

Transition State to Stalk Formation between Two Apposed Model Membranes Observed by Particle Simulation

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Stalk formation is an essential initial step in membrane fusion. It is a basic process involved in trafficking within the cell, exocytosis, synaptic release, as well as viral infection. The molecular mechanism, however, is only poorly understood. Using particle simulation of a soft, coarse-grained model we identify the minimum free energy path (MFEP) transforming two apposed bilayer membranes into a stalk, where an hourglass-shaped passage connects the two membranes. Due to the indistinguishability of identical amphiphiles in the fluid membrane, coordinates of individual bead-spring lipids cannot parameterize the transformation path, instead, we use the difference of hydrophilic and hydrophobic densities as order parameter, m . The explicit form of the free-energy $F[m]$ as a functional of the collective variable, m , is unknown, and an equation-free approach is adopted where MFEP is obtained by the on-the-fly string method. We use thermodynamic integration along this reversible transformation path to compute the excess free energy of the metastable stalk and the transition state. The transition state is confirmed by direct diagonalization of order-parameter fluctuations. The particle based simulations are quantitatively compared to predictions of self-consistent field theory using the same model but invoking a mean-field approximation. Matching the energy scale of our minimal coarse-grained model by requiring that the hydrophilic-hydrophobic interfaces of the model have the same tension than that between oil and water, we find that the stalk is metastable with an excess free energy of about 13 kT with respect to two apposed bilayers. The transition state towards stalk formation has a free energy barrier of 2.5 kT with respect to the metastable stalk and involves only a small number of lipids.