Understanding cytochrome *c*–nanoparticle interactions with molecular dynamics simulations

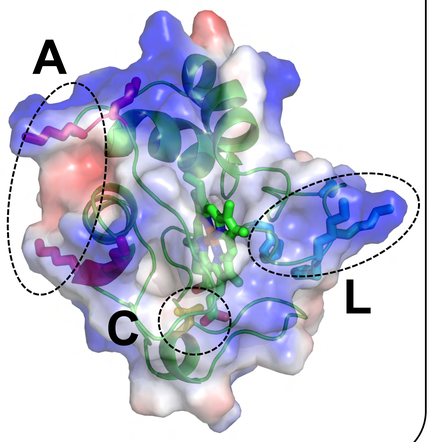
Nikita D. Rozanov,[1] Caley Allen,[1] Eric S. Melby,[2,3] Robert J. Hamers,[2] Joel A. Pedersen, and Rigoberto Hernandez[1]

[1]Johns Hopkins University, [2]University of Wisconsin – Madison, [3]Pacific Northwest National Laboratory

Motivation and Objectives

Understand the binding chemistry between cytochrome *c* and mercaptopropionic acid (MPA) coated gold nanoparticles (AuNP).

Cyt *c*, pictured along with its proposed binding sites, is a peripheral membrane protein that is a crucial element of respiratory chain and apoptosis pathway[7]. Previous experiments determined that cyt *c* causes MPA coated AuNPs to adhere to bilayers[1]. The significant health and safety implications of this process motivated a detailed molecular dynamics study of the system to gain insights into the underlying mechanism.

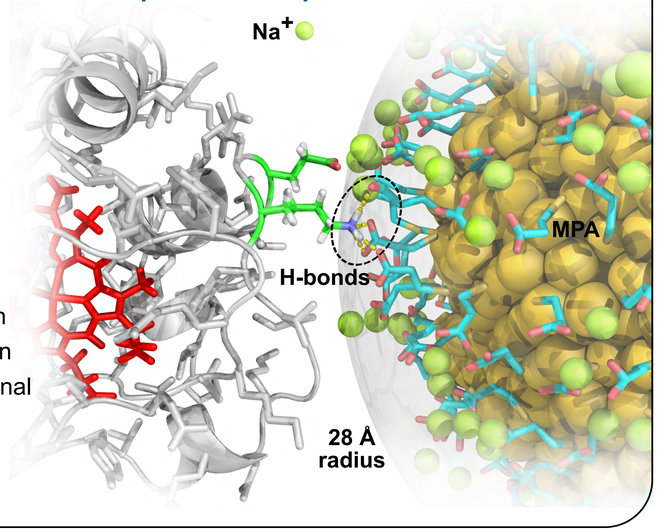


System Overview

Molecular dynamics simulations provide multiple methods to characterize the protein–nanoparticle interaction.

Observables

- Hydrogen bonding
- Proximity to nanoparticle
- Interaction energetics
- Sodium ion redistribution
- Reorientation
- Conformational changes



Experimental Methods

System Preparation

The protein (PDB 1akk)[2] was placed in six different starting configurations with respect to the AuNP using PyMOL[3]. Following, the combined system was placed in a water box and ionized using VMD[4]. To describe the forces in the system, we used the CHARMM36 force field[6].

Molecular dynamics simulations

Each configuration underwent an energy minimization, followed by one nanosecond *NPT* and *NVT* equilibrations, before proceeding to the production run. Each production simulation lasted for 50 nanoseconds, and was carried out using NAMD[5] on the MARCC supercomputer. The trajectories were subsequently analyzed using VMD[4].

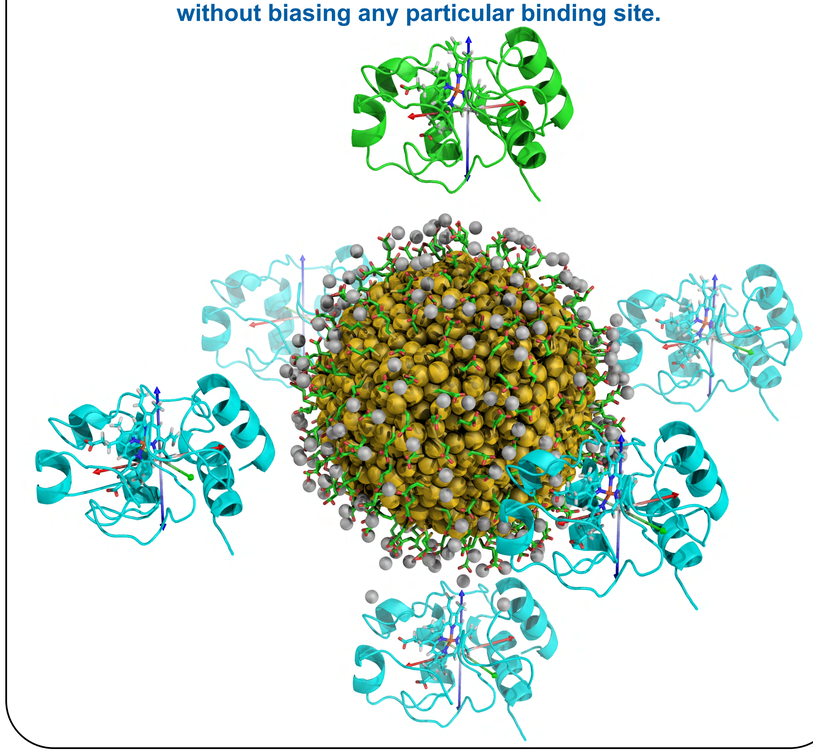
Connection to Experiment[1]

Different surface coatings have different effects on AuNP attachment to bilayers when cyt *c* is present.

- MPA coated AuNPs adhere to multiple bilayer types proportional to the amount of cyt *c* present
- Unlike MPA, EG6 ligands cause weaker attachment to the bilayer, and no attachment in some cases
- These differences are hypothesized to be associated with different binding configurations between the protein and bilayer

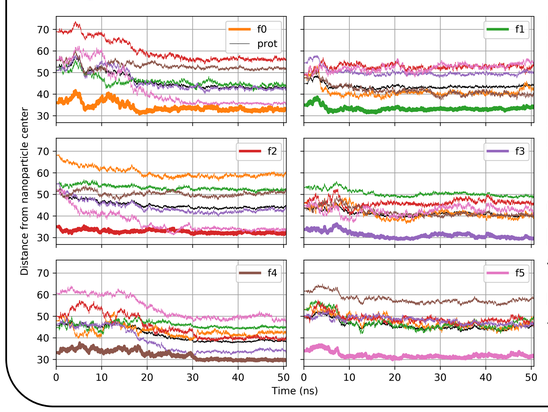
Summary of Starting Orientations

The different orientations attempt to capture the entire protein surface without biasing any particular binding site.



Tracking Protein Dynamics

Changes in protein face-to-AuNP distances show cyt *c* reorientations.

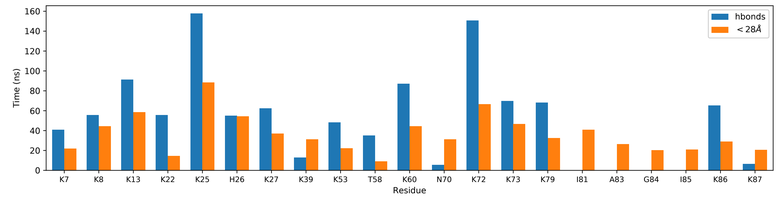


Face	Residues
f0	48 49 50 51 53 54
f1	37 38 58 60 61 62
f2	2 3 4 5 7 8
f3	13 16 28 72 79 81
f4	66 69 70 73 87 91
f5	21 22 23 24 25 26

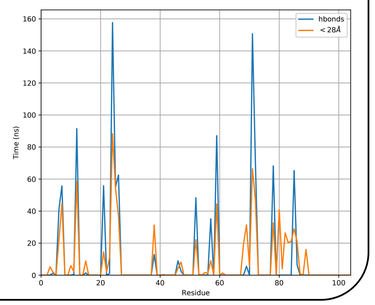
Center of mass distances between selected protein faces and the AuNP are measured with respect to time for each simulation.

Measuring Residue Affinity

Measuring H-bonding and proximity between cyt c and the AuNP across all simulations reveals the residues that interact most significantly with the nanoparticle.



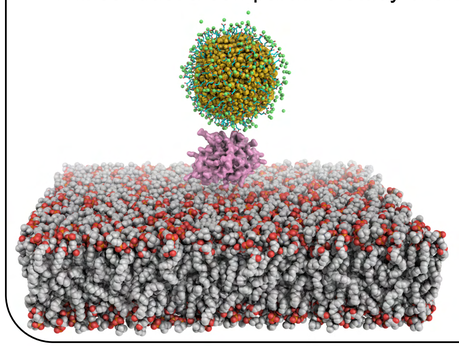
- Many of the interacting residues contain nitrogen, which can H-bond to MPA
- Some residues appear in multiple trajectories, indicating strong affinity to the AuNP
- They also significantly overlap with the proposed binding sites in cyt *c*, providing clues to how the protein influences AuNPs



Conclusions and Future Work

Gaining an understanding of the binding chemistry between gold nanoparticles and cyt *c* will provide vital information for ensuring nanoparticle safety.

- Completed molecular dynamics simulations to characterize cyt *c*–nanoparticle interactions, and extracted relevant information
- Will conduct a comparative study changing the AuNP coating to EG6



- Future study will combine the protein, nanoparticle, and bilayer into one system
- Plan to identify key binding sites as well as interaction mechanisms using data from the simulations

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