INTERNATIONAL JOURNAL FOR NUMERICAL METHODS IN FLUIDS
Int. J. Numer. Meth. Fluids 2007; **54**:831–840
Published online 28 February 2007 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/fld.1453

A meso-scale analysis of lipid bilayers with the dissipative particle dynamics method: Thermally fluctuating interfaces

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SUMMARY

We present a meso-scale simulation of lipid bilayers with the dissipative particle dynamics (DPD) method. The spectrums of the thermal undulation are analysed and the bending rigidity of the lipid bilayers is calculated. In order to define the position of the membrane, we apply a definition of the interface which has been newly proposed by Kikugawa *et al*. (*Comput. Fluids* 2007; **36**:69–76). We show the applicability of this method to the lipid bilayer system. By means of this definition, the roughness of the extracted interface can be varied and this effect is investigated. The spectral intensity is shown as a function of the undulatory wavenumber q. The spectral intensity in large-q regions is affected by the roughness of the interface. However, we find that the spectral intensity in small-q regions, where the bending rigidity can be calculated, is hardly affected. Moreover, the undulation spectrums show q^{-4} behaviour in small-q regions, which agrees with the theoretical prediction. The effects of the size of the computational cell are also investigated. All spectrums obtained in the differently sized cells agree well, although the observable range of the wavenumber depends on the cell size. The bending rigidity calculated by spectral intensity from the largest cell is in good agreement with experiments and molecular dynamics simulations in the literature. Copyright © 2007 John Wiley & Sons, Ltd.

Received 3 December 2006; Revised 26 December 2006; Accepted 27 December 2006

KEY WORDS: dissipative particle dynamics; lipid bilayers; interface; thermal undulation; spectral analysis; bending rigidity

1. INTRODUCTION

Lipid bilayer vesicles, even though appearing as spheres in an optical microscope, have a larger surface area than spheres of the same volume, because the lipid bilayers are 'folded' by thermal undulations. The difference of these two areas is called the excess area. The thermal undulations

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Contract/grant sponsor: Japan Society for the Promotion of Science
Contract/grant sponsor: Ministry of Education, Culture, Sports, Science and Technology, Japan

of lipid bilayers play an important role in many systems. For example, it is reported that the deformation of lipid bilayer vesicles in a shear flow can be explained by an expansion of the excess area, while area dilation, which is governed by the dilation modulus, is negligible [1]. Other papers have also reported the important role of the thermal fluctuation of bilayers, e.g. in multilayer systems [2] and vesicles adhering to solid substrates [3]. These imply that the microscopic undulations have significant effects on the macroscopic behaviour. Recently, therefore, thermal undulation has been investigated by molecular-scale simulations. Lindahl *et al*. [4] reported that the undulatory behaviour of the lipid bilayer agrees well with the theoretical prediction. This analysis used the molecular dynamics (MD) method with a large system containing up to 1024 lipid molecules. However, it is usually difficult to capture the continuum behaviour of lipid bilayers from the MD simulations because the spatial and time length of the simulation are limited. Therefore, in recent years, analyses of the undulation of bilayers or monolayers have been seen in various papers employing mesoscopic simulation methods, such as the coarse-grained MD method [5] and by the dissipative particle dynamics (DPD) method [6]. In the spectral analysis of the thermal undulation by these molecular simulations, one difficulty arises from the definition of the position of the bilayers. We find the definition to vary from one article to other (see References [5, 6] for example.)

In this study, we introduce a definition which is newly developed by Kikugawa *et al*. [7] to determine the lipid/water interface and consequently the position of the membrane. This method can capture the local and instantaneous structure of the interface and has an advantage that the characteristic features of the interface can be extracted more fully based on the instantaneous interface defined by the method than if based on the equimolar surface. Note that this method is generally applicable to particle-based simulations which include interfaces, although it is originally developed for a liquid–vapour interface. Using this definition, we determine the position of the bilayers and the thermal undulation is analysed. The DPD method, which is a mesoscopic simulation method originally proposed by Hoogerbrugge and Koelman [8], is used to simulate large systems. First, we show the validity of the DPD lipid model, and then show the applicability of the definition to the lipid bilayer system. The spectrums of the thermal undulation are analysed and the bending rigidity of the lipid bilayers is calculated from the spectrums. The effects of the computational cell size on the undulatory spectrum are also analysed.

The outline of this paper is as follows. In Section 2 we describe the simulation method and the molecular model. The definition of the interface is summarized in Section 3. The DPD results are compared with MD and partly with experiments in Section 4 to validate the DPD results. The spectrum analysis of the membrane undulation is also described in Section 4, and the conclusion of this paper is in Section 5.

2. SIMULATION METHOD AND MODEL

A DPD particle represents a cluster of several atoms. The total force on a DPD particle consists of a conservative force $\mathbf{F}_{ij}^{\mathrm{C}}$, a dissipative force $\mathbf{F}_{ij}^{\mathrm{D}}$, and a random force $\mathbf{F}_{ij}^{\mathrm{R}}$:

$$\begin{aligned}\mathbf{F}_{ij}^{\mathrm{C}} &= a_{ij}(1 - |\mathbf{r}_{ij}|/r_{\mathrm{c}})\mathbf{n}_{ij}\\ \mathbf{F}_{ij}^{\mathrm{D}} &= -\gamma\omega^{\mathrm{D}}(|\mathbf{r}_{ij}|)(\mathbf{n}_{ij}\cdot\mathbf{v}_{ij})\mathbf{n}_{ij}\\ \mathbf{F}_{ij}^{\mathrm{R}} &= \sigma\omega^{\mathrm{R}}(|\mathbf{r}_{ij}|)\zeta_{ij}\Delta t^{-1/2}\mathbf{n}_{ij}\end{aligned} \tag{1}$$

DOI: 10.1002/fld

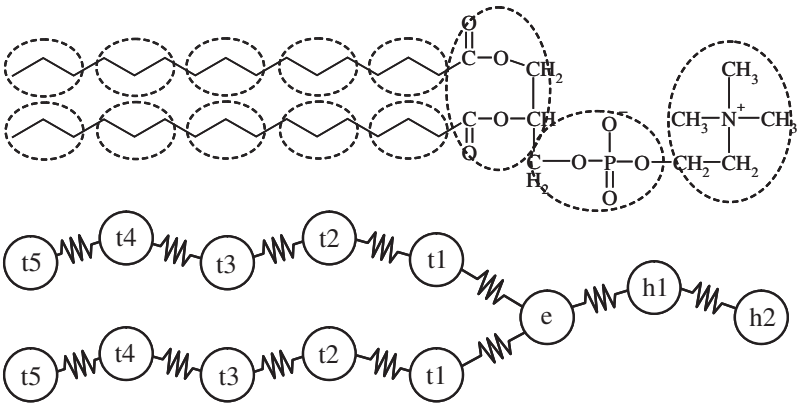

Figure 1. Molecular structure used in the MD simulation (DPPC) and the DPD simulation. Each dashed ellipse represents a group corresponding to one DPD bead.

Table I. The repulsion parameters a_{ij} from Groot and Rabone [10].

	w	t	e	h
w	78	104	79.3	75.8
t	104	78	86.7	104
e	79.3	86.7	78	79.3
h	75.8	104	79.3	86.7

w represents the water beads, t the tail beads, e the ester linkages, and h the head beads.

where $\mathbf{r}_{ij} = \mathbf{r}_i - \mathbf{r}_j$ for $\mathbf{r}_i$ is the position of particle i, $\mathbf{n}_{ij} = \mathbf{r}_{ij}/|\mathbf{r}_{ij}|$ and $\mathbf{v}_{ij} = \mathbf{v}_i - \mathbf{v}_j$ where $\mathbf{v}_i$ is the velocity of particle i. Note that $\mathbf{F}_{ij}^{\mathrm{C}} = \mathbf{F}_{ij}^{\mathrm{D}} = \mathbf{F}_{ij}^{\mathrm{R}} = 0$ for $|\mathbf{r}_{ij}| < r_{\mathrm{c}}$, r_{c} being the cut-off radius. The coefficient a_{ij} is a repulsion parameter which represents the maximum repulsion amplitude between particle i and j. The friction parameter is γ and the noise parameter is σ. According to Español and Warren [9], γ, σ, and the reduced temperature T should obey the relationship, $\sigma^2 = 2\gamma k_{\mathrm{B}} T$, where k_{B} is the Boltzmann constant. The random element ζ_{ij} is Gaussian white noise with zero mean and variance 1. The weight functions ω^{D} and ω^{R} satisfy the following relationship: $\omega^{\mathrm{D}}(|\mathbf{r}_{ij}|) = [\omega^{\mathrm{R}}(|\mathbf{r}_{ij}|)]^2$ [9]. We use reduced units with $k_{\mathrm{B}} T = m = r_{\mathrm{c}} = 1$. σ is chosen as 3, and density ρ as 3 following the literature [10]. The time step Δt is chosen as 0.05. The integration algorithm and the molecular structure of the lipid molecules are the same as Groot and Rabone [10]. The lipid structure is shown in Figure 1. The repulsion parameters a_{ij} are also taken from the literature [10] and listed in Table I. Note that this parameter set was originally developed for a realistic phospholipid molecule. In Section 4, we show results in physical units of length. They are converted using $r_{\mathrm{c}} = 6.4633$ Å, as described in [10]. The lipid molecules consists of DPD beads and are connected by an intra-molecular potential which consists of a bond potential and an angular potential. We use $U_r = \frac{1}{2} K_r (|\mathbf{r}_{ij}| - \mathbf{r}_{\mathrm{eq}})^2$ as the bond potential and $U_\theta = \frac{1}{2} K_\theta (\theta - \theta_{\mathrm{eq}})^2$ as the angular potential. Here K_r and K_θ are the constants, θ is the angle between the three connected DPD beads, and r_{eq} and θ_{eq} are the equilibrium length of the bonds and the equilibrium angles,

DOI: 10.1002/fld

Table II. Parameters for the angular potential from Kranenburg *et al*. [11].

	K_θ	θ_{eq} (deg.)
t–t–t	6	180
t–e–t	3	90

t represents the tail beads and *e* the ester linkages.

respectively. The parameters of the intra-molecular potential, K_r, K_θ, r_{eq}, and θ_{eq} are taken from [11]: $K_r = 100$, $r_{\mathrm{eq}} = 0.7$ in all bonds, and K_θ and θ_{eq} are listed in Table II.

We used four lipid bilayer systems where the numbers of lipid molecules, N_{lip}, were 64, 200, 800, and 3200. The number of water beads, N_{water}, was 534, 1667, 6668, and 26 672, respectively; the number of water molecules per lipid is about 25 in all cases. Note that one water bead represents three water molecules in this model. The 64 lipid system is used for comparison with the MD simulation in Section 4. Other larger systems are used for the spectral analysis of the membrane undulation. In order to obtain a tensionless state, we apply the constant tension scheme, which combines the DPD method (used for evolving the position of particles) with the Monte Carlo (MC) method (used for changing the size of the simulation cell) [12]. The size of the simulation cell was averaged over the constant surface tension ($\gamma = 0$) calculation, and thereafter a constant volume calculation was carried out using the obtained cell size. The resulting surface tension obtained from the constant volume calculation was almost zero. The last 60 000 steps were used for the analysis described below. The MD simulation consists of 64 DPPC lipid molecules and 1600 TIP3P water molecules and runs for 10 ns. The details of the MD simulation is described in an earlier article [13].

3. INTERFACE DEFINITION

To determine the interface, we use a new definition developed by Kikugawa *et al*. [7], in which the particle density is defined as a field quantity by smoothing the single particle density of particles by using a smoothed delta function. Computationally, the density field is defined on each orthogonal grid point generated in the MD cell by giving the following smoothed delta function on the centre of mass of the particles (water particles in this study):

$$D(\mathbf{r}^{\mathrm{g}} - \mathbf{r}_i) = \begin{cases} (2k\Delta x)^{-3} \prod_{d=1}^{3} \left\{ 1 + \cos \dfrac{\pi}{k\Delta x} (x_{i,d}^{\mathrm{g}} - x_{i,d}) \right\} & \text{if } |x_{i,d}^{\mathrm{g}} - x_{i,d}| < k\Delta x \\ 0 & \text{otherwise} \end{cases} \tag{2}$$

Here $x_{i,d}$ is the position of particle i in the d direction: $\mathbf{r}_i = (x_{i,1}, x_{i,2}, x_{i,3})$. $\mathbf{r}^g$ and Δx are the grid position and grid spacing in the simulation cell. k represents the broadening of the delta function and determines the roughness of the interface which is captured. The density of each grid point is calculated by summing the smoothed density of all particles. The position of the interface can be decided when the density value of the interface is determined. As reported in [7], the distribution function of the single particle density has typically two peaks. The two peaks indicate the membrane phase and the water phase in this study. The centre value between the

DOI: 10.1002/fld

two peaks was defined as the density value of the interface (for details, see [7]). In lipid bilayer systems such as in this study, two interfaces between lipids and water can be defined. We defined the midpoint of the two as the position of the membrane. We note again that this method was originally developed for a liquid–vapour interface, but is generally applicable for particle-based simulations which include interfaces.

4. RESULTS AND DISCUSSION

The number density profiles of the membrane simulated with the MD and DPD methods are shown in Figure 2. Here, z is the direction normal to the bilayers and the mid-plane of the membrane is set to $z = 0$. Both the DPD and MD simulations contain 64 lipid molecules. The distributions of MD simulations are calculated using the position of the centre of mass of the atoms which are accounted to belong to the corresponding DPD beads. Because of the softness of the intra-molecular potentials of DPD, the distributions of the lipid particles of DPD are rather broader than those of MD. For the same reason, the $t4$ particle shows a single-peaked distribution in DPD, whereas it is double peaked in MD. However, the positions of the peaks of the distributions except for the $t4$ bead are similar to the MD results. Especially, the peak-to-peak distances between the head beads are very similar.

The lateral diffusion coefficient of lipid molecules in the bilayer plane, which is an important dynamical property, was also calculated from the mean-square displacements (MSDs) of the centre of mass of the lipid molecules. The MSDs were fitted by straight line in the long-time region to

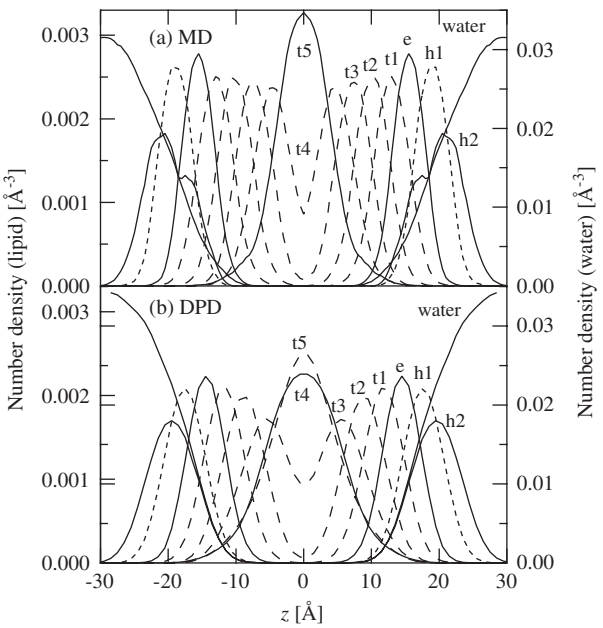

Figure 2. Number density profiles obtained from (a) MD and (b) DPD simulation. The distributions of the hydrophobic chains are shown per chain.

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obtain the lateral diffusion coefficients. The calculated diffusion coefficients were 2.0×10^{-11} m^2/s by DPD and 1.7×10^{-11} m^2/s by MD. Both results are in good agreement with those of other simulations and experiments of similar lipid bilayers, namely approximately (1–4) $\times 10^{-11}$ m^2/s (see [13] and references therein).

Next we show the spectral analysis of the membrane undulations. The spectral analysis of the undulation is important because the bending modulus, which is one of the most important physical properties of lipid bilayers, can be calculated from it as described below. In the planar membrane system, the local displacement of the membrane can be defined as $h(x, y) = z(x, y) - z_0$, where $z(x, y)$ is the local position of the membrane at (x, y) and z_0 is the averaged position of the membrane. The Fourier transform of $h(x, y)$, $\tilde{h}(q)$, and the wavenumber $q = 2\pi/\lambda$ where λ is the undulation wavelength, have the following relationship [14]:

$$\langle|\tilde{h}(q)|^2\rangle = \frac{k_B T}{A}(\gamma q^2 + \kappa q^4)^{-1} \tag{3}$$

where A is the membrane area, γ surface tension, and κ bending rigidity. This equation is derived from the energy equation of continuum bilayers and the equipartition principle and is not valid for short wavelengths. In this study, the surface tension γ is almost zero as described above and so the first term of the right-hand side of Equation (3) is negligible. This indicates that the spectral intensity is expected to obey a q^{-4} behaviour in the continuum limit.

A snapshot of the simulation and the interfaces calculated using the definition described in Section 3 are displayed in Figure 3. From Figure 3(b), we can see that the molecular-scale roughness of the interfaces can be captured well with smaller values of k ($k = 6$, meaning high resolution), whereas the roughness was smoothed with larger k ($k = 9$, meaning low resolution). Here we note that if in a simulation more than three interfaces were detected at (x, y) at a certain time step, in other words, $h(x, y)$ was not single-valued per interface at (x, y), for example, due to the protrusion of lipid molecules, then those results were not used for the spectral analysis. The mid-point of the two interfaces along the z-axis is defined as the position of the membrane $z(x, y)$ and the mid-plane of the computational cell, $z = 0$, is set as the averaged position z_0. Figure 4 shows the spectral intensities $S(q) = A\langle|\tilde{h}(q)|^2\rangle$ as a function of the wavenumber, q, with various k in the case of $N_{\text{lip}} = 3200$. Not surprisingly the spectral intensities for large q become small with an increase of k. This indicates that the small fluctuations are smoothed out with large k. On the other hand, the intensities for small q match well for all k value, indicating that spectral intensities corresponding to large-scale fluctuations are not affected by the resolution of the defined interface. These facts indicate that this definition seems inapplicable for investigation of large-q regions, such as for investigations of protrusions of lipids [4], but is well applicable for small-q regions, where the bending rigidity can be calculated. We again note that this interface definition has the advantage that the local and instantaneous interface can be determined and the characteristic features such as the number density and the dynamical properties near the interface can be extracted well [7]. Figure 4 also indicates that the spectral intensities show an asymptotic behaviour to q^{-4} for small q. This suggests that Equation (3) is valid in the continuum limit, as is reported similarly in several molecular simulations of bilayers [4–6, 15]. Figure 5 displays the spectral intensities calculated with various cell sizes with $k = 7$. Although the observable range of the wavenumber depends on the cell size, all spectrums agree well. This is interesting because it indicates that constraint of the cell area has little effect on the observed spectral intensity. We note that the effect of the cell height h_z was also tested using $N_{\text{lip}} = 800$ and $N_{\text{water}} = 40\,804$ (where h_z is three times larger than the original height) and the obtained spectrum is within the statistical error. In Figure 5, although

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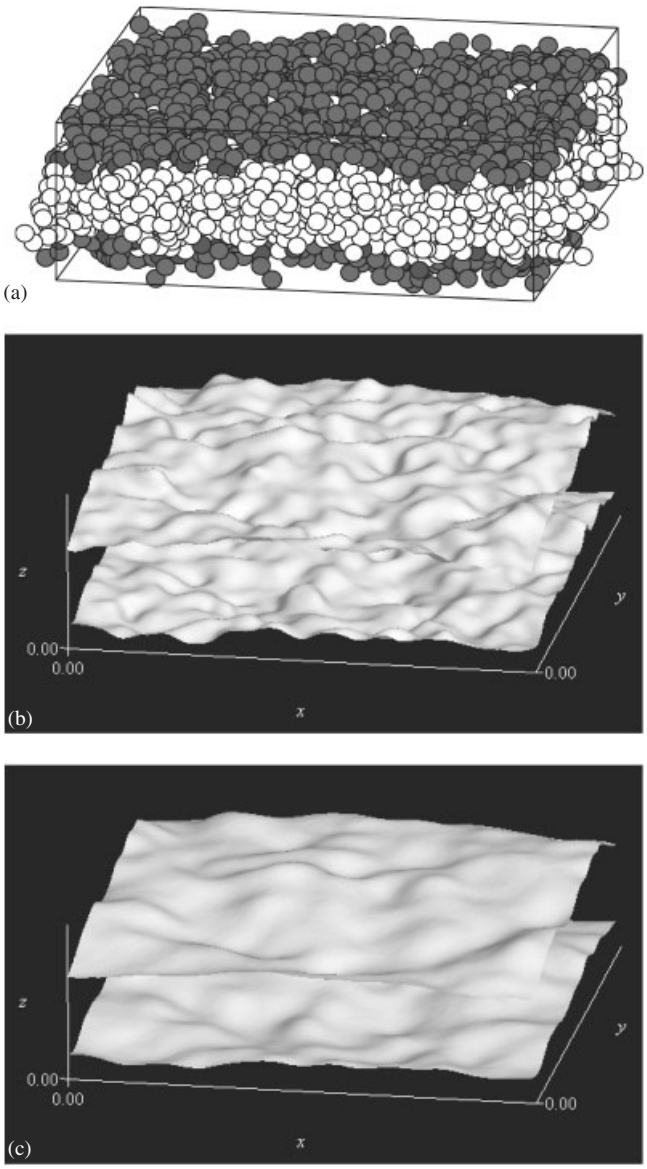

Figure 3. (a) A snapshot of the calculated lipid bilayer where $N_{\text{lip}} = 800$. The darker spheres represent the hydrophilic beads and the white spheres represent hydrophobic beads. The water beads are not shown. The corresponding lipid/water interfaces are shown in (b) and (c), where the parameter k is (b) 6 and (c) 9.

all spectrums seem to show an asymptotic behaviour to q^{-4} for small q, the bending rigidity is estimated more precisely with the larger system using Equation (3), because Equation (3) is valid in the continuum limit and the observable wavelength is limited in the smaller cells. In order to obtain the bending rigidity, we plotted $1/(S(q)q^2)$ *versus* q^2 in the case of $N_{\text{lip}} = 3200$ and $k = 7$,

DOI: 10.1002/fld

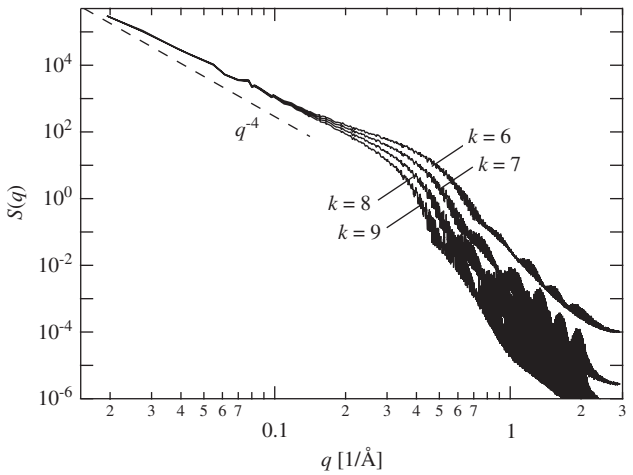

Figure 4. Spectral intensity of the thermal undulation as a function of wavenumber q for various values of k. The number of lipid molecules is 3200. The dashed line shows the q^{-4} behaviour.

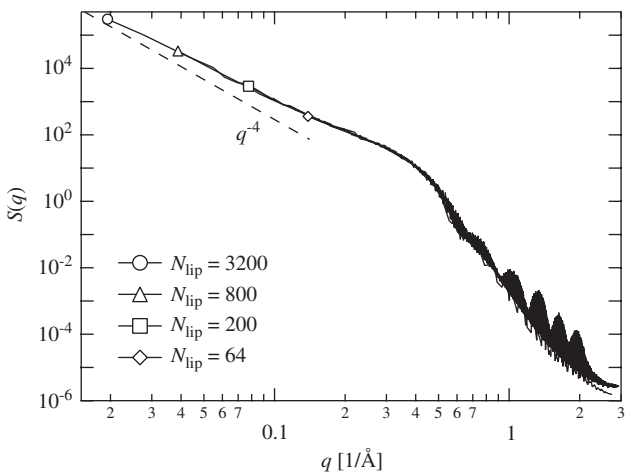

Figure 5. Spectral intensity of the thermal undulation as a function of wavenumber q with various cell sizes. The parameter k is 7 in all cases. On each line, the point at the smallest wavenumber is shown by a marker in order to clarify the observable range of the wavenumber with each simulation box. The dashed line shows the q^{-4} behaviour.

and fitted the first three points by straight line. This is a similar procedure to that reported in [6]. Supposing that the temperature is 300 K, the bending rigidity is calculated to be 5×10^{-20} J. This value is in good agreement with experiments ($5.6 \pm 0.6 \times 10^{-20}$ J for DMPC membrane [16]) and MD simulations (approximately 4×10^{-20} J [4, 15]).

DOI: 10.1002/fld

5. CONCLUSIONS

In this study, we investigated the thermal undulation of lipid bilayers by the DPD method. A recent definition of the interface was introduced into the lipid/water system in order to determine the interface between lipids and waters and subsequently the position of the bilayer. The undulation spectrums were investigated using the defined bilayer interfaces. The spectral intensity in large-q regions is affected by the smoothing parameter k, which defines the roughness of the interface. However, we found that the effects of this parameter k in small-q regions, where we can calculate the bending rigidity, is almost negligible. Moreover, the undulation spectrums show q^{-4} behaviour in the continuum limit and this coincides with the theoretical prediction. The effects of the size of the computational cell were also investigated. Although the observable range of the wavenumber depended on the cell size, all spectrums obtained with various cell sizes were in good agreement. This indicates that the observed spectrums are hardly affected by the constraint of the interface area. The calculated bending rigidity by the undulation spectrum showed good agreement with experiments and MD simulations in the literature.

ACKNOWLEDGEMENTS

This research was supported by Research Fellowships of the Japan Society for the Promotion of Science for Young Scientists, and by the 21st Century COE program, 'Mechanical System Innovation', by the Ministry of Education, Culture, Sports, Science and Technology, Japan. We wish to thank G. Kikugawa for many helpful discussions and P. L. Wilson for help in manuscript preparation.

REFERENCES

1. de Haas KH, Blom C, van den Ende D, Duits MHG, Mellema J. Deformation of giant lipid bilayer vesicles in shear flow. *Physical Review E* 1997; **56**:7132–7137.
2. Helfrich W. Steric interaction of fluid membranes in multilayer systems. *Zeitschrift für Naturforschung* 1978; **33a**:305–315.
3. Rädler JO, Feder TJ, Strey HH, Sackmann E. Fluctuation analysis of tension-controlled undulation forces between giant vesicles and solid substrates. *Physical Review E* 1995; **51**:4526–4536.
4. Lindahl E, Edholm O. Mesoscopic undulations and thickness fluctuations in lipid bilayers from molecular dynamics simulations. *Biophysical Journal* 2000; **79**:426–433.
5. Marrink SJ, Mark AE. Effect of undulations on surface tension in simulated bilayers. *The Journal of Physical Chemistry B* 2001; **105**:6122–6127.
6. Rekvig L, Hafskjold B, Smit B. Simulating the effect of surfactant structure on bending moduli of monolayers. *The Journal of Chemical Physics* 2004; **120**:4897–4905.
7. Kikugawa G, Takagi S, Matsumoto Y. A molecular dynamics study on liquid–vapor interface adsorbed by impurities. *Computers and Fluids* 2007; **36**:69–76.
8. Hoogerbrugge PJ, Koelman JMVA. Simulating microscopic hydrodynamic phenomena with dissipative particle dynamics. *Europhysics Letters* 1992; **19**:155–160.
9. Español P, Warren P. Statistical-mechanics of dissipative particle dynamics. *Europhysics Letters* 1995; **30**:191–196.
10. Groot RD, Rabone KL. Mesoscopic simulation of cell membrane damage, morphology change and rupture by nonionic surfactants. *Biophysical Journal* 2001; **81**:725–736.
11. Kranenburg M, Nicolas JP, Smit B. Comparison of mesoscopic phospholipid–water models. *Physical Chemistry Chemical Physics* 2004; **6**:4142–4151.
12. Venturoli M, Smit B. Simulating the self-assembly of model membranes. *PhysChemComm* 1999; **10**:45–49.
13. Sugii T, Takagi S, Matsumoto Y. A molecular-dynamics study of lipid bilayers: effects of the hydrocarbon chain length on permeability. *The Journal of Chemical Physics* 2005; **123**(18):184714.

DOI: 10.1002/fld

14. Safran SA. *Statistical Thermodynamics of Surfaces*, *Interfaces*, *and Membranes*. Addison-Wesley: Reading, MA, 1994.
15. Marrink SJ, de Vries AH, Mark AE. Coarse grained model for semiquantitative lipid simulations. *The Journal of Physical Chemistry B* 2004; **108**:750–760.
16. Evans E, Rawicz W. Entropy-driven tension and bending elasticity in condensed-fluid membranes. *Physical Review Letters* 1990; **64**:2094–2097.

DOI: 10.1002/fld