

Simulation of Phase and Component Segregation in Biological Membranes

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Received January 18, 2010; in final form, February 17, 2010

Abstract—Phase and component segregation in lipid membranes was studied by means of mathematical modeling. The time dependence of phase segregation on the lateral diffusion coefficient was calculated. The phase and component segregations were also simulated by multiparticle Monte-Carlo methods, and the phase diagrams of the system were obtained.

Key words: phase and component segregation, lipid membranes, phase field theory, asymptotic methods.

DOI: 10.3103/S002713491003015X

According to the model of Singer–Nicolson [1], the proteins and protein components of biological membranes are incorporated into a lipid bilayer. The protein and lipid microdomains that form under certain conditions at the surface of biological membranes substantially influence their functioning [2]. Experimental investigations of vesicles show the possibility of segregation at the surface of multicomponent lipid membranes, i.e., liquid–gel [3] and liquid–liquid [4] phase and component separations.

Segregation events can be described by the phenomenological phase (mean) field theory [5], where the order parameter φ is introduced: a value describing the phase condition of each point on the membrane surface. $\varphi = -1$ corresponds to the liquid phase and $\varphi = 1$ corresponds to the solid (gel-like) phase. The phase boundaries in the system characterize an abrupt transition layer between the levels $\varphi = -1$ and $\varphi = 1$.

Local structures that appear during phase and component segregation in the membranes can be studied by means of multiparticle models with different types of pair interactions. The equilibrium state in these systems may be obtained through total energy minimization using Monte-Carlo methods.

Application of the mean-field theory made it possible to qualitatively describe the segregation process and to estimate phase separation time in the two-dimensional lipid monolayer. The multiparticle Monte-Carlo membrane model was used to study phase segregation in single- and two-component lipid layers.

1. Estimation of Phase Separation Time

Lateral phase segregation in the membrane will be described using the mean-field theory, and the energy of the line tension of the lipid layer will be written as [6]

$$L(\phi, \eta) = \int_{\Omega} \delta \left[\frac{\lambda}{2} |\nabla \phi|^2 + \frac{1}{4\lambda} (\phi^2 - 1)^2 \right] \times \left[\frac{\xi}{2} |\nabla \eta|^2 + \frac{1}{4\xi} (\eta^2 - 1)^2 \right] dV. \quad (1)$$

Here, Ω is the volume under consideration δ is a constant, ϕ and $\eta \in [-1, 1]$ are order parameters describing lateral phase segregation and membrane shape, respectively, and λ and ξ are dimensionless quantities characterizing the width of the transition layer between the phases and membrane thickness, respectively. Below, only the phase segregation will be considered.

On calculating the variation of the functional (1) by ϕ and multiplying both parts of the obtained equation by λ , we come to the task

$$\frac{\delta L}{\delta \phi} \equiv \lambda^2 \Delta \phi - \phi(1 - \phi^2) = 0. \quad (2)$$

Stationary Eq. (2) leads to evolutionary

$$\lambda^2 \frac{\partial \phi}{\partial t} = \lambda^2 \Delta \phi - \phi(1 - \phi^2). \quad (3)$$

The transition layer between the phases is about 1–2 nm in width, while the lateral sizes of membranes may be up to tens of μm . Therefore, λ is a small parameter of the task and the solution of Eq. (3) should be sought as an abrupt transition layer between the levels $\phi = -1$ and $\phi = 1$. The parameter λ^2 in the

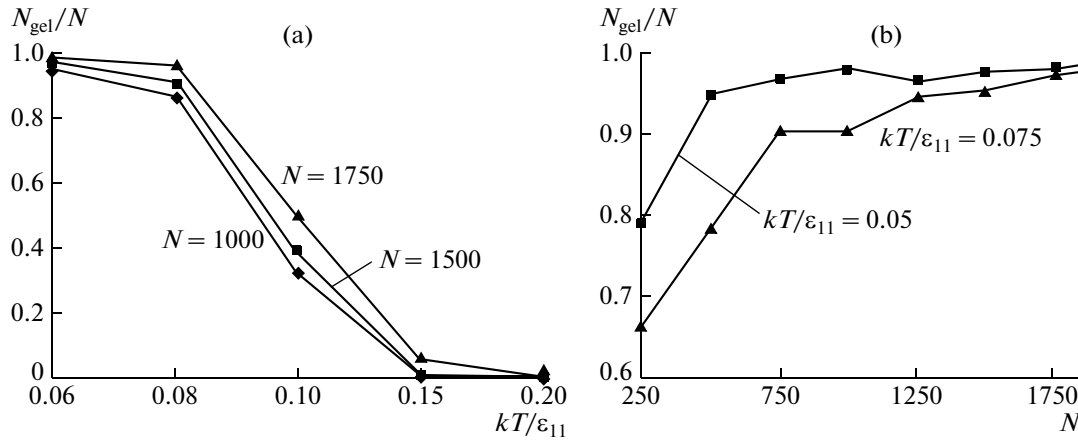


Fig. 1. The dependences of the dimensions of gel phase inclusion on the relative temperature kT/ε_{11} at $N = 1000, 1500,$ and 1750 (a) and the number of particles at $kT/\varepsilon_{11} = 0.05$ and 0.075 (b).

reaction–diffusion equation (3) stands for the higher derivative responsible for diffusion distribution; consequently, λ^2 characterizes the lateral diffusion coefficient of lipids.

A reaction–diffusion equation of type (3) was considered in [7]; investigation was carried out in the two-dimensional region. In this work, the time of formation of abrupt transition layers was estimated in the solutions of reaction–diffusion equations depending on the value of the small parameter λ . Application of the results of [7] to task (3) shows that lateral phase segregation in the lipid film will occur during a time of about

$$\tau(\lambda) = A\lambda^2 |\ln \lambda|. \quad (4)$$

Here, A is the calibration constant.

In [8], a polyatomic molecular–dynamic model of a lipid bilayer was considered. The lateral diffusion coefficient in the liquid–crystal state of the membrane varied from 10^{-8} to 10^{-6} cm²/s depending on the membrane composition, with characteristic times for the establishment of thermodynamic equilibrium from 0.3 to 3 ns. These data can be used for calibration of the expression (4), rewriting it as $\tau(D) = A/2D |\ln D|$; here, an allowance is made for $\lambda^2 = D$. The values of the calibration constant A vary from 3.26×10^{-4} to 4.34×10^{-3} s²/cm².

When deriving (4), it was a priori considered that regions of the coexistence of liquid and gel-like phases, which are separated from each other with an abrupt transition layer, could appear on the lipid membrane surface. Multiparticle membrane models make it possible to find the conditions of the appearance of phase and component segregation and thereby detect the limits of applicability of estimate (4).

2. Multiparticle Lipid Membrane Model

The Monte-Carlo method was used to investigate a lipid layer, with simulation on two-dimensional surfaces. The model region size was 25×25 nm.

The local structure of systems comprising several thousands of particles was determined using the following algorithm. The pattern of particle distribution in each of the numerical experiments was plotted by averaging the position of each of the particles for the last 1000 reference points (supposing that the configuration corresponding to the equilibrium state had already been found by that moment). Further, the positions of the closest neighbors were analyzed for each point of the system and it was determined whether they formed a hexagonal lattice with sufficient accuracy. Thus, it was possible to detect the lipids present in the gel (ordered) phase and those present in the liquid (unordered) phase.

The model describes a single- and two-component lipid membrane. Lipids are represented as particles interacting with each other by means of the Lennard–Jones potential:

$$V_{ij}(r) = \begin{cases} \varepsilon_{ij}[(\sigma/r)^{12} - (\sigma/r)^6], & r < R_c \\ 0, & r > R_c. \end{cases}$$

Here, r is the distance between the lipids, σ is a parameter characterizing the lipid radius, $R_c = 4\sigma$ is the distance at which the interaction between the lipids can be neglected, and ε_{ij} are the interaction constants. The configuration corresponding to the equilibrium distribution, i.e., the distribution with the lowest total energy, was sought using the Metropolis algorithm [9].

System parameters in the single-component variant were chosen as follows: $\sigma = 0.5$ nm, while during two-lipid film simulation the coefficients were $\sigma = 0.5$ nm, $\varepsilon_{22}/\varepsilon_{11} = 3$, and $\varepsilon_{12}/\varepsilon_{11} = 0.1$.

Diagrams of the ratio of the number of lipids in the gel phase N_{gel} to their total number N depending on relative temperature kT/ε_{11} and the number of particles N were plotted for the single-component lipid membrane model (Fig. 1).

A model comprising two types of lipids was used to study the phase and component segregation of the

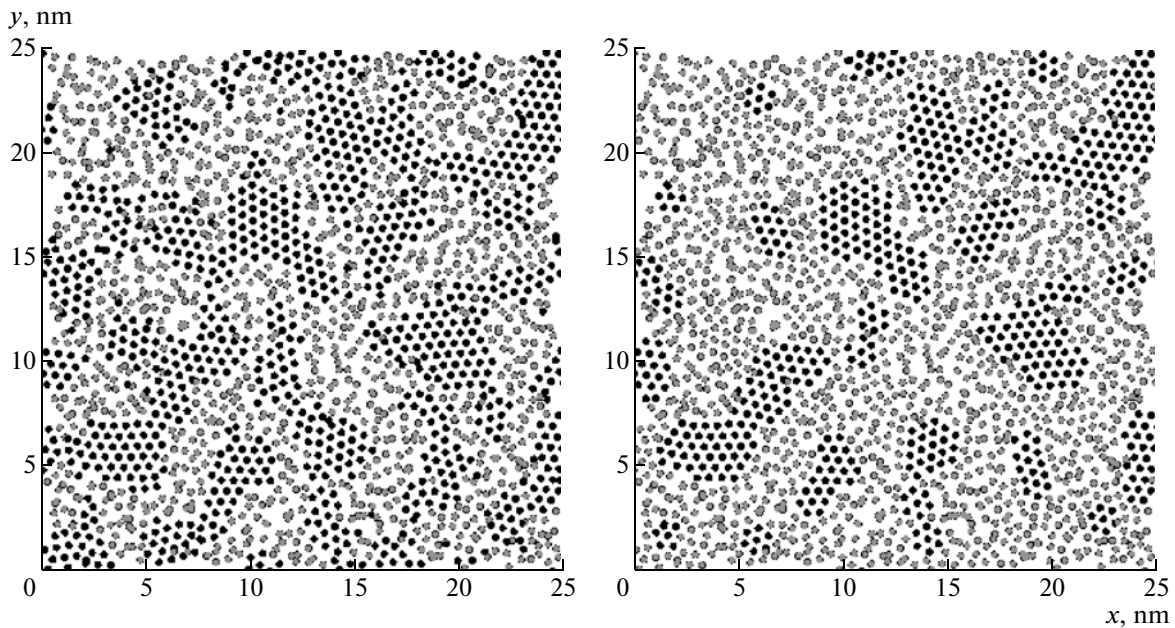


Fig. 2. On the left: Component segregation of a binary mixture; the two components are differently colored. On the right: phase segregation observed in the same binary mixture; the solid phase is in black and the liquid phase is in gray, $N = 2000$.

membranes. As can be seen from Fig. 2, the field of phase separation does not always coincide with the field of component separation.

A phase diagram was plotted for the two-component system (Fig. 3). It presents N_{gel}/N values at different temperatures and relative concentrations of the first component. The diagram demonstrates the existence of a range of system parameter values at which phase segregation is observed.

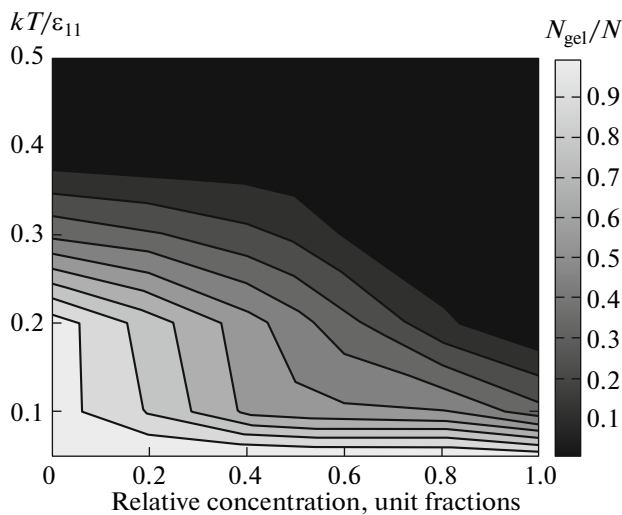


Fig. 3. Phase diagram of the temperature–concentration binary system. Regions with different ranges of N_{gel}/N values are colored differently.

CONCLUSIONS

Estimation of the time of phase segregation on a membrane surface was demonstrated. The results of publication [3] on asymptotic analysis of the reaction-diffusion equation are applicable to the task formulated using the phase field theory. The theoretical dependence was calibrated using experimental data.

The conditions of the appearance of phase segregation by the Monte-Carlo methods were determined using two-dimensional models of a single- and two-component membrane. The obtained phase diagrams of the systems showed the existence of phase and component segregation in membrane models.

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