FREE ENERGY SIMULATIONS OF PORE FORMATION

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Lipid membranes define biological cells by establishing a semi-permeable barrier. Pore formation plays a role in processes such as membrane fusion and fission, the killing of bacterial cells with antimicrobial peptides, and others. Although pores are heavily studied with a variety of methods, the free energy landscape of the initial stages of the pore formation is still not fully understood. We use molecular dynamics simulations to study the mechanisms and energetics of pore formation. We overcome the challenge of exploring the free energy landscape using umbrella sampling along a recently developed reaction coordinate[1, 2]. Here, we here study the effects (i) of electric fields on the free energies of pore formation, as applied during electroporation to allow cellular uptake of drugs or genes, and (ii) of the common small antifungal drug itraconazole and the solvent DMOS[3]. The potentials of mean force (PMFs) show that electric fields greatly stabilize open pores and lower the barrier for pore formation. We also compare two methods for establishing transmembrane potential in an MD simulation – external electric field and charge imbalance. Due to itraconazole low solubility in water there are several liposome-based formulations but the release mechanisms remain unclear. Interestingly, whereas itraconazole has only a small effect on the structure of planar, intact membranes, it strongly stabilized open pores[3].

[1] J. Hub and N. Awasthi, J. Chem. Theory Comput. 2017, 13, 2352-2366

[2] J. Hub, J. Chem. Theory Comput. 2021, 17, 1229−1239

[3] G. Kasparyan, C. Poojari, T. Róg, J. Hub, J. Phys. Chem.B, 124, 40, 8811–8821, Sept 2020