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Title: Selectivity and conduction studies in bacterial voltage-gated sodium channels by molecular dynamics simulations.

Abstract in Englisch

Voltage gated Na+ channels are essential for the generation of action potentials, and thus are vital for mediating heart rates, neuronal signal transductions and muscle contractions. Selective ion permeation is a critical biological function of these channels. Recently released 3-D crystal structures of bacterial voltage-gated sodium ion channels provide great opportunities to unravel key structural functions and mechanisms of their vertebrate counterparts at atomistic level.

This thesis presents three scientific publications, focusing on exploring the ion selectivity between sodium and calcium ions, sodium ion conductance mechanisms and structural dynamics as well as investigations of potential drug access pathways for charged channel blockers, in the vicinity of the selectivity filter domain via molecular dynamics simulations. This thesis elucidates the energetic differences between sodium and calcium ion permeations through the selectivity filter. A key structural configuration of the selectivity filter during outward transition simulations is discovered and suggested to be crucial in initiating channel slow inactivation. A potential external engineered access pathway for positive charged local anesthetics via a mutant in the selectivity filter is also proposed.

In summary, this thesis indicates the feasibilities of utilizing bacterial voltage gated sodium channels as templates to probe key channel functions of mammalian sodium channels and sheds light on key roles of the selectivity filter domain with regard to ion conduction, selectivity and drug access.