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Modeling and simulation of bacterial outer membranes and interactions with membrane proteins

Dhilon S Patel, Yifei Qi and Wonpil Im

The outer membrane (OM) of Gram-negative bacteria is composed of phospholipids in the periplasmic leaflet and lipopolysaccharides (LPS) in the external leaflet, along with β-barrel OM proteins (OMPs) and lipidated periplasmic lipoproteins. As a defensive barrier to toxic compounds, an LPS molecule has high antigenic diversity and unique combination of OM-anchored lipid A with core oligosaccharides and O-antigen polysaccharides, creating dynamic protein–LPS and LPS–LPS interactions. Here, we review recent efforts on modeling and simulation of native-like bacterial OMs to explore structures, dynamics, and interactions of different OM components and their roles in transportation of ions, substrates, and antibiotics across the OM and accessibility of monoclonal antibodies (mAbs) to surface epitopes. Simulation studies attempting to provide insight into the structural basis for LPS transport and OMP insertion in the bacterial OM are also highlighted.

Address

Department of Biological Sciences and Bioengineering Program, Lehigh University, PA 18015, USA

Corresponding author: Im, Wonpil (wonpil@lehigh.edu)

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Introduction

The Gram-negative bacterial OM is unique in biology with a well-pronounced asymmetric bilayer with LPS in the outer leaflet and phospholipids in the inner leaflet [1,2]. Exchange of molecular species across the OM is ensured by various *β*-barrel OMPs and periplasmic lipoproteins. The OM separates the periplasm from the external environment and functions as a selective barrier that prevents the entry of toxic molecules such as antibiotics and bile salts into the bacteria, which is crucial for survival of bacteria in diverse and hostile environments, but causes significant threats to the public health [3,4].

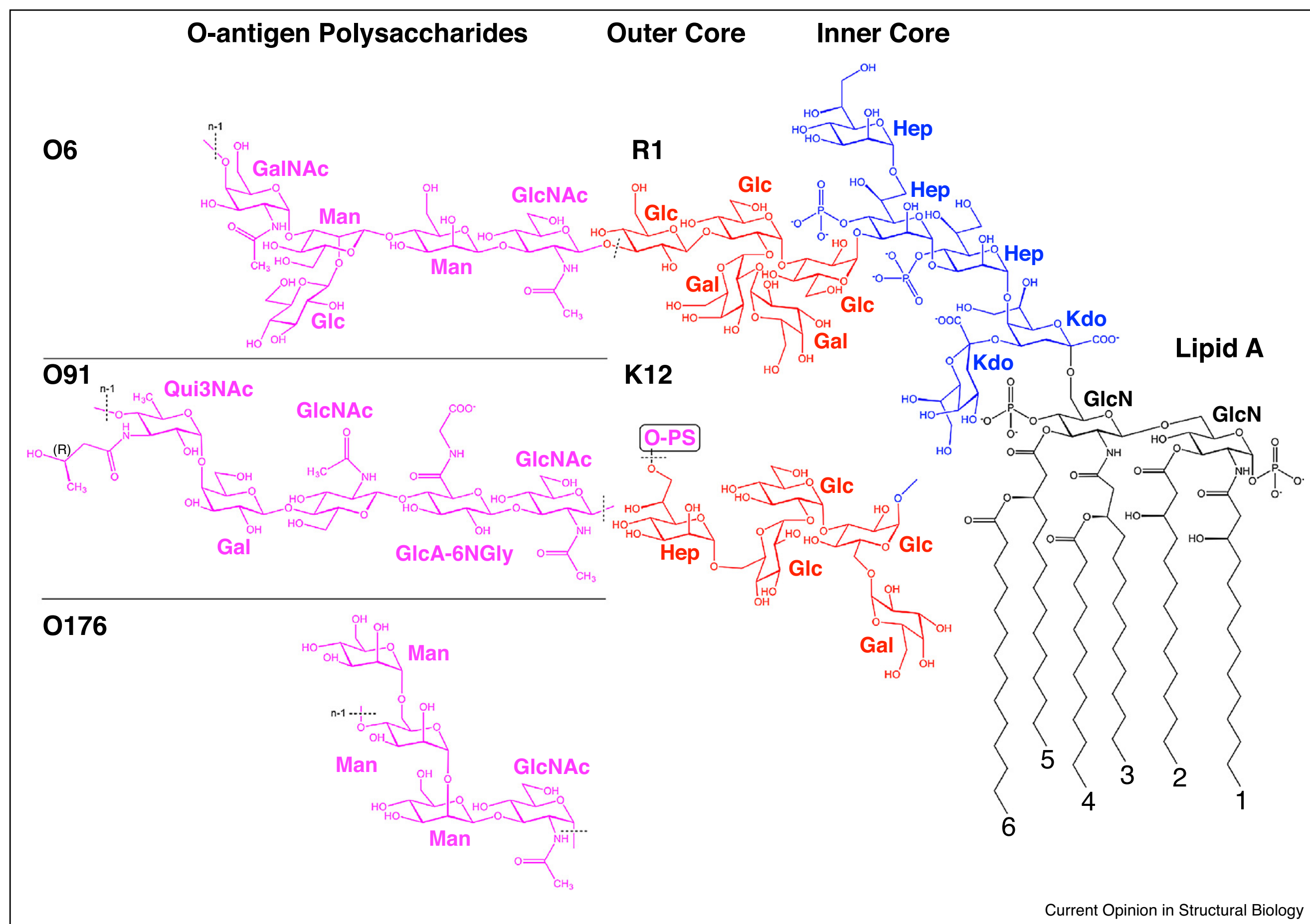
LPS is vital for both the structural and functional integrity of Gram-negative bacteria. It is composed of a phylogenetically conserved lipid A, a (inner and outer) core oligosaccharide, and highly diverse O-antigen polysaccharides with various lengths of repeating units that determine bacteria's antigenic diversity [5,6]. Most widely studied *Escherichia coli* OM has LPS molecules covering nearly three quarters of the OM surface per cell [7]. The bacterial growth conditions influence the phenotypic expression of surface determinants such as rough (absence of O-antigen polysaccharides) to smooth LPS (presence of O-antigen polysaccharides) [4]. For example, *E. coli* is reported to have five known core structures (R1-R4 and K12) and more than 180 O-antigen serotypes (Figure 1) [8•]. Clearly, the heterogeneity of core structures as well as O-antigen unit length and sequence diversity can create dynamic protein–LPS and LPS–LPS interactions. Understanding these interactions at the molecular level can provide insight into how bacteria restrict antibodies' access and increase antibiotic resistance, as well as how the permeability of the OM is affected even in different serological groups of the same species [9,10].

Advances in modeling and simulation of complex membrane models along with increasing computational resources and growing experimental data have made it possible to explore structural properties and dynamics of different OM components and their roles in transportation of ions, substrates, and antibiotics across the OM, as well as importance of protein–LPS interactions in mAb accessibility [11–13]. In this review, we highlight such modeling and simulation efforts together with computational studies of LPS transport and OMP insertion in the bacterial OM.

Structure, dynamics, and flexibility of LPS in the OM

Characterizing LPS structure and dynamics as well as physicochemical properties of the OM is crucial for understanding its biological roles, including the agonistic/antagonistic action on the host innate immune response. Lipid A, also known as endotoxin or pathogen associated molecular patterns, carries toxic properties of LPS and acts as a potent activator of the host innate immune system mainly via the TLR4/MD-2 receptor complex [14]. Lipid A possesses an archetypal structure of a *β*-(1 → 6)-linked D-GlcN disaccharide (Figure 1) that is acylated with four to eight fatty acids of different lengths, and there exist complex chemical substitutions

Figure 1



Chemical structures of *E. coli* R1.O6 LPS along with K12 core and two other O91 and O176 antigen structures (Kdo: 2-keto-3-deoxyoctulosonate; Hep: l-glycero-D-manno heptose; Man: D-mannose; Glc: D-glucose; Gal: D-galactose; GlcN: D-glucosamine; GlcNAc: *N*-acetyl-D-glucosamine; GalNAc: *N*-acetyl-D-galactosamine; GlcA-6NGly: D-Glucoronate-6-*N*-Glycine; Qui3NAc: D-Quinovose-(*R*)-3-hydroxybutyramido).

in lipid A from certain bacterial species [15]. How these variations affect the packing, rigidity, and permeability of LPS bilayers and their interactions with OMPs and small molecules is an interesting and emerging research topic.

Kim *et al.* [16] recently investigated the bilayer properties of 21 distinct lipid A types from 12 different bacterial species (having different acyl chain number (N_{CHAIN}) and length (L_{CHAIN}), and various chemical modifications) using all-atom molecular dynamics (MD) simulations and the CHARMM force field (FF) [17–21]. The area per lipid A increases as a function of N_{CHAIN} and the membrane thickness increases as a function of L_{CHAIN}. Influence of neutralizing ion type such as Ca^{2+}, K^+, and Na^+ on the stability and the integrity of lipid A bilayers appears to be minimal. However, the residence time of Ca^{2+} ions near the lipid A headgroups is longer than those of K^+ and Na^+ ion types, which is well correlated with lower lateral diffusion and higher compressibility of lipid A in Ca^{2+} neutralized systems. The effects of temperature, nature of cations, and chain numbers on the physicochemical properties of lipid A bilayers were also investigated using MD simulations with the GROMOS, GLYCAM, and AMBER FFs [22–25].

Wu *et al.* performed the MD simulation studies on *E. coli* LPS-only (Figure 2**a**) and OM-like bilayers (with and without OMPs (Figure 2**b** and **c**)) using different components of LPS, such as lipid A only, lipid A + R1-core (LPS0), LPS0 + 5 O6 antigen repeating units, and LPS0 + 10 O6 antigen repeating units [26,27]. Additions of LPS components indeed influence both LPS structures and its overall bilayer properties. Analyses of LPS-only simulations show that the area per lipid A increases, and bilayer order decreases as more LPS components are added, indicating slightly looser lipid A packing in the smooth LPS membrane compared to the rough LPS systems. Interestingly, more than 50% of the Ca^{2+} coordination sites are occupied by water molecules in the lipid A head

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