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DFPC Lipid Nanoparticle Interactions with Biofilms: Role of Gold Core Size, Kinetics, and Predictive Modeling

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Abstract:

Nanoparticles (NPs) play a crucial role in biomedical applications, especially as drug delivery carriers due to their versatility and modifiability. This study investigates the interactions between DFPC lipid-wrapped gold nanoparticles (LNPs) of varying core sizes and biofilms at the molecular level using coarse-grained molecular dynamics simulations. Results demonstrate that smaller gold core LNPs embed fully into biofilms, increasing membrane fluidity and disorder, while larger core LNPs remain adsorbed on the membrane surface without penetrating the bilayer. To enhance the predictive power and accelerate real-time evaluation of NP-biofilm interactions, this study further proposes a deep learning-assisted prediction framework. By training convolutional neural networks (CNNs) on molecular dynamics trajectory data, the model can predict nanoparticle penetration, embedding probability, and membrane response under varying particle sizes, lipid compositions, and environmental conditions. The combined simulation and deep learning framework establishes a scalable and adaptive tool for optimizing lipid nanoparticle design in drug delivery and nanomedicine.

Keywords:

Biomembrane; DFPC Lipid Nanoparticles; Molecular Dynamics; Deep Learning; Nanoparticle-Biofilm Interaction; Predictive Modeling

1. Introduction

Nanomaterials have shown tremendous potential in fields such as biosensors, electrochemical catalysis, optoelectronics, and the study of advanced physical and chemical properties. Among various nanomaterials, nanoparticles (NPs) have become one of the most intensively studied categories due to their tailorable surface properties, high surface-to-volume ratio, and versatility in functionalization[1-3]. Particularly in biomedical applications, NPs are considered promising drug carriers because of their structural stability and their ability to interact with biofilms in complex ways[4,5]. However, both experimental observations and molecular simulations indicate that NPs can cause disruption and structural damage to biofilms, raising concerns about their potential cytotoxicity[6,7]. This underscores the need to balance drug delivery efficiency with biofilm preservation, making it essential to better understand and control NP-biofilm interactions.

Recent studies highlight that the surface ligands on nanoparticles play a crucial role in modulating these interactions. Surface coatings—including organic compounds, polymers, and biomolecules (such as peptides)—not only reduce NP cytotoxicity but also improve drug delivery efficiency by enhancing biocompatibility and targeting specificity[8-10]. For example, Penades et al. designed carbohydrate-functionalized NPs to act as anti-adhesive scaffolds, preventing tumor cell adhesion and metastasis[11]. Similarly, protein-coated NPs have been shown to minimize cytotoxicity while maintaining effective drug delivery capabilities[12]. Emerging strategies, such as oligonucleotide-functionalized NPs, further illustrate the potential of surface engineering to regulate NP-biofilm interactions[13].

Ding et al. explored the influence of NP shape and size on cellular uptake processes, emphasizing how these properties affect NP-biofilm interactions after internalization[14]. In recent years, lipid nanoparticles (LNPs) have attracted considerable attention due to their biomimetic nature, which

offers improved biocompatibility compared to traditional inorganic nanoparticles. LNPs are particularly promising for targeted drug delivery, as they can encapsulate therapeutic molecules within a lipid shell, enhancing site-specific delivery efficiency. However, the molecular-scale mechanisms governing the interaction between lipid-coated NPs and lipid bilayers remain incompletely understood, warranting further investigation.

In this study, we explore the interactions between DFPC lipid-wrapped gold nanoparticles (LNPs) with different gold core sizes and biofilms using coarse-grained molecular dynamics (CGMD) simulations. To complement these simulations, we propose a deep learning-enhanced analysis framework that leverages time-series simulation data to train predictive models. By incorporating deep learning, we aim to establish a predictive system capable of forecasting the probability of NP embedding, the extent of membrane disruption, and the relationship between NP properties and biofilm responses under diverse environmental and design conditions. This combined approach offers new insights into the molecular mechanisms of NP-biofilm interactions while providing a scalable platform for intelligent nanoparticle design in biomedical application

2. Methods and Models

2.1 System Setup

As shown in Figure 1(a), this study employs dioctadecatrienoylphosphatidylcholine (DFPC) lipids to construct the lipid bilayer membrane. DFPC lipids consist of a hydrophilic head group linked via phosphate moieties and two hydrophobic tails formed by polyunsaturated fatty acid chains. These lipid molecules are loosely packed and exhibit high lateral mobility, which facilitates the insertion of nanoparticles (NPs) into the bilayer.

As illustrated in Figure 1(b), the nanoparticles used in this study consist of a gold (Au) core coated with DFPC lipid ligands. The gold core is functionalized with a monolayer of s-atoms, which serve as anchoring points for the lipid ligands. Two different gold core diameters are examined: 1.6 nm and 2.4 nm, referred to as NP1.6 and NP2.4, respectively. The DFPC lipid ligands are initially randomly dispersed in water. After a 40 ns equilibration simulation, the DFPC lipids spontaneously self-assemble onto the gold core surface, with hydrophobic tails binding to the s-atoms and hydrophilic heads exposed to water, achieving complete (100%) surface coverage.

Each simulation system contains approximately 25,820 coarse-grained water molecules, with an initial box size of 15 nm × 15 nm × 20 nm. Periodic boundary conditions are applied in all three spatial directions to simulate a continuous environment.

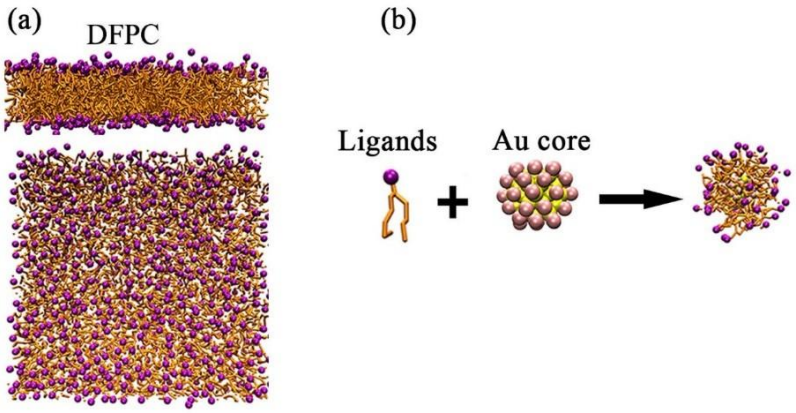

Fig 1. (a) The structure of DFPC lipid (b) The structure of the lipid ligands and the DFPC lipid NP

2.2 Simulation Methods

In this paper, the simulation method used in this paper is a coarse-grained molecular dynamics simulation. This method applies to an extensive range of molecular systems and has features such as

high sampling efficiency, which reduces the time required for the evolution of the whole system, so that we can consider the kinetic behavior of larger systems over a long time. We simulate the system at a controlled temperature of 310 K. All simulation groups will be balanced by 20 ns NPT simulation. The interactions between atoms in the system are described by potential functions, so the interactions between non-bonded atoms in the system are defined by a combination of Coulomb interactions and Lennard-Jones (LJ) potentials. We have done several sets of simulations, and the simulation time for each location was 10 μs or 20 μs to ensure the accuracy of the results. All simulation groups are listed in Table 1.

Table 1: All simulation groups

Nanoparticle	Au core sizes (nm)	Time (μs)
$NP_{1.6}$	1.6	10
$NP_{1.6}$	1.6	10
$NP_{1.6}$	1.6	20
$NP_{1.6}$	1.6	20
$NP_{2.4}$	2.4	10
$NP_{2.4}$	2.4	10
$NP_{2.4}$	2.4	20
$NP_{2.4}$	2.4	20

2.3 Data Analysis

To understand the interaction between DFPC lipid NPs and biological membranes and the kinetic processes, we observed the motion of NPs in the membrane at different moments using the molecular dynamics software VMD. Then we calculated the variation of the DFPC lipid NPs distance from the biofilm plasma center over time using the gmx distance tool in the GROMACS toolkit. Finally, we calculated the surface density of DFPC films using gmx density.

3. Results and Discussion

3.1 Effect of Gold Core Size on the Interaction between DFPC Lipid Nanoparticles and Biofilms

We investigated the interaction between DFPC lipid NPs of different Au core sizes and biofilms. Figure 1 shows the microkinetic processes of $NP_{1.6}$ and $NP_{2.4}$ with biofilm. In the initial moment of the simulation, we placed the NPs at 7 nm from the membrane surface. As shown in Figure 1(a), The $NP_{1.6}$ was adsorbed to the surface of the membrane after about 1.4 μs. At the end of the 1.5 μs simulation, we found that the $NP_{1.6}$ was wholly embedded in the biofilm, and this embedding state until the end of the simulation. It was also found that the lipid ligands were mixed with DFPC lipids because it was detached from the Au core and moved freely in the lipid bilayer so that after the $NP_{1.6}$ were fully embedded into the lipid bilayer, we could only observe the Au core independently in the bilayer. However, as shown in Figure 1(b), $NP_{2.4}$ is different from the phenomenon of $NP_{1.6}$, when the system was simulated to 1.4 μs, we observed that $NP_{2.4}$ was also adsorbed on the membrane surface, but this state continued until the end of the simulation, $NP_{2.4}$ still did not enter the lipid bilayer.

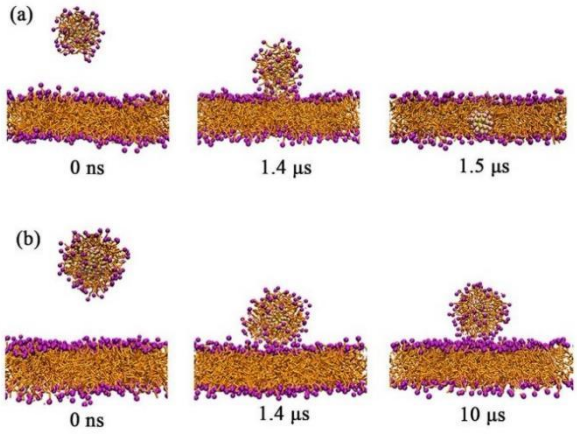

Fig 2. (a) The kinetic processes of $NP_{1.6}$ inserted into the DFPC bilayer (b) The kinetic processes of $NP_{2.4}$ adsorbed on the biofilms

Figure 3 shows the variation in the distance between DFPC lipid NPs and the biofilm plasma center with time. The results showed that the distance between the $NP_{1.6}$ particles and the center of mass of the lipid bilayer membrane tended to decrease at 1 μs, indicating that the nanoparticles began to embed in the biofilm at this time and reached 0 nm between the particles and the center of mass of the membrane at about 1.5 μs, which indicated that the lipid NPs were wholly embedded in the lipid bilayer at this time. However, the distance between the $NP_{2.4}$ and the lipid bilayer center of mass remained at 6 nm from the beginning to the end of the simulation, i.e., the NPs were adsorbed on the surface of the bilayer, which indicates that the $NP_{2.4}$ was not embedded into the lipid bilayer during the whole simulation, so we did not observe the $NP_{2.4}$ embedded into the lipid bilayer during the whole kinetic process.

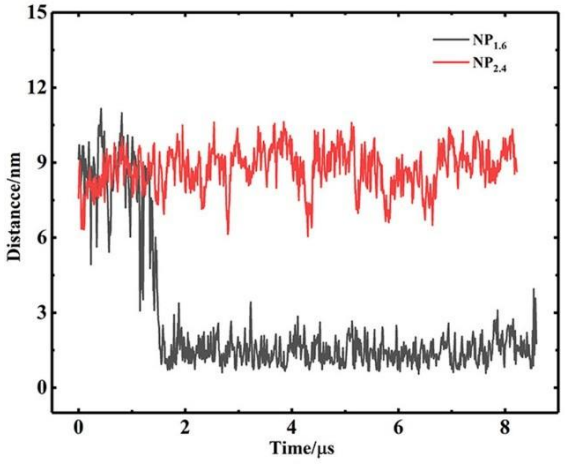

Fig 3. Variation of the distance between the center of mass of $NP_{1.6}$ and $NP_{2.4}$ and biofilm with time

Figure 4 compares the surface density of the DFPC bilayer distributed along the x-axis in the system of $NP_{1.6}$ and $NP_{2.4}$. The results showed that the $NP_{1.6}$ occupied the lipid sites from the time they first adsorbed onto the membrane surface to the time they ultimately entered the membrane, which resulted that the density decreasing at the NP entry site, thus, a significant nadir at approximately 9 nm. However, the surface density of the DFPC lipid bilayer in the $NP_{2.4}$ particle system was always stable, which suggests that $NP_{2.4}$ was not embedded in the biofilm throughout the kinetic process and had little effect on the surface density of the membrane. It indicates that lipid NPs with small Au core size make the lipid bilayer more loose and disordered.

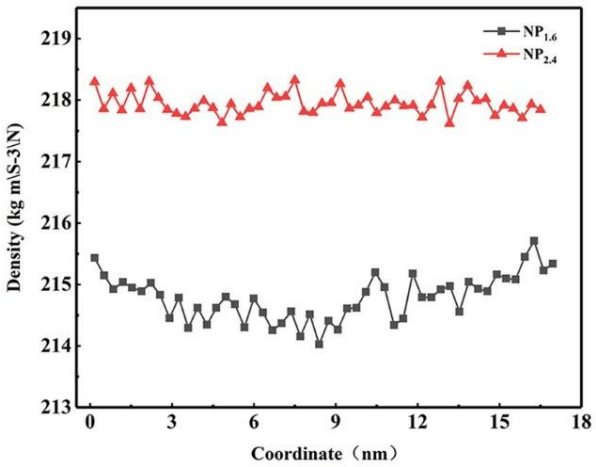

Fig 4. Surface density of DFPC bilayer for the $NP_{1.6}$ system and $NP_{2.4}$ system

4. Conclusion

This paper focuses on the effect of gold core size on the interaction between lipid NPs and biofilms under DFPC lipid wrapping. By observing the kinetic processes of DFPC lipid NPs in the system, we found that DFPC lipid NPs with smaller Au core sizes were wholly embedded within the biofilm and made the lipid bilayer more loose and disordered. In contrast, in the system of lipid NPs with larger Au core size, we did not find NPs embedded in the biofilm throughout the simulation. We showed that lipid NPs with smaller gold core sizes are more easily embedded in the membrane than lipid NPs with larger gold core sizes by calculating the center-of-mass distance between DFPC lipid NPs and biofilm and the surface density of the DFPC lipid bilayer. Thus, the Au core size pair may play a significant role in the kinetic process of the DFPC lipid nanoparticle-biofilm interactions. This paper provides a feasible scheme to regulate the interaction between lipid nanoparticles and biological membranes, which is a reference for applying lipid nanoparticles in fields such as nanomedicine.

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