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An Asymmetric Approach to Modeling Ion Channels Using Finite Element Analysis

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***Abstract*—Biological ion channels are water filled pores in the cell membrane. They regulate the flow of ions in and out of the cell. Modeling the dynamics of these channels and relating their structure to functionality is crucial in understanding the mechanisms by which they conduct. This paper proposes a novel Finite Element Method (FEM) based simulation framework for modeling of ion channels that does not assume channel symmetry. This is the first framework that allows the use of multiple dielectric constants inside such channels without assuming geometrical symmetry thus providing a more realistic model of the channel. Due to the run-time complexity of the problem, lookup tables must be constructed in memory to store pre-calculated electric potential information. The large number of elements involved in FEM and channel resolution requirements can potentially result in very large lookup tables leading to a performance "bottleneck".**

This paper answers the following question: Does the accuracy introduced by using an asymmetric model outweigh the inaccuracy caused by having to reduce the size and resolution of electric-field look-up tables? This paper compares the memory footprint of an ion channel simulator that assumes a symmetric channel model versus an asymmetric model. We show that currently available personal computers are sufficient for attaining reasonable levels of accuracy for both. Our results show diminishing returns in accuracy with tables sized greater than 8.5 GB for the asymmetric model.

Keywords-biological ion channels; Brownian Dynamics; ion permeation; Finite Element Method, Assymetric channel

I. INTRODUCTION

Biological ion channels regulate all electrical activities in the cell. Failure of these channels to function properly causes various diseases such as cystic fibrosis, epilepsy, diabetes, and migraines. Understanding their structural and functional properties will additionally provide insight into disorders of cellular electrical activity, the influence of drugs and hormones on the cell, properties of the muscular system, and the unique properties of the nervous system. Attaining dynamic information requires the construction of accurate computational models that consider all aspects of the ion channel system: the membrane bilayer, protein atoms that form the channel, water molecules inside the channel, and ions that go through the channel.

Modeling each of these components poses its own challenges, such as the correct representation of electrostatic and electrodynamic properties of the water molecules and ions inside the channel, the polarization and short-range effects in the channel, and construction of the system boundaries. Modeling challenges are further complicated by the time and special scales required for simulating ion channels. Because conductance, the only observable characteristic of ion channels, happens at a micro second time scale, simulations must be run for at least that duration (i.e. one micro second) in order to verify the model against experimental results. The time resolution required to represent the motion of ions is in the femto second range. Poisson's equation has to be solved every time step (i.e. femto second) in order to calculate the electric potential that is used to later calculate the position of the ion using Langevin equation [1]. Thus, a billion iterations of calculating the solution are required in order to run simulations for a micro second. This represents a challenging computational problem given that the channel has to be simulated at micromolar concentrations. On a spatial scale, the entire system is nanometer in size and the motion of ions must be resolved to the level of Angstroms.

There is a need for a computational framework that can accurately model the system with high spatial and temporal resolution that can perform simulation over a long enough simulation period to generate reliable information regarding the channel's functional properties. It has been shown that Brownian Dynamics (BD) provides the only computationally feasible model for which simulations can be run long enough to produce conduction events that can be compared against experimental data [1]. A major limitation of previous implementations of BD is that all regions inside the channel must be assigned the same dielectric constant [2]. This results in an unrealistic representation of the channel since the channel's geometry changes at different parts of the channel causing the polarization of water to change accordingly. Consequently, different parts of the channel should be modeled using different dielectric constants. Further, the work in [2] assumed geometrical symmetry in the channel's shape.

In [3] we proposed a novel FEM based simulation framework for simulating ion channels that allows the use of multiple dielectrics in the different regions in the channel. However, [3] assumed a symmetric geometry. The work proposed in this paper does not make any assumptions about the channel's geometry and as a result, the channel can have a completely irregular shape.

The use of an asymmetric model for the channel has significant implications on both the run-time complexity and space complexity at various stages of the simulation framework. The symmetric geometry used to perform FEM in [3] can be described very simply by abutting

cylindrically symmetric "rings" to form the channel. An asymmetric channel is more computationally demanding and requires a more sophisticated "marching" algorithm to construct the FEM geometry. This is discussed in detail in Section II.

More important than the space and run-time complexity of FEM geometry construction is the size of the look-up tables used to perform BD [3]. These tables constitute the "bottleneck" of the simulation framework with respect to memory. To accommodate the large number of simulation iterations needed to acquire relevant physical information, this set of tables must be entirely stored in memory and must provide constant run-time access to the BD simulator. Unfortunately, the size requirements of the look-up tables grow significantly for an asymmetric model. This will be discussed in detail in Sections III and IV.

Thus, the contributions of this paper are two-fold:

1) A FEM-based simulation framework that does not assume geometric symmetry is developed for modeling ion channels.
2) It is shown that the memory capacity of conventional workstations is sufficient for both the existing symmetric approach and the proposed asymmetric approach. More explicity, 0.5% accuracy is achieved with a 8.5 GB memory footprint.

This paper is organized as follows: Section II provides a description of our method for constructing the asymmetrical channel geometry. Section III provides an overview of the FEM-based framework. Section IV provides a feasibility study of the proposed framework with respect to run-time and memory constraints and Section V provides our conclusions.

II. Asymmetric Channel Geometry Construction

To construct the channel wall that defines the dielectric boundary between water and protein, the ion channel structure (i.e. the location of the atoms that make the channel) is first downloaded from the protein data-bank. This information is then used as an input to a Marching Cubes (MC) algorithm [2] which constructs the boundary while adhering to physical constraints. First, the channel should take on a roughly cylindrical shape with only two openings at both ends of the z-axis. Second, the boundary surface must be fully connected.

The basic steps of MC are the following:

1) Divide the space into a grid of cubes.
2) For each cube:
   a. Calculate the value of a threshold test function at the corner points of the cube. Determine if the value of this function is greater or less than a preset threshold thus determining if the boundary passes through this cube.
   b. If the boundary passes through the cube, replace the cube with an appropriate set of polygons.
3) Sum all polygons generated in order to generate a surface that approximates the surface described by the threshold test function.

Because the ion channel wall is defined by the field produced by the protein atoms that make the channel's wall, it is natural to use electrostatics for the threshold test function. In particular, the threshold function will be a summation of the individual electrostatic field contributions from all atoms that make up the protein.

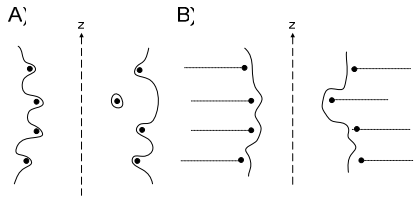

Figure 1: (A) A fragmented protein/water boundary at a high MCA threshold. (B) Fragmentation can be avoided using radial boundary conditions.

Boundary conditions are used to enforce the physical constraints. First, we want to guarantee that the channel is cylindrical in nature (i.e. it has openings on top and bottom along the z-axis). This can be achieved by defining a boundary condition that the z-axis is fixed to a particular voltage. At low threshold values, the channel would then appear as a perfect cylinder around the z-axis. As the threshold is raised, the radius of the cylinder surface generated by MC would continue to grow. Because the atoms are also part of the threshold test equation, their contribution towards the shape of the channel would increase. As the cylinder grows, it will be "pressed" against the atoms that form the protein thus taking on a smoothened shape of the boundary between the protein and water. If the threshold becomes too large, the cylinder could potentially grow beyond those atoms closes to the z-axis thus fragmenting the channel boundary (see Fig. 1(A)). This is a violation of the desired constraints that the channel wall stay connected as one surface. To fix this problem, we apply boundary conditions for each atom such that there is a line of fixed voltage extending radially from the location of each atom to infinity. This has the effect of preventing fragmentation of the surface as shown in Fig. 1(B).

Computationally, the MC approach requires more memory and run-time than the approach used in [3]. This does not reflect negatively on the use of an asymmetric channel because this phase of the simulation framework is not critical. This phase is executed only once offline before the more computationally demanding BD phase. The true bottleneck for the simulation framework is the memory footprint of the electric potential tables. This is discussed in the following sections.

III.FEM-based Simulation Framework

At the core of the simulation framework is Comsol [5] which is a commonly-used FEM solver used for electromagnetic, mechanics, thermodynamics, and fluid dynamics. At front-end of the framework, a CHARMm residue topology file (RTF) and a CHARMm coordinate file (CRD) [6] are provided as inputs to a channel surface

generator. CHARMm is a popularly used molecular dynamics tool developed by biophysicists. These files are generated from data available through the protein databank [7] and describe the structure of the protein macromolecules that define the ion channel. As discussed in Section II, an Outline Generator constructs a sharp boundary between the water and protein described in three dimensions. This geometry is subsequently used by the FEM solver which generates electric potential results for positions throughout the channel and stores them in a set of look-up tables structured in a way that minimizes access time while minimizing the memory footprint. These tables are subsequently used by a second-order time-discretization of Langevin's stochastic differential equation for the motion of the ions (see Gunsteren and Berendsen [8]).

Lookup tables are used to store 3-dimensional electric potential information generated by the FEM solver. In doing so, pre-calculated electric potential information is made available to the BD solver thus avoiding the high run-time cost of solving Poisson's equation for each iteration.

For each iteration of the BD simulation, the solver needs to determine the electrostatic potential acting on each ion injected into the channel. The forces acting upon each ion *i* in the system include self-potential due to surface charge induced by the ion itself, external potential due to the applied field, and fixed charges in the protein wall. A more detailed description of these forces is beyond the scope of this paper and is provided in [1] and [3].

The electric field is the gradient of the electric potential and is used to calculate the electrostatic force. By using the superposition principle, the electric field can be calculated for a system of many ions by adding together the contribution from each ion. Thus, only the following electrical field values need to be pre-calculated and stored as lookup tables:

$$\overline{E}_{3D}(r,\theta,z) = \overline{E}_{X,i}(r,\theta,z) \quad , \tag{1}$$

$$\overline{E}_{6D}(r_i,r_j,\theta_i,\theta_j,z_1,z_2) = \sum_{j\neq i}\overline{E}_I(r_i,r_j,\theta_i,\theta_j,z_1,z_2) + \sum_{j\neq i}\overline{E}_C(r_i,r_j,\theta_i,\theta_j,z_1,z_2) \quad , \tag{2}$$

where X denotes the electric field due to external charges, I denotes the electric field due to image charges, and C denotes the electric field due to Coulomb interactions. In Equation (2), the field acting on ion *i* due to ion *j* is being calculated.

The $\overline{E}_{3D}$ table is constructed from one FEM simulation where there are no ions and all external charges have been added. Electric field information is calculated by the solver at each mesh grid points throughout the channel and is stored in the table. Values in the table are indexed by the location in cylindrical coordinates, *(r,θ,z)*. The force acting on ion *i* by the external charges is therefore,

$$\overline{F}_i = q_i \cdot \overline{E}_{3D}(r_i,\theta_i,z_i) \tag{3}$$

The $\overline{E}_{6D}$ table stores the combined electrostatic field information acting on an ion *i* due the Coulomb potential and image potential due to ion j, respectively. When *i=j*, $\overline{E}_{6D}$ provides the electric field due to self-potential. Entries are indexed by $(r_i,r_j,\theta_i,\theta_j,z_1,z_2)$. To calculate the force acting on ion *i* caused by its self potential and by ion *j*,

$$\overline{F}_i = q_i \cdot \overline{E}_{6D}(r_i,r_j,\theta_i,\theta_j,z_1,z_2) \tag{4}$$

where q_j is the charge of ion *j*. The run-time complexities for accessing $\overline{E}_{3D}$ and $\overline{E}_{6D}$ are constant.

Equations (3) and (4) are suitable for storing electrical field information for an asymmetric channel. Previous work [3] assumed a symmetric channel could therefore make the assumption that the only the relative placement between any two ions is significant and not their absolute positions. Thus, equation (4) can be reduced to a 5-D table,

$$\overline{F}_i = q_i \cdot \overline{E}_{5D}(r_i,r_j,|\theta_i-\theta_j|,z_1,z_2) \tag{5}$$

It [3], it was determined whether or not the capacity of conventional workstations was sufficient to store the 5-D table in Equation (5) while achieving an interpolation accuracy better than 0.5%. In the following section, we will address the same issue but for the significantly larger 6-D table in Equation (4) used for the asymmetric case.

IV.Feasibility of the Asymmetric vs. Symmetric Model

As discussed in Section III, the simulation framework requires large lookup tables that reside in memory and store pre-calculated electric field information. Using the simulation framework discussed in the previous section, we now show the feasibility of the proposed framework by showing that reasonable levels of FEM accuracy can be achieved with modest table sizes.

We conducted experiments using a KcsA ion channel. The corresponding RTF file for KcsA channel was extracted from the Protein Databank [7]. External charges were extracted from a CRD file description. As described in the previous section, an asymmetric channel was constructed and used to conduct a FEM analysis to solve for electric potential and electric field throughout the channel.

The FEM solver was used for six different levels of grid spacing for both the symmetric and asymmetric model. Each level of spacing corresponds to five different properties which were adjusted in unison. These properties affect how the mesh is constructed when various obstacles are encountered such as small curved parts of the geometry. For simplicity in this paper, the levels of grid spacing are denoted by $\beta_1, \beta_2,\ldots,\beta_6$ for the symmetric model and $\alpha_1, \alpha_2,\ldots, \alpha_6$ for the asymmetric model.

Each level of grid spacing corresponds to a different number of total grid points per channel thus affecting the size of the table needed to store pre-calculated electric field information. 1 denotes the highest resolution number, and 6 denotes the lowest resolution number. For β_5, for example, each dimension of the 5-D table is of size 27 so the total size of the table in bytes is 21^5 table entries × 6 numbers/entry × 8 bytes/number = 657 MB assuming the use of double-precision numbers. The set of table sizes corresponding to β_1 through β_6 range from 350 MB which would be reasonable for most desktop computers to 22.5 GB which is well beyond the total memory capacity of current desktop computers.

Using the FEM solver, a table was constructed for each level of grid spacing. The accuracy of levels β_2 through β_6 were compared against β_1 on point by point bases. To facilitate such a comparison, all tables were constructed using the same mesh grid (same number of grid points). In the case of level β_1, 100% of the table entries were calculated using FEM. For levels β_2, β_3, β_4, β_5, and β_6, 50.6%, 31.9%, 23.3%, 17.3%, and 12.6% of the entries were calculated by FEM, respectively, and the remaining were interpolated using a multivariate linear interpolation. Effectively, the accuracy of interpolation is being determined as a function of the grid spacing. This is important because BD simulations must interpolate electric field information based on the tables each time an ion moves into a new location within the channel. This occurs for every time step of the simulation and for all ions in the system.

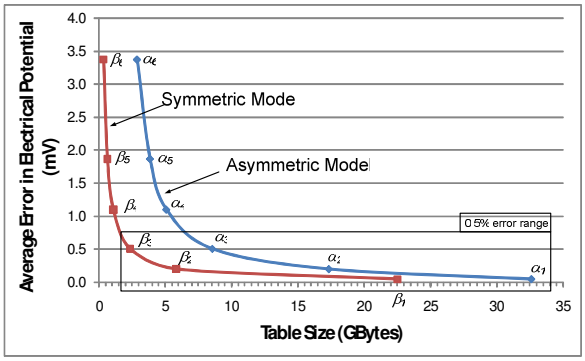

FIGURE 2: THE ERROR IN ELECTRIC POTENTIAL ESTIMATION AS A FUNCTION OF THE TABLE SIZE FOR SYMMETRIC AND ASYMMETRIC MODELS.

Fig. 2 shows the error in interpolated electric potential values as a function of table size. The shape of this curve appears to follow that of an exponential decay such that the proportional reduction in error diminishes as we construct larger tables. Thus, if we choose a grid spacing on the "knee" of the curve (i.e. β_3) then we can be relatively certain that larger table sizes will not result in significant improvements in accuracy. β_3 falls within the 0.5% error range which is highlighted in the figure. Further, β_3 corresponds to a table size of 2.2 GB which is certainly within the reach of many research workstations.

Similar experiments were conducted for the asymmetric model for six grid points labeled α_1 through α_6 ranging from 2.8 GB to 32.6 GB. Because the asymmetric model requires a much larger 6-D table, its curve is correspondingly shifted to the right in Fig. 2. The "knee" of the asymmetric curve is α_3 which falls within the 0.5% error range and requires 8.5 GB which is also within the reach of modern workstations.

This result supports the use of an asymmetric model for simulating ion channels using FEM. In particular, it shows that the use of asymmetric models in our simulation framework is computationally viable.

V.Conclusions

In this paper, we introduced a stochastic multi-particle simulation framework for ion channels. This comprises of solving Poisson's equation via a finite element analysis, together with the Langevin equation for the dynamics of the individual ions. We introduced a methodology for constructing an asymmetric geometry of the channel.

Due to the run-time complexity of the problem, large lookup tables must be constructed in memory to store pre-calculated electric potential information thus leading to a potential memory bottleneck. Results presented in this paper showed that the memory available on conventional workstations is sufficient for providing accurate estimates for both asymmetric and symmetric modeling approaches. These results help support the continued effort toward developing FEM-based modeling of ion channels. In recent work [9], we have used the BD algorithm to model how drugs interact with ion channels at the atomic level.

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