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Electronic Supplementary Information for

Large-scale dissipative particle dynamics simulations of self-assembly amphiphilic systems

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Contents

1	Methods and models		
	1.1	DPD formulation	1
	1.2	DPD model	2
		1.2.1 Amphiphilic molecule	2
		1.2.2Sickle hemoglobin (HbS) molecule	3
2	Simulation setup		
	2.1	Amphiphilic self-assembly in bulk solution	4
	2.2	Amphiphilic self-assembly under soft confinement	4
	2.3	Self-assembly of HbS molecules under soft confinement	5
3	Vide	Clips	7

1 Methods and models

1.1 DPD formulation

The DPD method is a particle-based mesoscopic simulation technique that allows modeling of fluids and soft matter. In a DPD simulation, a particle represents the center of mass in a cluster of atoms, and the position and momentum of the particle is updated in a continuous phase but spaced at discrete

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time steps. Particles i and j at positions r_i and r_j interact with each other via pairwise conservative, dissipative, and random forces, which are given by:

$$F_{ij}^{\mathsf{C}} = a_{ij}\omega(r_{ij})\mathbf{n}_{ij} \tag{1}$$

$$F_{ij}^{\mathbf{D}} = -\gamma \omega^2(r_{ij}) (\mathbf{n}_{ij} \cdot \mathbf{v}_{ij}) \mathbf{n}_{ij}$$
(2)

$$F_{ij}^{\mathbf{R}} = \sigma \omega(r_{ij}) \zeta_{ij} \Delta t^{-1/2} \mathbf{n}_{ij}$$
(3)

where $\mathbf{r}_{ij} = \mathbf{r}_i - \mathbf{r}_j$, $r_{ij} = |\mathbf{r}_{ij}|$, $\mathbf{n}_{ij} = \mathbf{r}_{ij}/r_{ij}$, and $\mathbf{v}_{ij} = \mathbf{v}_i - \mathbf{v}_j$. The coefficients a_{ij} , γ and σ define, respectively, the strength of conservative, dissipative and random forces. In DPD simulations, the values of γ and σ are equal to 4.5 and 3.0, respectively. In addition, ζ_{ij} is a random number with zero mean and unit variance. The weight function $\omega(r_{ij})$ is given by

$$\omega(r_{ij}) = \begin{cases} 1 - r_{ij}/r_c & r_{ij} < r_c \\ 0 & r_{ij} \ge r_c \end{cases}$$
(4)

where r_c is the cutoff radius, which gives the extent of the interaction range.

In the DPD method, the dissipative force and the random force act as heat sink and source respectively, and the combined effect of the two forces acts a thermostat, which conserves momentum and thus provides the correct description of hydrodynamics to the system. Also, a common choice of the soft repulsion for the conservative force permits us to use larger integration time steps than are usually allowed by the molecular dynamics (MD) simulation technique.

1.2 DPD model

1.2.1 Amphiphilic molecule

Within the mesoscopic approach, an amphiphilic molecule is represented by a coarse-grained model with hydrophilic particles (denoted by A) and hydrophobic particles (denoted by B) in our study. Specifically, in the present work, we focus on amphiphilies built from a hydrophilic head and two hydrophobic tails, i.e., an amphiphilic $A_3(B_2)_2$ block copolymer molecule is modeled, as shown in Figure S1. For the simulations of amphiphilic self-assembly under soft confinement, a large unlamellar vesicle (LUV) is first formed from amphiphilic $H_2(T_2)_2$ molecules, where the H particles are hydrophilic while the T particles are hydrophobic. We then place another type of amphiphilic molecule, $E_3(F_2)_2$, in the interior of the LUV membrane. Solvent particles (denoted by S) are included explicitly in the simulation.

By joining consecutively particles with a spring force, one can construct coarse-grained models of polymers [1]. The elastic contribution is expressed as,

$$F_{ij}^{S} = k_s (1 - r_{ij}/r_s)\hat{r}_{ij},$$
(5)

where $k_s = 500.0$ is the spring constant, and the equilibrium bond length between two consecutive particles, r_s , is set to $0.38r_c$.



Figure S1: Coarse-grained DPD models of amphiphilic molecules. Amphiphilic $A_3(B_2)_2$ and $E_3(F_2)_2$ molecules have the same structure and amphiphilic property but used for different simulation cases: For simulations of amphiphilic self-assembly in bulk solution, we employ the $A_3(B_2)_2$ model while for simulations of amphiphilic self-assembly in soft confinement, we use the $E_3(F_2)_2$ model. The amphiphilic $H_2(T_2)_2$ molecules are used to form the compliant LUV. In the figure, the A, E and H particles are hydrophilic while the B, F and T particles are hydropholic.

1.2.2 Sickle hemoglobin (HbS) molecule

In this study, a coarse-grained HbS model is constructed to match the physical description and structural properties of the HbS molecule. Specifically, one hemoglobin molecule is built with two hydrophilic particles (denoted by H_S) and two hydrophobic particles (denoted by T_S). The H_S and T_S particles represent the α - and β -subunits of HbS molecule. Cytosolic particles (denoted by C) are included explicitly to describe the crowding effect in the models. To control the HbS chain flexibility, an extra bond-bending force among three subsequent hydrophobic particles is added,

$$F^{\theta} = -\nabla V_{bend},\tag{6}$$

$$V_{bend} = \frac{1}{2}k_{\theta}(\theta - \theta_0)^2,\tag{7}$$

where k_{θ} and θ_0 are the bond-bending constant and the equilibrium angle, respectively.

According to Yang *et al.* [2], chain chirality is the reason for self-limited, self-assembled bundle sizes; thus, we need to also consider chiral interactions. We then include a tunable bending resistance interaction described by a bending finitely-extensible-nonlinear-elastic (FENE) force [3], which has the form

$$F_{bend} = k_{bend} \left[\frac{\theta - \theta_0}{1 - (\theta - \theta_0) / \Delta \theta_{max}} \right],\tag{8}$$

where $\Delta \theta_{max} = 0.3 \theta_0$ is the maximum allowable bending angle between these hydrophobic particles.

2 Simulation setup

In this study, the simulations are performed using the GPU-accelerated DPD $_{USER}MESO$ package [4]. The time integration of motion equations is done using a modified velocity–Verlet algorithm with $\lambda_{VV} = 0.5$ and time step $\Delta t = 0.01$ [1]. Here, we present details of the simulation setups for different cases.

2.1 Amphiphilic self-assembly in bulk solution

In the study, the simulation of amphiphilic self-assembly in bulk solution has been carried in a periodic boundary system containing amphiphilic molecules and solvents in several different system box of sizes ranged from $10r_c \times 10r_c \times 10r_c$ to $120r_c \times 120r_c \times 120r_c$. The particle number density is set at 5 and the concentration of amphiphilic molecules is 10.0 vol%. For example, in a small box of size $10r_c \times 10r_c \times 10r_c$, the total number of particles and amphiphilies used in the simulation is only 5 000 and 500, respectively. When we increase the the system box of size to $120r_c \times 120r_c \times 120r_c$, the total number of particles and amphiphilies in the simulation becomes 8 640 000 and 864 000, respectively.

In the amphiphilic self-assembly, interaction parameters for the conservative force between DPD particles are necessary for simulating amphiphilic systems. Based on previous computational studies [1, 5], the repulsive parameter related to the interaction between two like DPD particles is set at $a_{ii} = 15.00$ (i =A, B, S), causing the simulated compressibility of these DPD particles at room temperature to correspond to the experimental value. As suggested by Laradji and Kumar [6], the hydrophobic and hydrophilic interactions emerge from the relative interaction strengths a_{ij} . With this, the value of the parameter between two particles, one of which is hydrophilic and the other hydrophobic, is $a_{AB} = 120.0$, which is considered to be a sufficiently large value for the strong segregation [7]. To model the amphiphilic nature of amphiphilic molecules, the repulsion parameter between the hydrophilic A and solvent S particles is chosen to be the same the repulsion parameter between two alike particles. Likewise, the parameter related to the interaction between the hydrophobic B and solvent S particles is made larger than the repulsion parameter between two similar particles, which ensures that the hydrophobic block of amphiphilie is sufficiently shielded from the solvents. In the current study, we choose $a_{BS} = 120.0$. In summary, the repulsive interaction parameters between any two particles are given by,

$$a_{ij} = \begin{pmatrix} A & B & S \\ A & 15.0 & 120.0 & 15.0 \\ B & 120.0 & 15.0 & 120.0 \\ S & 15.0 & 120.0 & 15.0 \end{pmatrix}.$$
(9)

These amphiphilies and HbS molecules can self-assemble into complex microstructures including spheres, micelles and vesicles within these parameters.

2.2 Amphiphilic self-assembly under soft confinement

Simulations of the amphiphilic self-assembly under soft confinement have been carried in a compliant large unilammelar vesicle (LUV) containing a total of 55 000 solvent particles and 1120 amphiphilic molecules. The bilayer membrane of the LUV is formed by 67 824 DPD particles. The total number of particles used in the simulation is 625 000 at a particle density of 5 in a box of size $50r_c \times 50r_c \times$ $50r_c$ with periodic boundary conditions. The hydrophobic and hydrophilic interactions emerge from the



Figure S2: Sequential snapshots of spontaneous formation of toroidal vesicle from amphiphilic molecules in a compliant LUV at $a_{\text{HE}} = a_{\text{TF}} = 240.0$. The self-assembled amphiphilic vesicles and LUV are shown as green and red/white colors, respectively, and only half of the LUV is shown for clarity.



Figure S3: Transient change in the interaction energy associated with the amphiphilic molecules for the toroidal vesicle formation process in a compliant LUV at $a_{\text{HE}} = a_{\text{TF}} = 240.0$.

relative interaction strengths a_{ij} . Regarding the interaction parameters between the hydrophilic and hydrophobic parts of the amphiphilic molecules, we set $a_{HF} = a_{TE} = 240.0$ for the hydrophobic interaction. With this, the parameters chosen for the simulations are,

$$a_{ij} = \begin{pmatrix} H & T & E & F & S \\ H & 15.0 & 120.0 & a_{HE} & 240.0 & 15.0 \\ T & 120.0 & 15.0 & 240.0 & a_{TF} & 120.0 \\ E & a_{HE} & 240.0 & 15.0 & 120.0 & 15.0 \\ F & 240.0 & a_{TF} & 120.0 & 15.0 & 120.0 \\ S & 15.0 & 120.0 & 15.0 & 120.0 & 15.0 \end{pmatrix}.$$
 (10)

After these parameters are selected, we study the amphiphilic self-assembly under soft confinement at three simulation cases with different interaction parameters: (1) $a_{\text{HE}} = a_{\text{TF}} = 15.0$ such that the two types of amphiphilies can coexist in the simulation system; (2) $a_{\text{HE}} = a_{\text{TF}} = 50.0$ such that the two types of amphiphilies are in weak segregation regime; (3) $a_{\text{HE}} = a_{\text{TF}} = 240.0$ such that the two types of amphiphilies are put well outside the weak segregation limit, and fall into strong segregation regime.

These amphiphilies can self-assemble into complex microstructures including straight cylindrical vesicle (the shape of vesicle has a straight cylindrical topology), U-like vesicle (the shape of vesicle has a U-like topology) and toroidal vesicle (the shape of vesicle has a toroidal topology). Figure S2 together with the video clips in the Supplementary Information provide typical dynamic formation processes of the self-assembled vesicles.

2.3 Self-assembly of HbS molecules under soft confinement

Simulations of the self-assembly of HbS molecules under soft confinement have been carried in a compliant LUV containing a total of 450 000 solvent particles and 2090 HbS molecules. The bilayer membrane of the LUV is formed by 620 000 DPD particles. The total number of particles used in the simulation is 5 000 000 at a particle density of 5 in a box of size $100r_c \times 100r_c \times 100r_c$ with periodic

boundary conditions. The repulsive interaction parameters between any two particles are given by,

$$a_{ij} = \begin{pmatrix} H & T & H_{\rm S} & T_{\rm S} & C \\ H & 15.0 & 120.0 & 240.0 & 240.0 & 15.0 \\ T & 120.0 & 15.0 & 240.0 & 240.0 & 120.0 \\ H_{\rm S} & 240.0 & 240.0 & 15.0 & 120.0 & 7.5 \\ T_{\rm S} & 240.0 & 240.0 & 120.0 & 15.0 & 120.0 \\ C & 15.0 & 120.0 & 7.5 & 120.0 & 15.0 \end{pmatrix}.$$
 (11)

To simulate the self-assembly of HbS with chain chirality, the connections between two consecutive hydrophobic particles and one hydrophilic particle are constrained to a certain angle, $\theta_{H_ST_ST_S}$. Specifically, two different types of bond-bending interactions are included to control the chirality of HbS chain, one of which is exerted between one hydrophilic particle and two consecutive hydrophobic particles in HbS strand. They are applied in both directions with an equilibrium angle of $\theta_{H_ST_ST_S} \simeq 90^\circ$; the other is exerted between one hydrophilic particle and two consecutive hydrophobic particles in two different HbS strands with $\theta_{H_ST_ST_S}$ ranging from $120^\circ \sim 150^\circ$. Moreover, an additional FENE force, which is applied among three hydrophobic particles from two different HbS chains when the distance between their ends is less than a target distance, is also included to strengthen the bending rigidity of self-assembled HbS fibers.



Figure S4: (Left) Confinement effect on the HbS self-assembly. (Right) Functional dependence of ESF on ASF.

Following our previous study on HbS self-assembly under hard confinement [8], we employ the asphericity shape factor (ASF) and elliptical shape factor (ESF) to quantify the RBC membrane distortion. The ASF and ESF measure the deviation of the RBC from a spherical shape and the degree of the distortion on the two-dimensional plane, respectively. From the DPD simulations, we can compute

$$ASF = \frac{(R_1 - R_2)^2 + (R_2 - R_3)^2 + (R_3 - R_1)^2}{2(R_1 + R_2 + R_3)^2},$$
(12)

$$\mathbf{ESF} = R_1/R_2,\tag{13}$$

Figure S4(Right) shows functional dependence of ESF on ASF.

3 Video Clips

1. Video clip S1 illustrates the dynamic pathway in the formation of U-like vesicle from amphiphilic molecules under soft confinement at $a_{\text{HE}} = a_{\text{TF}} = 15.0$.

2. Video clip S2 illustrates the dynamic pathway in the formation of toroidal vesicle from amphiphilic molecules under soft confinement at $a_{\text{HE}} = a_{\text{TF}} = 50.0$.

3. Video clip S3 illustrates the dynamic pathway in the formation of toroidal vesicle from amphiphilic molecules under soft confinement at $a_{\text{HE}} = a_{\text{TF}} = 240.0$.

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