Identifying descriptors of the conductive state in small viral K^+ ion channels

Lars Schumann,[1] Martin Urban,[1] Kerri Kukovetz,[2] Oliver Rauh,[2] Indra Schröder,[3] Gerhard Thiel,[2] Stefan M. Kast[1]

[1]Fakultät für Chemie und Chemische Biologie, Technische Universität Dortmund, 44227 Dortmund, Germany

[2]Fachbereich Biologie, Technische Universität Darmstadt, 64287 Darmstadt, Germany

[3]Institut für Physiologie II, Universitätsklinikum Jena, 07743 Jena, Germany

Gating, the process of stochastic fluctuations between open and closed states of ion channels, is essential for regulating transmembrane ion fluxes in cells from all forms of live in the context of ion homeostasis and electrical signalling. The origin and intricacies of gating are not fully understood yet. The structure of a channel in its various gating states, which is controlled by its amino acid sequence, also directly influences ion selectivity. We here focus on a miniature model system for canonical tetrameric potassium channels, the virally coded $Kcv_{PBCV\text{-}1}$, comprised of only 94 amino acids per monomer. [1,2] In spite of its small size this channel protein still represents the highly conserved core pore module of all K^+ channels and shows all essential functional features like gating and selectivity.

To investigate the properties of ion channels in solution and embedded within a membrane environment molecular dynamics (MD) simulations are commonly utilized. Here, a homology model based on the NaK ion channel mutation NaK2K was used as initial structure. [3] By changing the K29 protonation state of $Kcv_{PBCV\text{-}1}$ to a neutral form, we were able to observe multiple ion transitions in µs-timescale MD simulations. The resulting computed conductivity is compatible to experimental results including data from a mutant (K29A) that neutralized the cationic amino acid. From the trajectory data representative structures were computed by means of simulated annealing, [4,5] allowing direct comparison of the thermodynamic properties of structures at different K29 protonation states simulated at 0 and +425 mV respectively. For the first time, we could characterize the properties of solvent species within the confined geometry of a highly conductive $Kcv_{PBCV\text{-}1}$ structure by means of the 3D Reference Interaction Site Model (3D RISM). [6]

Additionally, we could monitor and characterized the structural changes underlying a so-called "filter gating" in $Kcv_{PBCV\text{-}1}$. In this type of gating very negative voltages cause a fast inactivation of the channel. Here we find conformational changes of filter residues correlated with inactivation, consistent with literature. [7] The computed open channel time spans allow for the calculation of rate constants that can be directly compared to the corresponding values of channel fluctuations under similar conditions in experiments. The computational and experimental data are in good agreement, including the effect of modulating the KCl solvent concentration on the rate constant. Thus, we were able to successfully combine computational structure modelling and simulation with experimental functionality assessment in the same time window in a complementary manner.

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