Amgen Seminar Series in Chemical Engineering

in

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Molecular Modeling of Biological Systems: from a Force Field Study to Modeling of an Anti-Microbial Peptide in Water and a Complex *S. aureus* Membrane

By

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Interest in studying anti-microbial peptides (AMPs) has increased because of their potential as a future applicable antibiotic drug. In my research under supervision of Professor Greenfield, we attempt to understand the interaction of AMPs against membrane of bacteria. We are studying the structure of two novel hybrid AMPs LM7-1 and LM7-2 that were designed previously in Professor Martin's research group (Cell and Molecular Biology Department). These AMPs differ in sequence only at the 15th residue. Several experimental studies have been successfully investigated mechanisms of AMPs against bacteria, but there is still much uncertainty in the exact mechanisms because of experimental restrictions. Since molecular modeling provides atomistic details and 3D structure of a system, it can significantly contribute to investigating these mechanisms in more detail. In this talk, I will show how molecular modeling helps in understanding complex systems and deciphering biochemistry information that it is impossible to obtain by experiments. And since the precision of biomolecular modeling results is significantly based on force field (FF) parameters, the importance of developing FFs will be demonstrated in this talk.

Force Field development. Our simulation results on the basis of CHARMM36 (C36) FF show that the structures of two aromatic amino acids, Tryptophan (Trp) and Tyrosine (Tyr), deviate from planarity. Hence, we investigated the geometry, dynamics, and out-of-plane vibrations of atoms in these rings by imposing improper torsion and changing torsion angle force constants. To that end, molecular dynamics (MD) simulation and all-atom normal mode analysis (NMA) were implemented. We could match the pattern and frequencies of out-of-plane vibrations of these rings with Raman and infrared spectra, and decrease the extent of out-of-plane vibrations for atoms in these rings.

A Helical Peptide in water. AMPs usually have a helical structure on the membrane of bacteria. Some studies have stated that the flexible loop at the middle of helical AMPs, which leads peptide to bend and snap the lipid bilayer, has a direct effect on AMPs activity against bacteria. We computationally studied dynamics and vibrations of a helical and a helix-hinged-helix structure of a LM7-2 in solution. Although some vibrational experimental studies have been done on proteins or peptides, we show extended and interesting details about peptide vibrations by our study. We applied instantaneous NMA and Fourier Transform method to understand how a change in the structure of a peptide will affect peptide fluctuations. Raman and infrared spectra cannot indicate these motions that correspond to the low intensity measured frequencies.

A complex lipid membrane. Lipid bilayers play a crucial role in a peptide-membrane interactions. Therefore, more real system of lipids will provide more detail of this interaction. To that end, we have designed the most realistic *S. aureus* membrane by including 19 different types of lipids, compared to other simulations that implemented a range of 2-5 different lipids. We applied Reverse Monte Carlo method to match lipid bilayer composition to experimental results in the literature. Dynamics and membrane characteristics of this complex system were studied.

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