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Analysis of nanoprobe penetration through a lipid bilayer

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ABSTRACT

With the rapid development of nanotechnology and biotechnology, nanoscale structures are increasingly used in cellular biology. However, the interface between artificial materials and a biological membrane is not well understood, and the harm caused by the interaction is poorly controlled. Here, we utilize the dissipative particle dynamics simulation method to study the interface when a nanoscale probe penetrates the cell membrane, and propose that an appropriate surface architecture can reduce the harm experienced by a cell membrane. The simulation shows that a hydrophilic probe generates a hydrophilic hole around the probe while a hydrophobic probe leads to a 'T-junction' state as some lipid molecules move toward the two ends of the probe. Both types of probe significantly disrupt lipid bilayer organization as reflected by the large variations in free energy associated with penetration of the membrane. Considering the hydrophilic/hydrophobic nature of the lipid bilayer, three other hydrophilic/hydrophobic patterns – band pattern, axial pattern and random pattern – are discussed to reduce the damage to the lipid membrane. Both the free energy analysis and simulation studies show that the axial pattern and the random pattern can both minimize the variations in free energy with correspondingly smaller adverse effects on membrane function. These results suggest that the axial pattern or random pattern nanoprobe generates a mild interaction with the biological membrane, which should be considered when designing nondestructive nanoscale structures.

1. Introduction

Cell membranes consisting of a lipid bilayer are crucial for living cells providing protection of their interior from the surrounding environment [1]. With rapid advances in biotechnology such as gene injection, in-vitro-fertilization, and drug development, various biological effectors (small molecules, DNAs, RNAs, peptides, and proteins) are required to pass through a cell membrane. One of the promising methods for delivering biological effectors into a cell is to use nanoscale structures (ranging from several to hundreds of nanometers). For example, nanoparticles (<10 nm) [2–6], carbon nanotubes (1 ~ 5 nm) [7–9], and nanowires (~100 nm) [10,11] are considered to be effective methods for introducing multiple types of reagents into cells in high throughput. During delivery, some hydrophilic/hydrophobic molecules adhere to the nanostructures [2,12,13]. However, the lipid bilayer is a thin polar membrane made of two lipid leaflets with hydrophilic phosphate 'heads' on the surface and hydrophobic 'tails' segregated in the core. Because of this 'hydrophilic–hydrophobic–hydrophilic' structure, cell membranes present a formidable barrier to most polar molecules. This means an interface between the artificial materials and the lipid bilayer must be created and surfaces of nanostructures will progressively disrupt the organization of the biomolecules when they come into contact with cell membrane [14–19]. Though, numerous experimental platforms employing nanoscale structures have been constructed to deliver various molecules into different types of cells [2,5,11,20–23]. However, when building such platforms, researchers usually focus on their geometrical size [24], shape [25] or the biological effectors [2] coated on them, and typically pay little attention to the interfaces between the artificial materials and the biological bilayer or the damage experienced by the membrane. In reality, different interfaces will lead to different degrees of bilayer disruption [16,19,25] some causing cell death [22,26]. It is widely accepted that in many cases it is the coated molecules that are interacting with biological system [27–29]. Thus, we propose that an appropriate surface architecture can reduce the harm experienced by a cell membrane and thereby benefit the experimental results. In this paper, we consider a nanoscale probe penetrating the lipid bilayer as an example to study these interactions, with the hope of identifying a surface pattern that is minimally disruptive to cell membranes.

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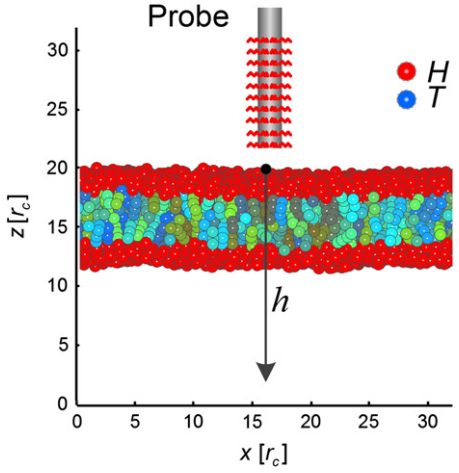

Fig. 1. The simulation model and its initial state, section view with $y = 16r_c$. The tail particles in different chain lipid molecules are colored differently so that they can be distinguished, and for clarity, the water particles are not shown. The probe is $2r_c$ above the membrane at the initial state, thus there is no interaction between the probe and the membrane.

2. Methods

2.1. Dissipative particle dynamics

To analyze the interfaces between the probe and the lipid bilayer, we use dissipative particle dynamics (DPD) simulation, a coarse grained method widely used to study bio-membrane systems [25,30–33]. In DPD, there are three types of interactive forces: a conservative force, a dissipative force and a random force. The three forces work together to describe the motion of the simulated particles. The conservative force between two particles i and j is

$$\mathrm{F}_{ij}^{C} = a_{ij}\left(1-r_{ij}/r_c\right)\hat{\mathrm{r}}_{ij} \qquad r_{ij}\le r_c \tag{1}$$

where r_{ij} is the distance between particles i and j, $\hat{\mathrm{r}}_{ij}$ is the unit vector connecting particle j to i, and a_{ij} is the conservative force parameter between particles i and j, representing the maximum repulsive force between two types of particles, which differs for different types of particles. The value of a_{ij} for water interacting with another type of particle defines the hydrophilic/hydrophobic character of this type of particle: the larger a_{ij}, the more hydrophobic is the particle. r_c is the cut-off radius; if $r_{ij} > r_c$, the conservative force is zero. r_c is also the length unit used in the simulations [34].

The dissipative force between two particles is linear in terms of their relative momentum and is described as

$$\mathrm{F}_{ij}^{D} = \gamma_{ij}\omega_{ij}^{D}\left(\hat{\mathrm{r}}_{ij}\cdot\mathrm{v}_{ij}\right)\hat{\mathrm{r}}_{ij} \qquad r_{ij}\le r_c \tag{2}$$

where γ_{ij} is the dissipative force parameter between particles i and j, and $\mathrm{v}_{ij} = \mathrm{v}_i - \mathrm{v}_j$ is their relative velocity. ω_{ij}^{D} is the dissipative r-dependent weighting function.

The random force between a particle pair is

$$\mathrm{F}_{ij}^{R} = \sigma_{ij}\omega_{ij}^{R}\theta_{ij}\frac{1}{\sqrt{\Delta t}}\hat{\mathrm{r}}_{ij} \qquad r_{ij}\le r_c \tag{3}$$

where σ_{ij} is the random force parameter, θ_{ij} is a randomly fluctuating variable with Gaussian statistics and ω_{ij}^{R} is the random r-dependent weighting function.

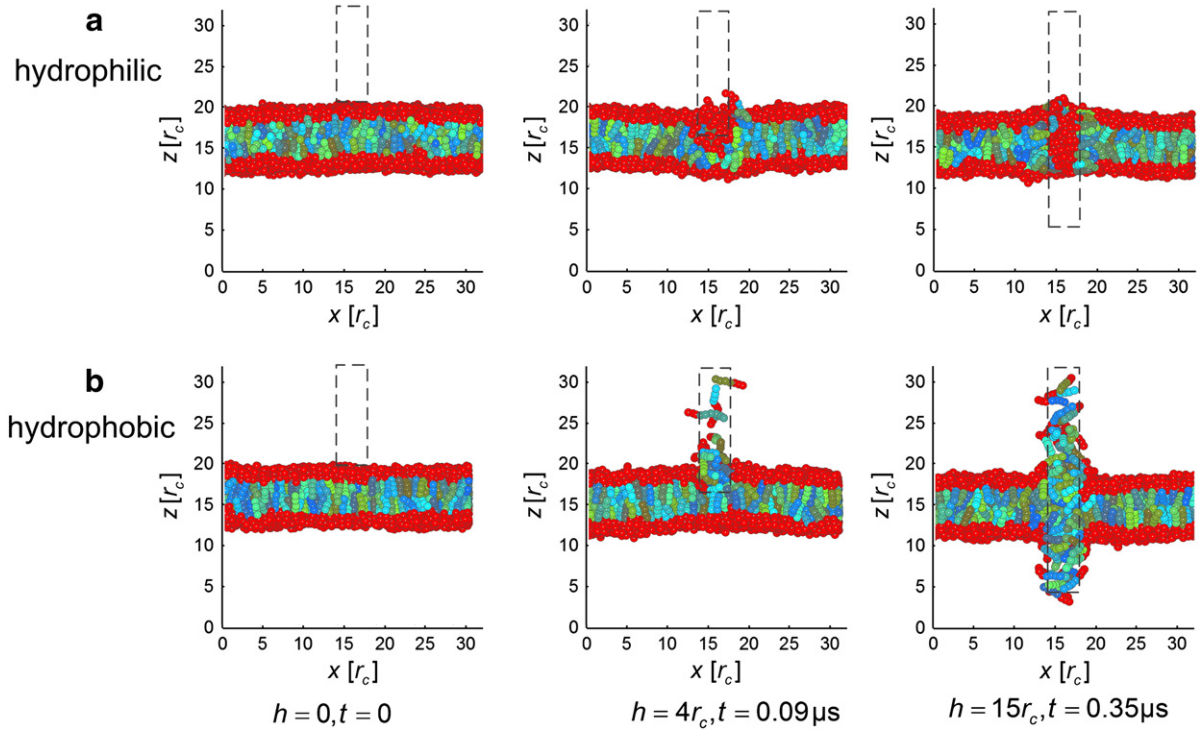

Fig. 2. Morphologies of the lipid bilayer penetrated by hydrophilic and hydrophobic probes, section view with $y = 16r_c$. The dashed rectangles represent the locations of the probe. (a) As the probe descends, for the hydrophilic pattern probe, the head particles of the membrane lipids gather around the probe, and some rotate from vertical to horizontal. (b) For the hydrophobic probe, the tail particles become disordered, and some adhere along the probe, leading to a 'T-junction' state.