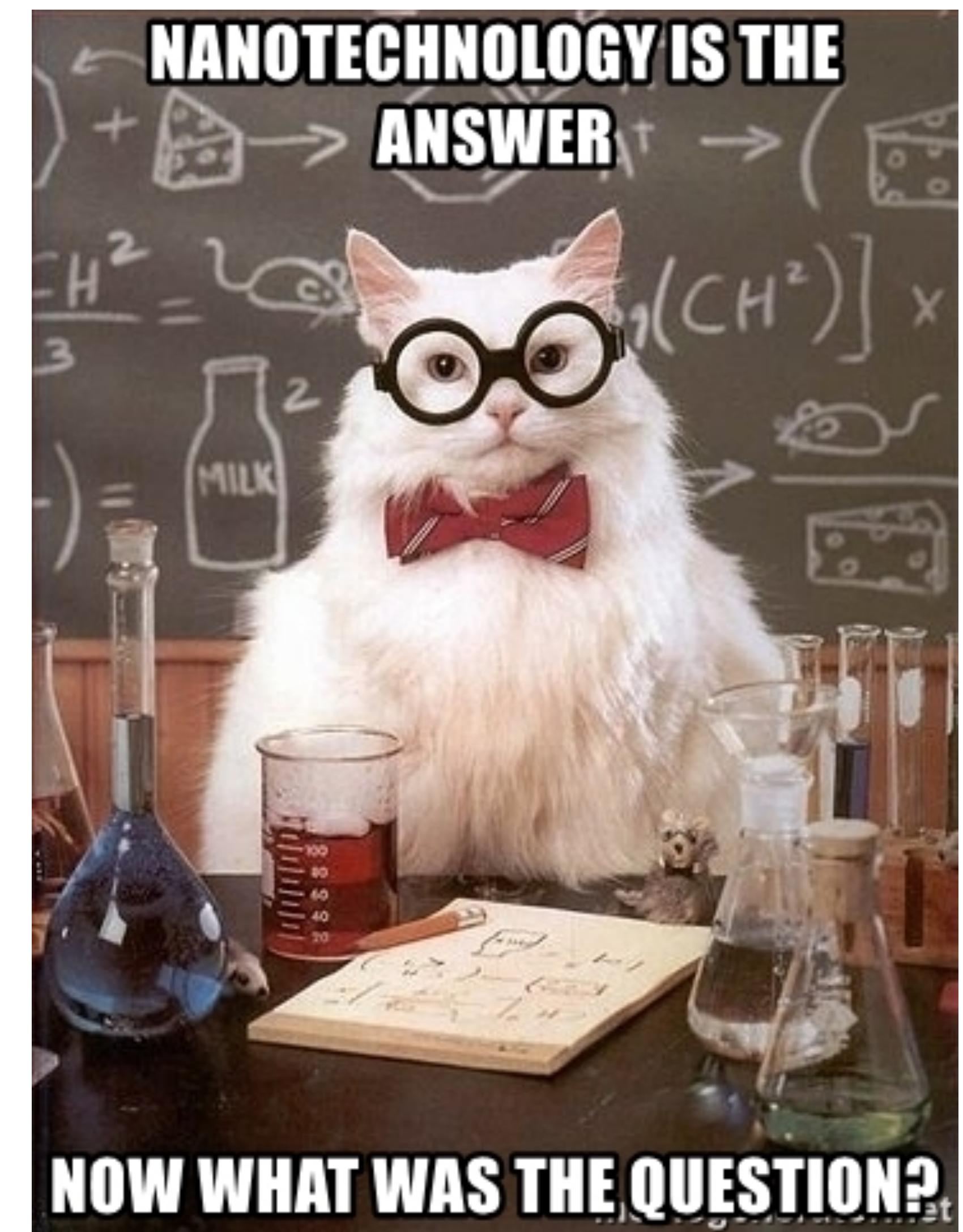


A molecular dynamics approach to understanding local lipid heat disruption by gold nanoparticles

Jahmal Ennis

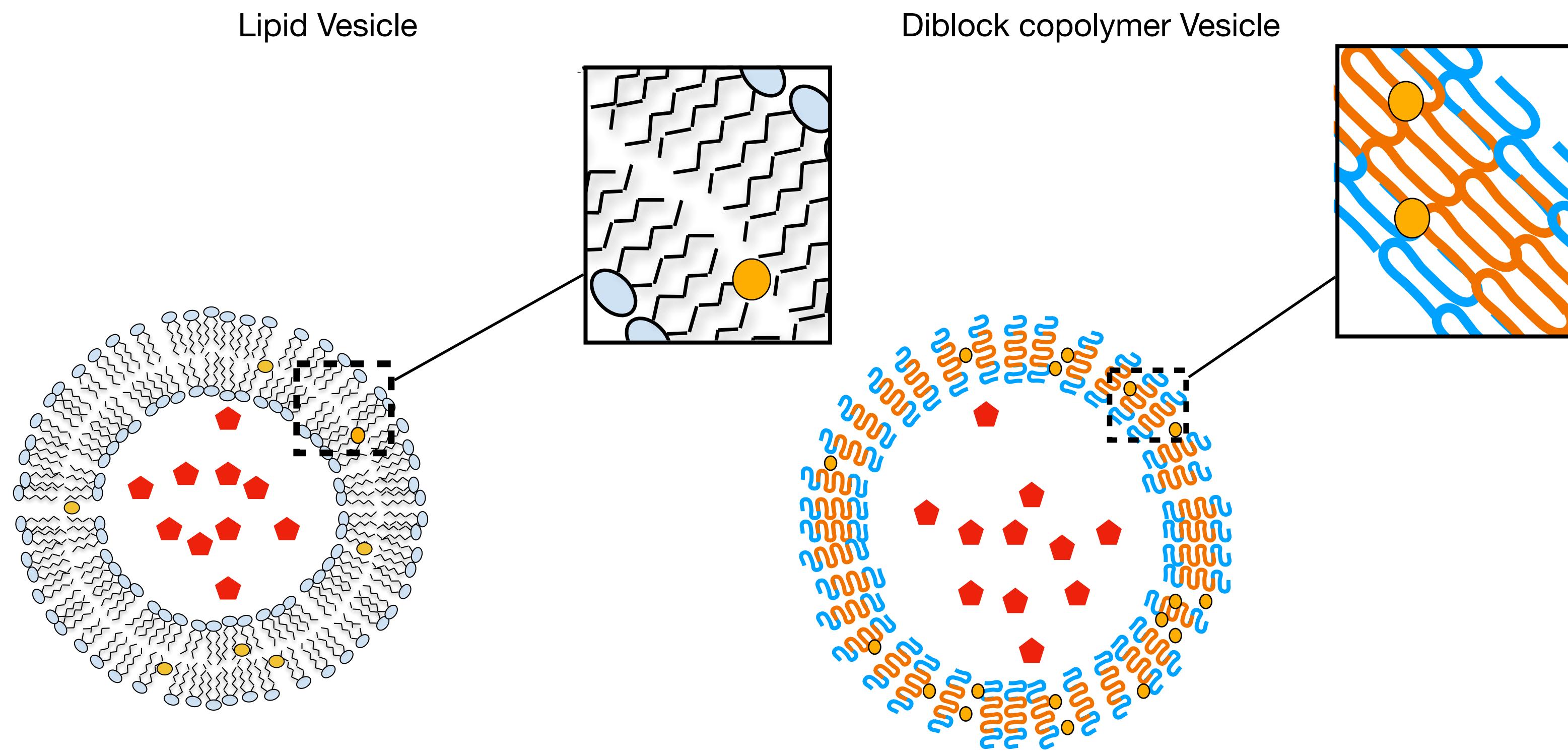


Background

Drug Delivery and Self-assembled vesicles

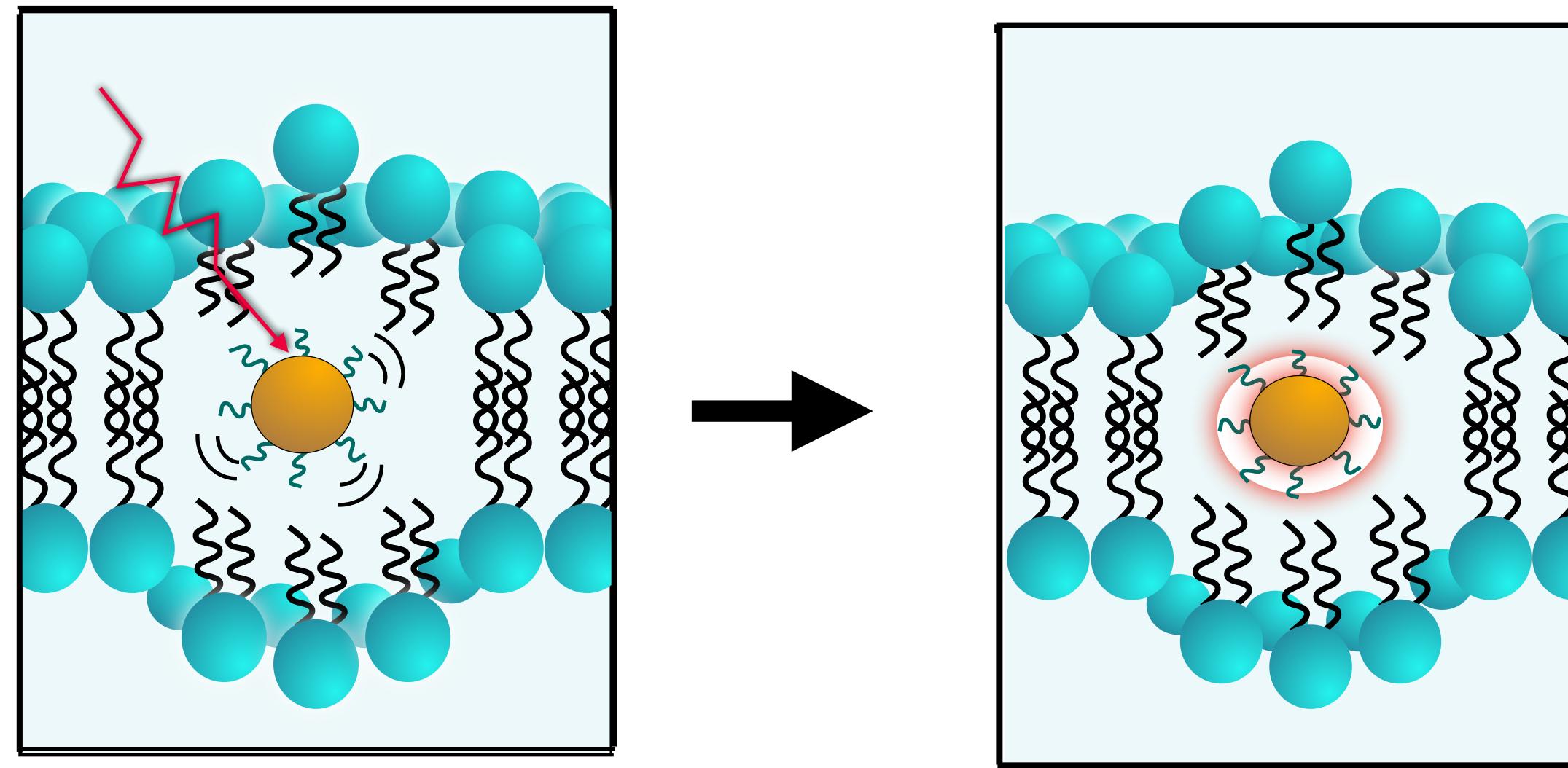
- Drug delivery industry is a multibillion dollar industry
- Methods for delivering drugs such as oral and injection are outdated
- Minimally invasive controlled delivery and drug release
- Self-assembled vesicles can improve upon current drug delivery methods
 - Easily trap and transfer small molecules
 - Spacial and temporal control during drug release
 - Tunable for multipurpose application

What are self-assembled vesicles?



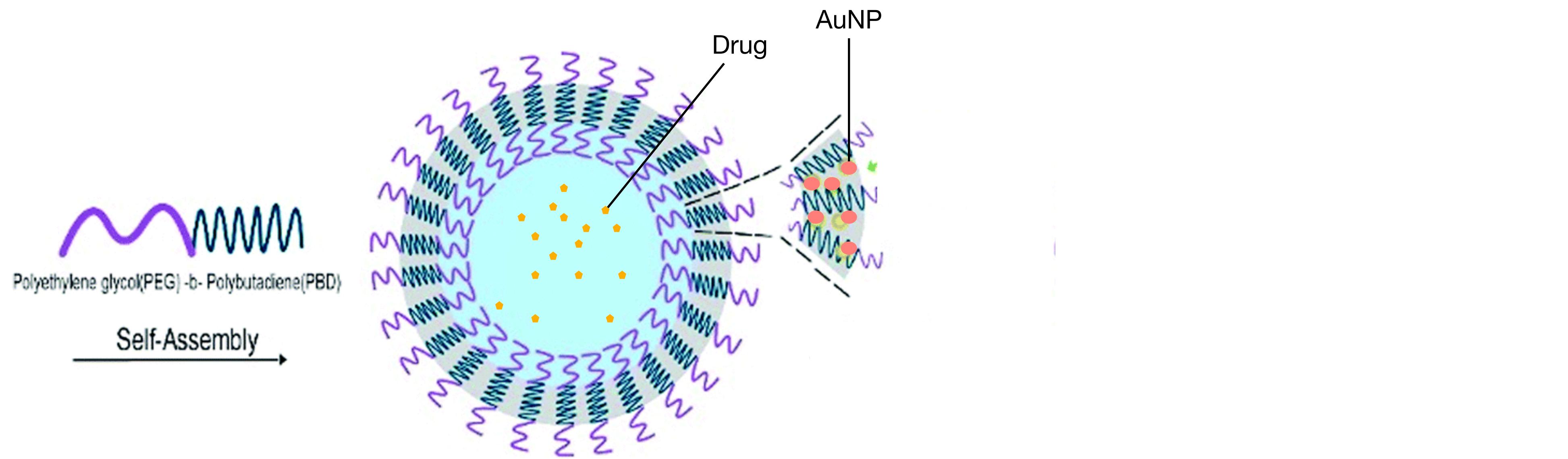
- Amphiphilic molecules
- Spontaneously rearrange to form an inside and outside
- Liposome building blocks are lipids
- Polymersome building blocks are Diblock copolymers

Light responsive gold nanoparticles

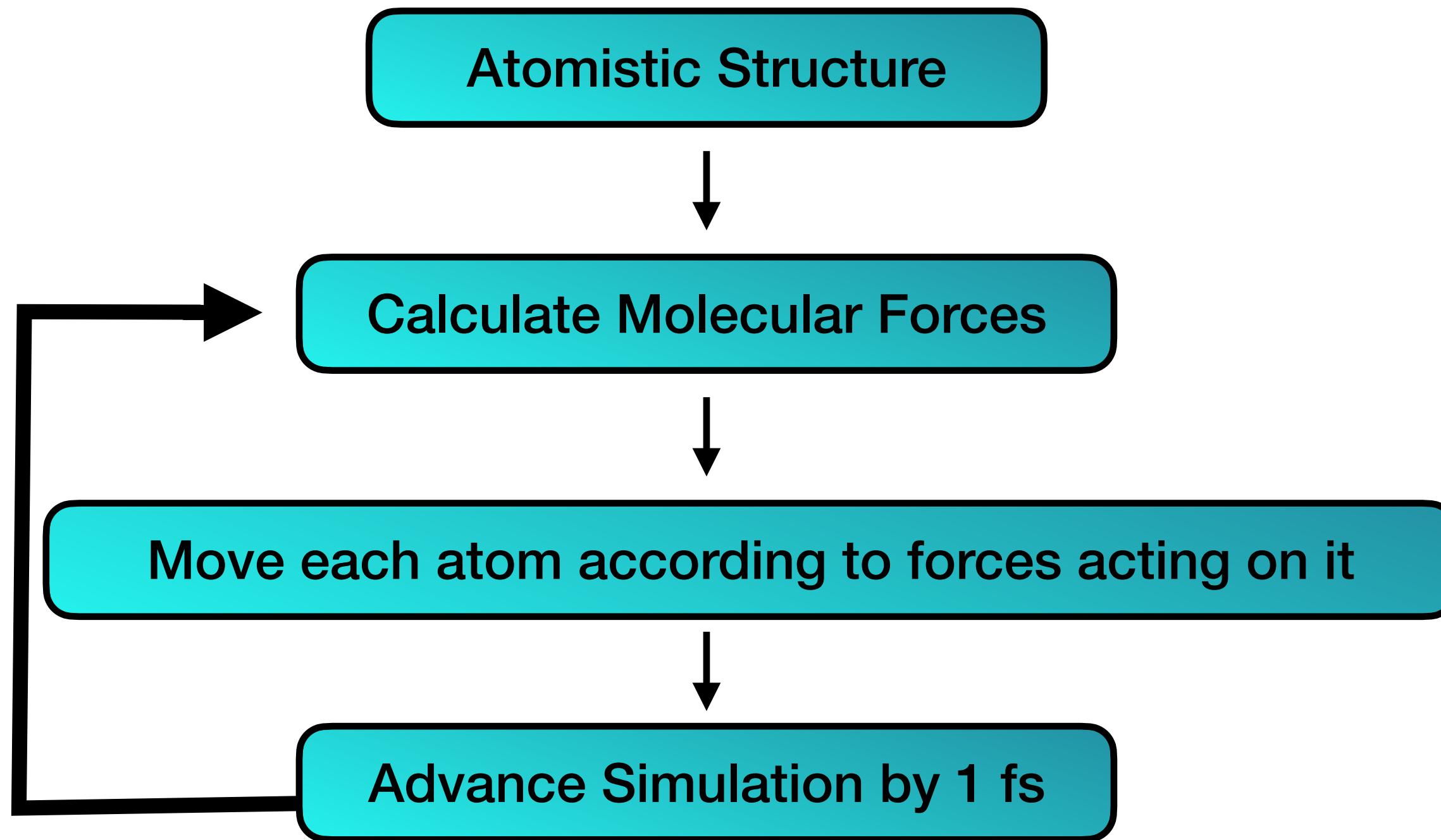


- Ligand coated gold nanoparticles
- Electrons on the surface of gold will oscillate causing strong excitation of the gold
- Surface plasmon resonance causes heating in membrane
- Can cause membrane disruptions

Polymersome Poration Schematic

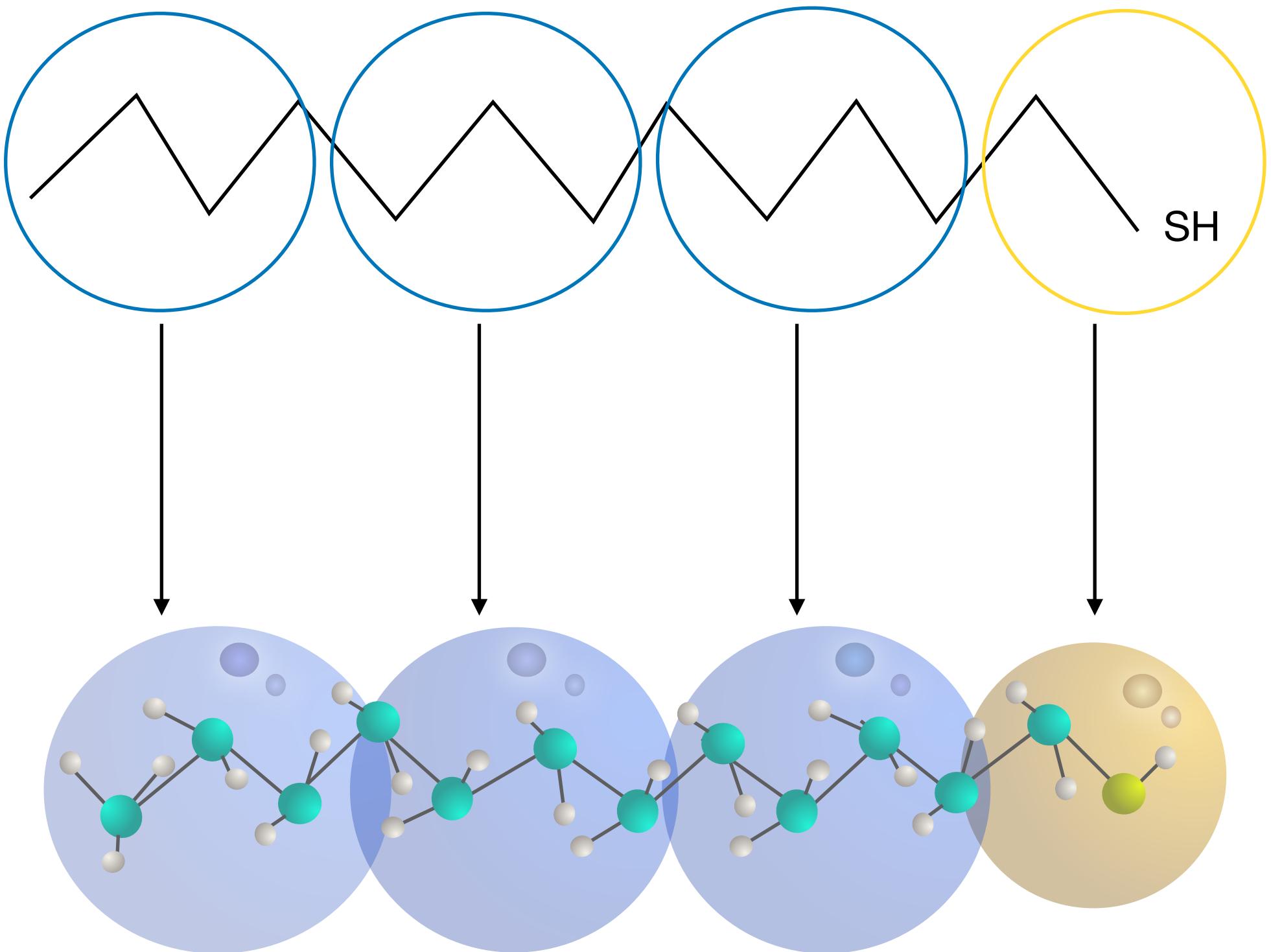


Molecular Dynamics as a Computational Microscope



- Capture the behavior of macromolecules with high resolution
- Simulate on the time-scales of biologically relevant events
- A method to observe events in real time

Coarse Grained Molecular Dynamics



- 4 to 1 mapping scheme for heavy atoms
- Bonded “Beads”
- Generalize electrostatic interactions
- Lower resolution trade-off for longer time scale

Main Question and Approach

- What factors effect local lipid membrane disruption caused by heat transfer from gold nanoparticles?

Aim 1

- Investigating the effects of membrane composition on nanoparticle organization

Aim 2

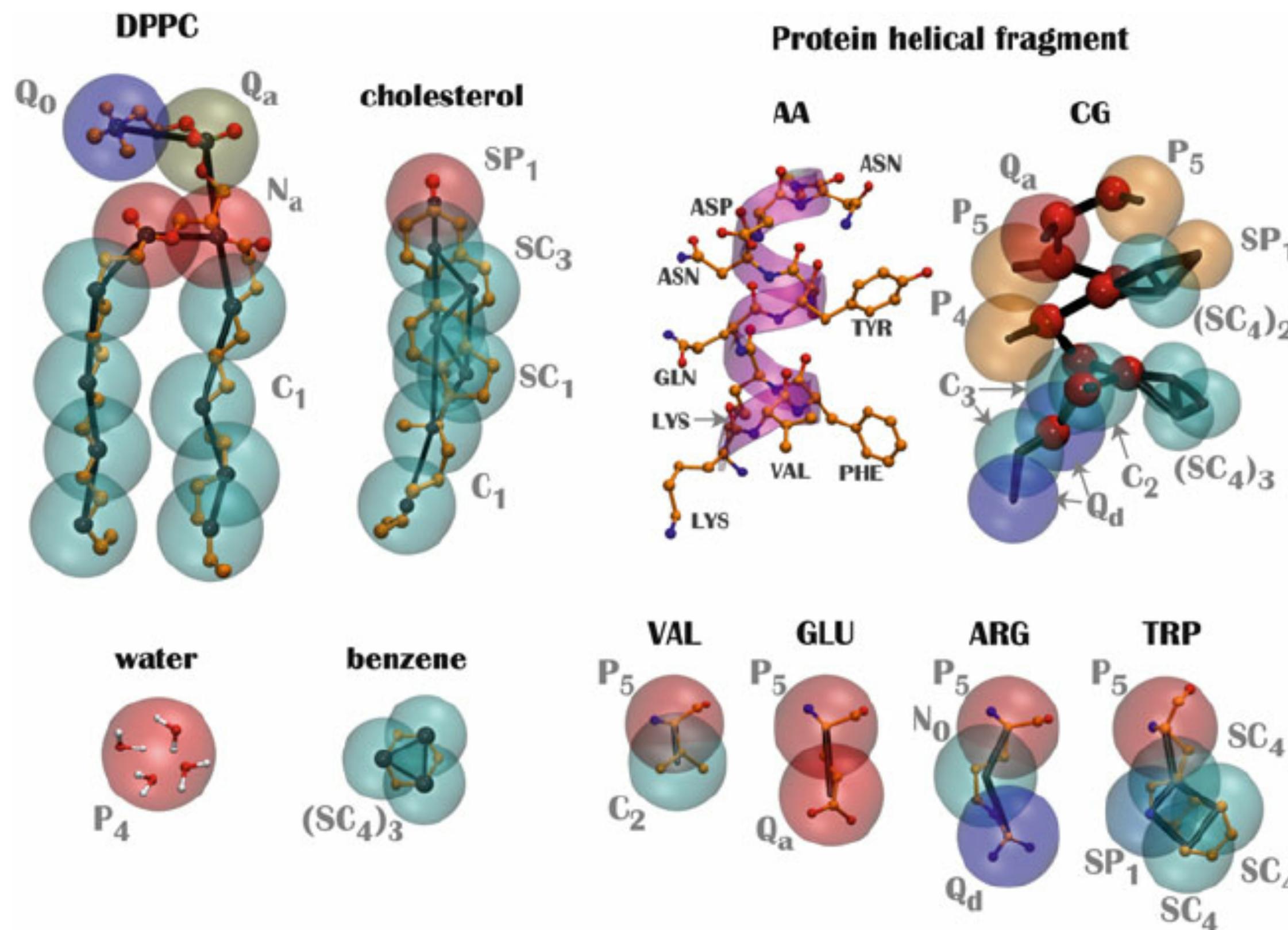
- Investigating the effects of nanoparticle temperature on aggregation and membrane structure

Preliminary Work

Preliminary Work Outline

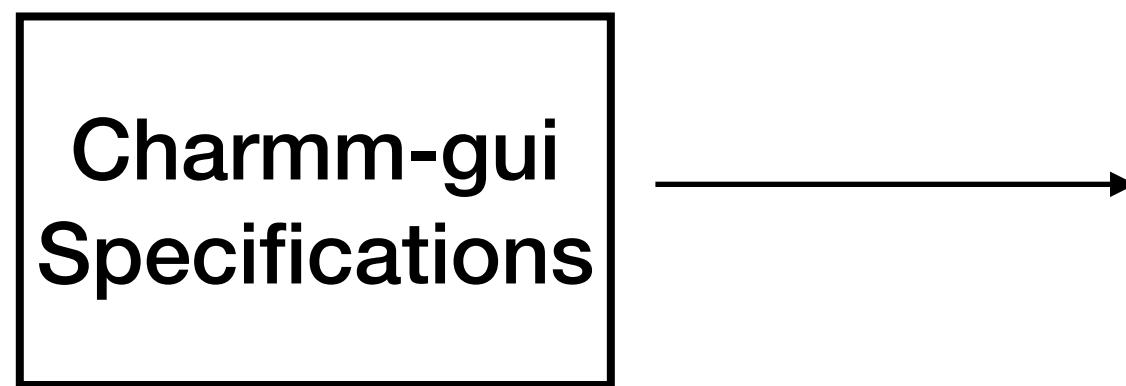
- Development of coarse grained gold nanoparticles
- Simulation of 613K nanoparticle in POPC membrane
- Simulation of two 313K nanoparticles aggregating
- Simulation of three AuNP aggregate system
- High concentration 36 AuNP aggregate system

Martini force field used to parameterize AuNP beads

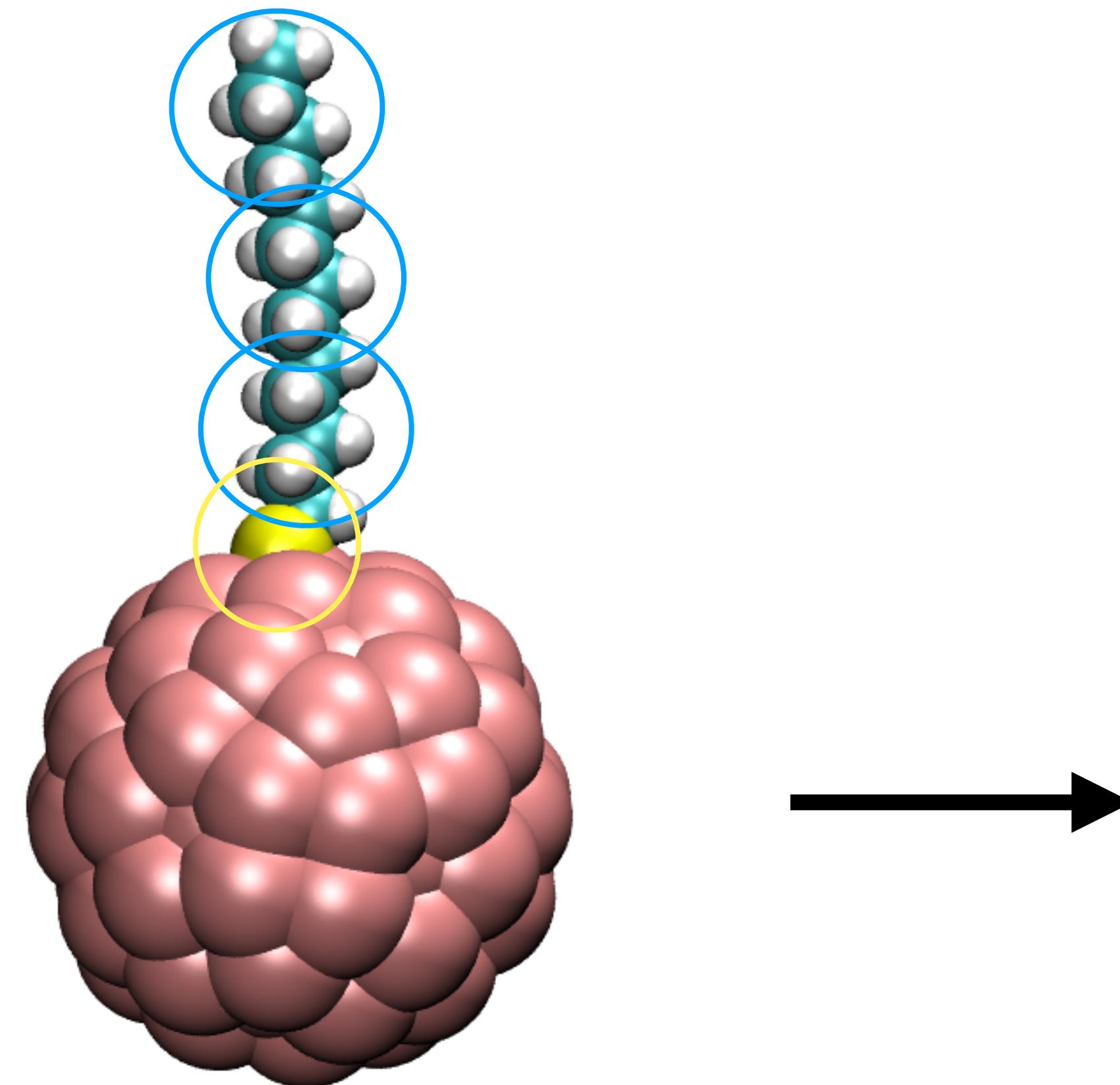


- 4 bead types Polar(P), Nonpolar(N), Apolar(C), Charged(Q), Polarity 1-5 and donor, acceptor groups
- Extensive well developed and validated lipid model
- Insane.py - Membrane building scripts

Development of pipeline to coarse grain gold AuNP's

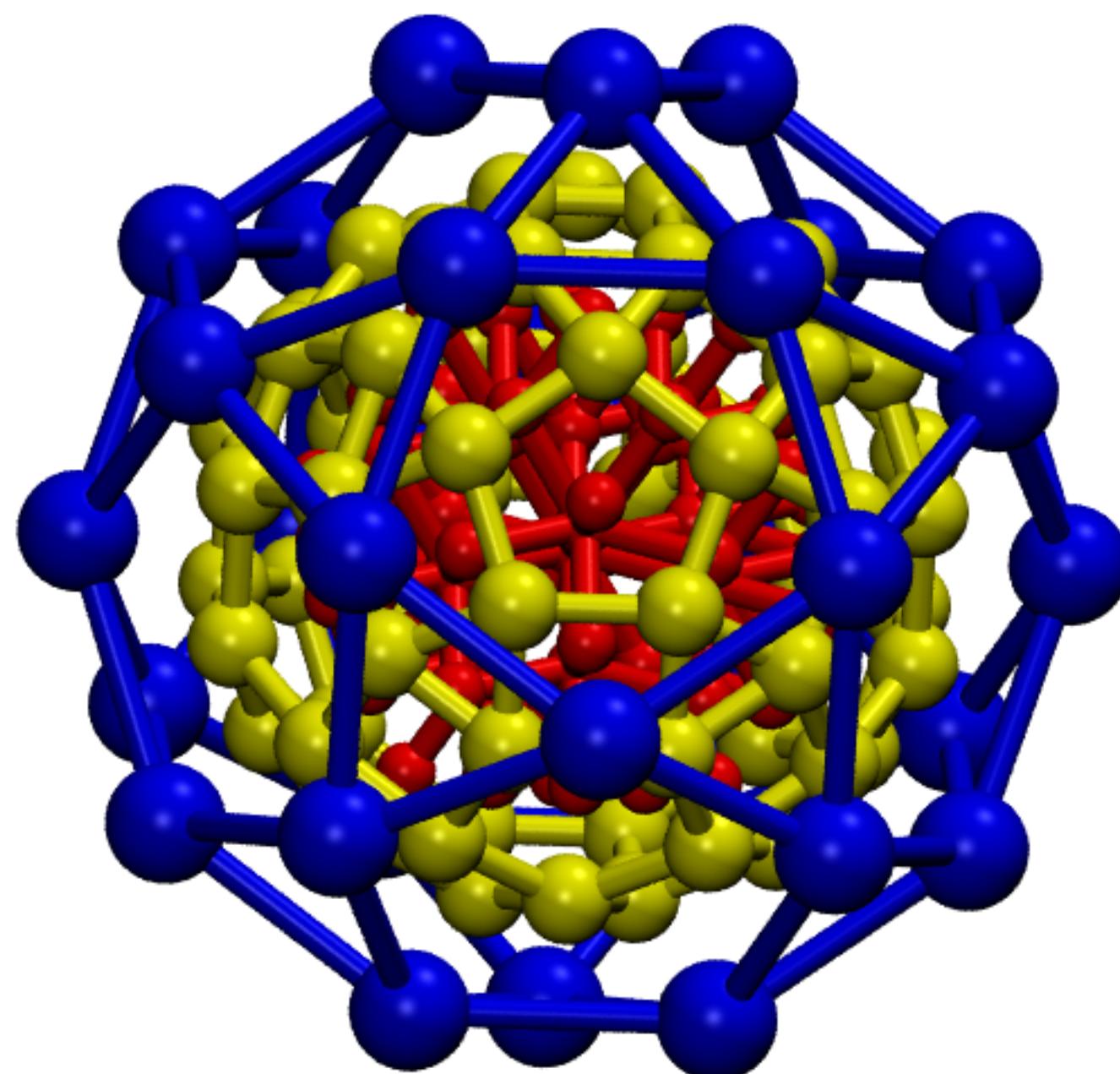


Coarse grained ligands on gold surface

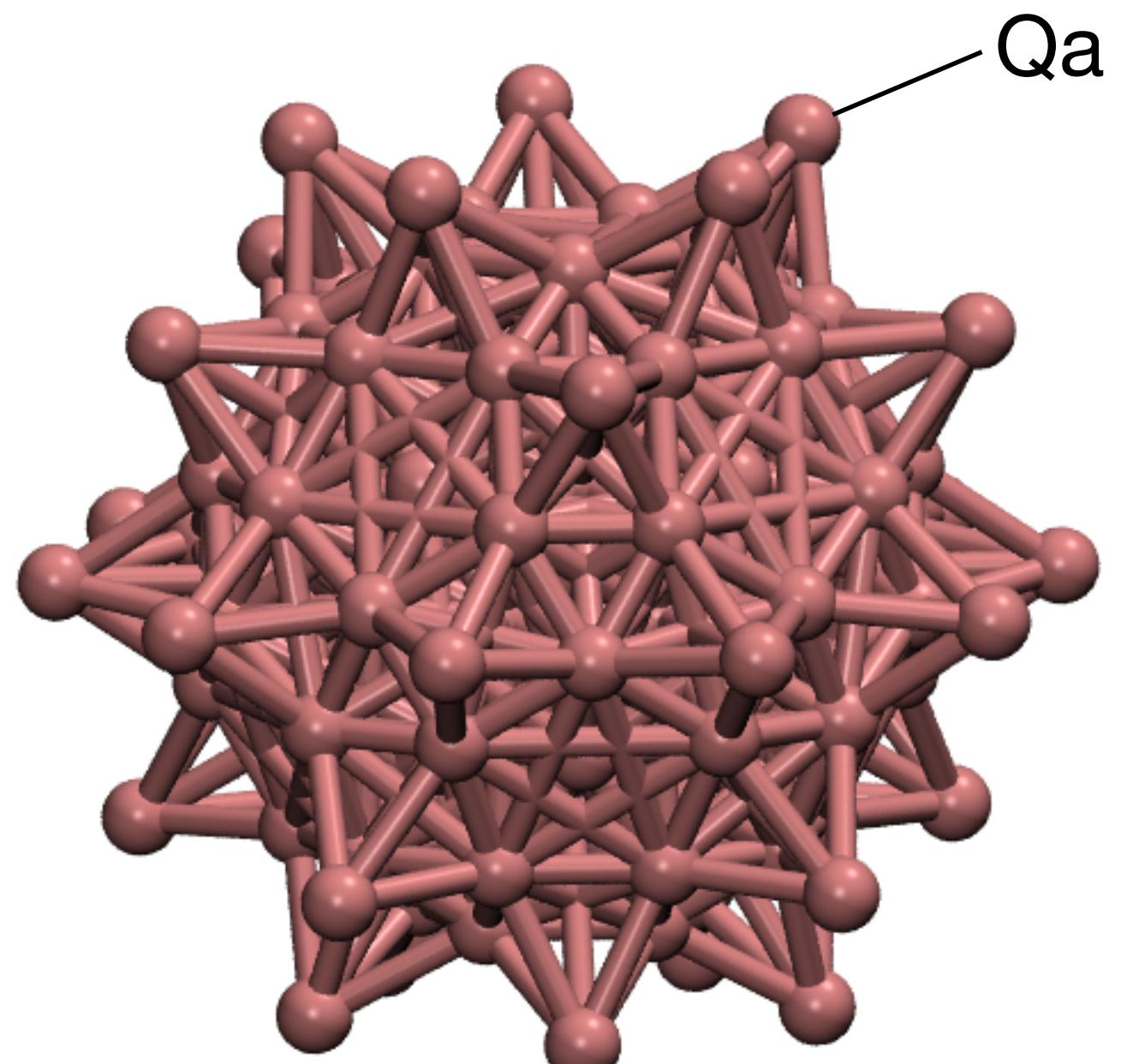


What are the parameters of an AuNP core?

Charmm-Gui Output Structure

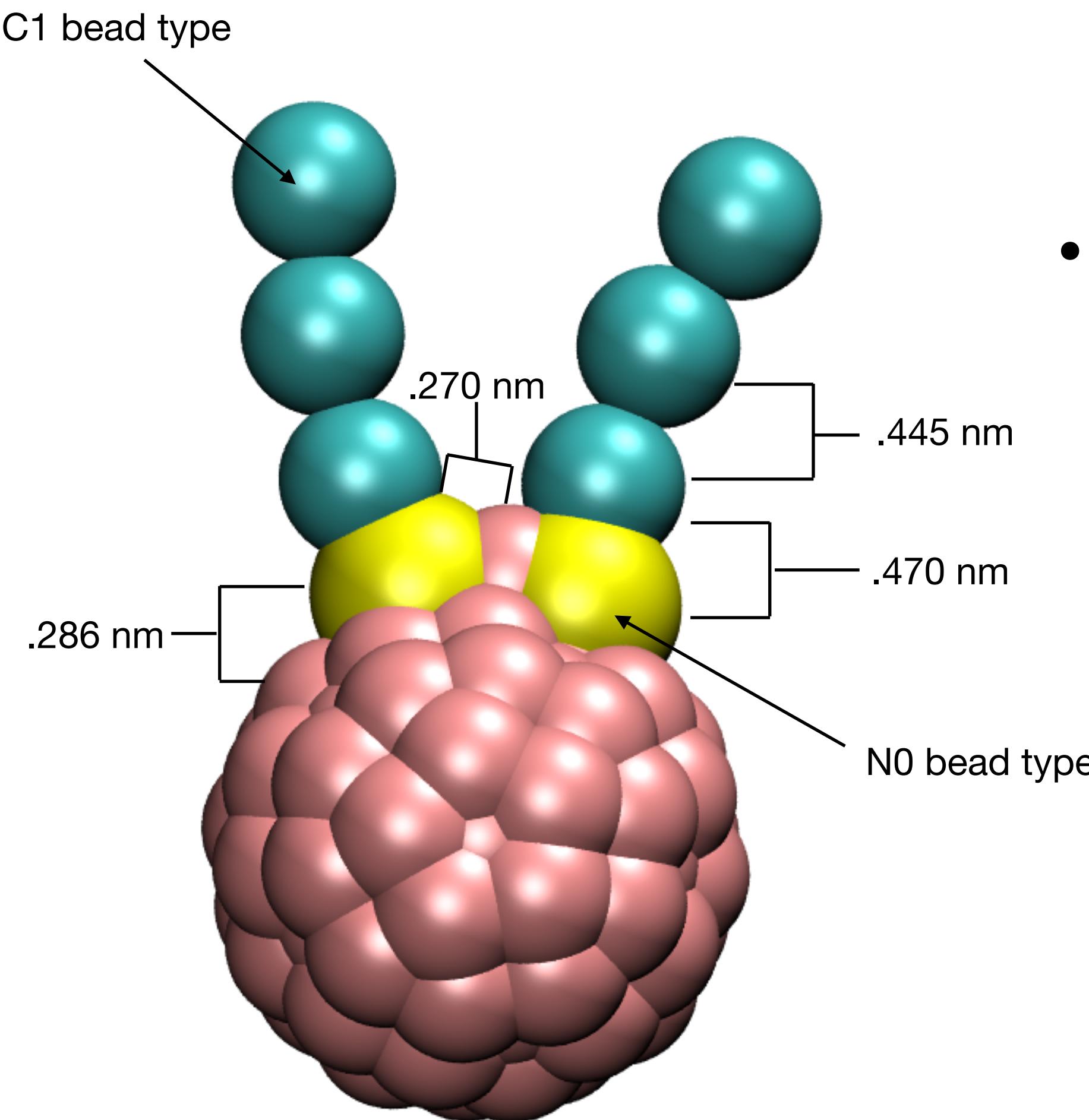
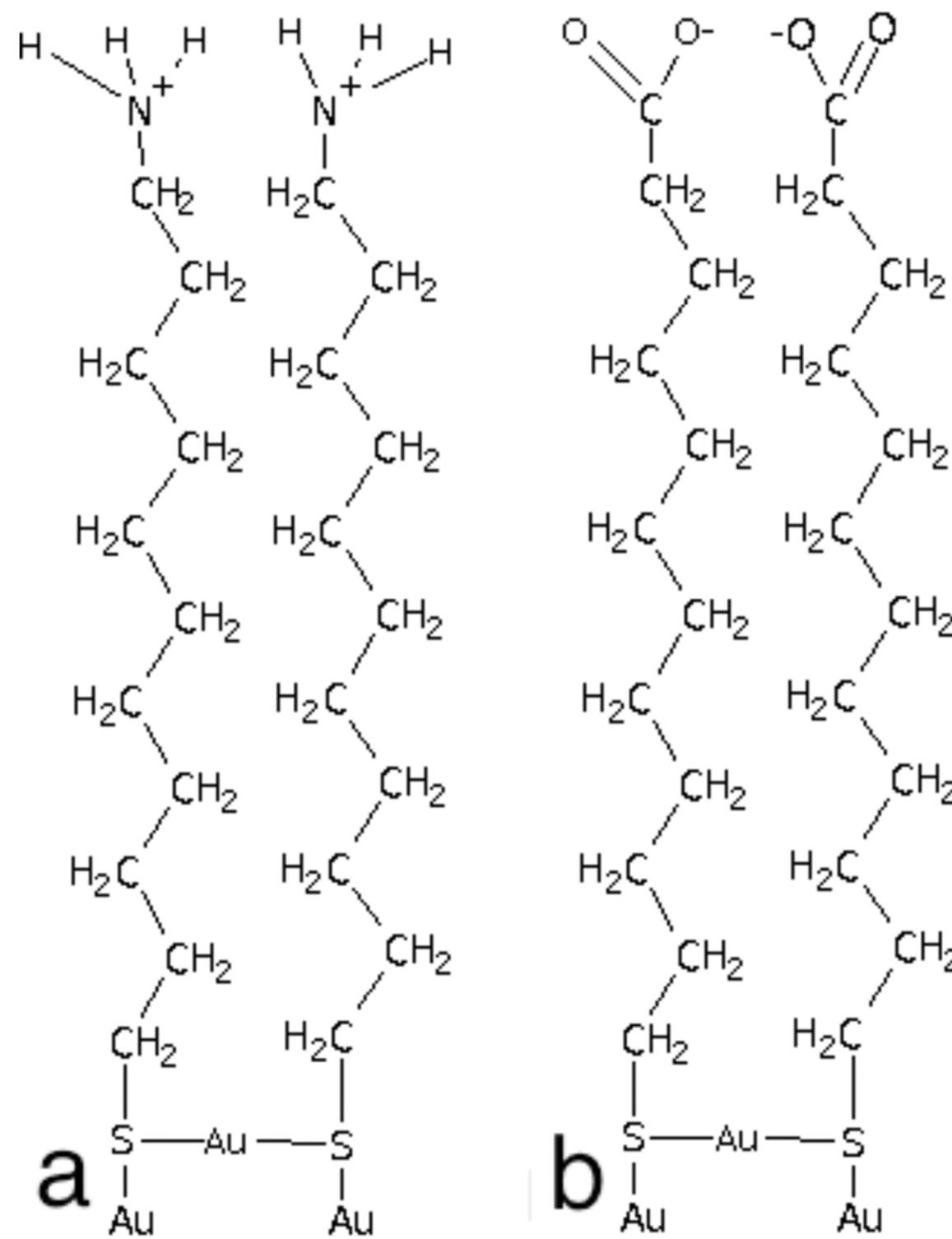


Applied Elastic network



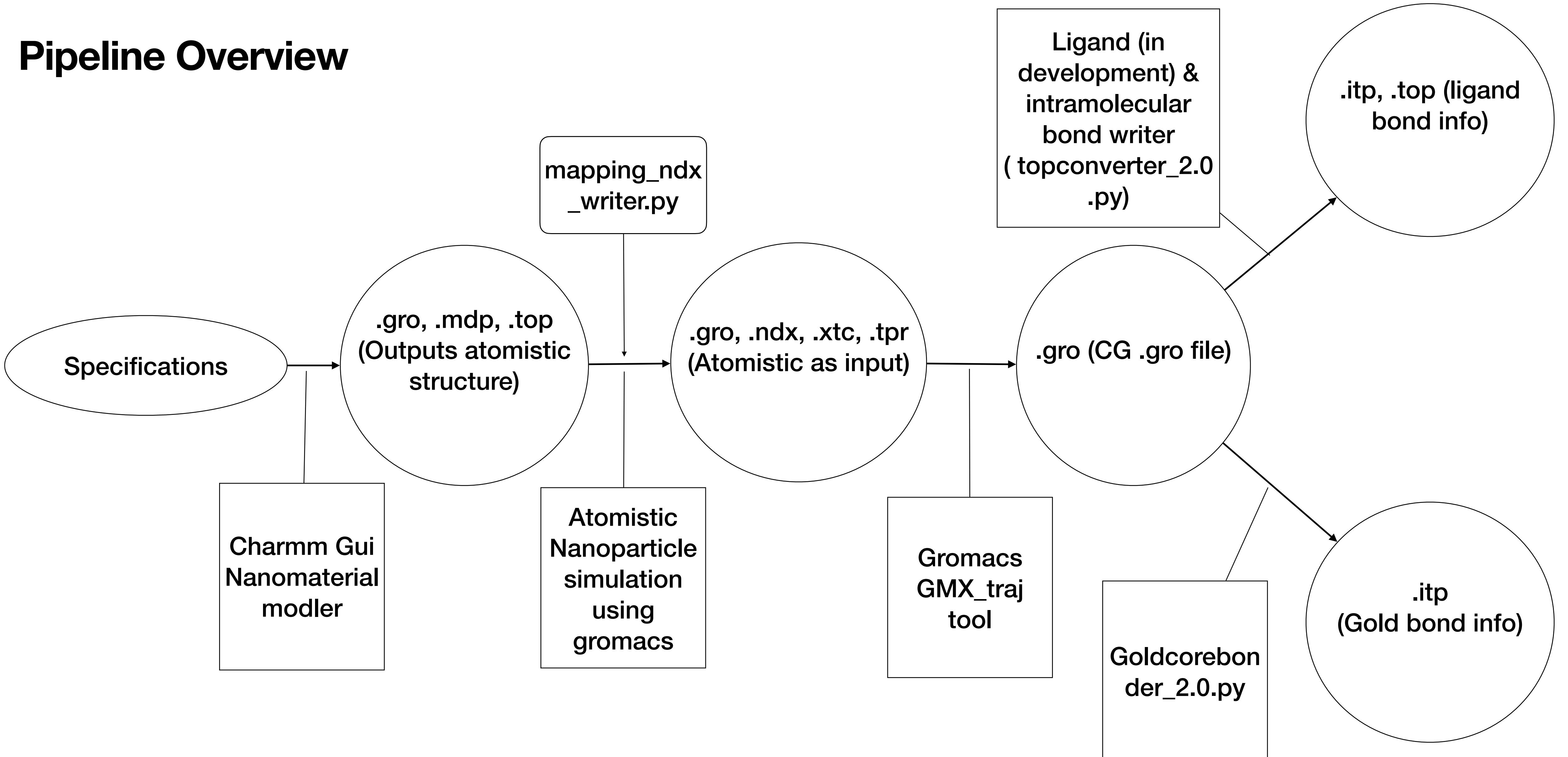
- Elastic network of bonds
- Beads within 5 Å are bonded
- Spring constant 3000 $Kj/(mol * nm^2)$

What is the parameterization of ligands on the gold surface?



- Spring constant 1250
 $Kj/(mol * nm^2)$

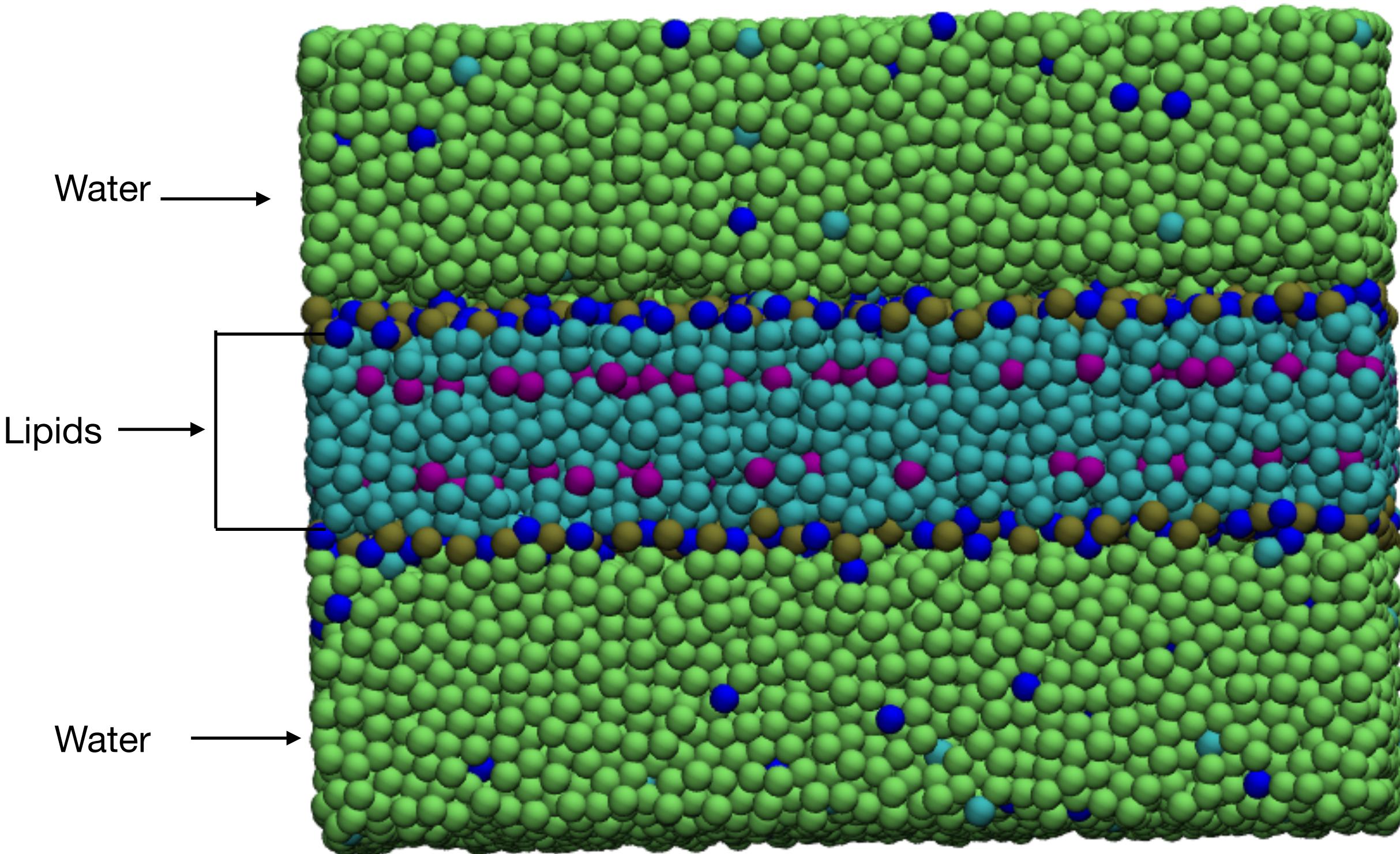
Pipeline Overview



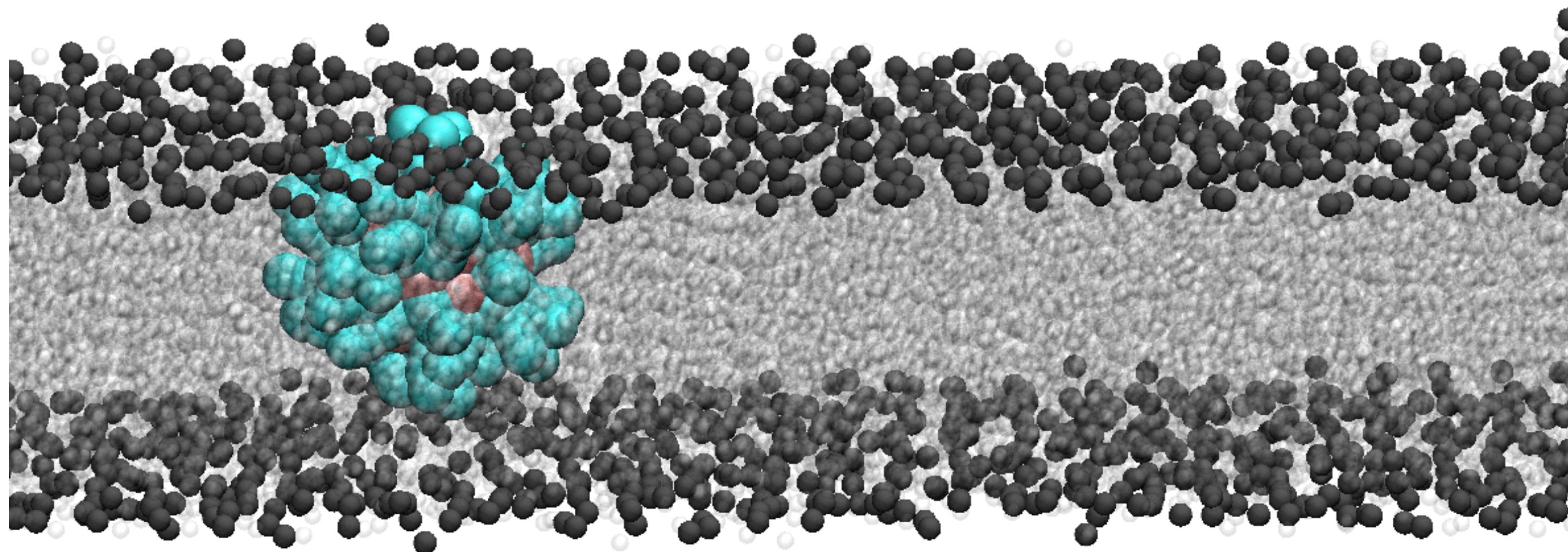
Mapping structure

Parameters/Connectivity

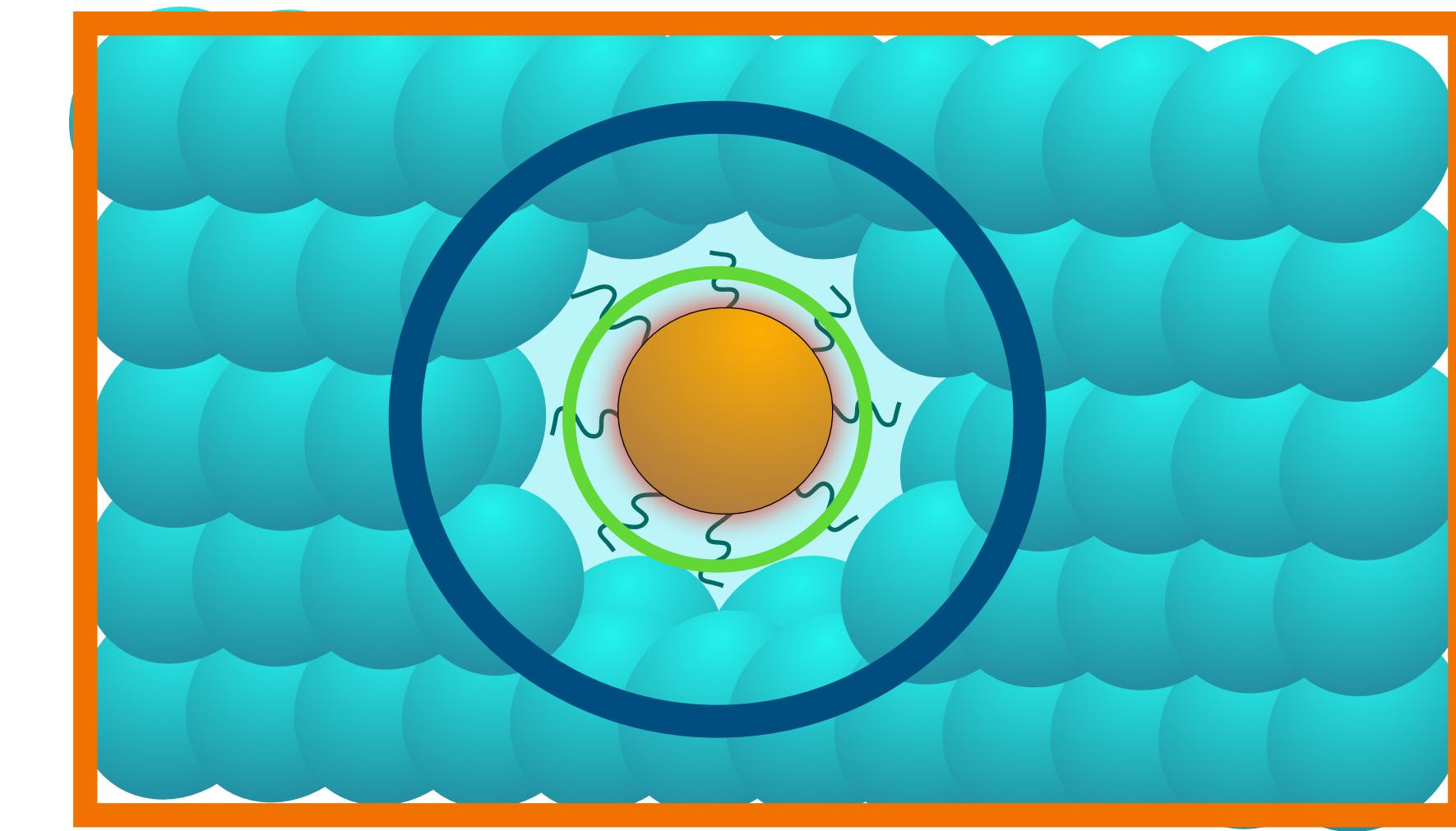
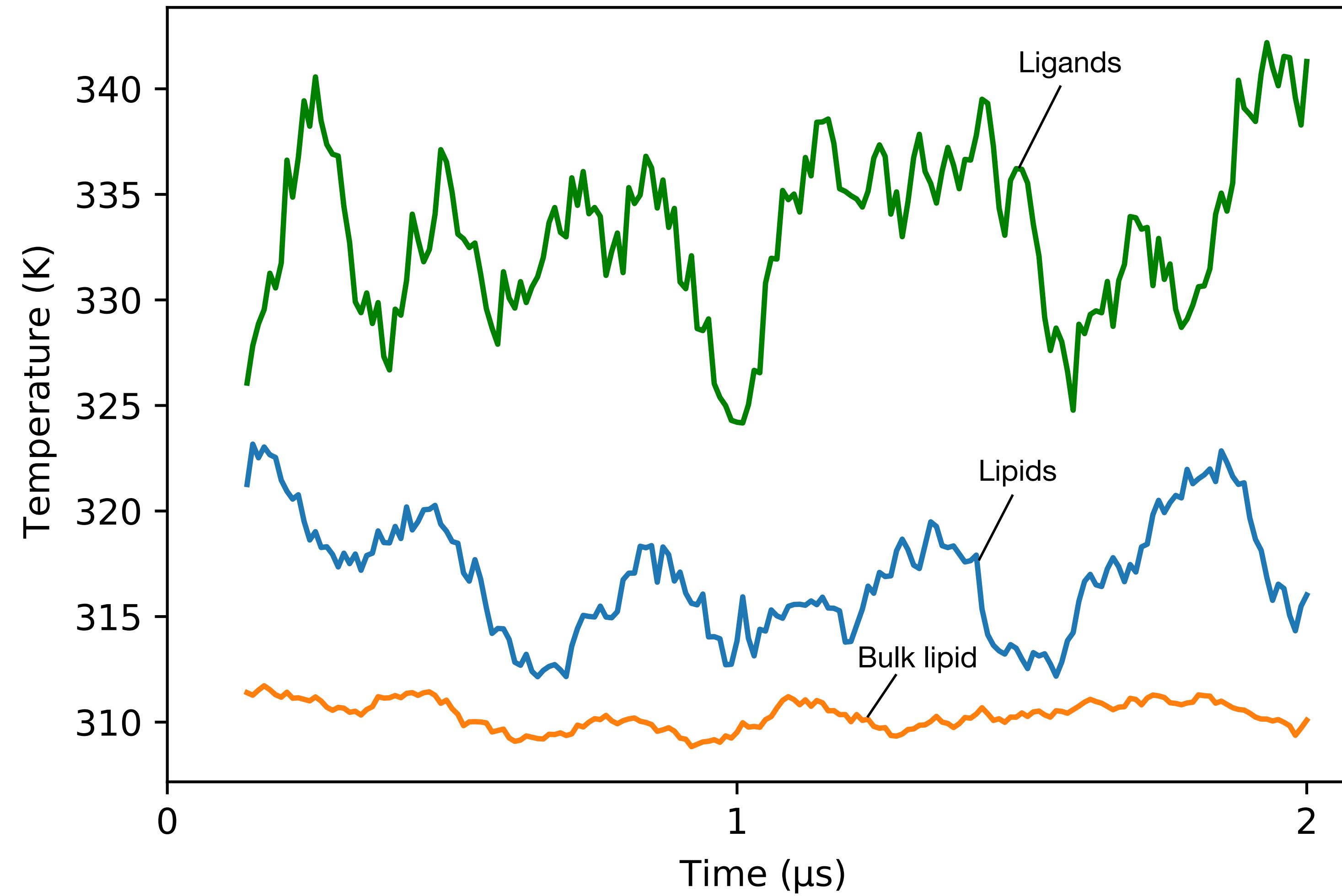
Representation of entire system



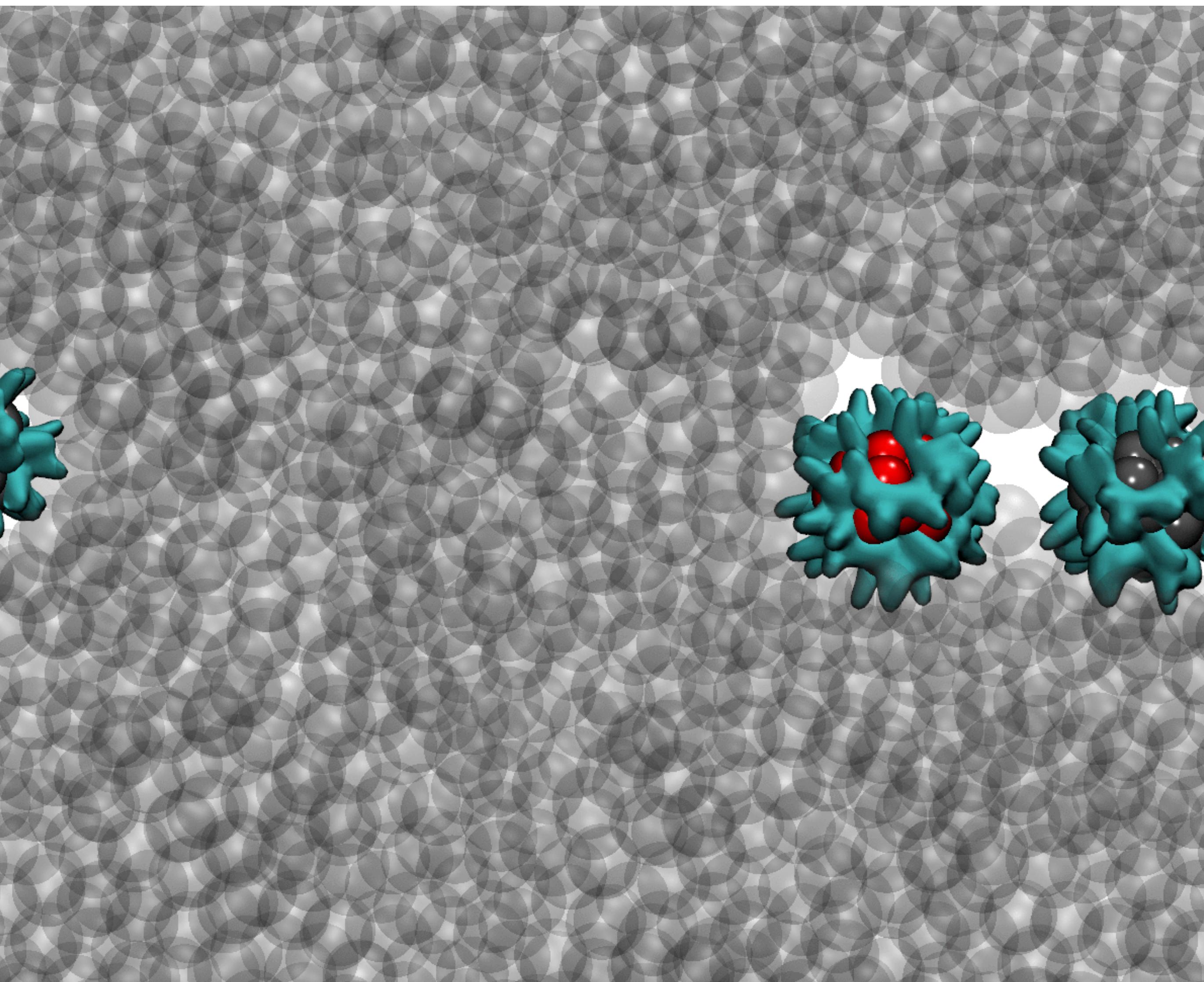
613K nanoparticle in POPC lipid membrane



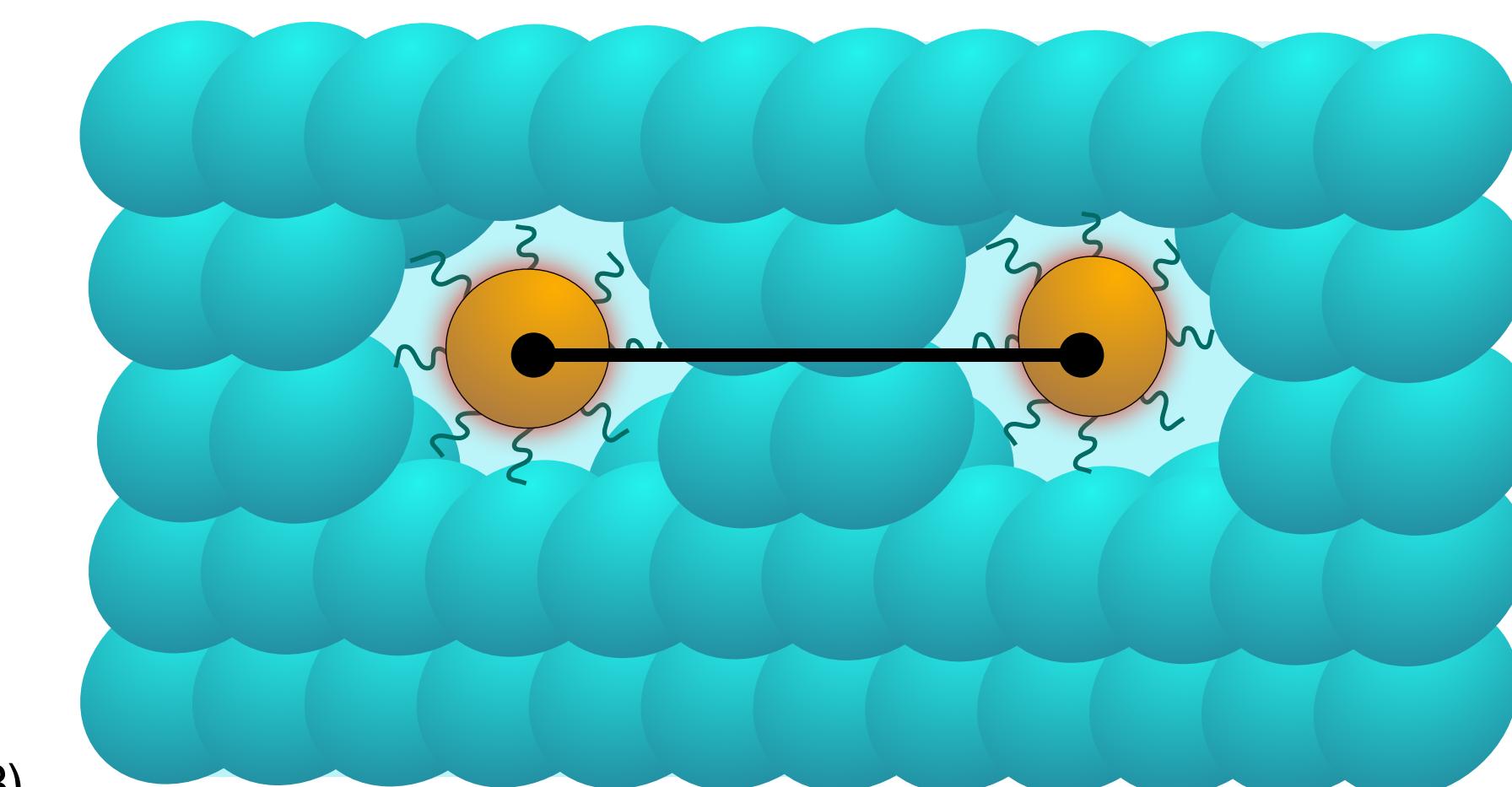
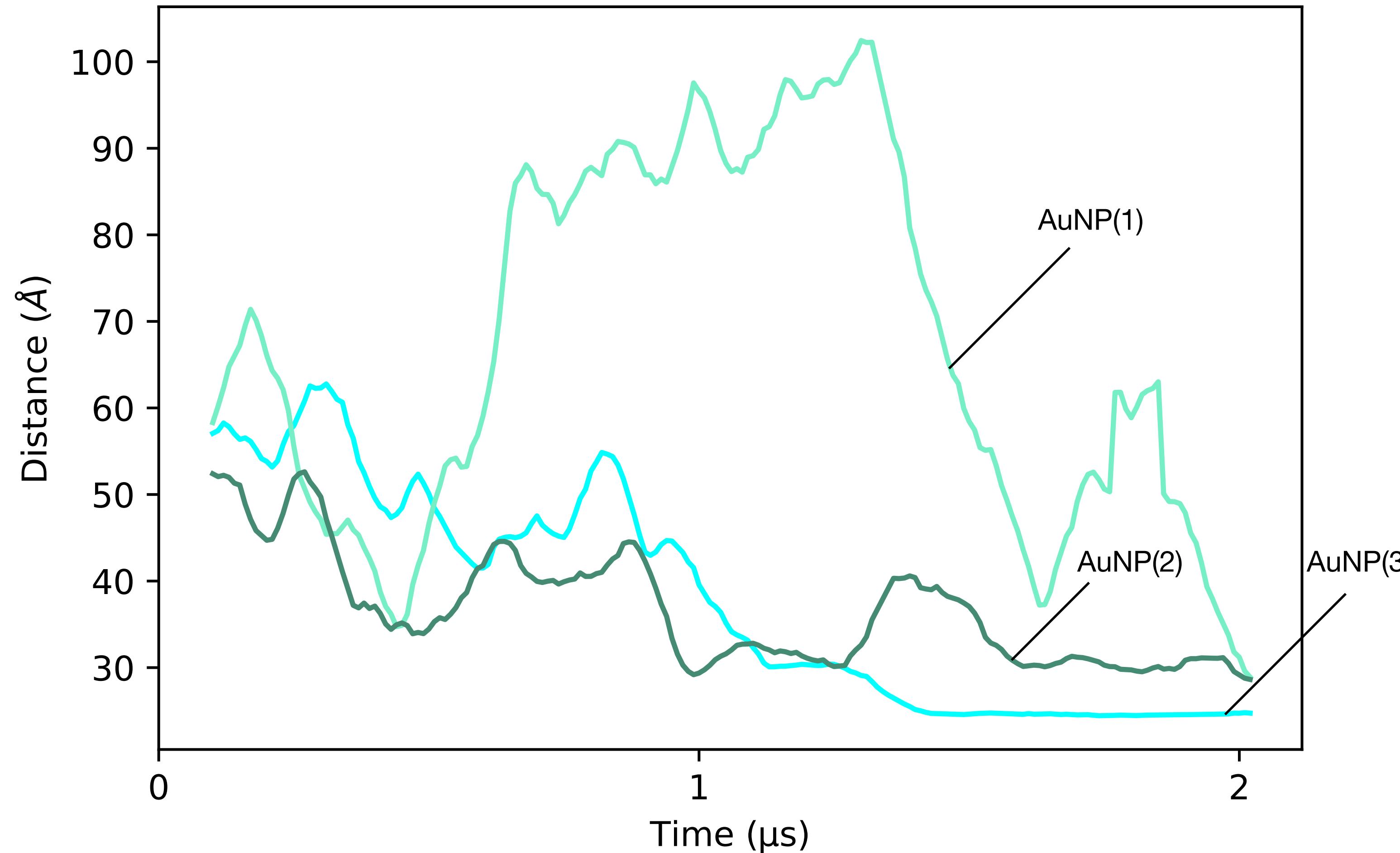
Analysis of local temperature around nanoparticle compared to bulk



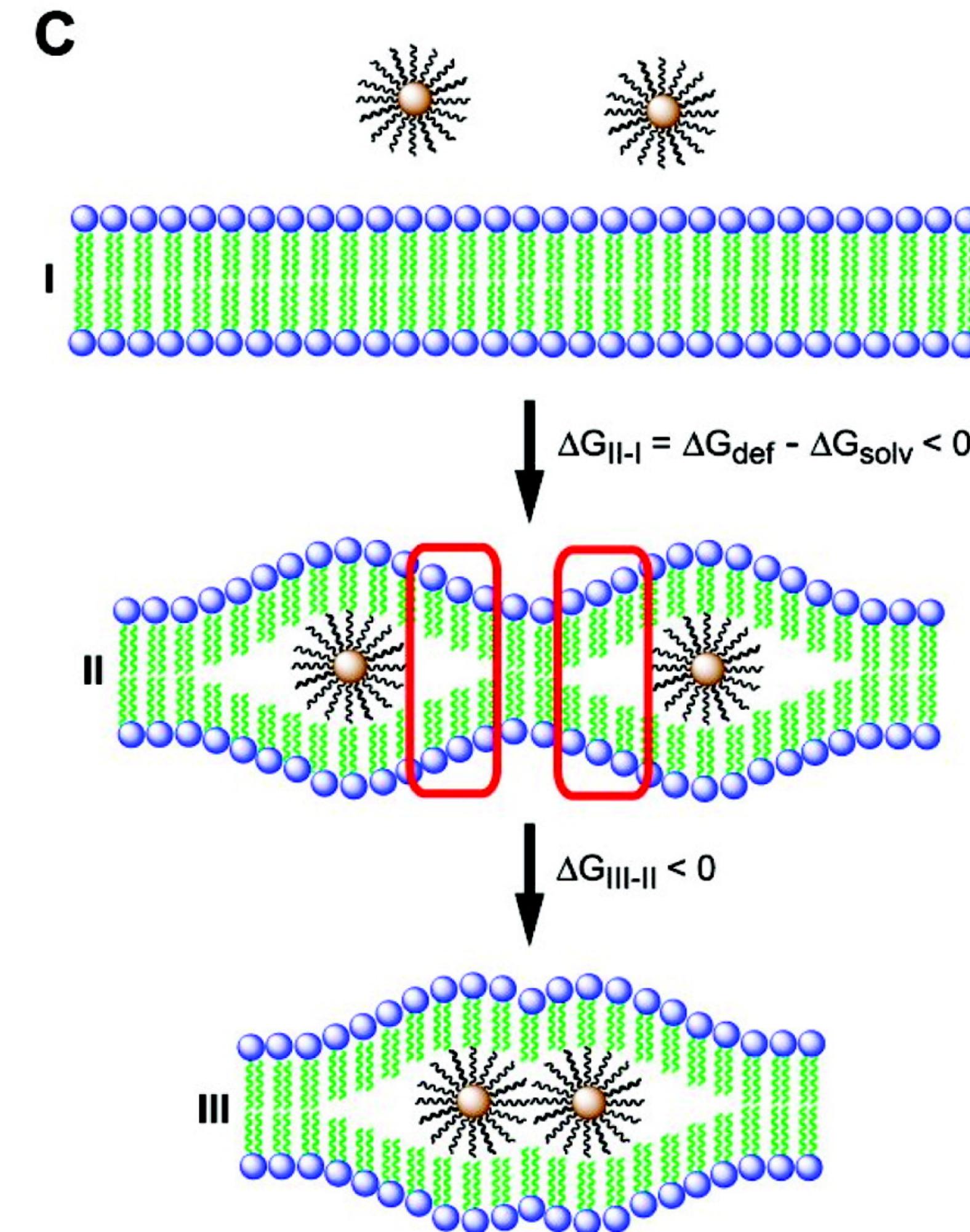
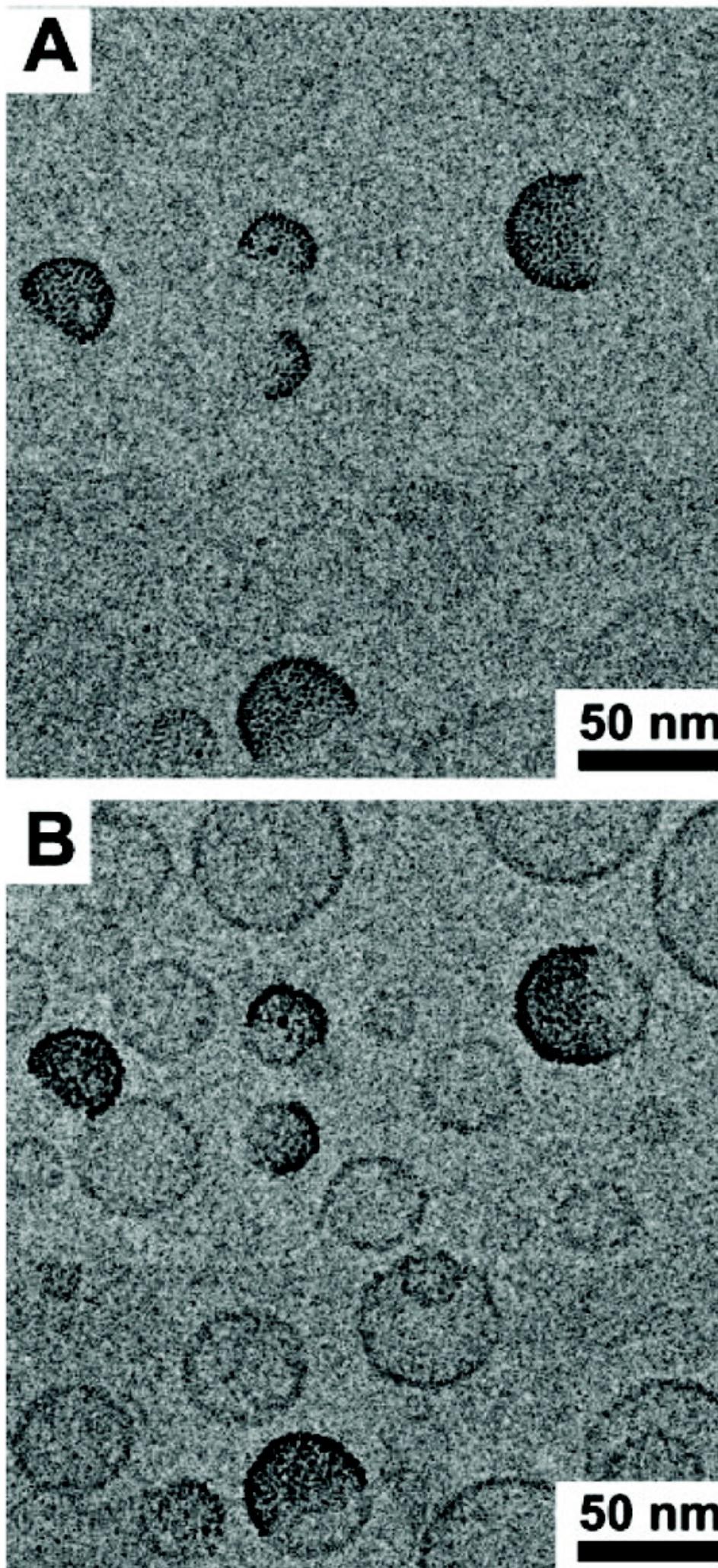
Simulation of nanoparticle aggregation with two 313K AuNP's



Three replicas of center of mass distance between two AuNP's

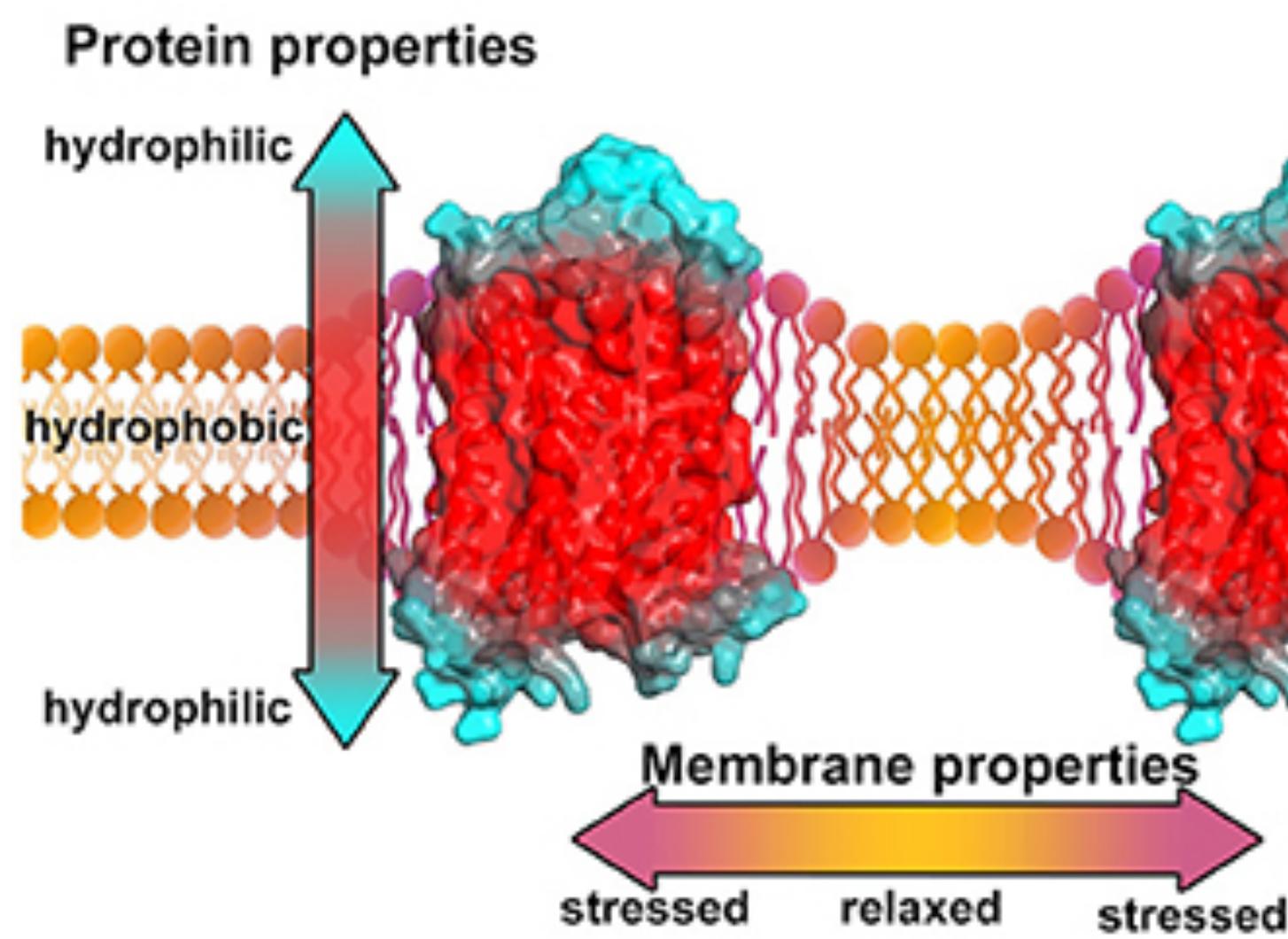


Potential causes of nanoparticle aggregation

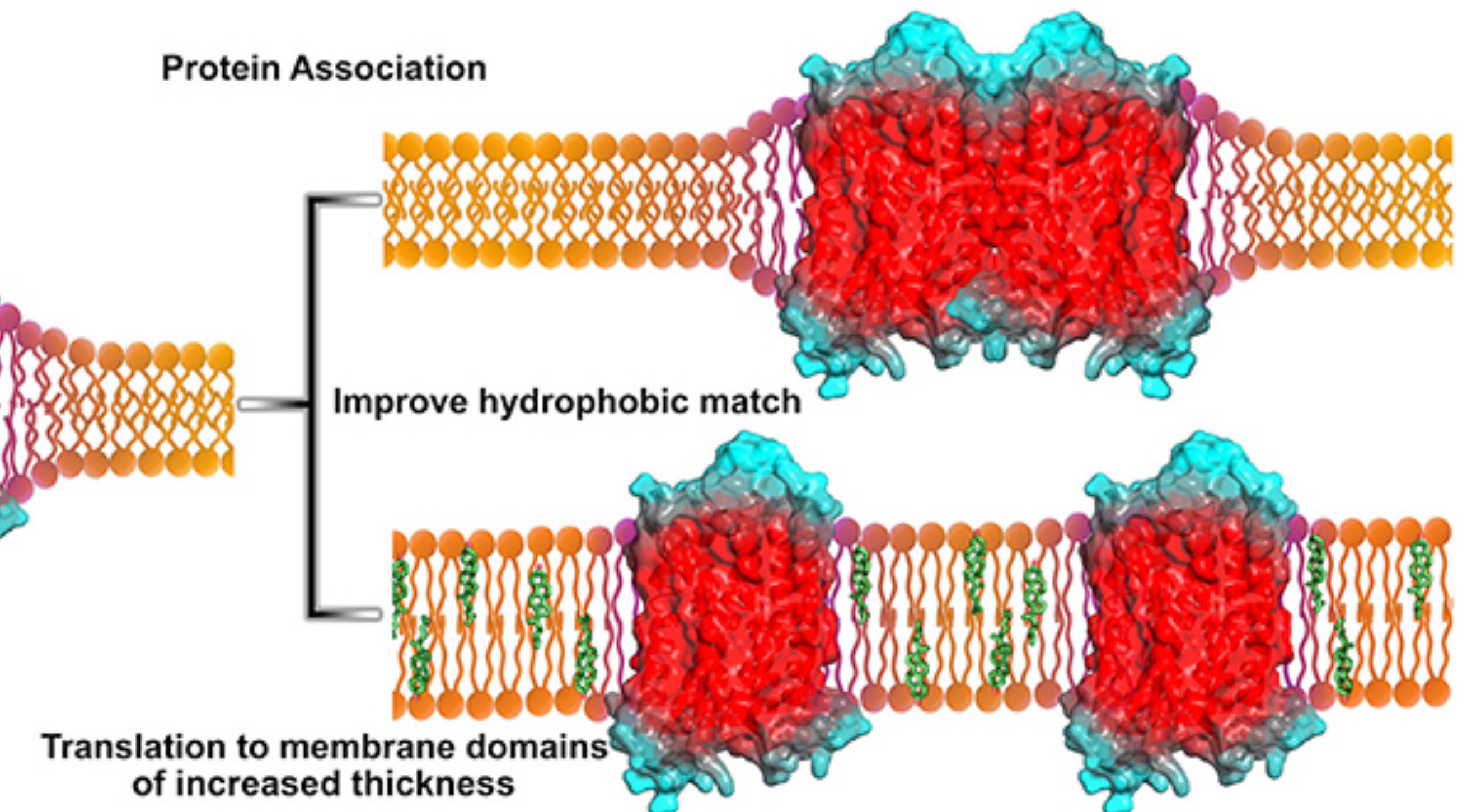


Similar aggregation models

Hydrophobic mismatch

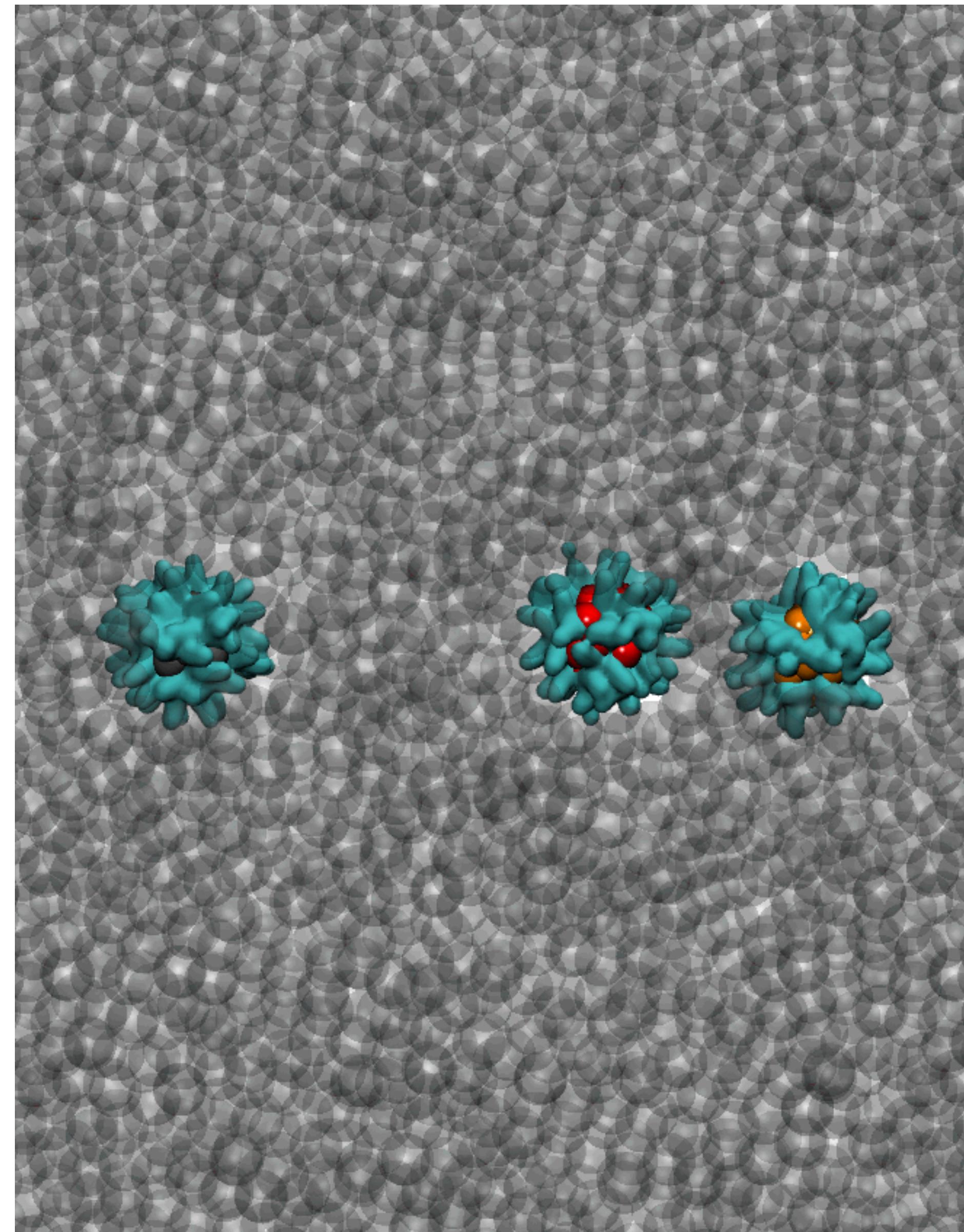


Protein Association

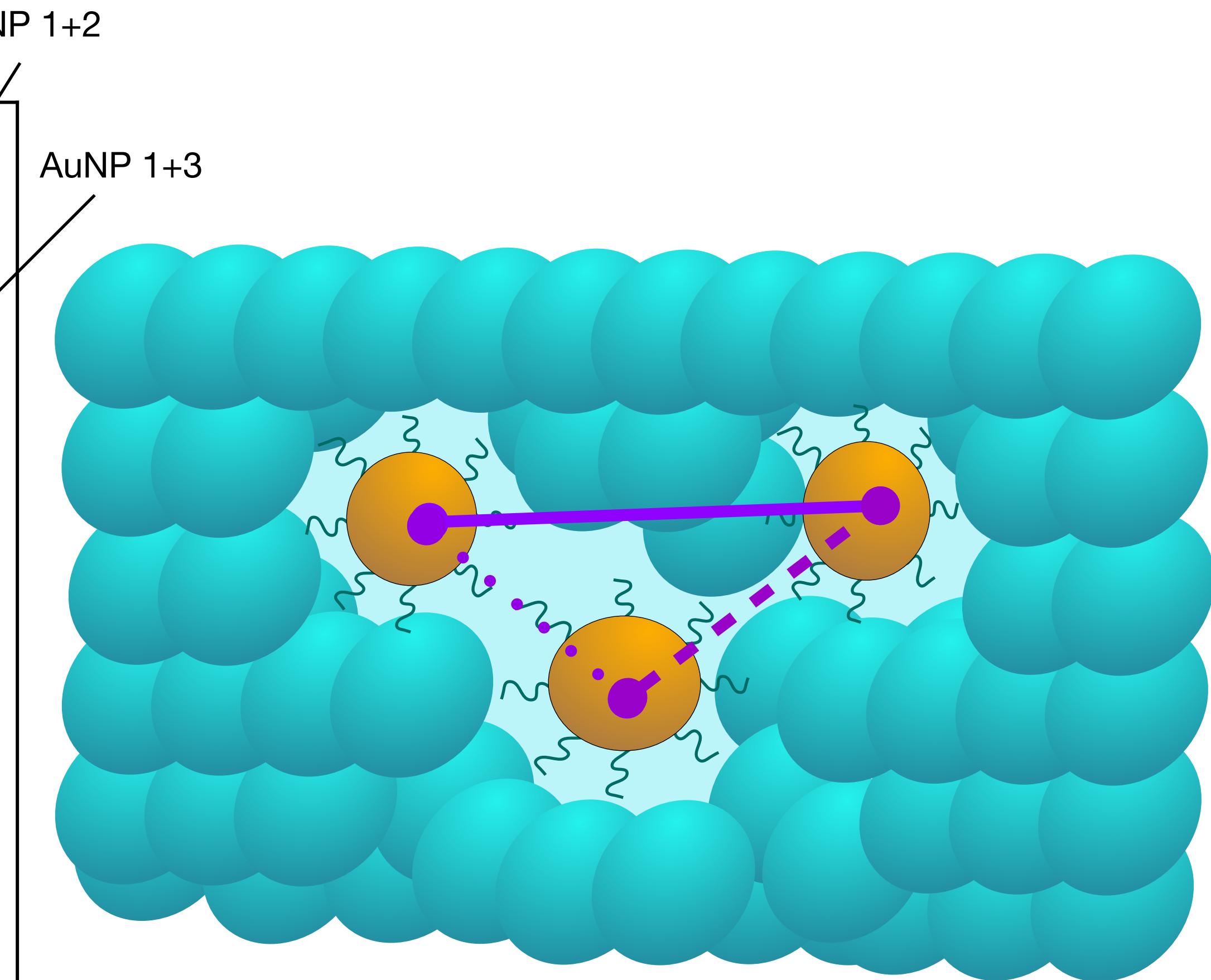
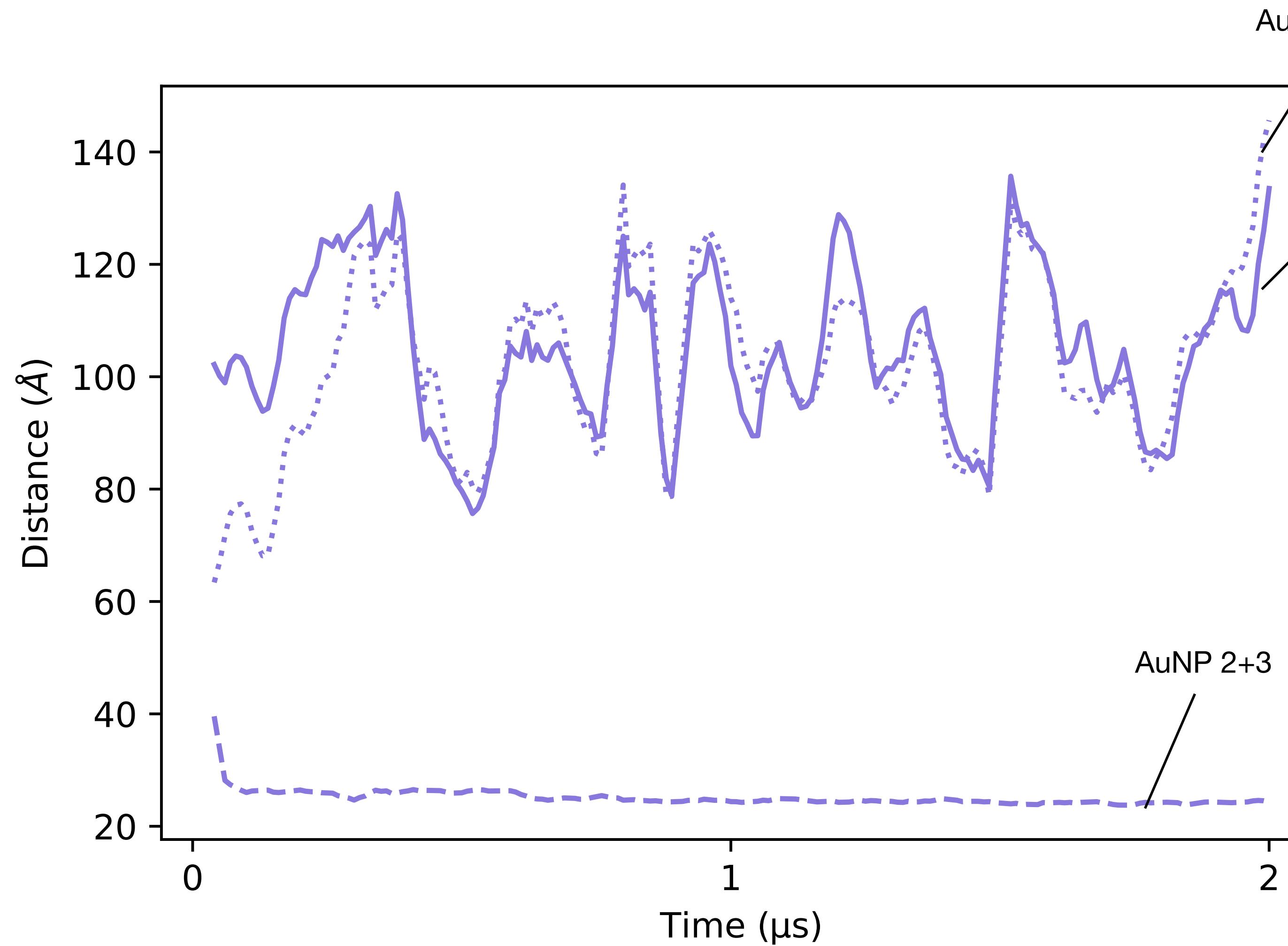


Mouritsen, O. G. (2013). "Membrane protein-lipid match and mismatch," in *Comprehensive Biophysics*, Vol. 5, ed E. H. Egelman (Amsterdam: Humana Press), 245–260.

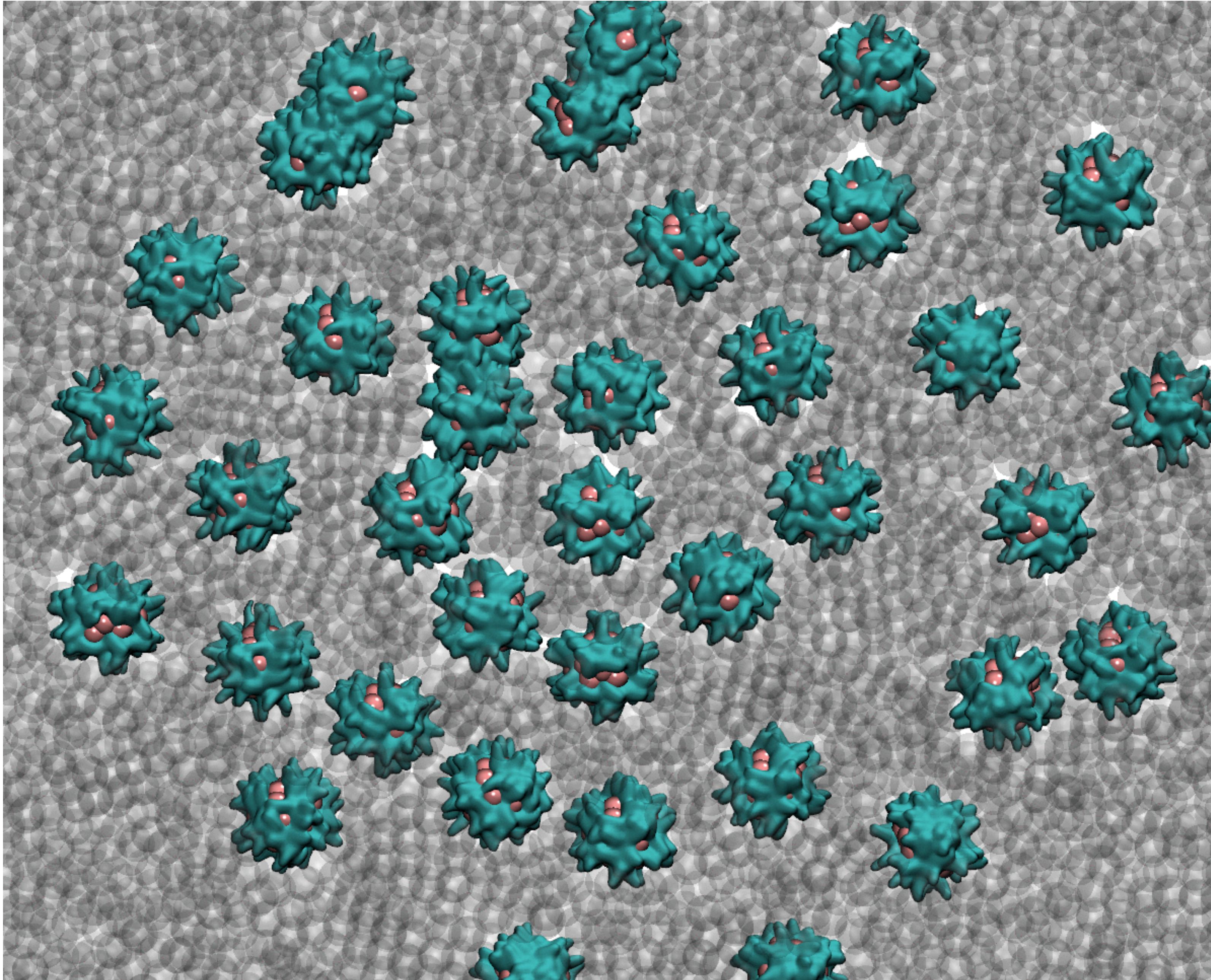
Simulation of 3 nanoparticles with two nanoparticles forming aggregates



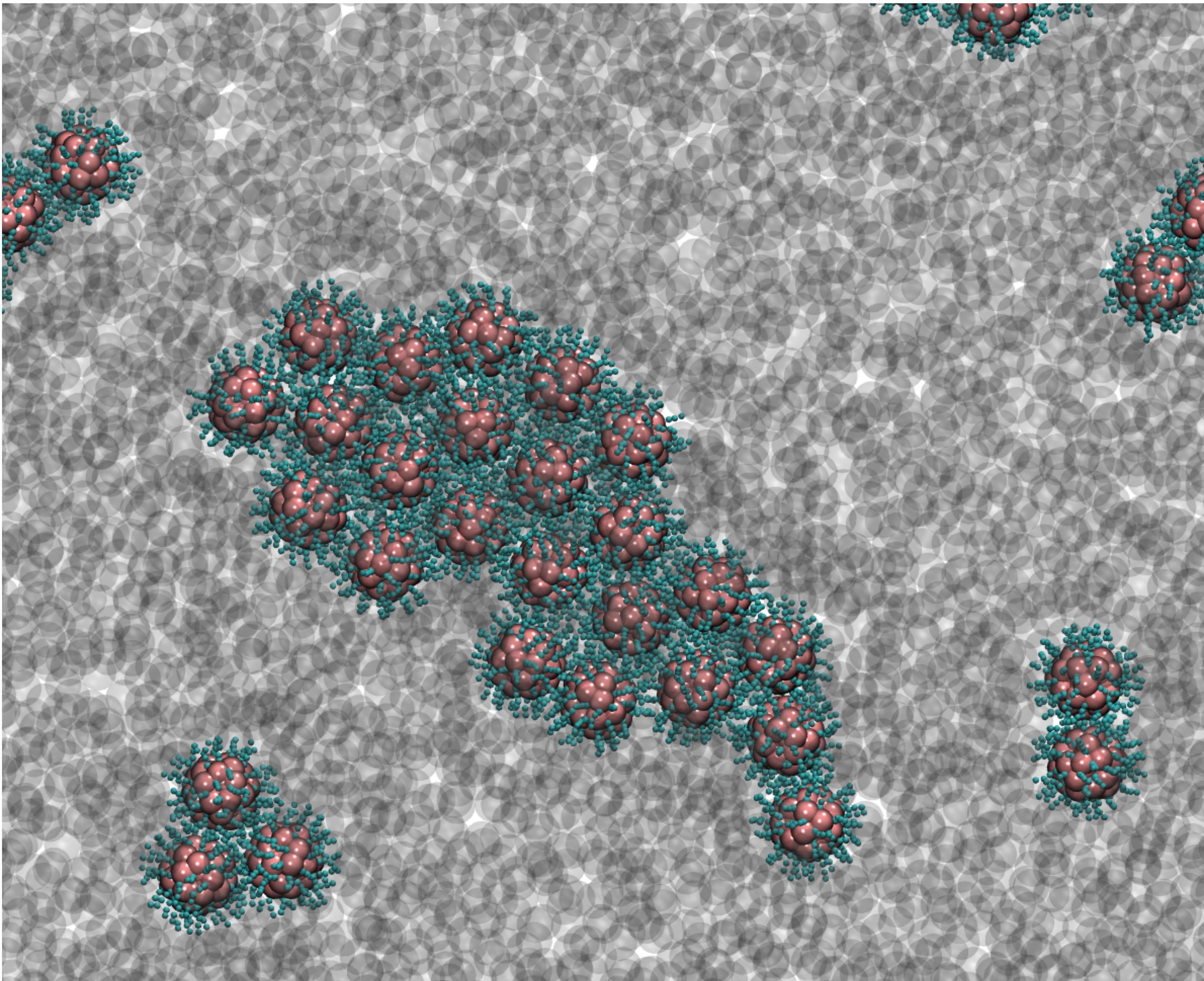
Center of mass distance between three individual nanoparticles



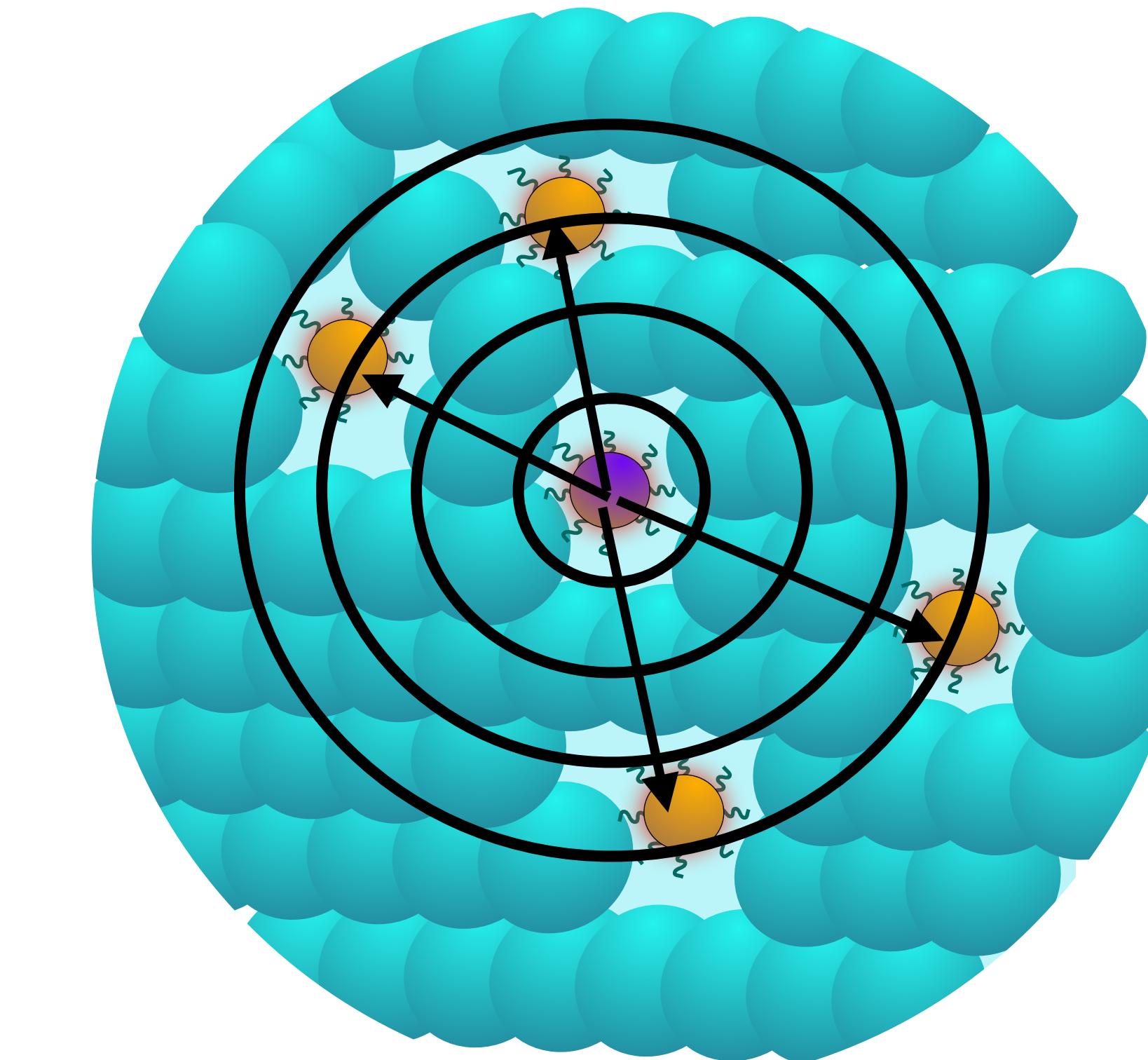
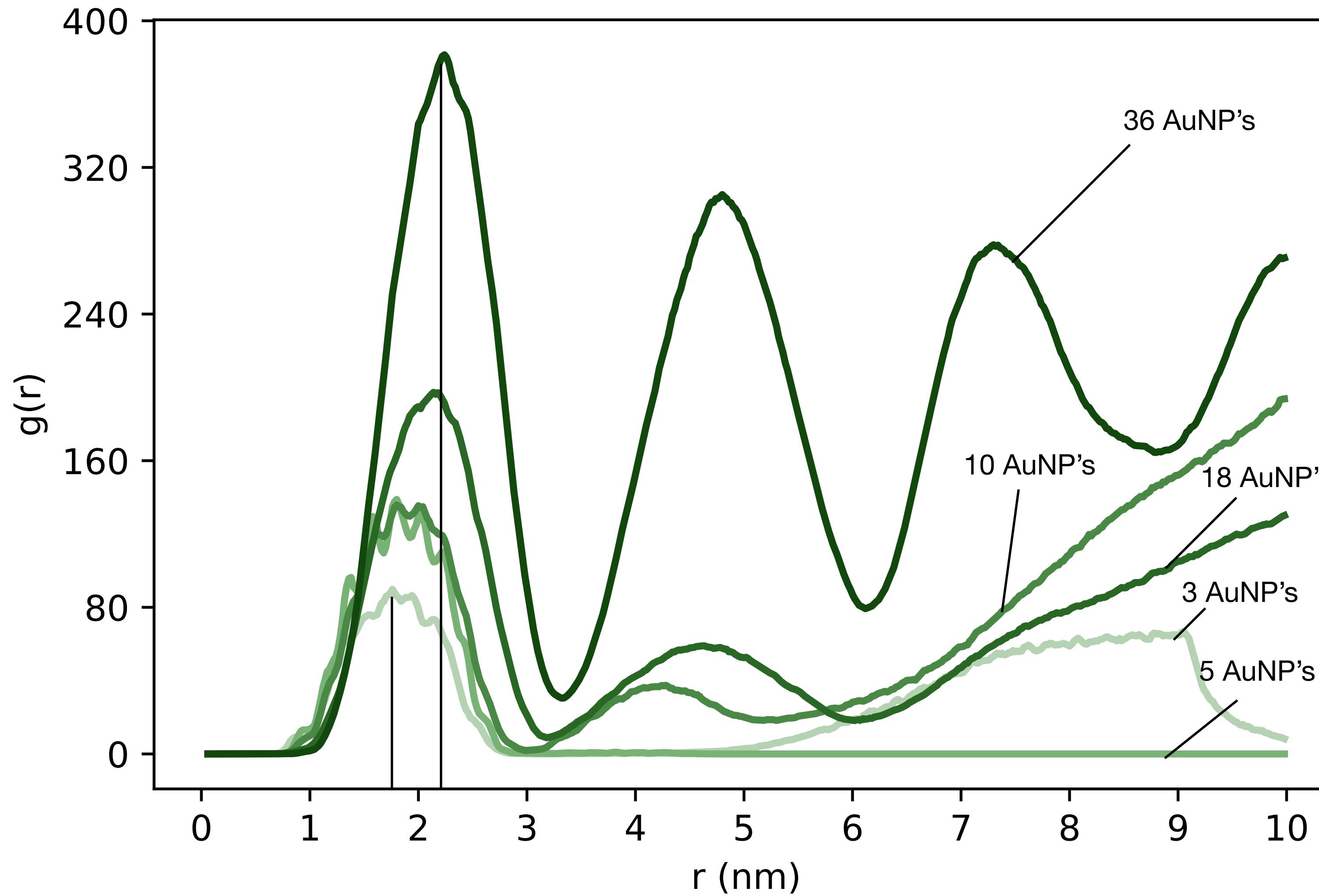
36 nanoparticle system exhibiting patterning



Gold core hexagonal patterning in lipid membrane



Radial distribution function of 313K nanoparticles at several different concentrations



Project Aims

**Aim 1: Investigating the effects
of membrane composition on
nanoparticle organization**

Aim 1: Rationale

- Nanoparticle aggregation is observed in simulation and experiments
- Heated aggregates may cause lipid disruption differently from single heated nanoparticles
- Membrane composition may play a role on aggregate formation and organization
- Understand the structure of cold nanoparticles before nanoparticle heating

Aim 1: Approach

Simulation Set 1: Vary lipid chain length and determine radial distribution function of nanoparticles and radius of gyration of aggregates

- Hypothesis: Decrease in acyl chain length will destabilize nanoparticle aggregates

Simulation Set 2: Vary nanoparticle concentration and determine radial distribution function of nanoparticles and radius of gyration of aggregates

- Hypothesis: Increased concentration will stabilize aggregates

Simulation Set 3: Vary nanoparticle size and determine radial distribution function of nanoparticles and radius of gyration of aggregates

Hypothesis: Larger nanoparticle will form clusters which are more stable

Simulation Set 4: Vary ligand chain length and determine the radial distribution function of nanoparticles and radius of gyration of aggregates

- Hypothesis : Ligands with longer chains will favor an aggregated state

Aim 2: Investigating the effect of nanoparticle temperature on aggregation and membrane structure

Aim 2: Rationale

- Aggregate heating affects lipid membrane structure
- Thermalization of the membrane may increase membrane disorder and disruption
- Membrane disorder may affect aggregate ordering in the membrane
- Understand the conditions of aggregate heating on membrane structure

Aim 2: Approach

Simulation Set 1: Vary heating of nanoparticles at two set temperatures, 313K and 513K

Analysis 0: Characterize the effect of nanoparticle temperature on aggregate organization over short time scales relevant to thermal transfer

- Aim 1 comparison

Analysis 1: Determine lipid tilt of lipids near aggregation

- Lipid tilt will increase with increased heating of the membrane

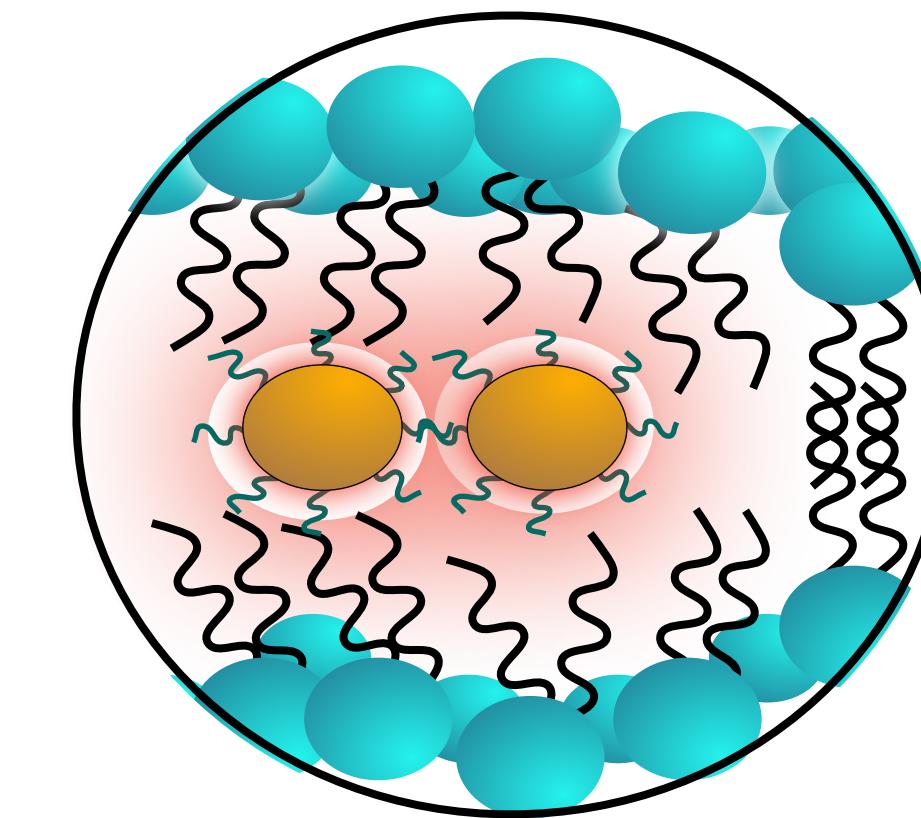
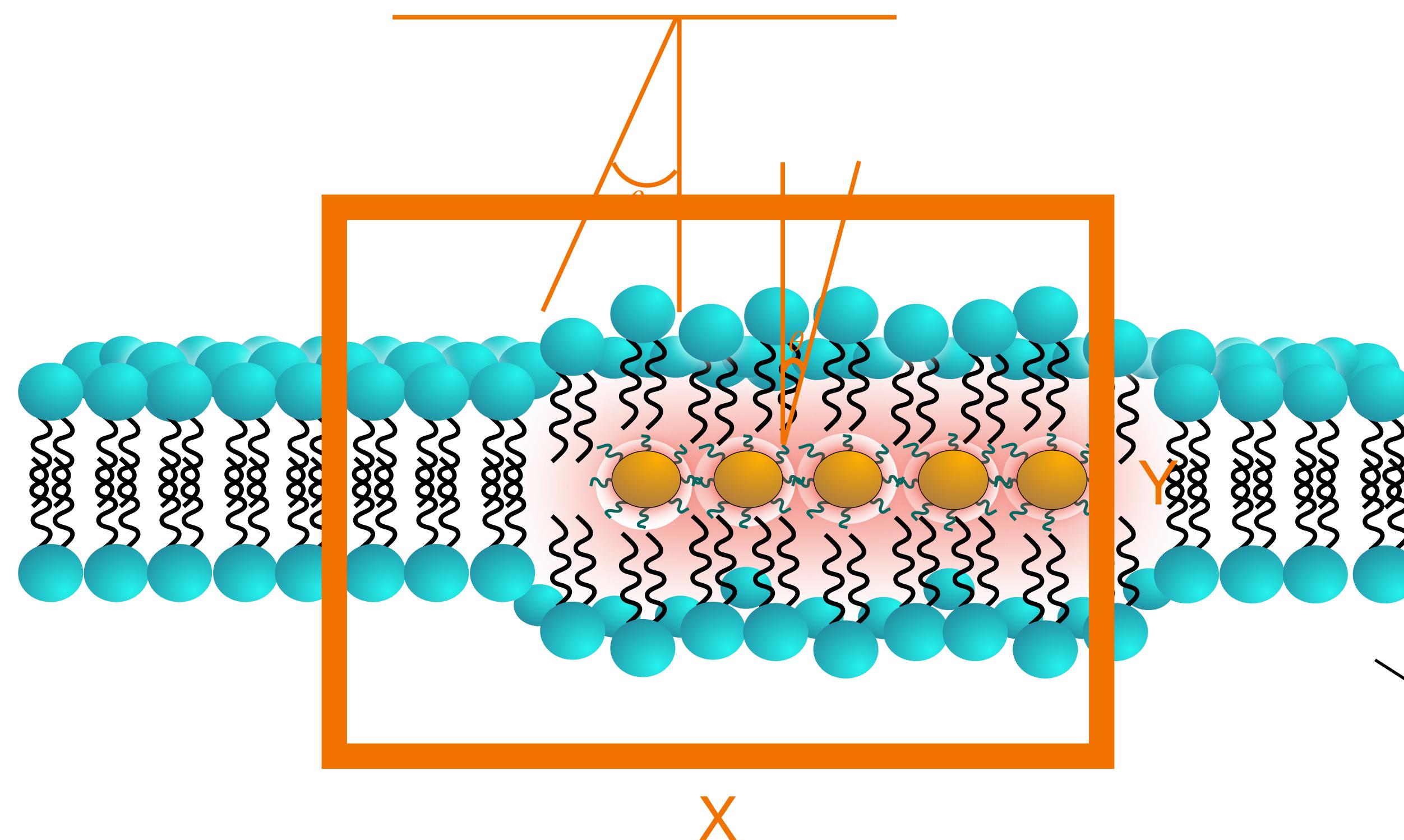
Analysis 2: Determine lipid chain order of lipids around the aggregation

- Lipid chains will become more disorder with an increase in nanoparticle temperature

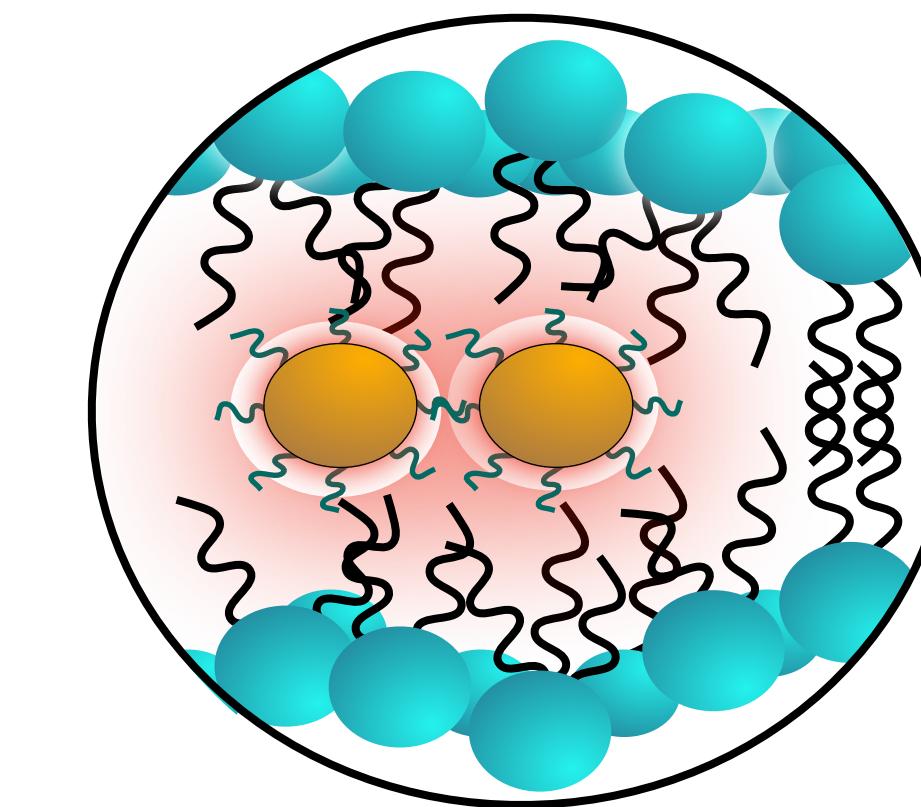
Analysis 3: Determine the area per lipid around the aggregation

- Area per lipid will increase due to thermal expansion of lipids

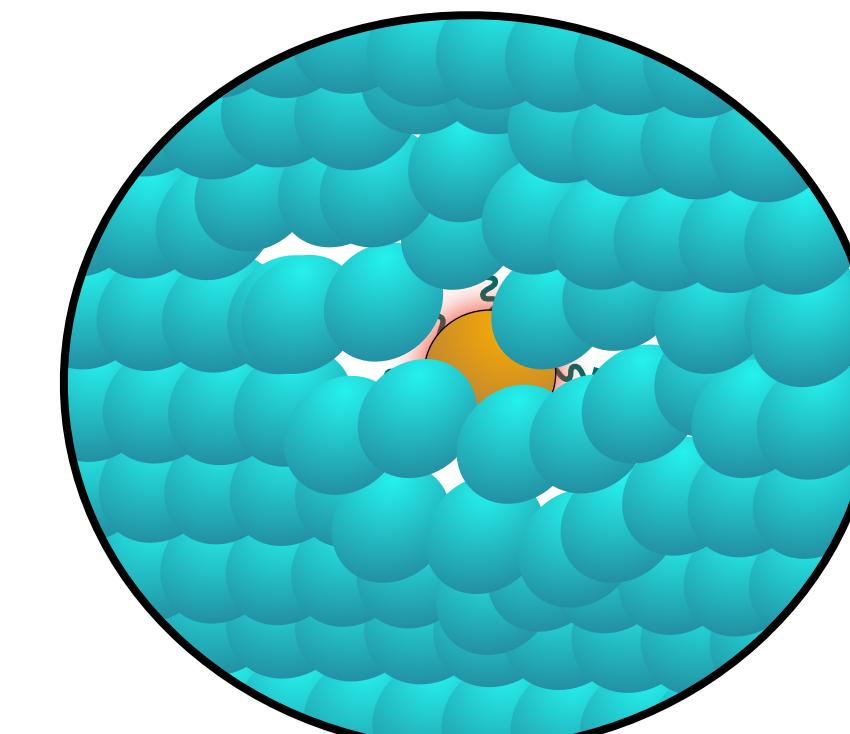
Aim 2 simulation setup and Analysis



Lipid Tilt



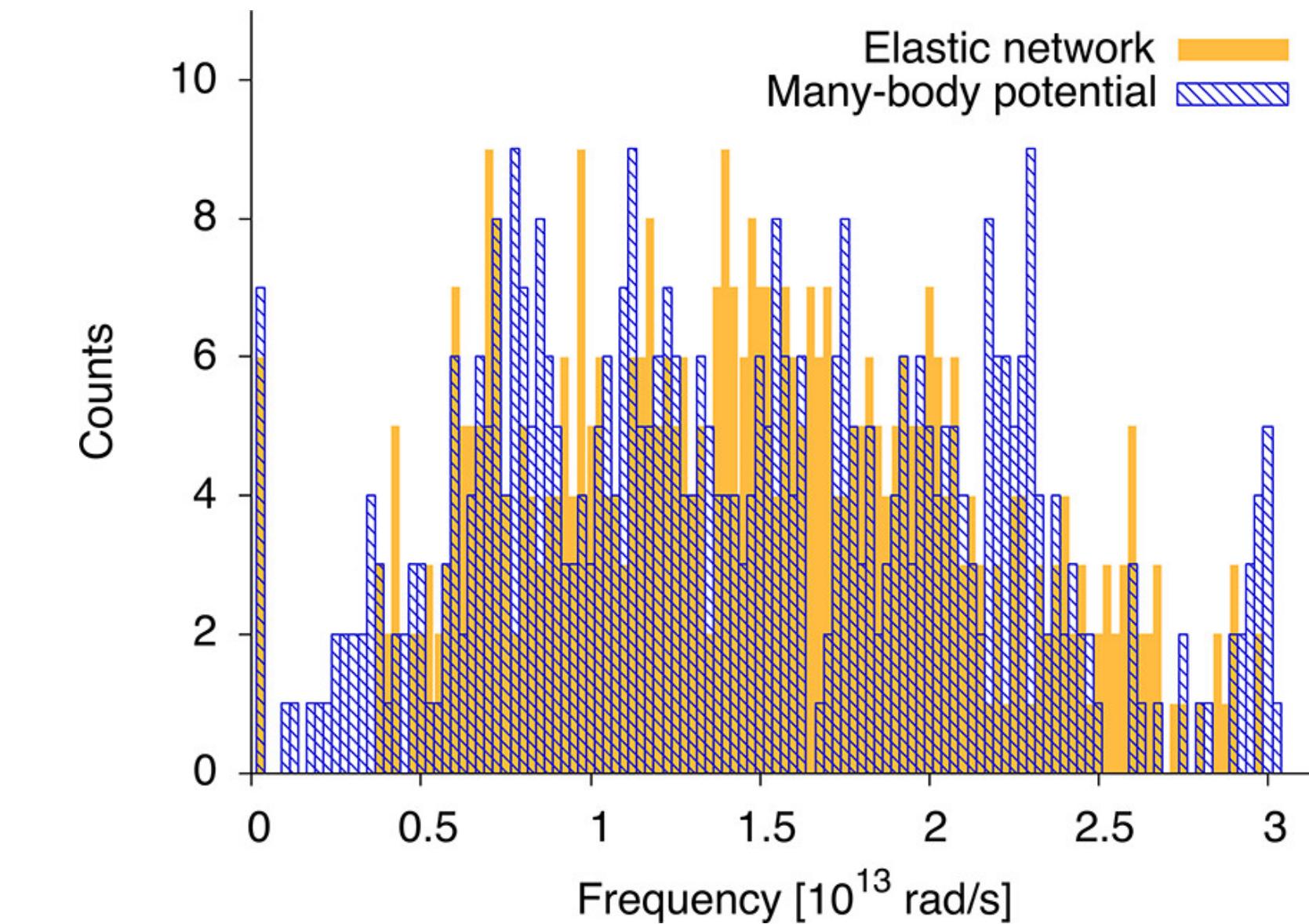
Lipid Chain Disorder



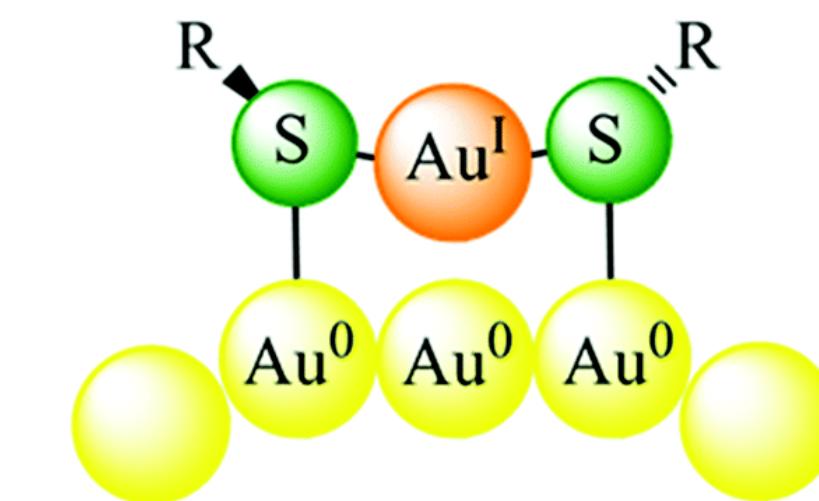
Area Per Lipid

Improvements to current model

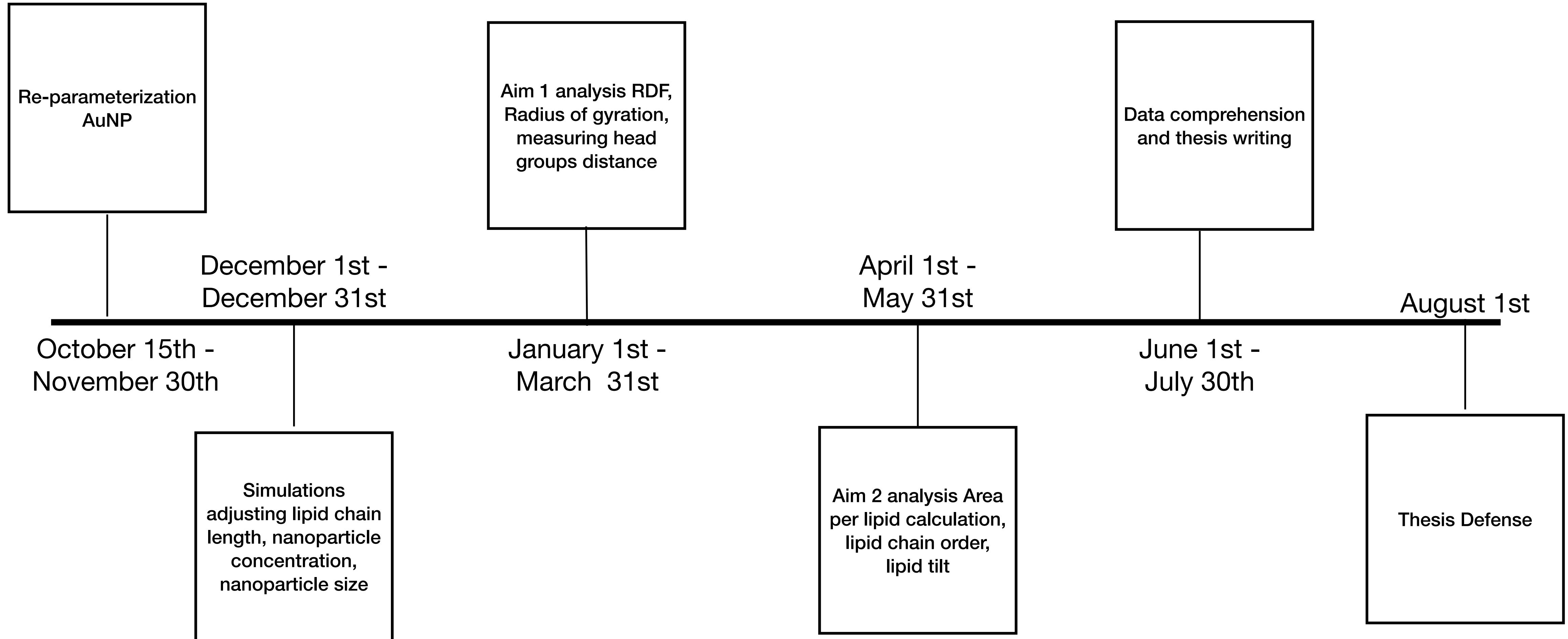
- Elastic network connectivity should be aligned with the vibrational spectra of gold
- $AUS_k = 325000Kj/(mol * nm)$, $AUC_k = 11000Kj/(mol * nm)$
- Surface charge of gold needs to be updated
- AUL beads have +1 charge



Andrea Torchia, Federica Simonelli, Riccardo Ferrando, and Giulia Rossi
ACS Nano 2017 11 (12), 12553-12561



Timeline



Summary

- Background
 - Self-assembled vesicles as an improvement to current drug delivery techniques
- Preliminary work
 - Nanoparticle heating, aggregation and patterning in POPC membranes
- Project Aims
 - Investigating the effects of membrane composition on nanoparticle organization
 - Investigating the effect of nanoparticle temperature on aggregation and membrane structure
- Timeline

Questions?