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Self-assembly Modeling of Biological Membranes by Dissipative Particle Dynamics Method

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Abstract
In this study, binary fluids consisting of ‘‘solvent’’ and ‘‘surfactant’’ molecules are studied as simplified model systems. Solutions of lipids in water are characterized by a wide range of length scales. Molecular Dynamics (MD) technique is used to study equilibrium and transport properties of biological membranes. However, classical molecular dynamics can deal with hundreds of thousands of atoms over a timescale of the order of 100 ns. For larger time and length scales the MD simulation becomes extremely expensive or even impossible. Recently, Dissipative Particle Dynamics (DPD) has been introduced as a mesoscopic simulation method that enables us to apply length and time scales that are significantly larger (several order of magnitude) than the one used in conventional MD simulations. The aim of this study is to simulate the self-assembly of the surfactant molecules into bilayer membranes by the DPD method. Our simulations verify that by using a periodic boundary condition and a fixed number of surfactants per area, a bilayer is formed which has a specific value of surface tension. Moreover, the surfactant consists of a hydrophilic head group and a hydrophobic tail group which was modeled by chains of particles interconnected by a harmonic bond potential. In this study the bending stiffness of these chains were incorporated. We were able to give to our surfactants a specific chemical structure and therefore, our membrane simulation result is closer to the physics. This makes our work quite distinct from most of previous studies. Eventually the effect of changes in the chain length and stiffness of the surfactants on the properties of the modeled membranes were studied. We observed that depending on the location of stiffness applied, the stiffness of chains have significant effect on the surfactant properties.

Keywords: Dpd, Biological Membrane, Lipid Bilayer

Introduction

Lipid bilayer membranes surround the living cells, protecting their interior from the outside world. They are much more than a static structural component, however, in that their composition and dynamics influence the membrane-bound proteins, and contribute to the remarkable material properties of cells such as red blood cells [1]. The dependence of the material properties of lipid bilayer membranes on the structure of their component molecules is biologically and commercially important. The plasma membrane that surrounds all living cells must be strong enough to prevent the permeation of unwanted ions and molecules, but also flexible enough so that, for example, red blood cells can squeeze through capillaries whose width is only one-third of the cell’s diameter [1]. Commercially, artificial lipid vesicles are potential vehicles for drug delivery systems [2]. On the other hand, the role of the lateral pressure profile in biological membranes has been the topic of discussions in the literature in the context of the structure and function of membrane proteins [3] or in the mechanism of anesthesia [4]. An important aspect in these discussions is that there are no experimental methods to determine a pressure profile. At present, we have to rely on simulations or theory [4]. Dynamic processes taking place within a membrane can involve cooperative changes over distances large compared to the molecular size, and occur on timescales much longer than molecular vibrational periods. By using molecular simulation it is, in principle, possible to study an all atom model of a membrane. Several theoretical approaches have been applied to this problem. Lattice-based Monte Carlo (MC) simulations have been used to study the development of microstructures in surfactant–water systems [5], the conformational chain properties of lipids within a bilayer composed of long or short chain molecules, and a mixture of both [6]. Several research groups have applied mean-field techniques to lipid bilayers [7], exploring the dependence of membrane stability on key lipid properties such as the area per head group [8], hydrocarbon tail length [6], and the variation of membrane bending stiffness with amphiphile tail length and head group area. Charged lipids and their interactions with ions near the solvent–membrane interface have also been investigated using a self-consistent field theory. Both these approaches have certain limitations. Lattice based simulations lack the full Galilean invariance of a fluid, while mean-field theories ignore fluctuations within a system. Furthermore, atomistic Molecular Dynamics (MD) simulations are restricted to small system sizes and short times [9]. Therefore, coarse-grained MD simulations have been used to extract the area compression modulus and bending modulus of single-component lipid bilayers and monolayers, and their lateral stress distribution [10]. Because even coarse-grained MD requires large

amounts of computer time to simulate sizable membrane patches, a new particle-based, mesoscopic simulation technique developed in the 1990s has recently been applied to the problem of simulating large membrane patches. Dissipative particle dynamics was introduced in 1992 by Hoogerbrugge and Koelman, who applied it to measuring the hydrodynamic drag on a cylinder in a moving fluid [11]. The algorithm was modified by Groot and Warren to study the phase separation of immiscible polymeric fluids [12].

In this work, we apply this method to simulate the self-assembly of a model membrane. Furthermore, we use a potential function that is much 'softer' than the Lennard-Jones potential conventionally used in MD simulations. By making these choices, we are able to use a time step that is significantly larger than the one used in conventional molecular dynamics simulations. Goetz and Lipowsky [10] have also shown that the use of periodic boundary conditions and a fixed number of surfactants per area leads to a bilayer that has a given surface tension. Biological membranes, however, have a state which is essentially tensionless. To ensure such a tensionless state, we performed several simulations to determine the area per bilayer lipid that gives a state of zero tension. Here, we show that we can mimic the experimental situation by a constant surface tension simulation [13]. We perform several simulations to locate the area of zero tension. We also present some results in which we study the effect of the chain length and stiffness of our model lipids on the properties of the bilayer.

SIMULATION METHODOLOGY

The elementary units in a DPD simulation are fluid elements or *soft beads*. A soft bead represents a volume of fluid that is large on a molecular scale, and hence contains at least several molecules or molecular groups, but still macroscopically small. Beads interact via effective forces chosen so as to reproduce the hydrodynamic behavior of the fluid without reference to its molecular structure. DPD differs in this respect from MD simulations, in which the forces are chosen to model the intermolecular interactions of a system as accurately as possible. Forces in DPD are pair wise additive, conserve momentum, have no hard core, and are short-ranged, where the range of the force is the size of the soft beads. The use of momentum-conserving forces also distinguishes DPD from Brownian Dynamics, in which each particle receives a random push independently of all other particles resulting in purely diffusive motion. All beads have the same mass, m_0, and radius, r_0, and these set the mass and length scales in the simulation. A time scale must be extracted from the dynamics of the relevant processes in the simulated fluid, such as the diffusion of a micelle's center of mass, or from the in-plane viscosity of a bilayer membrane.

In DPD the forces are composed of (soft) repulsion conservative forces, pair wise dissipation forces, and pair wise random forces. The force acting on a particle i is then given by:

$$f_i = \sum_{j \neq i} (F_{ij}^C + F_{ij}^D + F_{ij}^R) \tag{1}$$

where the sum runs over all other particles within a certain cut off radius r_c . For our simulations we have applied the soft-core repulsive force that has been used in many other DPD simulations [12]:

$$F_{ij}^C = \begin{cases} a_{ij}(1 - r_{ij}/r_c)\hat{r}_{ij} & (r_{ij} < r_c) \\ 0 & (r_{ij} \geq r_c) \end{cases} \tag{2}$$

where a_{ij} is a maximum repulsion between particle *i* and particle *j*, $r_{ij} = r_{ij} - r_i$ is the distance vector between particles i and j and $r_{ij} = |r_{ij}|$. According to Español and Warren [14] the DPD technique samples a Boltzmann distribution with a potential related to the conservative force:

$$F^C = -\nabla U \tag{3}$$

The remaining two forces are a dissipative or drag force and a random force. They are given by:

$$\begin{aligned} F_{ij}^D &= -\eta \omega^D(r_{ij})(\hat{r}_{ij}.v_{ij})\hat{r}_{ij} \quad , \\ F_{ij}^R &= \sigma \omega^R(r_{ij})\theta_{ij}\hat{r}_{ij} \end{aligned} \tag{4}$$

where ω^D and ω^R are *r*-dependent weight functions vanishing for $r > r_c$, $v_{ij} = v_j - v_i$ and $\theta_{ij}(t)$ is a randomly fluctuating variable with Gaussian statistics: $\langle \theta_{ij}(t) \rangle = 0$ and $\langle \theta_{ij}(t)\theta_{kl}(t') \rangle = (\delta_{ik}\delta_{jl} + \delta_{il}\delta_{jk})\delta(t - t')$ Español and Warren [14] showed that one of the two weight functions appearing in Eq.(4) can be chosen arbitrarily and then this choice fixes the other weight function. There is also a relation between the amplitudes and $k_B T$. In summary:

$$\omega^D(r) = [\omega^R(r)]^2, \quad \sigma^2 = 2\eta k_B T$$

This is called fluctuation–dissipation relation. As a simple choice we take:

$$\omega^D(r) = [\omega^R(r)]^2 = \begin{cases} (1 - r)^2 & (r < 1) \\ 0 & (r \geq 1) \end{cases} \tag{5}$$

We choose the particle mass, the temperature, and interaction range as units of mass, energy, and length. Hence $m = kT = r_c = 1$, and the simulated time is expressed in the natural unit of time

$$\tau = r_c \sqrt{m / kT} \tag{6}$$

The DPD method, in general, has been shown to produce a correct (*N*, *V*, *T*) ensemble if the fluctuation–dissipation relation is satisfied [12,14]. At every time step, the set of positions and velocities, $\{r_i, v_i\}$ is updated using a modified version of the velocity–Verlet algorithm:

$$\begin{aligned} r_i(t+\delta t) &= r_i(t) + \delta t v_i(t) + 1/2\delta t^2 f_i(t), \\ \tilde{v}_i(t+\lambda\delta t) &= \tilde{v}_i(t) + \lambda\delta t f_i(t), \\ f_i(t+\delta t) &= f_i(r_i(t+\delta t), \tilde{v}_i(t+\lambda\delta t)), \\ v_i(t+\delta t) &= v_i(t) + 1/2\delta t(f_i(t) + f_i(t+\delta t)). \end{aligned} \tag{7}$$

The force is updated once per iteration. Because the force depends on the velocity, the velocity in the next time step has to be estimated by a predictor method. This is done in the second step of our algorithm. The velocity is then corrected in the last step. If the parameter λ is set at λ=0.5, this scheme reduces to velocity–Verlet algorithm [15]. However, here we use λ=0.65, where we find a very accurate temperature control even at the time steps $dt = 0.06\tau$.

In the simulations, self-assembly of a bilayer is simulated in a periodic cell, where the bilayer is oriented perpendicular for example to the *x*-axis. Therefore, the local density of each component is measured in thin slabs perpendicular to the *x*-axis, and the stress tensor is averaged locally and over the whole system. The stress tensor leads to the surface tension via

$$\begin{aligned} \gamma &= \int p_{xx}(x) - 1/2\left(p_{yy}(x) + p_{zz}(x)\right)dx \\ &= A^{-1}\sum_{i<j}\left(F_{ij,x}x_{ij} - 1/2\left(F_{ij,y}y_{ij} + F_{ij,z}z_{ij}\right)\right) \end{aligned} \tag{8}$$

where *A* is the area of the *yz*-plane, and F_{ij} is the total conservative force between particles i and j. In our work we must measure γ and control it to provide a tensionless membrane.

The system that is simulated is composed of water and some special polymers. The structure of this kind of single chain polymers contains one chain of hydrocarbons connected to a phosphate group. Then In our simulations, we distinguish three types of particles that model water (w) and the hydrophilic head (h) and hydrophobic tail (t) segments of the surfactants. The molecule is shown in Fig. 1, together with its mapping on the coarse-grained DPD model.

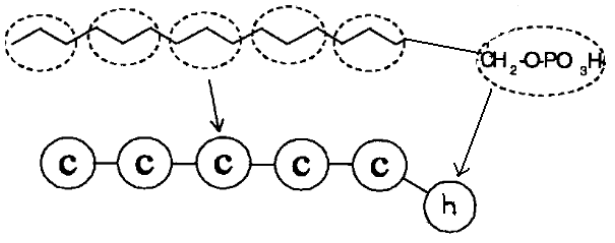

Figure 1 The simulated single chain and its mapping on the DPD model. Each bead represents roughly the same liquid volume.

In addition, the surfactant molecules are constructed by connecting the h and t atoms *via* harmonic springs:

$$U_{spring}(r_{i,i+1}) = \frac{k_r}{2}r_{i,i+1}^2 \tag{9}$$

with $k_r = 10$. This constant was chosen in order to have a bilayer with less surface tension. A surfactant molecule consists of a linear chain of h and t units. For example, a linear chain with one head group and seven tail units is denoted by ht_7. The effect of chain length on the bilayer's properties can be studied by changing the number of tail units.

Unsaturated carbon bonds can change the stiffness of a membrane lipid. We model the stiffness of the chain by introducing a bond bending potential:

$$\begin{aligned} U_{bend}(r_{i-1,i}, r_{i+1,i}) &= \frac{k_\theta}{2}(\theta - \theta_0)^2 \\ &= \frac{k_\theta}{2}\left(\frac{r_{i-1,i}.r_{i+1,i}}{|r_{i-1,i}||r_{i+1,i}|} - \theta_0\right)^2 \end{aligned} \tag{10}$$

where θ_0 is the angle between two consecutive bonds. We have used k_θ=0.1 and $\theta_0 = \pi$. The presence of the bond bending potential is shown by a capital T. For example, ht_2Tt indicates a chain of 5 beads in which the last three atoms of the tail have the bond bending potential. It is important to note that both the spring and bond-bending potential are part of the conservative forces for the DPD program.

All simulations have been performed at $k_BT = 1$, with 200 surfactants. C_s concentration of the surfactant, is defined as:

$$C_s = \frac{N_h + N_t}{N_w + N_h + N_t}$$

and was set in average equal to 0.49. N_h, N_t and N_w are the number of heads, tails and water particles, respectively. The volume of the box was chosen to have a density of about 3 (at such a density and concentration of surfactants the bilayer is formed).

To construct a mesoscopic model, we first need to determine the volume of the simulation beads, and hence determine the length scale. Applying coarse-graining, three carbon atoms are taken together and grouped into one bead. This mapping is justified by studying the partial volumes of $(CH_2)_3$ and water molecules. Because the volume of a water molecule is 30 $A^{\circ 3}$ and the water beads are to represent the same volume of 90 $A^{\circ 3}$, the water beads (w) must represent three water molecules, whose volume also adds up to 90

$A^{\circ 3}$. Hence each (w or c-) bead represents a liquid volume of 90 $A^{\circ 3}$.Because the simulated bead density is $\rho r_c^3 = 3$, a cube of r_c^3 contains three beads and therefore corresponds to a volume of 270 $A^{\circ 3}$. Thus, we find the physical size of the interaction radius,

$$r_c = \sqrt[3]{270}A^{\circ} = 6.4633A^{\circ} \tag{11}$$

Let, in general, a bead correspond to N_m water molecules. The number N_m can be viewed as a real-space renormalization factor. The case discussed above thus corresponds to the choice $N_m = 3$. Hence, a cube of volume r_c^3 represents ρN_m water molecules, where ρ is the number of DPD beads per cubic r_c. Because the physical volume of this cube is equal to $30\rho N_m A^{\circ 3}$, the length scale r_c follows as

$$r_c = 3.107\left(\rho N_m\right)^{1/3}[A^{\circ}] \tag{12}$$

For water, mass of each DPD particle, which is the reference mass, is given by,

$$m_{ref} = m_{DPD} = N_m \times m_{water} \tag{13}$$

where m_{water} is the mass of each water molecule, which is calculated to be $3.9\times10^{-26}\ kg$.

The reference time is the time taken by DPD particles to move a reference length r_c. It is defined as the ratio of r_c to the reference velocity of the system and is given by,

$$t_{ref} = t_{DPD} = \frac{r_c}{u_{ref}} \tag{14}$$

Many researchers have taken thermal velocity, $\sqrt{\frac{k_B T}{m_{DPD}}}$ as the reference velocity [14,16,17].

It is assumed that the repulsion parameter between equal beads is fixed at the value of a = 78, and that the bead density is fixed at $\rho = 3$. Following Groot and Warren [12], a modified velocity–Verlet algorithm is used that allows for time steps of $dt = 0.06\tau$ at this repulsion parameter.

To find in practice the interaction parameters for this model, we need to match the compressibility and solubility. It was previously proposed that the following relation should hold [12]:

$$\frac{1}{kT}\left(\frac{\partial p}{\partial \rho}\right)_{simulation} = \frac{1}{kT}\left(\frac{\partial p}{\partial n}\right)_{experiment} \tag{15}$$

where ρ is the bead density in the simulation, and n is the density of, e.g., water molecules in liquid water. However, this relation only holds if one DPD bead corresponds to one water molecule. In general, the system should satisfy

$$\frac{1}{kT}\left(\frac{\partial p}{\partial \rho}\right)_{simulation} = \frac{1}{kT}\left(\frac{\partial n}{\partial \rho}\right)\left(\frac{\partial p}{\partial n}\right)_{experiment} = \frac{N_m}{kT}\left(\frac{\partial p}{\partial n}\right)_{experiment} \tag{16}$$

where N_m is the number of water molecules per DPD bead. In the previous section, N_m has been chosen as $N_m = 3$. For this value, the compressibility of water at room temperature is matched if the repulsion parameter in Eq.2 is determined at [12]:

$$a_{ii} = 78, \tag{17}$$

where a_{ii} is the repulsion parameter between particles of the same type. Note that it is taken the same for all liquid components, because we actually simulate equal liquid volumes for all components.

The next observable to match is the mutual solubility. In polymer chemistry, this is usually expressed by specifying the Flory–Huggins χ-parameters. This parameter represents the excess free energy of mixing in the Flory–Huggins model. This is a cell model, where every cell is filled by a fraction ϕ of A molecules and by a fraction 1-ϕ of B molecules. Hence, the lattice is completely filled. If A is a polymer that occupies N_A cells and B is a solvent that occupies N_B cells, then the free energy per cell (disregarding constants and terms linear in ϕ) can be written as

$$\frac{f_v}{kT} = \frac{\phi \ln \phi}{N_A} + \frac{(1-\phi)\ln(1-\phi)}{N_B} + \chi\phi(1-\phi). \tag{18}$$

Eventually the Flory–Huggins χ-parameters can be written in this form:

$$\chi = (0.231 \pm 0.001)\Delta a \tag{19}$$

where $\Delta a = a_{AB} - a_{AA}$ is the excess repulsion [18]. The pertinent χ-parameters are determined by matching relevant thermodynamic data to the same Flory–Huggins model. According to Groot and Rabone[18]:

$$\chi = \begin{pmatrix} & \langle w \rangle & \langle t \rangle & \langle h \rangle \\ \langle w \rangle & 0 & 6 & -0.5 \\ \langle t \rangle & 6 & 0 & 6 \\ \langle h \rangle & -0.5 & 6 & 2 \end{pmatrix},$$

$$\chi = \begin{pmatrix} & \langle w \rangle & \langle t \rangle & \langle h \rangle \\ \langle w \rangle & 78 & 104 & 75.8 \\ \langle t \rangle & 104 & 78 & 104 \\ \langle h \rangle & 75.8 & 104 & 86.7 \end{pmatrix} \qquad (20)$$

Following Groot and Warren [12], we use the fixed noise amplitude $\sigma = 3$. This particular thermostat is special in that it conserves (angular) momentum, which leads to a correct description of hydrodynamics.

Results and Discussion

We start our simulation at the beginning with a random distribution of surfactants (see Fig. 2). The bilayer is formed after 34000 time steps and the assembly attains its final configuration by 50000 time steps as shown in Fig. 3.

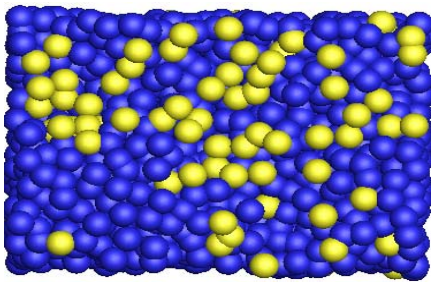

Figure 2. The initial configuration of the simulation of the self-assembly of a bilayer.

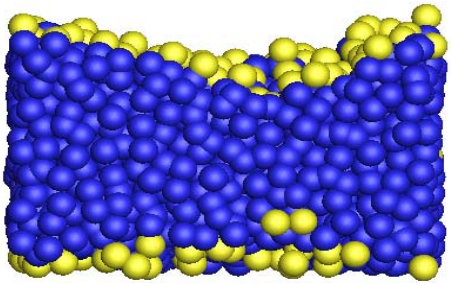

Figure 3. A bilayer starting from a random distribution of surfactants (hTt_9).

The density profiles for this bilayer which its surfactants consist of 10 beads and the bending potential is applied near their heads are presented in Fig. 4. Although the surfactant structure and the simulation parameters are different from those used in [18,19], the obtained results follow their work qualitatively.

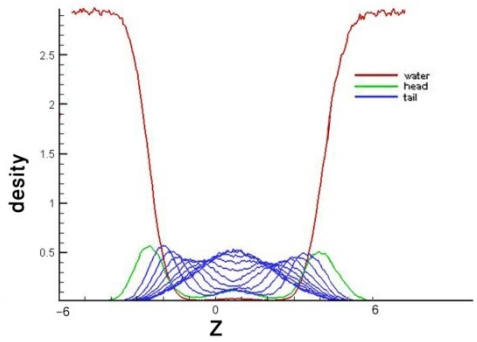

Figure 4. Density as functions of the distance from the middle of the bilayer z for 200 hTt_9 surfactants

A very important criterion for validation of simulating membranes is area per surfactant [18]. Experimental values for the area per head group of DPPC are reported to be 70 $A^{\circ 2}$ [20], or to vary from 57.6 to70.9 $A^{\circ 2}$ [21]. For DOPC, the value of 60 $A^{\circ 2}$ is reported [22, 23], and finally this parameter is reported to be 65.5 $A^{\circ 2}$ for simulations of POPC [24]. Our simulation estimates an averaged area of 64.7 $A^{\circ 2}$ per surfactant. This value is within the range observed in the experimental data. The area per surfactant was calculated by dividing the area by half of the number of surfactants, for a bilayer.

The effect of the tail length and stiffness on the average area per surfactant is shown in Fig. 5.

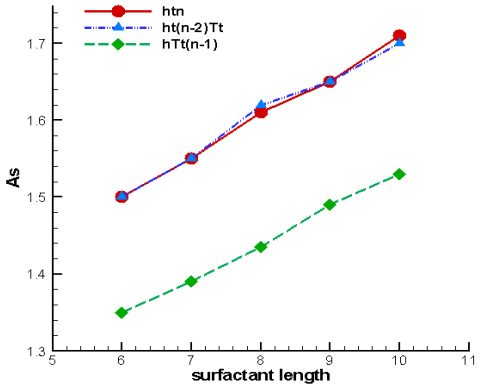

Figure 5. Effect of the surfactant structure on the area per surfactant.

It is obvious that when the tail length increases, the area per surfactant also increases. The behavior predicted by this simulation was already reported by other researcher [19]. A significant difference between our simulation and [19] is the structure of membrane. In our study, simulation is based on a special polymer with a specific chemistry structure.

In Fig. 5 we also compare the effect of the stiffness on the area per surfactant. This figure shows that the location of the bond bending potential affects the properties of membrane. When it is located at the end of the tail, the area per surfactant is approximately similar

to the flexible chains. In contrast, when the potential is near the head, the area becomes smaller. Similar conclusion was reported by Venturoli [19]. This means that the stiffness close to the head groups gives a stronger ordering of the molecules and as a result of the mutual interactions a more compact structure is formed.
It is interesting to compare these results with the theoretical calculations of Cantor [25] on a lattice model. To ensure similar length scales in all three studies, we have scaled the areas to give the same area per surfactant for chains with length 7. Fig. 6 shows that all studies predict that the area increases linearly with chain length and are in a very good agreement with each other.

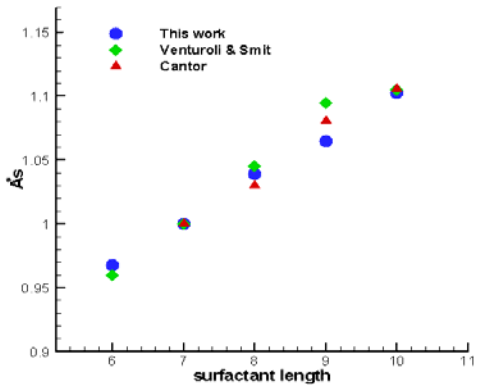

Figure 6. Comparison in our simulation results with the calculation of Cantor and venturoli's work, for completely flexible chains

Conclusions

In this work, we have shown that using DPD method, we can simulate the self-assembly of bilayers. We were also able to give a specific chemical structure to the membrane and this makes our membrane simulation more physical. In this regard, our work is quite distinct from previous studies. Then, we validated our results with previous simulations and theoretical works. We have also studied how changes in the structure of the surfactants affect the physical properties of the bilayer. An interesting conclusion is that the stiffness has a large effect on the properties, provided that this stiffness is located close to the head group of the surfactants.

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