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Asymmetric heat transfer from nanoparticles in lipid bilayers

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ABSTRACT

Here, we use molecular dynamics simulations to characterize the heat transfer properties of lipid bilayer – gold nanoparticle systems in which the nanoparticle acts as a heat source. The focus is on dipalmitoylphosphatidylcholine (DPPC) lipid bilayers and thiolated alcohol and alkyl functionalized nanoparticles as prototype hydrophilic and hydrophobic nanoparticles. We find hydrophilic nanoparticles which are partly in contact with the surrounding water environment are more efficient in transferring heat to the system than hydrophobic ones which reside surrounded by the membrane. This is because of the hydrogen bonding capability of the hydroxy pentanethiol and the more efficient heat conductivity through water than the lipid bilayer. Additionally, we find the heat conductance is strongly asymmetric and has a discontinuity between the bilayer leaflets. In total, the findings provide understanding on heat transport from localized heat sources in lipid bilayers and could bear significance, e.g., in engineering and controlling photoactivated triggering of liposomal systems.

1. Introduction

Triggered liposomal contents release is at key role in many drug targeting, diagnostics, and sensor applications. A trigger for the liposomal contents release can be provided, e.g., by magnetic field, ultrasound, or by local heating, see e.g. Refs. [1–4] for recent reviews. Of these, local heating can be achieved by e.g. photoactivation in which metallic, especially gold, nanoparticle heat up via surface plasmonic resonance [5,6]. In particular, photoactivated release via gold nanoparticles surface plasmonic resonance inducing local heating in the liposome has been demonstrated e.g. in Refs. [7–12].

In key role in the photoactivated liposomal content release process is the heat transfer from the nanoparticle to the liposome and its aqueous environment [13]. This heating drives the lipid bilayer from the liquid-ordered to the liquid-disordered phase [7,10,14] which has been demonstrated to release, e.g. calcein [10], berberine [15] or dyes such as carboxyfluorescein [16]. The physics involved in the plasmonic heating of gold nanoparticles and the heat transfer from them contains many open questions due to the interplay between optics and thermodynamics in the plasmonic heating and the nanoscopic, molecular scale at which all this occurs, see e.g. Refs. [5,17]. Nevertheless, the macroscopic effects due to photothermal heating, such as tissue damage, chemical reactions, or drug transport, have been demonstrated, see e.g. [5] for a review. However, at microscopic scale, many open questions remain. These include, for example, the amount of heat generated and its transfer into the environment of the nanoparticle. The latter is complicated further by the protective ligand coating of the nanoparticles which stabilizes the nanoparticle but also greatly affects the interactions of the gold nanoparticle with its environment. Experimentally characterizing the heat transfer relies on mapping the lipid bilayer response, e.g. via calorimetric or dissipation monitoring measurements [18–21] or scattering techniques [10,22], NMR [21], or FRET or fluorescence microscopy [23]. However, computer simulations provide a tool to characterize the nanoparticle interactions with the liposome and the heat transfer from it to the bilayer in otherwise unattainable high molecular level detail.

Therefore, it is not surprising that the effects of the gold nanoparticle on the structure and the dynamics of the lipid bilayer have been studied extensively by simulations, see e.g. Refs. [24–32] These works show that gold nanoparticles have a distinctive, ligand dependent influence on the bilayer characteristics [24,25,29–32]. The works also address the pathway the liposomes engulf the gold nanoparticles [27,29,32,33]. However, modeling heat transport has received much less attention both in lipid bilayers and from nanoparticle type local heat sources. Lipid bilayer heat conductance has been studied via molecular modeling in Refs. [34–36]. On the other hand, ligand coated nanoparticle heat transfer to molecular environment has been examined in Refs. [37,38]. These basic studies of heat transfer show, e.g., the asymmetric character of the lipid bilayer is at key role in the heat transport

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in lipid bilayers [36] and that the molecular coupling strength dominates the heat transfer [34,35]. For gold nanoparticles, Chen et al. [38] analyzed the heat transfer from a gold nanoparticle to water-pool and Lin et al. [37] nanoparticle heat transfer in an alanine membrane. Additionally, Lin et al. discuss the influence of the nanoparticle on the neighbouring water and bilayer environment [39] and on the bilayer transition temperature [40] via coarse grained computational studies. However, we are not aware of molecular modeling studies of heat transfer from nanoparticle type heat sources in lipid bilayer environment.

Therefore, in this work, we address via atomistic molecular dynamics simulations the heat transport characteristics of a lipid bilayer environment containing functionalized gold nanoparticles that act as the heat source. As said, the setup is motivated by liposomal systems in which photoactivated gold nanoparticles act as a trigger of liposomal content release. We address the heat transfer from the gold nanoparticle in this system and the effect of ligand functionalization on the observed heat transfer characteristics. Finally, we discuss the findings in terms of triggered liposomal content release.

2. Methods

The molecular dynamics simulations in this work were performed using the GROMACS 4.5.5 simulation package [41]. The heat transfer studies were performed in a system consisting of a lipid bilayer of 512 DPPC lipids and a functionalized gold nanoparticle of 144 Au atoms core and 60 thiolate ligands as surface functionalization all in explicit water. Such thiolated gold nanoparticle is typically referred to as $Au_{144}(SR)_{60}$. This particular nanoparticle size and functionalization density were chosen because it is one of the few particularly stable "magic" nanoparticle sizes in the size range of 1–3 nm that have been characterized to molecular precision both in Au atom and thiolate content [42]. In the simulations, the examined thiolate ligands SR are hydrophobic hexane thiol $S(CH_2)_5CH_3$ and hydrophilic hydroxy pentanethiol $S(CH_2)_5OH$, see Fig. 1. The functionalizations are identical except that the latter has the end methyl group replaced by an OH-group.

The DPPC lipids were described within the Berger lipid description [43] using the OPLS force-field compatible formulation of Ref. [44]. In line with the OPLS force-field, water is described by the TIP3P water model [45]. Thiolated ligands were constructed within the OPLS-ua force-field using the existing sulfur [46], alkane [47], and alcohol parameters [48] of the OPLS-ua force-field. The gold was described as a Lennard–Jones metal using the parameters of Heinz et al. [49]. Gold–sulfur interaction is modeled by Lennard–Jones interactions with $r_0 = 0.235$ nm ($\sigma = r_0/2^{1/6}$) and $\epsilon = 50$ kJ/mol. The r_0 value reflects the average gold–thiol bond length reported in [42]. The gold–sulfur bond is reported to be comparable in strength to the gold–gold bond in [42]. Our choice of ϵ corresponds to a slightly more stiff bond than the gold–gold bond. The partial charges for the thiolates were taken from the respective OPLS force field parameters [46–48] while a modest charge of 0.09 e is set for the gold atoms. This is to follow quantum chemical calculations of the charge distribution [50] and it also results in an overall nanoparticle charge in qualitative agreement with experiments, see e.g. Ref. [51].

The Berger description [43] is chosen to describe the lipids in this work because a compatible thiolated ligand parametrization can be constructed within this description. We are aware, some other lipid forcefields could provide a more accurate DPPC description in terms of finesse in lipid head group interactions and bilayer structural characteristics, see e.g. Refs. [52–54] for recent lipid force-field comparisons. However, as the heat transfer characteristics are dictated by the coupling strength between interactions, the heat transfer characteristics should thus be independent of minor details in the description.

A 512 DPPC lipid bilayer and the hydrophobic and hydrophilic nanoparticles are first constructed and relaxed separately in aqueous environment. The same bilayer configuration is used to generate both the hydrophobic and the hydrophilic nanoparticle setup initial configuration. The hydrophobic nanoparticle is embedded

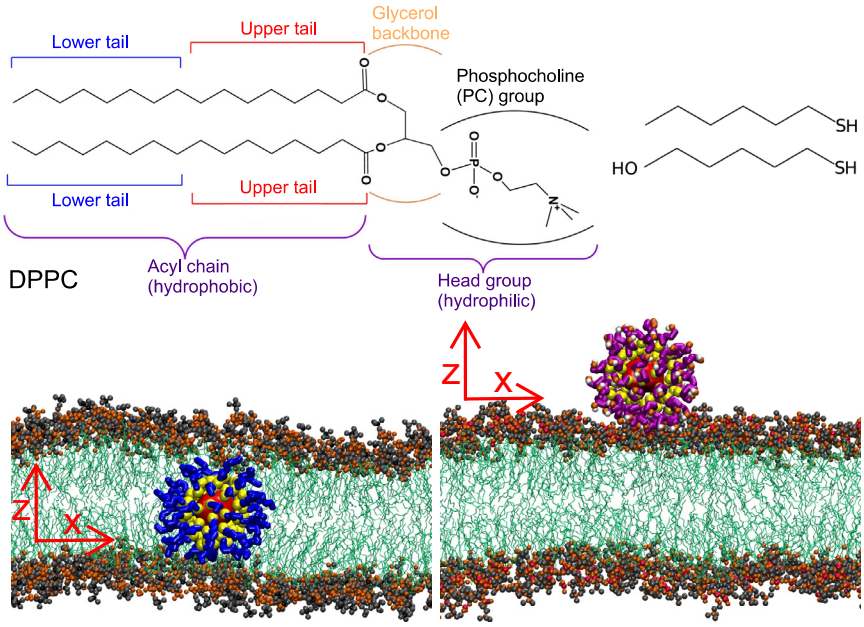

Fig. 1. At top, the DPPC lipid structure and the nanoparticle hydrophobic hexanethiol $S(CH_2)_5CH_3$ and hydrophilic hydroxy pentanethiol $S(CH_2)_5OH$ functionalizations. The labels refer to the different DPPC groups and the tail division used in the analysis. At bottom, the resulting relaxed configurations of the corresponding $Au_{144}(SR)_{60}$ nanoparticles in the DPPC bilayer system (hydrophobic nanoparticle at left and hydrophilic nanoparticle at right). Water, although explicitly present in the simulations, is omitted in the visualization. In the analysis, the cartesian coordinate axes are set so that the *z*-axis is along the bilayer normal and the bilayer plane coincides with the *xy*-plane.