Thermodynamic and kinetic ion selectivity of phospholamban

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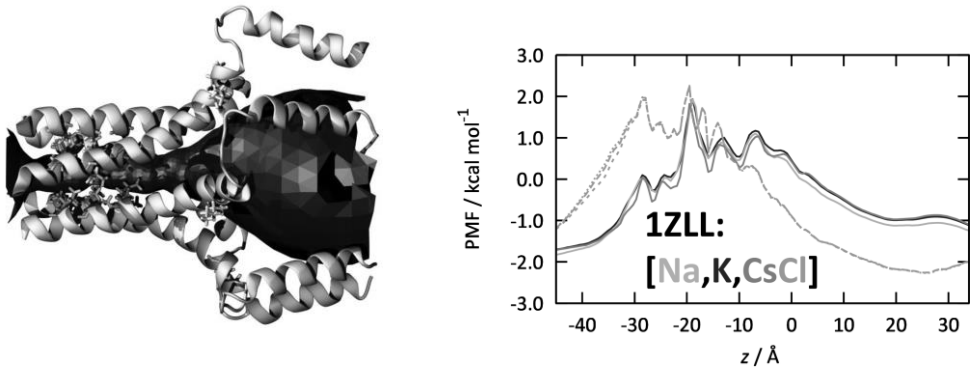
The membrane protein phospholamban is known to modulate the clearance of Ca^{2+} from the cytosol in muscle cells by blocking, in its monomeric form, the sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA). However, phospholamban also exists as a pentameric assembly whose function is controversially discussed. It might represent an inactive storage form but it was also demonstrated to function as a cation channel [1]. Structurally, a narrow hydrophobic constriction in the interior of the phospholamban pentamer forms an apparent barrier to ion translocation. Yet the protein apparently favors the larger Cs^+ over smaller cations.



Here we investigate into the ion translocation features by means of computations of the potential of mean force (PMF) at finite concentration conditions. The PMF is a key quantity for characterizing chemical and biological processes since it represents the free energy change along a given reaction coordinate. We employ the 3D reference interaction site model (3D RISM) integral equation theory, that yields correct K^+/Na^+ selectivity predictions for potassium channels [2]. In contrast to expensive molecular simulation approaches, 3D RISM theory allows for the direct, noise-free computation of the PMF in order to address the thermodynamic and kinetic ion preference of phospholamban for Cs^+, K^+ and Na^+. The link between PMF and ion conductance is provided by a simplified mean field theory [3].

The methodology is applied to two conformations of the putative phospholamban channel protein. We show that both thermodynamic and kinetic selectivity agree with experimental data from electrophysiology for one of the conformations treated (PDB code 1ZLL), while the other form (1XNU) is apparently impermeable. The calculations shed light on the molecular basis of phospholamban conductance by providing detailed maps of the PMF along the channel axis.

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