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Escaping the Cave: How a Computational Microscope Can Help Us Understand Membrane-Active Peptides

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One of the grand challenges of chemistry has been to develop the ability to characterize chemical and biological phenomena on length and timescales that span dozens of orders of magnitude. For example, understanding cell metastasis requires knowledge of the molecular interactions that facilitate cell growth and metabolism, or scale-up of the synthesis of small molecule inhibitors requires knowledge of the phase behavior of bulk quantities of the drug. Molecular dynamics (MD) simulations have emerged over the past 40 years as an invaluable tool in characterizing the "jigglings and wigglings" of biomolecules that lead to biological function, providing an atomistic level of detail that is often inaccessible even to techniques such as nuclear magnetic resonance (NMR) spectroscopy. The pH-Low Insertion Peptide (pHLIP) is a pH-sensitive peptide that traditionally had been thought to follow the partitioning-folding coupling paradigm of most membrane-active peptides: at physiological pH, pHLIP will bind to eukaryotic plasma membranes in a coiled state, but at acidic pH, it will fold and insert into the membrane. This model was largely developed based on circular dichroism (CD) and tryptophan fluorescence spectroscopy, two low-resolution techniques. Over the past four years, our lab has used MD simulations to more fully understand the behavior of pHLIP in environments typical of drug delivery (in solution, bound to a membrane surface, and inserted into a membrane). We have discovered that pHLIP does not completely conform to partitioning-folding coupling; rather, it is finely tuned to respond to changes in its environment, both as a function of pH, membrane composition, and peptide sequence. Together, these results are providing critical understanding of the mechanism of pHLIP that will allow for design of applications in diagnostic imaging and targeted drug delivery

Date: Wed, Nov. 28, 2018
Time: 4:30-5:30 pm
Location: 208 Clark Hall