Title: Computational studies on RNA: From structure prediction to drug design

Abstract: Visualizing the biology of cells in real time can transform our knowledge of the "rules of life," leading to pivotal insights on disease progression and solutions. For example, aberrations in RNA underlie nearly every disease, ranging from neurological diseases to viruses to cancer. Thus, developing computational models that can reliably predict the atomistic structure of RNA will have far reaching and profound effects on our ability to rapidly and accurately develop targeted pharmacotherapeutics for millions of Americans. Since the creation of modern computers, researchers have tried to harness computational power to speed up scientific discovery. Today, we can utilize computational methods and tools to describe chemical dynamics. For example, using molecular mechanics force fields, it is possible to perform molecular dynamics (MD) simulations in microseconds or faster time scales for biological systems like RNA. Application of these methods lets us compare the structural and thermodynamic properties of RNA with experimental data that can visually depict the atomistic details, which are hard to get with the current experimental techniques.

Current research has yielded better algorithms to study structural properties of biomolecular systems. Yet, computational models must be precisely refined to make reliable and effective predictions for scientific discovery, particularly for RNA based investigations. With a credible force field, one has the possibility to study the atomistic details and dynamics of biomolecules, which is challenging with the current experimental techniques. In the first part of my lecture, I will talk about the AMBER RNA force field, and how we improved several of the torsional parameters for RNA and showed that dramatic improvements are observed in our predictions (J. Chem. Theory and Comput. 6, 1520-1531, **2010;** J. Phys. Chem. B 121, 2989-2999, **2017**).

In the second part, I will talk about a novel method my lab is developing to provide a solution to the so-called 'RNA folding problem', where we are developing an algorithm to predict 3D RNA structures from sequence. Predicting 3D structures of RNA from sequence is one of the ambitions of researchers working in the field of computational chemistry. Yet, RNA folding is a challenging problem, which requires a proper understanding of physico-chemical properties of RNA. We address the use of physics-based approaches to provide a solution to the 'RNA folding' problem. By studying the energy landscapes of RNA dinucleotide monophosphates (DNMP), one can determine both the structural and thermodynamic properties for RNA DNMPs, which can be used to build an 'RNA dimer library'. These RNA fragments, then, can be used as LEGO pieces to predict the 3D structures. We applied our method to 21 RNA tetraloop hairpins, which yielded very promising results. We are currently creating a Monte Carlo Simulator for this purpose, as well as extending the work to investigate RNA internal loops.

In the last part of my talk, I will discuss the 'Dynamic Docking' approach my lab has been developing. As described above, a good quality RNA force field is crucial as it allows us to investigate biological important RNA systems, such as RNA internal loops, using computational methods. For example, expansion of r(CUG) repeats, which have periodic 1×1 UU internal loop motifs, is found in the non-coding regions of mRNA and cause myotonic dystrophy type 1 (DM1). Since these expansions are in non-coding regions, the diseases are caused by RNA gain-of-function mechanism where proteins such as muscleblind-like 1 protein (MBNL1) surround the expanded RNA repeats. Designing small molecules, which will target RNA, is one way to inhibit the RNA/MBNL1 complex and ameliorate the disease. There are many docking algorithms to study small molecule protein interactions, but these codes assume that the protein has a well-defined structure, which is not the case in RNA loops. Thus, a dynamic binding algorithm, which utilizes a physics-based approach, such as Molecular Mechanics, can be applied to study small molecule-RNA interaction. We showed that using such a dynamic approach, we can predict the experimental results of nine small molecules targeting RNA CUG repeats (Biophys. J. 122, 180-196, **2023**). Results are very promising as it allows one to study small molecule/RNA binding without the use of experimental approaches. We are currently extending this work, where we want to optimize lead compounds using *in silico* approaches.

About Me: I have training in theoretical and computational biophysics as well as in NMR spectroscopy specializing in RNA chemistry. I have received my Ph.D. in Physics from the University of Rochester and have had postdoctoral trainings at Northwestern University and the University of Cambridge. Currently, I am an Assistant Professor in the Department of Chemistry and Biochemistry at the Florida Atlantic University. Furthermore, I am affiliated with the UF-Scripps Research Institute Florida as a Professional Scientific Collaborator and the FAU Wilkes Honors College as an affiliate faculty and am a member at the MCIFAU FDoH Cancer Center of Excellence. My lab creates new computational methods and models to investigate the 3D structures of RNA, and how small molecules target functionally important RNA motifs. We actively collaborate with experimental researchers.