Insights into voltage gated sodium channel NavAb function from multi-microsecond molecular dynamics simulations

C. Boiteux,[1] I. Vorobyov[2] and T.W. Allen,[1,2] [1]Health Innovations Research Institute & School of Applied Science, RMIT University, GPO Box 2476V, Melbourne, VIC 3001, Australia and [2]Department of Chemistry, University of California, Davis, CA 95616, USA.

The recent solution of the X-ray structure of the bacterial channel NavAb has provided the first opportunity to study the functional mechanisms of a sodium channel at the atomistic level. This channel displays the typical voltage-gated ion channel structure, but possesses a selectivity filter reminiscent of a calcium channel, a characteristic of the NachBac family. Despite the relatively low level of ionic selectivity exhibited by this channel, it is important to understand how its particular structure and sequence controls the binding and permeation of Na ions. The available NavAb channel structure is in a pre-activated state (where its pore remains closed), making direct studies of permeation difficult. However, we have carried out multi-microsecond simulations (on the physiological timescale for permeation) to reveal the interactions responsible for the competitive binding of Na^+, K^+ and Ca^{2+} ions into the selectivity filter as a function of protonation state on the protein's EEEE locus. We describe the coordination environment for different multiple ion configurations and compute distributions and underlying thermodynamics to understand the binding and movements of ions within the channel. Within these lengthy trajectories we also observe a striking flexibility of the channel pore, including conformational changes to a structure consistent with that previously proposed to be an inactivated state. Our long simulations have provided insights that are being used to guide targeted computational investigations into permeation and selectivity for this unusual Na channel.