Eur Biophys J (2010) 39:1477–1482
DOI 10.1007/s00249-010-0604-0

ORIGINAL PAPER

Adsorption of proteins on a lipid bilayer

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Received: 11 November 2009 / Revised: 11 February 2010 / Accepted: 24 March 2010 / Published online: 13 April 2010

Abstract In our analysis of protein adsorption on a lipid bilayer, the protein surface is considered to contain one or a few charged spots, and the bilayer contains a significant amount of lipids with oppositely charged head groups. After adsorption, a folded protein is assumed to change its shape slightly due to the electrostatic attraction, so that one of the spots forms a flat contact with the oppositely charged lipid heads of the lipid bilayer. With realistic parameters, this model predicts that the contribution of electrostatic interactions to the protein adsorption energy per charged amino acid–lipid pair is 16–25 kJ/mol. Thus, a few (four or five) pairs is sufficient for irreversible adsorption.

Keywords Proteins · Lipids · Adsorption energy · Electrostatic interactions · Poisson–Boltzmann equation

Introduction

Protein adsorption on solid or soft-matter surfaces has long attracted the attention of researchers working both in the natural sciences and in industry, because it plays an important role in biology, medicine, and in numerous technical, pharmaceutical, and food-processing applications (Malmsten 2003; Gray 2004; Tsapikouni and Missirlis 2008). The kinetics of protein adsorption are often apparently simple, but in reality they are very complex, and their interpretation is usually far from straightforward due to diffusion limitations in solution, conformational changes, surface diffusion, ordering or aggregation of adsorbed proteins, complexity and multiplicity of binding sites, surface roughness, and a multitude of related microscopic factors. One of the latter is Coulomb interaction between charged amino acid residues of a protein, charged groups on the surface of the substrate, and the electrolyte (Gray 2004; Mulgrew-Nesbitt et al. 2006). If the protein charge is appreciable, this factor may determine the protein adsorption energy.

In this work, we estimate the electrostatic contribution to the energy of adsorption of folded globular proteins on a charged lipid bilayer. This case is obviously of interest from the viewpoint of cellular biology, because all proteins are charged to some extent except at the isoelectric point, but even there the protein is likely to have local charges, and the lipid membranes in cells always contain some charged lipids. In addition, as model systems, charged lipid bilayers may be formed on solid surfaces by adsorption and rupture of vesicles composed of mixtures of zwitterionic, negatively charged, and/or positively charged lipids (Richter et al. 2003; Richter and Brisson 2005). This makes it possible to study protein adsorption on charged lipid bilayers under well-defined conditions and to change systematically the governing parameters (e.g., the fraction of charged lipids) controlling the adsorption kinetics.

Compared with conventional solid surfaces with fixed location of charges (the case reviewed by Gray 2004 and Tsapikouni and Missirlis 2008), lipid bilayers allow rapid diffusion of lipids, and accordingly the adsorption of charged proteins in general and globular charged proteins in particular is expected to be accompanied by fast local lipid redistribution, optimizing the protein–lipid binding. Experimental information about this type of protein adsorption is

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currently limited. First, we may mention the measurements of the kinetics of the MARCKS (myristoylated alanine-rich C kinase substrate) protein adsorption by Michielin et al. (1998, 1999) and Ramsden and Vergeres (1999) (see also a review of this protein family by Arbuzova et al. 2002). This protein is not folded. Its highly basic part, located in the middle of the chain, interacts with the head groups of negatively charged lipids. The main contribution to the adsorption energy seems, however, to be related to the incorporation of its hydrophobic terminal part into the membrane (Michielin et al. 1998). More recently, Choi and Dimitriadis (2004) observed [by atomic force microscopy (AFM)] incorporation of cytochrome *c* into a supported anionic lipid bilayer. In another recent AFM study, Creutz and Edwardson (2009) observed adsorption of annexin (golobular protein) and copine (linear protein) on a supported lipid bilayer. In this case, the annexin–bilayer contact seems to be enriched by negatively charged lipids, and the binding of annexin promotes adsorption of copine.

The redistribution of lipids during adsorption of flexible unfolded charged macromolecules on mixed lipid membranes was theoretically studied by Dias et al. (2005) and Tzlil and Ben-Shaul (2005). The corresponding results may be of interest for interpretation of adsorption of cationic (e.g., antimicrobial) peptides onto anionic lipid bilayers (the related experiments have recently been reviewed by Bechinger 2009). The case of proteins is however different, because, despite partial denaturation, adsorbed proteins usually remain folded.

Concerning proteins, we may note that there are a few treatments (Harries et al. 2002; Dias and Linse 2008; Trusova and Gorbenko 2008) of adsorption of charged proteins on charged lipid bilayers assuming that the protein is spherical and does not change its shape during adsorption. In reality, proteins are often not fully symmetrical and in addition are fairly flexible, have a multiplicity of almost isoenergetic states, and can easily change their shape after adsorption. The corresponding conformational changes may range from local reconfiguration near the protein–surface contact to complete denaturation. For these reasons, proteins are often believed to form flat contact with the substrate. This case was analyzed by Heimburg et al. (1999), Mbamala et al. (2005), and Loew et al. (2009) with emphasis on the adsorption isotherms. The latter authors use phenomenological parameters and do not discuss the electrostatics in detail. The analysis by Heimburg et al. is focused on the role of electrolyte in the screening of charges of lipids and proteins (the protein–lipid interaction is not scrutinized). The model used by Mbamala et al. is general, but the final results are numerical and accordingly not fully transparent. In our work, we keep the analysis as simple as possible in order to obtain analytical results and articulate the physics behind and the applicability conditions of the model.

Model

In our model (Fig. 1), we assume that the charged amino acid residues form one or a few spots near or on the surface of a protein (the location of charges near the surface is usually energetically favorable). After adsorption, a protein changes its shape slightly so that one of the spots forms a flat contact with the oppositely charged lipid heads of the lipid bilayer. Using this model, we estimate the free energies of the system before and after adsorption with emphasis on the electrostatics. The difference of these energies is identified with the contribution of electrostatic interactions to the energy of protein adsorption on the lipid bilayer with charged head groups.

In our calculations, we consider that the charges of lipid heads on both surfaces of the lipid bilayer are screened by electrolyte (or partly by the charges located on the surface of a solid, if one of the sides of the bilayer contacts a solid) so that there is no electric field inside the bilayer (the formation of electric field there is energetically unfavorable, because the bilayer dielectric constant is low). As already noted, protein adsorption is assumed to occur on the interface between the lipid bilayer and solution. We do not consider partial or complete protein immersion into the bilayer via, for example, hydrophobic interactions (this field has recently been reviewed by Bechinger 2008). Our results may, however, be useful for understanding the latter process, because protein adsorption is its first step.

Lipid bilayer

To be specific, we analyze 1:1 electrolyte in water and use the conventional one-dimensional (1D) Poisson–Boltzmann equation to describe the screening of the charges of lipid

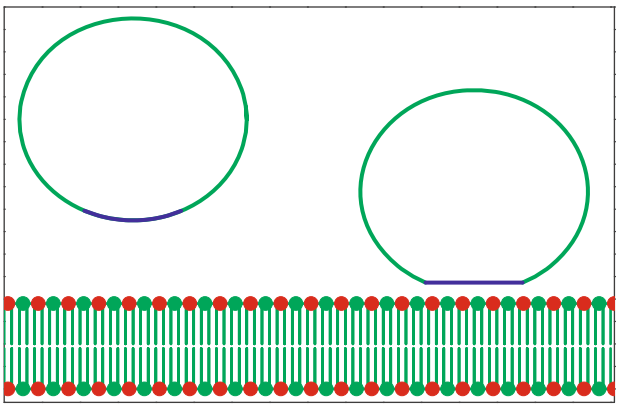

Fig. 1 Scheme of protein adsorption on a bilayer composed of lipids with neutral and charged heads. The charged amino acid residues form a spot on the surface of a protein. After adsorption, a protein changes its shape so that the charged spot forms a flat contact with the oppositely charged lipid heads of the lipid bilayer

heads located on the lipid–solution interface. This equation still forms a cornerstone of the electric double-layer theory (for recent modifications, see Ibarra-Armenta et al. 2009 and references therein). The 1D approximation holds provided that the concentration of charged lipids is appreciable and their discrete charges can be replaced by uniformly distributed charge. In this case, the potential in the solution is described as

$$\frac{\mathrm{d}^2\varphi}{\mathrm{d}x^2} = \frac{8\pi e_0 n_0}{\epsilon_s} \sin h\left(\frac{e_0\varphi}{k_\mathrm{B}T}\right), \tag{1}$$

where n_0 is the ion concentration far from the electrode, ε_s is the dielectric constant, and e_0 is the absolute value of the electron charge. This equation can easily be integrated (Bard and Faulkner 2001). In particular, we have

$$\frac{\mathrm{d}\varphi}{\mathrm{d}x} = -\left(\frac{32\pi n_0 k_\mathrm{B}T}{\epsilon_s}\right)^{1/2} \sin h\left(\frac{e_0\varphi}{2k_\mathrm{B}T}\right). \tag{2}$$

Near the lipid bilayer, the boundary condition for φ is

$$-\epsilon_s \left.\frac{\mathrm{d}\varphi}{\mathrm{d}x}\right|_{x=0} = 4\pi\rho_l, \tag{3}$$

where ρ_l is the bilayer surface charge concentration. Substituting Eq. 2 into Eq. 3 results in

$$\rho_l = \left(\frac{2\epsilon_s n_0 k_\mathrm{B}T}{\pi}\right)^{1/2} \sin h\left(\frac{e_0\varphi_l}{2k_\mathrm{B}T}\right), \tag{4}$$

where $\varphi_l \equiv \varphi(0)$ is the bilayer potential.

We are interested in the situation when the charge of the lipid layer is appreciable and $e_0\,|\varphi_l|$ is appreciably larger than $2k_\mathrm{B}\,T$. For example, we consider that ρ_l is positive, and φ_l is positive as well (our final results are equally applicable for $\rho_l < 0$). In this case, we have $\sin h[e_0\varphi_l/(2k_\mathrm{B}T)] \simeq \exp[e_0\varphi_l/(2k_\mathrm{B}T)]/2$, and Eq. 5 can be rewritten as

$$\rho_l \simeq \left(\frac{\epsilon_s n_0 k_\mathrm{B}T}{2\pi}\right)^{1/2} \exp\left(\frac{e_0\varphi_l}{2k_\mathrm{B}T}\right). \tag{5}$$

According to this equation, the dependence of φ_l on ρ_l is given by

$$\varphi_l \simeq \frac{k_\mathrm{B}T}{e_0} \ln\left(\frac{2\pi\rho_l^2}{\epsilon_s n_0 k_\mathrm{B}T}\right). \tag{6}$$

This simple expression is sufficient for our analysis (for more general expressions, see e.g. the treatments by Evans and Wennerström 1994 and Mengistu and May 2008).

The free energy per unit area of the bilayer is defined by Overbeek (1990) and Evans and Wennerström (1994) as

$$F_l = \int_0^{\rho_l} \varphi_l(\rho)\mathrm{d}\rho. \tag{7}$$

Note that, at first sight, this expression is purely electrostatic and might be associated with enthalpy. However, the potential defined by Eq. 1 depends on the charge distribution, which in turn is determined in the electrolyte by the interplay of electrostatic and entropic factors. For this reason, Eq. 7 represents free energy.

Substituting Eqs. 5 or 6 into Eq. 7, we obtain

$$F_l \simeq \rho_l\varphi_l(\rho_l) \simeq \frac{\rho_l k_\mathrm{B}T}{e_0} \ln\left(\frac{2\pi\rho_l^2}{\epsilon_s n_0 k_\mathrm{B}T}\right). \tag{8}$$

The charge concentration can be represented as $\rho_l = e_0/a_l$, where a_l is the surface area per charged lipid. Substituting this relation into Eq. 8 yields

$$F_l \simeq \frac{k_\mathrm{B}T}{a_l} \ln\left(\frac{2\pi e_0^2}{\epsilon_s n_0 a_l^2 k_\mathrm{B}T}\right). \tag{9}$$

The free energy per charged lipid is given by

$$f_l = a_l F_l \simeq k_\mathrm{B}T \ln\left(\frac{2\pi e_0^2}{\epsilon_s n_0 a_l^2 k_\mathrm{B}T}\right). \tag{10}$$

Protein in the solution

To describe the screening of the protein charge in the solution (far from the bilayer), we also use the Poisson–Boltzmann equation, neglect the corrections related to the deviations from the 1D geometry, and estimate the free energy per charged amino acid in analogy with Eq. 10 as

$$f_p \simeq k_\mathrm{B}T \ln\left(\frac{2\pi e_0^2}{\epsilon_s n_0 a_p^2 k_\mathrm{B}T}\right), \tag{11}$$

where a_p is the surface area per charged amino acid.

Protein–bilayer contact

In our analysis, as already noted, a protein is assumed to change its shape slightly after adsorption, so that one of the spots forms a flat contact with the oppositely charged lipid heads of the lipid bilayer. In other words, the charged lipids screen the protein charge located in the contact area. Physically, perfect screening by charged lipids is expected to be the most favorable, because otherwise an electric field would be formed in the protein or lipid layer with low dielectric constant and the energy of the protein–lipid complex would rapidly increase with decreasing number of charged lipids forming the contact (this point is illustrated in the Appendix). Under equilibrium, the chemical potential of charged lipids in the contact area should, however, be equal to that outside this area. In general, this condition is not compatible with perfect screening. Thus, screening by lipids can hardly be perfect, especially if the chemical potential of charged lipids is low. The latter means that the

concentration of charged lipids is very low. With this exception, the screening by charged lipids should be nearly perfect and for the purpose of estimation can be considered perfect. In particular, the electrostatic energy of interaction of an adsorbed protein with the bilayer can be estimated by employing the simplest capacitor model, i.e.,

$$F_a \simeq \frac{2\pi A h e_0^2}{\epsilon_a a_p^2}, \tag{12}$$

where A is the contact area, h is the distance between the charged surfaces, and ε_a is the dielectric constant in the space between these surfaces. In this approximation, the energy per charged amino acid is given by

$$f_a = F_a/N \simeq \frac{2\pi h e_0^2}{\epsilon_a a_p}, \tag{13}$$

where $N = A/a_p$ is the number of charged amino acids forming a contact with the bilayer.

Using Eq. 13 below in order to estimate the protein adsorption energy, we neglect the protein reconfiguration energy needed to form a flat contact with the lipid bilayer. This energy is expected to be often negligible, because proteins are well known to be fairly flexible. One of the manifestations of this peculiarity is that, under physiological conditions, the native state of a protein is only a few kcal/mol more stable than its unfolded state and that the folding kinetics are often rather rapid (Finkelstein and Galzitskaya 2004).

Note also that Eq. 13 does not take the change of the entropy of mixing of charged and uncharged lipids into account. The measure of the latter factor is a product of N and $\Delta\mu$, where $\Delta\mu \equiv k_B T \ln[\theta/(1-\theta)]$ is the corresponding contribution to the chemical potential of charged vesicles (θ is their fraction). If θ is not low (as noted in Sect. "Lipid bilayer," we are interested in this case), the role of the mixing entropy is minor.

Protein adsorption energy

After protein adsorption, the energy of N charged amino acid–lipid pairs located in the contact area is Nf_a. Before adsorption, the energy of the corresponding charged lipids and amino acids is $N(f_l + f_p)$. Thus, the contribution of electrostatic interactions to the protein adsorption energy is represented as

$$E_{\mathrm{ad}} = N\left(f_l + f_p - f_a\right). \tag{14}$$

Results of calculations

In our model, we have seven parameters: T, a_l, a_p, h, ε_s, ε_a, and n_0. To illustrate the model predictions, we use $T = 300$ K and $h = 1$ Å. The lateral distance, d, between nearest-neighbour lipids is about 5 Å. The area per charged lipid is $a_l \simeq \pi d^2/(4\theta)$, where θ is the fraction of charged lipids. Employing, for example, $\theta \simeq 0.3$, we obtain $a_l \simeq 60$ Å^2. The scale of a_a is expected to be the same, and we use $a_a = a_l = 60$ Å^2.

Far from the bilayer-solution interface, we have $\varepsilon_s \simeq 80$. Near the charged interface, ε_s is known to be appreciably lower. To show typical dependence of f_l (Eq. 10) on n_0, we use $\varepsilon_s = 80$ and 30 (Fig. 2). For 0.01 M $\leq n_0 \leq$ 0.1 M, f_l is seen to be 15–20 kJ/mol. The scale of f_p is similar.

The shape of amino acid residues does not perfectly fit the shape of lipid heads, and the interface between a protein and the lipid bilayer inevitably contains some amount of water. Due to this water, ε_a is expected to be appreciably larger than that in the protein or the lipid bilayer but lower than in water far from the surface. At present, the value we should use for ε_a is open for debate. To illustrate the role of this parameter, we have varied its value from 10 to 80 (Fig. 3). In this case, f_a is in the range from 2 to 10 kJ/mol. The adsorption energy per charged amino acid–lipid pair, $\Delta f \equiv f_l + f_p - f_a$, is accordingly in the range from 16 to 25 kJ/mol.

Conclusions

Our calculations indicate that, during adsorption of charged proteins onto an oppositely charged lipid bilayer, the contribution of each charged amino acid–lipid pair to the protein adsorption energy is 15–20 kJ/mol. Thus, a few (four or five) pairs seems to be sufficient for irreversible adsorption. Although for such a low number of pairs the model is not fully reliable, the scale of the energy is expected to be correct.

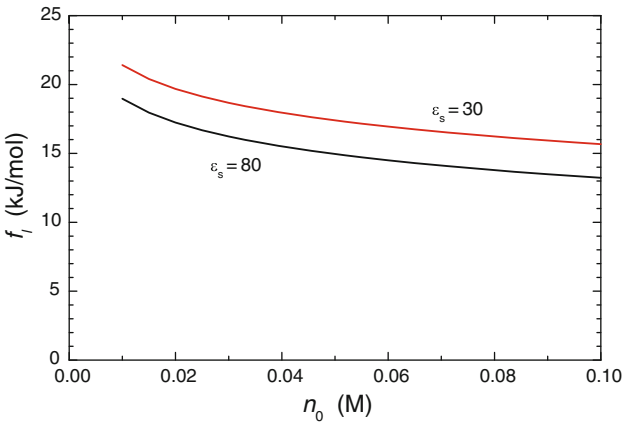

Fig. 2 Free energy per charged lipid as a function of electrolyte concentration (Eq. 10) for $\varepsilon_s = 80$ and 30. For the other parameters, see the text

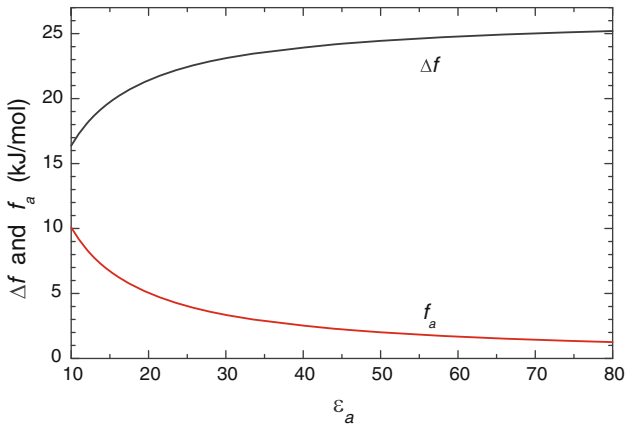

Fig. 3 Electrostatic energy, f_a, and adsorption energy, $\Delta f \equiv f_l + f_p - f_a$, per charged amino acid–lipid pair as a function of ε_a for $\varepsilon_s = 80$ and $N_0 = 0.1$ M. For the other parameters, see the text

Finally, we point out some implications of the results obtained for the kinetics of adsorption of charged proteins on a lipid bilayer with oppositely charged lipids. As the protein approaches the bilayer and comes within the Debye screening length, it will polarize, i.e., attract the charged lipids. Since the latter are very mobile, they will continuously adjust their positions to minimize the energy. If one lipid–amino acid electrostatic bond is formed with the above quoted binding energy, it leads to a short residence time on the surface before the protein desorbs. If a second charged lipid diffuses into the protein interaction zone within the residence time created by one bond, a second bond is established and a longer residence time is then generated, during which a third lipid can bind, etc. This scenario is expected to lead to quite interesting adsorption, desorption, and rearrangement kinetics of proteins on the bilayer (the corresponding model will be discussed elsewhere (Zhdanov and Kasemo 2010)), quite different from that on a surface with immobile charges and binding sites.

Appendix

Our presented treatment implies that, after protein adsorption, the charged amino acid residues forms a flat contact with the oppositely charged lipid heads of the lipid bilayer. In this case, as noted in Sect. "Protein–bilayer contact," perfect local screening of the amino acid charges by charged lipids is usually energetically favorable, because otherwise an electric field would be formed in the protein or lipid layer with low dielectric constant and the energy of the protein–lipid complex would rapidly increase with decreasing number of charged lipids forming the contact. Here, we illustrate this point by using the simplest model focused on the contact area. To be specific, we

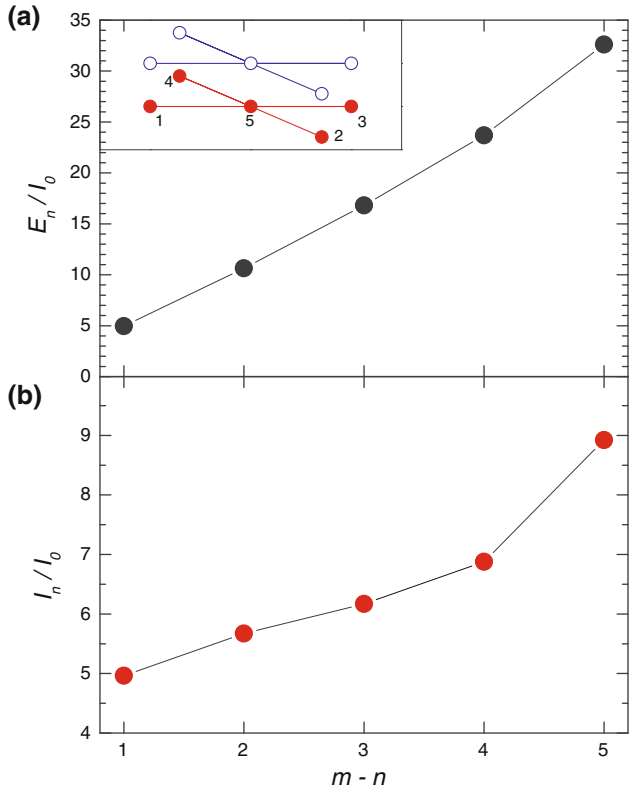

Fig. 4 Energies E_n (**a**) and I_n (**b**) as a function of $m - n$. The insert shows the charges in the protein−bilayer contact area. Five charged amino acid residues forming a cross are indicated by *filled circles*. The charged lipids located below are shown by *open circles*. The distance between nearest-neighbor protein (or bilayer) charges is a. The distance between the charged surfaces is h. The results are presented for $h = a/5$. To calculate I_n, the lipids were removed in the order indicated. The normalization constant is defined as $I_0 = e_0^2/a$.

consider that the protein has five ($m = 5$) charged amino acid residues located in the contact area, as shown in the inset to Fig. 4. The number of charged lipids is n ($n \leq m$). The local screening is perfect if $n = m$. The energy of this state is defined to be zero. If $m < n$, the local screening is imperfect. Globally, however, the charge will anyway be screened by the lipids not forming the contact and/or electrolyte. We neglect the interaction of the charges located in the contact area with those located beyond, because the distances between the former charges are shorter. In addition, we neglect the difference of the dielectric constants of the protein, lipid bilayer, and contact area (all these constants are set to be ε_a). For given n, the binding energy of a charged lipid, I_n, is defined as the energy needed to displace it to infinity, i.e.,

$$I_n = \sum_{i=1}^{m} \frac{e_0^2}{\epsilon_a r_i} - \sum_{i=1}^{n-1} \frac{e_0^2}{\epsilon_a r_i^*}, \tag{15}$$

where the first and second terms represent the Coulomb interaction of this lipid with the charged amino acid

residues and the other lipids, respectively (r_i and r_i^* are the distances between the charges). To form the state with n charged lipids, we should remove $m - n$ lipids. Thus, the energy of this state is given by

$$E_n = \sum_{i=n+1}^{m} I_i. \quad (16)$$

The increase of I_n and E_n with increasing $m - n$ is shown in Fig. 4.

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