

Membranes: A Field-Theoretic Description

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Introduction

Theoretical methods used to describe biological membranes are distinguished by the different length scales on which they examine the system. The method which has been used to a great extent in the past is a phenomenological one in which the length scale of interest is sufficiently large that all the details of the molecules which make up the membrane can be ignored. Consequently the membrane is described as a two-dimensional sheet of which the free energy can be characterized by a few elastic constants. The description has been quite successful in the regime of its validity. The text of Safran (Safran 2002) can be consulted for a good description and some applications. Its limitations are that changes in the membrane on small scales, typically the thickness of the membrane itself, are not described reliably, and the effects of molecular architecture are not clear. Presumably the architecture affects the elastic constants, but the calculation of the latter from the former is a separate one, and replete with its own difficulties.

At the other extreme is the description of the membrane as an assembly of molecules which are described in atomic detail. The system is then studied by some method of computer simulation, such as Molecular Dynamics. This has been an extremely successful technique, especially for examining the effects on the membrane of particular biological molecules. As computers become ever more powerful, more and more problems in Biology will be examined by simulation. Their limitation lies, of course, in the brief time interval over which the membrane can be studied. The existence of thermodynamic phases has to be inferred from small samples, and the calculation of thermodynamic quantities is rather difficult. Some of these problems can be overcome by coarse-graining the description of the molecules and replacing them with a few interaction centers. One thereby trades atomic detail for an increase in the time over which a process can be examined. The interested reader is referred to the review by Saiz and Klein (Saiz and Klein 2002).

Field-theory methods are, in principle, completely equivalent to particle-based methods. But rather than using the discrete positions \mathbf{r}_i , $i = 1, 2, \dots, N$ of all N particles as basic variables, the field theory describes the system in terms of a field, or fields, which are functions defined over all space \mathbf{r} . By adjusting the scale over which one chooses to characterize these fields, one adjusts the scale over which one examines the features of the system. Thus the description has great flexibility. Like its particle-based counterpart, the field theory can be simulated. Often one solves the theory within the self-

consistent field approximation, discussed below, which provides the ensemble average of quantities of interest, thereby sacrificing a knowledge of the effects of fluctuations. But if such effects are not of primary interest, then the approximation provides a relatively direct method for following processes over long times and for obtaining various thermodynamic quantities. This means, *inter alia*, that the free energies of different configurations or phases can be calculated and those of lowest free energy can be determined. To make clear the means by which a field theory is constructed, it is useful to consider a simple example. This one, and several others, are discussed in the excellent monograph by Fredrickson (Fredrickson 2006).

What is a field-theory?

The field theory which is most familiar is that which describes electromagnetism at zero temperature. Suppose one has a number, N , of discrete charges q located at position \mathbf{r}_i . Then the total energy of the system, U , can be written in terms of the particle density

$$\hat{\rho}(\mathbf{r}) = \sum_{i=1}^N \delta(\mathbf{r} - \mathbf{r}_i) \quad (1)$$

as

$$U = \frac{1}{2} \int \frac{q^2 \hat{\rho}(\mathbf{r}') \hat{\rho}(\mathbf{r}'')}{4\pi\epsilon_0 |\mathbf{r}' - \mathbf{r}''|} d\mathbf{r}' d\mathbf{r}'' \quad (2)$$

However one invariably introduces the electric potential

$$V(\mathbf{r}) = \int \frac{q \hat{\rho}(\mathbf{r}')}{4\pi\epsilon_0 |\mathbf{r} - \mathbf{r}'|} d\mathbf{r}', \quad (3)$$

which satisfies the Poisson equation

$$\nabla^2 V(\mathbf{r}) = -\frac{q \hat{\rho}(\mathbf{r})}{\epsilon_0}, \quad (4)$$

so that the energy becomes

$$U = \int \frac{1}{2} \int q \hat{\rho}(\mathbf{r}'') V(\mathbf{r}'') d\mathbf{r}'' \quad (5)$$

After using the Poisson equation to eliminate the charge density in terms of the potential and integrating by parts once, one obtains

$$U = \frac{\epsilon_0}{2} \int [\nabla V(\mathbf{r})]^2 d\mathbf{r}, \quad (6)$$

which expresses the energy entirely in terms of the field $V(\mathbf{r})$. This is often a far more convenient starting point for any calculation than the particle based expression Eq.(2).

A similar change in perspective can also be brought about in statistical mechanics where one is to calculate the configurational partition function of the N particle system in a volume V at temperature T ;

$$Z = \exp\{-\beta F(T, N, V)\} = \prod_i^N \int d\mathbf{r}_i \exp\{-\beta \int H[\hat{\rho}] d\mathbf{r}\} \quad (7)$$

where $\beta = 1/k_B T$ and the Hamiltonian $H[\hat{\rho}]$ is a functional of the particle density, eq. (1). We insert the identity

$$\int \mathcal{D}w \mathcal{D}\rho \exp\{\beta \int iw(\mathbf{r})(\rho(\mathbf{r}) - \hat{\rho}(\mathbf{r})) d\mathbf{r}\} = 1 \quad (8)$$

where $\mathcal{D}w$ and $\mathcal{D}\rho$ denote functional integrations (Binney et al. 1992), to obtain

$$\begin{aligned} \exp(-\beta F) &= \int \mathcal{D}\rho \mathcal{D}w \prod_i^N \int d\mathbf{r}_i \exp\{-i\beta \int w(\mathbf{r}) \hat{\rho}(\mathbf{r}) d\mathbf{r}\} \exp\{-\beta \int (H[\rho] - iw(\mathbf{r})\rho(\mathbf{r})) d\mathbf{r}\} \\ &= \int \mathcal{D}\rho \mathcal{D}w \exp\{-\beta(Nf[iw]) + \int (H[\rho] - iw(\mathbf{r})\rho(\mathbf{r})) d\mathbf{r}\} \end{aligned} \quad (9)$$

$$\equiv \int \mathcal{D}\rho \mathcal{D}w \exp\{-\beta \mathcal{F}(T, N, V, [w, \rho])\} \quad (10)$$

where

$$\exp(-\beta Nf[iw]) \equiv \prod_i^N \int d\mathbf{r}_i \exp\{-i\beta \int w(r) \hat{\rho}(\mathbf{r}) d\mathbf{r}\} \quad (11)$$

and $f[iw]$ is the free energy of a *single* object subject to the field $iw(r)$. The above transformations are exact, but the integrals over the fluctuating fields w and ρ cannot be carried out in general. The mean-field, or self-consistent field, approximation consists of approximating the exact partition function Z of eq. (10) by the value of the integrand at which it is stationary with

respect to variations in the fields; *i.e.* the exact free energy $F(T, N, V)$ is approximated by

$$\mathcal{F}(T, N, V, [w^*, \rho^*]) = Nf[iw^*] + \int (H[\rho^*] - iw^*(\mathbf{r})\rho^*(\mathbf{r}))d\mathbf{r} \quad (12)$$

where w^* and ρ^* are the solutions of the equations which express the condition that \mathcal{F} should be an extremum;

$$\frac{\delta \mathcal{F}}{\delta \rho} = 0 \quad \text{or} \quad iw^*(\mathbf{r}) = \left(\frac{\delta H}{\delta \rho} \right)_{\rho=\rho^*}, \quad (13)$$

$$\frac{\delta \mathcal{F}}{\delta w} = 0 \quad \text{or} \quad \rho^*(\mathbf{r}) = N \left(\frac{\delta f}{\delta iw} \right)_{iw=iw^*} \quad (14)$$

As the right-hand side of eq. (13) is real, one sees that the extremum of \mathcal{F} occurs at a value of w^* on the imaginary axis of the complex w plane. Second, one sees from eq. (11) that

$$\rho^*(\mathbf{r}) = \frac{\prod_i^N \int d\mathbf{r}_i \hat{\rho} \exp\{-i\beta \int w^*(\mathbf{r}) \hat{\rho}(\mathbf{r}) d\mathbf{r}\}}{\prod_i^N \int d\mathbf{r}_i \exp\{-i\beta \int w^*(\mathbf{r}) \hat{\rho}(\mathbf{r}) d\mathbf{r}\}} \quad (15)$$

$$= N \frac{\exp\{-i\beta w^*(\mathbf{r})\}}{\int d\mathbf{r} \exp\{-i\beta w^*(\mathbf{r})\}} \quad (16)$$

$$\equiv \langle \hat{\rho}(\mathbf{r}) \rangle. \quad (17)$$

Thus $\rho^*(\mathbf{r})$ is simply the average density calculated in the ensemble of a single particle in the real field $iw^*(\mathbf{r})$. But, from eq. (13) this field depends upon ρ^* itself. Thus the equations (13) and (14) are a set of self-consistent equations for the fields. Once they are known, the mean-field free energy of eq. (12) is also known. It is essentially Nf , *i.e.* N times the free energy of the single-particle system in the self-consistent field w^* corrected for some simple over counting of the interactions that the estimate Nf contains.

Results

Lipid Membranes

The mean-field theory description of membranes has a long history. As noted above, mean-field theory essentially approximates the problem of calculating

the partition function of a system of many interacting components by one in which the partition function of a single component in an external field is calculated. This field depends upon the average properties of the components as obtained from the single component partition function. The approximation is obviously better the better the description is of the single components and the better the calculation of the single-component partition function. Biological lipids present a problem in that they are much larger than simple atoms or molecules for which the partition function can be easily calculated, and they are much smaller than very long polymers for which the partition function can, in many cases, also be easily calculated. There are few alternatives to describing the many configurations of the molecule by means of some coarse-grained model and actually enumerating all possible configurations of the lipid and evaluating the partition function directly. One common method, pioneered by Szleifer, Ben-Shaul, and Gelbart (Szleifer et al. 1986) is to ignore the headgroups of the lipids and to focus only on their chains, to describe the thermal excitations in the chains by means of Flory's rotational isomeric states model (Flory 1969), and to describe the orientation of the chain by the values of three Euler angles. Such a description can encompass on the order of ten million configurations. Clearly the calculation of the partition function of the system in an external field is the necessary and difficult part of the approximation scheme. Lastly, Szleifer et al. modeled the hydrophobic part of the bilayer as a liquid, replacing all of the interactions in the system by a constraint that the density of this liquid be constant. This constraint is enforced by a field, which is the field in this field theory. As in any mean-field theory, it must be determined self-consistently; i.e. the field depends on the average densities which are determined from the partition function containing the field itself. There are alternative formulations of the basic ideas which are also useful (Leermakers and Scheutjens 1988; Khelashvili et al. 2005)

Because the description of the lipid-chains includes the angles between the carbons along the chain, one can readily obtain the average value of the angle between the normal to the bilayer and the vector from carbon number k to $k + 1$. An orientational order parameter directly related to this angle is measured by nuclear magnetic resonance, so that theoretical predictions can be directly compared to experiment. Further, the effect of the addition of double bonds on the order parameter can be calculated and the order parameter of the two different tails of common two-tailed lipids determined. These and other applications can be found in the review by Fattal and Ben-Shaul (Fattal and Ben-Shaul 1996).

Several years ago, the above theory was extended to include a second field. Just as the field introduced by Szleifer et al. was coupled to the number density, so a second field was introduced (Elliott et al. 2005) which coupled to the density of bonds of a specified angle. This permitted one to distinguish phases not only by their density, but also by the degree of order in their tails; *i.e.* to distinguish the gel phase from the liquid phase in a one-component system. It also permitted a calculation of the phase separation between liquid and gel phases which occurs in a mixture of saturated and unsaturated lipids. With the addition of a model cholesterol, the field theory was employed to obtain the phase diagram of the ternary mixture which displays, not only a gel phase, but *two* liquid phases (Elliott et al. 2006). All three such phases are commonly observed in such ternary mixtures (Veatch and Keller 2005). Such a phase diagram has only been obtained by field-theory methods. Again the calculation of thermodynamic quantities is precisely one of the strengths of these methods.

Polymeric Membranes

The fusion of biological membranes is a crucial process which takes place whenever anything leaves the cell or enters it, whenever material is exchanged between vesicles within the cell, during infection by viruses, during fertilization, and many other biological processes. It is not well understood, however. Some aspects are clear. Because the lipid headgroups interact favorably with water, it costs energy to remove the water between two vesicles in order to bring them close to one another. This has to be done by some outside agent. Because the removal of the water increases the free energy per unit area of the vesicle bilayers, *i.e.* increases its surface tension, the free energy can decrease if the vesicles can decrease their area, which they can do by fusing. But again, how does this come about? Over twenty years ago, it was proposed that the process began when the tails of some opposing amphiphiles flip over to forge a connection, denoted a “stalk,” which was modeled as axially symmetric (Kozlov and Markin 1983). Due to the surface tension, the stalk was assumed to spread radially, as shown in Fig. 1, leaving behind a hemifusion diaphragm consisting of the inner leaves of the opposing bilayers. Eventually a hole formed in this diaphragm producing the fusion pore. One way to investigate this process was to employ a field theory description of the bilayers, cause the system to follow the proposed pathway, and to monitor the free energy along the way. Again this can be done with field-theory

methods without difficulty.

Figure 1: Density profiles of the stalk-like structures shown in the r, z plane of cylindrical coordinates. (a) Two bilayers in solvent. There is no stalk between them. (b) The limit of stability of the initial stalk. (c) The metastable stalk itself. (d) The unstable transition state (saddle point) between the metastable stalk and the hemifusion diaphragm. (e) A small hemifusion diaphragm.

It would be advantageous, however, if this could be carried out in a system for which the evaluation of the single-component partition function could be evaluated more easily than by the direct enumeration of configurations described above for lipids. Amphiphilic lipids form bilayers because they afford a structure by which the hydrophobic tails can be shielded from unfavorable contacts with water by hydrophilic head groups which have favorable contacts. There are many other amphiphiles which form bilayers, and one suspects that many behaviors of membranes are universal in that they are displayed by all membranes, and not just the biological ones. Furthermore some amphiphiles lend themselves to theoretical calculation. That is the case with long, flexible, block copolymers which consist of a homopolymer of “A” monomers chemically joined to a homopolymer of “B” monomers. In a solvent of A homopolymers, which interact favorably with other As and unfavorably with Bs, these block copolymers form bilayer vesicles. Their advantage for theory is that the single-component partition function can be evaluated by solving a relatively simple, modified diffusion equation (Fredrickson 2006).

By utilizing such a theoretical system, and the field theory outlined above, one can relatively easily bring about the formation of all of the configurations involved in the formation of a stalk, the hemifusion diaphragm, and a pore (Katsov et al. 2004). Indeed, Fig. 1 shows the average density, $\rho(r)$, which was generated by the field theory. The free energy barriers encountered in the standard stalk-hemifusion diaphragm path to fusion could be compared to the barriers encountered in other proposed, non-standard, paths. Such a comparison showed that the barriers in the non-standard pathway were, in fact, smaller (Katsov et al. 2006).

Summary

This last example shows both the limitations and the advantages of the field-theoretic approach. As Fig. 1 was generated from a mean-field approach, one sees only the average densities, and none of the detail which would be produced by a simulation. On the other hand, it was relatively easy to calculate the free energies of different fusion pathways which had been proposed, and thereby determine which was the most favorable. For problems in which thermodynamic properties of membranes are paramount, as opposed to their microscopic structure, field-theoretic methods will continue to play an important role.

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