

University of Technology Sydney

Faculty of Engineering and Information Technology

Unravelling the Biophysical Mechanism of Lung Surfactant Monolayer Exposed to Gold Nanoparticles Using Molecular Dynamics Simulations

A thesis submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy in Mechanical Engineering

by

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Sydney, Australia

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CERTIFICATE OF ORIGINAL AUTHORSHIP

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ABSTRACT

Air-borne nanoparticles (NPs) can act as pollutants and have harmful effects, yet at the same time, the recent improvements in nanotechnology have enabled the design of NPs with specific properties, and their use in various biomedical applications. For example, gold NPs (AuNPs) found in mining dust or exhaust fumes can cause serious lung diseases but are also used as nanocarriers to improve the delivery of drugs into cells.

For air-borne NPs, the main route of entry to the body is via the lungs. After inhalation, the NPs come into contact with the inner surface of the lungs' alveolus, a component called the lung surfactant (LS). The main site of interaction of inhaled NPs is the LS monolayer, which is composed of lipids and proteins and forms the air-liquid interface of the lungs. Normal physiological lung function depends on the LS monolayer's capacity to act as a surface tension reducer. Despite exhaustive studies, the molecular-level mechanisms that underpin the adsorption, interaction and translocation/diffusion of AuNPs, either in their bare (pollutants) or phospholipid/ligand-coated (nanocarriers) states, into the LS monolayer are still poorly understood.

In this project, a series of coarse-grained molecular dynamics simulations are performed to elucidate the interaction of bare and phospholipid-wrapped AuNPs with LS monolayers, resulting in a number of key findings. First, bare AuNPs structurally deform the LS monolayer in a concentration-dependent manner, changing the biophysical properties of the monolayer, and creating pores in the monolayer. All of these changes are likely to interfere with normal lung functions such as maintaining physiological surface tensions at the interface. Second, the simulations reveal that the surfactant protein B (SP-B₁₋₂₅) found in LS monolayers, is important for monolayer stability and significantly increases AuNP aggregation in the monolayer. Third, phospholipid-wrapped AuNPs further increase the aggregation of SP-B₁₋₂₅, inducing buckle in the monolayer, and participating in the cholesterol sequestration. The studies also explore how the adsorption of phospholipid-wrapped AuNPs and monolayer perturbation are affected by the monolayer breathing conditions, monolayer lipid composition, and nature of the phospholipids used for wrapping.

In summary, the combined findings from these simulation studies have provided molecular-level insight into the structure and dynamics of the LS monolayer and how

bare or phospholipid-wrapped AuNPs interact with and diffuse into the LS monolayer. The molecular insights of these studies will facilitate the future design of nanocarriers for drug delivery and the assessment of AuNP as a pollutant and thus help to identify potential health risk in people exposed to bare AuNPs.

Keywords:

Lung surfactant; Gold nanoparticles; Surface tension; Coarse-grained molecular dynamics; Lipid monolayers; Lung surfactant monolayer; Surfactant peptide; Air-water interface; Lipid-wrapped gold nanoparticles; Model lung surfactant; MARTINI force field; Hydrophobic surfactant peptide.

DEDICATION

This thesis is dedicated to my parents, who love me, and who are those I love most. My parents (Sheikh Nazrul Islam and Tajmira Begum) are ordinary in their lifestyle, but extra-ordinary in their thought, in that they have always prompted my inspiration to be “human” from the early days of my life. I love you “Ma” (mother) and “Baba” (father).

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LIST OF PUBLICATIONS

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LIST OF CONFERENCES

- [1] **Sheikh I. Hossain**, Neha S. Gandhi, E. Sauret, Y.T. Gu, Suvash C. Saha, Molecular dynamics simulation study of a pulmonary surfactant monolayer with Gold nanoparticles, MM2017, 27-29th September 2017, Margaret River, Perth, Australia. (Poster presentation)
- [2] **Sheikh I. Hossain**, Neha S. Gandhi, Zak E. Hughes, Suvash C. Saha, Gold Nanoparticle Translocation into Lung Surfactant: Unraveling Its Mechanism at the Molecular Scale, MRS Fall Meeting and Exhibit, 25-30th November 2018, Boston, Massachusetts, USA. (Oral presentation)
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LIST OF ABBREVIATIONS, AND SYMBOLS

ABBREVIATIONS/SYMBOLS	DEFINITION
AFM	Atomic Force Microscopy
AgNPs	Silver Nanoparticles
APL	Area per Lipid
AuNP/AuNPs	Gold Nanoparticle/Nanoparticles
BaP	Benzo[a]pyrene
CDS	Constrained Drop Surfactometer
CG	Coarse-Grained
CGMD	Coarse-Grained Molecular Dynamics
CHOL	Cholesterol
CNT	Carbon Nanotubes
DHPC	Dihexanoylphosphatidylcholine
DPPC	Dipalmitoylphosphatidylcholine
GNs	Graphene Nanosheets
GO	Graphene Oxide
LC	Liquid Condensed
LE	Liquid Expanded
LS	Lung Surfactant
LWB	Langmuir-Wilhelmy balance
MD	Molecular Dynamics
MWCNT	Single-Walled Carbon Nanotubes
NP/NPs	Nanoparticle/Nanoparticles
PC	Phosphatidylcholine
PEG	Polyethylene Glycol
PG	Phosphatidylglycerol
PL/PLs	Phospholipid/Phospholipids

POPC	Palmitoyl-oleoylphosphatidylcholine
POPG	Palmitoyl-oleoyl-phosphatidylglycerol
SiO ₂	Silicon Dioxide
SP-A, SP-B, SP-C, SP-D	Surfactant Protein - A, B, C, D
SP-B ₁₋₂₅	Surfactant Peptide B residues (1-25)
SWCNT	Single-Walled Carbon Nanotubes
TiO ₂	Titanium Dioxide
w/v	Weight per volume
ZnO	Zinc Oxide