Biochimica et Biophysica Acta, 433 (1976) 264–270

BBA 77278

COMPUTER SIMULATION OF MODEL LIPID MEMBRANE DYNAMICS

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(Received September 25th, 1975)

SUMMARY

The motions of individual lipid molecules in a model membrane have been studied by computer simulation using the molecular dynamics technique. The intermolecular forces were of both the Lennard-Jones and the Coulomb type. The influence of temperature and electrical screening on the order-disorder transition was examined, and it was also found that this transition is initiated by the spontaneous generation of disclinations.

(1) INTRODUCTION

This communication is a preliminary report on what appears to be the first attempt to study the dynamics of a biological membrane by computer simulation. The studies were carried out using the technique of molecular dynamics, and the specific goal was an investigation of the physical processes which underly the temperature and pH dependence of the structural transition in the membrane. Recent experimental studies have revealed that both these factors have an influence on the diffusive properties of the phospholipid membrane [1]. The work also revealed details of the way in which the transition occurs.

The model used in this first investigation was highly idealized. Although biological membranes consist of two lipid layers, the present model was simply a monolayer. This approach is therefore strictly only applicable to the case in which the two layers function fairly independently. The individual molecules were in the form of rigid cylinders with a dumbell cross section, the two ends of the dumbell corresponding to the two hydrocarbon chains. The limitations imposed by the size of the computer memory precluded allowing for the flexibility of the individual hydrocarbon chains, but the effect of a *trans-gauche* rotation in any chain could be allowed for by changing some of the parameters in the local intermolecular interaction, as described later. The use of rigid cylinder molecules essentially reduces the problem to two dimensions, and the pictures appearing in Sections 2 and 3 of this paper are to be regarded as plan views of the membrane as seen from above.

Although the simulation is admittedly based on a grossly simplified model, it does reveal certain aspects of many-body behavior that are distinctly non-trivial.

Moreover, the effects observed are related specifically to the special conditions of geometry and intermolecular force that exist in a lipid membrane. Because of this, it is felt that the present study contributes to the understanding of the physical principles underlying membrane behavior. It also constitutes an appropriate starting point for the development of more realistic model studies using the same general approach.

(2) COMPUTER MODEL AND SIMULATIONAL TECHNIQUE

The zero-temperature structure of the model membrane was a crystalline lattice in which the hydrocarbon chains (i.e. the ends of the molecular dumbells) formed a regular hexagonal array. The polar head groups, which in the figures are represented by the lines joining pairs of hydrocarbon chains, were initially all parallel (see for instance ref. 2). Limitations of the size of the computer memory require one to use the device of periodic boundary conditions, so that the simulation is of a pseudo-infinite membrane. The initial situation is shown in Fig. 1, and the two pairs of lines (one pair horizontal and one pair vertical) indicate the periodic boundaries. These boundaries have, of course, no absolute position in space and can be drawn at any position so long as their relative distances and angles remain unchanged. In the present simulation the irreducible cell defined by the periodic boundaries contained 240 molecules.

The molecular dynamics simulational technique is simply an iterative digitalized method for solving the equations of motion of the individual molecules in a condensed assembly (see for example ref. 3). Each molecule is allowed to interact with all other molecules that lie within a given distance. This truncation of the inter-

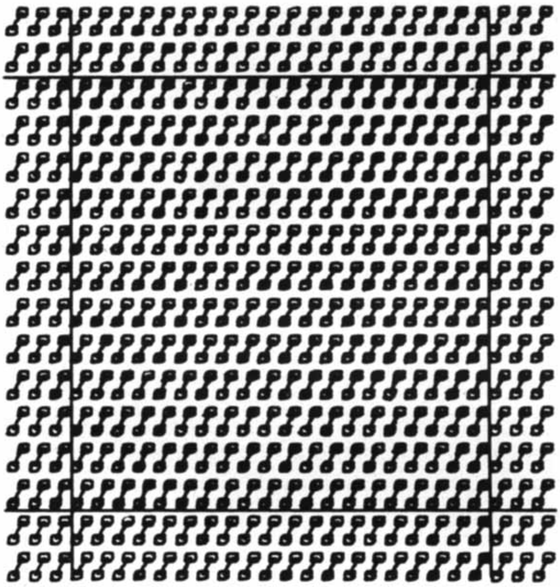

Fig. 1. The initial situation in the model membrane, showing the arrangement of the phospholipid molecules and the periodic boundaries.

action sphere keeps the computational time within manageable proportions. The intermolecular interactions were of two distinct types. Firstly it was assumed that the individual hydrocarbon chains interacted with one another with both short-range repulsions and longer-ranged Van der Waals attractions. These two factors were combined in the familiar way by using a Lennard-Jones potential of the form

$$V_{\mathrm{LJ}}(r_{ab}) = \varepsilon[(\sigma/r_{ab})^{12} - 2(\sigma/r_{ab})^{6}] \tag{1}$$

where r_{ab} is the distance between the a'th and b'th hydrocarbon chains, ε is an energy parameter (the well depth of the interaction), and σ is a distance parameter (approximately equal to the Pauling ionic radius). This potential applied to all interactions between hydrocarbon chains except the two chains within a given molecule, since the molecules were assumed to be perfectly rigid. The other interactions were those between the polar heads. Part of the head-head interaction does of course occur through the Lennard-Jones potential since the molecules are rigid. In addition there is the effect of the extra charges on the head groups, which produces a Coulomb interaction of the type

$$V_{\mathrm{C}}(r_{ij}) = q_i q_j / r_{ij} \tag{2}$$

where q_i and q_j are the effective charges on the i'th and j'th molecules, respectively, and r_{ij} is the separation distance between their centers of gravity. In the present situation all the charges always had the same sign and magnitude, so the Coulomb forces were always repulsive. A change in the magnitude of the charges simulates changes in pH since the latter alters the degree of screening of the polar head groups.

As a result of the various forces that act upon them, and because they are rigid, the individual molecules have both translational and rotational motion. The coupled simultaneous differential equations that apply to this situation are the Newton-Euler equations

$$\begin{aligned} F_{xi} &= M_i \ddot{x}_i \\ F_{yi} &= M_i \ddot{y}_i \\ N_i &= I_i \omega_i \end{aligned} \tag{3}$$

where F_{xi} and F_{yi} are the components of force on the i'th molecule in the x and y direction, respectively, N_i the corresponding torque, x_i and y_i the coordinates of the center of gravity of the i'th molecule, and ω its angular velocity ($= \mathrm{d}\theta/\mathrm{d}t$). M and I are, respectively, the mass and moment of inertia. The forces (and torques) are derived from

$$F_i = \sum_j -\mathrm{grad}\, V_{ij}(x_i, y_i, \theta_i, x_j, y_j, \theta_j) \tag{4}$$

where V_{ij} contains both the Lennard-Jones and Coulomb components. The increments in position and angle of the molecules are found by developing these parameters in a Taylor series, the final result being

$$\begin{aligned} r_i(t+\Delta t) &= 2\, r_i(t) - r_i(t-\Delta t) + r_i(t)(\Delta t)^2 \\ \omega_i(t+\Delta t) &= \omega_i(t) + N_i\, \Delta t / I_i \end{aligned} \tag{5}$$

where fourth and higher order terms have been neglected. The time step, Δt, can be used as a reduced variable, as discussed later. The temperature of the system, T, follows immediately (if one assumes completely classical behavior) from

$$2\,nk_{\mathrm{B}}T = \sum_i (M_i/2)\,(\dot{r}_i)^2 + \sum_i (I_i/2)\omega_i^2 \tag{6}$$

where n is the number of molecules in the irreducible cell and k_{B} is Boltzmann's constant. Finally, the pressure of the system, P, follows from Clausius' virial theorem and is given by

$$P = \rho k_{\mathrm{B}}T - \frac{\rho}{8n}\sum_i\sum_j r_i \frac{\delta}{\delta r_i} V_{ij} \tag{7}$$

ρ being the number density (i.e. number of molecules per unit area.) The temperature of the system can be varied simply by varying all the translational and angular velocities by the same factor, while the pressure in the system is varied by varying all the distances uniformly.

In an iterative computation of this type the maximum permissible size of the time increment is related to the highest instantaneous force that can occur in the system. The greater this force is the greater will be the tendency for the system to accumulate computational error. This latter usually manifests itself in a failure of the system to conserve energy (when no energy is being intentionally added to or withdrawn from it), and this is often accompanied by an "explosion" of the assembly of molecules. It is not difficult to show that the maximum allowable Δt is given by

$$\Delta t < 2\left(-\left(\frac{\mathrm{d}F}{\mathrm{d}r}\right)_{\max}\Big/ M\right)^{-\frac{1}{2}} \tag{8}$$

and by an analogous expression for the torques. $(\mathrm{d}F/\mathrm{d}r)_{\max}$ is the maximum derivative of the force. One sees that Δt can be increased both by increasing M and by lowering $(\mathrm{d}F/\mathrm{d}r)_{\max}$. The latter can in turn be achieved either by decreasing the strengths of the individual components of the potential or by simply making F a constant for all distances less than a certain precalculated radius. In the present calculation Δt was used in the form of a reduced variable, and the molecular mass and moment of inertia were adjusted so as to cause changes to occur in the system within the duration of computational runs of a few thousand time steps. Diffusive processes occur in real membranes on a time scale of 10^{-6}–10^{-8} s. The computational time step is therefore equivalent to approx. 10^{-10} s of real time. The other input variables were the well depth and distance parameter of the Lennard-Jones potential, and the effective charges on the head groups. For a variety of initial values the model was heated up until a transition was observed to a disordered state. By periodically plotting out all the molecular positions it was possible to follow the temporal evolution of the system.

(3) RESULTS

The technique described in the previous section has been used in a number of simulations with various relative values of the input parameters. In general it was found that an order-disorder transition occurred when the temperature rose above

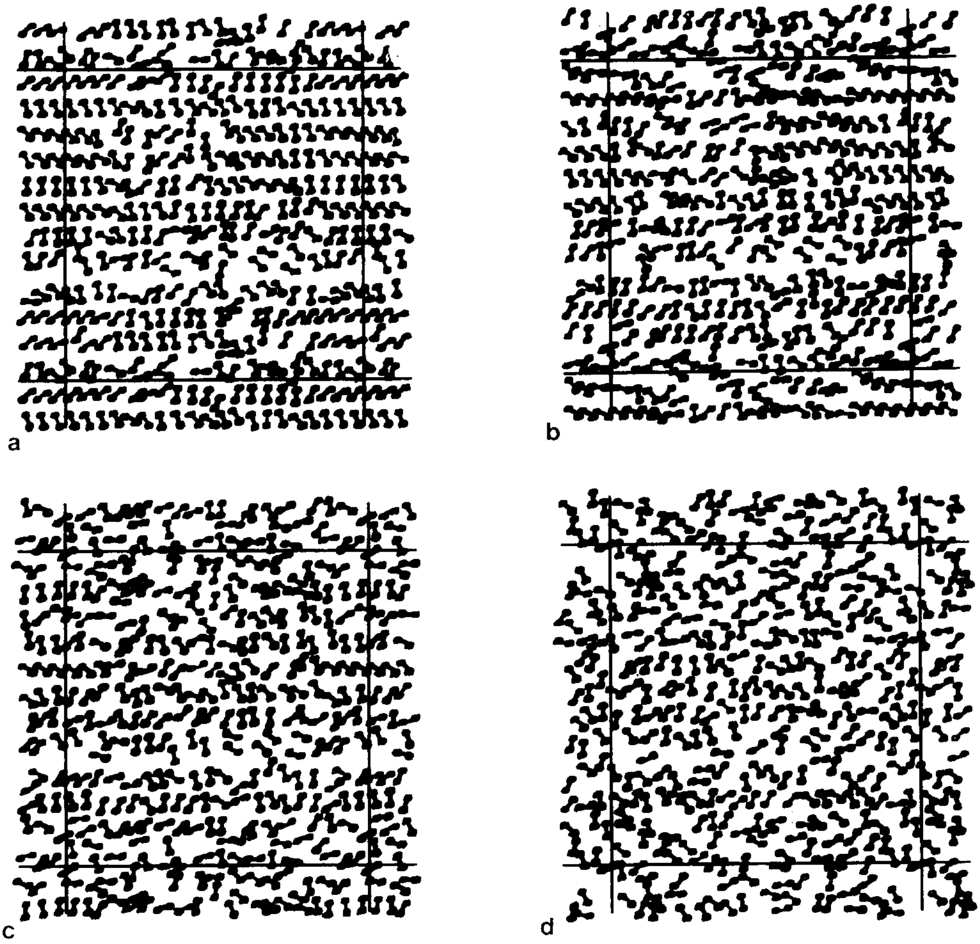

Fig. 2. Instantaneous situations during the order-disorder transition of a membrane near room temperature. The time interval between adjacent pictures in the sequence is approx. 10^2 time steps.

a certain value, this transition temperature being a function of the input variables as will be discussed below. The disorder invariably set in at one particular location and then rapidly spread to other parts of the model (usually within about 10^3 time steps). The sequence of Figs. 2a–2d shows an example of this occurring, the time interval between adjacent pictures in the sequence being 10^2 time steps. The simulations were run at constant pressure so it was possible to determine what changes of density are associated with the transition. It was found that for transition temperatures around room temperature the density falls by roughly 10 %. The disordered state was usually reminiscent of an isotropic and uniformly dense liquid. No tendency to form a two-dimensional liquid crystal was observed, but this does not rule out the possibility that such a state could exist under appropriate conditions.

The systematic study of the influence of the various initial parameters established the following trends: (i) An increase in the charges led to a decrease in the transition temperature. (ii) An increase in the well depth parameter of the

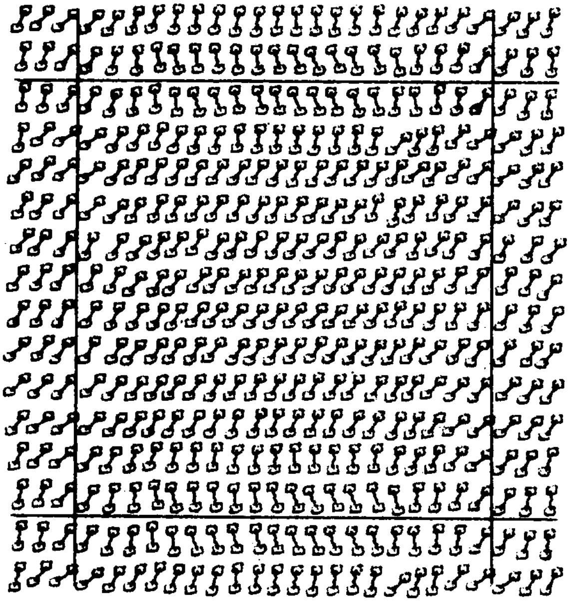

Fig. 3. Molecular arrangement at a very early stage of the disordering process. Note that portions of two of the rows of molecules have flipped over, producing disclinations.

Lennard-Jones interaction produced an increase in the transition temperature. (iii) Particularly interesting is the fact that transition temperatures in the vicinity of room temperature are obtained when the magnitudes of the Lennard-Jones and Coulomb forces are approximately equal for intermolecular separations in the range 80–100 % of the initial value at zero temperature.

A final point of interest concerns the observations of the very early stages of the order-disorder transition. Fig. 3 shows such a situation. It can be seen that some of the molecules have flipped over through about 60 degrees. This has happened to parts of the two rows along the horizontal periodic boundaries. (Their location near the boundaries is fortuitous, since the latter have no absolute locations.) This produces defects known as "disclinations" (i.e. dislocations of angle, see ref. 4), which are located at the terminations of the flipped-over regions. It is apparent from Fig. 3 that the defect marks a region in which the molecular density is slightly lower than elsewhere.

(4) DISCUSSION

The general features of the transitions observed in these studies appear to be in basic agreement with the experimental investigations of Trauble and Eibl [5]. They observed that the transition temperature, as monitored by changes in membrane transport properties, is influenced by changes in pH. This would be expected to change the degree of screening of the charges on the polar head groups and hence the strength of their mutual repulsions. Since the pH will not have any influence on the strength of the Lennard-Jones interaction, it appears that this could be the agency that nature uses to maintain a balance getween the different forces. For a given pH value the transition will occur at a particular temperature. Conversely, for a fixed (and sufficiently high) temperature changes of pH of the correct magnitude can themselves drive the transition in either direction. It would be expected, however, that the time constants would be quite different; the order-disorder transition would be much faster than the disorder-order transition, because for the former any site can serve as the nucleus whereas in the latter there is only one possible final state of complete order. Preliminary studies did indeed reveal that no recrystallization of the membrane occurs during cooling even for computer runs having a duration ten times larger than those used to study the order-disorder transition. Finally, one should note that there are both local and non-local features of the membrane behavior.

As the pH changes, the repulsive forces throughout the membrane are modified, and this changes the pressure or, at constant pressure, the density (i.e. the spacing between adjacent molecules). This is a global effect, but local inhomogeneities will nevertheless make certain sites favorable for the nucleation of the initial defects of the type shown in Fig. 3.

ACKNOWLEDGMENTS

It is a pleasure to acknowledge the benefit of stimulating discussions with Peter Overath, Ove Sten-Knudsen and Herman Trauble. The computations were made possible by generous support from Statens Naturvidenskabelige Forskningsråd

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