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### Short Communication

## Elasticity of Lipid Bilayer Interacting with Amphiphilic Helical Peptides

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**Abstract.** — Amphiphilic helical peptides exhibit an insertion transition when they interact with lipid bilayers. At low concentrations, the peptides adsorb at the hydrophilic-hydrophobic interface with the helical axes parallel to the bilayer surface. However, if the peptide concentration is above a critical value, a macroscopic fraction of the peptide molecules insert perpendicularly into the bilayer. The existence of a critical concentration for insertion is crucial to the peptides biological function. This phenomena can be understood in terms of the conventional theory of elasticity for a lipid bilayer.

### 1. Introduction

Interactions of amphiphilic helical peptides with lipid bilayers provide an interesting example of protein-membrane interactions that can be understood in terms of the elastic property of the lipid bilayers. In this Section I will describe the experimental observations. In the following Section I will show that the observed phenomena can be understood in the frame work of the conventional elasticity theory for a lipid bilayer.

A helical peptide of about 20 amino acids has a length comparable to the thickness of the hydrocarbon region of a phospholipid bilayer ( $\sim 30 \text{ \AA}$ ). The amino acids of an amphiphilic helical peptide are distributed in such a way that one side along the helix is hydrophilic and the other side hydrophobic. Such peptides have been found to associate with a bilayer in two ways: depending on conditions, the peptide either adsorbs parallel to the bilayer surface or inserts perpendicularly into the bilayer [1,2]. In the surface state, the peptide is presumably adsorbed at the hydrophilic-hydrophobic interface between the polar head group region and the hydrocarbon region of the bilayer [3]. Neutron in-plane scattering showed that, in the inserted state, the peptide forms pores in the barrel-stave fashion, that is, a number of helices surrounding a cylindrical aqueous pore [4].

At low peptide-to-lipid molar ratios ( $P/L$ ), the peptides are found to be in the surface state. Above a critical concentration  $P/L^*$ , there is a coexistence region in which a fraction of the peptide molecules are inserted and the rest remain on the surface. The inserted fraction

increases (from zero at  $P/L^*$ ) with  $P/L$ . In some cases the coexistence region ends at a higher  $P/L$  and beyond this concentration all peptide molecules are inserted. In other cases, the coexistence region extends to very high  $P/L$ 's and the completely inserted phase was not detected within the experimental limit. The value of the critical  $P/L^*$  for a given peptide varies with the lipid composition of the bilayer [1, 2].

The existence of a critical concentration for insertion (CCI) is crucial to the biological function of these peptides. In nature, these peptides are produced as antibiotics; they lyse bacterial cells without harming the host cells. In the activity assays, these peptides show critical concentrations for lysis [5–8]. Thus it was hypothesized [2] that the insertion transition is the mechanism of cytotoxicity and the cell selectivity is achieved, at least partly, by the dependence of the CCI on the lipid composition of the cell membranes.

The connection to the elasticity of the bilayer was revealed in a series of x-ray diffraction experiments [3, 9], in which peptides in the surface state were found to reduce the bilayer thickness. In all cases (two different peptides in three different lipid bilayers) the decrease of the bilayer thickness is proportional to the peptide concentration  $P/L$ .

We interpreted this result with a simple physical picture [3]. In a planar bilayer of pure lipid, the polar region (the head group and the associated water molecules) and the hydrocarbon chain region must maintain the same cross sectional area. Suppose now that some peptide molecules are inserted in the polar region. Then the added cross sectional area in the polar region due to the adsorbed peptide molecules must be matched by a corresponding area increase in the chain region. In general, the cross sectional area of a lipid is larger if its chains are more disordered. Since the volume of the chains is, to the first order, constant during an order-disorder transition (e.g., the volume change at the gel to  $L_\alpha$  phase transition is 4% for dipalmitoyl phosphatidylcholine [10]), the fractional increase in the cross section  $\Delta A/A_0$  (per lipid) equals the fractional decrease in the thickness  $-\Delta t/t_0$ .  $\Delta S = \Delta A(L/P)$  is then the expanded area due to each adsorbed peptide molecule. The experimental values of  $\Delta S$  calculated from the membrane thinning effect are approximately that of the cross sections of the adsorbed peptides [3, 9]. This is consistent with the assumption that the peptide is adsorbed at the interface and the adsorbing peptide pushes the lipid head groups laterally to create an additional area of  $\Delta S$  in the polar region.

## 2. Elasticity Theory

Consider a tensionless lipid bilayer, consisting of two identical monolayers, parallel to the  $x - y$  plane before peptide adsorption. Let  $u_\pm(x, y)$  be the displacement of the top and bottom interfaces from their equilibrium positions and  $a$  the equilibrium thickness of each monolayer. Then  $D(x, y) = u_+ - u_-$  is the change in the bilayer thickness (or more precisely the thickness of the hydrocarbon chain region) from the equilibrium value  $2a$  and  $M(x, y) = (u_+ + u_-)/2$  is the displacement of the mid-plane from its equilibrium position. The deformation free energy of the bilayer, per unit area of the unperturbed system, is given by [11]

$$f = aB \left( \frac{D}{2a} \right)^2 + \frac{K_c}{8} (\Delta D)^2 + \frac{K_c}{2} [\Delta M - C_0(x, y)]^2. \quad (1)$$

$B$  is the compressibility modulus of the bilayer (to be distinguished from the bulk modulus for layer compression of a multilayer stack [12]).  $K_c$  is Helfrich's bending rigidity for a bilayer [13].  $C_0(x, y)$  is the local spontaneous curvature [13] induced by peptide adsorption. At the moment, there is no reliable way of computing  $C_0(x, y)$ . However, in this model the D-mode and the M-mode are independent on each other. And we will be mainly concerned with the D-mode deformation. The deformation of the bilayer thickness is determined by  $(B/a)D +$

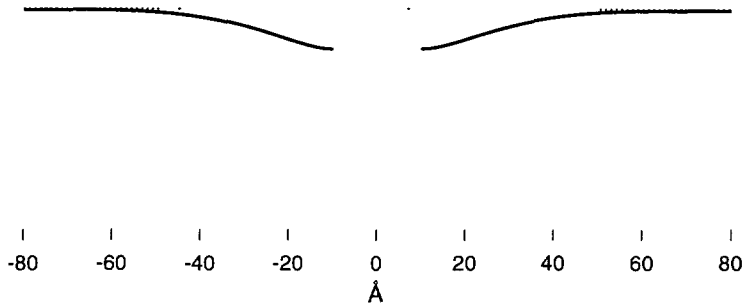


Fig. 1. — The profile of bilayer thickness change  $D(r) = u_+(r) - u_-(r)$  when a peptide molecule (shaded object) is adsorbed on it. The amplitude is magnified, the actual  $D_0$  is about  $-1.9 \text{ \AA}$  if the peptide cross section  $\Gamma$  is  $300 \text{ \AA}^2$

$(K_c/2)\Delta^2 D = 0$ . Let's first consider the effect of one peptide molecule. For mathematical simplicity, let's assume that the  $x - y$  cross section of a peptide adsorbed on the interface is a circular disk of radius  $r_0$ . The deformation induced by an adsorbed peptide is then described by  $D = c \text{ kei}(r/\lambda) + d \text{ ker}(r/\lambda)$  [14], with  $\lambda = (aK_c/2B)^{1/4}$ , and the total deformation energy  $F = (c^2 + d^2)\pi(BK_c/8a)^{1/2}I(r_0/\lambda)$  with  $I(z) = z[\text{kei}(z)\text{ker}'(z) - \text{ker}(z)\text{kei}'(z)]$ . The constants of integration  $c$  and  $d$  are determined by the boundary conditions at  $r = r_0$ . The thickness change at the boundary  $D(r_0) = D_0$  is determined by the area expansion due to the peptide adsorption as indicated above (and see below). The derivative at the boundary should be slightly negative (see Fig. 1), since we expect the boundary lipid molecules to tilt in such directions to fill the void created by the peptide. For simplicity we use the approximation  $D'(r_0) = 0$ . The profile of the thickness change is shown in Figure 1 with a magnified  $D_0$ .

The most important parameter determining the deformation is  $\lambda$ . For a numerical estimate, we use  $K_c = 50k_B T = 2 \times 10^{-12} \text{ erg}$  [15],  $B = 5 \times 10^8 \text{ ergcm}^{-3}$  [11, 16], and  $a = 15 \text{ \AA}$  [3] to obtain  $\lambda = 13 \text{ \AA}$  and we let  $r_0 = 10 \text{ \AA}$  so the cross section of an adsorbed peptide,  $\Gamma$ , is about  $300 \text{ \AA}^2$  [3]. As noted above, conservation of the chain volume implies  $\Gamma = (1/a) \int D dx dy$ , from which  $D_0$  is determined to be  $-1.9 \text{ \AA}$ . The total deformation energy  $F = 1.9k_B T$ . We note that the area of deformation by one adsorbed peptide is quite large, as much as  $100 \text{ \AA}$  in diameter. This, to some extent, justifies the use of continuum theory for discussing peptide-membrane interactions.

For the problems of more than one peptide molecule, we turn to the more manageable one-dimensional system. The thickness deformation is then determined by  $(B/a)D + (K_c/2)d^4 D/dx^4 = 0$  and a peptide molecule can be regarded as a point where  $D = D_0$  and  $dD/dx = 0$ . One can easily show that the deformation free energy due to two peptide molecules adsorbed at a distance  $r$  apart is  $F^{(2)} = 2F^{(1)}v(r)$ , where

$$v(r) = 2 \left\{ 1 + [\cos h(r/\sqrt{2}\lambda) - \cos(r/\sqrt{2}\lambda)] / [\sin h(r/\sqrt{2}\lambda) + \sin(r/\sqrt{2}\lambda)] \right\}^{-1}$$

and  $F^{(1)}$  is the energy due to one isolated peptide.  $v(r)$  is shown in Figure 2. It is a decreasing function from  $r = 0$  to  $r \sim 2\sqrt{2}\lambda$ . The potential is slightly attractive between  $r \sim 2\sqrt{2}\lambda$  and  $r \sim 5\sqrt{2}\lambda$ . However the depth of the potential well is insignificant, only about  $0.15k_B T$  (using  $F^{(1)} = 1.9k_B T$ ). Thus the membrane-mediated potential between two adsorbed peptide molecules is repulsive for  $r \leq 2\sqrt{2}\lambda$  ( $\sim 37 \text{ \AA}$ ) and essentially constant for  $r > 2\sqrt{2}\lambda$ . This is

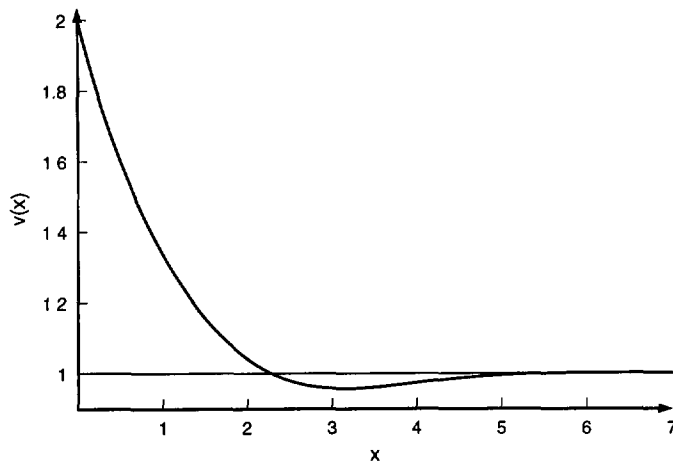


Fig. 2. — The function  $v(x) = 2/[1 + (\cos hx - \cos x)/(\sin hx + \sin x)]$

interesting because in most cases point defects in an elastic structure attract to each other, e.g. hydrogen in metals [17] or peptides inserted in a bilayer [11]. The concentration dependence of energy is as follows. If the peptide concentration is  $n$  per unit length, the deformation free energy per unit length is  $nF^{(1)}[\sin h(1/n\sqrt{2}\lambda) + \sin(1/n\sqrt{2}\lambda)]/[\cos h(1/n\sqrt{2}\lambda) - \cos(1/n\sqrt{2}\lambda)]$ . For peptide concentrations  $n$  less than  $1/2\sqrt{2}\lambda$ , it is simply  $nF^{(1)}$ . For concentrations greater than  $1/2\sqrt{2}\lambda$ , the energy is  $2\sqrt{2}\lambda n^2 F^{(1)}$ .

Experimentally membrane thinning was observable by X-ray lamellar diffraction for  $P/L$  as low as  $1/150$ , where the nearest-neighbor distances between uniformly distributed peptide molecules are  $\sim 100 \text{ \AA}$  [3, 9]. This is consistent with the implications of the theory that (1) the adsorbed peptide molecules are dispersed (rather than aggregated) on the membrane surface and (2) the deformation caused by peptide adsorption is long-ranged. The critical concentration for insertion can now be understood as follows. The free energy of adsorption consists of two parts, the energy of binding to the interface  $-\epsilon_B$  and the energy of membrane deformation  $f_M$ . At low  $P/L$ ,  $f_M = F^{(1)}$ . Our experiment implies  $-\epsilon_B + F^{(1)} < -\epsilon_I$ , the free energy of insertion, so that at low concentrations peptide is mostly on the surface. However, at high  $P/L$ ,  $f_M$  is proportional to  $P/L$ , or  $f_M = c(P/L)F^{(1)}$  with a constant  $c$ . Therefore at sufficiently high peptide concentrations, the energy of adsorption can exceed the energy of insertion. The critical concentration for insertion is defined by  $-\epsilon_B + c(P/L)F^{(1)} = -\epsilon_I$ .

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