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Molecular Dynamics Modelling of Biomolecular Interactions with Lipid Membranes

and

Novel Coarse Grain Lipid Model Development

A thesis presented in partial fulfilment of the
requirements for the degree of

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When I went to school, they asked me what I wanted to be when I grew up.
I wrote down 'happy'.

They told me I didn't understand the assignment
And I told them they didn't understand life.

- Unattributed

Abstract

Lipids comprise a key component of the cellular membrane and are essential to many biological processes. *In silico* investigations provide valuable opportunities to study the dynamics and structure of biological molecules, such as lipid membranes and the molecules that interact with them, at near atomic resolutions. In the context of this thesis three research projects were undertaken with a focus on lipid membrane simulations.

The structure and dynamics of the novel antibacterial battacin analogue peptides and their interactions with model membranes of the common pathogenic gram positive and gram negative bacterial species *Staphylococcus aureus* and *Escherichia coli* were studied. Antibacterial peptides are a key area of research due to their potential medicinal applications in overcoming the current antibiotic resistance crisis. However, detailed knowledge of their mode of action is often lacking. The peptides were to found to insert into the bacterial membranes, facilitated by the insertion of the fatty acid moiety, and showed strong affinity for all three types of membranes studied.

Antifreeze protein 1 (AFP1) is critical to cell survival at near freezing temperatures. Structural analysis of the behavior of AFP1 is presented, including a study of its possible aggregation. Interactions of AFP1 were studied in conjunction with a model of a typical cell membrane. AFP1 units were found to be flexible in solution, adopting a variety of non α-helical structures. In certain cases, two AFP1 proteins aggregated together and interacted with each other. Furthermore, AFP1 interacted with the unsaturated lipid membrane, coming to rest on its surface, providing insight into the freezing damage prevention mechanism.

Finally, in order to facilitate simulation of larger biological membrane systems, a novel supra-atomic phospholipid model was proposed, and model parameters developed for the common lipid 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC). The model is based on and ultimately compatible with the GROMOS 54a8 atomic-level force field[103] including the GROMOS coarse-grained water model[111]. It is also polarisable, unlike many popular supra-atomic models. The DPPC model was developed following a bottom-up approach, and is intended to pave a way for stepwise parameterisation of other lipids, to build a library of “plug and play” lipid parameters.

Thesis Outline

The scope of the thesis covers a variety of molecular dynamics simulation projects, centred on lipid membrane simulations, including novel coarse-graining methodology development, as well as utilising current atomistic modelling methods for biochemical investigations. The thesis is split into four chapters, each relating to a separate topic. The first chapter gives a brief overview of concepts involved in molecular dynamics simulations. The subsequent three chapters cover three separate projects. Each project chapter is split into several parts, including a specific literature review, results, methods, discussion and conclusion. Chapter 2 describes the investigation of novel anti-bacterial peptides and explores their behaviour in the context of lipid membranes. Chapter 3 is about investigation of winter flounder Antifreeze Protein 1 structure and aggregation in the context of lipid membranes. Chapter 4 deals with creation of novel coarse-grained modelling methodology for the lipid DPPC. A comprehensive list of combined and numbered references follows.

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Abbreviations

AFP1	Antifreeze protein 1
AL	Atomic level
CG	Coarse-grain
Dab	*α,γ*-diaminobutyric acid
DGDG	1,2-digalactosyldiacylglycerol
DMPC	1,2-dimyristoyl-sn-glycero-3-phosphocholine
DPPE	1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine
DPPC	1,2-dipalmitoyl-sn-glycero-3-phosphocholine
LJ	Lennard-Jones
LPS	Liposaccharide or cardiolipin
MD	Molecular dynamics
NVT	Constant moles, volume, temperature
NVP	Constant moles, volume, pressure
O17	Octapeptide 17
P30	Pentapeptide 30
POPC	1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine
POPE	1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanolamine
POPS	1-palmitoyl-2-oleoyl-sn-glycero-3-phospho-L-serine
RDF	Radial distribution function
RMSD	Root mean square deviation
RMSF	Root mean square fluctuation