School of Molecular Sciences
Arizona State University

SMS Spring 2023 Seminar Series

Friday Mar 31 | 3pm | Biodesign Auditorium

Modeling molecular recognition in flexible systems

Most macromolecules interreact with other molecules in order to carry out their biological role. By understanding the structures of complexes, the different binding modes and the interactions that drive binding we can design new molecules that promote or inhibit proteins. Computational modeling has played a significant role in predicting and identifying small molecule binding through techniques such as docking and alchemical free energy calculations. However, the success rate with flexible molecules is much lower.

In this talk I will present two directions in our efforts to combine information and simulations to predict the structures of complexes involving conformational changes. In the first example, we predict the structures of intrinsically disordered peptides that fold upon binding the extra terminal domain of bromo and extra terminal domain proteins – a class of proteins involved in cancer and viral infection. In the second example I will present our work on predict protein-nucleic acid complexes using generic information and our MELD simulation framework.

Alberto Perez, PhD

Assistant Professor, University of Florida

Alberto Perez is an assistant professor in the department of chemistry and quantum theory project at the University of Florida. His laboratory is interested in the structures, dynamics and functionality of proteins, peptides, and nucleic acids and how their interactions lead to functionality. Their interest in recent years has been the study of protein-protein interactions mediated through peptide epitopes that have a role in disease. These peptide-protein complexes are challenging to characterize both computationally and experimentally due to their large flexibility. They develop and apply computational tools to predict structures, relative binding affinities and mechanisms of action. During his post-doctoral training in Ken Dill's group he co-developed MELD (Modeling Employing Limited Data) to integrate sparse, ambiguous, and noisy data into simulations – which his group continues to develop. The approach significantly accelerates sampling of states compatible with subsets of data. At the University of Florida his group has established collaborations to incorporate new sources of experimental data such as CryoEM and NMR Chemical Shift perturbation towards structure determination. They combine these methods with more traditional simulation approaches to map the energy landscape of the biomolecules and understand their binding or folding landscapes. Finally, to identify strong peptide binders to proteins of interest, they developed a competitive binding approach using MELD. For the purposes of the proposed work, they have recently developed a high throughput competitive binding assay based on the AlphaFold machine learning approach that can rank peptides by their binding affinity.

*ZOOM option available: https://asu.zoom.us/j/89234740626