Free energies of stalk formation in the lipidomics era

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Many biological membranes are asymmetric and exhibit complex lipid composition, comprising hundreds
of distinct chemical species. Identifying the biological function and advantage of this complexity is a central goal of membrane biology. Here, we study how membrane complexity controls the energetics of the first steps of membrane fusions, that is, the formation of a stalk. We first present a computationally efficient method for simulating thermodynamically reversible pathways of stalk formation at coarse-grained resolution. The new method reveals that the inner leaflet of a typical plasma membrane is far more fusogenic than the outer leaflet, which is likely an adaptation to evolutionary pressure. To rationalize these findings by the distinct lipid compositions, we computed ~200 free energies of stalk formation in membranes with different lipid head groups, tail lengths, tail unsaturations, and sterol content. In summary, the simulations reveal a drastic influence of the lipid composition on stalk formation and a comprehensive fusogenicity map of many biologically relevant lipid classes.

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[2] JS Hub and N Awasthi, Probing a continuous polar defect: A reaction coordinate for pore formation in lipid membranes, J. Chem. Theory Comput., 13, 2352-2366 (2017)