Commentary: Surface Tension of Biomembranes

Benoît Roux
Groupe de Recherche en Transport Membranaire, Départements de physique et chimie, Université de Montréal, C.P. 6128, Succ. Centre-Ville, Montréal, Québec, Canada H3C 3J7

In this issue of the *Biophysical Journal*, molecular dynamics experts have expressed their views on a fundamental methodological question regarding the simulation of biomembranes. Fritz Jähnig elaborates on the reasons why bilayers should be simulated with zero surface tension, whereas Scott Feller and Richard Pastor discuss why it might be necessary to simulate bilayers under conditions of nonzero surface tension.

Since the pioneering work of van der Ploeg and Berendsen in 1983, the field of molecular dynamics simulations of lipid biomembranes has been expanding rapidly. Current computer simulations are usually based on all-atom models with realistic microscopic potentials, and water molecules are included explicitly. The simulated systems are generally organized as infinite lattices with periodic boundary conditions to reduce edge effects; the size and shape of the simulation cell may be allowed to vary and fluctuate in order to generate configurations corresponding to a system at constant pressure or at constant surface tension. Recently, questions concerning the nature of the periodic boundary conditions that should be applied during molecular dynamics simulations of lipid bilayer has become somewhat controversial. Chiu et al. (1995), as well as Feller et al. (1995), have argued that dynamical trajectories of bilayer should be generated in the presence of an applied external surface tension (actually stretching the membrane). On the other hand, Tu et al. (1995) have argued that the most realistic boundary condition is that of constant isotropic pressure with zero applied surface tension.

Is this a technical matter that should interest only practitioners of molecular dynamics simulations? Certainly not. The issue raises important questions for all scientists interested in a better understanding of the physical microstate of biological membranes and its role in biological processes. A few particular cases can help to illustrate this point. For example, the tension in lipid membranes is capable of activating some kinds of mechanosensitive ion channels, notably the 3-nS MscL channel cloned from *Escherichia coli*. (Sukharev et al., 1994). The mechanism of gating governing the opening and closing kinetics of the channel is not known. The activity of lipases provides another example. In monolayer studies, the catalytic activity of a β-isoform of phospholipase C activity is markedly affected by the area per lipid and the surface pressure, with reduced activity at extremes of initial pressure and with the most permissive pressures in the middle of the range investigated (James et al., 1994); the observed optimum surface pressure for hydrolysis was ~25 mN/m. A simple interpretation of such results is that a portion of each enzyme must insert into the monolayer before hydrolysis, doing work proportional to the enzyme area times the lateral pressure (Boguslavsky et al., 1994). Furthermore, it was recently shown that the activity of lytic peptides such as melittin is strongly influenced by the tension of vesicles under osmotic stress (Benachir and Lafleur, 1996); the ability of melittin to induce leakage of large unilamelar vesicles (LUV) is promoted when the outer solution is hypo-osmotic relative to the interior of the LUV. It was suggested that the structural perturbation caused by the osmotic pressure gradient loosens the compactness of the outer leaflet, which facilitates the melittin-induced change in membrane permeability. Finally, one might even speculate that the composition, the physical state, and the presence or absence of microtension could also play a role in the stable association of structural elements of membrane proteins or in membrane fusion. Such considerations highlight the importance of experimental measurements of the surface tension of phospholipid bilayers at the microscopic level. As stressed by the authors of both communications, it must be recognized that the local surface tension of bilayers has not been directly accessible by experiments.

In principle, molecular dynamics simulations based on realistic atomic models can provide a wealth of information at the microscopic level that is not easily accessible experimentally. However, for meaningful simulations it is essential to firmly establish the computational methodology upon which the molecular dynamics trajectories are based. Basically, the goal of the computationalist is to find the best way to construct an initial configuration and treat the finite simulation system (typically ranging from 5000 to 20,000 atoms) to realistically mimic a true molecular biomembrane. Experience has shown that stable simulations can be performed with the present models and efforts are continuously spent improving the force fields as the results from more simulations are compared with available experimental data (e.g., see Schlenkrich et al., 1996; Tu et al., 1995; and Venable et al., 1993). However, beyond the obvious limitations of the force fields, it is essential to establish molecular dynamics studies on rigorous methodological ground. What is the optimal treatment of the boundary conditions and the applied surface tension in simulations of bilayer membranes for meaningful studies (which can be compared to

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Address reprint requests to Dr. Benoît Roux, Chemistry Department, Université de Montréal, C. P. 6128, succ.A, Montréal, H3C 3J7 Canada. Tel.: 514-343-7105; Fax: 514-343-7586; E-mail: rouxb@ere.umontreal.ca.

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experiments)? Such a fundamental question concerns the formal correspondence of the properties of a finite system with those of an infinite one. In their communication, Feller and Pastor show explicitly that the calculated surface tension of a micropatch of membrane at constant surface area per lipid depends on the absolute size of the simulation system. This implies that the calculated surface tension in such systems does not behave as an extensive thermodynamic quantity. They attribute this variation to the change in out-of-plane fluctuations and membrane undulations. The present considerations regarding the correspondence of simulations with infinite systems are reminiscent of the confusion that existed for most of the 1970s concerning the formal treatments required to calculate of the bulk dielectric constant of polar fluids. In fact, the present situation is worse because there is a lack of direct measurements of the local surface tension of a micropatch of bilayer (contrary to the dielectric constant of polar liquids, which can be routinely measured). Most arguments are based on macroscopic measurements or on the interpretation of monolayer data. Fritz Jähnig stresses that, although the surface tension of a real bilayer is not accessible directly, such indirect measurements support the notion that it is zero.

The following discussion offers a unique opportunity to address a fundamental question concerning the surface tension of phospholipid bilayers. As members of the biophysics community, we are grateful to the authors of both communications for explaining their respective views on this issue.

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