Molecular simulations of protein-membrane interactions during membrane fusion

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Viral fusion proteins catalyze the fusion of the viral envelope with the host membrane, thereby allowing the virus to deliver its genome into the cytoplasm of the host cell. In this talk, a combined crystallographic and simulation study on the interactions of a class II fusion protein of rift valley fever virus is presented, which presents a major thread to humans and life stock throughout Africa. Both in the crystal and in MD simulations, we observe a specific recognition pocket for phosphatidylcholine (PC) lipids. Notably, the pocket is conserved throughout class II fusion proteins, suggesting that viruses do not merely anchor themselves into the hydrophobic membrane core, but that they may also sense the lipid composition of their host. Further. The simulations provide a atomic-level rationale for cholesterol-dependent membrane binding of the protein.[1]
The opening of the fusion pore has been suggested as the rate-limiting step during fusion. To rationalize such findings in energetic terms, and presented in the second part of the talk, we develop rigorous methods for computing the free-energy landscape of the opening and closing of membrane pores, so far with a focus on flat membranes. With these methods, we recently confirmed a 40-year old hypothesis on metastability (ability to live long) of membrane pores.[2,3]

[1] Guardado-Calvo, Atkovska,... , Hub, Rey, A glycerophospholipid-specific pocket in the RVFV class II fusion protein drives target- membrane insertion, Science, 2017, 358, 663–667
[2] Abidor, J. Electroanal. Chem. 104, 37 (1979). Chernomordik et al., Biochim. Biophys. Acta (1985, 1987)
[3] Ting, Awasthi, Müller, Hub, Metastable Prepores in Tension-Free Lipid Bilayers, Phys. Rev. Lett., 2018, 120, 128103. Hub and Awasthi, J. Chem. Theory Comput. 13, 2352 (2017).