Chemoeelastic Effect of Membranes
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Membrane, Elasticity, Erythrocyte, Enzyme Coupling

The elastic theory of a uniaxial membrane in an asymmetric environment predicts a spontaneous splay deformation. This spontaneous curvature of the membrane is discussed by the intrinsic splay of the membrane molecules (e.g., wedge shaped molecules) and their polar orientation. The chemoelastic effect is the polar orientation induced by the asymmetric environment in connection with the intrinsic splay. This effect is also discussed for polyelectrolytes where a small change of pH (~0.1) can lead to a spontaneous curvature of 10^4 cm^{-1}. The actual shape of red blood cells can be explained by the spontaneous splay and a change in environment induces the change in shape of these cells. A model is proposed for two conical bodies swimming in a uniaxial membrane which interact with each other through elastic coupling. The force between the bodies can be either attractive or repulsive. As an example of this model clustering of proteins is discussed.

1. Introduction

A biological membrane is mainly composed of a matrix of lipids and proteins\textsuperscript{1}. The term “lipid” stands for a wide range of natural products, as fatty acids and their derivatives, steroids, carotenoids, etc. These lipid molecules form a bilayer, and different proteins swim in this bilayer as shown schematically in Fig. 1. Due to the different molecular interactions between proteins, membrane and water, the proteins will have different positions in the membrane. For example, some proteins will swim like icebergs in the membrane and others are fixed with a foot at the membrane, as shown in Fig. 1, so that the main part of the proteins is in the water. The structure of a membrane becomes still more complicated because some proteins cluster and form subunits, and proteins can have an influence to the arrangement of the lipids, as shown in Fig. 1. A membrane with such a complicated structure can be characterized as a two dimensional alloy\textsuperscript{2}, and therefore the elastic properties can be mainly understood by treating the alloy as a continuum.

The elastic properties of membranes can be considered as an elastic shell with a preferred direction\textsuperscript{3} (see Fig. 2). This preferred direction is mainly given by the average direction of the elongated lipid molecules. If this preferred direction is identical with the normal of the membrane and if the center of mass of the molecules has no long range correlation, then the membrane can be described as a uniaxial membrane. The elastic properties of membranes can be easily understood, if one extrapolates the bulk elastic properties of liquid crystals to thin films. On one hand there exists the strain elasticity which connects stress and strain. It describes in solids the well-known elasticity and in isotropic fluids the compressibility. On the other

Fig. 1. Schematic representation of a biological membrane, composed of a lipid bilayer with different proteins.

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hand there exists the curvature or orientation elasticity which can be easily demonstrated by looking at a nematic liquid crystal. A nematic liquid crystal is a fluid with an anisotropic distribution of the long axes of the molecules and with no long range correlation of the center of mass. Therefore only spatial derivatives of the optical axis are connected with elastic properties. This curvature or orientation elasticity of nematic liquid crystals is described by three main elastic constants $k_{11}, k_{22}$ and $k_{33}$ which are referred as splay, twist and bend elastic constants, respectively. In a membrane where the preferred direction of the molecules $\mathbf{L}(|\mathbf{L}| = 1)$ is identical with the normal of the plane, only the splay elastic constant $K_1$ exists (see Fig. 2). But if the membrane or its environment is asymmetric, there exists a spontaneous splay elastic constant $k_s$ which will be discussed in details.

The spontaneous splay of a membrane is similar to the spontaneous twist of a cholesteric liquid crystal where an intrinsic twist, produced by chiral molecules, adds up to a macroscopic rotation of the optical axis. The topic of this section is to derive the intrinsic splay $c_s$ from a molecular model. In the next section the polar orientation $P_1$ will be discussed.

2. Spontaneous Splay of a Membrane

The curvature elastic energy per unit area of a uniaxial membrane can be derived from the symmetry of the system:

$$g_{\text{elastic}} = K_1 (\nabla \cdot \mathbf{L}) + \frac{1}{2} K_{11} (\nabla \cdot \mathbf{L})^2$$

or

$$g_{\text{elastic}} = \frac{1}{2} K_{11} (\nabla \cdot \mathbf{L} + c_0)^2 - \frac{1}{2} K_{11} c_0^2$$

with

$$c_0 = 1/r_0 = K_1/K_{11}.$$  (3)

The spontaneous splay elastic constant $K_1$ or the spontaneous curvature $c_0$ are zero for a symmetric membrane with a symmetric environment. But if the membrane and environment are asymmetric, $K_1$ and $c_0$ are non-zero. The spontaneous curvature $c_0$ can be described by an intrinsic splay $s_c$ which depends mainly on the intrinsic properties of the membrane and the polar orientation $P_1$ which is caused by the interaction between the membrane and the asymmetric environment:

$$c_0 = s_c \cdot P_1.$$  (4)

If the polar orientation is small enough, a linear relation exists between the spontaneous curvature and the polar orientation, so that the intrinsic splay is a constant. This linear relation is similar to Hooke’s law which describes a linearity between stress and strain.

The asymmetric membrane can be described by a polar molecular distribution $\mathbf{P}_1$. This means, the number of molecules of the same specimen which point up and down, is different ($n_+ \neq n_-$):

$$\mathbf{P}_1 = (n_+ - n_-)/(n_+ + n_-).$$  (5)

For wedge shaped molecules, as shown in Fig. 3, the polar distribution can be described by the average of the first Legendre polynomial $P_1 (= \cos \Theta)$.

$$\mathbf{P}_1 = \langle \cos \Theta \rangle.$$  (6)

The topic of this section is to derive the intrinsic splay $s_c$ from a molecular model. In the next section the polar orientation $P_1$ will be discussed.

The polar orientation leads to a bending of the membrane, if the molecules which form the membrane, have an anisotropic shape. Fig. 3 illustrates such a spontaneous splay deformation in the case where the molecular distribution is completely polar. The spontaneous curvature $c_0$ can be obtained from geometrical arguments:

$$c_0 = 1/r_0 = \Phi/b \quad (\mathbf{P}_1 = 1).$$  (7)

$b^2$ is the average area which one molecule occupies, and $\Phi$ is the average angle of the wedge shaped molecules. From Eqn (7) one could expect for the intrinsic splay:

$$s_c = \Phi/b.$$  (8)

This intrinsic splay belongs to a membrane with wedge shaped molecules which can flip under the influence of an asymmetric environment.
Another model for the intrinsic splay is that the molecules can not flip but they can change their surface as a function of the environment. This effect can occur if the membrane contains molecules which are polyelectrolytic. This means a neutral molecule changes at a certain pH value to a single charged and at another pH value to a double charged molecule and so on. It is possible that the larger ionised form of the molecule occupies a larger area than the lower ionised form due to the repulsive electrostatic forces. The spontaneous curvature for polyelectrolytes is (see Fig. 4):

\[ c_0 = \frac{1}{2} \frac{d}{(\Delta a/a)}. \]  

Fig. 4. Schematic representation of a spontaneous curvature (membrane is composed of polyelectrolytic molecules).

\( d \) is the thickness of the membrane and \( \Delta a/a \) is the relative change of the membrane surface. One expects from geometrical arguments the following intrinsic splay:

\[ s_c = \frac{1}{2} \frac{d}{(\Delta a/a)}. \]  

(10)

If the relative change of the area is expressed by a flip of wedge shaped molecules, one finds in the small angle approximation \((\Phi \sim \tan \Phi)\) that Eqn (10) is identical with Eqn (8). The polar orientation \( P_1 \) for polyelectrolytes is also given by Eqn (5) but the states up and down have now the meaning of different charged states.

This spontaneous curvature of a membrane is similar to the spontaneous twist of a cholesteric liquid crystal. In this case the intrinsic twist adds up to a macroscopic rotation of the optical axis (Fig. 5). A rotation of \( 2\pi \) defines the pitch \( p \) and the rotation power \( q \) which are related to the spontaneous twist elastic constant \( k_2 \) and the twist elastic constant \( k_{22} \) as

\[ q = 2\pi/p = t_c \frac{P_2}{P_1} d^{-1} = k_2 / k_{22}. \]  

(11)

Similar to the cholesteric liquid crystal the spontaneous splay elastic constant \( K_1 \) and the splay elastic constant \( K_{11} \) of an uniaxial membrane can be related to the spontaneous curvature \( c_0 \) as

\[ c_0 = 1/r = K_1 / K_{11}. \]  

(3)

The spontaneous curvature \( c_0 \) of a membrane which is built up with different molecules, can be expressed by:

\[ c_0 = s_{c1} P_{11} a_1 + s_{c2} P_{12} a_2 + \ldots \]  

(12)

\( s_{cn} \) and \( P_{1n} \) are the intrinsic splay and the polar orientation of the \( n \)-th specimen respectively. \( a_n \) is the area occupation

\[ a_n = \left( b_n^2 c_n \right) \left( b_1^2 c_1 + b_2^2 c_2 + \ldots \right)^{-1} \]  

where \( b_n^2 \) and \( c_n \) are the average area and the area concentration of the \( n \)-th specimen respectively (see e.g. Fig. 6).

Fig. 6. Spontaneous curvature of a membrane which is composed of different molecules.

The molecular models for a polarized membrane can be used to estimate the intrinsic splay \( s_c \). One finds for a small wedge shaped molecule \((\Phi = 0.1 \sim 10^\circ\) and \( b = 10^\circ \)) an intrinsic splay of \( \sim 10^6 \) cm\(^{-1}\). The intrinsic splay is \( 10^5 \) cm\(^{-1}\) for \( \Delta a/a \) of about 0.1 and for a membrane thickness \( d \) of 50 Å. If one assumes that the polar orientation is of the order of \( 10^{-3} \), the spontaneous curvature is of the order of \( 10^2 \) to \( 10^3 \) cm\(^{-1}\). The biconcave shape of red blood cells can be used to measure the spontaneous curvature of the membrane of red blood cells. Therefore the spontaneous curvature can be used to fit the actual shape of red blood cells by minimizing the total elastic energy. Helfrich and Deuling made such calculations and found an intrinsic splay of \( 10^5 \) cm\(^{-1}\) for the actual shape of red blood cells.

The intrinsic splay \( s_c \) influences not only the spontaneous splay elastic constant \( K_1 \) but also the splay elastic constant \( K_{11} \). This can easily be seen...
for the symmetric case where $K_1$ is zero. This case is discussed in detail for the nematic phase in ref. 10. If one applies a splay deformation to the membrane, then in steady state the deformation energy is reduced by the intrinsic deformation. Therefore the applied splay deformation produces by means of the intrinsic splay a polar orientation $\bar{P}_1$:

$$\bar{P}_1 = \frac{a_s P_s s_c \nabla \cdot \mathbf{L}}{3 k T} + \ldots \quad (14)$$

$a_s$ is a constant which describes how difficult it is to change the polar order of the molecules in the membrane. $P_s$, $k$ and $T$ are the degree of order of this membrane, the Boltzmann constant and the absolute temperature, respectively. This structural change of the membrane is connected with a time constant $\tau$, so that this relaxation process can be described by a generalized splay elastic constant:

$$K_{11}(\omega) = K_{11}(\infty) - \frac{K_{11}(\infty) - K_{11}(0)}{1 + i \omega \tau} \quad (15)$$

$K_{11}(\infty)$ and $K_{11}(0)$ describe two limits of the frequency dependent elastic constant, viz. the high and the low frequency limit. $K_{11}(\infty)$ is the splay elastic constant without structural changes. The change of the elastic constant is

$$\Delta K_{11} = K_{11}(\infty) - K_{11}(0) = N \frac{(a_s P_s s_c)^2}{3 k T} \quad (16)$$

where $N$ is the number of molecules per unit area.

In case the polar order of the membrane is fixed during the splay deformation by a constant environment, the change of the elastic constant $\Delta K_{11}$ will be zero. But if the environment is not fixed during the deformation, the splay deformation produces a polar order which influences the environment. In the next section relations between polar order and asymmetric environment are discussed. The induced polar order can change e.g. the $\mathrm{H}^+$ or other ion concentrations or the electric field strength across the membrane. This chemoelastic effect could be used for transporting information.

In general, the splay elastic constant $K_{11}$ is frequency dependent but because this dependence is induced by the intrinsic splay and the polar order of the membrane, $K_{11}$ depends also on the boundary conditions. This means for example that the polar order is constant in a fixed environment, so that an intrinsic splay never can reduce an applied splay. The splay elastic constant where the polar order is clamped, is identical with $K(\infty)$ because in both cases no structural changes can occur. Another extreme case is when the environment has no influence to the polar order of the membrane. This can be achieved by keeping the volume of the environment very small ($V \to 0$). In this case an applied splay can produce a change in the polar order (see Eqn (14)) so that $K_{11}$ of the free changeable polar order is identical with $K_{11}(0)$.

### 3. Chemoelastic Effect

The spontaneous curvature can be divided into two parts: the intrinsic splay $s_c$ and the polar orientation (see Eqn (4)). The intrinsic splay is only a property of the membrane whereas the polar orientation couples the membrane to the asymmetric environment. To calculate the polar order one has to know which interaction between membrane and environment is important.

For example, if the asymmetric environment produces an electric field across the membrane, this field $E$ aligns more or less the electric dipole $p$, which is fixed to the molecules of the membrane. The potential energy $U_e'$ of an electric dipole in an electric fields is

$$U_e' = - p \cdot E \quad (17)$$

Since the molecules are bound to the membrane, only the dipole component parallel to the molecular axis is effective

$$U_e = - p_{||} E \cos \theta \quad (18)$$

The average of $\cos \theta$ can be calculated if one assumes that the process obeys the Boltzmann statistic which leads to the following equation

$$\bar{P}_1 = \coth \frac{p_{||} E}{k T} - \frac{k T}{p_{||} E} \quad (19)$$

Here the actual problem is to calculate the electric field strength across the membrane.

Another chemoelastic coupling is that lipids and proteins can contain atoms capable of ionization. As a result, the state of such polyelectrolytes will be strongly influenced by the acid or basic properties of the environment, determined by the concentration of hydrogen ions $\mathrm{H}^+$ and the ionic strength. Because different charged molecules occupy different areas, one has a chemoelastic coupling (see Eqn (9)). The spontaneous curvature $c_0$ can be determined if one knows the areas $a_1, a_2$ and the area
concentrations $c_1$, $c_2$ of the single and double charged molecules of the membrane. The area concentrations can be calculated for a reaction of the type
\[ K \quad H A^- \xrightleftharpoons{\text{c}}{\text{c}} H^+ + A^{2-} \quad (20) \]
from the dissociation constant $K$ and the $H^+$ concentration, if one assumes furthermore that there is no jump mechanism for the molecules of the membrane.
\[ K = \frac{[H^+][A^{2-}]}{[HA^-]} \quad (21) \]
The brackets indicate volume concentrations. The relative change of the membrane areas is
\[ \Delta a/a = (1 - a) (1 + a)^{-1} \quad (22) \]
## The subscripts $i$ and $0$ indicate the $H^+$ concentrations on both sides of the membrane. One finds for small deviations $\Delta = [H_0^+] - [H_i^+]$ from the equilibrium value and for $K$ equal $[H_i^+]$
\[ \Delta a/a = 2(a_i - a_0) (a_i + a_0)^{-1}. \quad \Delta [H_i^+] \quad (24) \]
This equation, in connection with Eqn (9), shows the linear relation between the spontaneous curvature and the polar order (see Eqn (4))
\[ s_c = (a_i - a_0)/d(a_i + a_0) \quad (25) \]
\[ \bar{P}_1 = \Delta/2[H_i^+] \quad (26) \]

Fig. 7 shows the spontaneous curvature versus $pH_0$ for different dissociation constants. If $pH_i$ equals $pK$, the spontaneous curvature is an antisymmetric function with respect to the equilibrium $pH_i$ value. For $pH_i$ unequal $pK$ the spontaneous curvature is asymmetric with respect to the equilibrium $pH_i$ value. This means that by varying $pH_0$, the spontaneous curvature will have large values only for one sign of $c_0$. A remarkable feature of this chemoelastic effect is that small changes of $pH_0$ lead to large values of the spontaneous curvature. The chemoelastic effect was shown with the $H^+$ concentration but it is possible to get similar results with other ions.

As already mentioned, the spontaneous curvature can be determined by measuring the shape of vesicles, e.g. red blood cells. If there is a chemoelastic coupling between the environment and the membrane, then e.g. the shape of red blood cells can be changed with a changing environment.

Bessis\textsuperscript{16,17} reported from investigations on red blood cells where the shape was changed by a changing environment. For example, the biconcave shape of red cells can be driven by the environment to tri- or quadriconcave red cells. Even spheres with spikes pointing in or out, are possible. All these experiments indicate a strong chemoelastic effect, but it is necessary to make more detailed experiments on artificial membranes.

A membrane which contains different molecules has some similarity to a two-dimensional alloy as mentioned in the introduction. Therefore one has to distinguish between two different cases: first, the different molecules in the membrane are uniformly mixed, and second, the molecules form different phases in the membrane\textsuperscript{18}. In the case of phase separation the Eqs (9), (22) and (23) describe only the average value of the spontaneous curvature. In such a system the local spontaneous curvature would be very high, so that the form of the membrane in equilibrium will be very complicated. Bessis\textsuperscript{16} reported from observations on red blood cells where the proteins on the surface were partially removed: the shape of the cells can get spikes which point in or out due to different asymmetric environments. Such an effect could partially be explained by a strong non-uniform spontaneous curvature.

The chemoelastic effect of a membrane in an asymmetric environment can also be used to construct a muscle model. An estimation of the maximal work leads to about one erg per cm$^3$, if the cell
dimension is about $2 \times 10^{-4}$ cm and if $K_{11}$ is about $10^{-12}$ erg\(^n\). From this energy point of view it seems reasonable that such a model could only play a role in very small living systems (unicellular).

### 4. Elastic Coupling

By putting a conical body into a uniaxial membrane, the orientation of the membrane is disturbed which leads to an elastic energy. The total elastic energy can be increased or decreased if two orientation patterns are connected. This means that the force between such two conical bodies can be repulsive or attractive. To get more information about this elastic coupling, a closer look at the orientation pattern would be necessary.

If one describes the midplane of the membrane by the vector
\[ \mathbf{r} = r \mathbf{e}_r + \varphi \mathbf{e}_\varphi + f(r, \varphi) \mathbf{z} \] (27)
ther normal of the membrane is
\[ \mathbf{N} = \frac{\mathbf{r}_r \times \mathbf{r}}{|\mathbf{r}_r \times \mathbf{r}_\varphi|}. \] (28)

If the thickness of the membrane remains constant, the normal $\mathbf{N}$ is identical with the preferred direction of the uniaxial membrane $\mathbf{L}$. $\mathbf{N}$ equal to $\mathbf{L}$ is a good approximation, because a change of the thickness of the membrane needs much more energy than a simple splay deformation\(^3\). For a rotational symmetric disturbance the director $\mathbf{L}$ is
\[ \mathbf{L} = (1 + f^2)^{-1/2} \cdot (-f, \mathbf{e}_r + \mathbf{e}_\varphi). \] (29)

The orientation pattern of a uniaxial membrane with conical bodies should be similar to the orientation pattern induced by singularities in the nematic structure, since these line singularities create a two-dimensional distortion. Such line singularities in nematic phases are defined by a multiple change of $\pi$ of the preferred direction on a circuit taken around one of the lines. Therefore the disclination strength $n$ can have only discrete values and the energy of a nematic disclination is proportional to $n^2$. Similar to nematics the strength of the singularity can be defined as $\Phi/2\pi$. But in this case the strength of the singularity is not an integer as it is in the nematic case.

The orientation pattern of one conical body in the uniaxial membrane is shown in Fig. 8. Similar to the nematic case the disturbance can be positive or negative. For example the positive sign indicates that the thicker end of the body is on the upper side of the membrane. If two disclinations of a nematic phase are close enough together then it is possible to observe a movement of the disclinations. This movement is induced by attractive or repulsive force between the disclinations. If the signs are unequal than the force is attractive. Similar to disclinations of a nematic phase, a conical body in a membrane, in the elastic field of another conical body, experiences an attractive or repulsive force.

Since the two-dimensional elastic distortion decays very slow ($\log r$), the interaction between two conical bodies in a uniaxial membrane can go up to large distances. The exchange energy $W$ is positive for two positive or two negative orientation patterns and therefore it will increase the total elastic energy as it is shown in Fig. 9. If there are several conical bodies with the same sign in the membrane, then in equilibrium they will spread uniformly over the membrane, because the exchange energy $W$ is negative for a positive and a negative orientation pattern, so that the total elastic energy will be decreased. In this case the force between the conical bodies is attractive. If there is no additional
force then the two bodies will touch each other. But if the bodies are conical only in the first approximation, then high local distortions can create a repulsive term, so that they are at equilibrium at a certain distance as it is shown in Fig. 9. If there are several bodies with different signs in the membrane, then they can form subunits which are spread over the membrane.

Biomacromolecules with their complex shapes are built in membranes which form together a complex structure. These structures contain a great many kinds of proteins as well other constituents. All these constituents of the membrane and the environment must be organized in a highly specific way to generate the specific properties of the membrane (of the cell). This is a functional organization. The elastic coupling of biomolecules in a membrane, which act together, is a possible functional organization. For example the elastic coupling could be applied to enzymatic reactions where more than one reaction is involved for building up a compound. It is not much known about the arrangement of proteins in membranes but there is some evidence that some proteins as cytochrome c oxidase and the P 450 redox-system form subunits. Fig. 1 illustrates such possible arrangements of different proteins. The proteins on the left side act mainly outside of the membrane so that the proteins are only coupled with a foot to the membrane. The proteins on the right side act mainly inside the membrane. The possible crystalline structure around proteins can create a repulsive term, so that different proteins are fixed at the equilibrium distance $r_0$ as it is shown in Fig. 1.

Strobel reported from another functional organisation of proteins. He proposed a model for the passage of ions across the membrane, in which the protein is composed of four subunits. The arrangement of these units is in such a way that they create a transfer channel through the membrane. If the subunits are coupled together by elastic forces, a conformation change of the protein can control the transport mechanism.

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8. There is some evidence, proteins and different phospholipids are asymmetrically arranged in biological membranes: M. S. Bretcher, Science 181, 622 [1973].
11. The splay elastic constant of a uniaxial membrane can be estimated by the splay elastic constant of a nematic or smectic liquid crystal $k_{11}$: $K_{11} = k_{11} \cdot d = 10^{-12}$ erg for $k_{11} = 10^{-8}$ dyn $\cdot$ meter and $d = 100$ Å.