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Investigating the Selectivity of KcsA Channel by an Image Charge Solvation Method (ICSM) in Molecular Dynamics Simulations

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Abstract. In this paper, we study the selectivity of the potassium channel KcsA by a recently developed image-charge solvation method (ICSM) combined with molecular dynamics simulations. The hybrid solvation model in the ICSM is able to demonstrate atomistically the function of the selectivity filter of the KcsA channel when potassium and sodium ions are considered and their distributions inside the filter are simulated. Our study also shows that the reaction field effect, explicitly accounted for through image charge approximation in the ICSM model, is necessary in reproducing the correct selectivity property of the potassium channels.

AMS subject classifications: 31B05, 92C05, 65Z05

Key words: Potassium ion channel, selectivity, image charge solvation method, molecular dynamics.

1 Introduction

Ion channels are membrane-spanning proteins that form a pathway for the movement of ions through the cell membrane and they play significant roles in a wide variety of biological processes. Some examples of their many functions include the control of secretion of hormones into the bloodstream, generating electrical impulses that establish information transfer in the nervous system, and controlling the pace of the heart and other muscles [27]. The idea for assuming the existence of a means for transporting ions from the exterior of a cell to the interior was proposed 63 years ago with Hodgkin and Huxleyś study of the electrical activity in squid giant axon [17,20]. They showed that both sodium and potassium ions contributed to the ionic current and that their fluxes were in

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opposite directions. Twenty years later Hladky and Haydon used small antibiotic gramicidins to actually prove the existence of an ionic pathway [16,20]. Properties of ion channels and their functions in manipulating electric currents by conducting different ionic species heavily depend on their molecular structure in the presence of a complicated surrounding solvent environment. In past decades, great technical strides in many diverse areas of science culminated in the completion of x-ray crystal structures of ion channels. Meanwhile, for theoretical studies, a hierarchy of multi-scale mathematical models, from molecular dynamics [25,28], Brownian dynamics [10], and Poisson-Nernst-Planck (PNP) theories [9,11], were developed to study functions of ion channels.

Potassium channels are specialized proteins able to facilitate and regulate the conduction of ions, K^+ ions in particular, through cell membranes [13,27]. In 1998, MacKinnon et al. [17,20] successfully obtained the crystal structure of KcsA (potassium crystallographically sited activation) channel at a resolution of 2.0 Å, allowing a direct laboratory observation of the selectivity filter and binding sites of K^+ ions. KcsA is comprised of around 560 residues (Fig. 1) which form four identical subunits (Fig. 2), each containing two alpha-helices connected by a loop of approximately 30 amino acids. These proteins combine to form three primary sections of the channel: the opening pore on the cytoplasmic side of the cell interior, a small cavity (of 5Å in radius) filled with water and a mix of sodium (Na^+) and potassium (K^+) ions, and the selectivity filter. The selectivity filter, could be as narrow as 2Å in radius, comprised of four specific cation binding sites and formed by the backbone carbonyl groups of conserved residues threonine (T), valine (V), glycine (G), and tyrosine (Y), allows fast conduction of K^+ while being highly selective for potassium ions over sodium ions (Fig. 3) [13].

The relatively complete functioning components (gating, selectivity, conductance) and available high resolution structure of KcsA channel makes it the most interesting case attracting investigation in biological studies and mathematical modeling. However, modeling the selectivity of KcsA channel is extremely challenging due to the complicated ion-water-protein interactions. Counterintuitively, the Na^+ ion has the same ionic valence as the K^+ ion does but with a smaller ionic radius, nevertheless it is the one that is rejected by the narrow selectivity filter. In [12], it was suggested that the small diameter of the selectivity filter required dehydration of the cations entering the filter. To compensate for the cost of the dehydration, the carbonyl oxygen atoms from the amino acids in the filter take the place of the water oxygen atoms. The relative rigidity of the filter precludes this action in the case of the Na^+ ions with a smaller radius but stronger binding of water shell. However, a later study suggests that the selectivity can be explained by the fact that the smaller Na^+ does not bind to the K^+ sites in a thermodynamically favorable way [31].

To understand the selectivity mechanism of the filter, molecular dynamics (MD), being an explicit atomistic model, is a naturally suitable method to model these characteristics but the computation remains very expensive even with current computer powers due to the large number of degree of freedom and the necessarily small time step (10^{-15} seconds) versus the ion permeation time scale (10^{-6} seconds) [10]. The mean-field theory,