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Investigating Membrane Asymmetry Using Cryo-em and Molecular Dynamics Simulations

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The two leaflets of biological membranes can differ in both lipid composition and relative lipid abundance. Such bilayer asymmetries influence membrane properties and cellular functions, but the underlying molecular mechanisms are poorly understood. Abundance asymmetry, which occurs when there is an imbalance in the total number of lipids in the two leaflets, has proven particularly difficult to detect and characterize. We present an integrated experimental and computational framework to investigate lipid number asymmetry that arises naturally in very small vesicles. We used cryo-electron microscopy (cryo-EM) to characterize interleaflet lipid distributions in individual vesicles. We identified features in the intensity profiles across the bilayer that are sensitive to the number of lipids in each leaflet and confirmed the metric by analyzing large sets of liposomes with different diameters. At the same time, we use atomistic molecular dynamics (MD) to generate synthetic cryo-EM intensity profiles of simulated bilayers with varied number asymmetry for cross-validation with experimental data. Results from in vitro and in silico studies across various lipid compositions show similar trends with increasing number asymmetry but differences in absolute values, likely due to different interleaflet packing densities in the flat simulated bilayers and curved experimental membranes.