Commentary

Conformational dynamics of vesicles

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The transport of ions and molecules through membranes is a key ingredient to many biophysical processes. For example, contemporary attempts for gene therapy require transport of DNA fragments through the cellular and nuclear membranes (1); signaling depends on ionic transport through dynamic pores in membranes (see, for example, ref. 2); efficient drug delivery vehicles based on vesicular "baggies" (see, for example, ref. 3) or multilamellar "onions" (see, for example, ref. 4) assumes well-controllable drug release. These are but a few examples where understanding the fundamental processes that control and signal for transmembrane transport of ions, molecules, and macromolecules may be central for the development of new technological processes. While there exists a large body of empirical knowledge on this subject, there is little substantial comprehension of the physical principles involved. For example, are there multiple mechanisms? What is the origin of the specificity? What is the role of cooperativity? To approach providing answers to such questions, visualization of the dynamical steps involved could be an invaluable tool. The research reported in this issue of the *Proceedings* by Sandre, Moreaux, and Brochard-Wyart (5) represents an exciting advance in this direction.

Sandre *et al.* (5) have demonstrated specifically how to visualize the dynamics associated with pore opening and closing in tense vesicles. In this case, nonbiological vesicles with dimensions of tens of micrometers are produced by electroformation (6) and tension is induced by either adsorption on surfaces (using electrostatic coupling with multivalent ions or polylysine) or optical illumination in the presence of fluorescent probes embedded in the hydrophobic membrane core. In the absence of tension, the vesicle shape is controlled by curvature elasticity and the accompanying thermal undulation fluctuations (7, 8), and the appearance approximates that of a rough sphere. In the presence of tension, the surface becomes smooth and pores nucleate to reduce the surface area (thereby relaxing the tension). With the pores open, the sugar that is dissolved in the water repartitions to reduce the osmotic swelling pressure and the line tension, which originates at the pore edges, takes over and provides a driving mechanism for pore closure. Sandre *et al.* have derived theoretical expressions for this dynamics which are in accord with the observations. The driving surface and line tension forces on the pores are balanced by viscous drag in the solvent and membranes. Herein lies the clever trick that provides the opportunity to observe and follow the dynamics. The authors note that the time scale of the pore evolution is governed by the solvent viscosity; with this in mind, Sandre *et al.* simply increase the viscosity of the aqueous medium with glycerol up to about 32 centipoise, which provides sufficient slowing down to allow visual observations of the pore opening and closing. It is this accomplishment that may engender many derivative studies to shed light on transmembrane transport.

One important contribution of the Sandre *et al.* report (5) is to lead the way to visualization of dynamical processes in cell and plasma membranes; deep understanding of these functions has proven to be elusive. I shall briefly cite a few such examples.

Transmembrane transport of molecules and ions is often accomplished by means of membrane-bound proteins that self-assemble (often oligomers of three to six molecules) to form more-or-less selective pores. Such pores may, for example, allow the passage of linear molecules, both neutral (9) and charged such as single-stranded DNA (10). Detailed visualization of the molecules moving through the pores might well provide clues to unravel the specificity. Note, however, that such pores are typically in the nanometer size range, which is smaller than the optical range of the Sandre *et al.* study. Nevertheless one might well speculate about the possible extension of their investigation to shorter-wavelength probes, e.g., x-ray microscopy.

Exo- and endocytosis (see, for example, ref. 11) are processes in which the membrane deforms to encapsulate a foreign object (or molecule) and eventually buds off, thereby removing the intruder from the membrane. In endocytosis the net effect is to transport the object from the exterior to the interior of the cell (or vesicle). In exocytosis the object is removed to the exterior solvent. While much is now known about the interplay between concentration fluctuations in the membrane and the curvature elasticity that determines the cell shape, the detailed defect dynamics associated with the break-off step requires more elaboration.

Cellular adhesion and fusion (12) are processes that are stimulated and facilitated by membrane proteins. However, again the membrane fusion step requires the nucleation of defects. While there is considerable speculation on how this occurs, the specific defects involved remain unknown.

There exist a variety of cellular conformational reorganizations that have yet to be understood mechanistically. What provokes them? What is the physics that controls the time scales for the evolution? With the developments of Sandre *et al.* (5), the visualization of these processes becomes feasible.

1. Verma, I. M. & Somia, N. (1997) *Nature (London)* **389,** 239–242.
2. Hille, B. (1992) *Ionic Channels of Excitable Membranes* (Sinauer, Sunderland, MA), 2nd Ed.
3. Allen, T. (1996) *Curr. Opin. Colloid Interface Sci.* **1,** 645–651.
4. Panizza, P., Colin, A., Coulon, C. & Roux, D. (1998) *Eur. Phys. J. B* **4,** 65–74.
5. Sandre, O., Moreaux, L. & Brochard-Wyart, F. (1999) *Proc. Natl. Acad. Sci. USA* **96,** 10591–10596.
6. Angelova, M. I., Soléau, S., Méléard, P., Faucon, J. F. & Bothorel, P. (1992) *Prog. Colloid Polym. Sci.* **89,** 127–131.
7. Helfrich, W. & Servuss, R.-M. (1984) *Nuovo Cimento Soc. Ital. Fis. D* **3,** 137–151.
8. Milner, S. & Safran, S. A. (1987) *Phys. Rev. A* **36,** 4371–4379.
9. Bezrukov, S. M., Vodyanoy, I., Brutyan, R. A. & Kasianowicz, J. J. (1996) *Macromolecules* **29,** 8517–8522.
10. Kasianowicz, J. J., Brandin, E., Branton, D. & Deamer, D. W. (1996) *Proc. Natl. Acad. Sci. USA* **93,** 13770–13773.
11. Lindau, M. (1991) *Q. Rev. Biophys.* **24,** 75–101.
12. Zimmerberg, J., Vogel, S. S. & Chernomordik, L. V. (1993) *Annu. Rev. Biomol. Struct.* **22,** 433–466.

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