Small Ion Channel – Linking Molecular Simulations and Electrophysiology

Ion channels are pore-forming protein assemblies that mediate the transport of small ions across cell membranes. Otherwise, membrane bilayers would be almost impermeable to ions incapable to traverse the low dielectric constant, hydrophobic membrane core. Ion channels are ubiquitous to all life forms. In humans and other higher organisms they play the central role in conducting nerve impulses, cardiac functions, muscle contraction and apoptosis. On the other extreme of biological complexity, viral ion channels (viroporins) influence many stages of the virus infection cycle either through regulating virus replication, such as entry, assembly and release or modulating the electrochemical balance in the subcellular compartments of host cells.

Ion channels were crucial components of protocells. Their emergence facilitated adaptation of nascent life to different environmental conditions. The earliest ion channels must have been much simpler than most of their modern ancestors. Viral channels are among only a few naturally occurring models to study the structure, function and evolution of primordial channels. Experimental studies of these properties are difficult and often unreliable.

In principle, computational methods, and molecular dynamics (MD) simulations in particular, can aid in providing information about both the structure and the function of ion channels. However, MD suffers from its own problems, such as inability to access sufficiently long time scales or limited accuracy of force fields. It is, therefore, essential to determine the reliability of MD simulations. We propose to do so on the basis of two criteria. One is channel stability on time scales that extend for several microseconds or longer. The other is the ability to reproduce the measured ionic conductance as a function of applied voltage. If both the stability and the calculated ionic conductance are satisfactory it will greatly increase our confidence that the structure and the function of a channel are described sufficiently accurately. To our knowledge, long time scale stability ($\sim$10 μs) and the correct electrophysiology have been shown so far for only one channel – the synthetic LS3 hexamer). In this presentation, this approach will be discussed in application to two viral channels – Vpu, encoded by the HIV-1 genome and p7 of hepatitis C.