Determining the transbilayer structure of asymmetric bilayer membranes using small-angle scattering

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Cellular membranes are highly complex, composed of hundreds of distinct lipids and thousands of membrane proteins. Active transporter proteins drive an underlying asymmetry in the lipid composition of the inner and outer membrane leaflets. For example, in mammalian plasma membranes, outer leaflets are enriched in sphingolipids, while inner leaflets are enriched in several glycerophospholipids including phosphatidylethanolamines (PEs). Differences in leaflet composition likely result in transmembrane differences in fluidity and charge density; it remains unclear how these and other structural and mechanical properties of the two leaflets are coupled. Although controlled studies of asymmetry have long been technically challenging, recent advances in the preparation of asymmetric liposomes now allow such questions to be addressed systematically in a chemically well-defined system. Neutron scattering is particularly well suited for determining membrane structure due to the strong contrast between the stable hydrogen isotopes protium (^{1}H) and deuterium (^{2}H). Thus, the combined use of protiated and deuterated lipids can be used to generate interleaflet contrast and thereby elucidate the asymmetric matter distribution normal to the bilayer plane. Here, we present results from a diverse set of biophysical techniques, including SANS, SAXS, NMR, GC-MS, DSC, and Molecular Dynamics simulations, aimed at determining the transbilayer structure of asymmetric model membranes.