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PATTERN FORMATION OF TWO-DIMENSIONAL MODEL PHOSPHOLIPID MOLECULES BY MOLECULAR DYNAMICS SIMULATION

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ABSTRACT

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In this work, we aim to present a model for phospholipid monolayers that attempts to illustrate some basic characteristics of lipid membranes such as pattern formation and phase transitions as a function of characteristic system parameters and interaction with a foreign molecule in the membrane by employing the molecular dynamics simulation technique. Since interactions which cause structural changes usually occur in the head group region of the membrane, a quasi three-dimensional model is developed to represent the surface formed by the head group of the phospholipid molecules. Interactions between the parts of the different head groups are taken as Lennard-Jones and Coulomb type. After establishing a set of system parameters, pattern formation and phase transitions are studied as functions of the temperature. A scaling argument is used to relate different regions of the parameter space. Finally a bulky molecule (Gramicidin-A like) is placed into the model surface layer and changes in the transition temperature due to its presence are investigated.

Keywords:Phospholipids,Phospholipid Membranes,Model Membranes, Pattern Formation,Molecular Dynamics Simulation,Computer Simulation

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ÖZ

MOLEKÜLER DİNAMİK SİMULASYONU İLE İKİ BOYUTLU MODEL FOSFOLİPİD MOLEKÜLLERİNİN YAPI OLUŞTURMALARININ İNCELENMESİ

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Bu çalışmada fosfolipid membranlar için bir model önerilmiştir. Bu modelle gerçek membranların gösterdiği bazı temel özellikler ve davranışlar incelenmiştir. Bu özelliklerden bazıları model parametrelerine bağlı olarak değişik yapılar oluşturmaları, faz geçişleri ve membranın yapısında bulunan diğer moleküllerle olan etkileşmesi sonucu yapıda meydana gelen değişikliklerdir. Bu özellikler moleküler dinamik simulasyon metodu ile çalışılmıştır. Membranların yapısında bulunan diğer moleküllerle ve çevresi ile olan etkileşmeleri genellikle membranların yüzeyinde olduğundan, fosfolipid baş gruplarının oluşturduğu yüzey iki boyutlu bir model olarak çalışılmıştır. Baş grupları arasındaki etkileşmeler Lennard-Jones ve Coulomb tipi etkileşmelerdir. Sistem parametreleri seçildikten sonra yüzeydeki yapı oluşumları ve faz geçişleri sıcaklığın bir fonksiyonu olarak çalışılmıştır. Farklı parametre setleri arasında ilişki kuran matematiksel bir formülasyon geliştirilmiştir. Bu formülasyon, çalışılacak sistemlerin parametrelerini tayin etmede büyük kolaylık sağlamaktadır. Son olarak yüzeye yabancı bir molekül eklenerek, bu molekülün yüzeye ve faz geçiş sıcaklığına olan etkisine bakılmıştır.

Anahtar Kelimeler:Fosfolipidler,Fosfolipid Membranlar,Model Membranlar,Yapı Oluşumu,Moleküler Dinamik Simulasyonu,Kompütür Simulasyonu

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CHAPTER I

INTRODUCTION

One of the most interesting problems of biochemistry and biophysics deals with the determination of the structure and stability of biological membranes [1-3]. In addition to the immense amount of experimental data, theoretical approaches also provide useful information to our understanding of membrane structure. Due to the complexity of the problem of large number of particles, the quantum mechanical methods are still not feasible. However, with the rapid developments in computer technology, the classical many-body problems can easily be treated and the use of computer simulation methods has greatly extended the range of problems to which the methods of statistical mechanics can usefully be applied [4]. Once the interactions between the constituent particles which can be atoms, molecules or ions, are described, classical simulation methods can be applied to the system of interest. Computer simulation is a way from microscopic properties of the system to macroscopic properties. It is also called as computer experiment or numerical experiment and it is like a bridge between theory and theoretical models and real experiments [4].

The most important and widely used simulation techniques are of two types: Molecular Dynamics (MD) [5], and Monte Carlo (MC) [6]. MD method is mostly used for the study of time-dependent processes and the observable properties of the system are calculated as time averages over the trajectories. In MC method, no time scale is involved. It is a useful method if only static properties are required. The desired property of the system is then calculated as ensemble average of a function of the particle coordinates.

The first computer "experiment" on a model of a solid was the simulation by Fermi, Pasta and Ulam [7]. The appearance of the paper by Metropolis, Rosenbluth, Rosenbluth, Teller and Teller [8] in 1953 is considered as the birth of computer simulation as a statistical-mechanical technique. This paper is very well-known for its introduction of the Monte Carlo method for the study of systems of interacting particles. The article by Alder and Wainwright [9] in 1957 is the first article in the literature of a Molecular Dynamics simulation.

It is aim of this work to establish a simple model for a biomembrane in order to study typical processes like phase transitions and pattern formations as function of model parameters and as function of temperature. The model should be as simple as possible because of the hugh amount of computer time needed for the Molecular Dynamics computations but complex enough to show the typical behaviours observed in phospholipid bilayers. In particular, the model should be able to allow the study of the influence of bulky molecules (such as proteins and polypeptides) in the phase transition temperature.

1.1 Biological Membranes

Electronmicroscopy has shown that cells and cellular components such as the nucleus, mitochondria and ribosomes are surrounded by distinct membranes which play a vital role in many ion-transport and metabolic processes [1]. The biochemical functions of the membranes and orientational information of fragments can be obtained either through intrinsic markers like enzymes and receptors or from electronmicroscopy and histochemical characterization. Membranes have a thickness of only a few molecular layers, and can be isolated as separate entities. These flexible structures separate the cell from its environment.

Many membranes have similar physico-chemical properties such as thickness, surface tension, electrical resistance, electrical capacitance, and water permeability. They undergo first order temperature dependent phase transition from gel to liquid state. Phase transition characteristics of the lipid membranes are studied extensively both theoretically and experimentally [10-29].

Membranes serve as barriers for solutes and water as they are more permeable to substances soluble in nonpolar solvents than to water soluble compounds. Depending on the type of the membrane, they are the determining factor for phenomena such as active transport, facilitated diffusion, and the selective transport of ions. The properties of cells such as excitability, impulse conduction, secretion and cell - cell interactions may also depend on membranes. Although they display similar organizational structures, membranes do differ morphologically, physiologically, biochemically and compositionally. The composition of membranes in vivo is preserved metabolically by biosynthesis and degradation as well as by fusion and recycling [2].

Biological membranes essentially consist of a two-dimensional matrix made up of a phospholipid bilayer interrupted and coated by proteins (Fig.1). Bilayer matrix can accommodate the wide range of constraints required for an interface between the relatively stable internal milieu of a cell and its changing external environment.

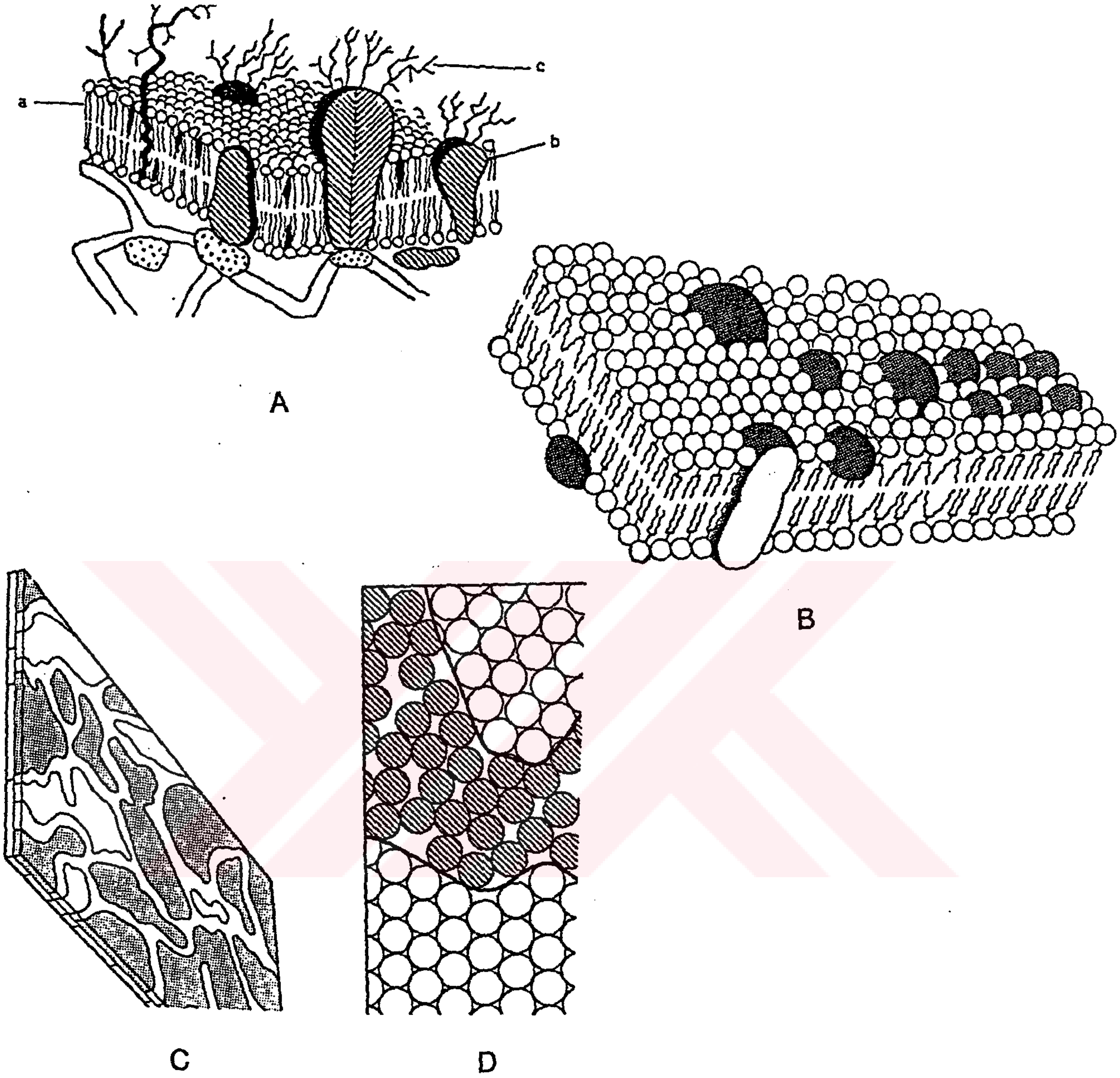


Figure 1. A) Lipid membrane with components (a) lipids (b) proteins (c) carbohydrates B) Organization of protein in bilayer matrix C) Topological view D) Top wiew of lipid molecules [2].

The interfacial region is usually more polar than the interior.Such an organization is a direct consequence of the hydrophobic effect, whereby the apolar acyl chain of lipids and the side chains of the nonpolar amino acid residues in proteins tend to be squeezed away from the aqueous phase. The forces which hold the components together in a bilayer matrix are largely of noncovalent nature. The hydrophobic effect as well as hydrogen bonding and electrostatic interactions make up the interaction energy which stabilizes the bilayer organization. The hydrophobic forces lead to energetically favourable conformations and self-aggregation of phospholipid molecules in a bilayer matrix.

Membrane lipids are arranged in two monomolecular layers (monolayers), in which the polar ends of the lipid molecules are directed outward and the nonpolar ends inward. The fatty acid chains of lipids in the membrane interior are most likely in a disordered state, approaching that of a liquid hydrocarbon. The disorder and fluidity of hydrocarbon chains in biological and model membranes depend mainly upon the temperature and length, the degree of unsaturation and the heterogeneity of the hydrocarbon chains.

The approximate size of membranes changes for different membranes and for different phases. The surface area per lipid molecule is in the range of 60-70 Å^2 at physiological temperature [1]. The inner and outer surface of membranes are asymmetric in structure and function. Some enzymes and antigens have been demonstrated to be present only on one side of the membrane. Electronmicroscopy of stained sections often shows differences in the density and width of the two layers (monolayers) of membranes.

The major components of the isolated membranes are lipid and protein. There is an excellent review of the theory of cooperative phenomena in lipid systems [30]. The predominant lipid fraction is phospholipid.

1.1.1 Phospholipids

Phospholipids are amphipathic molecules of approximately cylindrical shape with one polar group at one end of the long axis of the cylinder (Fig.2). One can notice the clear-cut difference between hydrophilic and hydrophobic (hydrocarbon chains) parts of the molecule. It also determines the tendency of phospholipid molecules to associate in the form of stacked bilayers.

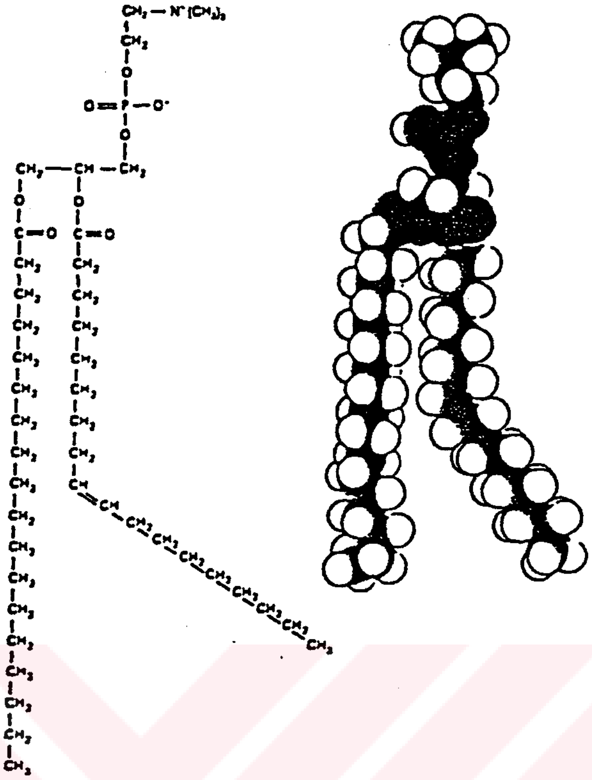


Figure 2. Phospholipid molecule

The nonpolar portion of the lipids in biomembranes is mostly made up of polymethylene chains. Covalently attached fatty acids form the bulk of the membrane lipids as acyl or alkyl derivatives. The polar head groups may be selected from a few distinct classes; however, it should be emphasized that the classes of lipids with the same polar groups but different fatty acids are truly different molecules with different metabolic and physical properties such as patterns of biosynthesis, transport, degradation and distribution. The functional differentiation of the structural variation in these lipids can be thought in terms of their stability and bipolarity, lower melting points due to branching, and the charged groups that could regulate the surface charge and hydration profiles of the bilayer. Still different classes of lipids found as membrane components have several features in common. They are amphipathic, i.e., the polar and apolar regions of the molecule are separate. In phospholipids, the polar regions comprise the glycerophosphocholine moiety and the two carboxyl ester groups. The apolar chains extend away from the plane of the head group (Fig.3).

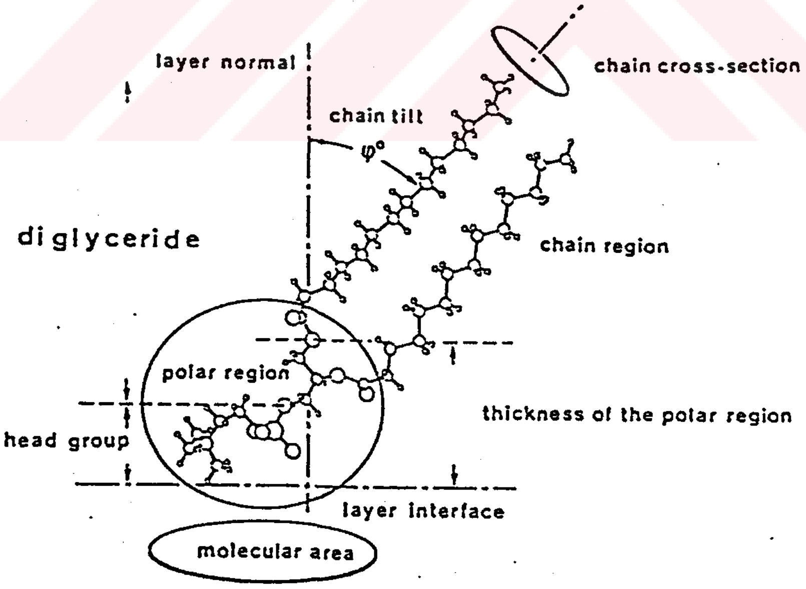


Figure 3. Anatomy of a phospholipid molecule [2].

It is possible to obtain detailed information on molecular conformation and packing of a variety of synthetic phospholipids from single crystal X-ray analysis [31-33], and also by spectroscopic methods which mainly work for solutions. Bilayer form is usually preferred in the crystalline anhydrous state as well as in aqueous dispersions with the hydrocarbon chains in crystals being stacked parallel to each other (Fig.4). The head group lies mostly parallel to the plane of the bilayer, and the chains are not equivalent. In such a packing, the projected area of the head group and that of the chains at the interface must match so as to achieve a cylindrical shape that is necessary for packing in a planar bilayer.

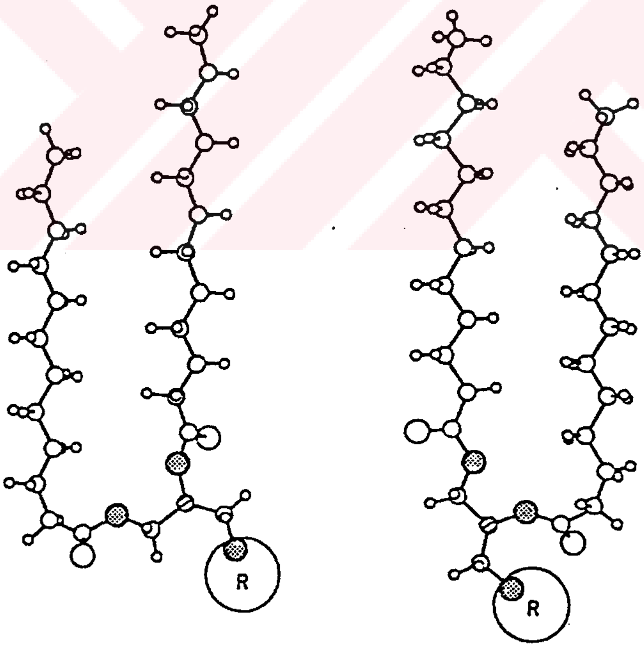


Figure 4. Preferred molecular conformations of different phospholipid molecules. R represents head group substituent [2].

The phase structures and phase transitions of lipids and biological membranes have been the subject of investigation for more than forty years. One of the primary justification for these studies has been to define the biological role of the lipid component of the biological membranes [34-42]. The interactions between lipids and membrane proteins or enzymes as well as metals can be studied by the use of phospholipid bilayer membranes. It is especially interesting to see how the interactions affect the structure and function of each component. One can obtain knowledge of the function of specific chemical constituents within the heterogenous membrane network.

1.1.2 Monolayers

Monolayers provide a very useful system to study the possible mechanism of action of anesthetic agents, drugs and toxins on cell membranes [43-49]. Reactions and interactions occurring during ion-exchange and ion transport phenomena in the membrane can be simply analyzed by monolayer techniques. Moreover, the molecular orientation, intermolecular spacing, molecular area and surface charge are well defined and can be precisely controlled in monolayers.

The surface reactions differ to a great extent from those occurring in bulk solutions as the dissolved molecules in bulk tend to have random orientations, whereas the molecules in monolayers have a more specific orientation. Because of these specific orientations the reactions in monolayers are often considerably faster than those in bulk solutions. The pH near a charged surface is often 2-3 pH unit different from the pH of the adjacent bulk solution, due to the attraction or repulsion between the H^+ ions and the fixed charges at the surface. Hence monolayers can simulate, to some extent, the conditions prevailing at the membrane surface.

Hydrocarbon chains normally do not form monolayer membranes if no polar groups are present. The well-oriented structures at the air-water surfaces only occur upon addition of surface active molecules possessing polar groups. The long hydrocarbon chain of sufficient length makes the molecule insoluble and the hydrophilic or polar group anchores it to the surface to form the insoluble monolayer. The molecules forming an insoluble monolayer can be considered as floating molecules.

The surface charge of the monolayer is determined by polar groups, which may be anionic, cationic, nonionic or zwitterionic. The intermolecular spacing between the molecules in a monolayer is determined by the nature of the polar groups and hydrocarbon chains such as the size and the charge distribution. The unsaturation or branching of hydrocarbon chains increases the area per molecule and, consequently, the spacing between the polar groups.

Monolayers can be thought as a two-dimensional state of matter, since their thickness (20 Å) is negligible compared to their length and width. Analogous to the state of matter in three dimensions, monolayers can exist as two dimensional solids, liquids or gases and can undergo temperature dependent phase transitions from one state to another. Phase transitions of lipid monolayers [50-52] have been studied extensively, mostly experimentally. Molecular dynamics simulation technique was also used to study disorder transitions in lipid monolayers [53].

CHAPTER II

COMPUTER SIMULATION

Computer Simulation is one of the new branches of science with a strong interdisciplinary character. It is based on an interplay between the traditional approaches of experiment and theory with the experimentalist being concerned with obtaining factual information concerning physical states and processes, and the theorist forming idealized models which are translated into a mathematical formulation. As is common in theoretical work, the investigator may find that the mathematical analysis is too complex, and is forced to make systematic simplifications in order to make predictions. Usually comparison of experimental and theoretical results is a difficult process which may be blamed on the uncertainty of the experimental interpretation, or the simplicity of the theoretical solution. The reality is generally a combination of both of these factors, and computer simulation methods fit in somewhere between these two extrema. They are usually called as " numerical experiments " since they are closer to the real life experiments than analytical theories and they are easier to manipulate than the laboratory experiments. Computer simulation is establishing its greatest value in those situations where the gap between laboratory measurement and theoretical explanation is large.

In contrast to analytical approaches, nonlinearity, lack of symmetry and a large number of degrees of freedom usually do not create insurmountable problems. Information not readily accessible to laboratory experiment is obtainable, and guidance for theoretical development is provided. It is the combination of computer experiment, laboratory experiment and theory which results in a very powerful approach for developing a better understanding of the physical world [54].

The starting point for a computer experiment is the development of a model for the physical system of interest. Then the problem is defined by fixing the boundary conditions and initial conditions. The method of solution or the algorithm can be selected from a number of possibilities considering the type of information sought and the physical problem and the laws governing it. Finally during the course of the computer runs, the parameters which control the experiment can be changed so that a real life experiment under different conditions can be simulated.

2.1 Molecular Dynamics Simulation

In this work, we have used the molecular dynamics simulation technique to study the surface dynamics of isolated model phospholipid monolayer. This technique is shown to be very effective in investigating dynamical properties of the systems of interest as well as static properties. The methodology has been developed [55-65] and extensively used in many branches of science since 1957. This method is also used to simulate phospholipids, monolayers, bilayers, lipid bilayers and biological membranes [66-79]. There are also a large number of Monte Carlo simulation studies of the same systems [80-89].

Molecular Dynamics method computes a trajectory of a N-particle system by solving Newton's equations of motion. A system of N-particles is positioned within a cell of fixed volume with the initial positions of the particles exactly known. A set of initial velocities is also assigned, usually in such a way that net momentum is zero. The subsequent trajectories of the particles are then calculated by stepwise numerical integration of the classical equations of motion. The particles are assumed to interact through some prescribed force, and at each step the force acting on each particle is calculated from the interaction potential of the system. The length of the time step depends on a number of factors: temperature, density, masses of the particles and the nature of the force employed. In the simulation of liquids such as lipids, for example, the time step is typically of the order of 10^{-15}

seconds, and the trajectories are followed for 10^3-10^5 steps, depending on the properties which are under investigation [90]. In MD, the total energy of the system is constant. The states arising at each step of calculation represent a sample from microcanonical ensemble where number of particles, volume, and total energy are constant. The solution of the equations of motion is, of course, a particularly efficient way of sampling phase space along a surface of constant total energy. Thermodynamic properties of the system are then calculated as averages over time.

For an isolated system, the total energy H is given by:

$$H=\sum_{i=1}^{N}\frac{P_i(t)^2}{2m_i}+V_N[r_1(t),\ldots\ldots,r_N(t)] \qquad (1)$$

H is a constant of motion. V_N represents the potential energy arising from the mutual interactions of the particles. p_i represents the momenta of the particles. For given initial conditions which specify the values of 6N coordinates and momenta at t=0, the positions at a later time can in principle be calculated from Hamilton's equations (eqn.2 and eqn.3).

Classical molecular dynamics solves Hamilton's equations of motion for a set of generalized coordinates q_i and momenta p_i :

$$\dot{q}_i = \frac{\partial H}{\partial p_i} \qquad (2)$$

$$\dot{p}_i = -\frac{\partial H}{\partial q_i} \qquad (3)$$

Using the definition of H we obtain Newton's equations:

$$\dot{p}_i = m_i \ddot{r}_i = -\frac{\partial H}{\partial r_i} = -\nabla_i V_N(r^N) \qquad (4)$$

Let us consider a set of N particles with masses m_i at cartesian positions $r_1,\ldots,r_N$. The particles are assumed to move according to the classical equations of motion:

$$\frac{d^2\vec{r}_i}{dt^2} = \frac{\vec{F}_i(\vec{r}_1,\ldots\ldots,\vec{r}_N)}{m_i} \qquad (5)$$

where

$$\vec{F}_i = -\vec{\nabla}_i V_N(\vec{r}_1,\ldots\ldots,\vec{r}_N) \qquad (6)$$

For simplicity, the force is assumed to be conservative, ie., it depends only on positions. The first problem we encounter is the computation of forces according to eqn.6.

If there is no external field,the general potential energy can be written as [4] :

$$V_N=\sum_{i=1}^{N}\sum_{j>i}^{N}V(r_i,r_j)+\sum_{i=1}^{N}\sum_{j>i}^{N}\sum_{k>j}^{N}V(r_i,r_j,r_k)+\ldots. \tag{7}$$

In principle, the effect of higher terms are included such that an effective two-body term can be employed:

$$V_N(\vec{r}_1,\ldots.,\vec{r}_N)\approx\sum_{i,j}^{N}V_{ij}(\vec{r}_{ij}) \tag{8}$$

If pair potential V_{ij} depends only on the magnitude of the pair separation, r_{ij} is defined as:

$$\vec{r}_{ij}=\vec{r}_i-\vec{r}_j \tag{9}$$

$$r_{ij}=|\vec{r}_{ij}| \tag{10}$$

MD pair potentials are often derived from experimental solid state properties for which analytical expressions are given in terms of two-body potentials. They include the average effects of many body forces [91].

Similarly, the force acting on particle i can also be written as a sum of the pair forces,

$$\vec{F}_i=\sum_{j\neq i}^{N}\vec{F}_{ij} \tag{11}$$

which can be derived from the pair potential:

$$\vec{F}_{ij}=-\vec{F}_{ji}=-\frac{\partial}{\partial\vec{r}_{ij}}V_{ij}(\vec{r}_{ij}) \tag{12}$$

In case the potential $V_{ij}(r_{ij})$ is of spherical symmetry, which is often the case when atom atom potentials are being used, $V_{ij}(r_{ij})$ is a function of r_{ij} only so that F_{ij} becomes

$$\vec{F}_{ij}=-\frac{dV_{ij}(r_{ij})}{dr_{ij}}\frac{\partial r_{ij}}{\partial\vec{r}_{ij}}=-\frac{dV_{ij}(r_{ij})}{dr_{ij}}\frac{\vec{r}_{ij}}{r_{ij}} \tag{13}$$

This expression is usually very simple to evaluate. The summation must be carried out in principle over all 1/2 N(N-1) pairs of particles.

Briefly an MD simulation consists of the following steps. From the positions and the definition of the potential function, forces acting on each particle for the time t are computed. Then using these forces, eqn.5 for every particle is integrated numerically to obtain new positions and their time derivatives at t+Δt. This procedure is repeated until sufficient information is collected.

Real-life experiments deal with Avogadro's number of particles. In order to simulate such events within a reasonable amount of computer time, only a minute portion of that system could be treated. Even then certain precautions must be taken to avoid artificial effects arising from these simplifications. At this point it is appropriate to define the boundary conditions of the simulated system. If we wish to simulate a bulk phase with a limited number of particles, the simulation of an isolated cluster or drop introduces unacceptable disturbances due to boundary effects of the finite size experiment. The common practice is to use periodic boundary conditions. The simulated particles are put in a volume of certain shape which is repeated in space in a regular fashion. Even though this unit cell can be of different shapes such as sphere or a tetrahedron, the standard practice is to use a cubic box. Then there exists 6 other identical boxes which neighbor the original box. With the idea that each box is also surrounded by 6 identical boxes, one can assume that an infinitely large system is being analyzed (Fig.5).

The implementation of the periodic boundary conditions go through two basic steps. For the closed systems such as NVE ensemble which is called as microcanonical ensemble where number of particles, volume and total energy are constant, or NVT ensemble which is called as canonical ensemble where number of particles, volume and temperature are constant, the number of particles doesn't change. That means any particle which leaves the box must reenter from an opposite side of the box. The other point of importance is in the computation of the interparticle distances. Since there are 7 (for cubic boundary conditions) identical particles, a minimum distance convention must be employed, that is some particles would not interact with all particles in the same box, and there would be some interactions with particles from neighboring cells. Both of these points require some care in implementation as would be discussed later.

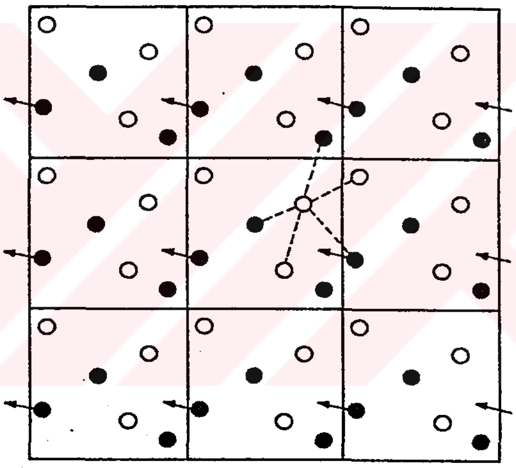


Figure 5. Periodic boundary conditions used in computer experiments [92].

Even for a system of a few hundred of particles, the simulation may be very costly in terms of computer time, and certain tricks of the trade must be used. One of the most practical ones is to employ a cutoff radius for the potential function. That means after some interparticle distance R_c, the potential is assumed to be zero. In accordance with this assumption, neighbor lists are also employed. The most time consuming step of an MD simulation is the computation of forces. Especially for the short range interactions, it is not necessary to compute all the terms in eqn.11 since most of the interparticle distances are too large to contribute to the potential and consequently to the forces. Therefore for every particle, a neighbor list which contains the names of particles which are close enough to contribute to the force significantly, is generated. The summation is carried out over not N-1 particles but only over those which are in the list. These factors and periodic boundary conditions must not contradict each other. For example, a particle should not simultaneously feel the interaction with another particle and with its image. Consequently the box size R_{box} should exceed twice the cut-off radius.

$$R_{box} > 2R_c \qquad (14)$$

For the force calculation only nearest image is taken into account. Complications arise if the potential of interactions is of such long range that it is not feasible to use a box size satisfying eqn.14.

In most cases forces are derived from pair interactions and the problem lies in the reduction of the number of pairs to consider. For short-range interactions a simple cut-off can be used at a radius that does not incorporate more than some hundred neighbors. The use of a cut-off radius produces truncation errors that manifest themselves as noise in the forces and extra fluctuation and/or drift in the total energy of the system. One may also modify the potential V(r) in such a way that both the potential and the force vanish at the cut-off radius.

$$V_{\mathrm{mod}}(r) = V(r) - V(R_c) - \left(\frac{\partial V}{\partial r}\right)_{R_c}(r - R_c) \tag{15}$$

Here V_{mod} is the modified potential and R_c is the cut-off radius. With a very large number of particles it is more efficient to produce a neighbor list once every so many steps (10 or 20) and use this list for force calculation for all steps between updates of the neighbor list. The neighbor list must at least contain all particles within the cut-off radius. This can be automatically taken care of if an interaction range for the construction of the neighbor list is chosen somewhat larger than R_c (e.g., 10% larger), while in every step the maximum particle displacement is monitored. As soon as this maximum displacement exceeds the difference between the range used for the neighbor list and R_c, the list is updated.

When interactions are intrinsically long range, use of a neighbor list becomes impractical. There are two possible solutions: i) One uses infinite summation methods, such as the Ewald Summation, or Fourier Methods [57]. Especially the latter are quite efficient but also complicated. ii) One uses two interaction ranges, a short one and a long one. While making up the neighbor list for the short range, the forces due to particles in the shell between the short and the long range are evaluated and stored per particle. This requires only one extra storage vector. This long range part is kept unchanged between updates of the neighbor list.

2.1.1 Solution of Şecond Order Ordinary Differential Equation of Motion

The essence of the method of computer simulation is to take advantage of the speed and accuracy of the modern digital computer to integrate numerically the equations of motion for hundreds or even thousands of molecules. There are many different ways of achieving this objective, with different efficiency and conveniency. The problem consists essentially in integrating ordinary second order differential equations by a finite difference approach. From the particle positions and velocities at time t, one attempts to obtain, with reasonable accuracy, the same quantities at a later time $t+\Delta t$.

Because of the finite step size, Δt, the solution will be only approximate; therefore the particle trajectories will not be precise, and will eventually diverge after some time. It is evident that the choice of Δt is important and depends on the solution method adopted, and on the simulated system. In all the proposed algorithms, one compromises between the desired accuracy of the trajectories and the size of the time step.

The equation to be solved is given in eqn.5 and eqn.6. Mathematically the problem constitutes an initial value problem [93] which can be simply formulated:

$$x'' = f(x) \tag{16}$$

$$x_0 = x(t_0) \tag{17}$$

$$x'_o = x'(t_0) \tag{18}$$

where x, x', x'' are 3N-dimensional vectors and their derivatives with respect to t. The most appropriate approach to solving such a problem is to use of a difference or step-by-step method. The solution is approximated by its value at a sequence of discrete mesh points. Normally these points are assumed to be equally spaced:

$$t_n-nh \qquad (19)$$

A step-by-step method provides a rule or algorithm for computing the approximation x_n at step t_n to $x(t_n)$ in terms of the values of x at t_{n-1} and possibly at preceding points. A k-value method uses k preceding values of solution depends on the properties of the function f and on the specified initial values of x_0 and x'_0.

The choice of the available difference methods is determined by the fact that the force calculation (the evaluation of f) is the most time consuming part of the computation, involving a double summation over particles. This rules out any method of solution (such as Runga-Kutta and extrapolation methods) that requires several function evaluations per step. General methods requiring only one force evaluation per step are multi-value predictor corrector methods.

2.1.1.1 Multi-Value Predictor-Corrector Method

Predictor-corrector methods generally rely on predicting the new positions and their derivatives for a short time step, and then correcting them from the forces computed at the new positions.

In a multi-value predictor-corrector method, the calculated values of position or its successive derivatives at a number of mesh points are used to aid in the computation at later points. A k-value method uses k previously calculated values of position or its derivatives. When these k-values are calculated at l previous mesh points, the method is called a l-step method. A multi-value method can be expressed using different representations. The representation is determined by the choice whether, for each mesh point, x or x′ or x″, etc. or combinations of them are used in the algorithm.

In the Nordsieck or N-representation, the column vector is written as

$$\vec{x}_n^N = [x_n, hx_n', \frac{h^2 x_n''}{2}, \ldots\ldots, \frac{h^{k-1} x_n^{k-1}}{(k-1)!}]^T \tag{20}$$

Predictor step is given by a matrix "A"

$$\vec{y}_{(n+1)}^N = A\vec{x}_n^N \tag{21}$$

The corrector step is expressed by a vector "a"

$$\vec{x}_{(n+1)}^N = \vec{y}_{(n+1)}^N + a\frac{h^2}{2}[f(y_{(n+1)}) - y''_{(n+1)}] \tag{22}$$

For "A" usually a Taylor expansion from the previous values is used; the values of "a" can be chosen for maximum stability and accuracy [93].

For k=4, involving the derivatives of force, the values are:

$$A = \begin{pmatrix} 1 & 1 & 1 & 1 \\ 0 & 1 & 2 & 3 \\ 0 & 0 & 1 & 3 \\ 0 & 0 & 0 & 1 \end{pmatrix} \qquad a = \begin{pmatrix} 1/6 \\ 5/6 \\ 1 \\ 1/3 \end{pmatrix}$$

One recognizes the binomial coefficients in the columns of "A"

Since the second derivatives or forces are actually computed at every step, it is convenient to use a representation in which the forces at previous steps are kept instead of higher derivatives at the previous steps and we call this the force (F) representation.

$$\vec{x}_n^{F} = [x_n, hx'_n, \frac{h^2}{2}x''_n, \frac{h^2}{2}x''_{(n-1)}, \ldots\ldots, \frac{h^2}{2}x''_{(n-k+3)}]^{T} \qquad \textbf{(23)}$$

Gear has shown that two different representations of the same k-value predictor-corrector algorithm are equivalent. This means that one representation can be converted into the other by a matrix transformation.

This transformation technique is a useful tool to compare the various existing algorithms. The comparison of different predictor-corrector algorithms are done in many publications. One of them is given in reference [57].

From a theoretical point of view, a multi-value (k-value) predictor-corrector algorithm with parameters obtained from stability and accuracy consideration as proposed by Gear [93] appears to be the best presently available algorithm for MD calculations. In the case of non-constraint dynamics the most suitable representation of the algorithm is the N-representation [59]. In our MD calculations, we used 6-th order Gear algorithm.

2.1.2 Equilibration

Initially, the particles are placed into the quasi-three dimensional box at a desired density such that they resemble a surface of an face centered cubic lattice. We use the term quasi-three dimensional, since the motion is on a two-dimensional surface but the head groups occupy a three-dimensional volume. The velocities are zero at the beginning. Surface density is defined as number of particles per unit surface area. It can be changed by changing the box sizes. Then the particles are allowed to follow the trajectories according to Newton's equations with the periodic boundary condition. If it is needed, the temperature of the system is rescaled to desired temperature. The statistical temperature T is calculated from the total kinetic energy of the system and monitored with some intervals. After a few ten thousand steps, the system shows no secular change in the temperature. This state is generally assumed to be a thermal equilibrium state. From this point on the system is assumed to be in equilibrium and the positions and also velocities of the particles are stored with some intervals for further analysis of the system.

2.1.3 Analysis

One of the things to be done is to plot the trajectories of the particles. So called trajectory plots provide direct information on the motion of the particles and their preferred locations at equilibrium. A trajectory plot is a trace of the path of each particle for the duration of simulation run. The diagram is constructed by connecting straight lines between successive positions of particles at time intervals of 100 Δt.

One of the most important static properties that can be obtained from MD simulations is the pair distribution function or G-function, since it is widely available from experimental measurements. It is a function usually written as G_{AB}, which gives the probability of finding a particle A at a distance r away from a particle B. The function is usually normalized to 1 at large r. It is the deviation of this function from uniformity that gives rise to the scattering of X-ray or neutrons. Therefore, the theoretical radial distribution functions can be compared to X-ray and/or neutron scattering data to check the reliability of the potential model. The calculation of this function is given in Appendix-A. G-function is often plotted since it provides insight to the liquid structures.

CHAPTER III

DESCRIPTION OF THE MODEL

In our numerical experiments, only the structure of the head surface of phospholipid membrane is simulated. The effects of tail groups are not considered since the interesting chemistry occurs at the head surface.

In the first two applications of the MD method to lipid monolayers, Cotterill and Toxvaerd [94-95] used a two-dimensional model and they considered the case in which the individual molecules are reduced to purely two-dimensional particles moving in the plane of monolayer. Later Kox et.al. [76] improved this by considering a little more realistic model in which lipids are represented by seven repeating units(-CH_2- groups). The first repeating unit of each chain is the head group which is constrained to move in a plane. However the interactions between the head groups are not completely considered. In a MC simulation, Scott [87] employed a model which takes into account the polar interactions of the head groups by aligning all the head groups with parallel dipole vectors within the x-y plane. Hussin and Scott [86] used a model in which the head groups are represented by two overlapping spheres carrying positive and negative charges. Although the study of Bareman et.al. [67] on the structural and dynamical behaviours in monolayers of long-chain molecules using MD technique, may be taken as a prototype for the tail-tail interactions, as Möhwald [96] states in his very recent review, the simulation of the interaction between the head groups is one of the most interesting and challenging aspects of the phospholipid monolayers. Therefore it is quite reasonable that lipid monolayers can be studied by studying two-dimensional surface formed by the head groups of the lipid molecules.

In our model, 120 lipid molecules which move on a two-dimensional surface are used to represent the system. Initial configurations are taken as two dimensional fcc lattices. The system is periodic only in x and y direction, with sides of 100 Å and 103 Å respectively. Individual centers of head groups have different z coordinates (quasi three-dimensional liquid) which do not change during the course of the simulation. The molecules are free to move in the x-y plane and rotate around the z axis which goes through the center of mass. Therefore the motion of each molecule is defined by three coordinates; x and y coordinates of the center of mass and a 2x2 Euler rotation angle in x-y plane. This angle is defined as the angle between the orientation of the actual head group and the initial configuration. A time step of 10 femptoseconds is used which results in a fluctuation of the total energy of about 7% of the kinetic energy fluctuation. Head group is composed of the three spheres fused together (Fig.6).

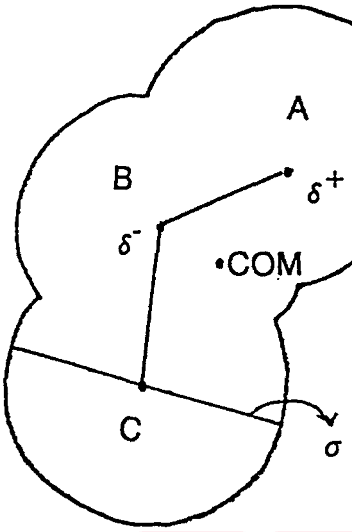


Figure 6. Projection of model head molecule on the surface (x-y plane). Rotation angle is zero.

Each sphere has the same diameter σ, and has a force center in its center of mass. The force center A is carrying positive charge while B has a negative charge with the total charge being zero. C is a neutral force center. Modelling the phospholipid head group, positively charged center refers to choline group, negatively charged center is the phosphate group in the middle, and the neutral group represents the ester group of the real phospholipid molecule. The point masses of the A, B, and C groups are 73, 109 and 75 atomic mass units, respectively. These numbers are found by mimicking the real molecule. Head molecule is a rigid body meaning that the vibrational motion is not considered. During the translational and rotational motion of the head molecule, the relative positions of A, B and C remain constant.

3.1 Interaction Potential

In Cotterill's model, interactions are 12-6 Lennard - Jones potential acting between the end points of rod-like molecules and Coulomb potential acting between the midpoints. Toxvaerd's interaction potential is a generalization of one proposed by Salem [97].

$$\phi(r)=\frac{\varepsilon}{q-1}\left[\left(\frac{\sigma}{r}\right)^{5q}-q\left(\frac{\sigma}{r}\right)^{5}\right] \qquad \textbf{(24)}$$

where ε and σ are parameters as in Lennard-Jones potential. Toxvaerd used q=5 and 2. Polar forces are accounted for as a perturbation.

In some recent MC studies [98-99], the head-head interaction is taken as a single parameter or it is taken as LJ plus Coulomb interactions [86-87] between each head groups as suggested by Fischer and Brickmann

[100]. We improve the modelling of phospholipid head group which has three force centers in 3-dimension rather than two force centers given in literature. Interactions between the heads and the force centers of heads are defined as LJ plus Coulomb which will be explained below.

In calculations, the total interaction potential of the system is taken as the sum of the effective pair potentials.

$$V_N(\vec{r}_1,\ldots,\vec{r}_i,\ldots,\vec{r}_N)=\sum_{i,j}^{N} V_{ij}(\vec{r}_{ij}) \tag{25}$$

The vector r_i indicates the position of the center of mass of i-th head group. The head groups interact with each other through the pair potential V_{ij} which depends not only the vector r_{ij} but also the orientation of the A, B, C groups (Fig.6) of the i-th and j-th centers. If the whole expression including orientational contributions is written explicitly, we obtain:

$$V_{ij}(\vec{r}_{ij})=V_{A_iA_j}+V_{B_iB_j}+V_{C_iC_j}+V_{A_iB_j}+V_{A_jB_i}+V_{A_iC_j}+V_{A_jC_i}+V_{B_iC_j}+V_{B_jC_i} \tag{26}$$

This equation can be rewritten as:

$$V_{ij}(\vec{r}_{ij})=\sum_{A=1}^{3}\sum_{B=1}^{3} V_{A_iB_j} \tag{27}$$

Double summation goes over the three groups of the model head molecule. Here, A and B are just the dummy indexes of the summations, and should not be confused with the name of the groups in Fig.6. The individual terms in eqn.26 are the interaction potential which depends on the pair separation between the groups of centers i and j.

$$V_{A_iB_j} = V(\vec{r}_{A_iB_j}) \tag{28}$$

The molecules in general interact with each other via short range repulsive forces and via longer range attractive van der Waals forces. In our model, since the distances between A, B, and C within a head group are kept fixed, the charges on each head form dipoles. Therefore, interaction between heads will be the sum of dipole - dipole, dipole - induced dipole, induced dipole - induced dipole types. We represent these interactions as Lennard-Jones plus Coulomb type potentials:

$$V_{A_iB_j} = 4\varepsilon_{AB}\left[\left(\frac{\sigma_{AB}}{r_{A_iB_j}}\right)^{12} - \left(\frac{\sigma_{AB}}{r_{A_iB_j}}\right)^{6}\right] + \frac{\delta_A\delta_B}{r_{A_iB_j}} \tag{29}$$

Here, the first term is the Lennard-Jones (LJ) potential and the second term is Coulomb potential. The Lennard-Jones parameters may be obtained from the well known Lorentz - Berthelot rules [4].

$$\varepsilon_{AB}=\sqrt{\varepsilon_{AA}\varepsilon_{BB}} \tag{30}$$

$$\sigma_{AB}=\frac{\sigma_{AA}+\sigma_{BB}}{2} \tag{31}$$

Our preliminary semi-empirical calculations indicated that the total charges on phosphate and amine groups of phospholipid molecule are approximately -1 and +1 respectively. In our monolayer calculations, charge is the parameter to be optimized. Before optimization, they are taken as ± 1. Same calculations also show that the volume of the spheres covering amine, phosphate and ester groups is approximately same and their hard sphere diameters are around 6 Å. This value is kept fixed throughout the calculations. Since the interactions of groups A or B or C are similar to each other then ε_{AA}, ε_{BB}, and ε_{CC} are taken as same and denoted by ε only.

CHAPTER IV

RESULTS AND DISCUSSIONS

4.1 Simulation of the Surface

When studying structural changes by Molecular Dynamics simulations, it is often very informative to study trajectory plots of the surface formed by model phospholipid head groups. These plots are obtained by superimposing the positions of particles at successive time intervals so that a clearer view of the motion of the system can be observed. This way one can monitor the equilibration process, and the formation of structures.

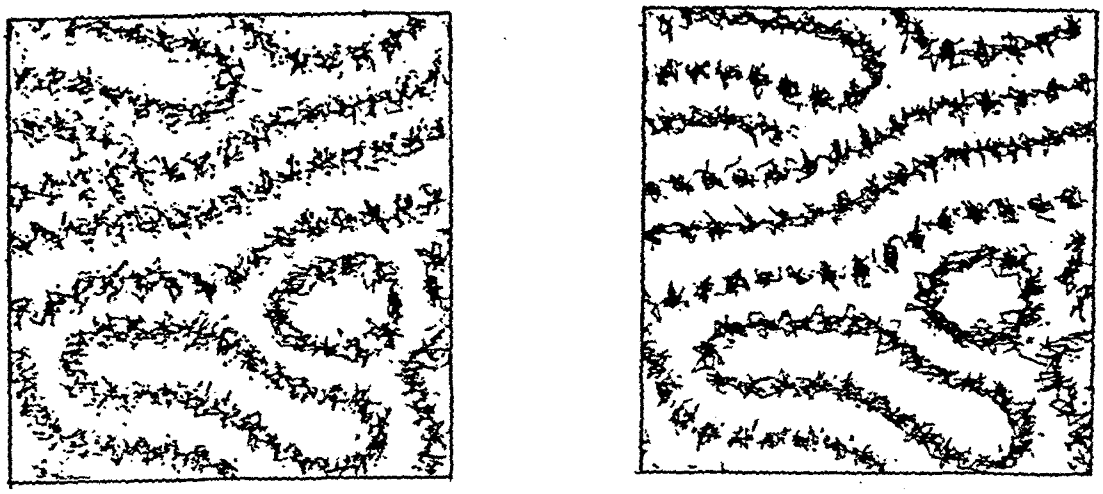
Our numerical experiments consist of four stages. The selection of the initial configuration, the equilibration, the actual simulation and the analysis of results. As mentioned before, 120 head molecules are used for the description of the monolayer surface. The center of masses of these molecules are placed on a surface of an FCC lattice. Their rotational orientations are chosen either randomly or in a semiregular order i.e. in the latter case every other molecule has 0 as initial rotational angle where the others have angles changing from -1.40 to 0.35 radians with increments of 0.25. After the initial configuration is selected, the system is brought to equilibrium with a proper temperature scaling. This process includes an initial 10,000 integration steps to relax the system and then an additional 50,000 steps with temperature scaling. Once the system is in equilibrium, a new run of 10,000 integration steps is carried out for the collection of history files. History files contain positions and velocities of each particle, usually sampled at every 10 time steps. The higher derivatives of the positions are not stored generally since most of the observable properties can be computed from positions and velocities only. Once the history files are created, one can analyze trajectory plots, g-functions and/or correlation functions. All these calculations are carried out in IBM 3090/200VF mainframe of Technische Hochschule Darmstadt and Silicon Graphics IRIS 4D/20G of Chemistry Department of METU. A typical equilibration is around 600 CPU sec. on IBM and around 24 hours on IRIS.

In this study we have followed the motion of the 120 head molecules for 100 picoseconds after the equilibration with the intervals of 0.1 ps. and in order to investigate conformations visually, trajectories are plotted for a few picoseconds after the equilibrium is reached.

The following ranges of the system parameters are studied. The temperature changes between 10-400 K, δ (charge) on the head group is between 0.25-1.0 au., and LJ energy parameter is varied starting from 0.2 to 10.0 (in units of 10^{-21} J). LJ hard sphere diameter is kept constant as 6.0 Å. These values are approximated from the results of semi-empirical quantum mechanical calculations. They are comparable to the values ($\delta=0.5$, $\sigma=5.4$, $\varepsilon=0.18$ in our units) used by Scott in his Monte Carlo calculations [87].

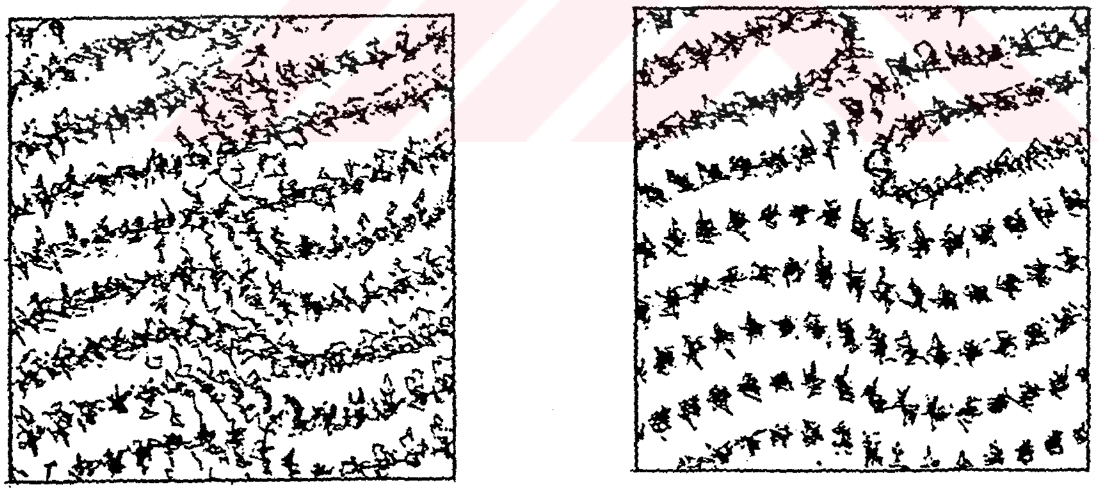
As the first step, we have studied the effect of the distribution of the rotational angles. In Fig.7a and 7b, trajectories for randomly distributed initial rotational angles at two different integration times are given . These plots are taken after the equilibrium is reached. The surface density is 0.01154 1/Å^2, the temperature is 300 K, the LJ potential parameter ε is 0.2 and the charge on cation and anion of the head group is ±1. Under these conditions, the surface molecules interact strongly due to the high point charges and they form chain type structure implying that dipole-dipole interaction is predominant. Fig.7c and 7d display the same behaviour for an ordered rotational angle distribution. Again the chain type structure formation is observed. In these figures, the rearrangement of the particles between 0.5 ps and 1.0 ps can be observed clearly. We can conclude that the equilibrium structures of our model system is independent of the initial distribution of the rotational angles of the surface molecules. However the random angular

Random distribution of rotation angles


(a) after 0.5 picoseconds

(b) after 1.0 picoseconds

Regular distribution of rotation angles


(c) after 0.5 picoseconds

(d) after 1.0 picoseconds

Figure 7. Trajectory plots of surface molecules at T=300 K, $\varepsilon=0.2$, $\delta=\mp1.0$, density=0.01154 Å^{-2}.

distribution as well as any spatial placement of molecules other than FCC lattice create stability problems at high density simulations. Hence we carried out the remaining runs with the ordered angular distribution on an FCC lattice.

In order to see the temperature effect, the parameters are fixed as mentioned above and the system is cooled slowly to 200 K and then to 100 K. The equilibrium structures at 200 K and 100 K display the same type behaviour, that is chain type structures are observed. In Fig.8, g-functions for A-A, B-B, C-C pairs at 300 K, 200 K, 100 K are plotted. As it is seen, the plots at three different temperatures are almost identical and they match quite accurately. This implies that the temperature up to 300 K does not affect the system in consideration, and there must be strong interactions which keep the molecules in ordered chains. It looks like that charge parameter is the cause of such rigidity. Therefore in order to see the effect of the charge on the configuration, we kept all the parameters the same as above, and at 300 K changed the charge from 1.0 to 0.25 with 0.25 intervals. Fig.9 shows the equilibrium structures as a function of the charge parameter. While the systems having charge value 1.0 and 0.75 are showing chain type ordered structures, the ones with the charge of 0.50 and 0.25 showed disordered structures. Therefore we carried out another simulation with charge 0.65 the result of which is also given in Fig.9. Since it shows neither ordered nor

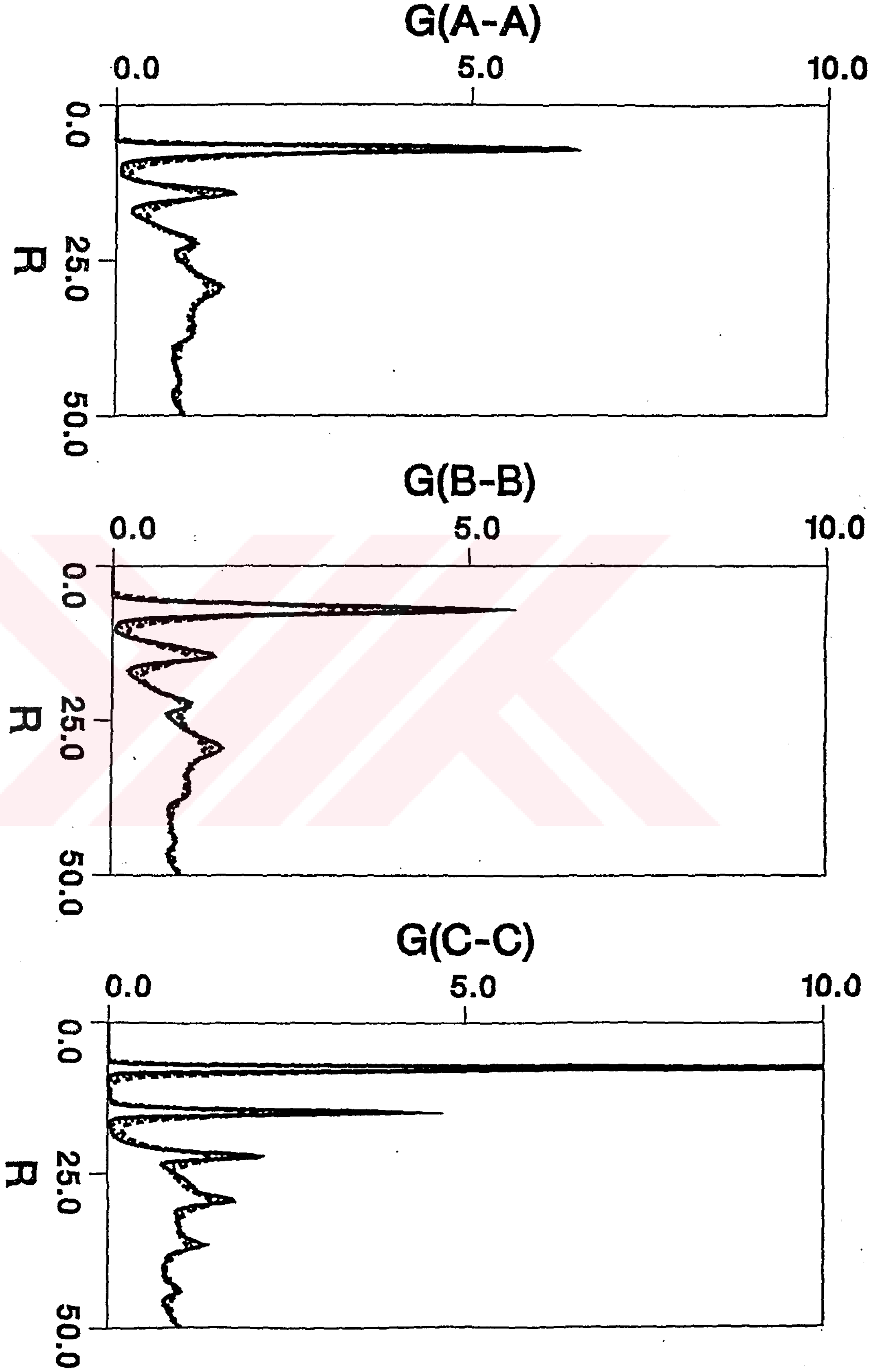


Figure 8. Radial distribution function of A-A, B-B, C-C type interactions at 300 K, 200 K, 100 K.

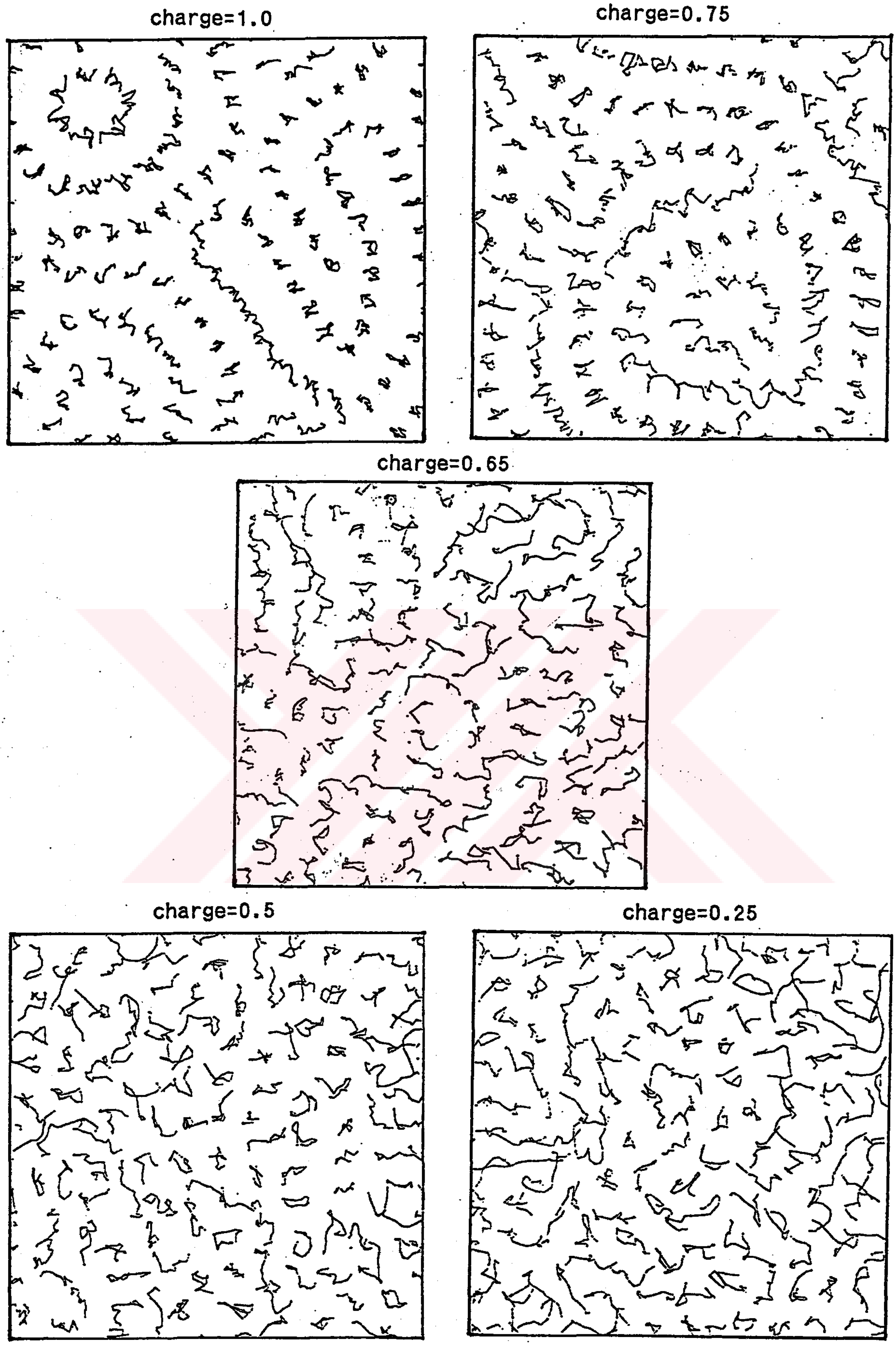


Figure 9. Trajectory plots of equilibrium structures surface molecules with changing charge where ε=0.2, T=300 K, density=0.01154 $\AA^{-2}$.

disordered structure at room temperature, for further calculations, the effective charge is set equal to 0.65. This value is slightly different from that used previously in the literature [86,87] and it is not an optimized value since there is no criteria for an optimization.

Another parameter which is investigated is the density of the surface. In order to find out the density, total energy of the system is plotted versus surface area (Fig.10). We observe that the total energy decreases with increasing area up to a certain point above which the total energy stays almost constant.

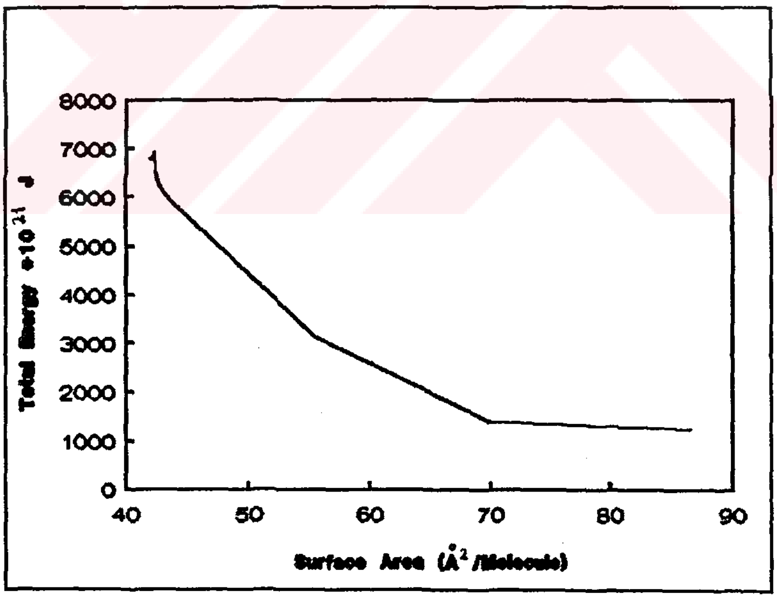


Figure 10. Change of total energy with surface area at 200 K.

Energetically favorable maximum density can be then found from the flat region of the curve. The resulting density is somewhat higher than the previous one. The new density is 0.01245 $1/\text{Å}^2$. The density optimization is done at 200 K while keeping the effective charge as 0.65 and ε as $0.2*10^{-21}$ J.

By using the new density, the effect of the variation of the charge is restudied to check whether ordered to disordered phase transition still occurs. The results are given in Fig.11. As it is obviously seen the transition occurs again in the range of 0.5-0.75. Old and new densities display the same type of transition at the same region of charge.The effect of the LJ energy parameter ε on the system is investigated at 300 K by setting the effective charge equal to 0.75 and 0.65 and varying the values of ε. Some representative results for $\delta=0.75$ are given in Fig.12. In all these figures we observe an ordered structure indicating that δ is still large and the effect of ε is not yet noticible. Then the value of δ is lowered to 0.65 and a wide range of ε is investigated. The representative trajectories corresponding to these simulations are given in Fig.13. The ordered structure persists up to $\varepsilon=0.8$ where heads move at cartesian trajectories indicating a liquid-like behaviour. The real sudden change is observed by $\varepsilon=8.0$ where the motion is restricted and after which we have solid type structure. It is clear that, increasing the ε has the same effect like decreasing the temperature. This brings out the conclusion that all the parameters can be written in terms of the other

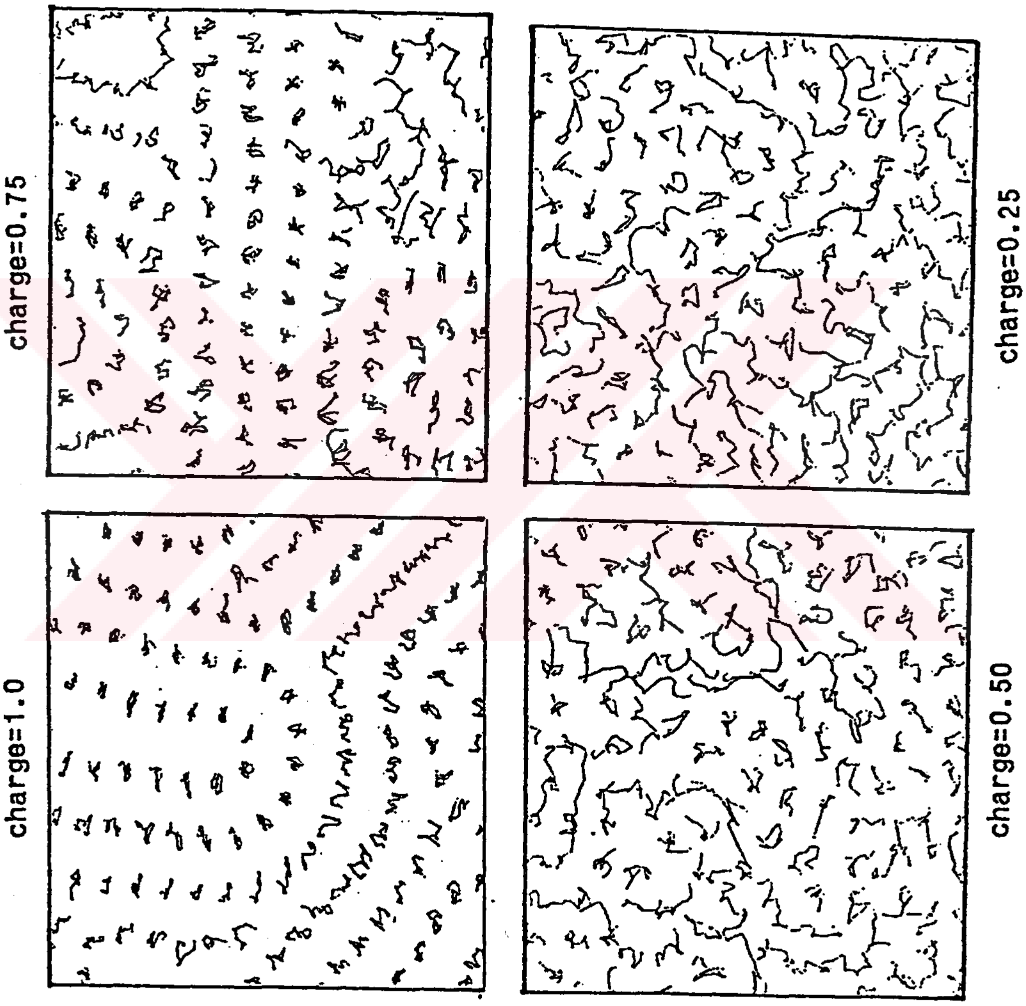


Figure 11. Trajectory plots of equilibrium structures of surface molecules with changing charge at new density of 0.01245 Å^{-2} at T=300 K, ε=0.2.

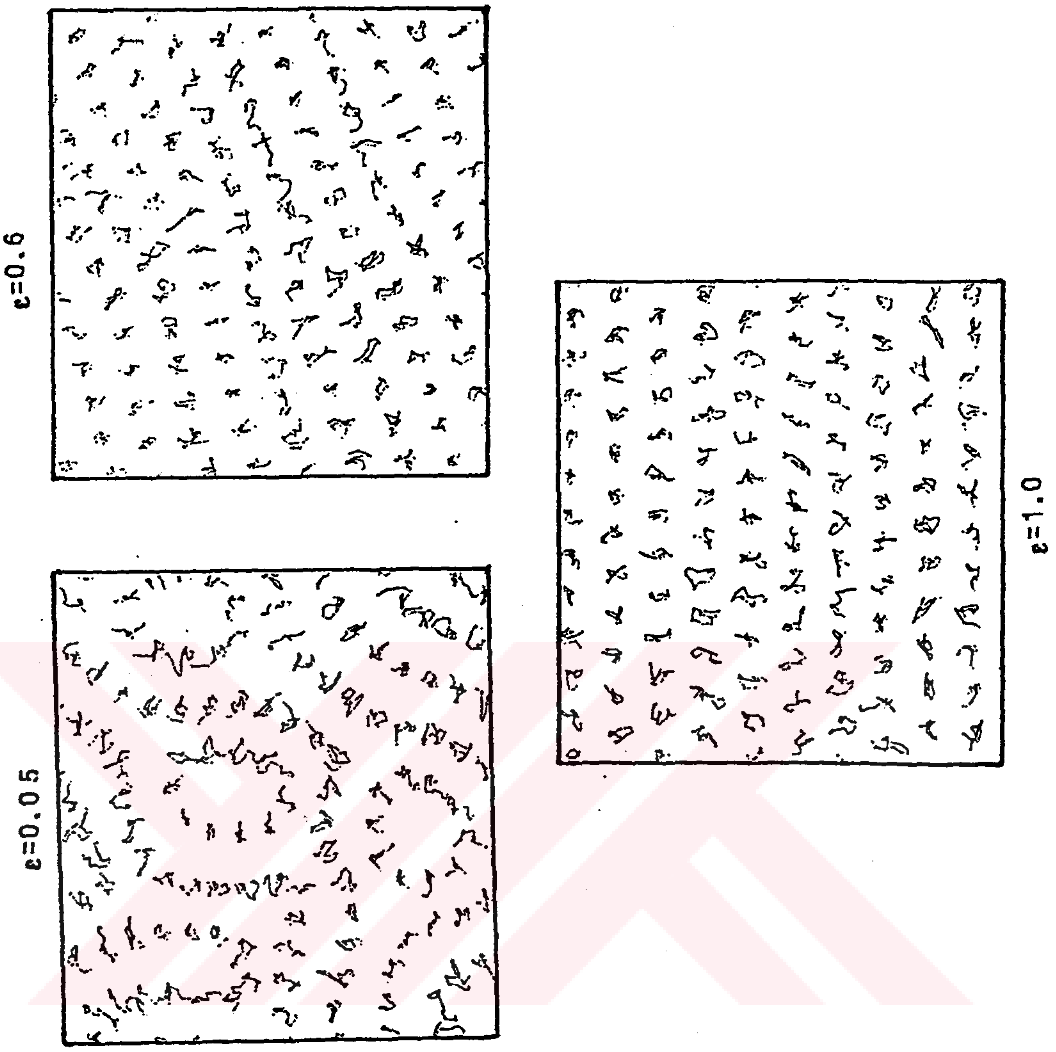


Figure 12. Change of structures with ε at $\delta=\mp 0.75$, T=300 K.

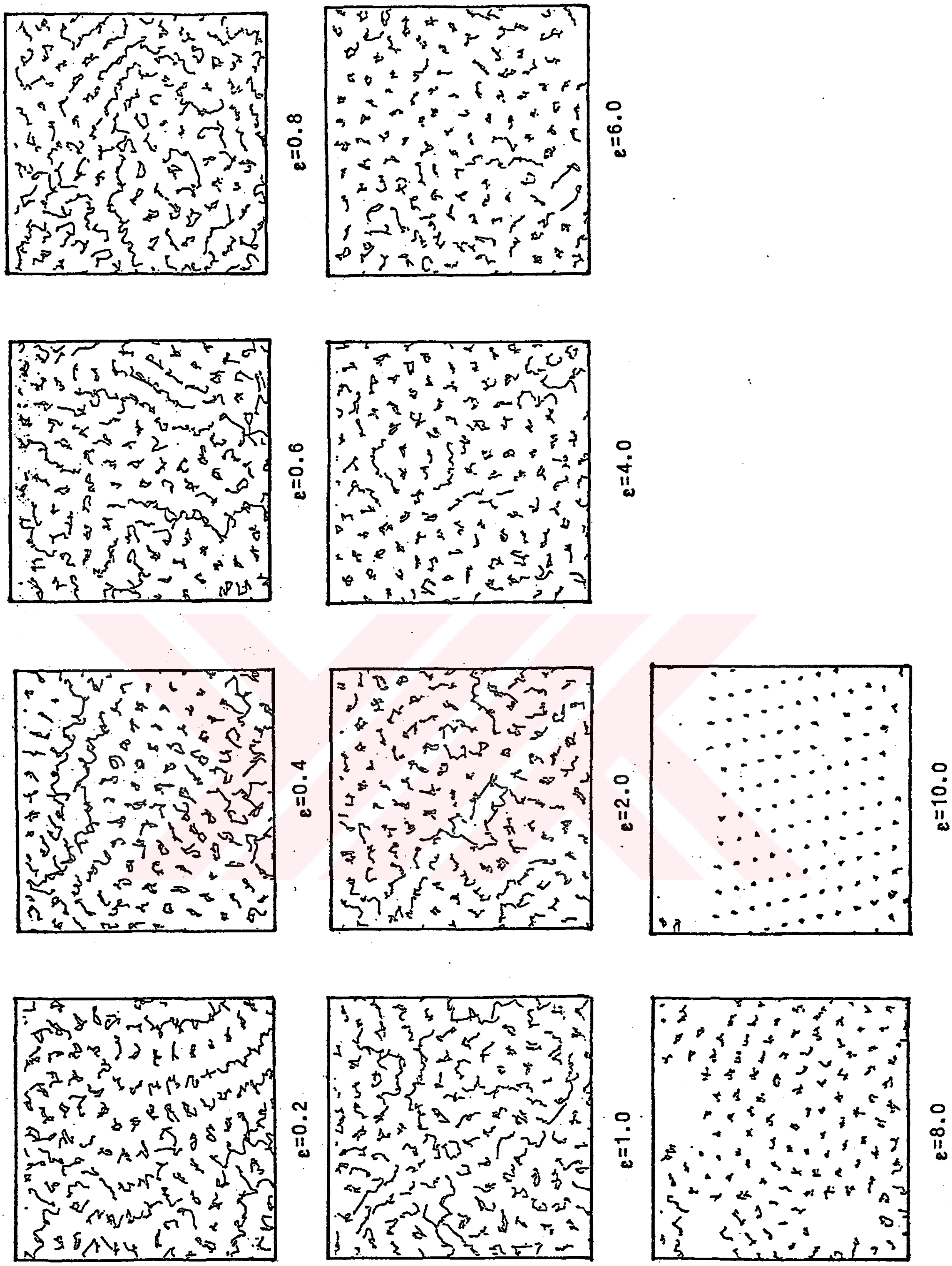


Figure 13. Change of structures with ε at $\delta=\mp 0.65$, T=300 K.

parameters. They must be transformable into each other by a scaling argument.

To summarize these experiments one can say that using this model, we are able to detect transitions from ordered to disordered structures by varying the model parameters. The most important parameter is the charge distribution of the head group where the temperature and the LJ energy parameters have somewhat smaller effects on the equilibrium structure.

4.2 Scaling of the Hamiltonian of the System

The total Hamiltonian of the system given in eqn.1, can be written in terms of our model potential as:

$$H=\sum_{i=1}^{N}\frac{p_i^2}{2m_i}+\sum_{i=1}^{N}\sum_{j>i}^{N}\sum_{A=1}^{3}\sum_{B=1}^{3}4\varepsilon\left[\left(\frac{\sigma}{r_{A_iB_j}}\right)^{12}-\left(\frac{\sigma}{r_{A_iB_j}}\right)^{6}\right]+\frac{\delta_A\delta_B}{r_{A_iB_j}} \qquad (32)$$

If we consider a new scaled coordinate system Q_i which is related to the old one q_i by the relation

$$Q_i=\frac{q_i}{\sigma} \qquad (33)$$

then the following transformation may be defined

$$R_{A_iB_j}=\frac{r_{A_iB_j}}{\sigma} \tag{34}$$

$$\lambda=\frac{\Omega^2}{\sigma\varepsilon} \tag{35}$$

$$\Omega_i=\frac{\delta_i}{\Omega} \tag{36}$$

where Ω is the absolute value of δ_i. Substituting these in the potential part of the Hamiltonian, we obtain:

$$V(q_i)=\varepsilon W(Q_i)=\varepsilon\sum_{i=1}^{N}\sum_{j>i}^{N}\sum_{A=1}^{3}\sum_{B=1}^{3}\left[4\left(R_{A_iB_j}{}^{-12}-R_{A_iB_j}{}^{-6}\right)+\lambda\frac{\Omega_A\Omega_B}{R_{A_iB_j}}\right] \tag{37}$$

Newton's equation (eqn.4) may be written as

$$\frac{dp_i}{dt}=-\frac{\partial H}{\partial q_i}=-\frac{\partial V}{\partial q_i}=-\frac{\varepsilon\partial W(Q_i)}{\sigma\partial Q_i} \tag{38}$$

which suggests that the definition of a scaled time

$$t'=\frac{\sqrt{\frac{\varepsilon}{m}}}{\sigma}t \tag{39}$$

and a unitless mass

$$M_i = \frac{m_i}{m} \tag{40}$$

yields

$$\frac{d}{dt} = \frac{\sqrt{\frac{\varepsilon}{m}}}{\sigma} \frac{d}{dt'} \tag{41}$$

and the scaled momentum

$$P_i = \frac{p_i}{\sqrt{m\varepsilon}} \tag{42}$$

Hence substitution of these in the kinetic energy part of the Hamiltonian expression yields

$$\sum_{i=1}^{N} \frac{p_i^2}{2m_i} = \varepsilon \sum_{i=1}^{N} \frac{P_i^2}{2M_i} = \varepsilon \Sigma_{kin} \tag{43}$$

and the total Hamiltonian takes the form

$$H = \varepsilon H' = \varepsilon\,(\Sigma_{kin} + W) \tag{44}$$

Based on the above scaling arguments, we can analyze the interplay between the LJ energy parameter and the temperature.

$$\frac{\langle E_{kin}\rangle}{N}=\frac{3}{2}kT=\frac{\varepsilon\langle\Sigma_{kin}\rangle}{N} \tag{45}$$

$$\frac{kT}{\varepsilon}=\frac{2}{3}\frac{\langle\Sigma_{kin}\rangle}{N} \tag{46}$$

Since the right hand side of the eqn.46 is parameter-free, then:

$$\frac{kT_1}{\varepsilon_1}=\frac{kT_2}{\varepsilon_2} \tag{47}$$

The final form is:

$$T_1\varepsilon_2=T_2\varepsilon_1 \tag{48}$$

A similar relation between the charges and the energy parameter can also be obtained from the potential energy definition:

$$\delta_2^2\varepsilon_1=\delta_1^2\varepsilon_2 \tag{49}$$

Now we can define a set of conditions such that the systems would behave similarly. This means that all the set of parameters which display phase transitions or certain pattern formations are related through a single control parameter. As a result of this argument, we notice that only one variable has to be defined and studied. Let us choose a set of parameters δ_1,ε_1 and T_1. If a second set has ε_2 as energy parameter, then T_2 and δ_2 can simply be written as:

$$\delta_2=\delta_1\sqrt{\frac{\varepsilon_2}{\varepsilon_1}} \tag{50}$$

$$T_2=T_1\frac{\varepsilon_2}{\varepsilon_1} \tag{51}$$

Similarly choosing temperature as the variable, we obtain:

$$\varepsilon_2=\varepsilon_1\frac{T_2}{T_1} \tag{52}$$

$$\delta_2=\delta_1\sqrt{\frac{T_2}{T_1}} \tag{53}$$

In the same fashion, when δ is the control variable, we write:

$$\varepsilon_2=\varepsilon_1\frac{\delta_2^2}{\delta_1^2} \tag{54}$$

$$T_2 - T_1\frac{\delta_2}{\delta_1} \qquad (55)$$

As it can be seen from Table.1, total energy goes to negative region starting from $\varepsilon=4.0$ and $\delta=0.65$. These values can be taken as a reference point where $\lambda=0.0176$. For this system, we changed the temperature from 400 K to 100 K and we observed phase transition between 200 K and 150 K (Fig.14). Another system with $\varepsilon=2.4$ and $\delta=0.50$ and the same λ was taken and cooled from 300 K to 50 K and it showed phase transition between 150 K and 100 K (Fig.15). Finally we studied the system with $\varepsilon=0.5919$ and $\delta=0.25$ (again representing $\lambda=0.0176$) between 10-400 K and the phase transition was observed around 100 K (Fig.16).

4.3 Modelling of Gramicidin-A Molecule

The modern view of a biological membrane is that of a cooperative system consisting of a lipid matrix, the lipid bilayer, where molecules such as proteins, cholesterol,.. are embedded. When a protein is incorporated in the lipid bilayer it may perturb the physical properties of the surrounding lipids [101-104]. One of the main questions to answer is

Table.1 Parameter Space

	epsilon ε (10^{-21}J)	charge δ (esu)	<total energy> (10^{-21} J)	<kinetic energy> (10^{-21} J)	<Temp.> (K)	lambda λ
	0.2	1.00	158.43	784.90	315.83	0.8333
	0.2	0.75	1131.46	731.63	294.40	0.4688
	0.2	0.65	1441.18	720.37	289.86	0.3521
	0.2	0.50	1650.91	812.83	327.07	0.2083
	0.2	0.25	1153.72	790.44	318.06	0.0521
	0.4	0.65	1479.94	730.25	293.84	0.1760
	0.6	0.65	1208.40	766.14	308.28	0.1174
	0.8	0.65	1108.40	690.69	277.92	0.0880
	1.0	0.65	1086.66	732.42	294.71	0.0704
	2.0	0.65	486.64	710.24	285.79	0.0352
	4.0	0.65	-1046.82	743.77	299.28	0.0176
	6.0	0.65	-2793.35	772.33	310.77	0.0117
	8.0	0.65	-5041.67	744.66	299.64	0.0088
	10.0	0.65	-8065.26	789.00	317.48	0.0070
	20.0	0.65	-19651.28	778.02	313.06	0.0035
	0.05	0.75	285.33	759.30	305.53	1.8750
	0.6	0.75	1173.60	719.43	289.49	0.1563
	1.0	0.75	1050.71	736.16	296.22	0.0938
	4.0	0.65	-648.59	992.44	399.34	0.0176
	4.0	0.65	-1046.82	775.40	312.00	0.0176
	4.0	0.65	-1607.92	473.80	190.65	0.0176
	4.0	0.65	-1927.13	313.85	146.41	0.0176
	4.0	0.65	-2276.72	263.34	105.96	0.0176
	2.3674	0.50	47.03	760.16	305.87	0.0176
	2.3674	0.50	-405.53	529.44	213.04	0.0176
	2.3674	0.50	-685.49	341.86	137.56	0.0176
	2.3674	0.50	-1003.92	246.37	99.14	0.0176
	2.3674	0.50	-1331.71	113.32	45.56	0.0176
	0.5919	0.25	1194.94	1008.01	405.61	0.0176
	0.5919	0.25	861.60	751.53	302.41	0.0176
	0.5919	0.25	479.33	497.64	200.24	0.0176
	0.5919	0.25	108.05	252.72	101.69	0.0176
	0.5919	0.25	-109.78	125.75	50.60	0.0176
	0.5919	0.25	-337.65	26.34	10.60	0.0176

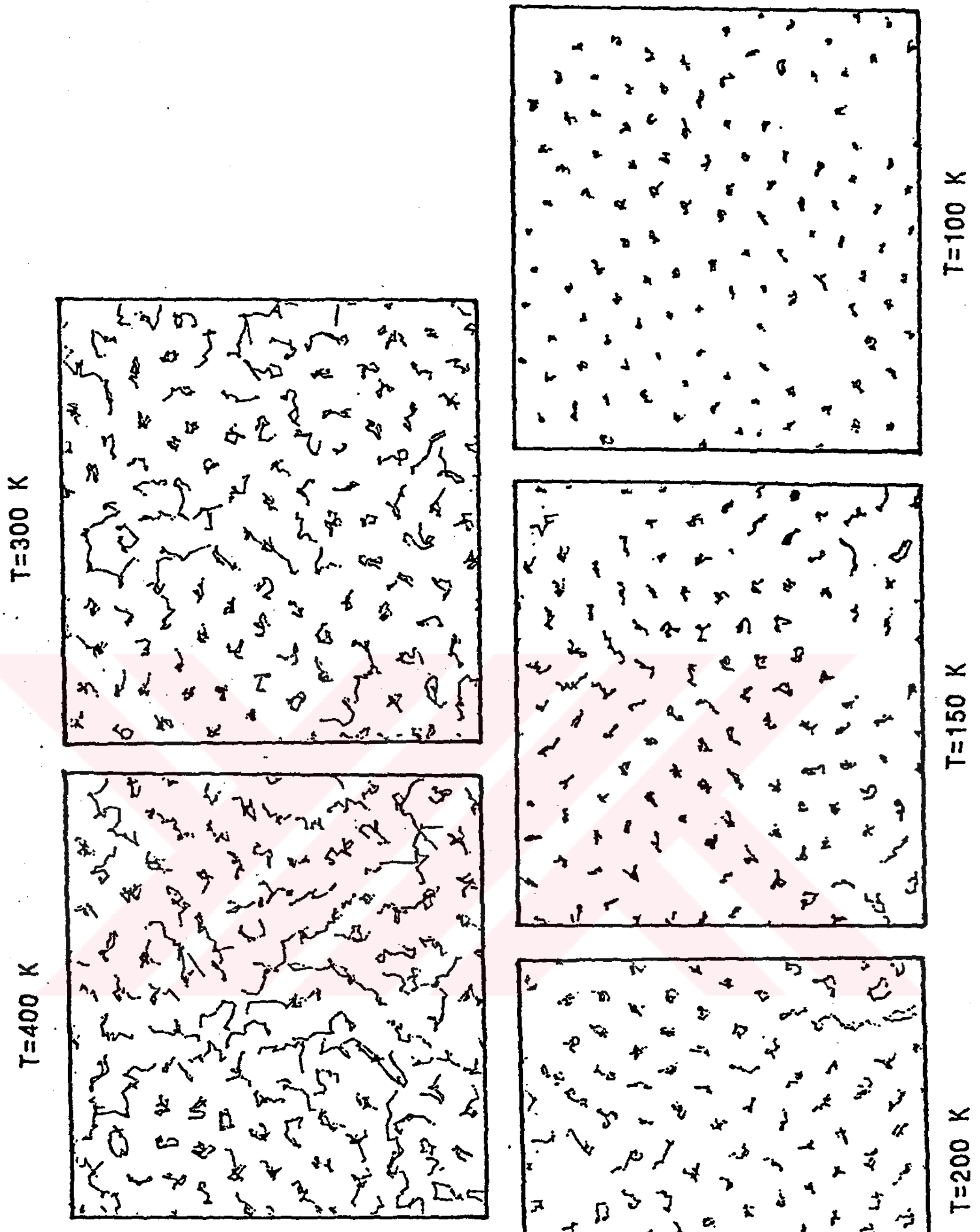


Figure 14. Change of structures with temperature at $\lambda=0.0176$, $\delta=\mp0.65$, $\varepsilon=4.0$, density=0.01245 $\AA^{-2}$.

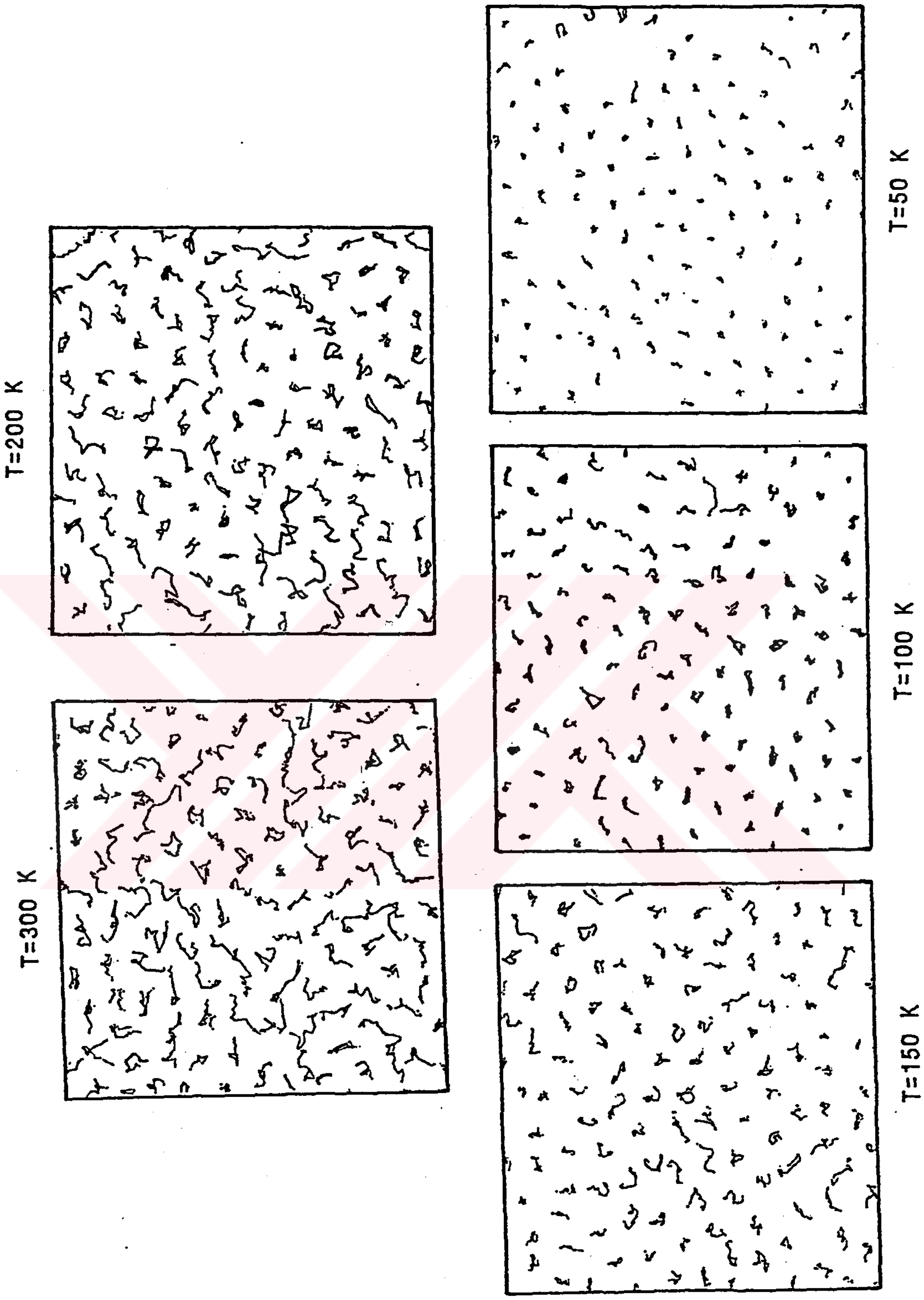


Figure 15. Change of structures with temperature at $\lambda=0.0176$, $\delta=\mp0.50$, $\varepsilon=2.3676$, density=0.01245 Å^{-2}.

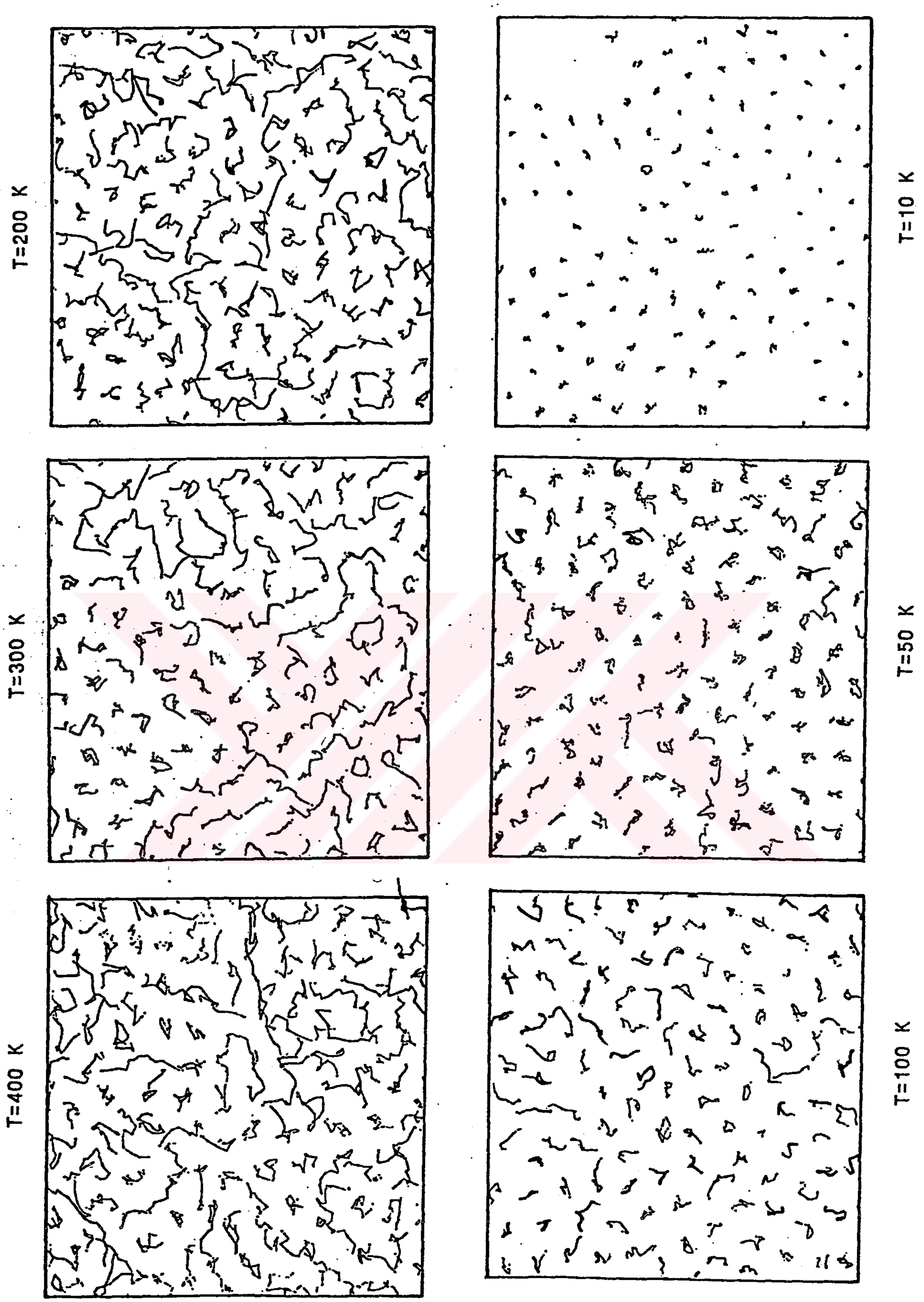


Figure 16. Change of structures with temperature at $\lambda=0.0176$, $\delta=\mp0.25$, $\varepsilon=0.5919$, density=0.01245 Å^{-2}.

whether this perturbation is restricted to a small neighborhood around the protein or if it has a long-range character as has been experimentally detected for some molecules in literature [88]. As already mentioned before, proteins are important constituents of the membranes. They play a vital role on the migration of the ions through biological membrane since they have ion-transport channel [105-109].

In this part of our study, in order to analyze the effect of such a large molecule on the membrane surface, a model resembling Gramicidin-A [110 -115] (Fig.17a,17b) was chosen and placed onto the surface. The choice of the Gramicidin molecule is because of its biological role in membrane. Transmembrane channels are formed by dimers of gramicidin molecule which is one of the best-characterized ion channels. These channels have proven to be excellent models for studying conductance, ion selectivity, water permeability, single-channel characteristics, and lipid-peptide and peptide-peptide interactions in bilayers. The biological role of gramicidin is related to the inhibition of RNA polymerase. Gramicidin channels are cation selective.

Gramicidin-A is a neutral linear pentadecapeptide (polypeptide) and its dimer gives rise to a 28 Å -long channel of about 4 Å internal diameter (Fig.17c). Previously several gramicidin-A-membrane system have

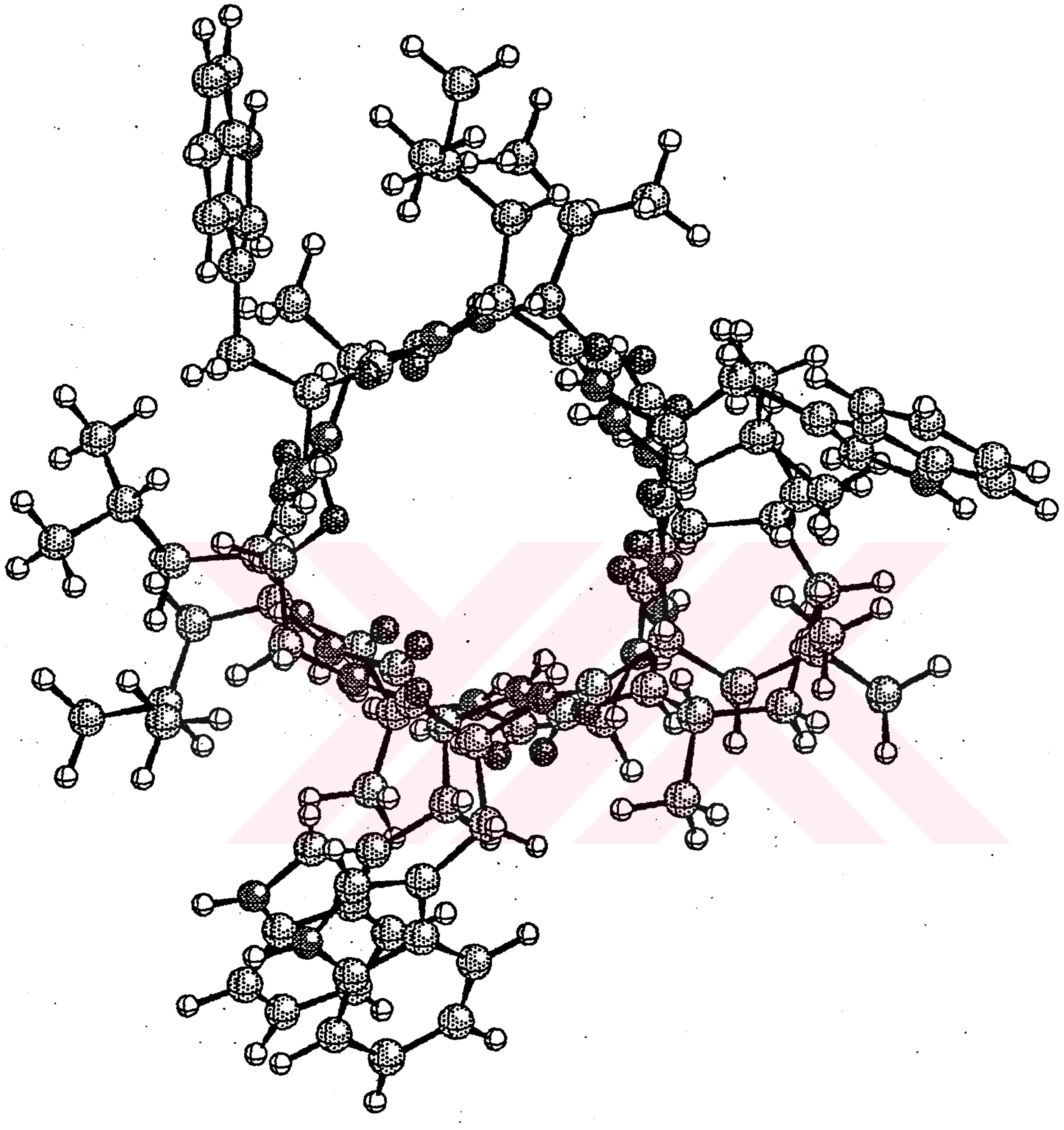


Figure 17.a. Top view of Gramicidin-A molecule. Ball and stick model.

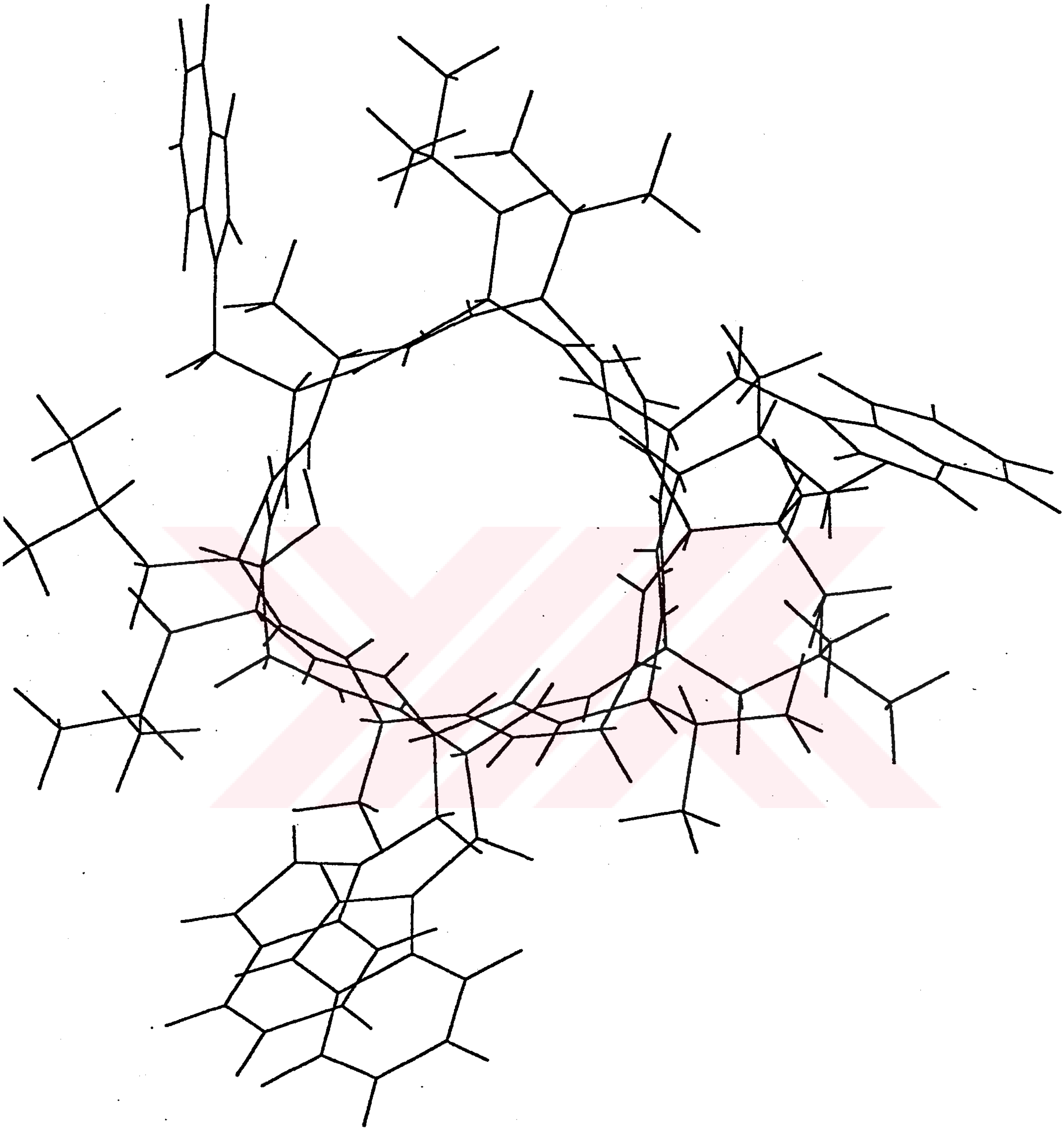


Figure 17.b. Top view of Gramicidin-A molecule. Wire model.

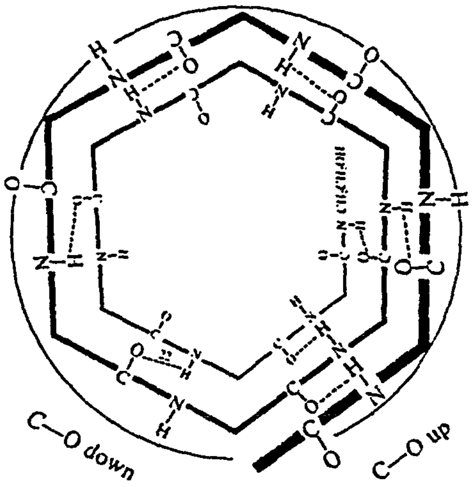


Figure 17.c. The primary sequence of Gramicidin.

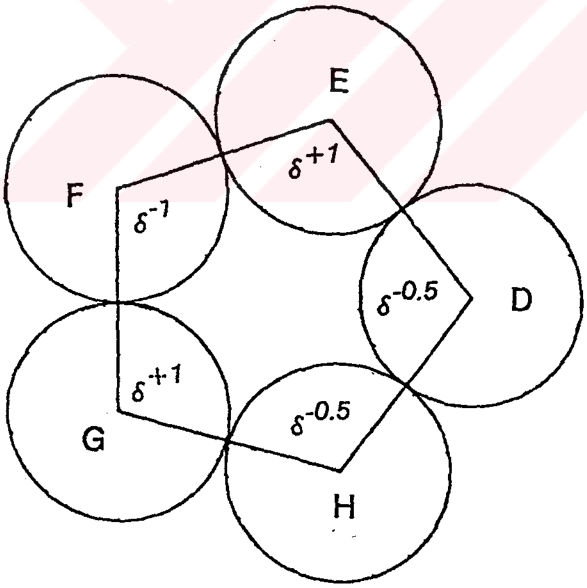


Figure 18. Model Gramicidin-A molecule.

been reported [116-125] including some findings also from the membrane-polypeptide combination [126]. The experimental work outnumbers the theoretical results due to the complexity of modelling such inhomogeneous systems. We have chosen our model protein as a pentagon having a point charge and a force center at each corner (Fig.18). These force centers with point masses of 150 amu. interact with the head molecules on the surface via electrostatic and van der Waals forces (eqn.27). After placement of only one model protein molecule to our initial surface, the number of the surface molecules is lowered from 120 to 115 in order to keep the surface density constant. Initially, the protein molecule is placed at the middle of the surface, then allowed to translate and rotate on the surface by interacting with neighboring surface molecules. Then the simulations are carried out as explained previously, that is after the equilibration, data is collected and the results are analyzed.

In Fig.19, the trajectory plots of the surface molecules are shown at three different temperatures. The empty space in each plot belongs to the area occupied by the protein molecule. We start with the system which is known to be ordered at 300 K with the parameters of charge is 1.0 and ε is 2.0 . It can be seen that the presence of the protein has no effect on the structure of the system. This is expected since the interactions between surface molecules are so strong that the presence of the protein cannot have

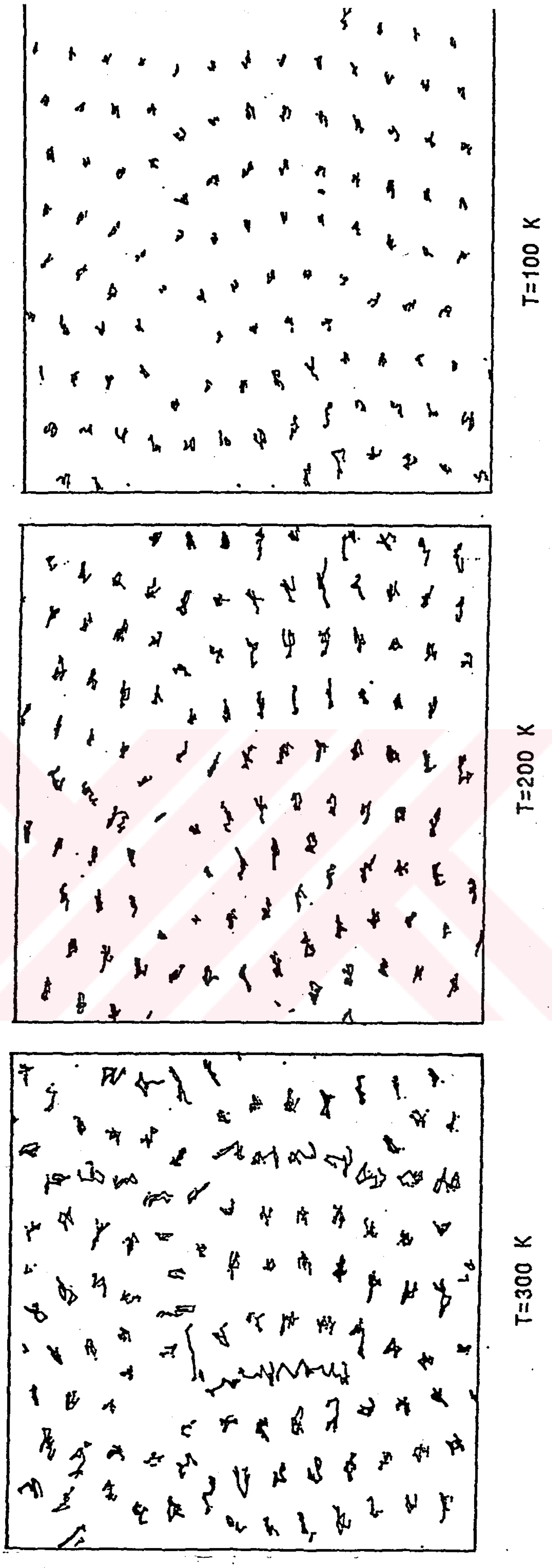


Figure 19. Change of structures of model Phospholipid-Gramicidin system with temperature at $\delta = \mp 1.0$, $\varepsilon = 2.0$.

any significant influence. At each temperature, the surface shows highly ordered structures. From the previous observations, we know that charge is a crucial parameter for our model system and the systems with high charges (larger than 0.65) shows ordered structure at 300 K. We study another ordered structure with the $\delta = 0.75$ and ε still 2.0 (Fig.20). The interaction of surface molecules with the protein still has no effect on the structure. We continue to reduce the charge of the system. Now the system parameters of $\delta = 0.5$ and $\varepsilon = 2.0$ (which has shown disordered structure at 300 K without the protein) shows ordered structure at 300 K, 200 K, 100 K (Fig.21). The effect of protein molecule is now becoming apparent especially for those surface molecules in the near vicinity. In order to see the effect of the protein molecule on the disordered to ordered phase transition, the previously studied set of parameters with $\lambda = 0.0176$ are taken. We observe that the transition temperature is increased by approximately 50 K due to the presence of protein molecule on the surface (Fig.22, Fig.23).

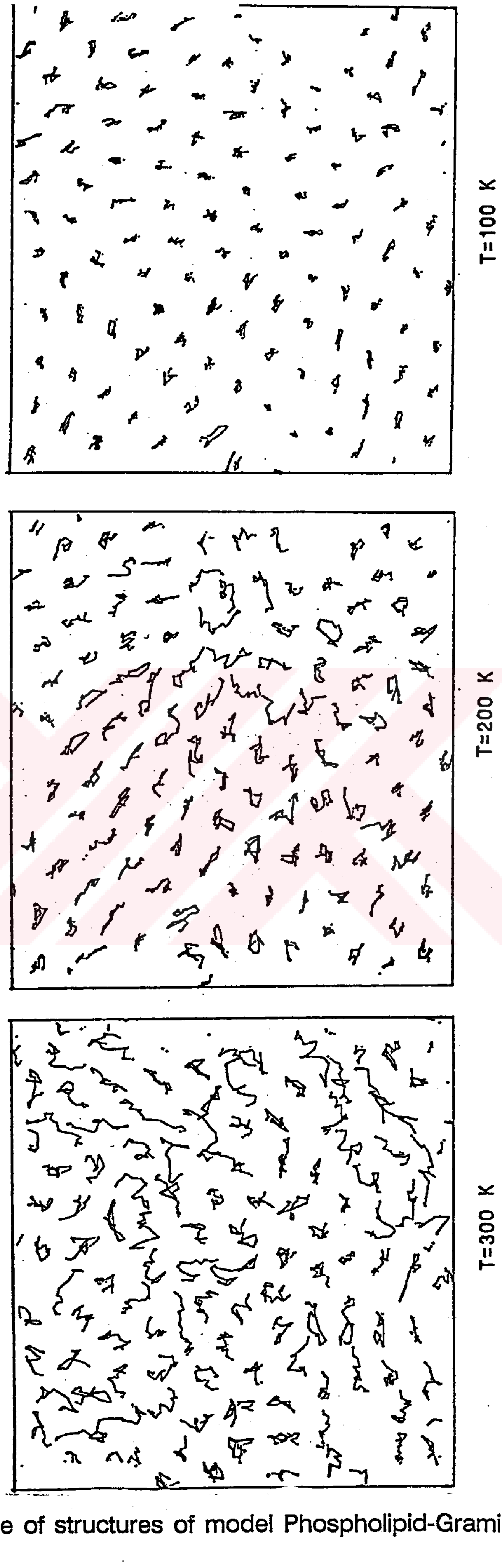


Figure 20. Change of structures of model Phospholipid-Gramicidin system with temperature at $\delta=\mp0.75$, $\varepsilon=2.0$.

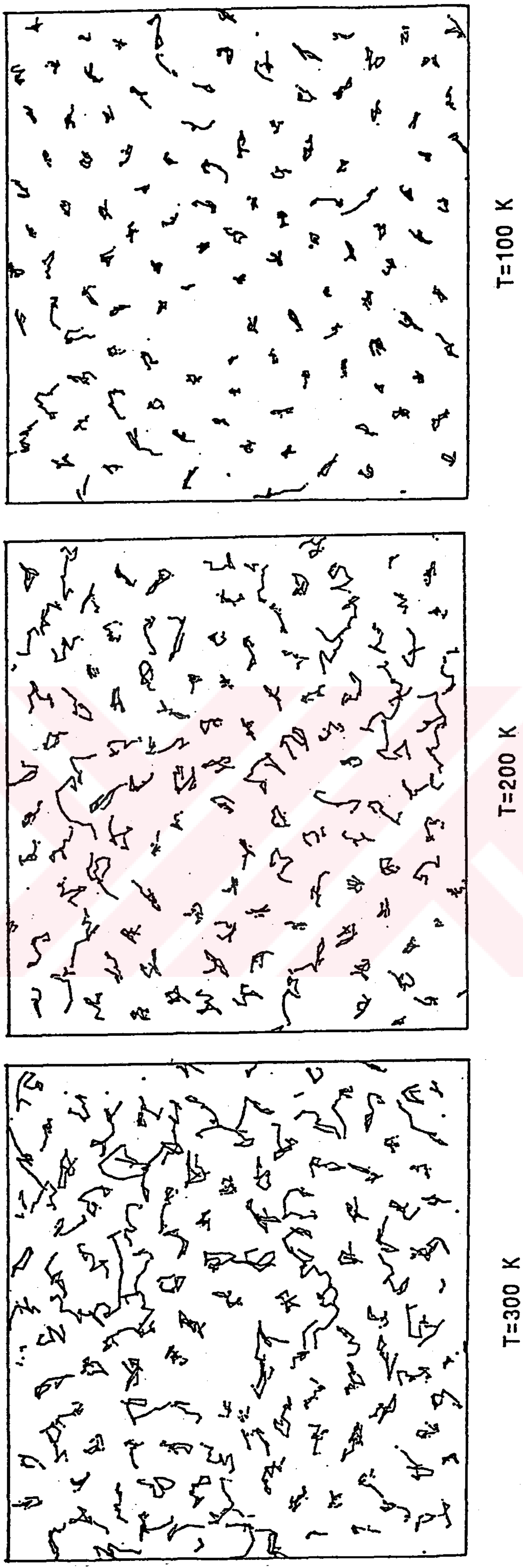


Figure 21. Change of structures of model Phospholipid-Gramicidin system with temperature at $\delta=\mp0.50$, $\varepsilon=2.0$.

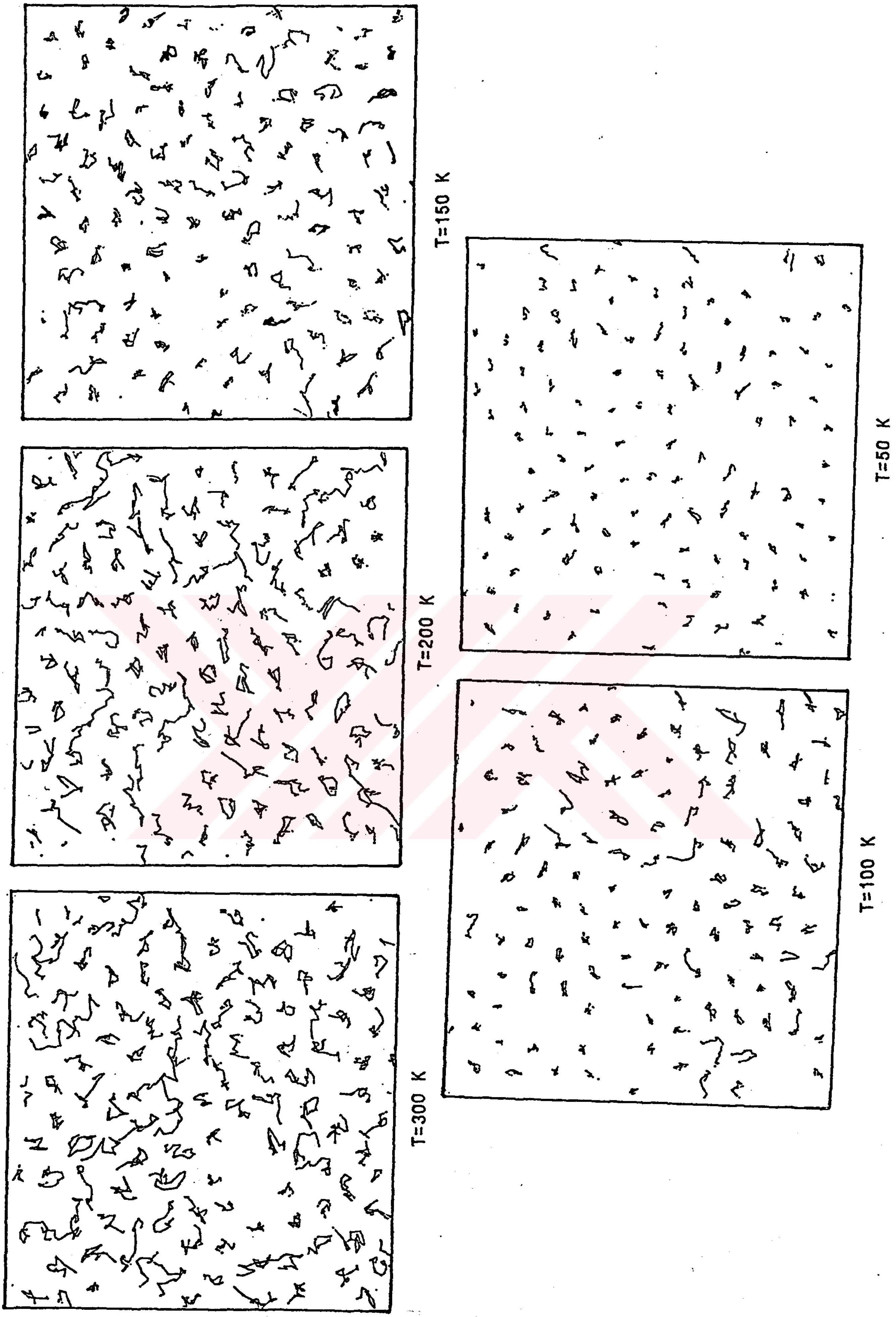


Figure 22. Change of structure of model Phospholipid-Gramicidin system with temperature at $\lambda=0.0176$, $\delta=\mp0.50$, $\varepsilon=2.3676$.

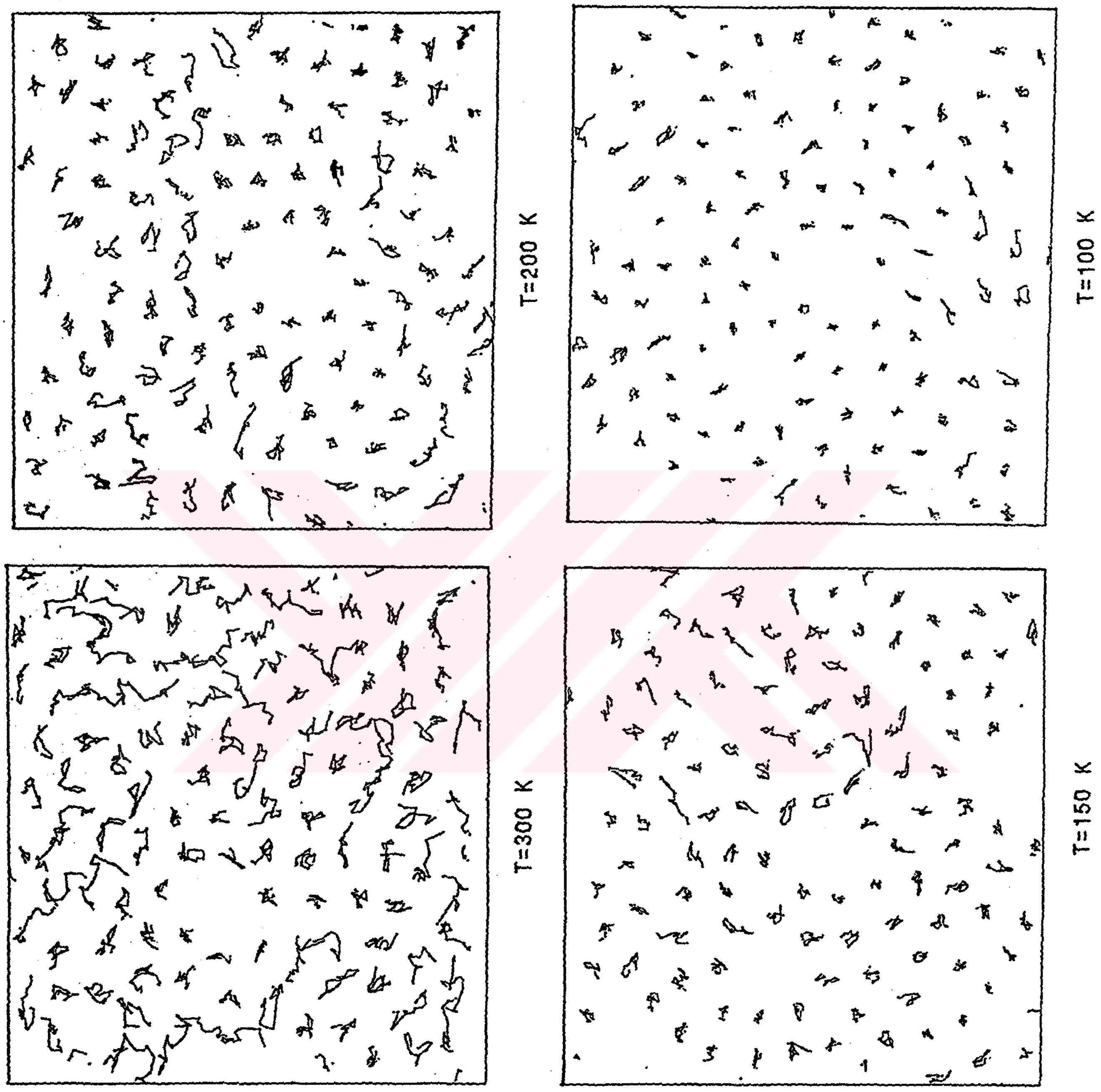


Figure 23. Change of structure of model Phospholipid-Gramicidin System with temperature at $\lambda=0.0176$, $\delta=\mp0.65$, $\varepsilon=4.0$.

CHAPTER V

CONCLUSION

In this study, we have analyzed in detail, the structural changes of a model lipid membrane surface using molecular dynamics simulation technique. The time-dependent equations governing the motion of molecules are solved numerically. By visual inspections of the individual trajectories of surface molecules, the formation of patterns are observed and their behaviour are noted as functions of interaction parameters and temperature of the system.

The computational aspects of the study includes the investigation of the equilibration process. Even though the conclusions are independent of the way the system was equilibrated, this process is extremely important since it is the most time consuming and sensitive part of the computational procedure. We have observed that this process is achieved by integration steps of around 10,000 steps. Fortunately the dependence on the initial configuration is substantially low so that certain regular structures can be used to initialize the system.

Upon the study of parameter space, it is observed that for high ε values, crystal like solid structures are obtained. They have rather low mobility and are discarded without further analysis. The interplay between other parameters is rather subtle, however it is very clear that, the point charge distribution of the surface molecule seems to be the most effective for the determination of the surface structure. For a given range of the charge, a definite change of the structure is seen. For the low polarity case, liquid-like structure is dominant but upon increasing the polarity of the molecule, chain like patterns start to form.

A scaling scheme is developed to incorporate and understand the effects of the different model parameters on the dynamical and structural behaviours of the system. A single parameter λ is defined which relates ε, δ and σ. Systems which are represented by the same λ, show similar temperature dependent phase transitions. In conclusion of these findings, we can state that once a certain λ corresponding to a specific behaviour is found, then the set of parameters which would also display similar behaviour can be determined easily without scanning the parameter space.

The biological membranes are not uniform in structure and they contain bulky molecules like proteins or polypeptides which play important role in ion-transport processes and in reactions with environment. Therefore a pentagon-type molecule which resembles gramicidin-A dimer is placed on the surface. The effects of the model molecule on the structural behaviour of the system are investigated. The simulations are repeated with the bulky molecule in the same manner explained above. The influence of the foreign molecule on the surface is noticible for the systems which show disordered, liquid type structure at room temperature. The effect of the molecule on phase transition temperature is studied. We observe that the transition temperature is incraesed by approximately 50 K due to the presence of this molecule. This can be interpreted that any perturbation on the system or breaking of the uniformity of the system causes an increase in the phase transition temperature.

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APPENDIX

APPENDIX A

The radial distribution functions can be calculated by dividing the interval within r=0 and cutoff radius (R_c) into segments of size δr and counting the number of pairs (AB) with distance falling in a given range. The results are to be averaged over different time steps. Let n(r) be the number of pairs which are r_i to $r_i + \delta r$ apart then

$$g_{AB}(r) = \frac{V}{N} \left< \frac{n(r)}{4\pi r^2 \delta r} \right>$$

where N is the number of particles and V is the simulation volume [127].

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