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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.

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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]

* Corresponding author. *E-mail address:* maria.sammalkorpi@aalto.fi (M. Sammalkorpi). 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 bilayer s 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







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 Au₁₄₄(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–Iones 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.

into the bilayer using InflateGRO to generate an opening for it, see Ref. [55]. The hydrophilic nanoparticle is placed in the vicinity of the DPPC bilayer into the aqueous phase. The initial distance of the hydrophilic nanoparticle from the DPPC bilayer is such that the ligand tips are barely in contact with the lipid membrane. Both setups are then solvated with water molecules (254 waters per lipid for the hydrophobic nanoparticle system and 252 water per lipid for hydrophilic system). This corresponds to a water slab of $\approx 24 \text{ nm}$ in thickness and a total system size of 12.55 nm \times 12.60 nm \times 29.47 nm for the hydrophobic system and 12.57 nm \times 12.62 nm \times 29.5 nm for the hydrophilic system. A relatively thick water slab is chosen to limit artefacts due to periodicity during the heat transfer study. Nevertheless, the periodic boundary conditions and the finite size of the system box do influence the outcome. The effects are carefully monitored for, and their influence discussed where appropriate.

While the heat transfer simulations are done without a thermostat or barostat influencing the bilayer and its aqueous environment energetics, the initial system relaxation and equilibration for 30 ns was performed in the NPT ensemble using a semi-isotropic Parinello-Rahman barostat with reference pressure of 1 bar, compressibility of 4.5×10^{-5} bar⁻¹, and a time constant of 5.0 ps. This equilibrates the bilayer properties, the nanoparticle position with respect to the bilayer center, and the lipid arrangement around the nanoparticle. During this initial equilibration, temperature was maintained at T = 323 K with water, lipids and nanoparticle coupled separately to the heat bath. The temperature was chosen so that it is clearly above the liquid-crystalline phase transition temperature for the lipid bilayer. Here, and in all following thermostating, the stochastic velocity rescale thermostat of Bussi et al. [56] is used with a time constant of 0.1 Xps. Notably, no such temperature control is used in the heat transfer production runs. Examples of resulting simulation configurations are presented in Fig. 1.

In studying heat transfer, the equilibrated configurations, see Fig. 1, are used as the starting configuration. Unlike in the initial relaxation, the system is decoupled from the barostat to prevent the barostat interference with the heat transfer. Thus the system volume is constrained to the volume corresponding to 1 bar pressure at T = 323 K. We emphasize the DPPC, as well as, water molecules are decoupled from any thermostat algorithm in these heat transfer simulations: the lipid and water molecule initial atom velocities originate from the relaxation simulation at T = 323 K and evolve without thermostat interference, see Fig. 2. Representing photoactivated heating, the thiolated nanoparticle acts as the heat source in the system and it is thermostated to 400 K temperature throughout the heat transfer simulations, again, see Fig. 2. Heat transfer from the nanoparticle is examined over a period of 10 ns.



Fig. 2. Time development of the DPPC bilayer temperature with hydrophobic and hydrophilic nanoparticles heating the system up.

In all simulations, a cut-off of 1.2 nm is used for van der Waals interactions. Long range electrostatics are described by the particle mesh Ewald (PME) method [57] with a real space cut-off of 1.2 nm. A time-step of 2 fs is used for all simulations. Water is constrained by the SETTLE algorithm [58] and LINCS is used for the bonds of the rest of the molecules in the system [59]. Periodic boundary conditions are imposed in all three directions. Throughout, double precision calculations are used to obtain more accurate convergence of the energy terms. For the same reason, the neighbourlist is updated every time step. Initial configurations are energy minimized with the steepest decent method. All simulation snapshots are generated by VMD [60].

3. Results

First, we equilibrated the lipid bilayer systems in the presence of the hydrophobic and hydrophilic nanoparticle. As expected, the hydrophobic nanoparticle prefers to reside within the hydrophobic core of the membrane whereas the hydrophilic nanoparticle relaxed its position to be at the peripheral region of the lipid bilayer facing both water and the lipid head groups. Both nanoparticles deform the membrane and influence its dynamics. Fig. 1 presents the configurations corresponding to relaxed bilayer structures with the nanoparticles used as the initial configurations for these simulations.

After obtaining equilibrated configurations, we moved to characterizing the overall heat transport of the lipid bilayer system containing a heated nanoparticle. In these simulations, the nanoparticle temperature is kept at 400 K representing, e.g., heating by light absorption. Notably, the rest of the system (meaning the bilayer and water) is decoupled from the thermostat to prevent the algorithm influencing the heat transfer behavior. The resulting time development of the temperature of the bilayer is presented in Fig. 2. Here and in the following, local temperature $T_{local} = \frac{2}{dk_B} \langle m_i v_i^2 \rangle$ in the simulated system is calculated based on the equipartition theory. In this, k_B is the Boltzmann constant, d the number of degrees of freedom, m_i the mass and v_i the velocity of particle *i*.

The data of Fig. 2 reveals that the DPPC bilayer heats up significantly faster if the nanoparticle heating the system up is hydrophilic. This reflects mostly the different positioning of the hydrophobic and hydrophilic nanoparticles with respect to the membrane. Whereas the hydrophobic nanoparticle is surrounded by the hydrophobic acyl chains of the lipids, see Fig. 1, the hydrophilic one resides at the peripheral region and is mostly surrounded by water and to a lesser degree by the lipid head groups. Besides the bilayer heat absorption, the stronger heat absorption into the system from the nanoparticle at the bilayer-water interface reflects also on the entire system heating faster (data not shown). We note the absolute heating rates and system behavior are dependent on the simulation system size. Furthermore, the periodic boundary conditions influence the outcome once the absorbed heat reaches the simulation box boundary. Nevertheless, the data enables us to conclude clearly the hydrophilic nanoparticle conveys heat more efficiently into the system.

To pinpoint the reason for this behavior and to characterize the system further, we analyzed the time development of the system temperature (1) perpendicular and (2) parallel to the bilayer plane. The temperature evolution perpendicular to the bilayer plane is calculated in discrete slabs whereas in the direction of the bilayer plane, the time evolution is calculated as a function of radial distance from the nanoparticle center of mass along the bilayer plane direction. In examining the temperature evolution, the thermostated nanoparticle heat source is omitted. That is, the

presented temperature data corresponds to the DPPC lipids and water molecules in the system, see Fig. 2 for the corresponding nanoparticle and spatially averaged DPPC lipid temperatures.

Fig. 3 presents the time development of the temperature distribution profile resulting from DPPC and water molecule contributions perpendicular to the bilayer plane for the two systems. Quite expectedly, the hydrophobic nanoparticle location shows as a minor peak in the hydrophobic system graph. Otherwise the graph is featureless and shows relatively uniform heating in time for both the DPPC and the water regions. Naturally, the near vicinity of the nanoparticle absorbs heat first. However, the hydrophilic nanoparticle induces a clear skew in the heat distribution. The heat absorption is heavily weighted to the side at which the nanoparticle resides. The asymmetry of the system is also reflected by the heat transport perpendicular to the bilayer plane. In this direction, a clear discontinuity at the center is observed. This is because the acyl chains face each other and their coupling is weak as no tails cross the pivotal plane.

Additionally, as heat transfer through covalent bonds (intramolecular heat transfer) is much more effective than heat transfer through non-covalent bonding (intermolecular heat transfer), the heating phenomenon shows first most strongly at the region close to the bilayer center plane. The reason for this is jointly a discontinuity in the heat transfer between the bilayer leaflets and the displacement of lipids and water from the volume the hydrophilic nanoparticle occupies. The displacement of lipids and water in the system happens near the level of the lipid head groups but close to the bilayer pivotal plane the hydrophobic lipid sections still need to fill the volume similar to an unperturbed lipid bilayer. As a consequence, much more of the mass of those lipids that are in direct contact with the nanoparticle resides near the bilayer center than elsewhere in the system including the locations where the lipids are in direct contact with the nanoparticle. As covalent bonds transfer the heat extremely fast, this leads to heat build up in the central region.

Corresponding to Fig. 3, the local temperature gradient of the DPPC and water subsystem as a function of time and the *z*-axis position representing the direction perpendicular to the membrane plane are presented in Fig. 4. As already indicated by Fig. 3, the temperature gradient of the system with a hydrophobic nanoparticle is almost constant throughout the simulation. The gradient has its highest values at the center of the bilayer which corresponds to also the nanoparticle center and the lipid tail-tail interface. On the other hand, the hydrophilic nanoparticle system has a prominent temperature gradient peak. This peak is at the lipid tail-tail



Fig. 3. Time development of lipid and water temperature perpendicular to the bilayer plane with hydrophobic (at left) and hydrophilic (at right) nanoparticles. The vertical dashed line represents the bilayer pivotal plane in the system and the *z*-axis is perpendicular to the bilayer plane, see Fig. 1 for the cartesian coordinate axes orientation in the system. The inset cartoons show the nanoparticle position, as well as, the qualitative density plots of lipids and water in the system in green and in red, respectively. Throughout the simulation, the nanoparticle is thermostated at 400 K. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



Fig. 4. Time development of the temperature gradient of lipids and water in the system as a function of *z*-axis position in the system containing a hydrophobic nanoparticle (at left) and a hydrophilic nanoparticle (at right). The *z*-axis represents the direction parallel to the bilayer normal, see Fig. 1 for cartesian axes orientation in the system.

interface and it reflects a discontinuity in the heat transport perpendicular to the lipid bilayer. Quite expectedly, the gradient decreases with the system heating up: the observed temperature gradient at the lipid tail-tail interface was 4.55 K/nm, 3.43 K/nm and 1.91 K/nm for 0–1 ns, 1–2 ns and 2–3 ns calculation intervals, respectively. For comparison, the hydrophobic nanoparticle induces a maximum gradient of ≈ 0.7 K/nm for the 0–1 ns time interval in the simulations.

The analysis of the temperature evolution in the system around the nanoparticle parallel to the bilayer plane was realized by calculating the temperature as a function of radial distance from the nanoparticle center of mass along the bilayer plane direction for the different molecular components. In this, guite expectedly due to the uniform character of the system in bilayer plane direction, no discontinuities or nonuniform behavior is observed (data included as supporting info). However, analysis of the system by components reveals differences in the molecular component carrying the heat in the two systems, see Fig. 5. The figure shows the temperature time evolution in a cylinder aligned perpendicular to the bilayer plane and radius of 2 nm centered at the nanoparticle center of mass. The temperature evolution is plotted separately for the two sides of the lipid bilayer for interfacial water (water within 2 nm of phosphatidylcholine groups), bulk water (all other water), the lipid phosphocholine (PC) head group, glycerol backbone, and the lipid tail analyzed in two halves, see Fig. 1. The lipid lower tail consists of the last 8 methyl groups and the upper tail region all other methyl groups. Notably, the data points corresponding to lipid section temperatures in the hydrophobic nanoparticle system have a larger scatter than those of the hydrophilic nanoparticle system. On the other hand, the hydrophilic nanoparticle occupies a significant volume of the analysis cylinder which reduces the number of lipids inside the analysis section; the hydrophilic nanoparticle displaces mostly water molecules which are numerous and hence the hydrophilic nanoparticle system data sets contain less scatter.

The nanoparticle first heats its local vicinity and the temperature rapidly increases radially. Fig. 5 shows in the hydrophobic system, the heat is absorbed and conveyed by the lipid tails as shown by these sections having a higher mean temperature in the graph. This results from the close vicinity of the lower lipid tails and the heated hydrophobic nanoparticle. On the other hand, in the system with the hydrophilic nanoparticle, the lipids in the close vicinity of the nanoparticle heat up fast. This efficiently drives the heat-up forward even though the heat distribution is skewed to the side at which the nanoparticle resides, see Fig. 3. Additionally, interfacial water at the side of the nanoparticle in the hydrophilic system heats up faster than in the hydrophobic system in which the water is shielded by the lipid bilayer in which the hydrophobic nanoparticle is embedded. This leads to much faster heating of the water region, and consequently the entire system. This reflects the efficient heat conductivity of the water phase.

In total, Figs. 2, 3 and 5 clearly indicate that the hydrophilic nanoparticle heats the system up significantly faster. Furthermore, the local temperature of lipid monolayers with hydrophobic nanoparticles is symmetrically distributed and significantly lower than that containing a hydrophilic nanoparticle (Fig. 3). On the contrary, monolayer temperatures in hydrophilic system vary with comparable temperature difference. The monolayer with heated nanoparticle shows much higher temperature than the opposite side and tends to transfer heat rapidly on the same side of monolayer. However, between the bilayer leaflets a discontinuity in the thermal conductance is observed. This observed thermal boundary resistance corresponds to the observations of Refs. [34,35].

Next, for the sake of simple comparison and connecting the observations to experimentally measurable characteristics, we calculate a coarse estimate for the thermal conductivity κ in both



Fig. 5. Temperature time evolution in the hydrophobic and hydrophilic nanoparticle (NP) systems in a cylinder of 2 nm in radius centered at the nanoparticle center of mass for bilayer interfacial water, bulk water, lipid phosphocholine (PC) group, glycerol backbone, lower tail and upper tail regions, see Fig. 1. For both systems, bilayer leaflet 1 is plotted at top and bilayer leaflet 2 at bottom; hydrophilic nanoparticle is directly in contact with leaflet 2. In the analysis, interfacial water is all water within than 2 nm from the phosphatidylcholine group mean position plane and bulk water is all other water. The lipid head group is divided into the phosphocholine head group and glycerol backbone sections while the lipid tail is analyzed in two halves with the tail end (lower tail) consists of the last 8 methyl groups and the central tail region (upper tail) all other methyl groups, see Fig. 1.

studied systems. The heat transfer can be considered in terms of Fourier's law for the energy current density

$$j_E = -\kappa \left(\frac{\partial T}{\partial r}\right) \tag{1}$$

Here, κ is thermal conductivity and we have assumed the temperature gradient is radial. Our heat source is radial but the bilayer system is strongly asymmetric; assuming a uniform, radial heat conductance here is a drastic simplification. Corresponding radial energy flux Φ_E is

$$\Phi_E = j_E \times A = -4\pi r^2 \kappa \left(\frac{\partial T}{\partial r}\right) \tag{2}$$

Here, *A* is the respective sphere shell area. As the nanoparticle pumps energy into the system, Φ_E is time dependent. However, for a simple approximation, we make an assumption that the flux can be considered momentarily equal for any shell of the sphere (independent of *r*). This assumption enables us to integrate Eq. 2 and obtain an estimate for the thermal conductivity κ for a sphere shell between two different sphere radii r_1 and r_2 (and corresponding temperatures T_1 and T_2):

$$\kappa = \Phi_E \left(\frac{1}{4\pi r_2} - \frac{1}{4\pi r_1} \right) \left(\frac{1}{T_2 - T_1} \right) \tag{3}$$

The above approach is for a steady state heat flux. If more accurate estimates or estimates valid over extended time periods are required, we emphasize the reader should consider time dependency in the system and transient solutions for the heat flux, see e.g. Refs. [61,62]. Here, however, we aim for a coarse estimate and examine momentary heating of the system at the early stages of the simulation.

We know the nanoparticle approximate radius r_1 and its temperature T_1 , and the simulations enable us to calculate mean temperature T_2 at any radial distance r_2 from the nanoparticle center of mass in the system. On the other hand, the corresponding total energy increase in the system tells us how much heat energy has been transferred from the nanoparticle to the system, see Fig. 6. The slope of this data corresponds to the rate of energy flow into the system $\frac{\partial E}{\partial t}$. At early stages of the simulation, the data curves are practically linear as expected for steady state flux in a uniform system and thus the figure presents also the slopes and linear data fits to the data at 0 ns -0.5 ns and 0 ns -1.0 ns time intervals. The slopes, together with the time intervals, give an approximate for the energy flux Φ_E into the system. The difference between the



Fig. 6. Time development of the total energy in the system. The energy gain results from the hydrophobic and hydrophilic nanoparticles (NP) acting as a heat source. The dotted lines represent linear fits to the data at 0 ns -0.5 ns and 0 ns -1.0 ns time intervals and show $\frac{\partial E}{\partial t}$ values for the systems at the early stages of the simulation.

slopes at the two presented intervals indicates that for the hydrophobic nanoparticle system $\frac{\partial E}{\partial t}$ is practically constant at time intervals shorter than 1 ns but for the hydrophilic system $\frac{\partial E}{\partial t}$ varies significantly. Nevertheless, using a linear approximation leads to less than 10% error in $\frac{\partial E}{\partial t}$ value during this period. At extended time periods, the periodic boundary conditions and the time dependency of the heat flux need to be taken into account.

As a very coarse estimate, if we consider the system a uniform sphere, the simulation box dimensions correspond to a sphere radius of $R_2 = 8.35$ nm. At 1 ns time, the hydrophilic system corresponding temperature is $T_{2,hydrophilic} = 347$ K and the hydrophobic system temperature is $T_{2,hydrophobic} = 335$ K. The gold nanoparticle (thiols excluded) has an approximate radius of $R_1 = 0.8$ nm, and due to the thermostat control, its temperature is approximately $T_1 = 400$ K. Plugging in these values in into Eq. 3 results in $\kappa_{hydrophilic} = 0.3 \text{ Wm}^{-1}\text{K}^{-1}$ and $\kappa_{hydrophobic} = 0.1 \text{ Wm}^{-1}\text{K}^{-1}$. Similar κ values are obtained for 0.5 ns time period. Whereas the former underestimates the κ of water by approximately half (see e.g. [63]), the latter is very close to values reported for various alkanes [64] and also values obtained for alcohols or oils. Actually, the hydrophilic nanoparticle is partially in contact with water and partially in contact with the bilayer. This means its heat is absorbed by both water environment and bilayer environment – hence mean κ is less than for pure water environment simulation would be.

The presented approximation forfeits the asymmetry, periodicity (finite simulation box size), and all time dependency in the heat flow into the system. With such a coarse approach to obtaining the mean κ values from the simulations here, this level of match with experimental values is fortuitous. We emphasize a much more rigorous approach should be taken if truly predictive values are desired from this type of calculation. However, the qualitative difference in the values reflects the heat conductivity difference in the two systems: when the nanoparticle is even partially in contact with the water phase, the mean heat conductivity in the system is significantly higher. Thus, even such a coarse approximation connects this type of simulational work to macroscopically measurable quantities.

4. Discussion

Here, we performed a molecular simulations study of heat transfer from a nanometer scale functionalized nanoparticle to a lipid bilayer. The results showed a hydrophilic nanoparticle residing at the lipid membrane peripheral region is significantly more efficient in heat transfer to the aqueous system than a hydrophobic one which prefers to reside embedded into the lipid membrane. The heat transfer takes place through absorption to the molecule sections in contact with the heated nanoparticle resulting in heating occurring through lipid tail ends in the hydrophobic nanoparticle system and through lipid heads and peripheral water in the hydrophilic nanoparticle system. Furthermore, in the heat transfer, we observe a significant discontinuity in the direction perpendicular to the lipid bilayer between the bilayer leaflets in the hydrophilic nanoparticle system.

The heat transfer from the hydrophilic nanoparticle to the system is more efficient because of the different environments the nanoparticles reside at. Whereas the hydrophilic nanoparticle is surrounded by water and lipid head groups, the hydrophobic one is embedded into the membrane and surrounded by lipid acyl chains. Two factors contribute to the hydrophilic nanoparticle heating the system up more efficiently. First, the hydrophilic functionalization couples more strongly to both DPPC head groups and water than the hydrophobic alkyl chain functionalization. This is because of the hydrogen bonding capability of the hydroxy pentanethiol. Second, the heat conductivity of water and lipid head groups are higher than that of the lipid membrane acyl chains. This enables heat transfer to take place efficiently into the entire system. Whereas water heat conductivity has been reported to be approximately $0.65 \text{ W m}^{-1} \text{ K}^{-1}$ at room temperature [63] for alkanes of varying length, values around $0.1 \text{ W m}^{-1} \text{ K}^{-1}$ have been reported [64].

Our oversimplified continuum treatment of the heat transport in the systems provided mean heat conductivity values κ of approximately half of the water heat conductivity for the hydrophilic nanoparticle system and very close to the alkane heat conductivity for the hydrophobic nanoparticle system. As already said, this level of agreement with the experimental heat conductivity values is fortuitous at the level of simplification done in the treatment. However, consideration of the system geometry and the magnitude difference obtained for the respective mean κ values reveals that the initial environment in which the nanoparticle resides in dominates its heat transfer characteristics: if the nanoparticle is surrounded by lipids, the system heats up like an alkane (or alcohol or oil) medium would whereas the stronger coupling to water in heat conductance and the better heat transport qualities of water dominate the behavior when the heat source is even partially in contact with water. Considering Fourier's law of thermal conductivity (Eq. 1), this is actually quite expected as the energy current density throughout depends on the local thermal conductivity and the local temperature gradient: if the medium absorbing heat from the heat source is inefficient in conducting heat, the entire heat absorption process is slowed whereas an efficient heat conduction medium spreads the heat into the system even if the heat source is only partially in contact with the more efficient heat conduction medium as is the case with our hydrophilic nanoparticles.

Besides the mean heating characteristics, the nanoparticle hydrophobicity plays a role also in the qualitative heat transfer characteristic of the lipid bilayer system. In particular, the hydrophobic particle conveys heat to the system through the lipid tail ends symmetrically whereas the hydrophilic nanoparticle convevs heat to the nearby lipids and water and leads to an asymmetric temperature distribution between the bilaver leaflets. This asymmetry in the lipid bilayer heat transfer characteristics has been previously reported for pure bilayer systems by Mueller and Mueller-Plathe [36] and by Nakano et al. [34]. They have characterized in detail the bilayer asymmetries, and guite expectedly, our findings on the hydrophilic nanoparticle as the heat source agree qualitatively. However, the nanoparticle is a localized, finite size heat source with spherical geometry as opposed to planar slab-like heat source and heat sink regions used in Refs. [34–36]. Consequently, we observe the bilayer section most in contact with the nanoparticle thiolates to heat up initially: whereas in the hydrophilic nanoparticle system heat is carried by the close-by lipids and the water, in the hydrophobic nanoparticle system, we find that the heat is absorbed and conveyed by the lipid tails and especially the tails ends. This is partially because of the nanoparticle positioning in the middle of the bilayer and its geometry: there is more contact to lipid tail ends than to, for example, lipid heads, for example, water is not in direct contact with the hydrophobic nanoparticle. The significance of this is that additional possibilities to control the heat conductance can be obtained via tailoring of the functionalization chemistry and through the thermal coupling.

As in our work the heat source is a nanoparticle which can reside also entirely within the membrane and spanning the heat conductivity discontinuity between the two bilayer leaflets, the hydrophobic nanoparticle system results provide an interesting comparison to the asymmetry results of Mueller and Mueller-Plathe [36] and those of Nakano et al. [34,35]. By spanning the bilayer pivotal plane by the heat source, the discontinuity in the heat transfer between the leaflets is masked. The bilayer leaflets, as well as, the water at both sides of the membrane heat up symmetrically when the nanoparticle is hydrophobic. Actually, Nakano et al. have also reported the thermal resistance at the bilayer pivotal plane is reduced by lipid chain length asymmetry [35]. Simplistic generalization of their observation joint with our membrane leaflet spanning nanoparticle results is that any membrane spanning molecule or particle that strengthens the inter-leaflet heat transfer coupling reduces the potential temperature profile asymmetry between the bilayer leaflets. This observation bears significance if, for example, symmetric thermophysical properties are desired. For example, a liposomal system has distinct inner and outer membrane leaflets - asymmetry in the leaflet heating leads to asymmetry between the inner and outer leaflet thermophysical response. This influences, e.g. phase transitions and molecular transport through the membrane. On the other hand, our findings reveal a heat source (such as a nanoparticle) spanning the plane between the two bilaver leaflets results in symmetric heating of the leaflets. However, in considering this asymmetry, it is important to keep in mind that our simulations indicate the hydrophilic nanoparticle is so much more efficient in transferring its heat to the aqueous lipid bilayer environment that despite the observed asymmetry in the heat transfer, both bilayer leaflets (the hotter and the colder) in the hydrophilic nanoparticle system exceed in temperature those of the hydrophobic nanoparticle system very fast.

5. Conclusion

Overall, our findings show that the specific functionalization of the gold nanoparticle plays a role in the heat transfer characteristics to the lipid bilayer. By tuning hydrophobicity and hydrophilicity, one can select the medium that primarily carries the heat assuming the nanoparticle heat sources are small enough to be engulfed by the bilayer. This primary heat carrier medium dictates the heat transfer efficiency which in turn can be used to control the total heating of the system. The heat source positioning can also be used to either induce a heating asymmetry between the bilayer leaflets in, for example, liposomal systems or to remove this asymmetry, which is characteristic to lipid bilayer heat conductance, via spanning the bilayer center plane by the heat sources so that the sources couple to both leaflets. In total, the findings here could provide additional means to tailor the thermophysical characteristics of lipid bilayers heated by nanoparticle type localized heat sources. Such heating occurs in, for example, photoactivated drug release.

Conflict of interest

There is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.chemphys.2015. 09.016.

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