CHEMISTRY & BIOCHEMISTRY COLLOQUIUM: Developing computational tools to study molecular interactions in protein dynamics trajectories

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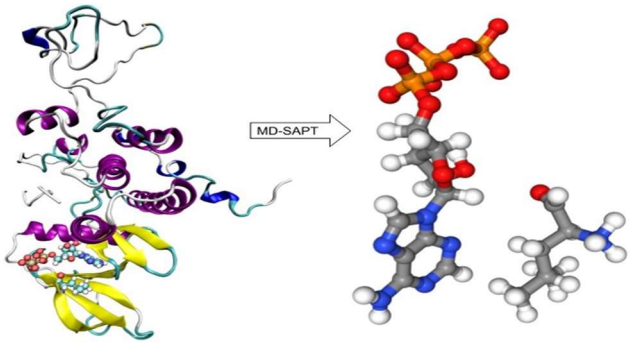
Date:
9/16/2022

Time:
1:30 PM-2:50 PM

Location:
COB 267

About The Speaker:

Ashley Ringer McDonald received her Ph.D. from Georgia Tech in 2009. After completing a post-doc at the University of Maryland School of Pharmacy, Dr. McDonald joined the faculty in the department of Chemistry & Biochemistry at California Polytechnic State University in 2011. She was tenured and promoted to associate professor at Cal Poly in 2017. She is a member of the Board of Directors at the Molecular Sciences Software Institute (the MolSSI; molssi.org) where she serves as the director for education, training, and faculty development. McDonald is the chair-elect for the American Chemical Society Division of Computers in Chemistry and an active member of the MERCURY Consortium.



Abstract:

This seminar will discuss our work on the MEK1 signaling protein and computational tools we have developed to study the molecular interactions in MEK1. MEK1 is a protein kinase in the MAPK cellular signaling pathway and is notable for its dual-specificity and its potential as a drug target for a variety of cancer therapies. While much is known about the key role of MEK1 in signaling events, understanding of the structural features that sustain MEK1 function remain limited due to absence of crystal or NMR structural insights into the phosphorylated and activated form of MEK1. In this work, homology modeling is used to overcome this limitation and generate computational models of the doubly-phosphorylated active MEK1 conformation. A variety of models were generated using crystal structures of active protein kinases as homology model templates. These models were equilibrated using molecular dynamics simulations, and each model was validated against several known st ructural characteristics of activated kinases. The best model structures were used in docking studies with ATP and a small peptide sequence that represents the activation loop of ERK2 to identify the most important residues in stabilizing protein docking and phosphorylation. These results provide insights for the pursuit of structure guided mutagenesis and drug design. To characterize the molecular interactions in MEK1 using quantum mechanics methods, we have developed MDSAPT, a python package designed to manage the entire workflow of analyzing molecular interactions in a molecular dynamics trajectory.

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