Application Of Grid Focusing Methodology To Transport Monte Carlo Model For Ion Channel Simulations

G. A. Kathawala, T. van der Straaten and U. Ravaioli

Beckman Institute of Advanced Research, University of Illinois at Urbana-Champaign
Room 3203 B, 405 N. Mathews Avenue, Urbana 61820, USA, gkathawa@uiuc.edu

ABSTRACT

Reduced order particle based models have become popular recently for the study of ion channels. One of the key computational challenge for these methods is the fast and accurate calculation of electrostatic forces acting on the mobile ions. We have applied the electrostatic focusing method to address this issue. We have validated our method using bulk simulations and comparing the pair correlation functions with single grid setup. Full channel simulations were performed for *ompF* porin channel and important channel behavior like asymmetry of the channel and loss of selectivity at high bath concentrations were observed. We also observed the separation of pathways for anions and cations as they traverse the channel. Using focus grid method, we obtained an overall speedup of more than 50 % for our channel simulations.

Keywords: Ion Channels, Porin, Monte Carlo, Simulation, Focus Grid

1 INTRODUCTION

Ion channels are a class of protein that have pores down their middle, found in nearly all membranes of biological cells. These channels control the transport of ions across the membranes and show exciting device properties like selectivity and gating. Although Molecular Dynamics simulations can resolve channel physics at atomistic level, the large time scales and the complexity of the channel proteins prohibit their use for calculation of steady-state currents. Reduced order models like Brownian Dynamics [1]-[3] and transport Monte Carlo methods [4] have been shown in the past as viable alternatives for studying the protein systems. Water is treated as an implicit medium with a specified dielectric constant and steric interactions are treated using a viscous force or a scattering mechanism, thereby speeding up these simulations.

One of the key computational issue related to the reduced order modeling of ion channels is the calculation of electrostatic force acting on the ions. The calculation of dielectric self force and also the ion-ion coulomb force become non-trivial in regions with spatially varying dielectric coefficients, such as the pore region of an ion channel. Different methods have been employed toward this goal with a trade-off between accuracy and computational performance. Edwards et. al. [2] in their work for simulation of Gramicidin channel assumed the axial symmetry of the channel to map the 3-D problem onto a 2-D grid, over which they solved the Poisson equation to calculate the electrostatic fields. This approach is not directly extensible to more complicated channels like *ompF* porin. Im and Roux [1] used a single solution of the Poisson-Boltzmann equation to calculate the long-range component of the electrostatic field and used coulomb interactions and a reaction field to calculate the ion-ion interaction forces and dielectric self force respectively. This approach is very appealing for generating fast simulation results but the tradeoff is in the limited accuracy for ion-ion interaction forces. Possible improvements are in the description of the coulomb forces in the presence of highly varying permittivity. There is also an issue when applying a Poisson–Boltzmann solution to a direct inter–ionic coulomb force evaluation, because screening effects might be double–counted.

In our model [4], we calculate the electrostatic forces self-consistently using P^3M methodology [5] by repeated solution of Poisson equation in conjunction with calculation of a short range term. The solution of the Poisson equation on a fine enough grid allows us to capture the effects of dielectric self force and accurately calculate the ion-ion electrostatic interactions. However, the computational costs associated with repeated solutions of Poisson equation are large, specially when one uses fine grid. To overcome these limitations, we propose the use of focus grid method for ion channel simulations in this paper. Electrostatic Focusing is a popular method in finite difference methods for generating a precise solution at a particular target sub domain lying within a large domain [6]. We have used our model to perform bulk and *ompF* porin channel simulations.

ompF porin is a trimeric protein channel that spans the outer membrane of the ecoli bacterium to allow the passive diffusion of small hydrophilic solutes. The three-dimensional molecular structure of porin has been determined from X-ray crystallography [7], [8] and is shown in Fig. 1. It exhibits many interesting properties. In particular, OmpF exhibits high selectivity toward cations at low salt concentration, but becomes weakly selective at

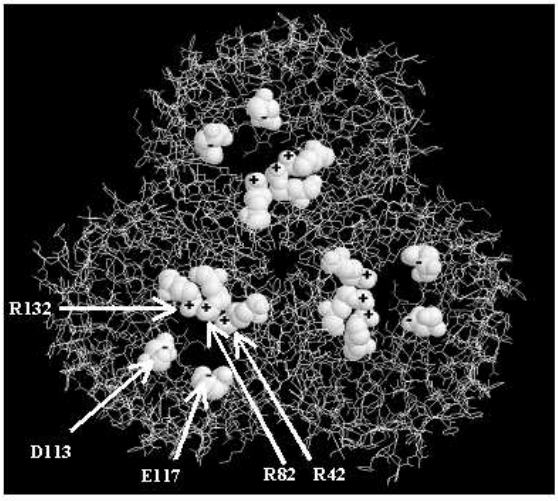

Figure 1: Molecular structure of *ompF* porin, projected along the length of the channel, showing the three-fold symmetry of the trimer. The five amino acids in the constriction region of each pore are highlighted.

concentration in the molar range. We investigate some of these properties using our model and present our results in this work. We will describe in detail our simulation model in the next section and results and discussion will be presented in the third section.

2 Method

In our Monte Carlo model BioMOCA, protein atoms are modeled as static charges occupying finite volume with a specified dielectric constant. The protein and lipid are treated as rigid structure and are inaccessible to the ions. Water is treated as an implicit medium. The steric interactions of ions with individual water molecules are modeled as a scattering mechanism. The forces acting on the particles are calculated using the P^{3}M methodology. In this scheme, the electrostatic field acting on the ions is obtained by adding the short-range Coulomb field (particle-particle interaction) to the field obtained from the solution of Poisson equation and subtracting a correction term to avoid double counting. The finite size of the ions are modeled using a truncated form of the pairwise Lennard-Jones potential. The model is described in more detail in our previous work [4].

Grid focusing method involves an initial solution of the Poisson equation in the complete domain on a coarse finite difference mesh. The boundary conditions for a finer discretized sub domain are defined from the initial coarse solution in order to obtain a more accurate calculation at the target sub domain. For ion channel simulations using Monte Carlo methodology, the presence of large baths of ions is a major requirement for accurate treatment of screening. The presence of these baths make the mesh domain of Poisson equation very large and lead to either large number of grid points with fine mesh resolution or a small mesh with very coarse discretization. From bulk simulations, we have observed that a coarse mesh is sufficient for describing baths using P^{3}M scheme. However, a fine resolution is required in the channel domain because of the highly charged nature of these regions and the presence of rapidly varying dielectric regions. Using the focusing methodology, it is possible to satisfy the requirement of large baths and fine grid resolution in channel at the same time in a computationally efficient way. This methodology also allows us to have multiple fine mesh domains which may be needed to describe the electrostatic behavior for channels with multiple pores like porin or an array of channels sharing common bath regions.

In focus grid method, we define two or more than two discretized meshes for the solution of Poisson equation. The first grid is a coarse mesh spanning the entire problem domain including the bath regions and the channel region. The second mesh is much finer and spans the channel region mainly. The Poisson equation is first solved on the coarse mesh using the finite difference method. The boundary conditions for the fine mesh is then obtained by interpolation from the coarse mesh solution along with some additional calculations. The coarse mesh solution results in incorrect short-range electrostatic forces. So, if a charged species is located near the boundary of the fine mesh, the boundary conditions derived from the coarser mesh will be slightly inaccurate. We use a form of P^{3}M methodology to overcome this deficiency. We calculate the two short–range potential assuming a coarse and fine mesh respectively and add the difference of the two to the interpolated potential. The potential used to derive the Dirichlet boundary conditions on the fine mesh is given by

$$
\begin{aligned}
{}^2V_{r_0}^{mesh} = \; & {}^1V_{r_0}^{mesh} + \sum_{j,r_j \in {}^1\Omega_{r_0}^{sr}} \left({}^1V_j^{coul} - {}^1V_j^{ref} \right) \\
& - \sum_{j,r_j \in {}^2\Omega_{r_0}^{sr}} \left({}^2V_j^{coul} - {}^2V_j^{ref} \right) \qquad (1)
\end{aligned}
$$

where the left superscripts 1 and 2 refer to coarse and fine grid respectively and V_i^{coul} is the coulombic potential at point r_0 due to ion i. V_i^{ref} is the reference potential given by

$$
V_j^{ref} = \frac{q_j}{\pi \epsilon r_{sr}} \left(-2 + \frac{2s^2}{r_{sr}^2} - \frac{s^3}{r_{sr}^3} \right) \quad r_j \in \Omega_{r_0}^{sr}, s = |r_j - r_0| \qquad (2)
$$

and $\Omega_{r_0}^{sr}$ is the short-range domain around point r_0. r_{sr} is the radius of the short-range domain and is equal to 1.5 times the local grid spacing. ${}^2V_{r_0}^{mesh}$ would be the correct mesh potential at point r_0 if ideal reference potentials are considered and therefore can be used to define the Dirichlet boundary conditions for the fine grid.

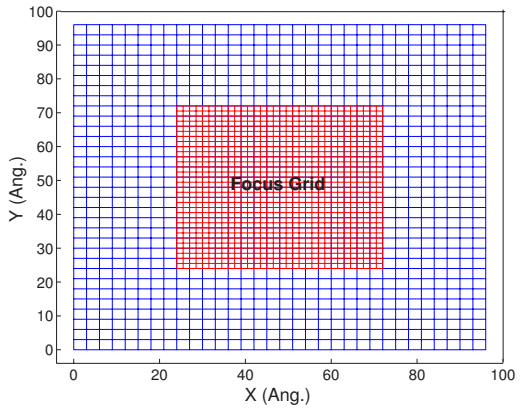

Figure 2: Focus grid setup for bulk simulations.

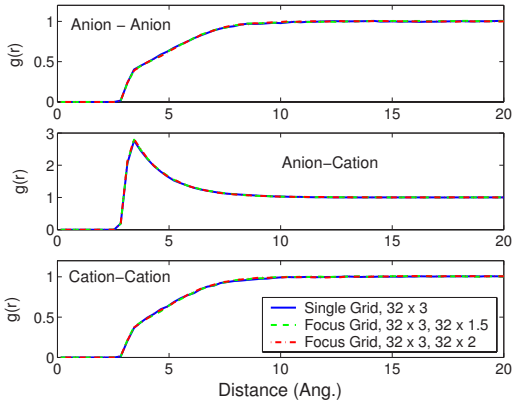

Figure 3: Pair correlation functions for a 1M electrolyte solution constituted of monovalent cations and anions, each having ionic radii of 1.5 Å for 3 different setups. Grid sizes are indicated in the legend.

3 Results and Discussion

The focus grid method discussed in the previous section was implemented in our Monte Carlo simulator BioMOCA and simulations were performed to test the validity of the method. As a first step, bulk simulation were performed with a grid setup shown in Fig. 2. We had a fine grid in the middle of a large coarse grid. The grid spacing of the large mesh was 3 Å and the grid spacing of the fine grid was either 2 Å or 1.5 Å. The pair correlation function $g(r)$ obtained for a 1 M bulk solution is plotted in Fig. 3. We can see that the pair correlation functions obtained using the focus grid agree well with the one obtained using single grid.

We used the focus grid methodology to study the *ompF* porin channel. *ompF* is unique in that it has three monomer units resulting in three identical pores. For this problem, we designed a focus grid scheme com-

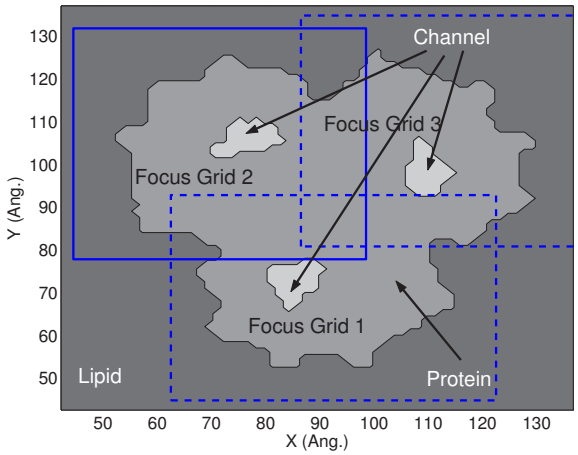

Figure 4: Focus grid setup for *ompF* porin simulations.

posed of one large grid and three focus grids. The $x-y$ cross-section of the three focus grids used in the simulation is shown in Fig. 4. The length of the focus grids in the z direction were 72 Å. The simulation domain dimensions were 96 Å across each direction. The course grid had a mesh spacing of 3 Å whereas the focus grids had a grid spacing of 1.5 Å. For single grid simulations used for comparison purposes, we used a grid with a uniform mesh spacing of 1.5 Å, unless otherwise stated. We used dielectric permittivies of 80, 5 and 2 for the aqueous region, protein and lipid respectively. The diffusion coefficients used for determining the scattering rates varied along the z-direction, with bulk diffusivities used in the bath regions and scaled down values used in the channel region, the scaling factor being 2.5.

Simulations were performed for 0.10 M KCl solution for a range of bias conditions and also for varying molar concentrations at 100 mV bias. Taking single grid simulations as the base case, for simulation of 0.1 KCl solution at 100 mV bias, we obtained an overall speedup of more than 50 % and a speedup of about 100 % for the portion of the code related to calculation of electrostatic forces for focus grid simulations. The speedup increased to approximately 150 % and 185 % respectively if we use grid schemes with grid spacings of 2 Å and 1 Å in place of 3 Å and 1.5 Å respectively, keeping the simulation domain the same.

ompF porin is a highly charged system with a net charge of -33 e on it. The constriction region of the channel is highly charged(see Fig. 1) and the arrangement of charges gives rise to very strong transverse electric fields leading to separation of ionic flow for cations and anions. In Fig. 5, we have plotted the net charge density due to mobile ions at $y = 101.5$ Å. We can observe that cations flow along the top surface of the channel whereas anions flow along the bottom surface. A detailed analysis of individual trajectories also showed the separate pathways for the two ionic species with anions always

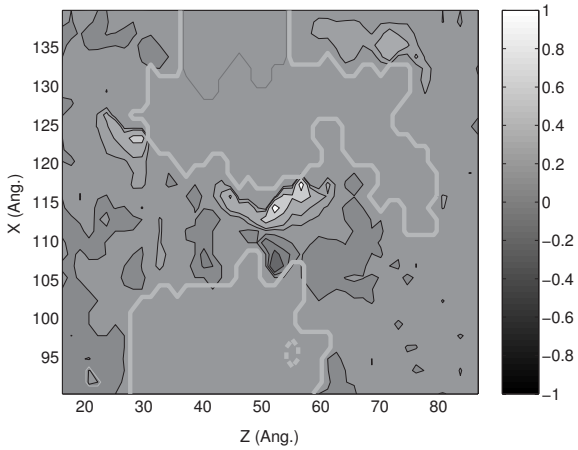

Figure 5: Net charge density in focus grid 3. The contour lines were drawn at concentrations of -1.0 M, -0.5 M, -0.2 M, -0.1 M, 0.0 M, 0.1 M, 0.2 M, 0.5 M and 1.0 M.

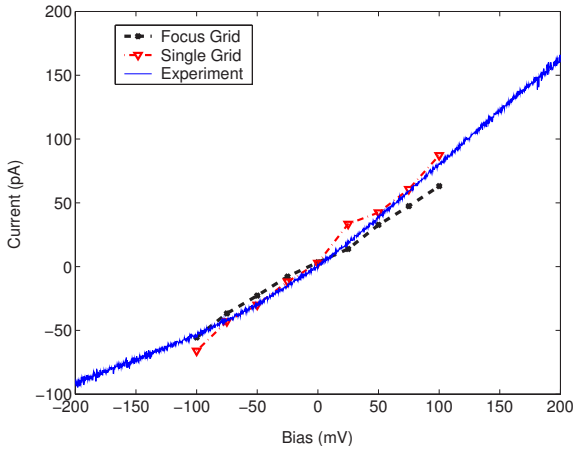

Figure 6: Channel current as a function of applied bias.

moving along the radially inward surface and cations moving along radially outward surface.

We also observed the asymmetric nature of the *ompF* porin channel current in Fig. 6, where the currents for negative bias are always lower than currents at positive bias for equal bias magnitude. Although we see a difference of about 10-20% between currents obtained from single grid and focus grid setup that are otherwise identical, there is in general a good match with the experimental data. In Fig. 7, we have plotted the ratio of cation current to anion current and we can observe the loss of selectivity at higher bath concentrations.

4 Conclusions

Grid focusing can be used to speed up the calculation of electrostatic force acting on ions in reduced order

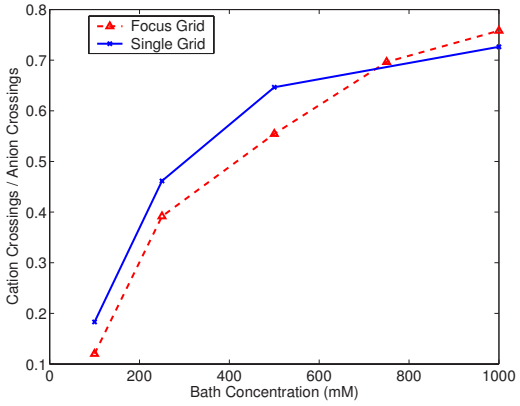

Figure 7: Ratio of number of anion crossings to number of cation crossings as a function of bath concentration. The bath concentrations were identical on both sides.

particle based methods. We have implemented the focus grid method into our ion channel simulator BioMOCA. The pair correlation function obtained using the focus grid scheme compares very well with single grid solution. Experimentally observed behavior of *ompF* porin channel like asymmetry and loss of selectivity has been reproduced in our simulations. An overall speed-up of over 50 % was obtained by using focus grid setup over single grid setup for equivalent simulations.

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REFERENCES

[1] W. Im and B. Roux, J. Mol. Bio., 322, 851, 2002.
[2] S. Edwards, B. Corry, S. Kuyucak, and S. Chung, Biophys. J., 83, 1348, 2002.
[3] S. Aboud, M. Saraniti, and R. Eisenberg, J. Comput. Elec., 2, 239, 2003.
[4] T. van der Straaten, G. Kathawala, A. Trellakis, R. Eisenberg, and U. Ravaioli, Molecular Simulations, 31, 151, 2005.
[5] R. W. Hockney, and J. W. Eastwood, Computer Simulation Using Particles, McGraw-Hill, 1981.
[6] N. A. Baker, D. Sept, S. Joseph, M. J. Holst, and J. A. McCammon, Proc. Natl. Acad. Sciences, 98, 10037, 2001.
[7] S. W. Cowan, T. Schirmer, G. Rummer, M. Steiert, R. Ghosh, R. A. Pauptit, J. N. Jansonius, and J. P. Rosenbusch, Nature, 358, 358, 1992.
[8] M. S. Weiss, and G. E. Schulz, J. Mol. Biol., 227, 493, 1992.
[9] T. A. van der Straaten, J. M. Tang, U. Ravaioli, R. S. Eisenberg, and N. R. Aluru, J. Comp. Elect., 1:3, 335, 2002.