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How the Antimicrobial Peptides Kill Bacteria: Computational Physics Insights

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Abstract. In the present article, coarse grained Dissipative Particle Dynamics simulation with implementation of electrostatic interactions is developed in constant pressure and surface tension ensemble to elucidate how the antimicrobial peptide molecules affect bilayer cell membrane structure and kill bacteria. We find that peptides with different chemical-physical properties exhibit different membrane obstructing mechanisms. Peptide molecules can destroy vital functions of the affected bacteria by translocating across their membranes via worm-holes, or by associating with membrane lipids to form hydrophilic cores trapped inside the hydrophobic domain of the membranes. In the latter model, the affected membranes are strongly buckled, in accord with very recent experimental observations [G. E. Fantner *et al.*, Nat. Nanotech., 5 (2010), pp. 280-285].

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1 Introduction

Lipid bilayer membranes consisting of zwitterionic or acidic lipids are the essential components of cells and their organelles. They play very important roles in the living cells [1]: They can protect cell interior from the outside world; They can also interact with proteins and peptides to control the transport of substances into the cell and determine the metabolism of cells [2]. Antimicrobial peptides (AmPs) are bio-molecules employed by plants and animals for their defense against bacteria [3, 4]. These short chain peptides secreted by organisms are typically composed of 12-45 amino acid residues that carry

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positive charges. When binding onto the outermost leaflet of negatively charged bacteria membrane by the aid of hydrophobic and electrostatic interactions, the antimicrobial peptides fold to amphipathic secondary structures, typically α-helices and β-sheets. Such peptides can kill the bacteria via either physical, chemical, or biological processes.

The vital function of the AmPs attracts both experimental and theoretical interest to elucidate their still elusive killing mechanisms. An appealing picture of this process was provided by the phenomenological Shai-Matsuzaki-Huang (SMH) model [5–7] which suggests that the peptides kill the cell by inserting into bacterial membrane to create holes that cause cellular content to leak out: When the peptides bind onto the surface of membrane, they displace the lipids and alter the membrane structure by thinning the bilayer and increasing the local surface tension of the bilayer. When the surface tension increases over a threshold value, the bilayer will rupture and permit the peptides permeate into the interior of the target cell. According to the structure of the insertion state, a number of models are suggested, such as "barrel-stave model", "carpet model", and "toroidal-pore model".

Many theoretical and numerical methods have also been used to study the molecular mechanism of the cell lysis by antimicrobial peptides, such as molecular- mean-field theory [8], all-atom molecular dynamics simulations [9–12], and coarse-grained simulations [13–17]. Most of these approaches support the SMH model that a physical hole in the membrane is stable and is an effective mechanism of antimicrobial activity.

In our recent paper [18], we reported a numerical study of the dynamic processes of cationic antimicrobial peptide translocation across a lipid bilayer membrane composed of both zwitterionic phospholipids and acidic phospholipids. Our study employed dissipative particle dynamics (DPD) simulations [19–21] in which both solvent and counterions are included explicitly. The advantage of the DPD method is that it allows simulations of large system in long time such that the full process of the peptide transport across the membrane becomes observable. Our study [18] also supports the SMH model, that the peptide can translocate across the bilayer membrane via a transmembrane hole. But the intermediate metastable peptide insertion state is composed of only one peptide. We also found that there are two mechanisms for peptide translocation: local tension increase and electrostatic attraction. Via electrostatic attraction, the peptide translocation is more reliable and, moreover, can occur at relatively low peptide concentrations.

In this article, first we give a review on how to apply DPD simulations to study the antimicrobial peptide-bilayer membrane interactions. Then we further develop the DPD simulation into constant particle number, surface tension, normal pressure, and temperature ($N\gamma_s P_\perp T$) ensemble [22, 23]. The NPT ensemble is usually more physically relevant ensemble than the NVT (constant volume) ensemble. By modifying the interaction strength between peptides and lipids as well as interactions between peptides and water, we investigate the effects of various physical-chemical properties of the peptide on the membrane obstructing mechanism. We find that besides creating metastable physical holes, the peptides can obstruct the integrity of the membrane by forming a hydrophilic core trapped inside the hydrophobic domain of the membrane. This novel structure is