Comment on "Cluster Formation of Transmembrane Proteins Due to Hydrophobic Mismatching"

Schmidt *et al.* [1] recently studied the interactions between proteins embedded in membranes. The key parameter in this study is the hydrophobic mismatch. Schmidt *et al.* computed the force components along the unit vector pointing from one protein to the other and determined via integration the pair potential $U(r)$ that the proteins experience. For all mismatches this pair potential shows a minimum in $U(r)$ when the proteins touch, while for increasing distances a high potential barrier emerges that is followed by 2–3 lower peaks.

In this Comment, we argue that the quantity of interest is, however, not the pair potential computed by Schmidt *et al.*, but the potential of mean force (PMF), which is defined as the reversible work needed to bring two proteins from infinity to a given distance. The difference between the PMF and the potential computed by Schmidt *et al.* is the sign, and as a consequence, the barriers observed by Schmidt *et al.* are, in fact, minima of the PMF. From a computational point of view, computing the PMF accurately, however, is not as simple as reversing the sign. The PMF force involves an integration over these forces and hence it is important to sample the maxima of the potential equally accurate as the minima, using, for example, the weighted histogram analysis method. Figure 1 shows the PMF potential for a similar protein-lipid model [2,3]. Indeed, if we reverse the sign in Fig. 3(a) of Schmidt *et al.*, we get a curve which is very similar to ours. These results show a long-range, lipid mediated, attraction for both the negative and positive mismatch, while for zero mismatch the interactions are less attractive. The potential of mean force shows a small repulsive barrier in the case of a strong positive and negative mismatch. Schmidt *et al.* argue that clustering of proteins is caused by the large repulsive barrier; the correct interpretation is, however, that clustering is caused by long-range attractive interactions.

If we compare our potential of mean force calculations with the theoretical predictions of Dan *et al.* [4] and Kralchevsky *et al.* [5], our conclusions are opposite from Schmidt *et al.*; i.e., we do not observe the high energy barrier observed in the calculations of Dan *et al.*. As pointed out by Kralchevsky *et al.* [5], in the case of zero surface tension, which is imposed in our simulations, the theory of Dan *et al.* should be very similar to the theory of Kralchevsky *et al.* In fact, depending on the choice of parameters, a repulsive barrier can be the result of the model of Kralchevsky *et al.*, if the lipid profile in between the two proteins differs very much from the single protein profile. However, in both theories it is assumed that the proteins do not tilt, which is a good approximation for proteins with a large diameter [2], but may not hold for proteins with a small diameter.

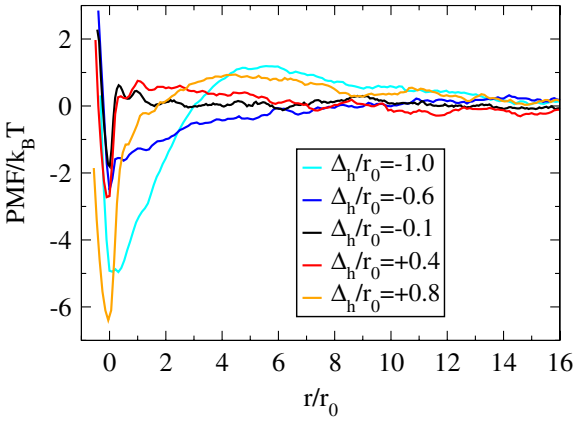

FIG. 1 (color online). Potential of mean force as a function of the distance between two proteins with negative (light blue and dark blue), no (black), and positive (orange and red) mismatch. The mismatch is defined as $\Delta_h = h - h_0$, with h the bilayer thickness at the surface of the protein and h_0 the unperturbed bilayer thickness. The mismatch is in units r_0, which is the interaction cutoff diameter. A mismatch of -1.0, -0.1, and 0.4 in our model corresponds to a similar mismatch in the model of Schmidt, i.e., $n = 3$, 5, and 6, respectively.

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