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Research paper

Dissipative particle dynamics (DPD) simulations with fragment molecular orbital (FMO) based effective parameters for 1-Palmitoyl-2-oleoyl phosphatidyl choline (POPC) membrane

Hideo Doi [a,*], Koji Okuwaki [a], Yuji Mochizuki [a,b], Taku Ozawa [c], Kenji Yasuoka [d]

[a] Department of Chemistry and Research Center for Smart Molecules, College of Science, Rikkyo University, 3-34-1 Nishi-ikebukuro, Toshima-ku, Tokyo 171-8501, Japan
[b] Institute of Industrial Science, The University of Tokyo, 4-6-1 Komaba, Meguro-ku, Tokyo 153-8503, Japan
[c] JSOL Corporation, 2-5-24 Harumi, Chuo-ku, Tokyo 104-0053, Japan
[d] Department of Mechanical Engineering, Keio University, Yokohama 223-8522, Japan

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ABSTRACT

In dissipative particle dynamics (DPD) simulations, it is necessary to use the so-called χ parameter set that express the effective interactions between particles. Recently, we have developed a new scheme to evaluate the χ parameters in a non-empirical way through a series of fragment molecular orbital (FMO) calculations. As a challenging test, we have performed the DPD simulations using the FMO-based χ parameters for a mixture of 1-Palmitoyl-2-oleoyl phosphatidyl choline (POPC) and water. The structures of both membrane and vesicle were formed successfully. The calculated structural parameters of membrane were in good agreement with experimental results.

1. Introduction

It has been widely recognized that computational simulations of molecules are powerful to model the given target system. In particular, molecular dynamics (MD) simulations have a wide range of applications to large molecular systems consisting of dozen thousands of atoms. Therefore, as reviewed in Refs. [1–3], a number of MD simulations for proteins, lipid membranes, and so on have been carried out, to date.

Many practical MD simulations have been based on molecular mechanical (MM) or classical force field (FF) parameters derived empirically from experimental data, since the full evaluation of forces through non-empirical or quantum mechanical (QM) calculations are impractical for large molecules at the prohibitive computational costs. Therefore, several MD codes with empirical FF parameters, e.g. CHARMM [4–6], AMBER [7,8], GROMOS [9], and OPLS [10,11], have been developed: QM calculations have also been partly used for small model systems in the parameter determination for such as partial charges [7,8].

For huge molecular systems, the simulation methods of coarse-grained MD (CGMD) and dissipative particle dynamics (DPD) have been used to reduce computational costs. In these methods, certain groups of atoms are treated as one particle, and the given target systems are modeled with effective FF parameters among such particles. CGMD simulations for lipid membranes have thus been carried out [12–14].

DPD has an advantage over usual CGMD in covering longer time steps. In addition, only short-range FFs (or soft potentials) are necessary to perform DPD simulations. These two features of DPD can provide longer simulation time of larger molecular systems relative to CGMD [15–21]. Hereafter, we would focus on DPD.

DPD simulations with empirical FF parameters could suffer from the following difficulties, however. First, there should be a considerable dependence on the available data of molecular structures and thermodynamic properties for the determination of parameters. Besides some exceptions, it would be hard to obtain non-crystalized molecular structures (just of lipid membranes). Second, the availability of experimental thermochemical data is generally limited relative to the case of structural data, especially for large molecules. When the type of target system differs from the postulated types for the empirical parameter set used, the reliability of simulation results should be degraded. In other words, there are potential needs to develop effective parameters without experimental data sets.

In 1992, Fan et al. proposed a revolutionary procedure to determine the effective interaction parameters for DPD simulations, the so-called χ parameters, without experimental values [22]. Fan's approach has a notable merit that it can directly estimate the contact energy between binary components (as described later). Nonetheless, the use of several empirical FF parameters was

* Corresponding author.
E-mail addresses: hideo-doi@rikkyo.ac.jp (H. Doi), fullmoon@rikkyo.ac.jp (Y. Mochizuki).

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necessary in this procedure. Thus, there should remain a difficulty addressed in the previous paragraph. Especially, when charge transfer and polarization are substantial in the target system, the validity of χ parameters estimated with MM/FF parameters can be limited.

Recently, we have developed a modified version of Fan's procedure to calculate the χ parameters [23], based on the fragment molecular orbital (FMO) method [24–26]. In our procedure [23], the crucial contact energies between components are evaluated with the interaction energies from the FMO calculations or without empirical FF parameters. Since FMO is a QM method, both charge transfer and polarization are straightforwardly incorporated. The DPD simulation with FMO-based χ parameters has been successfully applied to the electrolyte (for example, Nafion) membranes - water systems [27]. In this Letter, the FMO-DPD combinative simulation scheme is used for a lipid membrane system of 1-Palmitoyl-2-oleoyl phosphatidyl choline (POPC). Note here that the FF determination for lipids could be difficult in empirical ways because of relatively rare availability of crystal structures for lipid membranes. The remaining parts of this Letter are composed as follows. Section 2 summarizes the method of simulation (DPD and FMO-based χ parameter determination). The set-up of the present simulation of POPC is described in Section 3, and the simulated results are presented in Section 4. It will be shown that several fundamental properties of lipid bilayer are comparable well with the experimental data, indicating the versatility of our procedure.

2. Method of simulation

2.1. DPD simulation

In this subsection, we brief the DPD method. DPD is based on the dynamics of soft particles interacting by conservative, dissipative, and random forces [28,29]. The fundamental DPD scheme is extended to polymer systems by Groot et al. by introducing a bead-spring type particle model [30–32]. Here we describe the outline of Groot's DPD model as follows. The time evolution of the given system under forces is simulated by solving standard Newton's equation of motion

$$\frac{d\mathbf{r}_i}{dt} = \mathbf{v}_i, \tag{1}$$

and

$$m_i \frac{d\mathbf{r}_i}{dt} = \mathbf{f}_i, \tag{2}$$

where, $\mathbf{r}_i$, $\mathbf{v}_i$, and m_i are the position, velocity, and mass of the ith particle, respectively. For simplicity, the masses and diameters of particles are scaled relative to 1 to reduce units (dimensionless form). Force $\mathbf{f}_i$ consists of three parts in the original DPD formulation [28,29], and an additional spring force for polymer systems with bond connections [30–32]. The interaction between two particles is then written as the sum of these forces

$$\mathbf{f}_i = \sum_{j \neq i} (\mathbf{F}_{ij}^C + \mathbf{F}_{ij}^D + \mathbf{F}_{ij}^R + \mathbf{F}_{ij}^S). \tag{3}$$

The first three forces are considered within a certain radius r_c of short-range cut-off. The conservative force $\mathbf{F}_{ij}^C$ is a soft repulsion action as follows [30]

$$\mathbf{F}_{ij}^C = \begin{cases} -a_{ij}(1 - r_{ij})\mathbf{n}_{ij} & r_{ij} < 1 \\ 0 & r_{ij} \geq 1 \end{cases} \tag{4}$$

where a_{ij} is the maximum repulsion force between particles i and j, $\mathbf{r}_{ij} = \mathbf{r}_j - \mathbf{r}_i$, $r_{ij} = |\mathbf{r}_{ij}|$, and $\mathbf{n}_{ij} = \mathbf{r}_{ij}/|\mathbf{r}_{ij}|$. The repulsion parameters between particles of different types correspond to the mutual solubility, expressed as the Flory-Huggins χ parameter (as shown later). When the reduced density ρ is assumed to be 3, a linear relation with χ_{ij} is usually set like [30,31]

$$a_{ij} = a_{ii} + 3.27\chi_{ij} \tag{5}$$

Namely, when the set of χ parameters is prepared for the target system of DPD simulation, $\mathbf{F}_{ij}^C$ can be set up.

In Eq. (3), the dissipative force $\mathbf{F}_{ij}^D$ represents the hydrodynamic drags [30], and the random force $\mathbf{F}_{ij}^R$ corresponds to thermal noises of the Gaussian statics. When particles i and j are connected with a bond, a harmonic spring force $\mathbf{F}_{ij}^S$ is simply defined as

$$\mathbf{F}_{ij}^S = C\boldsymbol{r}_{ij} \tag{6}$$

where C is a proper force constant.

2.2. Determination of χ parameter

In the Flory-Huggins lattice theory, the free energy change (ΔG) for a binary component system at a given temperature T is expressed as follows [33]

$$\frac{\Delta G}{RT} = \frac{\varphi_1}{x_1}\ln\varphi_1 + \frac{\varphi_2}{x_2}\ln\varphi_2 + \chi\varphi_1\varphi_2 \tag{7}$$

where φ_i ($i = 1, 2$ for the two components) means the volume fraction and x_i is the chain length. By Fan's procedure [22], the crucialχ parameter is defined as

$$\chi = \frac{Z\Delta E_{12}}{RT}, \tag{8}$$

where Z is the coordination number of the model lattice and the temperature dependence is incorporated through the Monte Carlo sampling. The contact energy ΔE_{12} is given by the following equation

$$\Delta E_{12} = E_{12} - \frac{1}{2}(E_{11} + E_{22}). \tag{9}$$

E_{ij} is the interaction energy between the components i and j, and each of them is evaluated with empirical FF parameters. Actually, a large number of geometrical configurations (for example, a few thousands) are generated for 1-1, 2-2 and 1–2 pairs in the evaluation of interaction energies. If the number of components is three or more, all the possible combinations should be considered.

In our procedure [23], the FMO calculations [24–26] are used to evaluate the set of E_{ij} of Eq. (9) as the interaction energies among fragments. Each particle can be further divided into several fragments if it is too large. This flexibility is a merit of the FMO method. Actually, the distance parameters of FF set are modified with the results of MO calculations for model systems (or QM-based refinement), and this modification slightly alter both sample configurations (subjected to a series of FMO calculations) and the value of Z. In the present scheme, the particle - particle (or two-particle) interactions are included, but extensions to incorporate effective three particle interactions into two particle interactions (E_{ij}) can be naturally considered through the FMO calculations [26]. Full details of our procedure of χ parameter determination will be published elsewhere [23]. When necessary, the hydration effect for particles can be incorporated by a Poisson-Boltzmann (PB) model in the FMO framework (FMO-PB) [34].

3. Set-up of POPC simulation

3.1. Parameter evaluation

As shown in Fig. 1, the POPC molecule was expressed by six types of beads (or connected particles), where each bead corresponded to