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Second-order Poisson–Nernst–Planck solver for ion transport

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ABSTRACT

The Poisson–Nernst–Planck (PNP) theory is a simplified continuum model for a wide variety of chemical, physical and biological applications. Its ability of providing quantitative explanation and increasingly qualitative predictions of experimental measurements has earned itself much recognition in the research community. Numerous computational algorithms have been constructed for the solution of the PNP equations. However, in the realistic ion-channel context, no second-order convergent PNP algorithm has ever been reported in the literature, due to many numerical obstacles, including discontinuous coefficients, singular charges, geometric singularities, and nonlinear couplings. The present work introduces a number of numerical algorithms to overcome the abovementioned numerical challenges and constructs the first second-order convergent PNP solver in the ion-channel context. First, a Dirichlet to Neumann mapping (DNM) algorithm is designed to alleviate the charge singularity due to the protein structure. Additionally, the matched interface and boundary (MIB) method is reformulated for solving the PNP equations. The MIB method systematically enforces the interface jump conditions and achieves the second order accuracy in the presence of complex geometry and geometric singularities of molecular surfaces. Moreover, two iterative schemes are utilized to deal with the coupled nonlinear equations. Furthermore, extensive and rigorous numerical validations are carried out over a number of geometries, including a sphere, two proteins and an ion channel, to examine the numerical accuracy and convergence order of the present numerical algorithms. Finally, application is considered to a real transmembrane protein, the Gramicidin A channel protein. The performance of the proposed numerical techniques is tested against a number of factors, including mesh sizes, diffusion coefficient profiles, iterative schemes, ion concentrations, and applied voltages. Numerical predictions are compared with experimental measurements.

1. Introduction

All fundamental self-sustaining processes of living organisms are based on their ability to receive, process, create and transmit signals. Although biological signals are often referred to as hormones, growth factors etc., they can be as elementary as small ions whose motions create electrostatic potentials across the cell membrane. Electrochemical transmembrane gradient induces flow of ions in and out of cells through membrane proteins [34]. The membrane proteins that give rise to selective ion permeability are called ion channels. As their name implies, ion channels have pores that permit particular ions to cross the cellular membrane. Ion channels are essential to cell sustaining and control a wide variety of important

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physiological processes, ranging from nerve and muscle excitation, muscle contraction, action potential generation and resting, sensory transduction, cell volume and blood pressure regulation, cell proliferation, hormone secretion, fertilization, maintenance of salt and water balance, learning and memory, to programmed cell death [39]. Typical ion channels are voltage-gated or ligand-gated. Voltage-gated ion channels open or close depending on their response to the magnitude of the voltage gradient across the plasma membrane, while ligand-gated ion channels open or close depending on the binding or interaction of ligands with ion channels. Additionally, there are ion channels that are gated by extracellular chemical signals (e.g. neurotransmitters), or by intracellular signals (e.g. second messengers) [63]. Finally, mechanical or thermal stimuli, such as force or temperature, are increasingly recognized as regulators of ion channels and impact cell structure and function. Fig. 1(a) gives an illustration of a simple voltage-gated ion channel, the Gramicidin A channel.

A wide range of experimental techniques and methods have been developed for investigating the structure and function of ion channels over the past few decades [39]. For example, classical electrophysiology techniques are used to study ion channel responses to current injections. Crystallographic and nuclear magnetic resonance (NMR) spectroscopic techniques are often employed to determine the structure and/or structural features of ion channels. Genetic engineering techniques are utilized to identify the active site information of ion channels after the introduction of mutations. Pharmacological techniques are commonly used to elevate or suppress ion channel responses. Additionally, animal models usually serve as prototypes for human ion channel studies. The advances in experimental techniques have led to enormous progress in our understanding of the structure, function, dynamics and transport of ion channels.

The paramount importance and abundant experimental data have stimulated much theoretical and computational investigation in ion channels. Various theoretical and computational approaches, from fundamental to phenomenological, are also developed to understand the biological mechanism of ion channels. The most commonly used theoretical techniques in the field are stochastic models, ab initio molecular dynamics (MD) [58], classical molecular dynamics (MD), and continuum

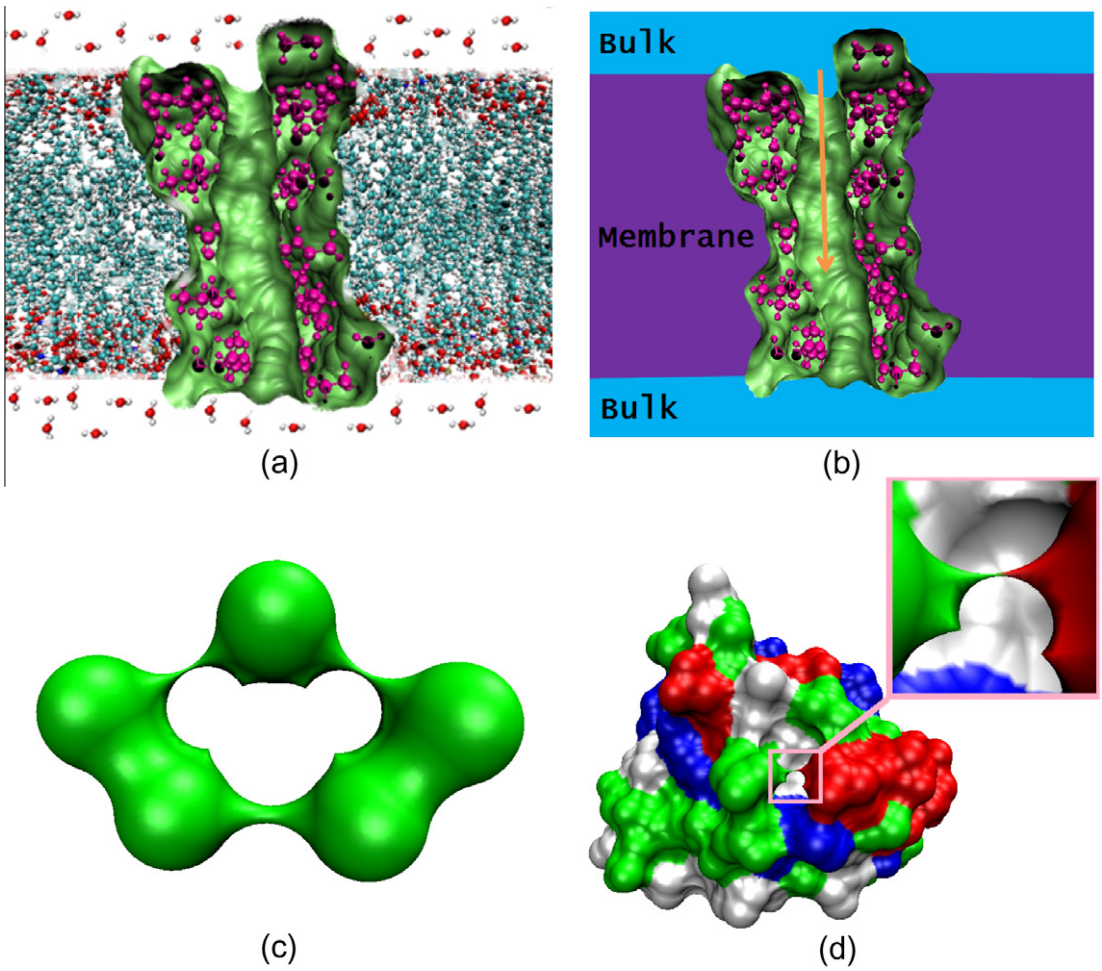

Fig. 1. Illustrations of ion channel geometry, computational setup, and geometric singularities. (a) Gramicidin A channel; (b) computational setup for the PNP system; (c) geometric singularities in the molecular surface of a five-atom structure; (d) geometric singularities in the molecular surface of protein 451c (color map indicates the residues). (For interpretation of the references to colours in this figure legend, the reader is referred to the web version of this paper.)