New and Notable

Toward a Realistic Theory of the Interaction of Membrane Inclusions

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An inclusion, like an integral membrane protein, necessarily perturbs local ordering of the bilayer in its vicinity. It is then a natural thought for a physicist to consider the indirect interaction between nearby inclusions induced by overlap of the perturbed regions of the bilayer. Such a phenomenon is familiar in simple or complex fluids including liquid crystals, or in any other ordered system perturbed by the presence of a surface or an impurity.

Although general principles may be straightforward, in the case of membranes the molecular detail of the perturbation at the site of the inclusion is complicated. Theoretical work in the past has concentrated on a particular choice from a possible range of effects, resulting in rather unrealistic models. In this issue of *Biophysical Journal*, May and Ben-Shaul (1999) present a model and a calculation based on all aspects of molecular rearrangement at the contact between an inclusion and the lipid matrix. The result is a realistic description with predictive capability and, thus, amenability to experimental testing.

How does an inclusion perturb the structure of the bilayer matrix? During the early 1970s, as bilayer membranes gradually became better understood, different approximate pictures emerged as useful. On a shorter length scale it is appropriate to consider a molecular picture in which the membrane interior consists of partially ordered chains. On length scales much larger than the average diameter of a lipid molecule, a very useful approximation is to describe membranes as continuous elastic sheets.

These views of the unperturbed bilayer membrane structure are naturally reflected in different models for the interaction between inclusions. Earlier models were more oriented toward a short-range view, where a perturbation is a local change in lipid ordering. More recently, continuum-elasticity theories appropriate for large length scales have dominated in published studies.

The models also depend, of course, on what is assumed to be the mechanism of the perturbation. There is no universal answer, but the two most important factors are the shape of the inclusion and the extent of its hydrophobic surface. The hydrophobic regions of a protein and the bilayer may match in thickness. If shape of the inclusion is cylindrical, the perturbation is restricted to short-range local change in lipid ordering and will be small (Shen et al., 1998).

When an inclusion is wedge-shaped and the hydrophobic regions match, curvature-elastic deformation is dominant and the simpler continuum model may be applicable. Corresponding to this deformation, the standard result is that elastic potential energy between two inclusions decreases with distance d as d^{-4}. But in a very recent complete investigation, Kim et al. (1998) find a surprising result: When more than two proteins are present, simpler pairwise theories are misleading because nonpairwise attractive forces are strong. For some five or more proteins, these forces can prevail and lead to the formation of stable aggregates.

When the extents of the hydrophobic regions of the membrane and inclusion do not match, the deformation also leads to local stretching (or shortening) and tilt of the chains. Another normally neglected factor is that major or minor lipid components of a bilayer may have their own preferred shapes, described macroscopically through the concept of spontaneous curvature. All these effects can no longer be treated in a macroscopic continuum theory, so molecular modeling becomes indispensable.

May and Ben-Shaul (1999) have now presented a realistic model of lipid-protein interaction, showing that in principle every effect is important and cannot be discarded without a quantitative argument. The starting position is the free energy expression, based on the understanding of self-assembling phospholipid structures accumulated over the years by many workers including the present authors. The free energy, which is formally a continuum theory, is expressed through molecular interaction parameters. This combination provides tractable formalism, which leads to valuable results for both the interaction between inclusions and the phase behavior of protein-lipid mixtures.

The ultimate test of a model is prediction of system behavior. The present work offers examples of protein-protein interaction weakened by tilt that need to be explored experimentally. More conclusive here is related recent work by May and Ben-Shaul (1997) on lipid-DNA aggregates. The work was performed in a similar spirit, with the electrostatic part of the free energy described by the Poisson-Boltzmann equation. The theory has successfully predicted that hexagonally packed complexes of DNA with cationic lipids will be increasingly stable as spontaneous curvature of the lipid tends to negative values and bending rigidity is small. Recent experimental work on cationic liposome-DNA complexes (Koltover et al., 1998) found that hexagonal complexes do indeed form in either of two ways: by adding to liposomes helper lipid-promoting negative curvature (dioleoyl phosphatidylethanolamine), or by adding

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cosurfactant-reducing membrane rigidity (hexanol). In this example biophysical insight is particularly important because hexagonally packed complexes are very effective as transfecting vehicles delivering extracellular DNA across the membrane.

An accurate description of a bilayer membrane is more easily accomplished than a similar description of the aqueous electrolyte at the membrane or macromolecular surface. It would be very useful to have molecular expressions of comparable accuracy for the free energy of the aqueous phase. In the last two years, even this goal has begun to appear closer with the introduction of ingenious new models for the hydrophobic part of the free energy of interaction between solutes (Garde et al., 1996). When such a description is fully accomplished, the art of biophysical prediction will become more useful and prevalent.

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