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Multiscale Simulations of Lipid Interactions with Integral Membrane Proteins: Aquaporins
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Membrane protein structural biology is one of the key biochemical challenges of the coming decade. With continuous improvements to the methods used by structural biologists there is a predicted exponential growth in the number of membrane proteins structures. Nevertheless, these biological assemblies are usually resolved in the absence of the native lipid environment. Coarse-Grained molecular dynamics (CGMD) simulations provide a means for assessing the assembly and interactions of molecular complexes at a reduced level of representation. This method has been shown to accurately predict the insertion position of proteins within a cell membrane. Previous studies enabled us to correlate predicted contacts to lipids with experimental data on lipid-exposed residues for a number of membrane proteins (e.g. LacY, rhodopsin, KcsA, MscL, FepA, BtuB). The recent determination of high resolution structures for aquaporins in a phospholipid bilayer environment (Aqp0: 2B6O and 3M9I; Aqp4: 2ZZ9) has provided an excellent test case. The CGMD approach has been used to simulate lipid/protein interactions for >30 members of the aquaporin family, revealing that patterns of protein/lipid headgroup interactions are conserved and are in good agreement with the lipids resolved in the electron crystallography structures. We have extended this further by using a multi-scale approach, investigating the interactions at atomic resolution. At this scale we may also consider hydrogen bonding interactions, which also show good agreement with the experimental structures. This methodology is being incorporated into a semi-automated high-throughput pipeline to enrich our database of CGMD membrane protein simulations (CGDB; http://sbcb.bioch.ox.ac.uk/cgdb).