both lattice and continuous percolation is the existence of a threshold. At a certain critical fraction of conducting sites, or critical area fraction of conducting material, long-range paths will be formed, and the conductivity of a macroscopic sample will increase markedly. In other words, there is a transition between a low-conductivity state, dominated by the conductivity of the insulating component, and a high-conductivity state, dominated by the conductivity of the conducting component (Pike et al., 1974).

For our purposes, the most important result of percolation theory is the critical area fraction, x_c, because it is not accurately predicted by effective-medium theories (Pike and Seager, 1974). (Note that we use x_c and "critical area fraction" to refer to the critical fraction of sites in lattice problems, and the critical area fraction in the continuous problem.)

The critical area fraction depends on the dimensionality of the system: As the dimensionality increases, more paths become available, and the fraction of conducting sites needed for conduction decreases. For a given dimensionality, the critical fraction of conducting sites decreases as the connectivity of the lattice increases. Furthermore, for a given lattice, the critical fraction of conducting sites decreases as the range of the interaction increases. (See Dalton et al., 1964; Kirkpatrick, 1976.)

These results for lattices give a qualitative understanding of the critical area fraction, but the results for a continuum are needed to describe lateral diffusion in membranes. For randomly distributed overlapping disks, values of x_c have been obtained by Monte Carlo calculations (Roberts, 1967; Pike and Seager, 1974; Ottavi and Gayda, 1974; Fremlin, 1976), by series expansion (Haan and Zwanzig, 1977), and by extrapolation of the results of Dalton et al. (1964) to infinite coordination number

(Shante and Kirkpatrick, 1971; Domb, 1972). The results are in reasonable agreement: $x_c = 0.641$ to 0.683, with an average value of 0.668 ± 0.016. (We exclude the value of Roberts, 1967; see Pike and Seager, 1974.) We shall adopt the value

$$x_c = 0.668. \tag{4}$$

Experimental results are available from measurements of the conductivity of thin films of sputtered metal as a function of the amount of metal deposited. Liang et al., (1976) obtained a value of 0.67 with a bismuth film, and Murti (1979) found a value of 0.60 for an indium film. One limitation of these experiments is that the sputtered film may be in fact three-dimensional instead of two-dimensional, giving a lower value of x_c than would be obtained in a strictly two-dimensional system. One must therefore interpret the observed x_c as a lower bound on the two-dimensional x_c; our value is thus consistent with the experimental values.

For diffusion on a cell surface, the critical area fraction ought to be slightly lower than this, because the surface is closed, creating some paths for diffusion not present in a planar system.

As in the effective-medium theories, the results of continuum percolation theory are insensitive to the shape of the conducting particles, unless the particles are elongated or dendritic (Pike and Seager, 1974). The average critical area fraction for uniform squares (Pike and Seager, 1974; Haan and Zwanzig, 1977) is 0.667, in excellent agreement with our average value 0.668 for uniform circles. Skal and Shklovskii (1974) found that the three-dimensional critical volume fraction was insensitive to shape for a wide variety of shapes.

Percolation theory (See the review of Kirkpatrick, 1973.) predicts that the conductivity within a region Δx around x_c has a power law dependence:

$$\sigma_c(x) \simeq \begin{cases} \sigma_0(x - x_c)^t & (x > x_c) \\ \sigma_1(x_c - x)^{-u} & (x < x_c) \end{cases} \tag{5}$$

Comparison of various determinations of the critical exponents and the width Δx of the critical region gives the following values (Watson and Leath, 1974; Liang et al., 1976; Levenshtein, 1977; Straley, 1977; Webman et al., 1977; Yuge and Onizuka, 1978):

$$\Delta x \simeq 0.1, \qquad s = 0.2, \qquad t = 1.2 \pm 0.1, \qquad u = 1.1. \tag{6}$$

The exponents are expected to depend principally on dimensionality; they are insensitive to the details of the lattice. The exponent t shows this clearly. The range of values quoted includes results from the bond problem on the square lattice, the site problem on the square lattice, and the continuous case as measured by sputtering experiments with a thin film of bismuth.

Relation of the Theories

How do the effective-medium theory and the percolation theory fit together? The connection between the two theories has not been analyzed for two-dimensional continuous percolation, but we shall summarize the results for cubic and square lattices (Kirkpatrick, 1971, 1973; Pike et al., 1974; Webman et al., 1975).

The effective-medium theory is a good approximation unless the ratio of the conductivities of solid and fluid, $r = \sigma_s/\sigma_f$, approaches zero. According to Pike et al. (1974), for the cubic lattice, the effective-medium theory holds when $r > 10^{-5}$, but Kirkpatrick (1971) showed that for the square lattice, the effective-medium result is inaccurate near $x \simeq x_c$ for $r = 10^{-5}$. We expect the Bruggeman-Landauer equation to hold for, say, $r \gtrsim 10^{-3}$. This equation is thus appropriate for diffusion in typical mixtures of solid and fluid lipids, as will be discussed later.

When r approaches zero, the situation becomes more complicated. The effective-medium theory is still a good approximation far from x_c, but in the neighborhood of x_c, the power-law expression (Eq. 5) from percolation theory is appropriate. The value of x_c predicted by the effective-medium theory, $x_c = 0.5$, is incorrect. This is a general property of effective-medium theories: neglect of correlations leads to inaccurate predictions of x_c (Pike et al., 1974).[1]

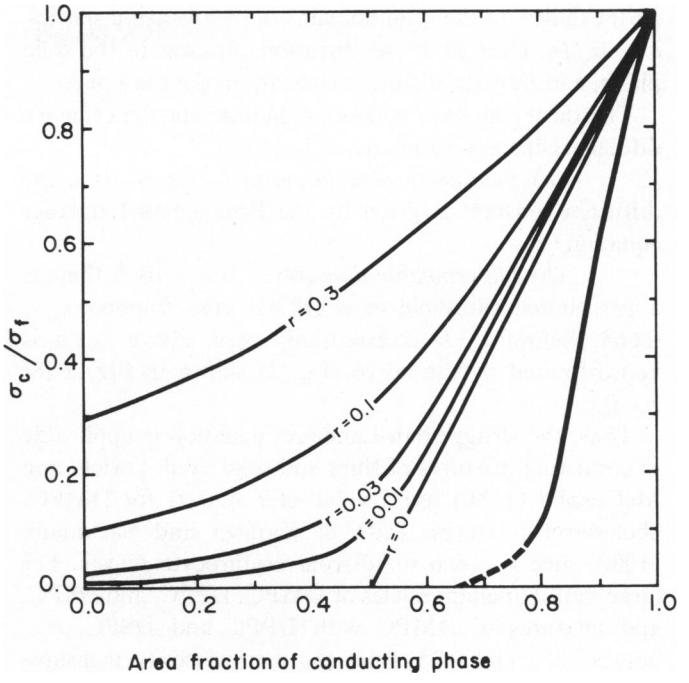

FIGURE 1 The normalized conductivity of the composite medium, $\sigma_c^* = \sigma_c/\sigma_f$, as a function of the area fraction of the conducting phase. The solid curves are from the Bruggeman-Landauer equation (2) for the indicated value of $r = \sigma_s/\sigma_f$. The dotted line shows the power law (Eq. 5), and the heavy line represents Eq. 7.

We construct a function interpolating between the two limits by assuming a cubic polynomial in x, and choosing the coefficients so that the polynomial and its derivative match the Bruggeman-Landauer equation (2) at $x = 1$, and the power-law expression (Eq. 5) at $x = x_c + \Delta x = 0.768$. The resulting curve, $\sigma_c^*(x) = 66.118311 - 231.07059\ x + 264.78625\ x^2 - 98.833971\ x^3$, (Eq. 7) is shown in Fig. 1. This curve is somewhat arbitrary, because the width of the critical region, $\Delta x = 0.1$ (Watson and Leath, 1974; Levenshtein, 1977), is not accurately known, and it is necessary to assume a functional form. But we expect the curve to be semi-quantitatively correct.

This case is important in biological systems, because an immobilized membrane protein is impenetrable to a diffusing molecule, giving the limit $r = 0$.

Freire and Snyder (1980) analyzed their Monte Carlo calculations on lipid bilayers in terms of percolation theory, though their treatment differs from ours in two important respects. First, they assume lattice percolation instead of continuum percolation. Second, they consider percolating channels of molecular dimensions; we assume channels wide enough that macroscopic lateral diffusion can occur in them.

BIOLOGICAL SIGNIFICANCE

The Theory section shows that the diffusion constant in a fluid membrane with solid domains depends on two parameters, the area fraction x of fluid lipid, and the relative

[1]Note that the theory of Owicki and McConnell (1980) shows no percolation threshold, because for $x > 0$, some fluid stripes are always aligned along the direction of diffusion.

permeability[2] of the solid domains to the diffusing species, $r = D_s/D_f$. Here D_s is the diffusion constant in the solid phase, and D_f is the diffusion constant in the fluid phase.

The theory makes two key predictions for the effective diffusion constant, summarized in Fig. 2:

(*a*) *Semipermeable domains.* If $r > 10^{-3}$, the diffusion constant is given by the Bruggeman-Landauer equation (2).

(*b*) *Impermeable domains.* If $r < 10^{-3}$, there is a percolation threshold at a critical area fraction $x_c = 0.668$. Below x_c, D is essentially zero; above x_c, it is approximated by the curve (Eq. 7) shown in Fig. 2 for $r = 0$.

Thus, the Bruggeman-Landauer equation is applicable to coexisting mixtures of fluid and solid lipid. Owicki and McConnell (1980) use a value of r = 0.01 for DMPC-cholesterol mixtures. Data of Kapitza and Sackmann (1980) give $r = 0.6$ for discoid erythrocyte ghosts. For large multilamellar vesicles of DMPC, DPPC, and DSPC, and mixtures of DMPC with DPPC and DSPC, r is between 0.1 and 0.25, from the microviscosity measurements of Lentz et al. (1976*a*, *b*). These values of r are well within the range of applicability of the effective-medium theory.

If the obstructions are immobilized proteins, they are likely to be impenetrable to a laterally diffusing molecule, and we have the second case, for which Eq. 7 applies.

It is important to remember that the observed diffusion rate in a composite medium depends on the distance over which diffusion is measured. Over short distances, a diffusing particle is unlikely to encounter an obstruction, and the diffusion constant is simply that of the fluid phase. Over long distances, the particle must take a tortuous path through the obstructions, and the diffusion constant is that of the composite.

To obtain an idea of the dimensions involved, we consider a membrane at the percolation threshold, with 33.2% of its lipid in the gel phase. If the radius of the solid domains is 10 nm (Sackmann et al., 1977), then there are 10^3 domains/μm^2, at an average separation of 30 nm, and the average channel width is 10 nm. If the area per lipid is 0.5 nm^2, the radius of the lipid is ~0.7 nm, and the channel is ~14 lipid molecules wide. If the radius of the solid domains is larger, as observed for various synthetic lipids and lipid mixtures (Hui and Parsons, 1975; Hui, 1981), the channel widths will be greater.

As stated earlier, we have assumed static percolation: the lifetime of the solid domains is long compared with the characteristic time for lateral diffusion. If the domains are transient, the values of the critical exponents may differ from those used here. Laguës (1979*a*, *b*) treated the three-dimensional case. This theory, adapted to two dimensions, would be appropriate to describe the effect on lateral diffusion of the transient solidlike clusters found in the fluid phase near the transition temperature (Lee et al., 1974; Lee, 1977; Freire and Biltonen, 1978. See also Ubbelohde, 1978, and references cited there.)

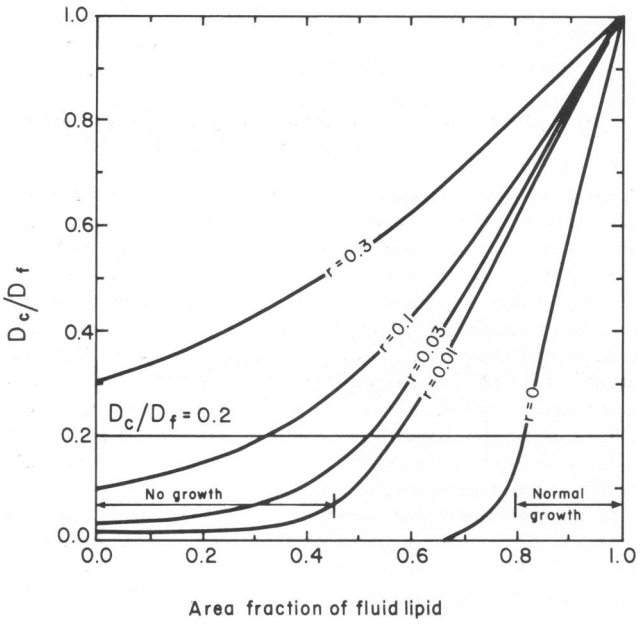

FIGURE 2 The normalized diffusion constant D_c^* as a function of the area fraction x of the fluid phase for various values of $r = D_s/D_f$, redrawn from Fig. 1 (in terms of diffusion coefficients rather than conductivities). The growth limits for *E. coli* are from Jackson and Cronan (1978).

Experimental Tests

An experimental test of the theory is possible using existing techniques, inasmuch as x, r, and D can be measured. The fraction x of fluid-phase lipid can be obtained from the phase diagram, or directly by electron microscopy (Hui, 1981), or from the partitioning of parinaric acid (Sklar et al., 1975, 1977*a*, 1977*b*, 1979; Tecoma et al., 1977), or 2′,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) (Shimshick et al., 1973; Shimshick and McConnell, 1973). Diffusion constants can be measured using fluorescence photobleaching recovery (Schlessinger et al., 1977; Wu et al., 1977, 1978; Smith and McConnell, 1978, for example) or the rate of excimer formation (Galla and Sackmann, 1974; Sackmann et al. 1977; Galla et al., 1979; Morgan et al., 1980). If the diffusion constants in solid and fluid phases are measured as a function of temperature, they can be extrapolated to give the values for both phases in the region of coexistence, so that the ratio r is known as a function of temperature.

Schindler et al. (1980) used fluorescence photobleaching recovery to measure the diffusion constants of a lipopolysaccharide and a lipid analog as a function of the concentration of *Escherichia coli* matrix protein in reconstituted multibilayers. (For a discussion of the interpretation of these results, see Jähnig, 1981, and Koppel et al.,

[2]Recall that we have assumed that the partition coefficient of the diffusing species is zero or unity. In general, if the partition coefficient of the diffusing species A is $K_A = [A]_{solid}/[A]_{fluid}$, then $r = K_A D_s/D_f$.

1981.) A plot[3] of the diffusion constants for lipopolysaccharide as a function of the area fraction of fluid shows two main features. First, their curve agrees with Eq. 7 for $x > 0.9$. Second, they find no percolation threshold in the measured range $x = 0.4$ to 1.0.

The absence of a percolation threshold is due to the fact that in *E. coli,* the matrix protein forms a periodic structure stabilized by strong protein-protein interactions (Steven et al., 1977). These interactions lead to aggregation of the proteins, lowering the value of the percolation threshold from that obtained for a random distribution of impermeable domains. If the distribution of the matrix protein were characterized, or if the experiments were repeated using weakly interacting membrane proteins, the data would provide an excellent test of our theory.

We emphasize that our values of D_c^* give the correction to the usual diffusion constant D_f for the effects of the composite medium alone. To predict the actual diffusion constant, other corrections may be necessary to allow for the dependence of the diffusion constant on the size of the diffusing species (Schindler et al., 1980; Saffman and Delbrück, 1975), the shape of the diffusing species (Crank, 1975), the concentration of diffusing species, and binding of the diffusing species by the immobile phase. It may be necessary to correct for the presence of immobilized boundary lipid and for the finite size of the diffusing species by defining an effective area fraction of fluid.

Minimum Requirement for Fluid Lipid

If long-range lateral diffusion is required for a cell to function normally, then our theory predicts that a certain minimum fraction of fluid lipid is also required. Percolation theory gives one limit: for $r = 0$, the area fraction of fluid lipid must be at least $x_c = 0.668$ for long-range diffusion to occur.

Even if the obstacles are permeable ($r > 0$), there is still likely to be a minimum fraction of fluid lipid required. Suppose that a fivefold reduction in the rate of some diffusion-controlled reaction would be disruptive enough to stop growth. Then the line $D_c^* = 0.2$ in Fig. 2 gives the critical area fraction for growth for the different values of r. If $r = 0.03$, for example, then the minimum area fraction of fluid is 0.53. Jackson and Cronan (1978) found that *E. coli* grows normally at $x > 0.80$, but growth stops at $x = 0.45$. Clearly we could fit their results using plausible values of r and D_c^*, but these growth experiments are not likely to be useful as a test of our theory.

Temperature Dependence of the Diffusion Constant

In the percolation limit, the temperature dependence of D below the percolation threshold will be approximately that of the solid, and the dependence above x_c will be approximately that of the fluid (Pike et al., 1974). For lipid mixtures undergoing lateral phase separations, the abrupt change in D will occur at the temperature corresponding to the critical area fraction x_c, as determined from the phase diagram.

For systems described by the Bruggeman-Landauer equation, D depends on temperature through both x and r. The principal dependence is, of course, through x.

Channeling of Diffusing Molecules

As mentioned in the introduction, several authors have suggested that the presence of solid regions of lipid will enhance lateral diffusion rates by channeling or "canalizing" the diffusing species. Two cases must be considered:

(*a*) Pure diffusion (the unimolecular case), as in fluorescence photobleaching recovery, or the intermixing of surface antigens on fused cells (Petit and Edidin, 1974).

(*b*) Bimolecular reactions, as in the formation of excimers of pyrene probe molecules in membranes (Galla and Sackmann, 1974), or the binding of two membrane constituents.

Assume that the diffusing species is excluded from the gel phase. Then, as the fraction x of fluid-phase lipid decreases, the concentration of the diffusing species in the fluid phase, $C = C_0/x$, increases, but the diffusion constant $D_c(x)$ decreases. The behavior of the rates depends on the ratio of the distance l_{obs} over which diffusion is observed to the average width l_f of a fluid channel. (In a bimolecular reaction, the distance over which diffusion is observed is the average separation of the reacting species.) If diffusion is observed over a short distance $l_{obs} \ll l_f$, then $D \simeq D_0$, as discussed earlier, and the rate increases sharply as the fraction of fluid decreases. For pure diffusion, the rate is

$$\mathcal{R}_1 \propto D(x)\, C(x) \propto D_0/x, \tag{8}$$

and for the bimolecular reaction

$$\mathcal{R}_2 \propto D(x)\, C(x)^2 \propto D_0/x^2. \tag{9}$$

Thus the effect of channeling is very pronounced over short distances, especially in the bimolecular case. The effect is diminished greatly when diffusion is observed over long distances $l_{obs} \gg l_f$, when the obstructions can hinder diffusion significantly. In this case,

$$\mathcal{R}_1 \propto D_c(x)/x, \tag{10}$$

and

$$\mathcal{R}_2 \propto D_c(x)/x^2. \tag{11}$$

Normalized rates for the unimolecular and bimolecular cases are shown in Figs. 3 and 4. (The case $l_{obs} \ll l_f$ corresponds to $r = 1$, because the diffusing particle does not then encounter any obstacles.) Note that if the solid phase is relatively impermeable, the channeling effect

[3]We have assumed that the area fraction of lipid is equal to the mass fraction of lipid.

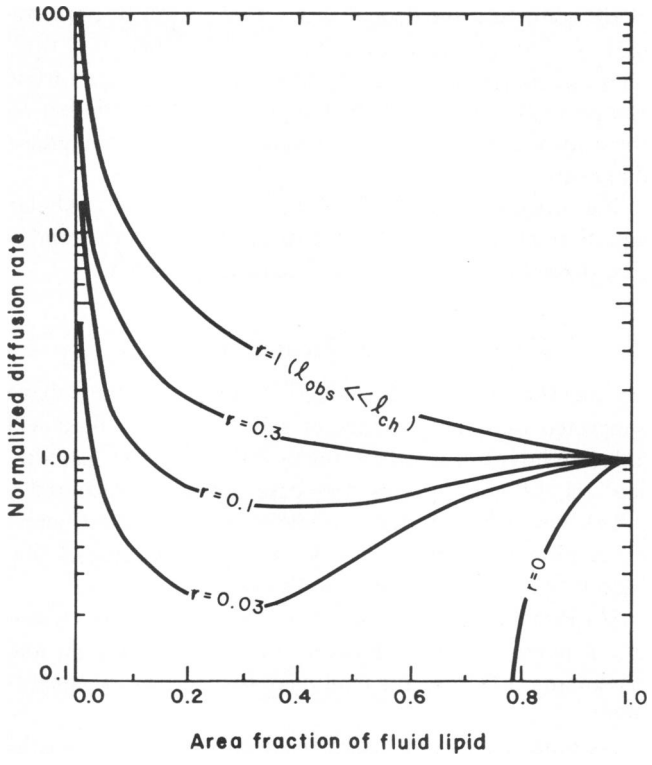

FIGURE 3 The effect of channeling on the diffusion rate.

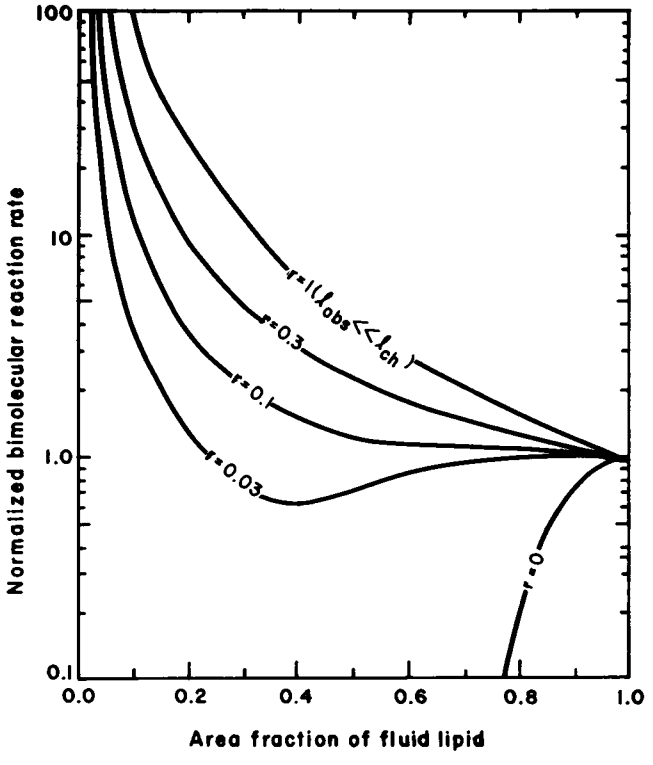

FIGURE 4 The effect of channeling on the bimolecular reaction rate.

enhances the rates only when most of the lipid has solidified. We conclude, then, that the channeling effect is unlikely to be important for long-distance diffusion, but it can be very important in short-distance diffusion.

Further Work

Further work in several areas would be useful: (*a*) Experimental tests of our theory in lipid mixtures, and protein-lipid mixtures, as discussed above; (*b*) detailed examination of the transition between effective-medium theory and percolation theory for the two-dimensional continuous case; (*c*) proof of the existence of the diffusion constant for a diffusing particle in a two-dimensional membrane; (*d*) extension of the work of Laguës (1979*a*, *b*) to describe percolation in two-dimensional systems with transient solid domains.

APPENDIX

Conceptual Questions about Two-Dimensional Diffusion

Two objections may be raised against our treatment, concerning the divergence of the two-dimensional diffusion constant, and the existence of the steady state in two dimensions.

The diffusion constant can be expressed as the integral of the velocity autocorrelation function

$$D = \int_0^\infty \langle v(t)\, v(0)\rangle\, dt. \tag{A1}$$

As shown by Alder and Wainwright (1967, 1970) by molecular dynamics calculations on hard disks and hard spheres, at long times,

$$\langle v(t)\, v(0)\rangle \simeq \begin{cases} t^{-1} \text{ in two dimensions} \\ t^{-3/2} \text{ in three dimensions} \end{cases} \tag{A2}$$

The integral for D therefore diverges in two dimensions, but converges in three dimensions. Alder and Wainwright (1969, 1970) showed that the divergence is due to a vortex flow pattern. (See Pusey, 1979 for later references.)

We do not believe that this divergence invalidates our treatment. The long-time tail, Eq. (A2), has been observed in molecular dynamics calculations for hard disks and hard spheres (Alder and Wainwright, 1967), and for particles with a purely repulsive Lennard-Jones potential (Levesque and Ashurst, 1974; Tresser et al., 1977). But the particles we are considering have an attractive potential and internal degrees of freedom. As Alder and Wainwright (1969) demonstrated, the average energy per particle in the vortex motion is small compared to kT, so that a small amount of cohesive energy can destroy the vortex structure.

Furthermore, the membrane is not in fact two-dimensional. From the standpoint of diffusion, it can be treated as two-dimensional, on account of the high activation energy needed to move an amphiphilic membrane component into the aqueous phase. But from the standpoint of hydrodynamics, the system is three-dimensional, with the bilayer coupled (at least weakly) to the aqueous medium, by hydrogen bonding between lipid headgroups and water, for example. (In their calculation of the diffusion constant of a cylinder in a lipid bilayer, Saffman and Delbrück (1975) assume a no-slip boundary condition, which provides for such coupling.) We expect, then, that the diffusion constant is well defined.

The other problem is the existence of the steady state for an infinite two-dimensional system (Emeis and Fehder, 1970; Razi Naqvi, 1974). For steady-state diffusion to a sink of radius a, the concentration is

$$C(r) = C_0 \frac{\ln(r/a)}{\ln(R/a)}, \tag{A3}$$

where R is the radius of the boundary. The flux at the boundary of the sink is then

$$\phi = \frac{4\pi D C_0 a}{\ln(R/a)}. \tag{A4}$$

The flux depends on the size of the system, and if we take the limit $R \to \infty$ we must take C_0 to be infinite. As Emeis and Fehder (1970) point out, two-dimensional diffusion does not provide enough reactant molecules to sustain a steady-state concentration gradient. If C_0 is finite and R is infinite, the flux decreases monotonically with time. (An expression for the time-dependent flux is given by Razi Naqvi [1974].)

We therefore take the system to be finite, with dimensions large compared to the size of the obstructions and their separation.

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Recent calculations for the two-dimensional continuum give more accurate values of the critical exponents. (See E. T. Gawlinski and H. E. Stanley, *J. Phys. A.* 1981. 14:L291–L299, and the references cited there.) They found a percolation threshold of 0.676 ± 0.002, and a connectivity length exponent ν of 1.343 ± 0.019. According to the scaling law of Levinshtein, Shur, and Efros (1975. *Zh. Eksp. Teor. Fiz.* 69:2203–2211; [in English] 1976. *Sov. Phys. JETP.* 42:1120–1124), in two dimensions, $t = \nu$.

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