Computational Studies of the Concealed Gating Pathways and Electrophysiological Function of the Human Cardiac IKs Channel

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Abstract

Following the completion of the human genome, relating protein molecular structure to its physiological function remains a challenge for the next decade and beyond. Protein malfunction underlies many debilitating and life-threatening diseases. A framework relating protein structure-to-function is necessary for elucidating disease molecular mechanisms. Current techniques have limited ability to explore this relationship in atomic detail at physiological timescales. We formulate a modeling schema that overcomes this limitation through applications of Machine Learning. Using this approach, we study molecular processes of ion-channel gating using IKs as a paradigm. The simulations reproduce experimentally recorded saturation of gating charge displacement at positive membrane voltages, two-step voltage sensor movement shown by fluorescence, ion-channel statistics, and current-voltage relationships. Additionally, ligand modulation (by PIP2) of IKs and its role in cardiac action potential duration shortening during β-adrenergic stimulation was also studied. Channel subconductances are shown to depend on the pore energy profile and entire protein structure. The Machine Learning approach is applicable to atomistic-scale studies of any protein structure-to-function relationship on timescales of physiological function.