Stochastic Multi-particle Brownian Dynamics Simulation of Biological Ion Channels: A Finite Element Approach

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***Abstract*—Biological ion channels are protein tubes that span the cell membrane. They provide a conduction pathway and regulate the flow of ions though the low dielectric membrane. Modeling the dynamics of these channels is crucial in understanding their functionality. This paper proposes a novel simulation framework for modeling ion channels that is based on Finite Element Method (FEM). By using FEM, this is the first framework to allow the use of multiple dielectric constants inside the channel 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. Because of the large number of elements involved in FEM and channel resolution requirements there is the potential for very large lookup tables leading to a performance "bottleneck". This paper discusses strategies for minimizing table size and shows that currently available personal computers are sufficient for attaining reasonable levels of accuracy. For the framework proposed, results show diminishing returns in accuracy with tables sized greater than 2.2 GB.**

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

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 electrodynamics 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 femtosecond 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. 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 the need for a computational framework that can accurately model the system with high spatial and temporal resolution over enough iterations to simulation over a long enough simulation period to generate reliable information regarding the channel's functional properties. There are various techniques that make different levels of abstractions when replacing the real physiological system with a model. Each of these techniques has its own strengths and limitations. It has been shown that Brownian Dynamics (BD) provides the only computationally feasible model using which simulations can be run for long enough to produce conduction events that can be compared against experimental data [1]. In BD, protein, membrane and water are treated as continuum dielectric media with each having its own dielectric constant. Electric field numbers are computed by solving the Poisson partial differential equation at regular time steps, and are typically stored in memory to be used subsequently for ion motion simulation using the Langevin stochastic differential equation of motion. This data storage and access time are major computational challenges for BD implementations.

A major limitation of previous implementations of BD is that all regions inside the channel must be assigned the same dielectric constant. This results in an unrealistic representation of the channel since the channel's geometry changes at different parts of the channel causing the polarity of water to change accordingly. Consequently, different parts of the channel should be modeled using different dielectric constants. Previous work solves Poisson's

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equation using a variant of the boundary-element method [2] which does not allow for the use of multiple dielectric constants across the channel. Thus, a major contribution of this paper is the development of a framework that instead uses finite-element-modeling (FEM) thus allowing for multiple dielectric strengths.

Due to the large number of simulation iterations required, lookup tables must be constructed in memory to store previously calculated electric-field information. Because of the large number of elements involved in FEM, there is a potential for lookup tables to become a "bottleneck" for further improvements to performance. Thus, strategies must be used to minimize the size of these lookup tables. Once defined, the framework must be evaluated to determine its feasibility with respect to run-time and memory requirements. This must be determined in the context of the speed and memory capabilities of computers currently available to potential users of the framework.

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

1) A framework is developed for simulating ion channels using FEM.
2) The feasibility of a FEM-based approach is explored with respect to memory and run-time requirements.

This paper is organized as follows: Section II provides background information on methods for solving Poisson's equation for electrostatics. 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. Brownian Dynamics Simulations Set up

The iterative approach in [2] first constructs a channel wall that defines the dielectric boundary between water and protein. This is obtained by first downloading the ion channel structure from the protein data-bank. Two large cylindrical reservoirs are attached to the ion channel. These reservoirs mimic the extracellular and intracellular space. An outline of the boundary is constructed and discretized into tiles which are subsequently used to model induced surface charge. The field at the centre of tile due to permanent charges in the system is calculated for the centre of each tile. From this, the surface charge density can be calculated for all tiles. The electric field due to all surface charges is calculated and added to the field due to permanent charges. A new value for the electric field will result in new calculations for the surface charges which will subsequently lead to new estimates for the electric field. This process of iteratively updating the surface charge and the electric field continues until the difference in surface charge for a given iteration ceases to change beyond a predefined threshold.

The iterative approach taken by [2] assumes that the water and protein each maintain a constant dielectric constant. It has been suggested that relaxing the assumption of a constant dielectric strength throughout the channel would lead to a more accurate electrostatic model. In particular, the dielectric strength of the water in the bulk likely differs from that of the narrow pore.

It is difficult to expand the iterative approach to allow for varying dielectric strengths throughout the channel. It would require a new tiling approach for each dielectric domain within the channel. Further, the complexity of the iterative algorithm would grow with the number of domains and with the complexity of their shape. An alternative to this approach is the Finite Element Method (FEM).

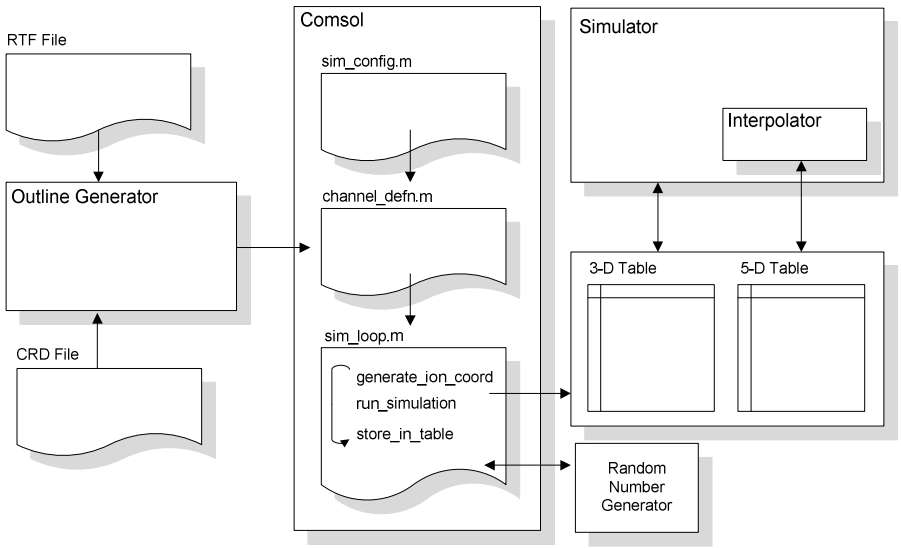

Figure 1: Brownian Dynamics Simulation Framework with FEM Poisson Solver

III. FEM-BASED SIMULATION FRAMEWORK

Figure 1 shows our proposed simulation framework based on a FEM solver for Poisson's equation coupled with a Langevin equation for the dynamics of the ions. At the core of the framework is Comsol [3] 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) [4] are provided as inputs to an outline generator. CHARMm is a popularly used molecular dynamics tool developed by biophysicists. These files are generated from data available through the protein databank [5] and describe the structure of the protein macromolecules that define the ion channel. The Outline Generator constructs a sharp boundary between the water and protein described in three dimensions. This is converted to a Comsol geometry which is subsequently used by the FEM solver. The FEM solver generates electric potential results for positions throughout the channel and stores them in a set of 3-dimensional and 6-dimensional tables structured in a way that maximizes 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 [6]).

To represent the channel, a sharp boundary must be created in 3-dimensions to define the di-electric interface between water and protein. To construct this boundary into a geometric format usable for the FEM solver, a number of steps must be followed. First, topological information for the channel is read into the channel construction tool. Second, a course boundary is constructed in 2-dimensions based on atom radius information which is then smoothed to improve FEM analysis. This boundary represents the pore of the channel and must be appended to a protein outline constructed from a set of parametric equations. Third, this 2-dimensional boundary is revolved into a cylindrically symmetric 3-dimensional geometry. Figure 2 shows an illustration of the 3-dimensional channel geometry.

These steps are similar to those found in [2]; however, the channel geometry is targeted for use in FEM analysis rather than an iterative solver. There are two major distinctions between the approach taken in [2] and the approach taken in this paper. Rather than tiling the boundary in order to iteratively assign surface charges, the boundary is simply defined by a set of rings. Both approaches retain the same level of channel resolution and both assume cylindrical symmetry. A second distinction is that the approach taken in this paper allows for the channel pores to be divided into several geometric objects each with their own dielectric strength.

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 BD iteration.

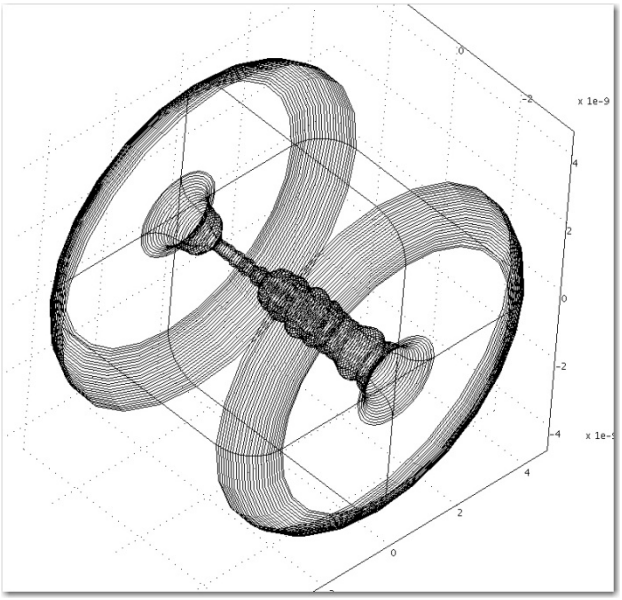

Figure 2: An 3-dimensional outline generated from protein topological information from the protein databank [Error! Bookmark not defined.].

For each iteration of the BD simulation, the solver needs to determine the electrostatic potential acting on each ion injected into the channel. The force experienced by each ion i in the system can be expressed as,

$$V_i = V_{S,i} + V_{X,i} + \sum_{j \neq i} V_{I,ij} + \sum_{j \neq i} V_{C,ij} \,, \qquad (1)$$

where $V_{S,i}$ represents the self-potential due to the surface charge induced by ion i on the channel boundary, $V_{X,i}$ represents the external potential due to the applied field, fixed charges in the protein wall, and charges induced by these. The third and fourth terms in equation (1) represent the potential caused by ion j acting on ion i. The third term is the image potential due to the surface charges induced by ion j. The fourth term is the Coulomb potential and has the computed from,

$$V_{C,ij} = \frac{1}{4\pi\varepsilon_0} \frac{q_j}{\varepsilon \left| \bar{r}_i - \bar{r}_j \right|} \,. \qquad (2)$$

The electric field is the gradient of the potential defined by (1) and will be used to calculate the electrostatic force. By using the superposition principle, equation (1) 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:

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

$$\overline{E}_{5D}(r_i,r_j,|\theta_i-\theta_j|,z_1,z_2) = \sum_{j\neq i}\overline{E}_I(r_i,r_j,|\theta_i-\theta_j|,z_1,z_2) + \sum_{j\neq i}\overline{E}_C(r_i,r_j,|\theta_i-\theta_j|,z_1,z_2) \quad , \tag{4}$$

The $\overline{E}_{3D}$ table is constructed from one FEM simulation for which 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 which is implemented as a hash-function. 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,

$$\overline{F}_i = q_i \cdot \overline{E}_{3D}(r_i,\theta_i,z_i) \tag{5}$$

The $\overline{E}_{5D}$ 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*, $\overline{E}_{5D}$ provides the electric field due to self-potential. Entries are indexed by $(r_i,r_j,|\theta_i-\theta_j|,z_1,z_2)$ which assumes a cylindrically symmetric channel. To calculate the force acting on ion *i* caused by its self potential and by ion *j*,

$$\overline{F}_i = q_i \cdot \overline{E}_{5D}(r_i,r_j,|\theta_i-\theta_j|,z_1,z_2) \tag{6}$$

where q_j is the charge of ion *j*. The run-time complexities for accessing $\overline{E}_{3D}$ and $\overline{E}_{5D}$ are constant.

IV. Feasibility of the FEM-based Framework

As suggested in the introduction, we propose the use of FEM for solving Poisson's equation when modeling ion channels. This approach requires the use of 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 [5]. External charges were extracted from a CRD file description. As described in the previous section, a symmetric channel was constructed and used to conduct a FEM analysis to solve for electric potential and electric field throughout the channel.

Figure 3 shows a cross sectional view of the channel which includes the pore, vestibules, and the protein outline. The channel is colored according to the electric potential values found using the FEM solver and has a range between -1000 mV with 400mV. The highest potential occurs at both openings of the channel and the lowest potential occurs at the narrow part of the pore (called the selectivity filter). This trend and the range of electric potential values are consistent with that found using the iterative approach [2].

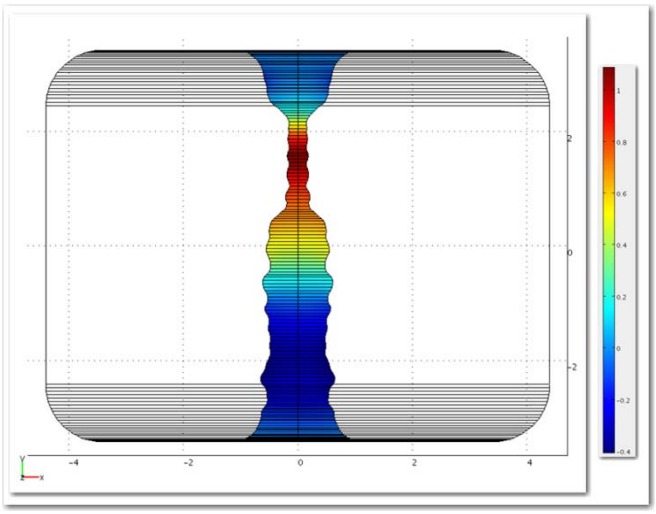

Figure 3: Cross sectional view of the electric potential in the ion channel.

The FEM solver was used for six different levels of grid spacing with each level corresponding 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 $\beta_1, \beta_2, \ldots, \beta_6$.

TABLE 1: SIX DIFFERENT LEVELS OF GRID SPACING WITH THEIR CORRESPONDING TABLE SIZE. THE DEFAULT SETTING FOR THE FEM SOLVER IS HIGHLIGHTED.

GRID LEVEL	β_1	β_2	β_3	β_4	β_5	β_6
GRID POINTS/CHANNEL	22004	11130	7030	5128	3816	2765
TABLE SIZE (MB)	22164	5671	2262	1204	667	350

As shown in Table 1, each level of grid spacing resulted in a different number of grid points to be evaluated. The default settings for the FEM solver are highlighted with a box and correspond to β_5. 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. For β_5, there are 3816 grid points in the channel so the table size is 3816 ion

positions × 3816 grid point entries × 6 numbers/entry × 8 bytes/number = 667 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 just over 21 GB which is well beyond the total memory capacity of current desktop computers.

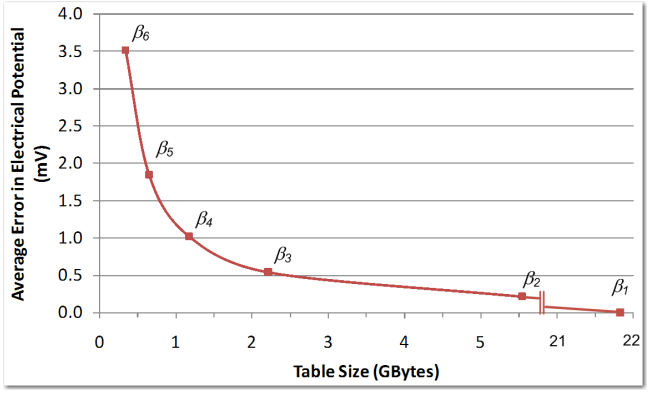

FIGURE 4: THE ERROR IN ELECTRIC POTENTIAL ESTIMATION AS A FUNCTION OF THE TABLE SIZE.

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 such a comparison, all tables were constructed using the same mesh grid (same number of grid points). In the case of level β_1, all table entries were calculated using FEM. For levels β_2 through β_6, only some of the tables were calculated by FEM and the remaining entries were interpolated. Effectively, we are determining the accuracy of interpolation 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 will occur every time step of the simulation and for all ions in the system.

Figure 4 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 an the proportional reduction in error diminishes as we construct larger tables. Thus, if we choose a grid spacing on the "elbow" 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. In the case of β_3, the corresponding table size is 2.2 GB which is certainly within the reach of many research workstations.

Normalized run-time results for the FEM analysis are shown in Figure 5. In the figure, a larger table size corresponds to more grid points during the FEM analysis thus leading to a longer run-time. The relationship between the number of grid points and the size of the table follows an exponential decay thus the run-time follows the same pattern. In this figure, a table size of 2.2 GB results in a significant drop in run-time over larger table sizes. This result supports the claim that β_3 is a good choice for grid spacing.

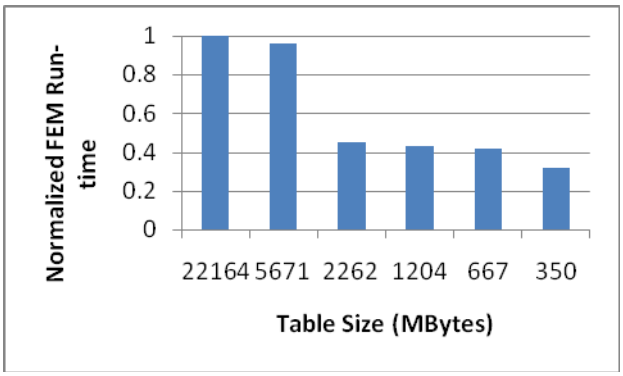

FIGURE 5: THE NORMALIZED RUN-TIME REQUIRED TO RUN THE FEM ANALYSIS AS A FUNCTION OF THE TABLE SIZE.

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. 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. Experiments presented in this paper showed that the memory available on conventional research computers is sufficient for providing accurate estimates of the electric field while minimizing run-time. These results helps support the continued effort toward developing FEM-based modeling of ion channels. In recent work [7], we have used the BD algorithm to model how drugs interact with ion channels at the atomic level.

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