Computational analysis of ion distributions in K^+ channels

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Classical molecular dynamics (MD) simulations are a computational tool for modeling structure, dynamics, and thermodynamics of nanometer-sized biomolecular systems on time scales of nanoseconds up to microseconds. Due to its atomic resolution, MD simulations are used to reveal principles of biochemical mechanisms and interactions which are difficult to be obtained by experimental techniques [1-3]. Ion translocation in membrane-bound potassium channels is, however, a comparatively slow process which requires alternative theoretical approaches in order to understand structure-function correlates.

Here we present a modeling workflow which facilitates the rapid screening of point mutation effects on ion concentration profiles along channel protein pores. We use the viral potassium channel Kcv as a suitable model system since it represents an extremely short, yet fully functional structural K^+ channel motif [4]. The basis structure for virtual mutation scanning is taken from a homology model of the wild-type channel that has been extensively refined by fully atomistic MD simulations of the protein in a solvated, explicit lipid bilayer system. Starting with structures obtained from these simulations, the workflow consists of a sequence of homology modeling steps for introducing the point mutations and subsequent 3D-RISM ("reference interaction site model") integral equation calculations [5]. The latter provide data about equilibrium ion distributions within the channel pore that yield concentration profiles upon radial integration [6]. Analysis of the integrated concentration profiles as a function of the mutation state yields important information to correlate apparent experimental conductance data with the amino acid sequence. These correlations can be used to design functional mutant channels with desired properties.

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