

# Themed issue: membrane biophysics

Biomembranes are thermodynamic ensembles with interesting features beyond the scope of single molecules. The role of thermodynamic observables, susceptibilities, and how they are influenced by the thermodynamic variables is the most prominent topic of this themed issue on membrane biophysics.

DOI: 10.1039/b912987c

Biological membranes are essential components of cells and their organelles. They mainly consist of lipids and proteins. The basic structure is a double layer of lipids of about 5 nm thickness into which proteins are embedded (Fig. 1). Membranes determine the boundary between the inside and outside of cellular compartments, and their respective ion and protein concentrations. They also control the transport of substances into the cell and are important players in the metabolism of cells. Furthermore, due to the presence of enzymatic proteins, the large overall surface of membranes gives rise to a plethora of catalytic properties.

Studies on membranes are clearly a topic of biology and biophysics. However, membranes are also ensembles of many molecules and as such have features well-known in other areas, *e.g.*, the fields of liquid crystals, polymer science, nanoscience and solid-state physics. Similar physical, physical chemistry and thermodynamic concepts to other disciplines concerned with soft matter are used, including phase behavior, diffusion, adhesion and adsorption. The field of membrane biophysics is a very important one for *Soft Matter* and we hereby highlight some of the more important and recent developments in this themed issue.

The basis for the understanding of biomembranes was gradually laid during the last 120 years. Overton<sup>1</sup> proposed that the layer-separating cell organelles have the properties of a fat, Gorter and Grendel<sup>2</sup> proposed the double-layer structure, Danielli and Davson<sup>3</sup> suggested that the double-layer lipid membrane is covered by surface proteins, while Singer and Nicolson<sup>4</sup> considered the membrane as a two-dimensional liquid with proteins being adsorbed to the membrane surface or spanning through the membrane interior. With time it became clear that membranes are not only homogeneous

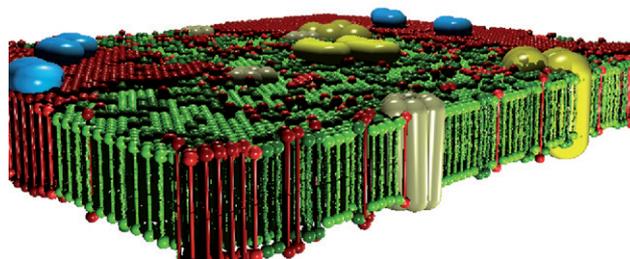
thin sheets separating two aqueous volumes, but that they possess an interesting structure with locally varying physical properties. Already in their important paper from 1972, Singer and Nicolson considered protein clusters, and Mouritsen and Bloom<sup>5</sup> proposed that capillary forces can exist between lipids and proteins leading to domains and aggregates. We now know that membranes are laterally inhomogeneous and display phase behavior, lipid domains, protein clusters, and compositional asymmetry between both lipid monolayers (Fig. 1). As is true for interfaces in general, membranes have in some sense a physics of their own that can be considered separate from the 3D environment.

In this themed issue, several articles address the lateral heterogeneity of biomembranes, *i.e.*, phase behavior and domain formation, for example the reviews by Semrau and Schmidt (DOI: 10.1039/b901587f), and Kumar and Bagatolli (DOI: 10.1039/b901866b), and the articles by Wieser *et al.* (DOI: 10.1039/b902266j) and Lipowsky *et al.* (DOI: 10.1039/b902036e). The transmembrane compositional asymmetry is addressed by May (emerging areas: DOI: 10.1039/b901647c), the review by Carrer *et al.* (DOI: 10.1039/b901883b) and the article by Sapay *et al.* (DOI: 10.1039/b902376c).

In an attempt to improve understanding of the function of biomembranes, much of biomembrane research in the recent decade has focused on single molecules, for example, the structure and function of individual membrane proteins, receptors or channel proteins. Seemingly, knowing more molecular detail also yields more insight into biological function. This is possibly true for molecules that act locally, *e.g.*, enzymes. However, knowledge obtained exclusively on the molecular scale obscures important features that emerge on larger scales, for instance, elastic constants, relaxation time scales, phase behavior, domain formation, and other kinds of cooperative behavior.

This themed issue of *Soft Matter* is especially dedicated to the phenomena emerging on mesoscopic and microscopic scales. The physical theory describing such systems is thermodynamics. The second law of thermodynamics implies that the most likely state of the system occurs most often. As Einstein noted in 1910<sup>6</sup> this statement would be trivial if one did not consider the states in the proximity of the entropy maximum, *i.e.*, the fluctuations of the system and their amplitude.

A problem with focussing on molecular scales is that one may not consider the thermodynamics of the system correctly.



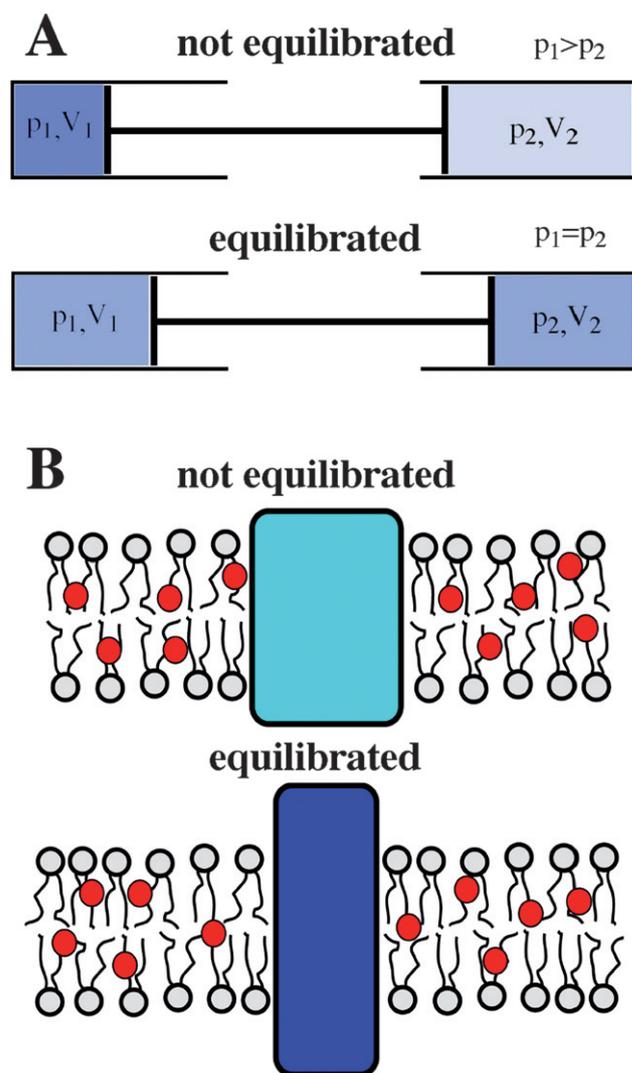
**Fig. 1** The present understanding of biomembrane structure is summarized in this image. The membrane consists mainly of lipids and proteins. Lipids arrange in domains and clusters and display different physical states, *e.g.*, solid-ordered (red), liquid-ordered and liquid-disordered (green). Proteins (yellow, blue and white) are distributed differently in the various domains. Courtesy of Heiko Seeger (Copenhagen).

The second law is only valid for the complete system under investigation, *e.g.*, the cell membrane as a whole, but not generally for arbitrarily selected subsystems within this membrane, *e.g.*, a protein or an individual lipid, if one looks at them in the context of the cellular environment. One can easily construct examples that demonstrate that. Fig. 2A (top) shows two gas containers with different pressures that are coupled by a piston. This system is not at equilibrium. At equilibrium, the pressures in both containers are the same [Fig. 2A, (bottom)]. In order to approach the equilibrated state, the entropy of one container increases while that of the other container decreases. This

implies that in this situation the second law does not hold for the individual containers but only for the total, coupled system. One can construct similar examples from membranes interacting with proteins and drugs. For instance, the article by Cantor *et al* (DOI: 10.1039/b822075a) discusses the influence of the lateral pressure created by anaesthetics dissolved in membranes on protein structure and function (schematically shown in Fig. 2B). Even though proteins are influenced by their structure, it is still the entropy maximum of the complete membrane that determines the protein state in the presence and absence of anaesthetics. A further example is the

article by Weikl *et al.* (DOI: 10.1039/b902036e) that shows that ligand–receptor equilibria are influenced by thermal curvature fluctuations of the membrane. This effect introduces cooperativity into membrane adhesion to surfaces. Obviously, a system is not only more than, but also different from, the sum of its parts. Thus, it seems wise under many conditions not to consider single-molecule properties, but rather system features. In thermodynamics, all the couplings between different system variables are expressed in Maxwell's relations, and there are as many of them as there are possible molecular interactions.

The susceptibilities are also functions that cannot be understood on the level of individual molecules. Some of them are the heat capacity (fluctuations in enthalpy), the volume and area compressibility (fluctuations in volume or area), bending elasticity (fluctuations in curvature), and capacitance (fluctuations in charge). Heat capacities are discussed in Wodzinska *et al.* (DOI: 10.1039/b909877a) and elastic constants of membranes by Fine *et al.* (DOI: 10.1039/b901714c). Fluctuations in particle numbers may lead to domain formation, and are discussed by Semrau and Schmidt (DOI: 10.1039/b901587f), Kumar and Bagatolli (DOI: 10.1039/b901866b), Weikl *et al.* (DOI: 10.1039/b902036e), May (DOI: 10.1039/b901647c), Wieser *et al.* (DOI: 10.1039/b902266j) and Lipowsky *et al.* (DOI: 10.1039/b902017a). Examples of the influence of large fluctuations are the papers by Brünig *et al.* (DOI: 10.1039/b901389j) on the critical slowing-down membrane transitions and the fluctuations in domain size. The paper by Wodzinska *et al.* (DOI: 10.1039/b909877a) shows that fluctuations in the lipid membrane result in the occurrence of ion-channel-like current events indistinguishable from protein channels in the regime of large-area fluctuations. The consideration of transport through lipid channels is contrasted by transport through protein channels (Schmitt *et al.*, DOI: 10.1039/b901587f) and peptide transport through membranes (Gao and Fang, DOI: 10.1039/b902971k). The tutorial review by Westh (DOI: 10.1039/b901659c) gives an introduction to the chemical potential of water in connection with the interaction of drugs with membranes.



**Fig. 2** A: Two gas containers with different pressures are connected by a piston. When the systems equilibrate, one gas container increases its entropy while the entropy of the gas in the second container decreases. The equilibrated system represents the state of maximum entropy for the total system only. Adapted from ref. 7. B: A similar situation for a protein in a membrane. The red circles denote small molecules dissolved in a membrane, *e.g.*, anaesthetics. They exert a lateral pressure on the protein that may influence the protein conformation (*cf.* Cantor *et al.*, DOI: 10.1039/b822075a).

Often, temperature-dependent changes are studied. However, there are many other intensive variables, such as pressure, electrostatic potential and chemical potential. In an equilibrated system they are homogeneous throughout the experimental sample, as shown in Fig. 2 for equilibrated coupled gas containers or for the lateral pressure of membranes and proteins. The review by Winter and Je-worrek (DOI: 10.1039/b901690b) focuses on the influence of hydrostatic pressure on the phase behavior of membranes, while the review of Sparr *et al.* (DOI: 10.1039/b901737b) treats gradients in chemical potentials across membranes and their influence on phase behavior, and the review of Dimova *et al.* (DOI: 10.1039/b901963d) considers the electrostatic potential and its influence on vesicles. The papers by Cantor *et al.* (DOI: 10.1039/b822075a) and Xing *et al.* (DOI: 10.1039/b901664c) focus on the lateral pressure profile in membranes.

Finally, lipid vesicles are also used in drug delivery, as, for example, shown in the review of Koynova and Tenchov (DOI: 10.1039/b902027f) on the transfection properties of cationic lipids. Bunge *et al.* (DOI: 10.1039/b902264c) study bilayers on solid supports.

A number of excellent experts in the field of membrane biophysics contrib-

uted to this special issue of *Soft Matter*. We are grateful to all the authors that made this volume possible. We believe that it gives a fair insight into the present understanding of membrane biophysics and the thermodynamic couplings from a physical and physical chemistry point of view.



Thomas Heimburg, Denmark

## References

- 1 E. Overton, *Vierteljahresschr. Naturforsch. Ges. Zuerich*, 1895, **40**, 159.
- 2 E. Gorter and F. Grendel, *J. Exp. Med.*, 1925, **41**, 439.
- 3 J. F. Danielli and H. Davson, *J. Cell. Comp. Physiol.*, 1935, **5**, 495.
- 4 S. J. Singer and G. L. Nicolson, *Science*, 1972, **175**, 720.
- 5 O. G. Mouritsen and M. Bloom, *Biophys. J.*, 1984, **46**, 141.
- 6 A. Einstein, *Ann. Phys.*, 1910, **338**, 1275.
- 7 T. Heimburg and A. D. Jackson, in *Structure and Dynamics of Membranous Interfaces*, ed. K. Nag, Wiley, Hoboken, New Jersey, 2008, pp. 317–339.