Adaptive Brownian Dynamics for Shape Estimation of Sodium Ion Channels

Vikram Krishnamurthy* Taira Vora† Shin-Ho Chung‡

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Abstract

Ion channels are protein macromolecules that form biological nanotubes across the membranes of living cells. Given many possible geometrical shapes of an ion channel, we propose a computational scheme of selecting the model that best replicates experimental observations, using adaptive Brownian dynamics simulations together with discrete optimization algorithms. Brownian dynamics simulations emulate the propagation of individual ions through the sodium ion channel nanotube at a femto time second time scale and Angstrom unit (10^{-10} meter) spatial scale.

*Department of Electrical and Computer Engineering, University of British Columbia, Vancouver, V6T 1Z4, Canada. email: vikramk@ece.ubc.ca. fax: +1 604 822 5949

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‡Department of Theoretical Physics, Research School of Physical Sciences, The Australian National University, Canberra, ACT 0200, Australia. email: taira.vora@anu.edu.au and shin-ho.chung@anu.edu.au

1 Introduction

Ion channels are biological nanotubes formed by protein macromolecules residing within the cell membrane of all living organisms. They regulate all electrical activities of a cell by controlling the passage of ions into and out of the cell, thus maintaining the resting membrane potentials and, when needed, causing the generation and propagation of action potentials. Understanding the structure and dynamics of ion channels is a fundamental problem in biology. It is now known that genetic alterations of some of the genes synthesizing channel proteins are known to be associated with many inherited disorders, such as epilepsy, muscular disorders, cystic fibrosis and diabetes [8]. Elucidation of how single ion channels work will ultimately help neurobiologists find the causes of, and possibly cures for, a number of neurological and muscular disorders.

Recently the structures of several bacterial ion channels have been determined by crystallographic analyses [5, 6]. These discoveries have led to several recent papers where *Brownian dynamics modelling* and *Brownian dynamics simulations* of ion channels have been used to unravel structural properties of similar ion channels. Brownian dynamics (BD) modelling of an ion channel captures the dynamics of ions both within the ion channel and in the vicinity of the ion channel as a large scale interacting particle stochastic dynamical system. The modeling method deals with the computer simulation of this large scale stochastic dynamical system at an Å spatial scale and femto-second time scale resolution. The dynamics (velocity) of individual ions of this large scale stochastic dynamical system evolve according to a large dimensional vector stochastic differential equation called the Langevin equation. The Langevin equation also takes into account of systematic forces acting on ions within the nanotube of the ion channel – these systematic forces are a function of the structure of the ion channel, such as charge of amino acids lining the inner wall of the ion channel and the three dimensional shape of the channel. Thus the average time taken for an ion to cross the ion channel depends on these structural properties. It logically follows that by optimizing the fit between the Brownian dynamics simulated ion channel current (charge per unit time) and the experimentally measured ion channel currents, one can estimate the structural properties of an ion channel. This is the underlying idea of the paper.

The key idea in this paper is to derive a novel discrete stochastic approximation based algorithm to dynamically control the behaviour of the BD simulation. The resulting algorithm yields the optimal estimate of the shape of an ion channel by optimizing the match between the BD simulated ion channel current and experimentally determined current. By using a parameterized structure, we formulate the problem of estimating the shape of an ion channel the discrete stochastic optimization problem.

The paper is organized as follows. We begin by formulating the BD algorithm to calculate currents through ion channels. We then discuss the optimization algorithms devised to search and converge on the optimal shape of the pore for sodium channels. We then provide a numerical analysis of the performance of our algorithms.

2 Sodium Ion Channel Model and Brownian Dynamics Ion Permeation Model

2.1 Construction of Sodium Ion Channel Structural Model

The aim of this subsection if to carefully construct a finite number of feasible structural shapes for a sodium ion channel. These feasible shapes need to capture the following unique properties of the sodium ion channel. First, the sodium ion channel allows over 10^6 ions through the channel every second, and yet is able to distinguish between sodium and other ions. Second, it has a high affinity for monovalent ions, is rapidly blocked by divalent ions and allows no anions through. Third, the channel exhibits a symmetric, linear current–voltage curve when there is symmetric concentrations of NaCl in the intra-cellular and extra-cellular regions, and the current rapidly saturates with increasing concentrations. Finally, the channel is completely blocked when divalent ions are present in the external solution, but only marginally reduced in presence of intracellular divalent ions.

In order to model the sodium ion channel, and due to the lack of data available on its atomic structure, feasible models for the sodium channel must take into account the above properties and successfully reproduce available experimental current–voltage and current–concentration responses of the channel.

A sodium ion channel comprises of four functional components: *external vestibule*, *selectivity filter*, *internal pore* and *internal entrance region*. The family of sodium ion channels are believed to be structurally similar to the family of potassium ion channels. Thus, we have based the feasible shapes of the sodium channel on the KcsA potassium channel, the structure of which was recently crystallized by Doyle et al. [5]. We have shortened the selectivity filter and added an external vestibule to the existing potassium channel shape. Below we describe in detail how by carefully varying the dimensions of the above structural components there are a finite number of distinct possibilities for the shape. The candidate channels are depicted in Fig.1 and the various parameters of these candidate channels are given in Table 1

(i) *Outer Vestibule:* The outer regions making up the sodium channel protein are believed to be composed of the P loops of the protein that form a conical outer vestibule [8, 15].

(ii) *Selectivity filter:* Similar to the KcsA, we include a short selectivity filter followed by an internal pore region. All channel models contain a selectivity filter with a radius of $r = 2.2$ Å derived from permeant cation studies by Hille [10]. As the length of the filter is unknown, we vary this parameter to fit the current. We use only the two charged rings suspected to lie in the selectivity filter, and known from mutation studies to have a large effect on selectivity and conductance of the sodium channel [9, 19, 21]. The two charged rings are placed around the filter region as point charges, 1 Å behind the protein boundary, at a distance of $z = 14$ Å and $z = 18.5$ Å from the central axis of the channel. The inner ring contains a positively charged lysine and a negatively charged glutamate and aspartate amino acid group, and the outer ring contains two negatively charged glutamates and two negatively charged aspartates. The positive lysine in the inner ring is fully charged, but we believe that more than one negative residue is likely to be protonated. For the position and charged states of these residues we have used the data of [22]. They find that two residues must be protonated at any given time to reproduce the experimental

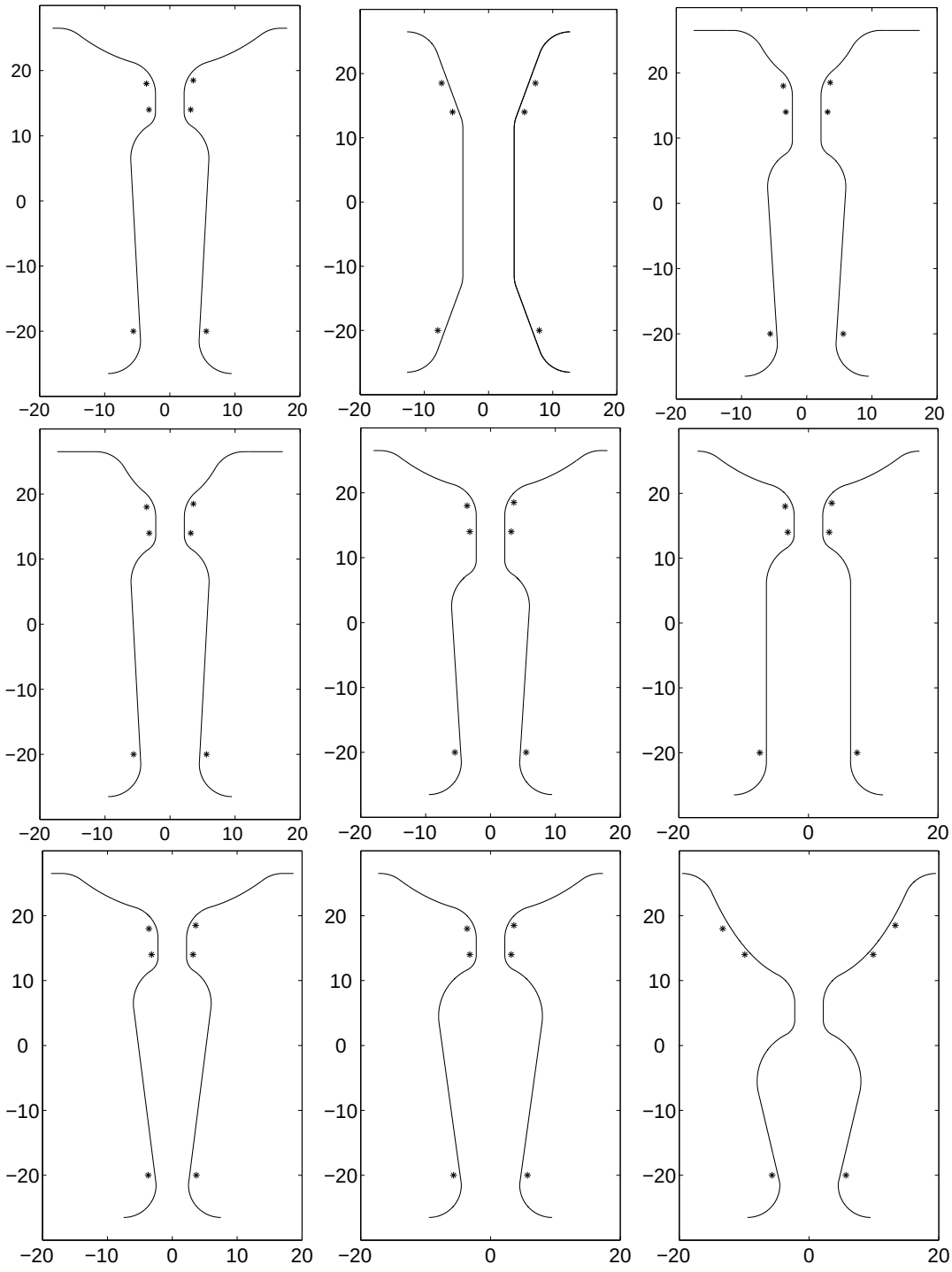

Figure 1: Nine Candidate Channel shapes for the sodium ion channel Nanotube considered in this paper. The 6 dots in each figure denote point charges in the protein lining the inner wall of the nanotube – all units are in angstrom units Å (1 Å = 10^{-10} m). The upper four dots represent the point charge approximations of the two charged rings in the selectivity filter, and the bottom two dots in the internal entrance of the ion channel represent the dipole charges that mimic the intracellular helix dipoles of the sodium channel protein. For further details on charge types, magnitudes and positions see Sec.2.1.