Study of the lipids lateral diffusion associated with structural changes in cytoplasmic membranes

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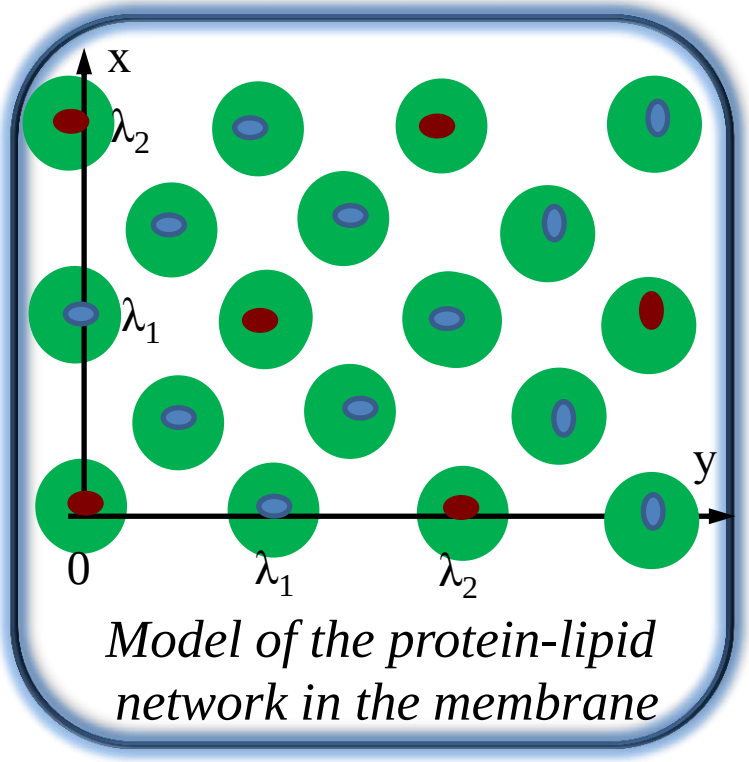
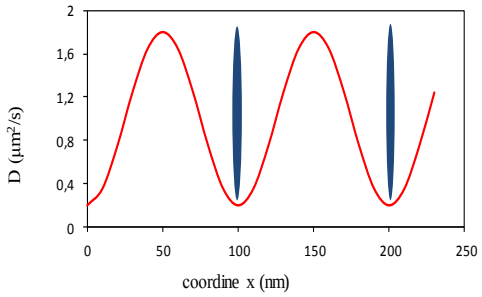
To date, it has been experimentally established that the diffusion of lipids in cytoplasmic membranes is complex. There are several qualitatively different types of lipid diffusion: slowed, confined, simple-Brownian, directed and hop diffusion. This paper presents a model of lipid diffusion in heterogeneous native cytoplasmic membranes. The lipid distribution function in a inhomogeneous membrane is analytically obtained. Criteria have been obtained for the implementation of which hop diffusion is observed in the membrane. It has been shown that the appearance of various types of lipid diffusion mentioned above is associated with structural changes in cytoplasmic membranes. When interacting with some ligands, a stationary periodic coordinate network of protein-lipid domains is formed in the cytoplasmic membrane, in which the lipid diffusion coefficient is lower than in the lipid bilayer between the domains.



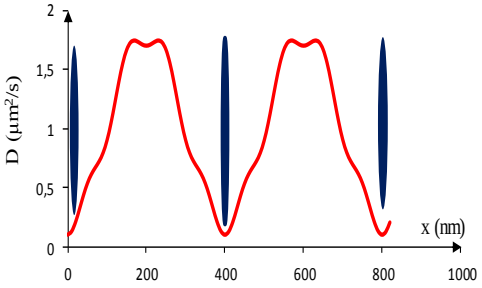
Model of the protein-lipid network in the membrane

A model of an infinite flat layer with an inhomogeneous, periodic diffusion coefficient D is considered. Two cases were studied – one and two sublattices of harmonic dependences of the diffusion coefficient D on the coordinate:

$$D = D_0 - D_1 cos(k_1 x) cos(k_1 y)$$



$$D = D_0 - \tilde{D}_1 cos(k_1 x) cos(k_1 y) - \tilde{D}_2 cos(k_2 x) cos(k_2 y)$$



where $D_0, \tilde{D}_1, \tilde{D}_2$ are the first, second and third diffusion coefficients, respectively, $k_1 = 2\pi/\lambda_1$, $k_2 = 2\pi/\lambda_2$, λ_1=100 nm is the distance between the nearest membrane proteins that have slightly changed their conformational state, λ_2 is the distance between the nearest membrane proteins that have greatly changed their conformational state.

The function of lipids distribution by coordinates is introduced:

$$\Psi(x,y,t)\,dxdy = dn(x,y,t)$$

Due to the diffusive nature of the movement of lipids in the membrane, the distribution function must satisfy the diffusion equation:

$$\frac{\partial\Psi(x,y,t)}{\partial t} = \frac{\partial}{\partial x}\left(D(x,y)\frac{\partial\Psi(x,y,t)}{\partial x}\right) + \frac{\partial}{\partial y}\left(D(x,y)\frac{\partial\Psi(x,y,t)}{\partial y}\right)$$

The diffusion of lipids in an infinite plane is considered. If at the initial moment of time the Brownian particles were at a point with coordinates (c,d), then $\Psi(x,y,0) = N_p\delta(c,d)$, where N_p is the number of particles, $\delta(x,y)$ is the delta function. We obtain a solution to this equation using the Fourier transform:

$$\Psi(x,y,t) = \frac{N_p}{4\pi G_1}exp\left\{-\frac{\left[\tilde{u}_1 t-(x-c)\right]^2+\left[\tilde{u}_2 t-(y-c)\right]^2}{4G_1}\right\}\text{, where}$$

$$G_1 = \left\{D_0 - \frac{\tilde{D}_1}{2}\left(cos\left(k_1(x-y)\right)+cos\left(k_1(x+y)\right)\right) - \frac{\tilde{D}_2}{2}\left(cos\left(k_2(x-y)\right)+cos\left(k_2(x+y)\right)\right)\right\}t$$

$$\tilde{u}_1 = \frac{\tilde{D}_1}{2}k_0\left(sin\left(k_1(x-y)\right)+sin\left(k_1(x+y)\right)\right) + \frac{\tilde{D}_2}{2}k_2\left(sin\left(k_2(x-y)\right)+sin\left(k_2(x+y)\right)\right)$$

$$\tilde{u}_2 = \frac{\tilde{D}_1}{2}k_0\left(-sin\left(k_1(x-y)\right)+sin\left(k_1(x+y)\right)\right) + \frac{\tilde{D}_2}{2}k_2\left(-sin\left(k_2(x-y)\right)+sin\left(k_2(x+y)\right)\right)$$

Where $\tilde{u}_1, \tilde{u}_2$ are the components of the two-dimensional vector **u** of the lipid advection velocity (drift velocity) along the x-axis and y-axis, respectively. The formula describes advection-diffusion in a flat layer.

We obtain analytically a condition when drift at advection of lipids X= |**u**|t is greater than dispersion $\sqrt{4G_1 t}$, i.e. when hop diffusion will be visible in experiments.

Consider the time evolution of the central maximum distribution functions $\frac{\partial \Psi(x,t)}{\partial x} = 0.$

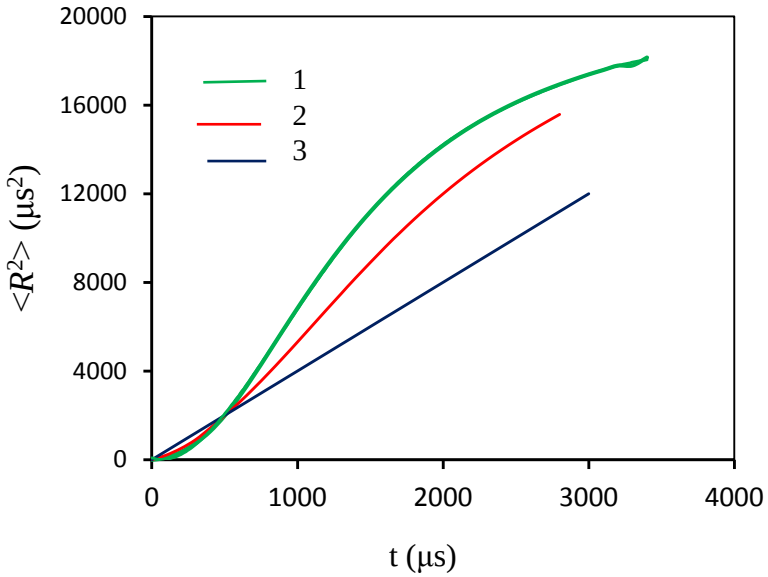
It is analytically shown that there is no advection in the initial time interval, but only diffusion exists. Then there comes a period of time when there is both advection and diffusion. Then there comes again a gap only of the diffusion movement of lipids and so on.

In experiments in a layer with two sublattices, advection is visible when

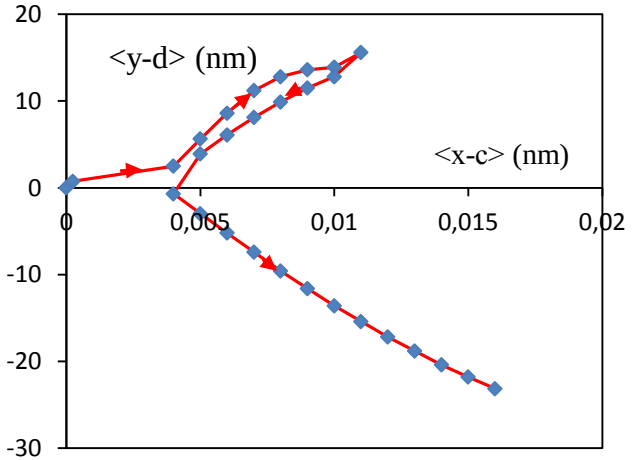
$\frac{(\beta_2 + \beta_3 q)^2}{\beta_2 + \beta_3 q^2} \geq 4(1 - \beta_2 - \beta_3)$ where $\beta_2 = \tilde{D}_1 / D_0, \beta_3 = \tilde{D}_2 / D_0, q = k_2 / k_1.$

In experiments in a layer with a single lattice, advection is visible when $\frac{D_1}{D_0} > 0{,}8.$

The results of numerical calculations confirm the conclusions of the analytical analysis. Initially, the particles move in a slow diffusion mode. At this time interval, the average displacement of the particle along the axes OX and OY is zero. Further, starting from the time of 1000 μs, advection is carried out, the average displacement of the particle is not zero. There is a local transfer of lipids to the center of attraction. The figure shows the evolution of the root-mean-square displacement of a particle for its two different initial coordinates.



Evolution of the mean square displacement of the lipid. Curve 1 - lipid started from the protein-lipid domain, curve 2 - lipid started between domain, line 3 - simple Brownian diffusion



The average displacement of a lipid from time. Lipid started between domain, which corresponds to curve 2 in the figure on the left

conclusion

- **This model explains well on a qualitative level the experimental results of measuring the movement of lipids in the cytoplasmic membrane**

- **It has been shown that the lateral diffusion of lipids in the cytoplasmic membrane is determined by structural changes in the membrane the appearance or disappearance of a stationary periodic network of protein-lipid domains associated with the cytoskeleton**

- **Criteria have been analytically obtained, when fulfilled, hop diffusion is observed in the membrane**

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