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## The simulation studies of the interplay of peptides with lipids

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# Chapter 1

## **Introduction to This Thesis**

### **1.1 Membrane active peptides**

#### *1.1.1 Peptide-membrane interactions are diverse in nature*

Peptide–membrane interactions play a critical role in a series of important biological processes, such as antimicrobial defense mechanisms, membrane remodelling, membrane fusion, ion channel formation, membrane protein insertion and folding, hormone-receptor interactions, and membrane-mediated amyloid aggregation.

The interplay between peptides and membranes gives rise to a rich and diverse behavior which is affected by the properties of the peptide, membrane, as well as external environment. Different kinds of peptides will trigger different membrane responses. Some peptides lead to local membrane defects, such as membrane pores (1, 2), membrane disorder (3, 4), lipid segregation (5, 6), and lipid protrusion (7). Other peptides alter the preferential curvature of membranes, and are able to induce shape transformations such as buckling or tubulation (8, 9). However, understanding the mechanisms of peptides interacting with membranes at the molecular level is still challenging.

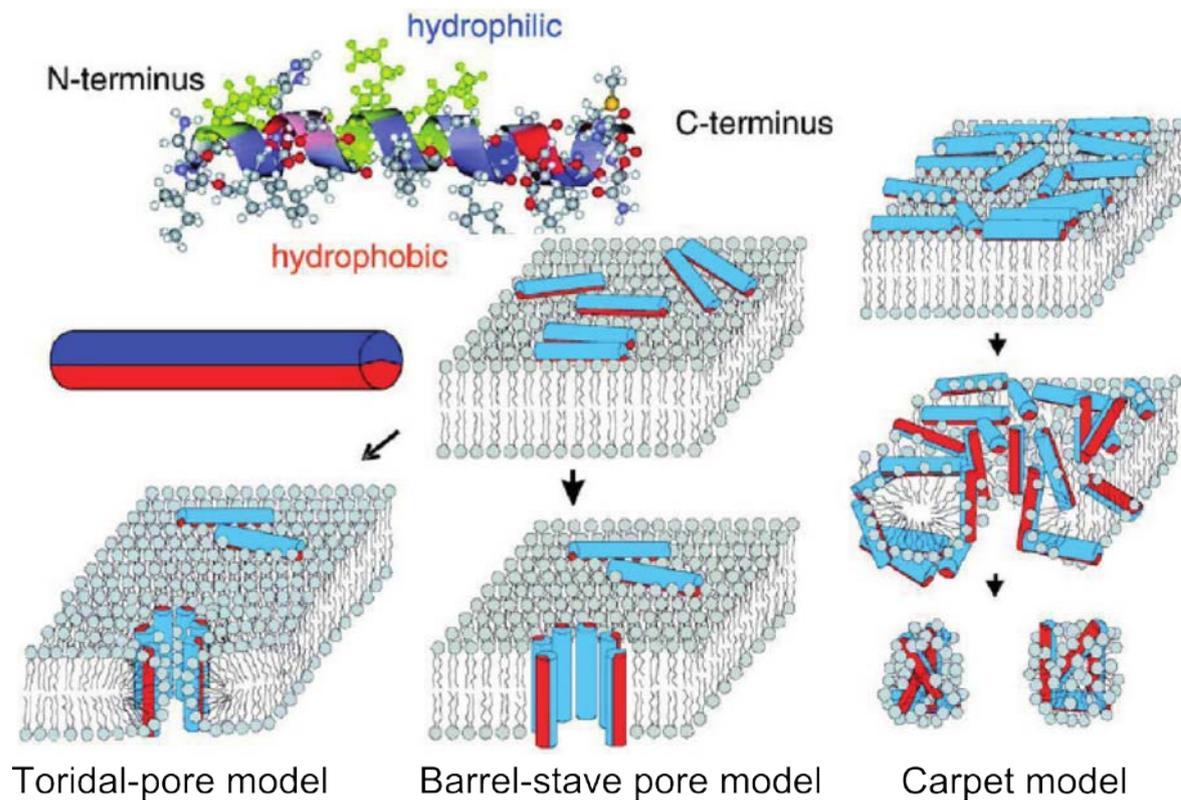
In this thesis, the interplay between two classes of membrane active peptides and membranes are investigated, namely the antimicrobial peptides Magainin 2, BP100, MSI-103, and MSI-78 involved in membrane rupture, and the amphipathic peptide Pex11-Amph involved in membrane remodelling during peroxisomal fission.

#### *1.1.2 Antimicrobial peptides in action*

Antimicrobial peptides (AMPs) typically are short cationic peptides with broad spectrum antimicrobial activity against bacteria, viruses, and fungi. They can be used as a promising substitute for conventional antibiotics that suffer from decreasing efficiency because of the rapid emergence of antibiotic-resistant bacterial strains (10, 11). Characteristics such as peptide charge (cationic or anionic), size, primary sequence, conformation, hydrophobicity, and amphipathicity are essential for antimicrobial activity and the mechanism of action (12, 13). However, up to now the mechanism of AMPs in action is not so clear yet. Several models have been proposed to explain membrane disruptions by AMPs, such as barrel-stave, toroidal, and carpet models, see Figure 1.1.

The “barrel-stave” model suggests that peptides bind to the membrane surface as monomers, followed by their oligomerization and the formation of transmembrane

pores by their direct insertion into the lipidic core of the target membrane (14). In the “toroidal-pore” model, insertion of peptides into the membrane eventually induces a self-connection between the two leaflets. The lipid monolayer bends continuously through the pore so that the water core is lined by both the peptides and the lipid head groups (15). In the “carpet model” the peptides accumulate at the membrane surface until a threshold concentration is reached. The adsorbed peptides then disintegrate the membrane into micelles in a detergent-like manner (16-18).



**Figure 1.1** Schematic description for proposed models of the mechanism of antimicrobial peptides (AMPs) in action. (Top, left) Many AMPs fold into amphipathic  $\alpha$ -helices with hydrophilic and hydrophobic sides when adsorbed to a lipid membrane. This conformation is here schematically represented as an amphiphilic cylinder, with hydrophobic (red) and hydrophilic (blue) halves. (Center) AMPs bind to the membrane surface with the hydrophobic side groups anchored in the hydrophobic lipidic core of the bilayer, leading to different outcomes. (Bottom, left) The toroidal pore model. (Bottom, center) The barrel-stave model. (Bottom, right) The carpet model. The figure is reproduced from reference (19).

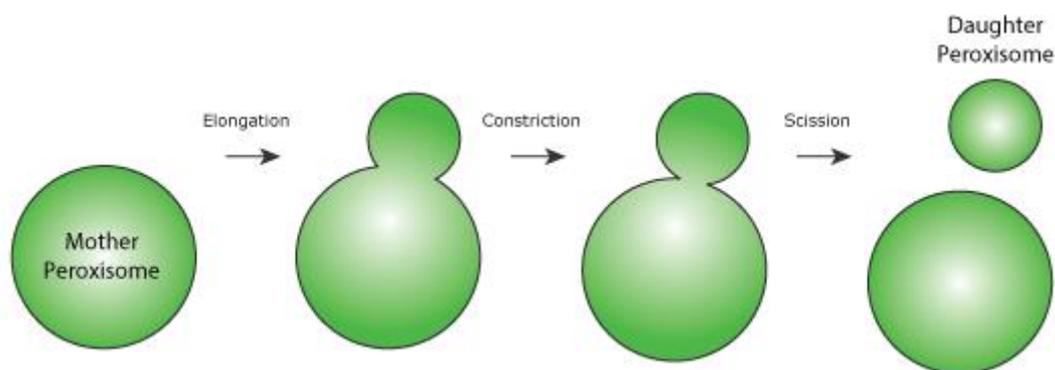
Although these models of AMP action have been proposed, as well as a number of different ways to sub-classify these peptides (20), an increasing number of studies (21) show that these models might be too simplistic, and that instead several concurrent factors—not necessarily the same across the AMP spectrum—might be responsible

for antimicrobial action. The AMP-mediated lateral segregation of anionic lipids in a membrane is one of the aforementioned disruptive factors. It has been observed for different peptides (22, 23) and, although probably not a lethal event by itself, it is a destabilizing feature of AMP behavior that might act in synergy with other mechanisms (24).

Real cellular membranes comprise hundreds of different lipid types and are distinctly heterogeneous in lateral organization as expressed by the 'raft' concept (25). Yet, in studying AMPs interacting with lipid bilayer, pure phase lipid membranes have been used more commonly. A more realistic model system would consist of ternary mixtures of cholesterol, saturated lipids and unsaturated lipids. Lipid membranes formed by these components exhibit coexisting fluid lipid phases: the liquid ordered (Lo) and liquid disordered (Ld) phases (26-28) as a model for lipid rafts. Understanding how lipid phase separated membranes might affect the behavior of AMPs is an important step to provide a better understanding of the action of AMPs in vivo.

### *1.1.3 The role of PEX11 in peroxisomal fission*

Peroxisomes are found in all eukaryotes. Failures in peroxisome formation in human cells result in biogenesis disorders such as the Zellweger syndrome (29). Peroxisome proliferation is a multistep process including elongation, constriction and scission (30), see Figure 1.2. The Pex11 protein is the most abundant peroxisomal membrane protein, known as the key player in peroxisome elongation. However, the molecular mechanism of Pex11 function in peroxisome proliferations is poorly understood. It is difficult to observe the dynamic process of the elongation in molecular detail, because in experiment, the maintenance of the shape of organelles is usually performed by regulating the membrane's properties.



**Figure 1.2** Schematic representation of the peroxisomal fission process.

Opaliński et al. found that the N-terminus of Pex11 contains a conserved amphipathic helix, termed Pex11-Amph, that can bind to membranes and alter the shape of liposomes, leading to tubulation (9). They discovered that amphipathic properties of Pex11-Amph are crucial for the function of Pex11 in peroxisome proliferation by employing mutants in experiments.

There are some commonly-used models to explain protein-induced membrane curvature: protein scaffolding (8), protein-protein crowding (31), and protein insertion. Both models of protein scaffolding and protein-protein crowding have the membrane asymmetry caused by binding of proteins on the surface of one membrane monolayer. Scaffolding proteins deform a membrane by bracing it like a scaffold, such as some BAR domain proteins (32, 33). Protein-protein crowding model suggests lateral pressure generated by collisions between bound proteins drives membrane bending. The insertion of hydrophobic or amphipathic protein domains into the membrane matrix can generate membrane curvature if membrane asymmetry appeared by the insertion. Some studies (34-36) showed shallow protein insertions are much more powerful in generating membrane curvatures than integral insertions.

In case of most peptides, including the Pex11-Amph peptides, the mechanism of inducing curvature in membranes is not clear due to the resolution limitations of experimental methods. Therefore, in studying the interplay of peptides with membranes, no matter AMPs or Pex11-Amph, it is important and necessary to employ computational modelling techniques. Computer simulations are able to provide the crucial/important information at the molecular level. In particular, the method of molecular dynamics (MD) is widely applied in the field of biomembranes, providing both structural details at atomistic resolution and dynamic behavior of molecules at the relevant time and length scales (37). In this thesis we use MD to unravel the interactions of various AMPs and Pex11-Amph with multi-component lipid membranes.

## **1.2 Computational Modelling**

### *1.2.1 Molecular Dynamics*

Molecular dynamics (MD) simulation has become an important and widely used theoretical tool which allows researchers in chemistry, physics, and biology to study the detailed microscopic dynamical behavior of various systems. A large number of MD simulations have been employed successfully to investigate the interactions of peptides with lipids, including many different AMPs (38-40) as well as a variety of membrane peptides and proteins causing tubulation (41, 42).

The MD methodology is founded upon the basic principles of classical mechanics. In a MD simulation, Newton's laws of motion are applied to each atom to determine the net force and acceleration experienced by each atom. MD generates the dynamical trajectories of a system of a fixed number of particles by integrating Newton's equations of motion, with suitable initial and boundary conditions, and proper interatomic potentials, while satisfying thermodynamic (macroscopic) constraints. Analyzing the trajectory gives molecular information that experiments often cannot provide.

The interactions between particles in a system are described by force fields. There are different levels of resolution to describe the interactions. When electronic degrees of freedom are important (e.g., to model chemical reactions) quantum methods are used. In quantum mechanics/molecular mechanics (QM/MM), the region of the system in which the chemical process takes place is treated at an appropriate level of quantum chemistry theory, while the remainder is described by a molecular mechanics classical force field. When electronic degrees of freedom are unimportant, classical MD simulations can be used, either using the atoms as primary interactions centers (atomistic, or all-atom MD) or by grouping several atoms together in clusters, or beads (coarse-grain MD). In this thesis we used classical MD simulations, both at all-atom and coarse-grain level of resolution. As coarse-grained models group a few atoms to one bead, the total number of particles in simulations decreases, thus speeding up computations drastically comparing with atomistic simulations (43).

At the heart of classical MD is the force field, which defines the interaction strength between all of the interaction centers. Commonly used all-atom force fields in the biomolecular area are OPLS-AA (44), AMBER (45), CHARMM (46), and GROMOS (47). Guvench et al. (48) performed a brief overview for these force fields, with respect to the modelling of lipid, proteins and other compounds. At the CG level of resolution, the most popular force field is the Martini model, explained in more detail in the following section.

### *1.2.2 MARTINI Force Field*

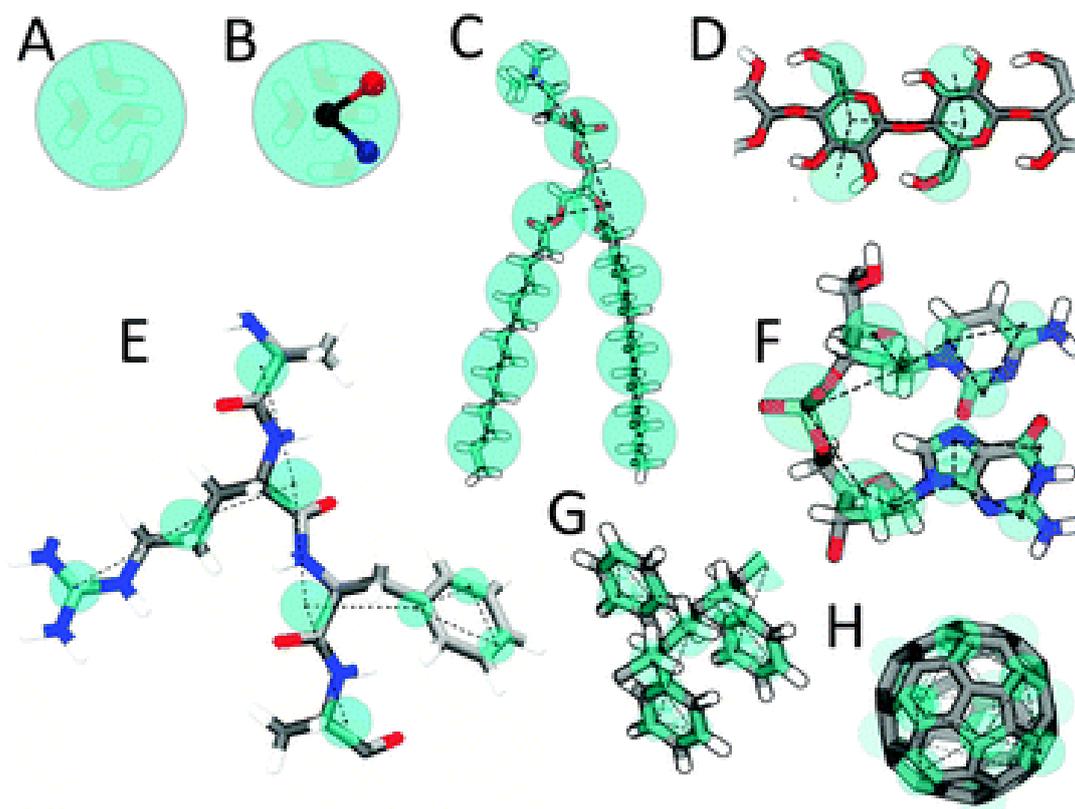
The MARTINI force field is a widely used coarse grained model in the biomolecular field which was developed by Marrink et al. (49, 50) in Groningen. It maps on average 4 heavy non-hydrogen atoms to one CG bead as the interaction center. The mapping concept consists of dividing a molecule into several small chemical building blocks. The parameterization of MARTINI force field has the target to reproduce thermodynamic data. There are in total 18 different types of beads including 4 main types: polar (P), non-polar (N), apolar (C), and charged (Q). Each main type bead has its own subtypes: polar and non-polar types were divided into 5 different types based on the degree of polarity, apolar and charged types have 4 subtypes by describing

denoting the hydrogen-bonding capabilities (d =donor, a =acceptor, da = both, 0= none).

The strength of interaction between beads is central in a force field. Similar to other force fields, MARTINI has two types of interactions: bonded and non-bonded. The bonded interactions were optimized by taking atomistic simulations as references. The non-bonded interactions between the beads were described by 10 levels of Lennard-Jones (LJ) 12-6 potentials. The 10 different strengths of interactions, which are defined by the value of the LJ well depth  $\epsilon$ , were obtained by reproducing experimental partitioning free energies of solutes between polar and non-polar solvents, and also the densities of liquids. In addition, charged beads bear charges and interact through a Coulomb potential with a relative dielectric screening constant  $\epsilon_r = 15$ .

The applications of the MARTINI force field have dramatically increased during the last 10 years, although this force field was originally developed for simulating lipids. One big advantage of the MARTINI model is its transferability that stems from the building block philosophy. This building block principle helps building MARTINI models of different classes of molecules that are compatible with each other. Apart from the original lipid membrane applications, the MARTINI model has been extended to polymers (51-53), DNA (54), carbohydrates (55), and carbon nanoparticles (56), see mapping examples in Figure 1.3. Plenty of studies (57-59) have shown that the MARTINI force field is a useful tool to investigate the interplay of protein/peptides-membranes, thus we applied this model to study interplay of AMPs and Pex11-Amph with lipid membranes.

Like other models, MARTINI model has its own shortcomings. It is important to know these drawbacks before one applies it to their systems. Firstly, due to the nature of coarse grain models, the MARTINI force field has a loss in chemical resolution. Whenever it needs to capture these details, such as receptor-ligand binding and ligand-induced conformational changes, which strictly require an accurate description with atomistic detail, an all-atom model would be preferred. Using a hybrid atomistic/coarse-grained model might be a solution, which is under development. Secondly, MARTINI proteins have their secondary structure constrained as the MARTINI model cannot account for the directionality of hydrogen bonds. Thirdly, MARTINI water (which maps 4 water molecules into one bead) is too much ordered (60). One consequence is that the formation of a water pore in a lipid bilayer is too unfavourable, which makes this mode of action of AMPs more difficult to study (61). However, this might be improved by applying a softer interaction potential to water beads in the future, which makes water interact less strongly and allow them to more easily permeate into the membrane and form pores.



**Figure 1.3** MARTINI mapping examples of selected molecules. (A) Standard water particle representing four water molecules. (B) Polarizable water molecule with embedded charges. (C) DMPC lipid. (D) Polysaccharide fragment. (E) Peptide. (F) DNA fragment. (G) Polystyrene fragment. (H) Fullerene molecule. In all cases Martini CG beads are shown as cyan transparent beads overlaying the atomistic structure. The figure is reproduced from reference (60).

### 1.3 Overview

In this thesis, we study the interplay of peptides with membrane lipids using large scale and high-throughput MD simulations. We mostly use CG models as the work horse, and refine our results using more detailed all-atom models. The mechanism of AMPs in killing bacteria is not clear yet, especially in molecular detail. MD simulations step into this field to offer a view on the dynamic behavior of interactions of AMPs with lipids. In Chapter 2 we focus on the AMP-mediated lateral segregation of anionic lipids in a membrane, one of the aforementioned disruptive factors in the mode of action of AMPs. We present a multiscale MD study of peptide binding and segregation, using the AMPs Magainin 2, BP100, and MSI-103 in interaction with a POPE/cardiolipin bilayer. In Chapter 3 we study the partitioning of AMPs on Ld/Lo phase separated membranes. We address the question whether AMPs have a preferential binding mode to either Ld or Lo domains, and to what extent the AMPs can disrupt the phase segregation. In Chapter 4 we investigated the interplay of

Pex11-Amph with peroxisomal model membranes. The simulations reveal how Pex11-Amph interacts with the membrane, and which residues are responsible for inducing membrane curvature. An outlook and summary conclude this thesis.

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