Hidden barriers in membrane-ion penetration

Debashree Chakraborty[1], Bratin Kumar Das and Anjana V M

[1]Department of Chemistry, National Institute of Technology Karnataka, India.

The development of computational models to predict the permeability of small molecules and ions through membrane is of considerable scientific and public health interest as this information are required for the progress of the drug candidates that progress to clinical trials. The permeation of small molecules through a membrane can be understood by the solubility–diffusion model of permeation. It consists of three main steps. The first step includes the passage of the small molecule from the solvent/aqueous phase to the lipid bilayer, the second step involves the diffusion of the small molecule across the lipid bilayer and the third step involves exit of the small molecule out of the lipid bilayer into the solvent/aqueous phase. As the ion-penetration is a rare event, Umbrella sampling simulations can be used as an efficient technique to determine the free energy cost for penetration of the ions along a reaction coordinate in a biased fashion. Therefore, defining a proper reaction coordinate to depict the mechanism of the ion penetration is very important. The ion-penetration mechanism depends on the type of the ion, type of the membrane and also on the membrane thickness. We performed a series of Umbrella sampling simulations for three different aniions, F^-, Cl^- and I^- in two different membranes (DNPC and DPPC) to find out the contributing factors for the ion-penetrations. It is found that the ion permeation consists of two main barriers. One from the upper leaflet and another from the lower leaflet. These two barriers are different in nature and water palys an important role in the permeation pathway. The dehydration pathway was observed more in the case of the thicker membrane (DPPC).

1) “Passive permeation of halides across the lipid bilayers: Understanding the mechanism by umbrella sampling simulation with modified reaction coordinates.” Bratin Kumar Das, Anjana V Mathath, Debashree Chakraborty*. (manuscript under preparation).