Computational structure analysis for membrane-bound potassium channels

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Ion channels fluctuate stochastically between "open" and "closed" states, which determine the ion flux through biological membranes, also known as "gating". This crucial feature of ion channels is necessary in cellular, biological systems to regulate the ion concentration level, which is essential for the processes of homeostasis or second messaging. Yet the origin of gating is not fully understood. The structure of a channel in its various gating states, which is controlled by its amino acid sequence, plays a vital role for ion selectivity. We here focus on tetrameric potassium channels, for which very short, miniature systems exist. These ideal model systems, Kcv_{PBCV-1} and Kcv_{ATCV-1} that are found in *chlorella* viruses comprise of only 94 and 82 amino acids per monomer [1-3] and play an important role for determining elementary structure-function relations. Although these channels are comparably small, they show all essential features like gating and selectivity.

Many experimental and computational studies have shown that small changes in the sequences of these ion channels can change their functionality drastically, ultimately leading to an inversion of the open/closed probability. [4] Commonly used molecular dynamics (MD) simulations allow for a dynamic characterization of these channels in their gating states but typically cannot be used to directly observe spontaneous gating transitions due to time scale limitations. Other approaches, like integral equation theory are able to predict ion distributions within channels and therefore allow for calculations of thermodynamic properties like free energy surfaces governing ion translocation, but require reasonable average structures as a basis. In the absence of experimentally available structures, MD simulations can fill the gap based on homology models derived from suitable template structures.

A useful method to generate reasonable structures from simulations of homology models is given by the workflow developed by Tayefeh *et al*. [5,6] which utilizes a mean-field simulated annealing approach to satisfy distance distributions. Currently available computer and GPU power nowadays allows for much longer simulation time scales than were possible at the time of first application of this workflow. We apply this protocol to our Kcv model systems and mutants embedded in solvated lipid bilayers in order to generate structures based on MD simulations reaching μs time scales. Structural and thermodynamic analyses of these more refined data are compared to properties and structural features obtained from limited MD data in order to characterize the effort required for reliable results.

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