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

October 2020

CERTIFICATE OF ORIGINAL AUTHORSHIP

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Sheikh Imamul Hossain, declare that this thesis is submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the School of Mechanical and Mechatronic Engineering, Faculty of Engineering and Information Technology at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

This document has not been submitted for qualifications at any other academic institution.

This research is supported by the Australian Government Research Training Program.

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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 ($SP\text{-}B_{1\text{-}25}$) 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 $SP\text{-}B_{1\text{-}25}$, 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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ACKNOWLEDGEMENTS

When I was thinking about who I should acknowledge, many names came to my mind. Up to now, I have passed through many different academic stages of my life and currently, I am in its most important phase. First, I would like to pay my deepest respect and gratefulness to all my educators, mentors, and well-wishers for nurturing, caring, and advising me. Among these fantastic and exceptional people, I would like to mention the names of a few individuals. I would like to begin with my primary supervisor, regardless of formalities, Dr Suvash C. Saha, for his support, guidance, wisdom, encouragement, and motivation. I would like to express my gratitude and respect to him for choosing me as a potential PhD student and keeping trust in me by giving me freedom in my research. I am also grateful to my co-supervisors, Dr Neha S. Gandhi, Dr Zak E. Hughes, and Dr Evelyne Deplazes, for their support, patience, enthusiasm, and constructive criticism throughout the completion of this thesis. I know that a massive thankyou is insufficient for them because of the effort and guidance they provided, but stating my gratitude will remind me to be thankful for the rest of my life. I still remember the days when I started learning Molecular Dynamics and without my mentors, I would have never explored the world of molecular modelling.

I would like to acknowledge the days I passed at Queensland University of Technology (QUT). I thank the LAMSES group members, especially Prof Yuantong Gu, for the support and advice I received during my early days with them.

I would also like to acknowledge professional editor, Diane Kolomeitz, for proofreading services according to the national guidelines for editing research theses.

I am indebted to all the members of our Lung group at UTS for constructive comments, sharing ideas, and skills in every weekly meeting. I am thankful to Dr Saidul Islam, Mohammad Zohurul Islam, Dr Tanvir Ahmed, S M Arifuzzaman, Salman Al Zahrani, Md Bellal Hossain and my other friends at UTS and QUT in the Sydney and Brisbane area, for their support and advice. These people never failed me when I felt loneliness.
I want to thank the UTS authority for providing me with the UTS FEIT Research Scholarship, UTS IRS, and overseas health cover. I would also like to thank Dr Michael

Lake for supporting and guiding me with the computational facilities provided by the UTS eResearch High-Performance Computer Cluster, UTS iHPC and NCI Australia.

Finally, it is time to thank my family members-my parents and siblings. Without their endless support, sympathy, tolerance, prayers and unconditional love, it would be impossible to continue a PhD journey. All these reasons inspire me to dedicate and credit my thesis to them.

LIST OF PUBLICATIONS

[1] **Sheikh I. Hossain**, Neha S. Gandhi, Zak E. Hughes, Suvash C. Saha, Computational Modelling of the Interaction of Gold Nanoparticle with Lung Surfactant Monolayer, *MRS Advances*, 4 (20), 1177-1185, 2019. doi.org/10.1557/adv.2019.93. **Published**

[2] **Sheikh I. Hossain**, Neha S. Gandhi, Zak E. Hughes, Y.T. Gu, Suvash C. Saha, Molecular insights on the interference of simplified lung surfactant models by gold nanoparticle pollutants, *Biochimica et Biophysica Acta (BBA) – Biomembranes*, 1861 (8), 1458-1467, 2019. doi.org/10.1016/j.bbamem.2019.06.001. **Published**

[3] M. Z. Islam, **Sheikh I. Hossain**, E. Deplazes, S. Bhowmick and Suvash C. Saha "Molecular Dynamics Study of Prednisolone Concentration on Cholesterol Based Lung Surfactant Monolayer" *AIP Conference Proceedings*, 2020. **Accepted**

[4] **Sheikh I. Hossain**, Neha S. Gandhi, Zak E. Hughes, Suvash C. Saha, The role of SP-$B_{1–25}$ peptides in lung surfactant monolayers exposed to gold nanoparticles. *Physical Chemistry Chemical Physics*, 22(27), 15231-15241, 2020. doi.org/10.1039/D0CP00268B. **Published**

[5] **Sheikh I. Hossain**, Neha S. Gandhi, Zak E. Hughes, Suvash C. Saha, Computational Studies of Lipid Wrapped Gold Nanoparticle Transport Through Model Lung Surfactant Monolayers, *Nanoscale*. **To be submitted**

CONTRIBUTION TO PUBLICATIONS

Paper 1	**Sheikh I. Hossain**, Neha S. Gandhi, Zak E. Hughes, Suvash C. Saha, Computational Modelling of the Interaction of Gold Nanoparticle with Lung Surfactant Monolayer, *MRS Advances*, 4 (20), 1177-1185, 2019. **Published**
Authors' contributions	S.I.H. developed model, performed simulations, analysed data and drafted the manuscript. S.C.S. coordinated the study, N.S.G. conceived the study, Z.E.H. helped in concept clarification, and S.C.S., N.S.G., and Z.E.H. helped draft the manuscript.
Paper 2	**Sheikh I. Hossain**, Neha S. Gandhi, Zak E. Hughes, Y.T. Gu, Suvash C. Saha, Molecular insights on the interference of simplified lung surfactant models by gold nanoparticle pollutants, *Biochimica et Biophysica Acta (BBA) – Biomembranes*, 1861 (8), 1458-1467, 2019. **Published**
Authors' contributions	S.I.H. developed model, performed simulations, analysed data and drafted the manuscript. S.C.S. coordinated the study, N.S.G. conceived the study, Z.E.H. helped in concept clarification, and Y.T.G. provided comments on the manuscript. S.C.S., N.S.G., Z.E.H. and Y.T.G. helped draft the manuscript.
Paper 3	M. Z. Islam, **Sheikh I. Hossain**, E. Deplazes, S. Bhowmick and Suvash C. Saha "Molecular Dynamics Study of Prednisolone Concentration on Cholesterol Based Lung Surfactant Monolayer" *AIP Conference Proceedings*, 2020. **Accepted**
Authors' contributions	M.Z.I. developed model, performed simulations, analysed data and drafted the manuscript. S.C.S. coordinated the study, S.I.H. conceived the study, and E.D. helped in concept clarification and S.B. presented the paper at the conference, S.C.S., S.I.H., and E.D. helped draft and provided comments on the manuscript.
Paper 4	**Sheikh I. Hossain**, Neha S. Gandhi, Zak E. Hughes, Suvash C. Saha, The role of SP-$B_{1–25}$ peptides in lung surfactant monolayers

	exposed to gold nanoparticles. *Physical Chemistry Chemical Physics*, *22*(27), 15231-15241, 2020. doi.org/10.1039/D0CP00268B. **Published**
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Paper 5	**Sheikh I. Hossain**, Neha S. Gandhi, Zak E. Hughes, Suvash C. Saha, Computational Studies of Lipid Wrapped Gold Nanoparticle Transport Through Model Lung Surfactant Monolayers, *Nanoscale*, **To be submitted**
Authors' contributions	S.I.H. developed model, performed simulations, analysed data and drafted the manuscript. S.C.S. coordinated the study, N.S.G. conceived the study, Z.E.H. helped in concept clarification, and S.C.S., N.S.G., and Z.E.H. helped draft the manuscript.

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Confirmation from principal supervisor (corresponding author of the publications)

As the corresponding author of each publication listed above, I am confirming the contributions of all co-authors and their authorship.

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Signature removed prior to publication. 22/09/2020

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[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)

[3] **Sheikh I. Hossain**, Neha S. Gandhi, Zak E. Hughes, E. Deplazes, Suvash C. Saha, Dual Role of Gold Nanoparticles in Lung Surfactant Monolayer: A Molecular Dynamics Study, 36th Combined Health Science Conference Sydney New Horizons, 14-15th November 2019, University of Technology Sydney, Sydney, Australia. (Poster presentation)

[4] **Sheikh I. Hossain**, and Suvash C. Saha, Molecular Dynamics Study of Lung Surfactant Monolayer with Phospholipid-coated Gold Nanoparticles, The Fourth Australasian Conference on Computational Mechanics, 28-29th November 2019, University of Tasmania, Sandy Nay Campus, Tasmania, Australia. (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	Palmitoyloleoylphosphatidylcholine
POPG	Palmitoyl-oleoyl-phosphatidylglycerol
SiO_2	Silicon Dioxide
SP-A, SP-B, SP-C, SP-D	Surfactant Protein - A, B, C, D
$SP\text{-}B_{1\text{-}25}$	Surfactant Peptide B residues (1-25)
SWCNT	Single-Walled Carbon Nanotubes
TiO_2	Titanium Dioxide
w/v	Weight per volume
Z_nO	Zinc Oxide