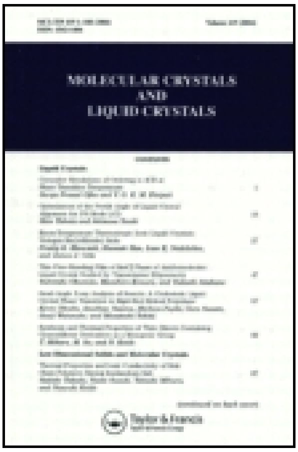

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MEMBRANE SELFOSCILLATIONS MODEL FOR THE TRANSBILAYER STATISTICAL PORES AND FLIP-FLOP DIFFUSION

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Abstract. The possibility of stochastic pores appearance through the lipidic bilayers, in absence of the electric field, is demostrated. The thickness fluctuations due to structural inhomogeneities and the dynamic of amphiphile molecules can determine the perforation of the bilayer.All possible evolution ways of the membrane after pore formation are studied and the flip-flop diffusion coefficient is calculated.

Keywords: membranes, oscillations, pores, diffusion

INTRODUCTION

The biological membranes and lipid bilayers, change their ionic permeability when they are subjected to short electric impulses or to a stationary electric field whose strength does not overcome a certain critical value[1,2]. If the electric field is stronger than a critical value, then the bilayer breaks down[3,4].Both phenomena have been connecting by the presence of the external field. In my opinion, the pores through the lipid bilayers may also appear in the absence of the electric field. They are stochastically in nature and are named statistical pores

Two mechanisms are possible for the appearance of a pore through a lipid bilayer: a) the evolution of structurally defects existing in the bilayer[5]; b) the self oscillation of the membrane surface due to own dynamics state[6]. The energy barrier for the appearance of a pore through a lipid bilayer for each of the two possible ways was calculated and their values are approximately equal[7].

Also, the formation of the statistical pores through lipid bilayers constitutes a new possibility for the explanation of transversal diffusion of lipid molecules through bilayers.

THE MEMBRANE SELFOSCILLATION SIDES

At the microscopic level, the lipid bilayer surface is neither smooth, nor static. The perpendicular oscillations of lipid molecules corroborated with the movement of the ions in the external electrolitic solution account for rugged look of the bilayer surface which is a succesion of valleys and peaks whose dimensions and position on the surface are continually modified.

It is very probable that two valleys, one on each side of the bilayer, are thinning sufficiently enough to be perforated, the result being a pore (**Figure** 1).

We suppose that these fluctuations from planeness have the form of the spherical caps, with a radius r_o and a maximum angle θ_m inside or outside the bilayer (Figure 1)

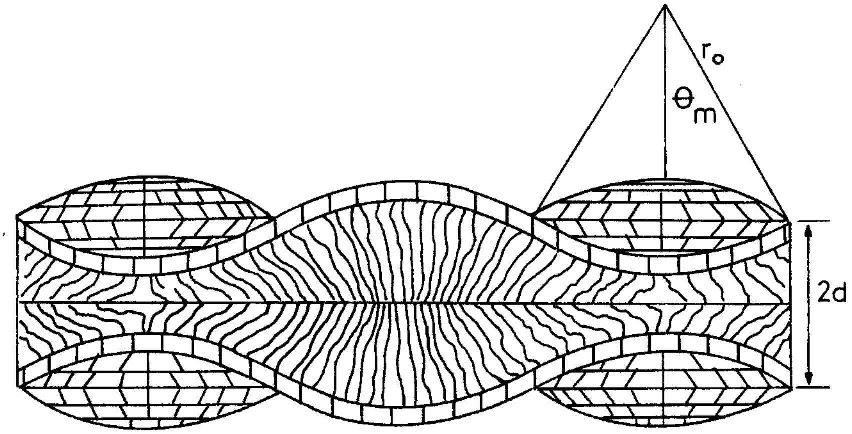

FIGURE 1. Selfoscillation of the lipid bilayer

The surface of a valley will be covered by n molecules each of them having an area a_o, and we can write[8]:

$$\bar{d} = nv/A \tag{1}$$

$$d_{max} = \bar{d} + r_o(1 - \cos\theta_m) \tag{2}$$

$$d_{min} = \bar{d} - r_o(1 - \cos\theta_m) \tag{3}$$

where, v is the volume of hydrocarbon chains, A is the area of spherical cap base, d is the mean thickness of the region affected by fluctuations, d_{max} and d_{min} are the maximum and the minimum thickness of the selfoscillating bilayer.

From the following conditions:

1. $d_{max} \leq l_{max}$ (the chain length in the extended state);
2. $d_{min} = c_p$ (the thickness of the polar region);
3. the volume change which results following the formation of a valley must not be greater than the volume of the "ring" of molecules at the edge of the spherical cap,

we can calculate the selfoscillation sizes.

FREE ENERGY CHANGE OF THE PERFORATED BILAYER

The phases of the evolution of the pore are represented in the Figure 2. The transbilayer pore formed by the mechanism of the thickness fluctuations will have an elliptic semitoroidal surface. The free energy change of the bilayer following the formation of an elliptic semitoroidal pore of radius r = R - b takes the form:

$$\Delta F = \Delta F_m + \Delta F_{sp} + \Delta F_{st} \tag{4}$$

ΔF_m is the free energy change due to membrane disappearance following the formation of a pore:

$$\Delta F_m = -2\pi R^2 \gamma_m \tag{5}$$

ΔF_{st} is the free energy change determined by the formation of the toroidal surface of the transbilayer pore. It is composed of two parts:

$$\Delta F_{st} = W_o + W_1 \tag{6}$$

$$W_o = N a_o \gamma_m \tag{7}$$

$$W_1 = \begin{cases} N(a - a_o)\gamma_h & \text{if } a(\theta,\varphi) \leq a_o \\ N(a_o - a)\gamma_m & \text{if } a(\theta,\varphi) > a_o \end{cases} \tag{8}$$

where, $_m$ and are the interfacial free energy per unit area for plane bilayer/water interface, respectively for

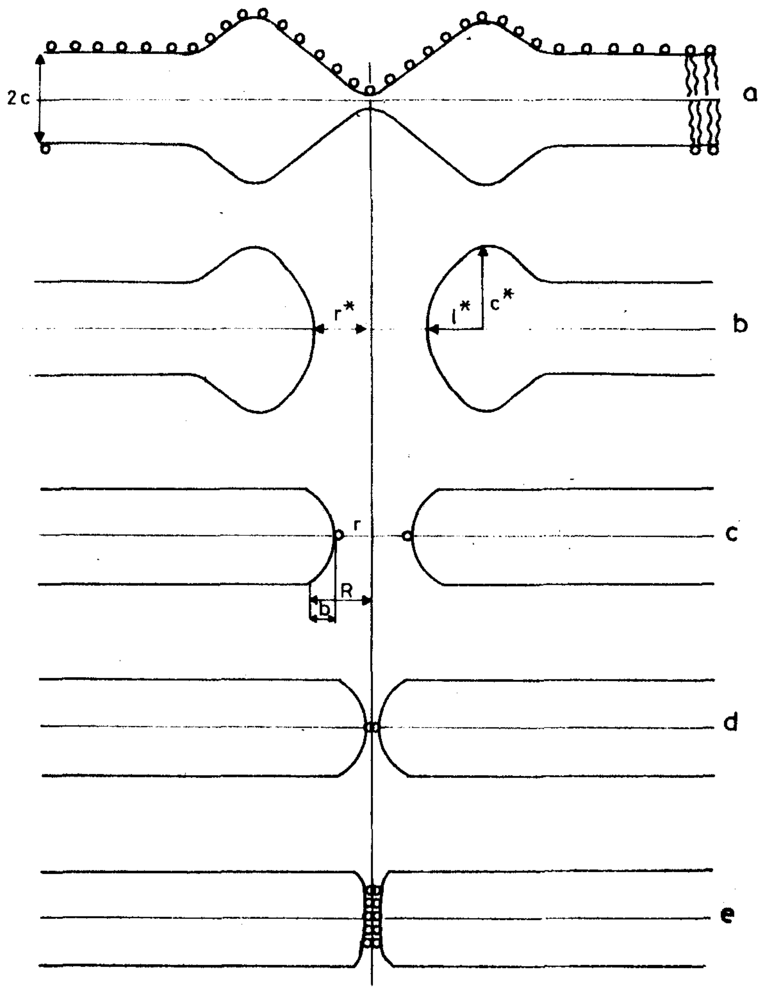

FIGURE 2 The phases of the formation, stabilisation and disappearance of a statistical pore in a bilayer. a) The phase of oscillation of the bilayer. b) Breaking of the bilayer. The two surfaces can be brought closer together or moved wider apart. In both cases the bilayer is in a state of striking lack of equilibrium. c) The stabilised pore. d) External causes or even thickness fluctuations in other places of the bilayer can bring about the disappearance of the pore. e) Pore closed like a zipper.

the hydrocarbon core/water interface. The signifiance of the geometrical parameters: R,r,b,c is given on the Figure 2. The superficial free energy W_o is due to the N molecules that cover the toroidal surface and are considered to have the same area per molecule a_o corresponding to the plane bilayer. The free energy change, W_1 is due to the increasing (or decreasing) of the contact surface between water and the hydrophobic core, by the change from the plane surface to the curved surface of the pore.[6] The final expressions of the free energy W_o and W_1 are:

$$W_o = Va_o\gamma_m/v = \begin{cases} 2\pi bc\gamma_m\,[y+(\pi/2-2/3)x] & \text{if } c<b\leq l_{max} \\ 2\pi c^2\gamma_m\,[y+(\pi/2-4/3)x+2/3] & \text{if } 0\leq b<c \end{cases} \tag{9}$$

$$W_1 = \begin{cases} (A - Na_o)\gamma_h = 2\pi c^2\gamma_h[(4I - x)y + (2I - f)x - \\ \qquad -(\pi/2 + 1/3)x^2] & \text{if } c<b\leq l_{max} \\ (Na_o - A)\gamma_m = 2\ c^2\gamma_m[(\pi/2 - 4I)y + (\pi/2 - 2I + f \\ \qquad - 4/3)x + x^2 + 2/3] & \text{if } 0\leq b\leq c \end{cases} \tag{10}$$

where, I is an elliptical integral,

$$I = \int_0^{\pi/2} \sqrt{1 - (1 - b^2/c^2).\sin^2 t}\ dt \tag{11}$$

f is defined as:

$$f = \begin{cases} \sin^{-1}(e) & e = \sqrt{1 - b^2/c^2} \quad \text{if } 0\leq b\leq c \\ \ln(k + b/c)/k & k = \sqrt{b^2/c^2 - 1} \quad \text{if } c<b\leq l_{max} \end{cases} \tag{12}$$

and $x = b/c$, $y = r/2c$ are normalized dimensions of the pore surface.

Fore the case when $b\leq c$ the occupation of a volume in the plane region by the hydrocarbon chains of the molecules with their head groups on the toroidal surface, determines a rarefying of molecules in a plane zone round of the pore like a disc whose width grows at the same time with the decreasing of the semiaxe b. In this way the contact area between water and the hydrophobic chains is growing, the result being a contribution ΔF_{sp} to the total variation of free energy of the bilayer following of the pore:

$$\Delta F_{sp} = 2\pi c^2(1-x)\left[\pi y+(\pi/2 -2/3)x +2/3\right] (\gamma_h - \gamma_m) \qquad (13)$$

RESULTS AND CONCLUSIONS

In Figure 3 the free energy change of the lipid bilayer due to the pore formation is represented:

$$\begin{aligned} z &= F(x,y)/kT \\ x &= b/c \ ; \quad x \geqslant 0 \\ y &= r/2c; \quad y \geqslant 0 \end{aligned} \qquad (14)$$

The numerical calculations have been made for lipid bilayer formed from 2,3-dimyristoyl-D-glycero-1-phosphoryl choline (DMPC), using the following data[9] : $a_o = 38.6$ Å^2, $v = 615.67$ Å^3, $c = 15.95$ Å, $l_{max} = 21.87$ Å, $c_p = 7.9$ Å, $\gamma_m = 0.02$ J/m^2 and $\gamma_h = 0.5$ J/m^2.
The following oscillation sizes have been calculated: $r_o = 231.67$ Å, $\theta_m = 14.1°$, $\bar{d} = 14.885$ Å.
There is a sadle-like point of coordinate $x = 1$; $y = 9.7$; $z = 2234$ on the plot from the Figure 3.

Each state of a pore is represented by a point on the surface (14). If the point is on the right of the plane $y = 9.7$ then the bilayer will evoluate towards breaking, and if the point is on the left of the plane then the pore will evoluate towards a stable state. This state is reached for $y = 0.0$ and $x = 1.0$, when the pore sheet has a common point in the middle plane of the bilayer (Fig.2d)

The fluctuation around this stable state can give birth to an open state or to a "more closed" state for $x \leqslant 0.1$. As it can be seen in Figure 4 and Figure 2c, for $x \leqslant 0.1$ the thickness of the contact region is equal to the thickness of the bilayer. From this state the molecules (few enough in number) whose polar heads make up the pore can redistribute themselves between the two monolayers, bilayer getting healthy.

Another possibility consists in the reorientation of

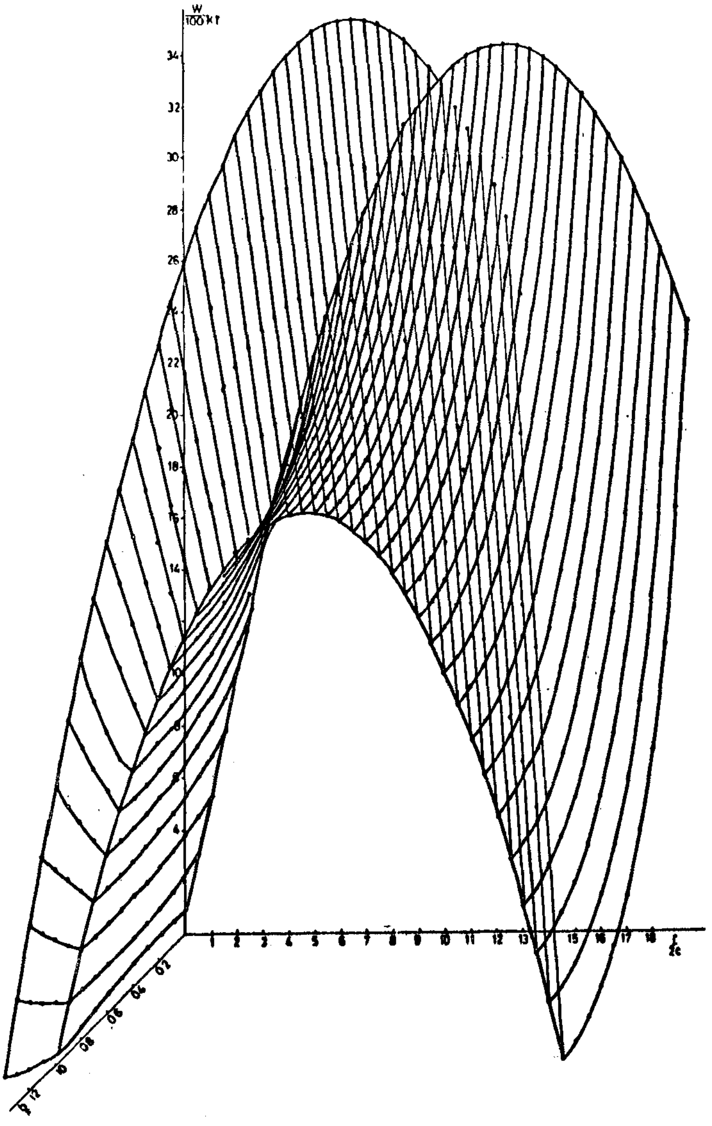

FIGURE 3 Plot of the function $z = \Delta F(x,y)/kT$, which gives the dependence of the free energy in scaled dimensions of the pore $(x=b/c, y=r/2c)$

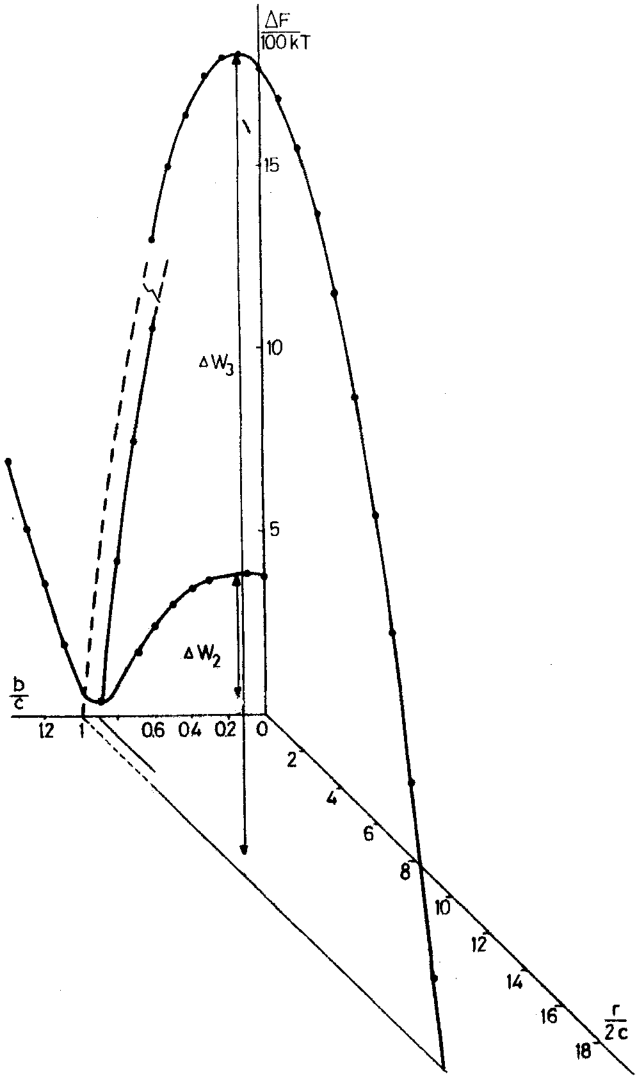

FIGURE 4 Important sections through the surface $z = \Delta F(x,y)/kT$ in Fig.3. The section with the plane $y = 0$ gives the energy barrier for the pore dissapearance, the lipid bilayer becomes healthy. For more clarity, their plot was modified by the liniar transformation $z = 5z' - 4z_o$, z_o is the real value of the minimum. The section through the saddle point of the surface with the plane $x = 1$, gives the energy barrier for the bilayer breaking, ΔW_3.

the polar head groups themselves on the surface of the pore making up a couple between their dipoles. This is a closed zipper-like pore[10]. Inside this pore there is a "thread" of water molecules. Also this pore should open.

The lateral diffusion of lipid molecules on the pore surface when the pore is open and the redistribution molecules when the pore disappears, can explain the flip-flop diffusion. From Figure 4 we can see that there are two energy barriers for:

a) The disappearance of the pore, when the bilayer become healthy, $\Delta W_2 = 74.193$ kT;

b) The breaking of the bilayer, $\Delta W_3 = 2344$ kT.

The free energy for the appearance of the pore, immediately after the perforation of the bilayer was calculated with the relation (4) in which $c^* = l_{max} = 21.87$ Å, $b^* = 18.78$ Å, $r^* = 2r_o \sin\theta_m - b^* = 8.74$ Å and $\Delta F_{sp} = 0.0$, because in this state of the bilayer, the phospholipid molecules did not have time to redistribute themselves between the plan and curved surface. The small semiaxis b^*,can be measured out on the condition that the inflexion points of the valley that determine the initial pore must be found on the ellipse whose big semiaxis is c^*. It has been found that energy barrier for bilayer perforation is $\Delta W_1 = 101.25$ kT.

Starting from these results we have calculated the flip-flop diffusion coefficient $D_{ff} = 10^{-23}$ m^2/s. If we consider a formula for D_{ff} that is similar to that for the translation diffusion, $D_{ff} = \bar{r}^2/4\tau$ and adopt the model of the jumps in an ordered two-dimensional network, then $\sqrt{\bar{r}^2}$ will be the thickness of the hydrophobic core and is the duration of the jump from one monolayer onto the other[11]. Considering a bilayer with the thickness of 32 Å it results $\tau = 2.56\ 10^5$ s. This value is comparable with lifetime of the phospholipid molecules in a lipid bilayer.

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