Membrane bilayers separate organelles from the cytoplasm and nucleoplasm of cells, and cells from their extracellular milieu. The mechanical compliance and tension of these membranes play a central role in their biological functions. For instance, the plasma membrane (which contains both lipid molecules and proteins and is physically connected to the underlying actin-rich cytoskeleton meshwork of the cell through linker proteins) regulates the cell’s ability to spread, deform, and migrate (1–4).

Because of its physiological importance, membrane mechanics has long been an important subject of biophysical research, studied using complementary systems and models, including live cells and biomimetic systems. The exquisite versatility and control of biomimetic, in vitro systems (mainly liposomes), which make use of purified lipids and proteins, have made these systems highly attractive to determine the complex physical laws that govern membrane mechanics and identify important molecular contributors.

Work with liposomes has long suggested that changes in cytoskeleton content, myosin-based activity, and cytoskeletal coupling to the membrane all significantly impact membrane stiffness and dynamics. In particular, the friction between the two leaflets of a plasma membrane was supposed to be as small as the friction of a lipid membrane, and thus has been considered to contribute little to overall membrane mechanics (5).

In this issue of the *Biophysical Journal*, Campillo et al. (6) revisit this assumption and elegantly demonstrate that minuscule changes in the molecular composition of lipid bilayers, such as the oil content in the hydrophobic interleaflet space, can have dramatic effects on their dynamic micromechanical properties. Using the well-established nanotube extrusion assay, introduced by Evans and Yeung (7) more than two decades ago, and theoretical analysis, these authors measure the static and dynamic force-deformation response functions of liposomes obtained either by inverted emulsion (IE) method or electro-formation (EF)—two commonly used methods of liposome formation, as well as plasma membrane spheres obtained directly from cell blebs. Nanotubes extracted from IE- and EF-obtained liposomes display nearly identical static properties: same membrane thickness and similar bending modulus, independently of cholesterol content and presence of an actin cortex. However, IE and EF nanotubes display fundamentally different time-dependent force response to preset deformation by optical tweezers.

Through the ingenious application of a ramp elongation to nanotubes extruded from IE liposomes, Campillo et al. (6) observe a fast increase in force followed by a decrease in force best described by two relaxation times: A fast relaxation time ranging between 1 and 10 s, which decreases with extrusion speed; and a much longer, novel relaxation ranging between tens of seconds and tens of minutes, which increases linearly with the square of the maximum length of the tether, presumably due to nonlocal bending effects. This slow relaxation is largely absent in EF liposomes. The same ramp-elongation experiment on plasma membrane spheres detached from cells that do not contain an actin cortex give rise to force-traces that quantitatively resemble those of IE liposomes, including this exceedingly slow force relaxation. Addition of a reconstituted actin cortex to IE liposomes, which add frictional forces between lipids and the cytoskeleton, fully recapitulate the dynamic force response of blebs subjected to the same time-dependent elongation.

The authors’ results suggest that the culprit(s) for this fundamentally different dynamic response between EF and IE liposomes are alkane chains that are present in liposomes prepared by IE (5). These molecules localize in the hydrophobic region of the membrane, in between the two leaflets, and would collectively affect internal friction of the membrane. For liposomes obtained from cell blebs (plasma membrane spheres), the membrane-spanning molecules promoting high viscous friction between leaflets would be transmembrane proteins.

What could mediate enhanced friction and modulate the dynamic properties of the plasma membranes in live cells? Ezrin, radixin, and moesin are prototypical members of a large family of proteins that physically and dynamically crosslink the cytoskeleton to the plasma membrane (8). Ezrin, radixin, and moesin molecules added to liposomes could modulate the effective friction between membrane and cytoskeleton and, in turn, greatly affect the force response during tether extrusion. Moreover, organelles and cells feature a remarkably high number of different lipids (9). It would be interesting to assess how lipid composition itself may affect dynamic micromechanical properties through their specific interactions with lipid-binding proteins of the cytoskeleton and membrane-spanning proteins.

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