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MONTE CARLO STUDIES OF THE LATERAL ORGANIZATION OF MOLECULES IN TWO-COMPONENT LIPID BILAYERS

ERNESTO FREIRE and BRIAN SNYDER

Department of Biochemistry, University of Virginia School of Medicine, Charlottesville, VA 22908 (U.S.A.)

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Summary

The lateral organization of two-component phosphatidylcholine bilayers has been investigated using Monte Carlo calculations based upon non-ideality parameters deduced from the phase diagrams of these mixtures. The results are used to develop a quantitative description of the distribution and spatial localization of compositional regions along the bilayer plane in both the gel and liquid crystalline phases. In particular, a detailed analysis of the physical extension (lateral connectivity) and compactness of the compositional clusters is made. It is concluded that the chemical composition of the membrane, the physical state of the bilayer and the interaction energies between molecules greatly influence the lateral connectivity and compactness of compositional regions and that these parameters might play an important role in the formation of diffusional pathways along the membrane plane.

Introduction

In the past few years considerable effort has been directed towards investigating physicochemical properties of selected mixtures of lipids in order to obtain information regarding the organization of these molecules within the bilayer and to establish correlations with selected functional properties of the membrane [1—3]. These studies have demonstrated that many membrane constituents do not behave ideally and that lateral phase separation, lateral species separation and other types of nonideal phenomena are often associated with lipid-lipid and protein-lipid mixtures [4—6].

The lateral organization of molecules within the bilayer is generally thought of in terms of domains or clusters of specific composition the average size of

which depends on the concentration and the interaction potential between molecules of a given type [7—10]. While this cluster representation is intrinsically correct it might, however, result in a distorted physical picture of the bilayer due to the fact that the distribution of cluster sizes is not homogeneous and that, in two dimensions, molecular clusters of a given size can have many different shapes and be formed with a different number of bonds or connections between molecules.

In a previous communication [11] we have shown that the phase diagrams of lipid mixtures in conjunction with Monte Carlo calculations can be used to generate molecular distributions from which the lateral organization of the bilayer can be deduced at any composition. In this article those studies are extended and the results are used to develop a more complete quantitative description of the lateral distribution of molecules in lipid bilayers. This description introduces new statistical mechanical variables to describe the lateral connectivity of the bilayer, the compactness of the compositional clusters and the relation of these parameters with the formation of diffusional pathways along the plane of the bilayer. While these Monte Carlo calculations are directed to describe the equilibrium organization of the bilayer, they also provide important clues regarding microscopic mechanisms of reorganization phenomena in lipid bilayers.

Methods

The Monte Carlo techniques used in this article have been described in detail in a previous communication [11]. In this model of the bilayer, the lipid molecules are assumed to be hexagonally packed in a triangular lattice and only nearest neighbor interactions are considered. A binary lipid system is represented by a $m \times n$ matrix with periodic boundary conditions, where each matrix element $D_{i,j}$ represents a lattice position which can be occupied by a lipid molecule of type A or type B. Molecular interactions are introduced by proper assignment of the six nearest neighbors of each lipid molecule.

Computer experiments as a function of the molar composition of the mixture are performed by a replacement technique. Each experiment is initialized with all the lattice positions occupied by lipid molecules of the same type (A molecules). Then a second type of lipid molecule, B, progressively replaces A molecules until the bilayer contains only B molecules. The relative intrinsic probability of a substitution at a given site is determined by the occupancies of the nearest neighbor positions of that site and can be expressed in terms of a single parameter P. Accordingly, each lattice position $D_{i,j}$ may assume one of the following values:

$D_{i,j} = 0$; if the site is occupied by a B molecule
$D_{i,j} = P^k$; if the site is occupied by an A molecule and k nearest neighbors are B molecules.

The parameter $P = \exp(\Delta E_m/RT)$ is a Boltzmann exponent proportional to $\Delta E_m = E_{AB} - \frac{1}{2} E_{AA} - \frac{1}{2} E_{BB}$, the excess energy of mixing. If ΔE_m is positive the formation of A-B bonds will be difficult and like molecules will have the tendency to aggregate; in this case $P > 1$. If, on the other hand, $\Delta E_m < 0$ A-B

bonds will be energetically preferred over A-A and B-B bonds. The case for which $\Delta E_m = 0$ ($P = 1$) defines the ideal mixture in which the molecules are distributed randomly. Thus, by appropriately selecting the value of P, molecular distributions as a function of the composition and neighbor-neighbor interactions can be obtained.

Theory

Consider a multicomponent lipid bilayer of N_T lipid molecules of which N_k are of species k. The distribution of these molecules along the plane of each monolayer will create clusters or domains of various compositions and sizes. A molecular cluster of type k and size n_k can be formally defined as a collection of n molecules of type k linked together by nearest-neighbor bonds, such that no k molecule outside the cluster is joined by a path of k-k bonds to any of the molecules inside the cluster; i.e., two k molecules belong to the same cluster, if and only if they are connected by at least one path of k-k bonds. Obviously, N_k satisfies the relation

$$N_k = \sum_{n_k} n_k M(n_k) \tag{1}$$

where $M(n_k)$ is the number of k clusters of size n. A straightforward generalization for the total number of molecules gives,

$$N_T = \sum_k N_k = \sum_k \sum_{n_k} n_k M(n_k) \tag{2}$$

The set of numbers $M(n_k)$ defines the cluster distribution function of the system. For binary mixtures of lipids these numbers can be deduced from Monte Carlo calculations based upon the parameters obtained from the experimental phase diagrams of these mixtures [11]. Typical cluster distributions for the gel and liquid crystalline phases of dimyristoyl-distearoyl phosphatidylcholine are schematically shown in Fig. 1. In this figure, the number of dimyristoyl phosphatidylcholine lipid molecules in clusters of size n in a 70×70 lipid monolayer has been plotted as a function of the cluster size for various dimyristoyl phosphatidylcholine mole fractions. This lipid mixture was chosen because it behaves almost ideally in the liquid crystalline phase but shows significant amounts of lateral species separation in the gel phase. Previously [11] we have calculated P as 1.35 for the liquid crystalline phase and P as 3.0 for the gel phase of dimyristoyl-distearoyl phosphatidylcholine.

Several features can be deduced from the distributions shown in Fig. 1. At low concentrations ($X_{DMPC} = 0.2$) most of the lipid molecules exist either in the monomeric state or form very small clusters. As the concentration increases ($X_{DMPC} = 0.4$), clusters of larger sizes begin to appear; the greater the value of P, the larger the number of molecules populating these clusters. It must be noted that none of these clusters contains a significant fraction of the total number of molecules; as shown in the figure, this concentration region is chacterized by the presence of a relatively large number of clusters of medium size. At $X_{DMPC} = 0.5$ a drastic change in the distribution pattern occurs. This change is characterized by a very rapid increase in the fraction of lipids popu-

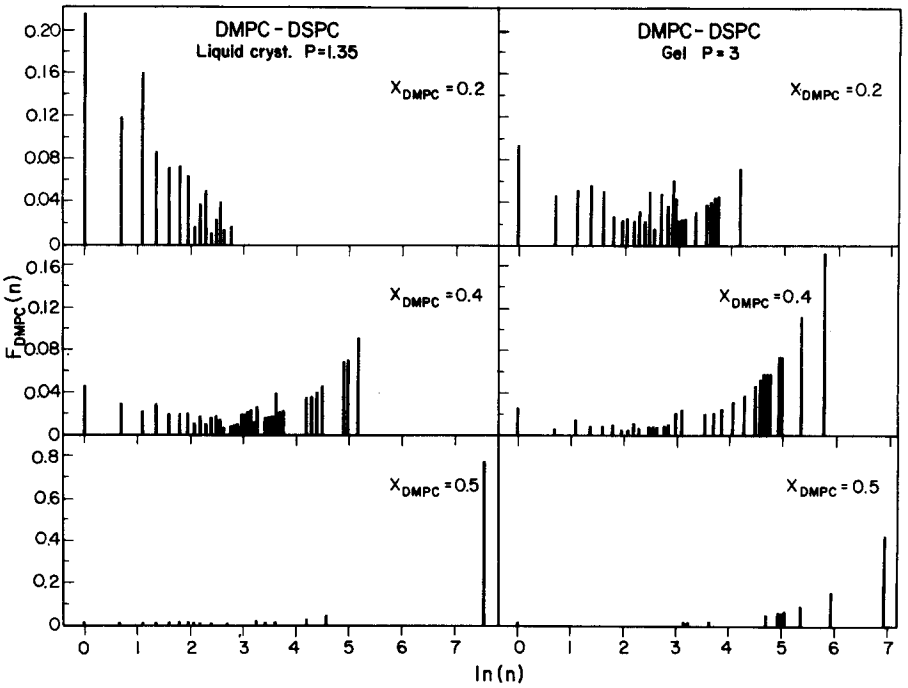

Fig. 1. Typical cluster distribution for dimyristoyl phosphatidylcholine (DMPC) in dimyristoyl-distearoyl phosphatidylcholine (DMPC-DSPC) mixtures of various compositions. Shown are the fractions of dimyristoyl phosphatidylcholine molecules in clusters of size *n* as a function of ln(*n*) in the gel and liquid crystalline phases.

lating the largest cluster and is more dramatic for the liquid crystalline (P = 1.35) than for the gel phase (P = 3.0). The concentration at which this phenomenon occurs defines the percolation point [12] which for a triangular lattice and P equal to 1 is exactly 0.5. At the critical percolation concentration the probability that all molecules belong to the same cluster and the probability that any two points are connected by a path of nearest neighbor bonds are finite. This behavior is dramatically illustrated in Fig. 2, where the fraction of

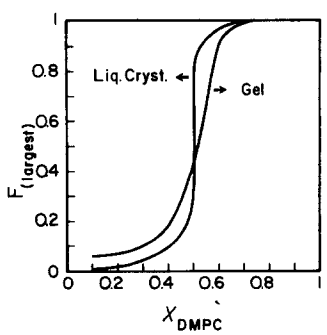

Fig. 2. Fraction of dimyristoyl phosphatidylcholine (DMPC) molecules in the largest dimyristoyl phosphatidylcholine cluster as a function of the mole fraction of dimyristoyl phosphatidylcholine for dimyristoyl-distearoyl phosphatidylcholine (DMPC-DSPC) in the gel and liquid crystalline phases.

TABLE I

LATERAL DISTRIBUTION PARAMETERS FOR DIMYRISTOYL-DISTEAROYL PHOSPHATIDYLCHOLINE IN THE GEL AND LIQUID CRYSTALLINE PHASES

$X_{DMPC\text{-}DMPC}$, fraction of DMPC-DMPC contacts. $\langle l_{DMPC} \rangle$, average cluster size. λ_{DMPC}, coefficient of compactness. ξ_{DMPC}, correlation length. $\xi_{C,DMPC}$, connectedness length.

X_{DMPC}	$X_{DMPC\text{-}DMPC}$		$\langle l_{DMPC} \rangle$		λ_{DMPC}		ξ_{DMPC}		$\xi_{C,DMPC}$	
	Gel	Liquid Crystal.	Gel	Liquid Crystal.	Gel	Liquid Crystal.	Gel	Liquid Crystal.	Gel	Liquid Crystal.
0.2	0.49	0.25	5.1	2.5	0.60	0.20	1.4	1.2	3.8	2.2
0.4	0.70	0.48	18.7	10.6	0.71	0.32	1.9	1.4	6.8	7.3
0.5	0.77	0.57	39.3	29.8	0.75	0.38	2.6	1.7	12.7	19.9

molecules in the largest dimyristoyl phosphatidylcholine cluster has been plotted as a function of the molar composition of the mixture.

As shown in Fig. 1, the size of the largest cluster, at $X_{DMPC} = 0.5$, is greater for the liquid crystalline than for the gel phase, even though the number of dimyristoyl-distearoyl phosphatidylcholine contacts is larger in the gel phase. This behavior, which is summarized in Table I, is a consequence of the fact that clusters of a given size can be formed with different number of bonds. In the gel phase, compositional clusters of a given size are, on the average, formed with a larger number of internal bonds than in the liquid crystalline phase; therefore, these clusters are more compact and have a smaller perimeter/surface ratio. In the liquid crystalline phase the compositional clusters are more ramified and therefore they extend over longer distances than in the gel phase. These differences in the compactness and connectivity properties of the compositional clusters and the changes in the correlation length are the most important differences in the equilibrium lateral distribution of molecules in the gel and liquid crystalline phases of phosphatidylcholine mixtures.

Cyclomatic number

The degree of compactness or ramification of a cluster can be studied by considering the relations between the number of like nearest-neighbor bonds (n_{kk}) and the number of molecules forming a cluster. These relations have been theoretically studied within the context of graph theory and can be expressed in terms of the cyclomatic number $C(n_k, n_{kk})$ of a cluster of size n_k . $C(n_k, n_{kk})$ is defined by the equation [13]

$$C(n_k, n_{kk}) = n_{kk} - n_k + 1 \tag{3}$$

and is equal to zero for a linear or completely ramified cluster and equal to one for a simply polygon. The coefficient of compactness of a cluster, λ, is defined as [13]

$$\lambda = \frac{C(n_k, n_{kk})}{C(n_k, \max)} \tag{4}$$

where $C(n_k, \max)$ is the cyclomatic number of the most compact configuration

CONFIGURATION	n_{kk}	$C(7,n_{kk})$	λ
	6	0	0
	7	1	$\frac{1}{6}$
	8	2	$\frac{1}{3}$
	9	3	$\frac{1}{2}$
	10	4	$\frac{2}{3}$
	11	5	$\frac{5}{6}$
	12	6	1

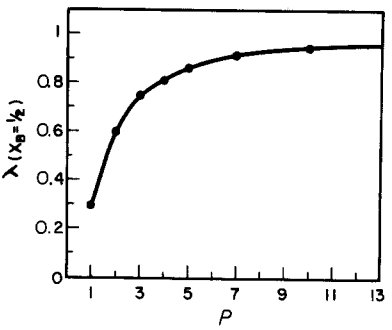

Fig. 3. Typical configurations of a cluster of seven molecules and n_{kk} bonds. The cyclomatic number and the coefficient of compactness are shown on the right side of the figure.

Fig. 4. Average coefficient of compactness, λ, as a function of the Boltzmann exponent, P, for an equimolar mixture.

of a cluster of size n_k. This quantity is equal to zero for a completely ramified cluster and equal to one for the most compact cluster. These concepts are illustrated in Fig. 3 for a cluster of seven molecules. On a triangular lattice with $n_k > 6$ the cyclomatic number of the most compact cluster can be approximated by the formula (see Appendix):

$$C(n_k, \max) = 2(n_k - 1) - 3[(1 + \tfrac{4}{3}(n_k - 1))^{1/2} - 1] \tag{5}$$

The above expression is exact for $n_k = 1 + 3b(b + 1)$ [$b = 1, 2, 3, \ldots$] so that no systematic deviations are observed in any size range.

In Fig. 4 the average coefficient of compactness λ has been plotted as a function of the Boltzmann factor, P, for an equimolar mixture ($X_B = X_A = 0.5$). As can be deduced from the figure, λ is a very sensitive function of P within the range $1 \leqslant P \leqslant 5$, which is precisely the range where most P values for phosphatidylcholines are found [11]. As noted before, the mean cluster size is, within this P range, a very insensitive function of P, however, the compactness of the clusters changes drastically. For the liquid crystalline phase of dimyristoyl-distearoyl phosphatidylcholine we estimate $\lambda = 0.38$ at $X_{DMPC} = 0.5$, whereas for the gel phase $\lambda = 0.75$; i.e. in the gel phase the compositional clusters are about twice as compact as in the liquid crystalline phase.

In general, equimolar mixtures of lipids with $P \sim 1$ are characterized by the presence of a large number of small clusters and a single, very ramified percolating cluster which contains most of the lipid molecules and extends over most of the bilayer. As discussed before, an increase in the value of P will increase the number of contacts between like molecules, creating a larger number of clusters of intermediate size with a higher degree of compactness. This process is achieved by joining small clusters into larger clusters and by breaking

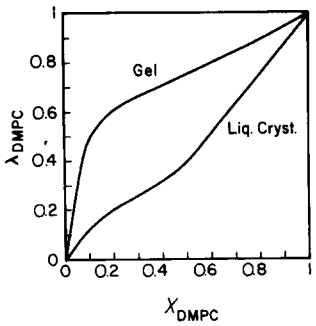

Fig. 5. Coefficient of compactness of dimyristoyl phosphatidylcholine (DMPC) clusters as a function of the mole fraction of dimyristoyl phosphatidylcholine for dimyristoyl-distearoyl phosphatidylcholine (DMPC-DSPC) mixtures in the gel and liquid crystalline phases.

the highly ramified percolating cluster into smaller but more compact clusters. For a small increase of P the number of clusters remains about the same and therefore the average cluster size does not change appreciably. This situation characterizes the liquid crystalline to gel transformation of equimolar mixtures of phosphatidylcholines.

As summarized in Table I, the coefficient of compactness is an increasing function of the molar composition of the mixtures. For a given value of P the compactness of the compositional clusters is smaller at low molecular densities and increases steadily until reaching its final value of unity for the pure system. As shown in Fig. 5 the dependence of λ on the composition is also a function of P. In this figure, the average coefficient of compactness of dimyristoyl phosphatidylcholine clusters in the gel and liquid crystalline phases of dimyristoyl-distearoyl phosphatidylcholine has been plotted as a function of X_{DMPC}. This graph allows calculation of compactness changes accompanying the gel-liquid crystalline transition at any dimyristoyl phosphatidylcholine mole fraction.

Pair correlation and pair connectedness functions

At fixed molecular compositions, changes in the compactness or ramification of the compositional clusters will greatly influence the physical extension of the compositional regions along the plane of the bilayer. In this respect, the existence of a highly ramified percolating cluster insures that most of the membrane surface will be covered by a network of nearest-neighbor bonds between like molecules. Conversely, the presence of highly compact clusters will define regions of very specific composition resembling compositional islands within the bilalyer lattice. Thus, changes in cluster compactness are intimately related to changes in the lateral connectivity of compositional regions.

These properties of the bilayer can be studied in terms of the pair correlation and pair connectedness functions. The pair correlation function, $g_{k,k}(d)$, is defined by the equation [11]

$$P_{k,k}(d) = X_k^2 g_{k,k}(d) \tag{6}$$

and is related to the probability $P_{k,k}(d)$ that two molecules at distance, d, are k molecules. $g_{k,k}(d)$ is equal to one for a random mixture and greater than one for an attractive potential. The pair connectedness function $C_{k,k}(d)$ is equal to the probability that two k molecules separated by a distance d belong to the same cluster (i.e. the probability that two k molecules at a distance d are connected by a path of k-k bonds). Thus, $C_{k,k}(d)$ measures the physical extension of the compositional clusters. $C_{k,k}(d)$ can be written in terms of Eqn. 6 as:

$$P_{k,k}(d) = X_k^2 g_{k,k}(d)[C_{k,k}(d) + D_{k,k}(d)] \tag{7}$$

where $C_{k,k}(d) + D_{k,k}(d) = 1$. $D_{k,k}(d)$ is called a blocking function [14] and is, by definition, equal to the probability that two k molecules at a distance d are not connected by a path of k-k bonds. The correlation length, ξ_k, and the connectedness length $\xi_{c,k}$ are defined by the equations [11,14,15]

$$\xi_k^2 = \frac{\sum_d d^2 (g_{k,k}(d) - 1)}{\sum_d (g_{k,k}(d) - 1)} \tag{8}$$

$$\xi_{c,k}^2 = \frac{\sum_d d^2 C_{k,k}(d)}{\sum_d C_{k,k}(d)} \tag{9}$$

and can be calculated by counting directly the total number of like molecules separated by a distance d, and the number of these molecules that belong to the same cluster. The pair correlation function and the correlation length for dimyristoyl phosphatidylcholine in the gel and liquid crystalline phases of

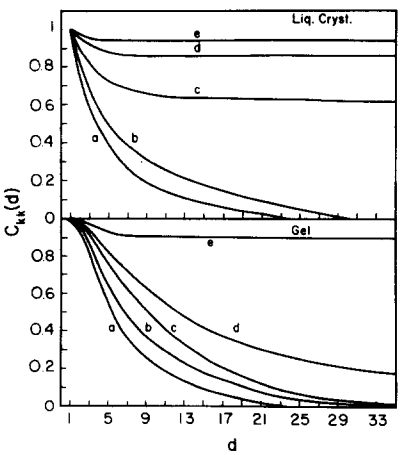

Fig. 6. Pair connectedness function $C_{kk}(d)$ as a function of the separation distance, d, (in number of molecules) for dimyristoyl-distearoyl phosphatidylcholine (DMPC-DSPC) in the gel and liquid crystalline phases. The dimyristoyl phosphatidylcholine (DMPC) mole fractions are a, 0.4; b, 0.45; c, 0.5; d, 0.55 and e, 0.6.

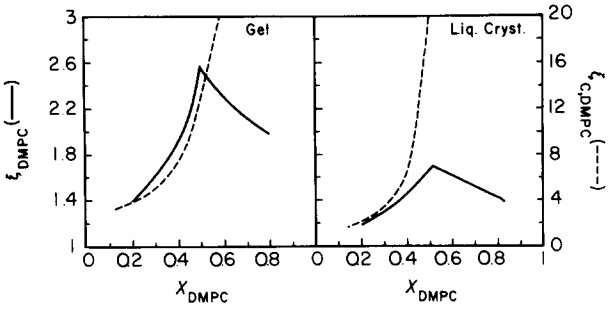

Fig. 7. Correlation length, ξ_{DMPC}, (solid line) and connectedness length, $\xi_{C,DMPC}$, (dotted line) as a function of the mole fraction of dimyristoyl phosphatidylcholine (DMPC) for dimyristoyl-distearoyl phosphatidylcholine (DMPC-DSPC) mixtures in the gel and liquid crystalline phases.

dimyristoyl-distearoyl phosphatidylcholine mixtures of various molar compositions have been analyzed in a previous communication [11]. The pair correlation function has a pronounced maximum at the nearest neighbor separation distance and decays asymptotically to 1 as the separation between molecules increases. For a random mixture, in which each molecule behaves independently of the others, the pair correlation function is equal to 1 at any distance. Thus, the correlation length defines the effective ditance over which a molecule influences the behavior of another molecule and as such it measures the magnitude of the cooperative interactions.

The pair connectedness function, as opposed to the pair correlation function, measures the physical extension of the compositional clusters. As shown in fig. 6, at low dimyristoyl phosphatidylcholine mole fractions $C_{k,k}(d)$ decays asymptotically to zero with distance; however, at some critical dimyristoyl phosphatidylcholine mole fraction the pair connectedness function no longer decays to zero but to some finite positive value. This critical mole fraction coincides with the percolation point and is characterized by the fact that most of the dimyristoyl phosphatidylcholine molecules are connected by a network of nearest neighbor bonds which extends over the entire bilayer. As illustrated in the figure, the critical percolation point occurs at a lower dimyristoyl phosphatidylcholine mole fraction in the liquid crystalline phase.

In Fig. 7 the correlation length and the connectedness length have been plotted as a function of X_{DMPC} for the gel and liquid crystalline phases of dimyristoyl-distearoyl phosphatidylcholine. As can be observed in the figure, the connectedness length is always greater than the correlation length, in agreement with recent theoretical results by Coniglio et al. [14,16]. At low dimyristoyl phosphatidylcholine mole fractions the connectedness length is larger in the gel than in the liquid crystalline phase; however, this behavior is reversed at higher concentrations. At the critical percolation point, the connectedness length diverges, indicating that most of the dimyristoyl phosphatidylcholine molecules belong to a single percolating cluster which extends over the entire bilayer surface. At this point the lateral connectivity of the bilayer is also maximal.

Discussion

Recently, several attempts have been made to characterize the lateral distribution of molecules in binary mixtures of lipids and single component bilayers undergoing a phase transition. Those studies have primarily focused on the calculation of phase boundaries and average cluster sizes under different physicochemical conditions [7—11,17]. While the cluster model appears to be an adequate representation of the bilayer, the specification of only two parameters is not sufficient for a complete characterization of the system. The inadequacy of the average cluster size to provide by itself an accurate representation of the bilayer can be demonstrated by examining the cluster distribution function. The character of this distribution is such that the most probable cluster size is not equal to the arithmetic mean and as such this latter quantity is not representative of the 'average cluster'. As we have shown, it is possible to induce relatively large changes in the organization of the bilayer without affecting the average cluster size.

The lateral distribution of molecules in a lipid bilayer is dictated by the energetics of the interactions between components. The magnitude of these interactions, which can be expressed in terms of the excess energy of mixing, ΔE_m, or the Boltzmann exponent $P = \exp(\Delta E_m/kT)$, will determine the total number of like and unlike contacts between molecules. This excess energy of mixing can be affected by changes in the physical state of the bilayer and/or changes in external physicochemical variables, thus triggering lateral reorganization processes within the membrane.

Since each lipid molecule has on the average six nearest neighbors, the system will respond to a change in ΔE_m by changing the number of bonds with which clusters of a given size are formed and by changing the total number of clusters. The first of these processes leaves the number of clusters invariant and therefore does not affect the average cluster size. The second process will increase or decrease the average cluster size depending on the sign of the change in ΔE_m. The overall characteristics of the lateral reorganization will depend on the balance between these two processes. Small changes in ΔE_m ($1 \leqslant P \leqslant 5$), like those associated with the phase transitions of phosphatidylcholine mixtures, will affect primarily the compactness of the compositional clusters and the shape of the cluster distribution without a major effect on the average cluster size.

Changes in the number of bonds with which clusters of a given size are formed will affect the physical extension of the compositional domains within the bilayer. In general, highly compact clusters will be constrained to small regions of the bilayer whereas highly ramified clusters will extend over longer distances. As shown in Figs. 2 and 7, there is a critical molar composition at which the connectedness length diverges and a network of like molecules connected by nearest-neighbor bonds covers the entire bilayer. This percolation process occurs very abruptly over a very narrow composition range and is influenced by the magnitude of ΔE_m.

Previously, different transport processes in biological membranes have been associated with parameters describing the lateral distribution of molecules within the bilayer. In particular, permeability processes across the membrane

have been associated with phase boundaries and local density fluctuations. These quantities are maximal at the phase transition or under conditions of phase separation and as such they have been correlated with the enhanced bilayer permeability observed at the transition temperature. This enhanced permeability, however, might not be the only process affected by the organization of the bilayer. Recently, Galla et al. [18] have suggested that the spread of solute molecules within the plane of the bilayer via lateral diffusion will also be affected by the lateral organization of the membrane. For example, it is conceivable that the efficiency with which a solute molecule is spread throughout the membrane will be maximal at the percolation point of the lipid component in which the solute molecule has a maximal solubility. A highly ramified network of lipid molecules will be much more effective in distributing a solute molecule over the entire membrane than highly compact domains localized to smaller regions of the membrane.

These studies constitute an initial attempt to develop a unified theory of the lateral organization of the membrane in terms of the size distribution and spatial localization of compositional domains. As we have shown for the case of phosphatidylcholine mixtures, this characterization can be achieved by defining the cluster distribution function, the coefficient of compactness and the pair correlation and pair connectedness functions. For binary mixtures these quantities can be estimated from phase diagrams or the composition dependence of other physicochemical parameters (Snyder, B. and Freire, E., unpublished data). More complex systems can also be analyzed with this formalism. Recently, Pearson et al. [19] have demonstrated that the radial distribution function for intramembranous particles in red blood cells can be evaluated from freeze-fracture electron micrographs. This type of analysis is similar to the one developed here and provides the basis for a rigorous characterization of the organization of biological membranes.

Appendix

The most compact configuration of a cluster. The most compact configuration of a cluster of n_k molecules of type k in a triangular lattice is an hexagon. This configuration can only be achieved when n_k satisfy the relation $n_k = 1 + 3b(b + 1)$, $[b = 1, 2, 3, ...]$, from which it follows that the smallest hexagon can be formed with seven molecules (see Fig. 3). For this hexagonal configuration, n_k and the number of molecules at the boundary of the cluster, n_{bound}, are related by the equation:

$$n_{bound} = 3\,[(1 + \tfrac{4}{3}(n_k - 1))^{1/2} - 1]$$

Similarily, the number of bonds between like molecules, n_{kk}, is equal to:

$$n_{kk} = 3n_k - \tfrac{1}{2}\,n_{ky}$$

where n_{ky} is the number of bonds between unlike molecules and is equal to

$$n_{ky} = 6 + 2\,n_{bound}$$

It follows that the cyclomatic number of the most compact configuration is:

$$C(n_{k,max}) = n_{kk} - n_k + 1$$
$$= 2(n_k - 1) - 3[(1 + \tfrac{4}{3}(n_k - 1))^{1/2} - 1]$$

which is the equation used in the text.

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