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Na^+ permeation through its protein channels, from molecular dynamics to continuum modeling

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Abstract. Researchers can reach important information about cell cycles such as migration, growth and muscle contraction, by studying the change of ion concentrations in animal cells. In the current work we have proposed three different techniques to study the passive ions motion in protein channels on different time scales. Molecular dynamics, Langevin dynamics and continuum models of mass transport are used to investigate ion transport from small to large time scales. We have used molecular dynamics to compute diffusivity and potential of mean force profile of NA^+transport across its protein channel. The diffusivity and potential of mean force of NA^+ in this condition was 1.06 $Å^2$/ns and 18 kcal/mol, respectively. Then diffusivity and potential of mean force profile of NA^+ calculated from molecular dynamics simulation is incorporated in Langevin dynamics equation of motion to study NA^+ transport across a group of channels working in parallel. Our results show that ion concentration distribution in the membrane protein channel is close to the phase-lagging model prediction. The achieved shock propagation speed in NA^+ channel is $v = 1.2$ nm/ns and indicates that an inherent lag exists in the biological systems. The proposed method can be used in multiscale modeling of NA^+ diffusion across cell membranes.

1. Introduction

Variance of ion concentration in animal cells is of crucial physiological importance to describe cell cycles as cell growth, contraction of muscle cells and cell migration [1-3]. The main function of the cell membrane separates the cell from its surroundings. However, continuous feed of nutrition across the cell membrane is vital for cell biological activities such as cell contraction and cell signaling. The hydrophobic and hydrophilic nature of lipid bilayer is an energetic barrier against diffusion of charge and polar molecules. Excluding the endocytosis and exocytosis which are the main mechanisms of macromolecule transport, passive transport across cell lipid bilayer, passive transport via protein channel and active transport via protein pumps are three other mechanisms for ions and polar molecule transport across cell membranes.

Ion permeation through protein channels is a topic of considerable interest [4,5]. Protein channels, in all cell membranes, regulate the flow of ions and a small group of small polar molecules across the membrane in all living cells [6]. Diffusivity and potential of mean free force (PMF) which is the Landaun free energy profile along a reaction coordinate are two transport parameters describing the ion permeation. Since these parameters are very sensitive to the computational method, they are computed often by means of all-atom Molecular Dynamics (MD) simulation.

All-atom molecular dynamics simulations will become increasingly valuable for understanding the dynamic properties of membrane proteins. Traditionally,

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Equilibrium Molecular Dynamics (EMD) is used to discover the ion permeation in protein channels. The time scale of the ion passing through its assigned channel is about 10 to 100 ns. Since the equilibrium molecular dynamics simulation works only by a small time step size, the number of time steps needed to perform an EMD simulation for finding the whole ion path and its transport properties will be very large which makes the EMD method hugely time consuming. Hence, the traditional expensive simulation of EMD becomes inefficient, and equilibrium biasing MD methods have emerged over time. One of these biasing MD methods is called Umbrella Sampling in which several EMD simulations should be done and cause high computational cost [7,8]. Steered MD (SMD) is an alternative method in which several non-equilibrium biasing MD simulations are used in one or two directions along the channel [9]. Using this method, computational cost of obtaining transport properties will be decreased. Cuendet [10], using Forward-Reverse Constant Velocity Steered Molecular Dynamics (FR-CV-SMD) simulation, computed effective potential energy involved in membrane receptors motion. Liu et al. [11] investigated Na^+ permeation through Gramicidin channel using eight one-directional simulations. Jensen et al. [12] studied sugar transport across lactose permease using FR-CV-SMD simulation. De Fabriitis et al. [13] calculated diffusivity of K^+ through Gramicidin channel using 25 simulations of FR-CV-SMD method and estimated the required number of simulations to achieve sufficient accuracy of results [14]. Kosztin et al. [15] used this method, for the first time, to obtain diffusivity and PMF for the permeation of water molecules through a single wall nanotube.

In this paper, Na^+ permeation through its protein channel is simulated on different scales - from the molecular to continuum scales. In the molecular time scale, we have simulated Na^+ transport across its protein channel applying 20 FR-CV-SMD simulations to obtain transport properties of Na^+ in this condition. Then in order to simulate a group of parallel protein channels placed in the membrane lipid bilayer in meso time scale, we have used the Langevin Dynamics (LD) equation and calculated dynamic properties of ion motion in protein channel from all-atom FR-CV-SMD results. We have developed an in-house LD Fortran Parallel code using OpenMP API [16] (LD-FP) for this case. Finally using LD-FP, ions permeation in larger time scale is studied and a phase-lagging model is proposed for this phenomenon.

Lumped parameter models such as a mass transport model are used to simulate the cell behavior in continuum medium. Fick's model admits instantaneous propagation within the continuum while in phase-lagging model, the speed of propagation is finite. There are other models for transport phenomena like the Cattaneo's model [17] of heat transfer, the flux limited diffusion model [18] of radiation energy and the Narayan's model [19] of mass transport phenomenon. In phase-lagging models, there is a time delay between flux and its driving force. Researchers have shown that the shock propagation speed in biological medium is less than that in other mediums which is equal to the speed of sound [20,21]. The apparent difference between classical and phase-lagging models of transport phenomena is the existence of shock, which is predicted by the phase-lagging models. Therefore we have used a phase-lagging model to determine the transport properties of Na^+.

We have discussed our approach in the following three sections. In the first section the theoretical concept and details of the developed all-atom MD method are described and, in the next sections, governing equations of LD simulation and phase-lagging model of mass transport, respectively, are expressed. Finally, the results are presented.

2. Materials and methods

2.1. All-atom molecular dynamics simulation

In this part, the approach to find diffusivity and PMF of Na^+ transport across its protein channel using FR-CV-SMD method is explained.

2.1.1. Diffusivity and PMF

In SMD simulation, a target molecule that we intend to discover its diffusivity and PMF is pulled along the reaction coordinate at a constant velocity as shown in Figure 1. In this condition the work done by dissipative

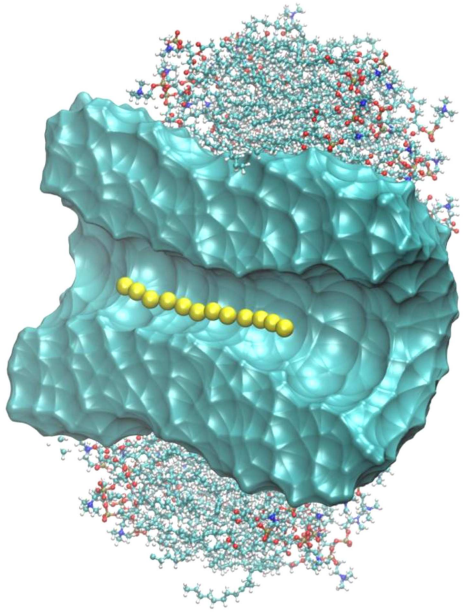

Figure 1. Trace of steered ion through stiff-spring pulling.

forces can be calculated by:

$$W_d = W - F, \tag{1}$$

where W_d is the dissipative work originated from motion irreversibility, W is the external work, and F is the free energy difference. If the velocity of target molecule goes to zero, then the motion of system is in equilibrium and the simulation results converge to the real phenomenon.

The method used to obtain the diffusivity and PMF of the protein channel is the FR-CV-SMD. In this method, a stiff-spring is connected to the target molecule and the other side of spring is pulled by a constant velocity.

The harmonic potential of spring and external work done to drive the molecule from z_0 to z, along the reaction coordinate, can be calculated, respectively, by:

$$V = \frac{k}{2}(z - z_0 - vt)^2, \tag{2}$$

$$W(t) = \int_0^t \frac{\partial V}{\partial t'} dt' = -kv \int_0^t (z - z_0 - vt')dt'. \tag{3}$$

In the above equations, v is the pulling velocity, and t is the time required to traverse the coordinate from z_0 to z. The initial length of the spring is assumed to be zero.

According to Kosztin et al. [20], using stiff-spring approximation:

$$k \gg \max\left[\frac{2\alpha}{(\delta z)^2}, \frac{2U_{\max}}{(\delta z)^2}\right],$$

where δz is the spatial resolution desired for the PMF, $\alpha \gg 1$, and $U_{\max}$ is the corresponding maximum energetic barrier, the diffusivity and PMF of the channel can be written as:

$$\text{PMF} = \left\langle \frac{(W_f - W_r)}{2} - \frac{(V_f - V_r)}{2} \right\rangle, \tag{4}$$

$$W_d = \left\langle \frac{(W_f + W_r)}{2} - \frac{(V_f + V_r)}{2} \right\rangle. \tag{5}$$

Here the f and r indices respectively, refer to forward and reverse path. The angular brackets represent an average over all the reactive trajectories.

In order to calculate diffusivity, the well-known Einstein relation is used [13]:

$$D = \frac{k_B T}{\gamma} = \frac{k_B T v}{\left(\frac{dW_d}{dz}\right)}, \tag{6}$$

where $\gamma = \frac{1}{v}\frac{dW_d}{dz}$ the position dependent friction coefficient.

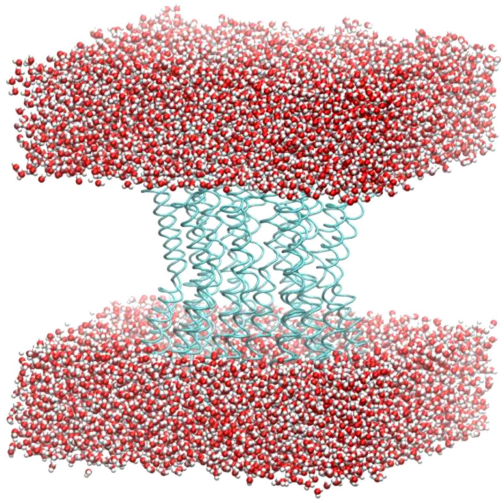

Figure 2. Arrangement of the protein channel solvated in water molecules.

2.1.2. Molecular modeling

The starting structure was obtained from protein data bank (PDB ID:1YCE [22]). Then, we embedded it in 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) lipid bilayer, which was generated by VMD membrane builder plugin [15], with a cross sectional area of 94 × 94 Å^2 made up of 232 lipids before and 128 lipids after locating the protein channel using VMD [23]. We choose POPC membrane model because this model was used in the previous simulations, and it had provided good results [24]. This structure is dissolved with 14414 TIP4P water molecules and ionic strength of 140 mM Na+Cl$^-$. The final simulation box contains 75282 atoms and its height is 100 Å. Figure 2 shows the arrangement of the protein channel and the water molecules. First of all, the lipid bilayer is melting for 1 ns in the NPT ensemble at 1 atm and 310 K using Langevin thermostat and barostat with friction of 1 ps^{-1}.

Two sets of 20 SMD simulations are performed after initial equilibrium simulation. The runs are executed with the CHARMM27 [25] force field in the NVT ensemble using Langevin thermostat with friction of 1 ps^{-1}. According to [13], the time step size is set by 1 fs with the pulling velocity of 30 Å/ns for 1 ns each run. The spring stiffness is set to 250 kcal/mol.Å^2 to satisfy the stiff-spring approximation. We employed NAMD 2.9 program [26], with particle-mesh Ewald electrostatics [27] and cubic periodic boundary conditions. According to [13], we applied a harmonic restraining potential to the center of mass of the $C\alpha$ atoms of the protein located at the central plane of the channel, shown in Figure 3, in order to avoid the protein channel atoms to protrude through the membrane caused by external force applied on the system. Our computer system is an Intel i5 2500 k (4 × 3.3 GHz) with 8 GB RAM and a NVIDIA GeForce

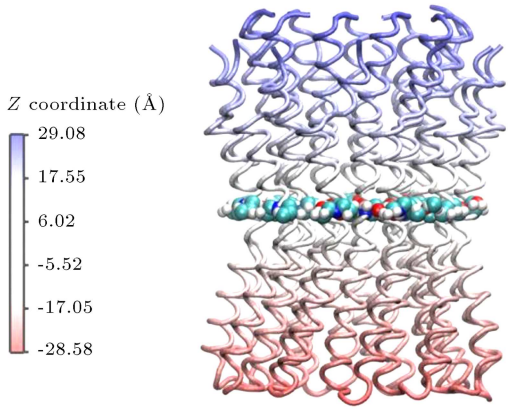

Figure 3. Fixed protein $C\alpha$ atoms (in the center of protein) during FR-CV-SMD simulation; z axis coordinate is shown in the contour.

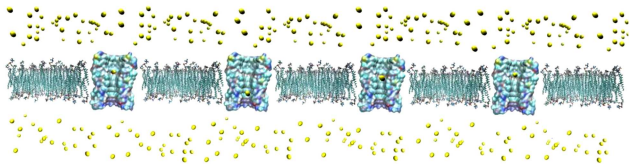

Figure 4. The ions permeation through parallel channels.

GTX-580. Computational speed is 0.626 days/ns to track a Na^+ in its channel.

2.2. LD simulation

This method can be exploited to simulate the ion diffusion across the membrane in the time scale of traverse of one or more ions through the channel. The results of simulations in the molecular and continuum medium can be connected in the LD simulation as a meso scale. To study the ion permeation in a group of protein channels working in parallel as shown in Figure 4, we can use the LD equation as:

$$ma = -\nabla U - m\gamma v + \sqrt{2m\gamma k_b T}N(t), \tag{7}$$

where U, γ, k_b, T, m, a and v are applied potential, friction coefficient obtained from Eq. (6), Boltzmann constant, temperature, mass, acceleration and speed of Na^+, respectively. $N(t)$ is a random number with Gaussian probability distribution function that satisfies the conditions:

$$\langle N(t)\rangle = 0, \tag{8}$$

$$\langle N(t)N(t')\rangle = \delta(t-t'). \tag{9}$$

According to Eqs. (6) and (7), atom acceleration can be achieved by:

$$a = -\frac{\nabla U}{m} - \gamma v + k_b T\sqrt{\frac{2}{mD}}N(t). \tag{10}$$

In this equation, D is diffusivity of the desired atom.

In order to track dynamic motion of ions through the parallel channels, 10000 Na^+ are located at the entrance ($x = 0$) of a virtual channel with 20 Å length. This simulation is equivalent to the transport of the 10000 NA^+ through 10000 parallel channels. We have implemented the zero mass flux and constant concentration boundary conditions at the end and entrance of the channel, respectively. In LD equation, the Brownian, dissipative force and constant potential gradient are applied for 1 ns simulation using velocity-Verlet integration algorithm [28] with a time step of 1 fs. These simulations are performed on the above mentioned system using LD-FP code.

2.3. Continuum modeling

Lumped parameter models, sometimes, are used to investigate some of the cell behaviors such as cell contractions. Most of mass diffusion problems are described and analyzed by Fick's law. It is well known that this classical diffusion theory may break down when one is interested in the transient problems in an extremely short period of time, very high flux, or in very low temperatures. Then, a modified flux model for the transfer processes with a finite speed wave, called phase-lagging model, is suggested [29]. In this model, the speed of propagation is finite and mass flux is related to concentration gradient as:

$$J(r,t) + \tau\frac{\partial J(r,t)}{\partial t} = -D\nabla n(r,t), \tag{11}$$

where J is the mass flux and τ is the relaxation time which is related to shock propagation speed by:

$$V_m = \sqrt{\frac{D}{\tau}}. \tag{12}$$

At the end, the diffusivity and PMF resulted from all-atom MD simulation are substituted in LD-FP code to estimate the speed of shock propagation in the phase-lagging model of Na^+ transport across the protein channel.

3. Results

3.1. All-atom MD results

PMF and the work done by dissipative force along the Na^+ channel are shown in Figures 5 and 6. In these figures, each of the dash lines corresponds to a forward-reverse simulation and the solid line shows their average.

As discussed previously, we can derive PMF and dissipative work, using Eqs. (4) and (5), in which $W_{f/r}$ and $V_{f/r}$ can be calculated from Eqs. (2) and (3). It should be noted that t is omitted from these equations considering $z = z(t)$. The resulting PMF and W_d are shown in Figures 5 and 6, respectively.

According to Figure 5, the free energy barrier

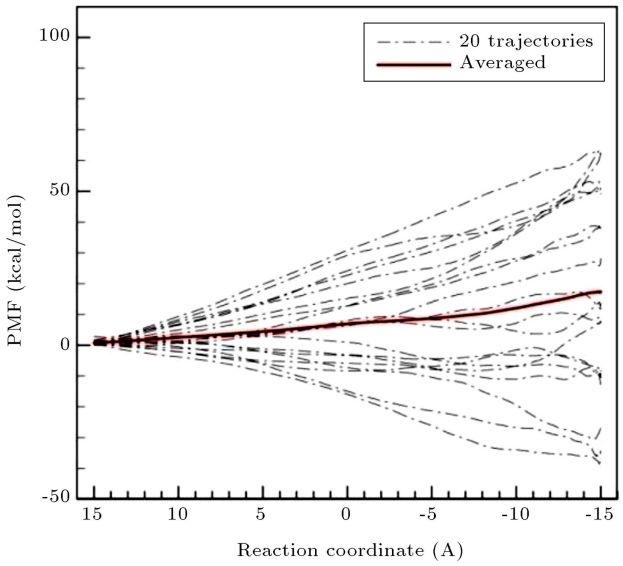

Figure 5. Free energy profile obtained from Eq. (4).

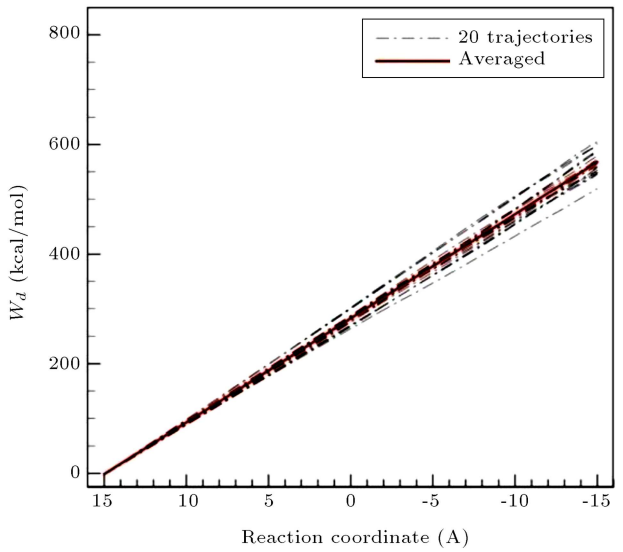

Figure 6. Dissipated work performed on the ion within the channel reconstructed from Eq. (5).

can be obtained from the maximum of the PMF experienced by the Na^+ ion across the channel which is equal to 18 kcal/mol.

Also, according to Figure 6, the dissipated work can be expressed by a linear function related to the channel coordinate. We can find the diffusivity using the derivative of W_d as stated in Eq. (6). The calculated value of the Na^+ diffusivity in its channel is 1.06 $Å^2$/ns.

3.2. Ion permeation through its protein channel using LD

By calculation of Na^+ diffusivity and channel PMF, we can investigate ion permeation in the protein channel using LD equation, without expensive all-atom simulation.

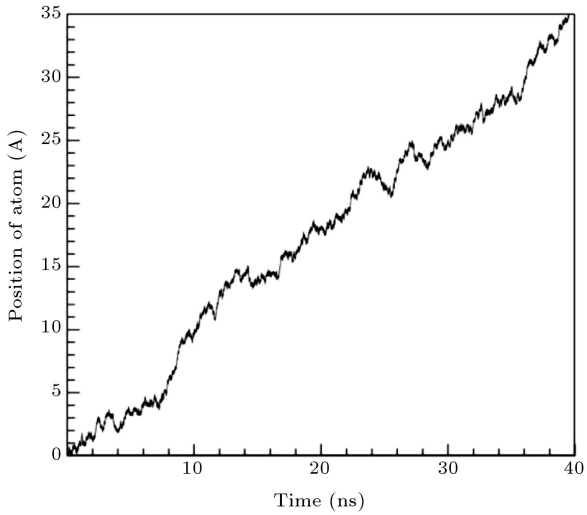

Figure 7. NA^+ trace in its channel using Langevin dynamics simulation.

We have incorporated the results of FR-CV-SMD simulation into Langevin equation and performed a LD simulation. It is noteworthy that the computational speed to track a Na^+ in its channel, in this approach, is 1.57×10^{-5} days/ns, which is very fast in comparison with all-atom method. The resulting track of Na^+ through channel with this method is shown in Figure 7. As shown, it takes 40 ns for an ion to traverse 3.5 nm of the channel length. Therefore, with this method, we can find the time order of ion transport across the channel.

3.3. Continuum transport properties of Na^+ permeation through its channel

In order to obtain the speed of shock propagation defined by Eqs. (11) and (12), we have tracked 10^4 Na^+ ions in a 20 Å virtual channel using an LD simulation under the effect of Brownian force with the diffusivity of 1.06 $Å^2$/ns and a 100 pN force representative of linear potential through channel.

The dimensionless distribution of ion concentration along the channel is shown in Figure 8. The dimensionless reaction coordinate and concentration was obtained by dividing with the channel length and initial concentration, respectively. Since the concentration gradient along the channel is very steep, a phase-lagging model, like Eq. (11), can describe the mass transport on this time scale.

The shock velocity is the measure of information propagation through the channel length. Considering Figure 8, the shock velocity can be approximately obtained by dividing the evidence position of the sharp concentration gradient to the corresponding simulation time. In Figure 8, we have plotted dimensionless concentration profiles for times of 0, 0.5 and 1 ns corresponding the dimensionless shock positions of 0, 0.3 and 0.6, respectively. This

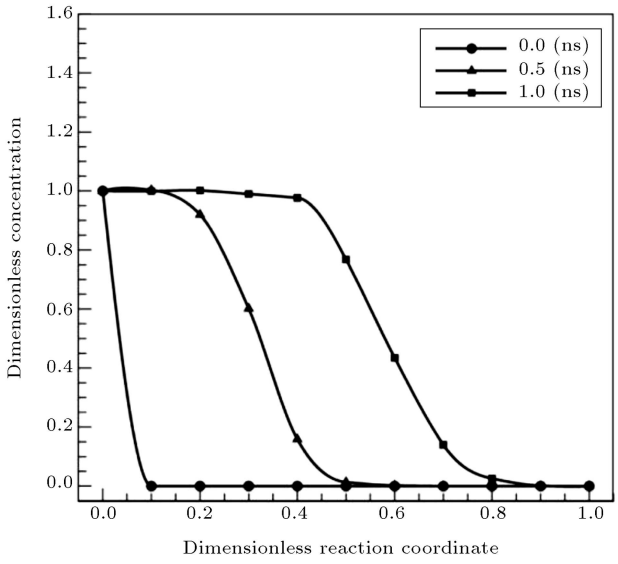

Figure 8. The Na^+ concentration through its channel using Langevin dynamics Fortran parallel code.

shows that the shock propagation velocity is about 1.2 nm/ns.

The velocity of information propagation is different in different materials. This velocity in Cu, Ag, Au and Pb is 1.56×10^4, 1.46×10^4, 1.26×10^4 and 2.67×10^4 nm/ns, respectively, as discussed in [30]. In this study, the velocity of information propagation in protein channel is obtained to be 1.2 nm/ns which is very small compared with other materials. This low speed in protein channel indicates that an inherent time lag exists in the biological systems.

4. Discussion and conclusion

The linear free energy profile for Na^+ transport through the protein originates from the relatively large diameter of its pore channel (approximately 15 Å). In fact, because of the large diameter of the pore, channel shape has no significant effect on Na^+ transport and the effective force applied to water molecules and Na^+ is the long-range electrostatic force. This implies that the protein channel distributes the electrostatic forces uniformly along the reaction coordinate and consequently the linear profile of PMF is a result of the ion concentration gradient across the cell membrane. Because of linear slope of the dissipated work (Figure 6), the diffusion of Na^+ is constant across the membrane. The order of magnitude of the resulting value of diffusivity is in agreement with similar ion simulations [13].

The LD simulation shows that it takes 40 ns for an ion to traverse 3.5 nm of the channel length. Therefore, with this method we can find the time order of ion transport across the channel. The natural ion motion through the protein channel can be investigated using the FR-CV-SMD, while by means of the EMD such computation is very time consuming. Although LD simulation is not capable to obtain diffusivity and PMF accurately, it can then be coupled with particle models of the cell to simulate transport phenomenon across cell boundaries.

In the phase-lagging model, there is a shock in the concentration gradient along the channel which is not previewed in Fick's model. This is due to finite speed of propagation in phase-lagging model. The result shows that the phase-lagging model can predict mass transport phenomenon more accurately in this case. The computed shock propagation speed in the Na^+ protein channels as a biological system is 1.2 nm/ns. Thus, using a phase-lagging model has a distinct advantage over classical Fick's model of mass transport in the lumps modeling of cell activities.

Using an accurate model for ion permeation in the protein channels is requisite to achieve valid results from cell cycle simulations. In this work, we have proposed three techniques to investigate ion permeation through its protein channel in different time scales. In order to achieve this purpose, we have performed an expensive set of FR-CV-SMD simulations. Since molecular systems consist of a large number of atoms, in this case 75282 atoms, all-atom MD simulations have many limitations. Thus we have developed an in-house LD-FP code to simulate ion permeation for a longer time. The computational speed of all atom MD and LD-FP simulation to track a Na^+ across the specific length of its protein channel, are 0.626 days/ns and 1.57×10^{-5} days/ns, respectively. It shows that we have reached an ultra-high computing capability to model ion permeation by means of the LD simulation. In addition, since in the LD simulations, the interaction between particles is absent, we can benefit from parallel processing without focusing on these details. In this regard, we have developed our in-house LD-FP code using the OpenMP API to model diffusion of a large number of ions through a set of protein channels working in parallel, simultaneously. In fact, LD can be used as a bridge connecting between molecular and continuum scales. Therefore three different techniques presented in this paper can be employed to investigate the different mass transport phenomena in the cell membranes.

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