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Computational Study on Hysteresis of Ion Channels: Multiple Solutions to Steady-State Poisson-Nernst-Planck Equations

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Abstract. The steady-state Poisson-Nernst-Planck (ssPNP) equations are an effective model for the description of ionic transport in ion channels. It is observed that an ion channel exhibits voltage-dependent switching between open and closed states. Different conductance states of a channel imply that the ssPNP equations probably have multiple solutions with different level of currents. We propose numerical approaches to study multiple solutions to the ssPNP equations with multiple ionic species. To find complete current-voltage (I-V) and current-concentration (I-C) curves, we reformulate the ssPNP equations into four different boundary value problems (BVPs). Numerical continuation approaches are developed to provide good initial guesses for iteratively solving algebraic equations resulting from discretization. Numerical continuations on V, I, and boundary concentrations result in S-shaped and double S-shaped (I-V and I-C) curves for the ssPNP equations with multiple species of ions. There are five solutions to the ssPNP equations with five ionic species, when an applied voltage is given in certain intervals. Remarkably, the current through ion channels responds hysteretically to varying applied voltages and boundary concentrations, showing a memory effect. In addition, we propose a useful computational approach to locate turning points of an I-V curve. With obtained locations, we are able to determine critical threshold values for hysteresis to occur and the interval for V in which the ssPNP equations have multiple solutions. Our numerical results indicate that the developed numerical approaches have a promising potential in studying hysteretic conductance states of ion channels.

AMS subject classifications: 70K50, 92C05, 37N30, 65M99, 97M10

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Key words: Poisson-Nernst-Planck equations, multiple solutions, *I-V* curve, turning point, continuation, hysteresis, memory effect.

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1 Introduction

Essential for life, ion channels are protein molecules with a narrow spanning pore across membranes, regulating various crucial biological functions [18, 43, 65]. They play fundamental roles in exchanging ions across cell membranes, propagating electric impulses in nerves, and maintaining excitability of membrane [21, 56]. Ion channels switch their conductance states in response to variation of transmembrane voltages as well as ionic concentrations of cells and extracellular medium [14, 17, 28, 47, 51, 52, 57]. For instance, lysenin channels that are inserted into a planar bilayer lipid membrane show voltage regulations with slowly changing external voltages [14]. Voltage-dependent anion channels exhibit hysteretic response to a varying voltage with frequency of different magnitudes [51]. Ionic concentrations also have significant impacts on the switching of conductance states of voltage-gated channels. An L-type voltage-gated calcium channel shows distinct gating modes when different concentrations of charge carriers are applied [52].

Hysteresis phenomenon is ubiquitous in optical devices [16], many-body systems [8], and biological systems [7]. In recent years, there has been a growing interest in understanding hysteretic response of ion channels to varying applied voltages [3, 9, 14, 31, 44, 48, 51, 60]. Hysteresis of ions channels is of physiological significance, since it involves many human physiological processes [9, 44, 60]. One distinct feature of hysteresis is the memory effect when the system undergoes transitions between different states. In the context of voltage-gated ion channels, the current through channels increases and decreases along different paths when applied voltages periodically ascend and descend, respectively [3, 9, 14, 48, 51]. It is pointed out that hysteresis takes place when frequency of an applied oscillating voltage is competing to typical relaxation time of transitions between different conductance states [9, 14, 48]. To explore such a hysteretic response, several discrete state Markov models have been developed [2, 9, 13, 19–22, 44, 48]. In such models, ion channels are assumed to have certain number of states, representing closed and open states. In addition, Markovian properties are assumed in the transitions between different states with certain transition rates. The master equation of stochastic processes is derived to describe the probability of the channel being in each state with respect to time. It should be noted that hysteresis exhibited in voltage-gated ion channels is often associated with stochastic conformational changes of ion channel proteins. In this work, we also observe hysteretic response of currents to the varying applied voltages as well as ionic concentrations, using a deterministic model of ionic transport, rather than a stochastic description of different conductance states. Our results imply that, in addition to its stochastic nature, the gating phenomenon may possibly have deterministic factors associated to multiple states of ionic transport current through open channels.