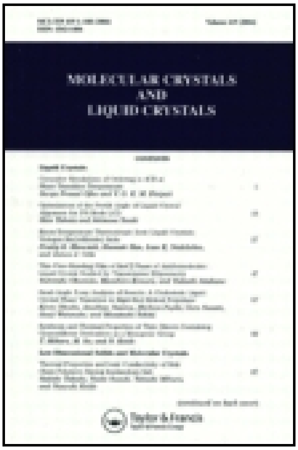

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Temperature Region of Meierane Activity

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TEMPERATURE REGION OF MEMBRANE ACTIVITY

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Abstract The functional model describing cell membrane properties is discussed in the case of four-site anisotropic interaction between lipid molecules. The lipids can appear in two conformational states and a phase transition from the phase with two states to the phase with one state only can be expected. Then the order parameter is different from zero in some temperature interval which can be considered as a region of the membrane activity in biological systems. In particular, the cation conductance through cell membranes is confined by the temperature of this transition as the lower limit while the upper limit is predicted by transition to the phase with disordered configurations.

1. INTRODUCTION

A functional activity of biological systems appear almost always in some intervals of values for physical parameters describing properties of these systems. The most typical and evident behaviour of this kind of activity in biological systems is observed as a function of temperature. In this paper we formulate a functional model which reflects this natural property by means of the order parameter, properly chosen, and different from zero only in a given temperature region. The approach is based on assumption concerning the interactions between elements of the considered system. Calculations for the order parameter corresponding to a given function of the system lead to the determination of this parameter, behaviour which shows that the function in question can appear in some limited temperature region only. The discussion is presented in the case of functional model[8] for the description of biological cell membranes.

In order to formulate the model in question we consider properties of the lipid bilayer in connection with the structure and its possible conformations. The physical background of this functional model is then given by the interactions of lipids which can appear in different conformational states stabilized by the coupling between the neighbouring molecules with different states. Of course, all the considered configurations can occur in all the network sites, but we assume that these exist in certain sites which are more probable for the appearence of a given kind of configurations. Therefore we introduce two sublattices for the lipid sites and we assume the interaction between lipids belonging to both sublattices. The model is usually formulated in the language of the projection operators for a given conformational state[1] and determined by the Hamiltonian like those used in the lattice gas[1] or interacting spins[3] theories. Of course, this analogy is very useful in mathematical treatment of the problem.

The description of cation conductance through cell membranes within the functional model as an example of its application was earlier formulated and temporal behaviour of the conductance was analyzed[9]. In the present paper we extend this model in order to explain that the membrane activity can be possible only in a given temperature region as a consequence of the membrane construction. Namely, we apply the extended model for membranes to the discussion of phase transitions in the function of proteins. Then the conductance state determined by the open and closed channels connected with the protein states can be treated as an example of the nature of cooperative phenomena and their links with the temperature confinement of biological activity.

2. MODEL OF A MEMBRANE

We repeat now the assumptions made for the model of a membrane used in[9] and we introduce an additional, more detailed description of the elements occuring in the model. We assume that a membrane forms three layers with the surface layer network sites covered by lipids and the internal layer occupied by proteins randomly distributed and interacting with lipids. There is no direct interaction between proteins. The lipids can appear in two conformational states and can be situated in two kinds of the network sites. The short-range interactions between lipids in different network sites are different. Moreover, the interaction is strongly anisotropic and it is of four-site anisotropy character. This kind of anisotropy is a new element of the functional model. Its appearance is connected with the discussion of the behaviour for two conformational sublattices.

Generally speaking, the Hamiltonian written in terms of the projection operators contains in fact the expressions for all powers with respect to the projection operators. The bilinear form discussed up to now is one of the simplest realizations of lipid-lipid interactions[1]. The next step should contain terms of higher order. Taking Hamiltonian concerning the conservation symmetry and time invariance we can see that the Hamiltonian should contain the terms with four projection operators. In particular, we require that the Hamiltonian should describe a possibility of transition

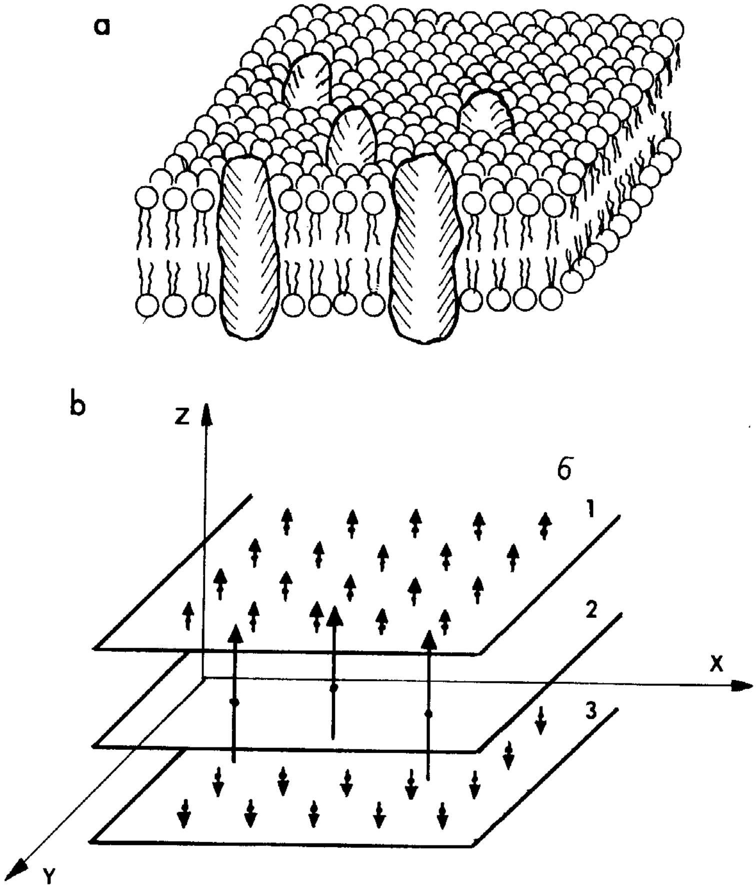

FIGURE 1. The model of biological membrane.

a) Structure of membrane according to the liquid mosaic.

b) Biological membrane in functional model presented in this paper: the proteins and lipids are placed by the pseudospins which interact with one another. The layered structure of the membrane is mapped by the layers ($\sigma=1, 2, 3$) related to the lipids and proteins.

from the phase with two conformations to the phase with one conformation only. This fact allows us to choose the anisotropic term in the form of four-site anisotropy by means of the analogous arguments as those applied in the theory of metamagnetics where the phase transition from antiferromagnetic to ferromagnetic phase is expected[4].

Next, we would like to mention that the distribution of lipids with different conformations plays an important role for the construction of the Hamiltonian because of the interaction between two different sublattices. There are no predictions enabling us to establish this structure precisely. Therefore we suggest to discuss this question in variants. The choice of one of possible variants should be confirmed by comparison with experiments.

In this paper we confine our discussion to one possible configuration by assuming two sublattices occupied by lipids with two different conformational states of molecules. In the simplest case when the sublattices are equivalent to inner and outer layers forming a membrane the interaction is different in the plane and between two planes. It is easy to show that this configuration is topologically equivalent within the molecular field approximation to the configuration where we have the nearest neighbours belonging to the different sublattice with respect to the element considered.

Of course, the above interpretation seems to be quite probable, but it serves only as an illustrative mechanism. It has no essential influence on the applicability of the presented model in general to the considered questions while it allows us to discuss some properties in a concrete form.

The structure of the lipid bilayer and random distribution of proteins in the middle plane is shown on Figure 1. The structure of polymers which are perpendicular to the

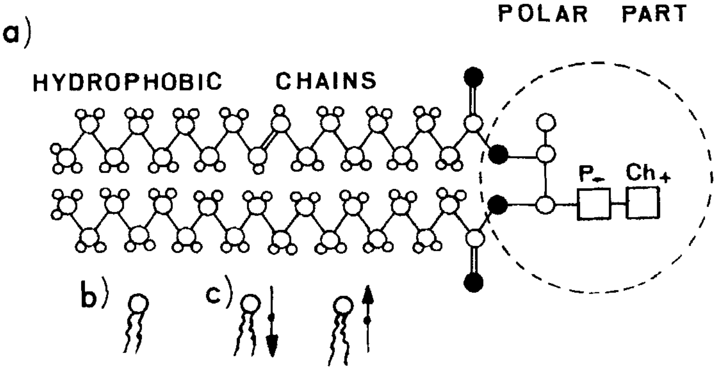

Figure 2. a) One kind of phospholipid molecule: ○ - carbon, o- hydrogen, ●- oxygen, ch - choline group, p - phosphate group[6].

b) Symbolic presentation of phospholipid molecule.

c) The conformational states of lipids with their pseudospin notation in functional model presented in this paper.

membrane surface and form the bilayer is presented on Figure 2. At the same time the figures indicate the notation of the symbols used here according to our previous paper[9].

3. EQUATIONS FOR ORDER PARAMETERS

The system of two lipid conformational sublattices and one protein sublattice can be described by means of three order parameters: two for the lipid conformations and one for the protein permeability proportional to the probability of the appearance of open channels[9]. We define them as the average values of the projection operators, namely $\langle S_1^z \rangle$ and $\langle S_3^z \rangle$ refer to the order of two conformations which are connected with two sublattices determined as the outer ($\sigma=1$) and inner ($\sigma=3$) layers. The protein order is described then by $\langle S^z_2 \rangle$. Usually, the order parameter $m=0.5(\langle S^z_1\rangle + \langle S^z_2\rangle)$ characterizing the degree of the order of conformation distribution is introduced.

The behaviour of the order parameters is described by means of the Hamiltonian of the system, which is now assumed in the form

$$H=H^0 + H^a \tag{1}$$

where according to[9]

$$H^0 = - \sum_{\sigma j \neq \sigma' j'} I_{\sigma\sigma'} S^z_{\sigma j} S^z_{\sigma' j'} - \sum_{\sigma j} B_\sigma S^z_{\sigma j} \tag{2}$$

and

$$\begin{aligned} H^a = {} & \frac{1}{2} \sum_{\substack{1j3j \\ 1j'1j''}} D\, S^z_{1j} S^z_{3j} S^z_{1j'} S^z_{1j''} \\ & + \frac{1}{2} \sum_{\substack{3j1j \\ 3j'3j''}} D\, S^z_{3j} S^z_{1j} S^z_{3j'} S^z_{3j''} \end{aligned} \tag{3}$$

with j standing for the two-dimensional position vectors belonging to the sublattice σ. The interaction elements $I_{11}=I_{33}=I_s$, $I_{22}=0$, $I_{12}=I_{23}=I_p$, $I_{13}=I_{31}=I_a$, $B\sigma=0$, while I_s, I_p, I_a, D are the parameters of the theory at the level of calculation.

The solution of the Hamiltonian (1) for the order parameters is mathematically equivalent to the solution of the Hamiltonian for metamagnetics[5]. Taking into account this equivalence we write the free energy F in the form

$$f=\frac{F}{Nk_BT_c}=\frac{SA}{2}\ [\alpha(x^2+y^2)+2xy+2\beta cz(x+y)$$

$$-\ 3dxy(x^2+y^2)]\ -\ t\sum_{\sigma}\ln\frac{\sinh(S+\frac{1}{2})y}{\sinh\frac{1}{2}\ y} \tag{4}$$

where T_c denotes the critical temperature for which the values $\langle S_1\rangle$ and $\langle S_3\rangle$ are equal zero, k_B is the Boltzmann constant while

$$y_1=\frac{A}{t}\ [\alpha x+y+\beta cz-\frac{1}{2}\ y(3x^2+y^2)d] \tag{5}$$

$$y_2=\frac{A}{t}\ [\beta(x+y)] \tag{6}$$

$$y_3=\frac{A}{t}\ [\alpha y+x+\beta cz-\frac{1}{2}\ x(3y^2+x^2)d] \tag{7}$$

and $t=T/T_c$, $A=3/[(S+1)(\alpha+1)]$, $\alpha=I_s/I_a$, $\beta=I_p/I_a$, $d=DS^2/I_a$, $x=\langle S_1\rangle/S$, $y=\langle S_3\rangle/S$, $z=\langle S_2\rangle/S$. The formula (4) reduces to that obtained in[5] for $\beta=0$. Minimizing the free energy with respect to x, y, z we obtain

$$x=B_s(y_1);\qquad y=B_s(y_3);\qquad cz=B_s(y_2) \tag{8}$$

with c denoting the concentration of proteins. The quantity cz is a measure of the cation permeability. In the eq. (8) the Brillouin function $B_s(y)$ has the form

$$B_s(y)=\frac{2S+1}{2S}\operatorname{ctgh}\left[\frac{(2S+1)y}{2S}\right]-\frac{1}{2S}\operatorname{ctgh}\left(\frac{y}{2S}\right)$$

which is the solution of the equation

$$\langle S_j^z\rangle=\frac{T_rS_j^z\exp(-\frac{H}{kT})}{T_r\exp(-\frac{H}{kT})}$$

with Hamiltonian H in molecular field approximation.

The eqs (8) have two solutions below $t=1$ ($T=T_c$) and one solution ($x=0$, $y=0$, $z=0$) above $t=1$. It means that the lipid conformations are completly disordered above the phase transition temperature T_c which plays now the role of the temperature for the transition from the ordered to disordered phase. Below T_c ($t=1$) one of the solutions is also of this character ($x=0$, $y=0$, $z=0$), but the second solution is different from zero for $0<t<1$ and has the property $|x|=|y|$ while both variants are possible, ie. (a) $x=-y$, and (b) $x=y$. In the case (a) we can speak about the appearance of two conformations which are easily distinguished. Then the total order parameter $m=0$, and $z=B_s(2\beta mSA)=0$. In the case (b) both sublattices are occupied by the some conformation. It is rather difficult to distinguish between them and we can speak about the phase with one conformation only. The order parameter $m=0$ shows that the phase is ordered. Then $cz=B_s(2\beta ma/t)$ *is different from zero. In our example this* case corresponds to the active state of protein channels.

The realization of one of two possible cases (a) or (b) depends on the minimum of the free energy f with respect to the corresponding solutions ($x=-y$) or ($x=y$). In general, the free energy varies in tempetature, so that we can expect the transition from one case to another. The transition temperature t is determined by the condition $f_a(t_M)=f_b(t_M)$. Taking into account our example concerning the cation conductance we find that this phase transition corresponds to the transition from phase with $z=0$ to the phase with $z\neq 0$. We mention here that the phase transition at temperature T_c means the transition from the phase with $z\neq 0$ to the phase $z=0$. Thus we can expect that the protein channel activity is confined by two phase transition points.

4.DISCUSSION OF SOLUTIONS

As an example of our calculations we present in Figure 3a the free energy as a function of reduced temperature. The curves denoted on the Figure as 2 and 3 have a common point, which is connected with temperature t_M. All these three curves have the common point in the reduced temperature t=1 and this point is connected with the phase transition between ordered and disordered conformational state. In Figure 3b the quantity cz is presented, which describes the activity of biological membrane. As we see, this quantity is different from zero in the temperature region $t_M<t<t_c$ which

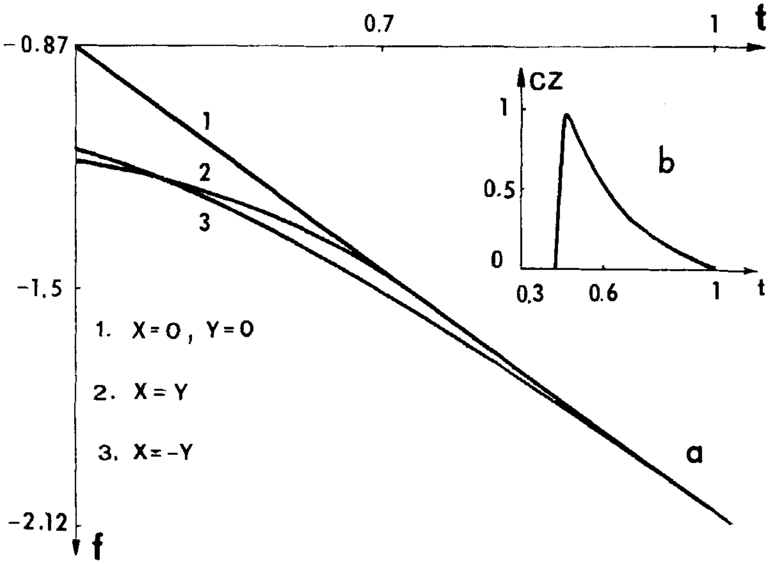

FIGURE 3. a) The free energy as a function of reduced temperature t.

b) The normalized quantity cz connected with the membrane activity as a function of reduced temperature t. The calculation were done for the α=5, d=1.2, β=0.01

can be considered as the region of membrane activity. Figure 4 presents the quantity cz but for different parameters whose values are described under the Figure. The state represented by the curve denoted on Figure 4 as 1 has only

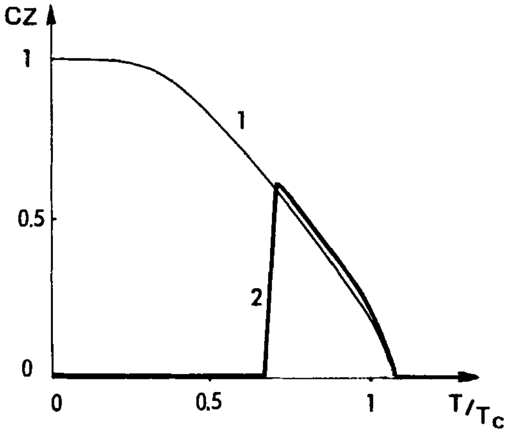

FIGURE 4 The quantity cz calculated as a function of reduced temperature t - the curve 1 was calculated for the parameters $\alpha=5$, $d=1.2$, $\beta=1$; the curve 2 for $\alpha=10$, $d=3$, $\beta=2$.

one phase transition point butthat given by curve 2 has two phase transition points. Our numerical calculations showed that the relations between all parameters are not simple and detailed calculations arenecessary to conclude finally about their behaviour.

5. DECORATION OF MEMBRANE

The interaction of small molecules with biological membranes is of interest in understanding the mechanism of membrane functions. In particular, this interaction is important in the case of anasthesia[4]. The theory of this phenomenon is based mainly on the assumption that the anasthetics lower order-disorder temperature and increase the cation permeability. There are several slightly different approaches to his question, in particular, the model presented by Nagle[2] and its generalization including an interaction with small molecules[7]. The idea of surface decoration is very close to the functional mode here presented, mainly in the case of the sorption theory taken into account. Therefore we consider a membrane decorated at it surface by small molecules sorbed by polymers forming a biological bilayer. The aim of this procedure is connected with two aspects: (1) to formulate a consistent approach to the decoration process within one functional model in order to treat the comparison of the results as a test for the functional theory, (2) to consider a shift to both phase transition temperature T standing for order-disorder temperature which is also analysed in other models[2] and T_M connected with the conformational phase transition. The behaviour of T_M in a function of sorption is then one of additional tests conforming the proper choice of the model assumption and its effectiveness. The application of the sorption sites are identified with the outer sublattice sites and interactions are determined by the coupling between the sorption operators c_{1j} and projection operators S_{1j} for a given conformation. Then the total Hamiltonian H_t consists of two parts H given by (1) and[7]

$$H_S=K\sum_j S^z_{1j}\ C_{1j} + (E-\mu)\sum_j C_{1j} \tag{9}$$

where μ denotes the chemical potential, K is the interaction parameter and $E(E<0)$ denotes the sorption energy. In the molecular field approximation the Hamiltonian (9) adds the expression

$$y' = \frac{A}{t}(-\ae\theta) \qquad (10)$$

to y_1 given by (5) and

$$\frac{F'}{Nk_BT_c} = As\ae\theta x - t\ \ln\frac{\sinh(s+\frac{1}{2})y_\theta}{\sinh\frac{1}{2}y_\theta} \qquad (11)$$

with

$$y_\theta = \frac{A}{t}[-\ae x - (E-\mu)/I_a] \qquad (12)$$

to the free energy given by (4). The symbols have the following meaning: $\ae = K/I_a$, $\theta = \langle C_1\rangle/S$ - plays the role of the sorption concentration. The solution is found as

$$\theta = B_S(y_\theta) \qquad (13)$$

while the sorption concentration is determined by the energy E which is releted to the so-called sorbate activity determined by $\gamma = \exp[-(E-\mu)/K'T]$, where $K' = I_s/2T_c$. This parameter appears in the formula (12) like the applied field term so that does not vanish for any temperature independently of the coupling with x. The parameter x does not vanish now because of the argument $y_1 + y'$ in (8). In the case $x \to 0$ we have

$$\theta = (\gamma - 1 - A\ae xt^{-1})(1+\gamma)^{-1} \qquad \text{for} \quad s = \frac{1}{2}$$

Substituting this expression to (8) we can see that the effective parameter

$$\alpha \to \alpha' = \alpha + \frac{A}{t(1+\gamma)}\ae^2 < \alpha$$

Thus the phase transition temperature T'_c should be expected as $T'_c > T_c$.

The present paper gives a possibility to discuss the sorption influence on the phase transition temperature T_M This discussion requires numerical analysis of the free energy considered in a function of θ. The results are presented on Figure 5. We can see that the sorption does not

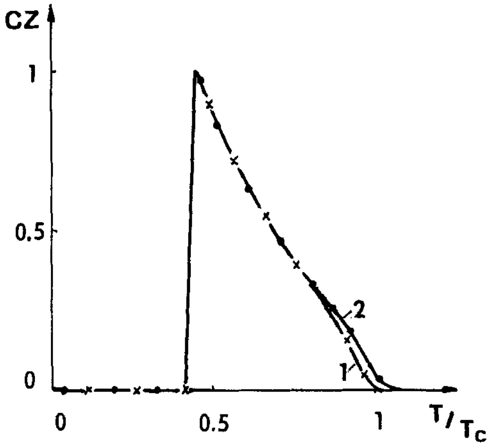

FIGURE 5 The quantity cz as a function of reduced temperature: curve 1 - $\alpha=5$, $d=1.2$, $\beta=0.01$; curve 2 - $\alpha=5$, $d=1.2$, $\beta=0.01$, $æ= -0.5$, $(E - \mu)/I_a = -0.15$ (this curve was calculated from the model with sorbed molecules on the surface).

shift the point T_m and is rather connected with the temperature T_c. Thus the temperature region of biological activity is shifted towards higher temperature and it is expected to be larger under the sorption influence. Of course, the shift depends on the interaction parameters, which means a dependence on the type of sorbed molecules.

6. CONCLUSIONS

The analysis of the free energy for cell membranes described by the functional model with four-site anisotropy shows that the conformational phase transition in a lipid bilayer appears for some values of the interaction parameters. The phase transition temperature T_M depends on the anisotropy constants and belongs to the interval: $(0, T_c)$. Such behaviour of the free energy leads to the apperance of the total order parameter m in a definite temperature region (T_M, T_c) only.

In our example considered in connection with the cation conductance the parameter m determines the protein activity, so that this activity occurs in a definite temperature region. We showed also that this region can be shifted by the sorbed molecules at the surface of a membrane.

The results obtained and their interpretation presented here allow us to state that it is possible to describe the membrane properties by means of a parameter showing that a membrane is active in some temperature interval. This means the existence of a temperature region for biological activity of living systems. We think that the presented considerations are of general character as far as they can enable us to generalize their conclusion for arbitrary biological objects.

Apart from the particular conclusions concerning the existence of the temperature phase transitions and their mechanisms in membranes the present work allows us to suggest that the construction of the functional model assures its wide applicability to various problems. The physical background leads to the proper Hamiltonian whose general form can be found by succesive approximations. The collective character of important features of biological systems is reflected by the model itself. The fact of the collectivity realized by conformational states, their coexistence and transitions between various conformations seems to be a basis of living processes. It is natural that the questions of the distributions between various topological configurations or excited states, their role and mainly their competition in considered phenomena should be discussed within the functional model. In the light of the above analysis the model is open for such investigations.

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