Understanding the Mechanisms of Decorated Nanoparticle Aggregation In Lipid Membranes

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Abstract

Gold nanoparticles are a ubiquitous photosensitizer with a broad range of applications in microscopy and targeted drug delivery. Vesicles photosensitized with gold nanoparticles are promising as targeted drug delivery vehicles due to their non-invasive rupture mechanism. Controlling the vesicle properties increases control of the spatial-temporal release of cargo and drug dosage. The aggregation of gold nanoparticles affects the photoporation of these vesicles by interfering with peak SPR wavelengths. These nanoparticles cause leaflet bending deformations on the order of the nanoparticle size, while ligand chains may also disrupt local packing of lipid chains. Aggregation may be driven by the need to minimize one or both effects, but their relative contributions are unknown. In order to test the contributions of these two perturbations to membrane structure, we simulated multi-nanoparticle systems in lipid membranes of varying compositions. We used coarse-grained molecular dynamics simulation via the MARTINI forcefield to simulate simple spherical nanoparticles with a decorated ligand exterior. We found that large-scale nanoparticle aggregation depends more on ligand chain length than nanoparticle size, suggesting that aggregation of gold nanoparticles is dominated by microscopic perturbations to lipid packing.

Hydrophobic nanoparticle size regime determines aggregation mechanism

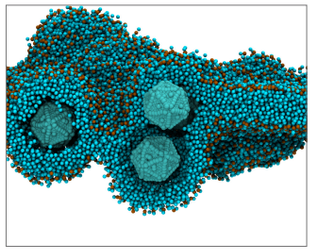


Fig 2. Visualization of a lipid membrane with hydrophobic 5nm nanoparticles. Lipids are in cyan, phosphate bead in orange, and nanoparticles in blue. Ligands and nanoparticle surface beads are not shown

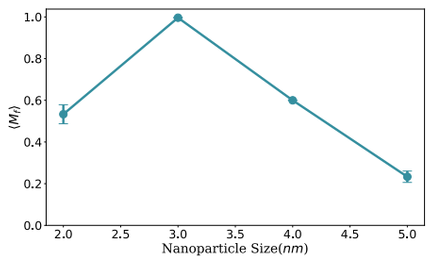


Fig 4. Fraction of nanoparticle monomers in systems with varying NP diameters. Each system has 3 replicas that ran for 5μ s, analysis was averaged over the final 1μ s. Systems contain 10 nanoparticles, lipid-nanoparticle ratio is held constant.

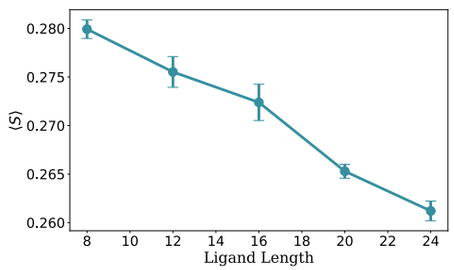


Fig 5. Lipid order parameter dependence on nanoparticle ligand length. Systems contain single, 2n m nanoparticles and ran for 20μ s, analysis was averaged over the final 1μ s. A negative monotonic trend is observed as ligand length increases.

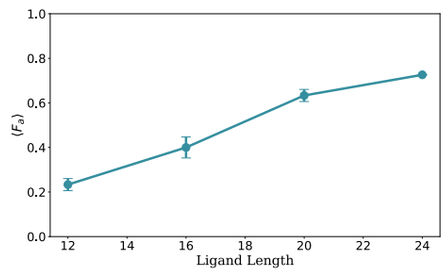


Fig 6. Fraction of nanoparticles in the largest aggregate in systems of varying ligand length. Each system has 3 replicas that ran for 5μ s, analysis was averaged over the final 1μ s. Systems contain sets of 10, 2n m nanoparticles held at constant lipid-nanoparticle ratio.

Background

- Ligand coated nanoparticles (NPs, Figure 1) are multipurpose tools used in biosensing, biolabelling, and controlled drug delivery[1]
- Nanoparticle aggregation in lipid membranes poses a challenge for many applications
- The mechanism of ligand coated nanoparticle aggregation is not well understood.
- We use coarse grained molecular dynamics to study the aggregation mechanism due to two types of deformations, membrane bending and acyl chain bending

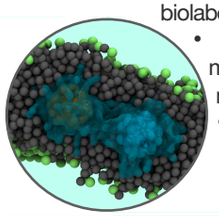


Fig 1. Visualization of 2 nm charged nanoparticles aggregating. Ligands in blue, nanoparticles in ochre and blue, lipid heads in green, lipids in grey.

Research Questions

1. What is the primary mechanism of aggregation for charged and hydrophobic ligand coated nanoparticles in phosphatidylcholine membranes?
2. Is the nanoparticle aggregation mechanism dependent on the nanoparticle regime?
3. How do charged interactions affect nanoparticle aggregation?

Charge influences small NP aggregation

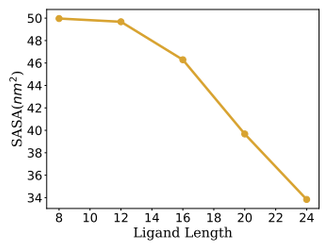


Fig 7. Solvent accesible surface area at varying ligand length in single nanoparticle systems. Systems contain 2n m nanoparticles and ran for 20μ s, analysis was averaged over the final 5 μ s. A negative monotonic trend is observed with increasing ligand length.

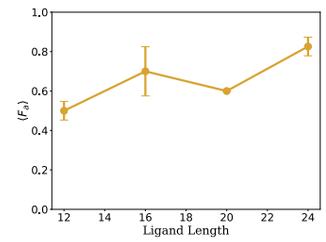


Fig 8. Fraction of nanoparticles in the largest aggregate dependence on the ligand length of charged nanoparticles. System contain 10 nanoparticles held at a fixed ratio with lipids. 3 replicas of each system ran for 5 μ s, analysis was averaged over the final 1 μ s.

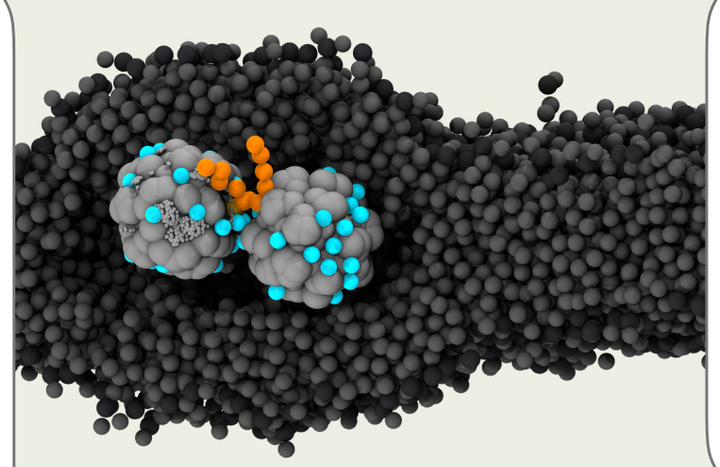
Methods

- Simulation software: Gromacs 2016[3], Force Field: Martini 2.2[2]
- POPC Membranes constructed with insane.py[4]
- # of NP's in largest aggregate (n)
- Total # of nanoparticles in the system (n_{tot})
- Total number of single nanoparticle in the system (n_s)

Largest Aggregate Fraction $F_a = \frac{n}{n_{tot}}$

Monomer Fraction $M_f = \frac{n_s}{n_{tot}}$

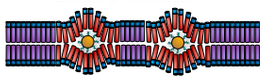
Order Parameter $S = \frac{3\langle cos^2\theta \rangle - 1}{2}$



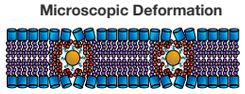
Approach

- CG-MD simulations of hydrophobic and charged nanoparticles.
- Simulating nanoparticles at 4 different diameters to understand nanoparticle induced membrane deformation impact on aggregation.
- Simulating nanoparticles at 5 different ligand length to understand nanoparticle induced lipid deformations impact on aggregation.

Elastic Deformation



Microscopic Deformation



Summary

- Bare hydrophobic nanoparticle aggregation in lipid membranes has been shown in other works to be primarily driven by membrane deformations, however, ligand coated nanoparticle aggregation is driven by both elastic membrane deformations (large NP regime) and microscopic packing deformations.[5,6]
- Nanoparticle aggregation is dependent on the degree of local lipid chain disorder.
- At short ligand lengths, the charged nanoparticle surface is more exposed.
- Charged nanoparticles coated by short (but not long) form larger aggregates than the equivalent hydrophobic nanoparticles, likely reflecting increased exposure.

References

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