Free energy simulations of potassium channels - KcsA, Shaker and HERG

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There are by now several potassium channel structures available both in the open and closed states. Using these structures in free energy molecular dynamics simulations, it is possible to study the structure-function relations in potassium channels in a rigorous fashion. Here we use free energy simulations in a comparative study of KcsA, Shaker and HERG potassium channels. Some of the issues to be considered are:

i) Role of the cmap terms in the CHARMM force field in stabilizing the structure of the selectivity filter: The cmap dihedral terms are relatively new addition to the CHARMM force field. We find that these terms play an essential role in keeping the C=O carbonyl dipoles in the selectivity filter directed towards the channel axis as observed in the crystal structures of potassium channels, and necessary for providing a complete hydration shell for the permeating K^+ ions.

ii) Comparison of the filter structures in KcsA, Shaker and HERG channels: KcsA is known to have a very stable filter structure, which leads to a large selectivity margin for permeation of K^+ *vs* Na^+ ions. Loss of the some of the H-bonds in other potassium channels results in a less selective channel, e.g., in HERG channel, K/Na selectivity is completely lost due to the flexibility of the S1 binding site. Nevertheless selectivity is retained in the other (S2-S4) binding sites.

iii) Energetics of ion permeation in KcsA and Shaker channels from potential of mean force (PMF) calculations: It is well established that 3 K^+ ions can occupy the S0, S2 and S4 sites in the KcsA channel.

Here we demonstrate that this is the only stable configuration for 3 K^+ ions in the filter by constructing PMF's of a K^+ ion while the filter is occupied by other 2 K^+ ions. A much higher PMF is found when the two K^+ ions are at the S1-S3 sites compared to that of S0-S2, which indicates that simultaneous occupation of the S1, S3, and S4 sites is not energetically feasible. Similar PMF results are obtained for the corresponding PMF calculations in the Shaker filter, reinforcing the homology of the filter structures among the potassium channels from the bacterial to the mammalian.