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Efficient Collective Variables for Estimating the Free Energy of Pore Formation in Lipid Membranes

Denys Biriukov [1], Timothée Rivel [1], Ivo Kabelka [1], Robert Vácha [1]

Masaryk University, Brno, Czech Republic [(1)]

Understanding the molecular mechanisms of pore formation is vital for deciphering fundamental biological processes and designing new therapeutic strategies. Although experimental methods offer valuable insights, they often lack the temporal and spatial resolution needed to capture the dynamic and complex stages of pore formation. In this work, we introduce two collective variables (CVs) to characterize membrane pore behavior—particularly its energetics—through molecular dynamics simulations. The first CV, termed Full-Path, effectively tracks both the nucleation and expansion phases of pore formation. The second, called Rapid, is tailored to assess pore expansion in the regime of large pores, offering a quick and reliable method for evaluating membrane line tension, which defines the free energy landscape in this regime. Our results show that both CVs yield consistent line tension predictions that qualitatively agree with experimental data for POPC, POPS, and POPG membranes. These experimental trends are accurately captured by the all-atom CHARMM36 and prosECCo75 force fields. In contrast, the all-atom Slipids and the coarse-grained Martini 2 and Martini 3 models show varying levels of agreement with experiments. Overall, our developed CVs can be easily adapted to different MD simulation engines, providing a versatile tool for advancing research in membrane biophysics.