ADAPTIVE CONTROLLED BROWNIAN DYNAMICS APPROACH FOR PERMEATION IN BIO-NANOTUBES

*Vikram Krishnamurthy**

Department of Electrical Engineering
University of British Columbia, Vancouver,
V6T 1Z4, Canada.
email: vikramk@ece.ubc.ca

Shin-Ho Chung

Biophysics Group,
Department of Theoretical Physics
Anustralian National University
Canberra, ACT 0200, Australia.

ABSTRACT

Ion channels are biological nanotubes formed by large protein molecules. In this paper we address the permeation problem which deals with the propagation of individual ions in an ion channel at an Angstrom unit spatial scale and femto second time scale. We present an adaptive controlled Brownian dynamics simulation approach to predict the structure of an ion channel. The Brownian dynamics algorithm is coupled with a stochastic gradient algorithm to match the simulated current with experimentally determined currents.

1. INTRODUCTION

All living cells are surrounded by a cell membrane, composed of two layers of phospholipid molecules, called the lipid bilayer. Ion channels are biological nanotubes in the cell membrane formed by large protein molecules, that allow ions to propagate into and out of the cell. These ion channel biological nanotubes – although they are typically the size of angstrom units (10^{-10} m), i.e., an order of magnitude smaller in radius and length compared to carbon nanotubes that are used in nano-devices. All electrical activities in a cell are controlled by ion channels. Furthermore several diseases such as epilepsy, Parkinson's disease, etc are caused by malfunctioning ion channels.

Recently there have been enormous strides in our understanding of the structure-function relationships in biological ion channels. For example, the 1991 Nobel prize in medicine went to Neher and Sakmann who invented the patch-clamp device – which can isolate a single ion channel and measure the current across it. In recent breakthroughs, the crystal structures of the bacterial potassium channel, mechanosensitive channel and chloride channel have been determined from crystallographic analysis [1, 2]. The 2003 Nobel prize in Chemistry was awarded to Prof. McKinnon who determined the structure of a Potassium ion channel.

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The aim of this paper is to show how controlled Brownian dynamics simulation can be used to estimate structural information about an ion channel. BD simulation for ion channel structure prediction is currently a hot area in biophysics – we show in this paper that ideas in statistical signal processing such as Markov Chain Monte Carlo and stochastic gradient schemes can be profitably used to efficiently estimate these structural parameters of an ion channel. We refer the reader to [3, 4, 5] and the special issue [6] for details on ion channels written by experts in the area.

2. LEVELS OF ABSTRACTION FOR MODELLING ION CHANNELS

The ultimate aim of theoretical biophysicists is to provide a comprehensive physical description of biological ion channels. At the lowest level of abstraction is the *ab initio* quantum mechanical approach, in which the interactions between the atoms are determined from first-principles electronic structure calculations. Due to the extremely demanding nature of computations, its applications are limited to very small systems at present. A higher level of modeling abstraction is to use classical molecular dynamics. Here, simulations are carried out using empirically-determined pair-wise interaction potentials between the atoms, via ordinary differential equations (Newton's equation of motion). However, it is not computationally feasible to simulate the ion channel long enough to see permeation of ions across a model channel. For that purpose, one has to go up one further step in abstraction to stochastic dynamics, of which Brownian dynamics (BD) is the simplest form, where water molecules that form the bulk of the system in ion channels are stochastically averaged and only the ions themselves are explicitly simulated. Thus, instead of considering the dynamics of individual water molecules, one considers their average effect as a random force or Brownian motion on the ions. This treatment of water molecules can be viewed as a functional central limit theorem approximation. In BD, it is further as-

sumed that the protein is rigid. Thus, in BD, the motion of each individual ion is modeled as the evolution of a stochastic differential equation, known as the Langevin's equation.

A still higher level of abstraction is the Poisson-Nernst-Planck (PNP) theory which is based on the continuum hypothesis of electrostatics and the mean-field approximation. Here, ions are treated not as discrete entities but as continuous charge densities that represent the space-time average of the microscopic motion of ions. For narrow ion channels where continuum electrostatics does not hold – the PNP theory does not adequately explain ion permeation.

Remark. Bio-Nanotube Ion Channel vs. Carbon Nanotube: There has recently been much work in the nano-technology literature on carbon nanotubes and their use in field effect transistors (FETs). BD ion channel models are more complex than that of a carbon nanotube. Biological ion channels have radii of between 2 Å to 6 Å . In these narrow conduits formed by the protein wall, the force impinging on a permeating ion from induced surface charges on the water-protein interface becomes a significant factor. This force becomes insignificant in carbon nanotubes used in FETs with radius of approximately 100 Å , which is large compared to the Debye length of electrons or holes in Si. Thus the key difference is that while in carbon nanotubes point charge approximations and continuum electrostatics holds, in ion channels the discrete finite nature of each ion needs to be considered.

3. BROWNIAN DYNAMICS SIMULATION MODEL OF AN ION CHANNEL

3.1. Brownian Dynamics Simulation Setup

The aim is to obtain structural information, i.e., determine channel geometry and charges in the protein that form the ion channel. Fig.1 shows a schematic illustration of a BD simulation assembly for a particular example of an antibiotic ion channel called a gramicidin-A ion channel. The ion channel is placed at the center of the assembly. The atoms forming the ion channel are represented as a homogeneous medium with a dielectric constant of 2 (shaded in Fig.1). Then, a large reservoir with a fixed number of positive ions (e.g., K^+ or Na^+ ions) and negative ions (e.g., Cl^- ions) is attached at each end of the ion channel. The electrolyte in the two reservoirs comprises of 55 M (moles) of H_2O , and 150 mM concentrations of Na^+ and Cl^- ions.

3.2. Mesoscopic Permeation Model of Ion Channel

Our permeation model for the ion channel comprises of 2 cylindrical reservoirs $\mathcal{R}_1$ and $\mathcal{R}_2$ connected by the ion channel $\mathcal{C}$ as depicted in Fig.1, in which $2N$ ions are inserted (N denotes a positive integer). In Fig.1, as an example we have chosen a gramicidin-A antibiotic ion channel – although the results below hold for any ion channel. These

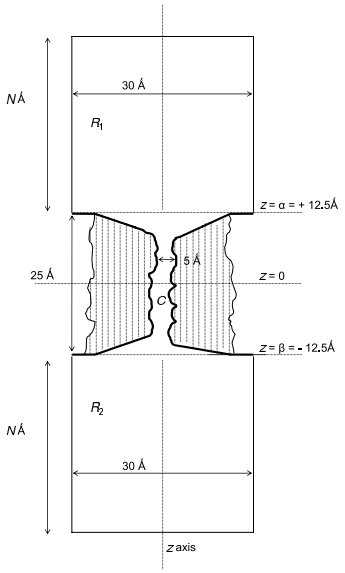

Fig. 1. Gramicidin-A Ion Channel Model

$2N$ ions comprise of (i) N positive charged ions indexed by $i = 1, 2, \ldots, N$. Of these, $N/2$ ions indexed by $i = 1, 2, \ldots N/2$ are in $\mathcal{R}_1$ and $N/2$ ions indexed by $i = N/2 + 1, \ldots, 2N$ are in $\mathcal{R}_2$. Each Na^+ ion has charge q^+, mass $m^{(i)} = m^+ = 3.8 \times 10^{-26}$ kg and frictional coefficient $m^+\gamma^+$, and radius r^+. (ii) N negative charge ions ions indexed by $i = N+1, N+2, \ldots, 2N$. Of these, $N/2$ ions indexed by $i = N = 1, \ldots 3N/2$ are placed in $\mathcal{R}_1$ and the remaining $N/2$ ions indexed by $i = 3N/2 + 1, \ldots, 2N$ are placed in $\mathcal{R}_2$. Each negative ion has charge $q^{(i)} = q^-$, mass $m^{(i)} = m^-$, frictional coefficient $m^-\gamma^-$ and radius r^-. $\mathcal{R} = \mathcal{R}_1 \cup \mathcal{R}_2 \cup \mathcal{C}$ denotes the open set comprised of the interior of the reservoirs and ion channel.

Let $t \geq 0$ denote continuous time. Each ion i, moves in 3-dimensional space over time. Let $\mathbf{x}_t^{(i)} = (x_t^{(i)}, y_t^{(i)}, z_t^{(i)})' \in \mathcal{R}$ and $\mathbf{v}_t^{(i)} \in \mathbb{R}^3$ denote the position and velocity of ion i and time t. The three components $x_t^{(i)}, y_t^{(i)}, z_t^{(i)}$ of $\mathbf{x}_t^{(i)} \in \mathcal{R}$ are, respectively, the x, y and z position coordinates. An external potential $\Phi_\lambda^{\text{ext}}(\mathbf{x})$ is applied along the z axis of Fig.1, i.e., with $\mathbf{x} = (x, y, z)$, $\Phi_\lambda^{\text{ext}}(\mathbf{x}) = \lambda z, \quad \lambda \in \Lambda$. Here Λ denotes a finite set of applied potentials. Typically $\Lambda = \{-200, -180, \ldots, 0, \ldots, 180, 200\}$ mV/m. Due to this applied external potential, the Na^+ ions drift from reservoir $\mathcal{R}_1$ to $\mathcal{R}_2$ via the ion channel $\mathcal{C}$ in Fig.1. Let $\mathbf{X}_t = \left(\mathbf{x}_t^{(1)\prime}, \mathbf{x}_t^{(2)\prime}, \mathbf{x}_t^{(3)\prime}, \ldots, \mathbf{x}_t^{(2N)\prime}\right)' \in \mathcal{R}^{2N}$ and $\mathbf{V}_t = \left(\mathbf{v}_t^{(1)\prime}, \mathbf{v}_t^{(2)\prime}, \mathbf{v}_t^{(3)\prime}, \ldots, \mathbf{v}_t^{(2N)\prime}\right)' \in \mathbb{R}^{6N}$ denote the velocities of of all the $2N$ ions. The position and velocity of each individual ion evolves according to the following continu-

ous time stochastic dynamical system:

$$\mathbf{x}_t^{(i)} = \mathbf{x}_0^{(i)} + \int_0^t \mathbf{v}_s^{(i)} ds \tag{1}$$

$$m^+ \mathbf{v}_t^{(i)} = m^+ \mathbf{v}_0^{(i)} - \int_0^t m^+ \gamma^+ \mathbf{v}_s^{(i)} ds + \int_0^t F_{\theta,\lambda}^{(i)}(\mathbf{X}_s) ds + b^+ \mathbf{w}_t^{(i)}, \quad i \in \{1, 2, \ldots, N\} \tag{2}$$

$$m^- \mathbf{v}_t^{(i)} = m^- \mathbf{v}_0^{(i)} - \int_0^t m^- \gamma^+ \mathbf{v}_s^{(i)} ds + \int_0^t F_{\theta,\lambda}^{(i)}(\mathbf{X}_s) ds + b^- \mathbf{w}_t^{(i)}, \quad i \in \{N+1, N+2, \ldots, 2N\}. \tag{3}$$

Equations (2) and (3) constitute the well known *Langevin* equations. The process $\{\mathbf{w}_t^{(i)}\}$ denotes a 3 dimensional Brownian motion, which is component wise independent. The constants b^+ and b^- are, respectively, ${b^+}^2 = 2m^+\gamma^+ kT$, ${b^-}^2 = 2m^-\gamma^- kT$. In (2), (3), $F_{\theta,\lambda}^{(i)}(\mathbf{X}_t) = -q^{(i)} \nabla_{\mathbf{x}_t^{(i)}} \Phi_{\theta,\lambda}^{(i)}(\mathbf{X}_t)$ represents the *systematic force* acting on ion i, where the scalar valued process $\Phi_{\theta,\lambda}^{(i)}(\mathbf{X}_t)$ is the total electric potential experienced by ion i given the position $\mathbf{X}_t$ of the $2N$ ions. λ is the applied external potential. The potential $\Phi_{\theta,\lambda}^{(i)}(\mathbf{X}_t)$ experienced by each ion i comprises of 5 components

$$\Phi_{\theta,\lambda}^{(i)}(\mathbf{X}_t) = U_\theta(\mathbf{x}_t^{(i)}) + \Phi_\lambda^{\text{ext}}(\mathbf{x}_t^{(i)}) + \Phi^{IW}(\mathbf{x}_t^{(i)}) + \Phi^{C,i} + \Phi^{SR,i}. \tag{4}$$

The *Potential of mean force* (PMF) denoted $U_\theta(\mathbf{x}_t^{(i)})$ in (4), comprises of electric forces acting on ion i when it is in or near the ion channel (nanotube $\mathcal{C}$ in Fig.1). The PMF U_θ is a smooth function of the ion position $\mathbf{x}_t^{(i)}$ and depends on the structure of the ion channel. Therefore estimating $U_\theta(\cdot)$ yields structural information about the ion channel. $\Phi_\lambda^{\text{ext}}(\mathbf{x}) = \lambda z$ denotes the potential on ion i due to the applied external field, $\Phi^{C,i}(\mathbf{X}_t)$ denotes the Coulomb interaction between ion i and all the other ions; Φ^{IW} also called the *Lennard-Jones potential* ensures that the position $\mathbf{x}_t^{(i)}$ of all ions $i = 1, \ldots, 2N$ lie in $\mathcal{R}^o$. Finally, in (4) $\Phi^{SR,i}(\mathbf{X}_t)$ denotes the short range Coulomb interaction.

Remark: The BD approach is a stochastic averaging theory framework that models the average effect of water molecules:
1. The friction term $m\gamma \mathbf{v}_t^{(i)} dt$ captures the average effect of the ions driven by the applied external electrical field bumping into the water molecules every few femto seconds. The frictional coefficient is given from Einstein's relation.
2. The Brownian motion term $\mathbf{w}_t^{(i)}$ also captures the effect of the random motion of ions bumping into water molecules and is given from the *fluctuation-dissipation* theorem.

4. CONSISTENCY OF BD SIMULATIONS

Assume that the system (1), (2), (3) comprising $2N$ ions has attained stationarity with the ion channel $\mathcal{C}$ closed. It is proved [3, 4], that this system is positive Harris recurrent and converges to its stationary distribution exponentially fast. Then the ion channel is opened so that ions can diffuse into it. Let $\tau_{\mathcal{R}_1,\mathcal{R}_2}^{(\theta,\lambda)}$ denote the mean minimum time for any of the $N/2$ Na^+ ions in $\mathcal{R}_1$ to travel to $\mathcal{R}_2$ via the ion channel $\mathcal{C}$, and $\tau_{\mathcal{R}_2,R_1}^{(\theta,\lambda)}$ denote the minimum time for any of the $N/2$ Na^+ ions in $\mathcal{R}_2$ to travel to R_1:It can be shown [3] that the mean first passage times $\tau_{\mathcal{R}_1,\mathcal{R}_2}^{(\theta,\lambda)}$ and $\tau_{\mathcal{R}_2,R_1}^{(\theta,\lambda)}$ satisfy a boundary valued partial differential equation. The mean current flowing from $\mathcal{R}_1$ via the ion channel $\mathcal{C}$ into $\mathcal{R}_2$ is

$$I^{(\theta,\lambda)} = q^+ \left(1/\tau_{\mathcal{R}_1,\mathcal{R}_2}^{(\theta,\lambda)} - 1/\tau_{\mathcal{R}_2,R_1}^{(\theta,\lambda)}\right) \tag{5}$$

It is not possible to obtain explicit closed form expressions for the mean first passage times $\tau_{\mathcal{R}_2,R_1}^{(\theta,\lambda)}$ and $\tau_{\mathcal{R}_2,R_1}^{(\theta,\lambda)}$ and hence the current $I(\theta)$ in (5). The aim of BD simulation is to estimate these quantities by simulating the stochastic dynamical system (1), (2), (3). In this section we show show that the current estimates $\hat{I}^{(\theta,\lambda)}(L)$ (defined below) obtained from a BD simulation are statistically consistent.

Each iteration l, $l = 1, 2, \ldots, L$, of the BD algorithm runs for a random number of discrete-time steps until an ion crosses the channel. Denote these random first passage times as $\hat{\tau}_{\mathcal{R}_1,\mathcal{R}_2}^{(l)}$ and $\hat{\tau}_{\mathcal{R}_2,\mathcal{R}_1}^{(l)}$. $L_{\mathcal{R}_1,\mathcal{R}_2}$ counts how many Na^+ ions have crossed from $\mathcal{R}_1$ to $\mathcal{R}_2$ and $L_{\mathcal{R}_2,\mathcal{R}_1}$ counts how many Na^+ ions have crossed from $\mathcal{R}_2$ to $\mathcal{R}_1$. Note $L_{\mathcal{R}_1,\mathcal{R}_2} + L_{\mathcal{R}_2,\mathcal{R}_1} = L$.

Algorithm 1 Brownian Dynamics Simulation Algorithm

- Input parameters θ for PMF and λ external potential.
- For $l = 1$ to L iterations:
  Step 1. Initialize all $2N$ ions according to stationary distribution $\pi_\infty^{(\theta,\lambda)}$. Open ion channel at discrete time $k = 0$ and set $k = 1$.
  Step 2. Propagate all $2N$ ions according to BD system until time k^* when ion crosses channel.
  - If ion k^* crossed ion channel from $\mathcal{R}_1$ to $\mathcal{R}_2$, set $\hat{\tau}_{\mathcal{R}_1,\mathcal{R}_2}^{(l)} = k^*$. Update $L_{\mathcal{R}_1,\mathcal{R}_2} = L_{\mathcal{R}_1,\mathcal{R}_2} + 1$.
  - If ion crossed ion channel from $\mathcal{R}_2$ to $\mathcal{R}_1$, set $\hat{\tau}_{\mathcal{R}_2,\mathcal{R}_1}^{(l)} = k^*$. Update $L_{\mathcal{R}_2,\mathcal{R}_1} = L_{\mathcal{R}_2,\mathcal{R}_1} + 1$.
- Compute the mean first passage time $\hat{\tau}_{\mathcal{R}_1,\mathcal{R}_2}^{(\theta,\lambda)}(L)$, $\hat{\tau}_{\mathcal{R}_2,R_1}^{(\theta,\lambda)}(L)$ and mean current estimate after L iterations as

$$\hat{I}^{(\theta,\lambda)}(L) = q^+ \left(1/\hat{\tau}_{\mathcal{R}_1,\mathcal{R}_2}^{(\theta,\lambda)}(L) - 1/\hat{\tau}_{\mathcal{R}_2,R_1}^{(\theta,\lambda)}(L)\right).$$

Theorem 1 (Consistency of BD) *For fixed PMF $\theta \in \Theta$ and external potential $\lambda \in \Lambda$, the ion channel current estimate $\hat{I}^{(\theta,\lambda)}(L)$ obtained from the BD simulation Algorithm 1 is strongly consistent, i.e., $\lim_{L\to\infty} \hat{I}^{(\theta,\lambda)}(L) = I^{(\theta,\lambda)}$ w.p.1 where $I^{(\theta,\lambda)}$ is the mean current defined in (5).*

5. CONTROLLED BD FOR PMF ESTIMATION

In this section, we outline a novel extension of BD simulation for estimating the PMF of an ion channel. This extension involves a simulation based learning control algorithm that dynamically adapts the evolution of the BD simulation. The complete formalism, convergence proofs and numerical results are presented in [3, 4].

We estimate the PMF U_θ parameterized by a finite dimensional parameter θ (e.g., θ are the means variances and mixture weights of a Gaussian basis function), by computing the parameter θ that optimizes the fit between the mean current $I^{(\theta,\lambda)}$ (defined above in (5)) and the experimentally observed current $y(\lambda)$ defined below. There are two reasons why estimating the PMF U_θ is useful: First, it allows us to determine the position and depth of the potential wells and barriers in the ion channel. Second, estimating the PMF permits us to compute the effective surface charge density along the protein of the inside surface of the ion channel that reproduces the PMF U_θ, see [3, 4] for details.

From experimental data, an accurate estimate of the I-V curve of an ion channel can be obtained. This I-V curve depicts the the actual current $y(\lambda)$ flowing through an ion channel for various external applied potentials $\lambda \in \Lambda$. For fixed applied field $\lambda \in \Lambda$, define the square error loss function between the mathematically defined mean current $I^{(\theta,\lambda)}$ in (5) and the true current $y(\lambda)$ as $\mathcal{Q}(\theta,\lambda) = |I^{(\theta,\lambda)} - y(\lambda)|^2$. Define the total loss function obtained by adding the square error over all the applied fields $\lambda \in \Lambda$ on the I-V curve as $\mathcal{Q}(\theta) = \sum_{\lambda\in\Lambda} \mathcal{Q}(\theta,\lambda)$. The optimal PMF U_{θ^*} is determined by the parameter θ^* that best fits the mean current $I^{(\theta,\lambda)}$ to the experimentally determined I-V curve of an ion channel, i.e., $\theta^* = \arg\min_{\theta\in\Theta} \mathcal{Q}(\theta)$. However, this deterministic optimization cannot be directly carried out, since it is not possible to obtain explicit closed form expressions for the current $I^{(\theta,\lambda)}$. This motivates us to formulate the estimation of the PMF as a stochastic optimization problem where $I^{(\theta,\lambda)}$ is replaced by estimates from BD simulation.

Suppose that the BD simulation Algorithm 1 is run in batches indexed by batch number $n = 1, 2, \ldots$. In each batch n, the PMF parameter θ_n is selected, the BD Algorithm 1 is run over L iterations, and the estimated current $\hat{I}_n^{(\theta,\lambda)}$ is computed. Since as proved in Theorem 1 these estimates are asymptotically unbiased,, we can re-express the objective function $\mathcal{Q}(\theta,\lambda) = |I^{(\theta,\lambda)} - y(\lambda)|^2$ as

$$\mathcal{Q}(\theta,\lambda) = \left(\mathbf{E}\left\{\hat{I}_n^{(\theta,\lambda)}\right\} - y(\lambda)\right)^2, \quad \mathcal{Q}(\theta) = \sum_{\lambda\in\Lambda} \mathcal{Q}(\theta,\lambda). \tag{6}$$

To solve the stochastic optimization problem by a simulation based optimization approach, we need to evaluate unbiased estimates $\mathcal{Q}_n(\theta,\lambda)$ of the loss function and derivative estimates $\widehat{\nabla}_\theta \mathcal{Q}_n(\theta,\lambda)$. The estimation of the derivative $\widehat{\nabla}_\theta \mathcal{Q}_n(\theta,\lambda)$ involves using recent sophisticated techniques in Monte-Carlo gradient estimation [7]. In [4] we present several such algorithms including the Kiefer Wolfowitz algorithm which evaluates derivate estimates as finite differences, Simultaneous Perturbation Stochastic Approximation (SPSA) which evaluates the derivatives in random directions (and thus saves computational cost), and pathwise infinitesimal perturbation analysis (IPA) gradient estimators, see [4] for complete details and convergence proofs.

The controlled BD simulation algorithm for estimating the PMF is schematically depicted in Fig.2 where $n = 0, 1, \ldots$, denotes batch number.

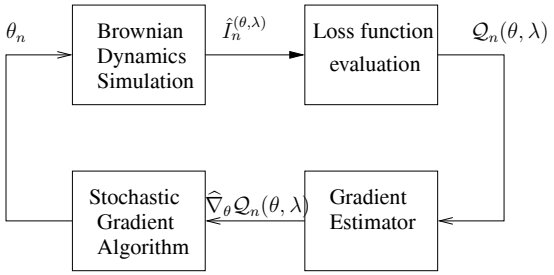

Fig. 2. Controlled BD Simulation for PMF Estimation

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