

MOLECULAR DYNAMICS STUDY OF PERMEATION PROCESS OF SMALL MOLECULES THROUGH A LIPID BILAYER

Taisuke SUGII*, Shu TAKAGI*, and Yoichiro MATSUMOTO*

*Dept. of Mech. Eng., The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo, 113-8656, Japan

Summary In this study, the transport characteristics on the lipid bilayer were analyzed using the molecular dynamics method. We calculated the free energy profiles of several small molecules across the three kinds of lipid bilayers using the cavity insertion Widom method. Furthermore, the three dimensional instantaneous potential field (van del Waals potential field and electrostatic potential field) was also calculated.

INTRODUCTION

The self-assembled amphipathic molecules in water solutions, such as surfactants or lipids, form micelles or bilayers, etc. Especially in a living body, the lipid bilayer forms the basic structure of bio-membranes and supports the various life activities. For example, considering the transport phenomena by simple diffusion, permeation of water molecules or carbon dioxide through a bio-membrane plays an important role. Furthermore, a liposome, that is a vesicle formed from lipid molecules, is useful for an investigation of biological membranes. And many applications are proposed, for instance, the Drug Delivery System and the artificial oxygen carrier. Although the elucidation of the molecular transportation through a lipid bilayer membrane is very important in such biochemical processes, experimental observation has much difficulty and even the mechanism of the molecular penetration is not understood clearly. Hence, in this research, we investigate the transport phenomena through a lipid bilayer. Recently, a cell membrane and a liposome are actively studied in various fields. Marrink et al. calculated the free energy profile of H₂O, NH₃, O₂ and the LJ particles with various radii across the DPPC membrane using the molecular dynamics method [1, 2]. For calculating the free energy, they used several different methods in the different region. More recently, Jedlovsky et al. [3] calculated the profile of the several small molecules using DMPC membrane by the Monte Carlo method. These results indicated that the non-polar molecules exist stably inside the lipid membrane while the interior hydrophobic region works as the energy barrier for the polar molecules. In this research, using the molecular dynamics method, the free energy profiles of small molecules (O₂, CO, NO, H₂O, and several artificial diatomic molecules) across the three kinds of pure lipid membranes (DLPC, DMPC, and DPPC) were calculated. Moreover, we calculated the vdW potential field and the electrostatic potential field of water-membrane system. The potential field is very important for an investigation of transport phenomena because it can represent the local and instantaneous state of the system.

CALCULATION METHODS

We used the three kinds of pure lipid membranes, which consist of DLPC, DMPC, and DPPC molecules, respectively. The difference between the three lipid molecules is the hydrocarbon chain length, that is, DLPC, DMPC, and DPPC molecules have 12, 14, and 16 carbons in each chain, respectively. The each system consists of 64 lipid molecules and 1600 TIP3P water molecules. The potential parameter was taken from Smondyrev et al [4]. The lipid bilayer was constructed using the molecular coordinates of DMPC crystal structure obtained from the x-ray analysis and added two carbons to each hydrocarbon chain for DPPC and reduced two carbons for DLPC. We carried out the calculation in NP_nγT ensemble [5]. We set the reference normal pressure P_{n0} , the reference surface tension γ_0 , and the reference temperature T_0 to 1 atm, 0 dyn/cm, and 320 K, respectively. The total calculation time was 2.0 ns.

We calculated the free energy profiles across the membrane using the cavity insertion Widom method [3, 6]. According to this method, the excess chemical potential at position z (z is the normal direction to the membrane.) is calculated as,

$$\mu^{\text{exc}}(z) = -kT \ln \left\langle \exp \left[-\beta v_{N+1}(\mathbf{r}^N) \right] \right\rangle - kT \ln \left\langle P_{\text{cav}}(z) \right\rangle . \quad (1)$$

Here, $\mu^{\text{exc}}(z)$ is the excess chemical potential at position z . $v_{N+1}(\mathbf{r}^N)$ is the potential energy interacting between the test particle inserted in the system and the rest particles. $P_{\text{cav}}(z)$ is the probability of finding the cavity of the radius R_{cav} in the system. We used the results of last 240 ps for calculating the free energy profiles.

The free energy profile mentioned above is an averaged feature over the time and the space. However, when considering the transportation phenomena of the small molecules, the local and instantaneous change of the potential field is also important. Hence, we calculated the vdW potential field (not shown here) and the electrostatic potential field by inserting the test particle into the grid points in the simulation cell. In the calculation of the electrostatic potential field, we used the smoothed particle charges by the Gaussian function [7]. The electrostatic potential becomes,

$$\phi_{\text{elec}}(\mathbf{r}) = \frac{1}{4\pi\epsilon_0} \sum_i \sum_n q_i \frac{\text{erfc}[a_d |\mathbf{r}_i + \mathbf{R} - \mathbf{r}|] - \text{erfc}[a |\mathbf{r}_i + \mathbf{R} - \mathbf{r}|]}{|\mathbf{r}_i + \mathbf{R} - \mathbf{r}|} + \frac{1}{V\epsilon_0} \sum_i q_i \sum_{\mathbf{G} \neq 0} \frac{1}{|\mathbf{G}|^2} \exp \left(-\frac{|\mathbf{G}|^2}{4a_d^2} \right) \exp[i\mathbf{G} \cdot (\mathbf{r} - \mathbf{r}_i)] . \quad (2)$$

Here, a is a constant number representing the envelope of the Gaussian function. The above expression includes some modifications to the usual Ewald method.

RESULTS AND DISCUSSION

The snapshot of the simulated DMPC membrane is shown in Fig. 1. Our results show good agreement with the other experiments and simulations, for example, about the order parameter of hydrocarbon chains and the electron density profiles. The calculated free energy profiles are shown in Fig. 2. Here, the mid-plane of the lipid bilayer was set to $z = 0$. We investigated the transport phenomena in two ways, that is, changing the solute molecules and changing the membrane molecules. Figure 2 (a) shows the free energy profiles of O_2 (non-polar) and the artificial molecules across the DMPC membrane. The artificial diatomic molecules have the dipole moment of 0.5 D, 1.0 D, 1.5 D, and 2.0 D in addition to the vdW potential parameter same as O_2 . The results clearly indicate that the non-polar molecule is stable in the center region of the bilayers, and becomes unstable relative to the outside of the membrane (bulk water) with increasing the dipole moment. Accordingly, the stable region (free energy minimum) appears near the lipid/water interface region with an increase of the dipole moment. And in the center region of the membrane, the polarity of the solute molecules has little effect on the profiles. The interface region works as a relatively higher energy barrier in all case. Figure 2 (b) shows the free energy profiles of H_2O across the DLPC, DMPC, and DPPC membrane. The energy barrier at the interface is not found in this case. The width of the energy barrier inside the membrane spreads with increasing the chain length, though the height doesn't almost change. This is probably because the distance from the lipid/water interface is the dominant factor in deciding the free energy of the polar solute.

Figure 3 shows the electrostatic potential field at $x = 0$ plane of DMPC/water system. The figures correspond to the results for the contribution of (a) the water molecules, (b) the lipid molecules, and (c) all of the molecules, respectively. It is shown that the water molecules make positive potential field inside and negative outside the membrane, and the lipid molecules work oppositely. This result qualitatively agrees with the statistical calculation results of the electrostatic potential by Shinoda et al [8]. Moreover, it is clear that each kind of molecules is counteracting each other, especially around the head groups of the lipid molecules. The total potential due to all molecules is slightly positive inside. Besides, the potential field of the water molecules has small fluctuation spatially while that of the lipid molecules has large fluctuation.

References

- [1] Marrink S. J., and Berendsen H. J. C., *J. Phys. Chem.*, **98**, 4155, 1994.
- [2] Marrink S. J., and Berendsen H. J. C., *J. Phys. Chem.*, **100**, 16729, 1996.
- [3] Jedlovsky P., and Mezei M., *J. Am. Chem. Soc.*, **122**, 5125, 2000.
- [4] Smondyrev A. M., and Berkowitz M. L., *J. Comp. Chem.*, **20**, 531, 1999.
- [5] Zhang Y., Feller S. E., Brooks B. R., and Pastor R. W., *J. Chem. Phys.*, **103**, 10252, 1995.
- [6] Pohorille A., and Wilson M. A., *J. Chem. Phys.*, **104**, 3760, 1996.
- [7] Takagi S., Uda T., Kikugawa G., and Matsumoto Y., *Proceedings of 3rd European-Japanese Two-Phase Flow Group Meeting, CD-ROM*, 2003.
- [8] Shinoda W., Shimizu M., and Okazaki S., *J. Phys. Chem. B*, **102**, 6647, 1998.

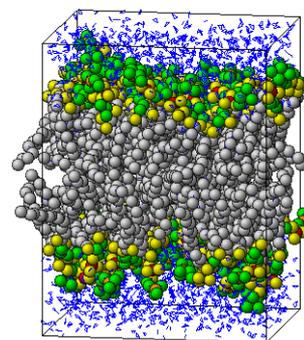


Fig. 1. Snapshot of the simulated membrane. The spheres and the blue line show the lipid molecules and the water molecules, respectively. The coloring scheme is P: Red, N: Orange, C: Green, O: Yellow, and Gray: hydrocarbon chains.

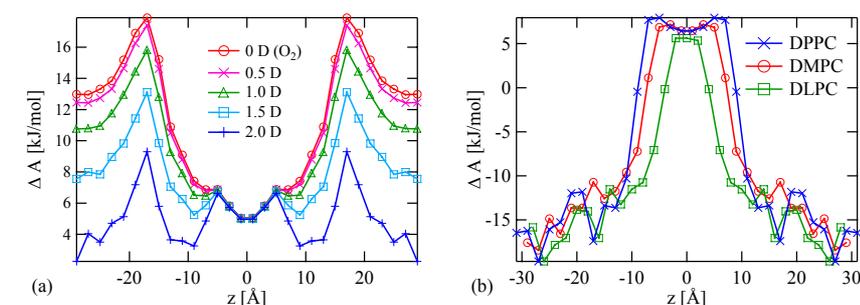


Fig. 2. (a) The free energy profiles of O_2 and the artificial molecules across the DMPC membrane. (b) The free energy profiles of H_2O across the DLPC, DMPC, and DPPC membrane.

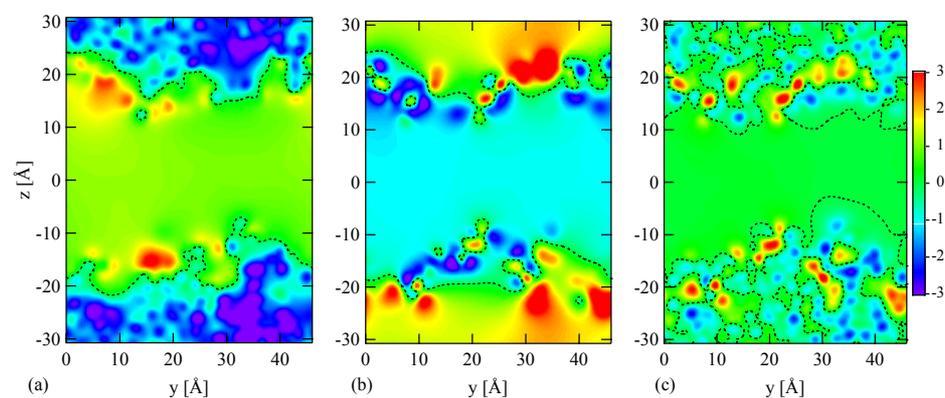


Fig. 3. The electrostatic potential field at $x = 0$, $t = 2.0$ ns. The contribution from (a) the water molecules, (b) the lipid molecules, (c) the all molecules, respectively. The black dashed line is 0 electrostatic potential surface.