419c Investigations of Hydrophobic Mismatch in Lipid/Peptide Systems by Molecular Dynamics Simulations

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Membrane proteins constitute a significant fraction of the genome. It has been proposed that it is energetically favorable for the membrane protein to match the hydrophobic thickness of the surrounding lipid bilayer with a similar length of hydrophobic domain of the constituent peptides. When a hydrophobic mismatch exists, the peptide-lipid system undergoes compensatory adjustments to mitigate the energetically unfavorable mismatch in lengths. Such adjustments in structure or orientation of peptides or lipids could play important roles in membrane protein activity. Due to the highly hydrophobic nature of the membrane proteins, experimental determination of structure and function is difficult. Molecular dynamics simulations are a valuable tool to investigate such mechanisms.

We have performed a systematic, large scale (>100ns) molecular dynamics simulation study of the interactions of model transmembrane KALP peptides in model lipid bilayers. Peptides and lipids of several lengths were studied, yielding a wide range of positive and negative mismatch conditions. Peptide tilt was found to be the dominant mechanism of mimatch alleviation under positive mismatch conditions, while a combination of local bilayer bending and side chain snorkeling was found to be the dominant mechanism of alleviation under negative mismatch conditions. Our results predict larger tilt angles of the peptides under positive mismatch conditions than do NMR experiments. To explain these discrepancies, work is under progress to investigate the various oligomerization states of these model peptides.